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Environmental Factors, Metabolic Profile, Hormones and Breast and Endometrial Cancer Risk

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Tromsø 2004

Institute of Community Medicine
University of Tromsø, Norway

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CONTENTS

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The medical program at the University of Tromsø (UiTø) integrated disease prevention as an essential part of medical practice, and I learned the great difference epidemiological evidence has made in this field.

In several prospective studies, Inger Thune has demonstrated that physical activity and body weight influence the risk of cancer at several sites, including the breast. My work has been inspired by her ideas about plausible biological links between energy balance, in particular, and breast cancer and her strong belief in energy balance as an important modifiable risk factor for breast cancer. Seeking a better understanding of the biological mechanisms underlying the observed associations between lifestyle and cancer risk, Inger Thune designed the Energy Balance and Breast Cancer Aspects (EBBA)-study, which provided unique data for part of my thesis. Inger Thune also introduced me to the large Norwegian three-county cohort conducting further research on energy balance, metabolic profile and risk of breast and endometrial cancer. I am deeply grateful to Inger Thune for generously sharing her knowledge and ideas with me and for thoroughly supporting me in all phases of my PhD study. I especially appreciate how she cared for all aspects of my life, including my family.

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LIST OF PAPERS

This thesis is based on the following papers

I Furberg A-S, Sandanger T, Thune I, Burkov IC, Lund E. Fish consumption and plasma levels of organochlorines in a female population in Northern Norway. *Journal of Environmental Monitoring* 2002;4:175-181.

II Furberg A-S, Jasienska G, Bjurstam N, Torjesen PA, Emaus A, Lipson SF, Ellison PT, Thune I. Metabolic syndrome and hormonal profile – serum high-density lipoprotein cholesterol as a plausible biomarker of breast cancer risk. The Norwegian EBBA-study. *Conditionally accepted by Cancer Epidemiology, Biomarkers and Prevention.*

III Furberg A-S, Thune I. Metabolic abnormalities (hypertension, hyperglycemia and overweight), lifestyle (high energy intake and physical inactivity) and endometrial cancer risk in a Norwegian cohort. *International Journal of Cancer* 2003;104:669-76.

IV Furberg A-S, Veierød MB, Wilsgaard T, Bernstein L, Thune I. Serum high-density lipoprotein cholesterol, metabolic syndrome, and breast cancer risk. *Conditionally accepted by the Journal of the National Cancer Institute.*

The papers will be referred to by their Roman numerals in the text.

1. INTRODUCTION

Breast cancer is the leading cancer among women in the Western world. In Norway, 2,503 cases of female breast cancer were diagnosed in 2000, which corresponds to an age-adjusted incidence rate of 72.1 per 100,000 women per year (1). The risk of breast cancer increases with age from puberty, doubling about every 10 years until the menopause, when the rate of increase slows dramatically and a flattening of the age-specific incidence curve is observed in some populations (1). In general, breast cancer spreads to distant organs and progresses to fatal disease more rapidly the younger the woman is at the time of diagnosis (2). This has made breast cancer the leading cause of death among Norwegian women aged 35–55 years in 2001 (3). Endometrial cancer is the most common type of malignant tumour in the uterine corpus. In Norway, 554 cases of corpus uteri cancer were diagnosed in 2000, which corresponds to an age-adjusted incidence rate of 14.6 per 100,000 women per year (1). In contrast to breast cancer, endometrial cancer is entirely a disease of middle-aged and elderly women.

There is however, considerable variations in the age-adjusted incidence rates of breast and endometrial across counties of Norway; counties with the largest proportions of urban population (i.e. Oslo) have incidence rates above the national average, whereas less urban areas, such as Finnmark, have lower incidence rates as these figures demonstrate; age-adjusted incidence rates 1996–2000 per 100,000 women per year for breast cancer in Oslo, 70.2, and in Finnmark, 54.7, and age-adjusted incidence rates 1996–2000 per 100,000 women per year for corpus uteri cancer in Oslo, 14.2, and in Finnmark, 12.7 (1). Similarly, breast and endometrial cancer are more frequent among women in industrialized countries than among women of the same age in developing countries worldwide [i.e. updated estimates of age-adjusted incidence rates to the year 2000 (per 100,000 women per year); Breast cancer: Northern America, 90.4 and Eastern Africa, 20.2; Corpus uteri cancer: Northern America, 15.5 and Eastern Africa, 3.4] (4,5). During the past 50 years, there has been a steady increase in the number of both breast and endometrial cancers diagnosed each year in Western countries, which can only partly be explained by aging of the total population (4).

Migrant studies suggest that environmental factors account for some of the observed differences in incidence rates of breast and endometrial cancer across populations and for the increase in breast and endometrial cancer rates in the Western world (6,7). A broad definition

of environmental factors includes dietary, social and cultural practises. Due to the universal nature of environmental factors, even a weak biological effect on carcinogenesis may have a large impact on the breast and endometrial cancer burden at the population level. Therefore, the investigation of environmental exposures that may have an impact on breast and endometrial cancer etiology should be considered, and studies should seek to identify modifiable risk factors that may reduce breast and endometrial cancer related suffering and death and especially the threat to women in mid-life.

Both the breast and the endometrium are epithelial organs that are dependent on sex hormones for development, growth, maturation and cyclic function. It is generally thought that cancers in these organs result from a subtle imbalance in the complex regulatory cycles to which the breast and endometrial tissue are exposed (8,9). It has been hypothesised that environmental factors may promote breast and endometrial cancer mainly by facilitating a hormonal milieu that stimulates the mitotic rate of the epithelial cells and increases the genetic instability of the cells through reduced DNA-repair, among other factors (9-11). Yet, some environmental factors may cause direct DNA damage (10) and contribute to the malignant transformation of the epithelial cell and the initiation of breast and endometrial cancer.

In most cases, the development of breast and endometrial cancer with environmental agents is a long and complex process that involves the mutation of multiple genes; the induction period between exposure and disease occurrence may be 10–20 years. For breast cancer specifically, evidence from both animal and epidemiological studies suggests that there may be vulnerable periods, perhaps in utero, during adolescence, or between menarche and birth of first child, when exposure is most important (12-14). Thus, an ideal basis for the development of effective ways to prevent breast and endometrial cancer would be an understanding of the natural history of the malignancies including identification and quantification of important environmental factors, and timing in relation to induction period, and timing in relation to age of the tissue (i.e. development and maturation of the breast and the endometrium) and life cycle development.

Environmental factors

1.1 Fish consumption and organochlorines

Fishing has been an essential activity for humans historically. Today, fish and marine mammals are still a traditional food source in certain coastal populations, particularly in Norway; besides being an important source of nutrition, this traditional food serves as a focus for cultural and social activities (15). Among the general population, seafood is promoted as part of a healthy diet with frequent references to the cardio-protective effect of ω-3 fatty acids (16). A steady supply of fresh and frozen fish and shellfish maintains a relatively high consumption of seafood in Norway of 65 g per day per capita (17). Because of this widespread use of seafood, reports on environmental contaminants in marine organisms have raised questions about possible harmful effects on human health. The topic was recently actualised by a study of dioxins in salmon including a risk analysis indicating that consumption of farmed Atlantic salmon may pose health risks that detract from the beneficial effects of fish consumption (18).

Dioxins belong to a mixed group of synthetic, halogenated aromatic compounds called organochlorines (19). Organochlorines are characterized by high resistance to biodegradation and high lipophilicity and accumulate in the fatty tissues of living organisms. Organochlorines were introduced into the market around 1930, and have been extensively used as industrial products or as pesticides since that time. For example, polychlorinated biphenyls (PCBs) are a group of 209 congeners that are used in electrical transformers, in paint, plastics and sealants. Additionally, 2,2′-bis(*p*-chlorophenyl)-1,1-dichloroethylene (*p,p′*-DDE) is metabolised from 2,2′-bis(*p*-chlorophenyl)-1,1,1-trichloroethane (*p,p′*-DDT) which was commonly used as a pesticide on a variety of agricultural crops and is still in use for the control of mosquitoes that spreads malaria.

Despite restrictions in the use of organochlorines in the 1970s in Europe and North America, these organochlorines persist in the environment due to their long half-lives; studies of highly exposed occupational groups of people have found a PCB half-life in the range 5–40 years, depending on specific congener make-up of the PCB mixtures (20). Furthermore, organochlorines still spill into the ecosystem from continued use in developing countries and are spread worldwide by atmospheric and oceanic streams. In the Northern Hemisphere interaction of geographical and climatic factors and biochemical properties of the

organochlorines, in particular, brings a burden to the Arctic ecosystem. Due to biomagnification of organochlorines in marine food webs, humans are exposed to these contaminants mainly through diets containing marine mammals, birds, eggs and fish (15).

In animal studies, many organochlorines are genotoxic or tumor promoters (21-25). Increased cancer incidence and mortality have been found among humans exposed to high levels of organochlorines either accidentally or as industrial workers (26,27). The International Agency for Research on Cancer (IARC) has classified the most toxic organochlorine TCDD (2,3,7,8-tetrachlorodibenzo-*para*-dioxin) as carcinogenic to humans, whereas others are considered as possible human carcinogens (28).

In recent years, organochlorines have attracted increasing attention in breast and endometrial cancer research because, in addition to their persistence and carcinogenicity, certain organochlorines are able to mimic the activity of reproductive hormones in laboratory tests and in wildlife (29,30). For example, experimental studies suggest that a DDT metabolite (i.e. o,p'-DDT) is an estrogen agonist, which increases DNA-synthesis and epithelial cell proliferation in the breast and endometrium. This compound promotes mammary gland development and uterine growth (29,31) and precipitates precocious puberty in female animals. PCBs have exhibited estrogenic as well as anti-estrogenic activity in vitro and in vivo, depending on the congener studied (32,33).

Consequently, organochlorines are often referred to as "endocrine disruptors". An endocrine disruptor is a chemical that interferes with the function of the endocrine system by mimicking a hormone, blocking the effects of a hormone, or by stimulating or inhibiting the production or transport of hormones (34). In 1993, Davis et al. (35) hypothesized that endocrine disruptors might play a role in breast cancer in the general population and that reductions in exposure might provide an opportunity for primary prevention of the disease.

While there have been several studies of subgroups heavily exposed to organochlorines either accidentally, occupationally or through dependence on contaminated food sources for life (15,26,27) less is known about the levels of organochlorines in the general population.

1.2 Energy intake, physical activity, and metabolic profile

Eating behaviours bridge the gap between the nutritional environment and the biological mechanisms for weight control (36). The quantity and the quality of the food consumed, the frequency of meal consumption, and the factors motivating one to eat are important aspects of food and energy intake regulation. Due to this complexity in the determinants of diet, energy intake may be regarded as a multifaceted exposure with large variation throughout human history and between people of different societies.

More than 80 years ago, Hoffman suggested that overnutrition was a major factor in carcinogenesis (37). Ecological studies support the idea that a high energy diet may represent a risk factor for cancer (38). In a relatively recent ecological study among women from five populations, mean salivary progesterone concentration during an entire menstrual cycle was positively related to both mean total energy intake and to breast cancer incidence (39). Several studies have found that energy restriction inhibits the growth of spontaneous, transplanted or induced tumours in rodents (40,41). Furthermore, experimental evidence is consistent with the hypothesis that energy restriction enhances DNA repair, moderates oxidative damage to DNA and reduces oncogene expression (42). Despite this suggested potent anti-tumor action of energy restriction, most case-control and cohort studies do not support its role in breast and endometrial cancer, as well as in other cancers in humans (43-46).

Physical activity is defined as any bodily movement produced by contraction of skeletal muscle that substantially increases energy expenditure. The energy expended during physical activity may represent between 15 and 50% of total energy expenditure, depending on the amount of physical activity performed and the body mass (47). Leisure-time or recreational physical activity is a broad description of the activities one participates in during free time, based on personal interests and needs. Occupational physical activity is that associated with the performance of a job, usually within the time frame of an 8-hour workday.

Today it is generally thought that physical activity is good for health. Besides the well-known beneficial effects of physical activity on the respiratory and cardiovascular systems, musculature and bones, other metabolic and physiological changes, in particular, link physical activity to cancer risk. These include alterations of immune status and hormonal balance. Greater levels of energy expended in physical activity per week have been associated with reduced levels of ovarian hormones (48,49). However, evidence that upholds physical activity

for cancer prevention in humans has accumulated only during the last two decades. For example, there is evidence from a majority of larger epidemiological studies, including a prospective study in Norway (46), that both leisure-time and occupational physical activity are associated with approximately a 30% reduction in the risk of breast cancer (50,51). Observations from a growing but limited number of studies on endometrial cancer suggest a protective effect of physical activity. There is inconsistent evidence regarding the type of activity (i.e. leisure-time or occupational physical activity) (50,51), and this relationship has only recently been studied among Norwegian women (52).

The modern social environment of industrialized societies promotes sedentary lifestyles through increased automation, and there is a natural decline in physical activity by increasing age. Thus, as the westernised lifestyle is spreading and people are getting older worldwide, we should attempt to understand more about what kinds, how much, how frequent, how intense, and for whom, physical activity should be prescribed, even if the effect on cancer risk in most studies is small.

Besides being possible independent risk factors for breast and endometrial cancer per se, energy intake and physical activity are major determinants of energy balance and body mass, which should be evaluated as an independent exposure. Obesity is caused by a positive energy balance brought about by a complex interplay between biological (age, sex, genes) and environmental factors. However, it has been suggested that the current overweight and obesity epidemics have been caused primarily by a general reduction in the level of physical activity in the population (53).

The World Health Organization (WHO) has provided a classification of individuals based on weight relative to height (body mass index, BMI) as a gauge of obesity that applies to both women and men and to all adult age-groups (Table 1) (54). In community studies the classification scheme has been simplified and the use of overweight (BMI, 25.0 to 29.9 kg/m^2) and obesity (BMI, $\geq$ 30.0 kg/m^2) as boundaries has been justified in terms of the differences in aetiology and morbidity and mortality rates of the conditions. In general, obese individuals have experienced a more pronounced positive energy balance (excessive energy intake relative to energy expenditure) that has been sustained for a longer period of time, than overweight people. Obesity is established as one of the most prevalent risk factors for

common chronic diseases as cardiovascular diseases and non-insulin-dependent diabetes mellitus (55,56), and early death (57,58), and more recently of cancer at several sites (50).

Table 1. World Health Organization (WHO) Classification of adults by Body Mass Index (BMI) (54)

WHO classification	BMI (kg/m^2)	Associated health risk
Underweight	< 18.5	Low (but risk of other clinical problems increased)
Normal range	18.5–24.9	Average
Overweight	25.0 or higher	
Pre-obese	25.0–29.9	Increased
Obese class I	30.0–34.9	Moderately increased
Obese class II	35.0–39.9	Severely increased
Obese class III	≥ 40.0	Very severely increased

Data from almost all countries of the industrialized world, and even those from the third world, reveal that a growing proportion of children and adults are overweight or obese (59). Presently, 64.5% of United States adults age 20 years and older are overweight and 30.5% are obese (60). Now in many European countries significantly more than half the adult population is overweight and up to 30% of adults are obese (61). There has been a dramatic increase in the prevalence of obesity in the last decades. It is also commonly observed that those who are in the upper ranges of BMI are heavier now than they were in the past (60,61).

Although overweight and obesity are established risk factors for chronic diseases most people who have a BMI above these cut-offs will never experience any major health threat because of their weight. However, studies have shown that morbidity and mortality rates are increased among overweight and obese individuals with additional metabolic abnormalities. This has stimulated the development of diagnostic criteria for clusters of metabolic abnormalities in order to improve risk assessment and prevention of cardiovascular disease in particular. The term "metabolic syndrome" originates from Reaven's work in 1988 (62), which initiated research on the relevant metabolic variables.

Table 2. According to WHO criteria (63), an individual has the metabolic syndrome if she or he has:

1. Diabetes, impaired glucose tolerance, impaired fasting glucose, or insulin resistance		
2. Plus two or more of the following abnormalities:		
	A. High blood pressure	≥ 160/90 mmHg
	B. Hyperlipidemia	triglyceride concentration ≥ 1.695 mmol/l and/or HDL-C* < 1.0 mmol/l in women and < 0.9 mmol/l in men
	C. Central obesity	waist-to-hip ratio > 0.85 in women and > 0.90 in men and/or BMI > 30 kg/m^2
	D. Microalbuminuria	urinary albumin excretion rate ≥ 20 µg/min or albumin-to-creatinine ratio ≥ 20 mg/g

*HDL-C = high-density lipoprotein cholesterol

However, in a new working definition of the metabolic syndrome by a national expert panel in the USA, the threshold for high blood pressure is set at 130/85 mmHg (64) and in the blood pressure classification for people aged 18 years or older, values above 140/90 mmHg is defined as hypertension (65).

Hormonal changes in women with excess body weight in general and in women with hyperinsulinemia, in particular form plausible physiological links to breast and endometrial cancer development. A chronic increase in estrogen exposure is thought to be the major etiologic factor in overweight and obesity induced breast and endometrial cancer (66). Excessive overweight may suppress ovarian function in predisposed premenopausal women (67), while in postmenopausal women overweight and obesity are generally associated with an increase in biologically active estrogen due to increased production of estrogens in peripheral fat tissue and reduced production of sex hormone binding globulin (SHBG) (66). Adipose women and especially women with abdominal adiposity tend to develop insulin resistance and hyperinsulinemia (68). Besides being a key mediator of changes in estrogen levels in obese women, insulin is a growth factor for tumour formation itself (69,70) and increases the levels of other mitogens [i.e. androgens, insulin-like growth factor (IGF)-I, leptin] (71-73) by affecting the production of hormones and their binding-proteins [SHBG, IGF-binding proteins (IGFBPs)] (74-76).

The overweight and obesity epidemics are escalating in all parts of the world and the incidence rates of breast and endometrial cancer are expected to increase concurrently (53,59). This allows for the development of strategies, including biological markers (biomarkers), to identify individuals at high risk of breast and endometrial cancer, in particular, among overweight and obese women. A biomarker is any substance, structure or process that can be measured in the human body or its products and may influence or predict the incidence or outcome of disease (77). The metabolic syndrome might be associated with an unfavourable hormonal profile and increased levels of estrogens and insulin, in particular. Thus, epidemiological studies should attempt to evaluate aspects of the metabolic syndrome as potential biomarkers of breast and endometrial cancer risk.

2. AIMS OF THE THESIS

To examine the relationships between environmental exposures including diet as a potential source of organochlorines, dietary energy intake and physical activity, metabolic abnormalities related to excess body weight, hormonal activity and the risk of breast and endometrial cancer in women was the main aim of this thesis. Two cross-sectional studies and two prospective cohort studies with repeated assessments of some of these variables address the following questions:

1. Are plasma levels of organochlorines among women living on the northwest coast of Norway related to fish consumption and suggestive of fish consumption as a source of endocrine disruptors of importance for breast and endometrial cancer risk?

2. Are there any relationships between salivary estradiol and progesterone concentrations throughout an entire menstrual cycle and metabolic profile, characterized by BMI and serum high-density lipoprotein cholesterol (HDL-C), and serum levels of androgens, insulin, IGF-I, and leptin? Are these characteristics of ovarian function and metabolic profile of importance for mammographic parenchymal pattern, a surrogate endpoint for breast cancer risk?

3. Are there any relationships between endometrial cancer risk and environmental factors as energy intake and physical activity, and metabolic profile, characterized by BMI, serum glucose and blood pressure? If any associations are observed, to what extent may these associations indicate causal relationships or reflect true biomarkers of risk?

4. Is serum high-density lipoprotein cholesterol (HDL-C), as an important variable in metabolic syndrome, associated with breast cancer risk? If an association is observed, to what extent may this association reflect a true biomarker of risk?

3. SUBJECTS AND METHODS

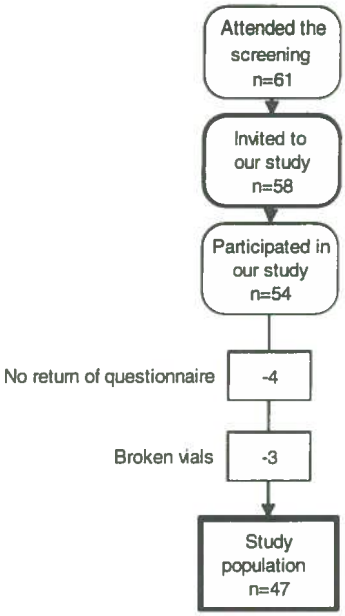
3.1 Paper I – The cross-sectional study of fish consumption as a potential source of organochlorines and exogenous sex steroid activity

3.1.1 Study population

Since 1985, the National Health Screening Service has screened individuals between the ages of 40–42 years in 18 out of the 19 counties of Norway to explore the association of lifestyle with chronic diseases (78). In November 1997, all women born in 1955–1957 and living in the municipality of Vestvågøy, in the county of Nordland were invited to participate in the screening. The attendance rate was 71.6%.

We invited women who attended this screening in November 1997, to participate in our study. We began to include participants on the first day of the screening and finished when 61 women in total had attended. A written invitation was handed to 58 of these women at the screening centre and 54 (93%) of them agreed to take part. The women were asked to fill in a self-administered questionnaire and to give an extra blood sample. Altogether, 47 of the 58 invited women (81%) were included; four women did not return the questionnaire and for three women the vials containing the samples were broken (Figure 1). Informed consent was obtained from all participants and the Regional Committee for Medical Research Ethics approved the design of the study.

Figure 1. Creation of the study population in Paper I



3.1.2 Questionnaire – ascertainment of environmental factors

As a basis for the majority of the questions, a semi-quantitative food frequency questionnaire (FFQ) developed for a Norwegian cohort study of breast cancer, was used (79). The FFQ collected data on habitual intake of three fat-containing food categories, namely fish, meat and milk, corresponding to a total of 67 different food items (Appendix A). Thirty-four questions on use of seafood were categorized into lean fish (cod, pollack, saithe, haddock), fatty fish (salmon, trout, redfish, redfish's head, herring, catfish, flatfish, halibut, mackerel), fish liver, roe, shellfish, whale meat, seal meat, and seagull's eggs. We asked for the consumption of lean and fatty fish filet by season. We also asked about age, height, weight, reproductive history, place of birth, duration of residency in the municipality of Vestvågøy, and occupation, in a separate section of the questionnaire. BMI (kg/m^2) was used to estimate relative weight.

3.1.3 Blood sample analyses - ascertainment of possible biomarkers

Non-fasting blood samples were drawn and plasma separated and frozen at –20°C until analysis. Plasma was analysed for the concentration of seven PCB congeners, *p,p'*-DDE, *β*-hexachlorocyclohexane (*β*-HCH), *cis*- and *trans*-chlordane (*c*-CD and *t*-CD), and the

toxaphenes Parlar 26 and 50. The Norwegian Institute for Air Research (NILU) selected organochlorines for the study according to the list of organochlorines considered to be relevant by the Arctic Monitoring and Assessment Program (AMAP) (19). All laboratory analyses were conducted at NILU by procedures described in Paper I.

3.1.4 Statistical analyses

The relationship between fish consumption and plasma concentrations of organochlorines was studied in order to determine whether fish consumption could be a source of exogenous steroid activity of importance for breast and endometrial cancer risk in the study population. We calculated descriptive statistics for plasma concentrations of organochlorines in the total population and in subgroups with different habitual intake of fatty fish fillet (i.e. non-consumers, moderate consumers and high consumers).

The associations between consumption of seafood and other predictor variables, and concentrations of PCBs and *p,p'*-DDE in plasma were analysed in linear regression models. Plasma levels of PCBs were left-skewed and therefore we used logarithmic transformed values in the regression analysis. The associations between consumption of seafood and other predictor variables, and concentrations of β-HCH and chlordanes were analysed in logistic regression models because a large group of observations were below the detection limits. The toxaphenes were excluded from statistical analyses because most of the observations were below the detection limits. Plots of residuals were used to confirm that data fitted to the regression models. All statistical tests were two-tailed and the level of statistical significance was set at 5 percent.

3.2 Paper II – The cross-sectional study of HDL-C, metabolic syndrome, hormonal activity and breast density

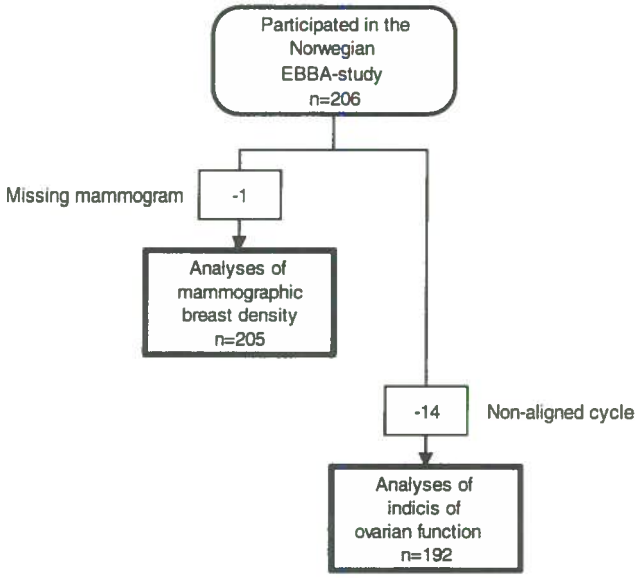
3.2.1 Study population

The Energy Balance and Breast Cancer Aspects (EBBA)-study is an international collaborative project exploring the association between lifestyle, ovarian function and breast cancer risk among Polish and Norwegian women. Parallel studies were run at the University of Tromsø, Norway, and at Jagiellonian University, Krakow, Poland, during 2000–2003 and 206 women were recruited in Tromsø, Norway, and 186 women were recruited in Poland. Sex steroids in saliva samples from the participants were measured at Harvard University,

Cambridge, MA, USA. The Norwegian data were used in Paper II (Figure 2). A detailed description of the study is given elsewhere (80).

The women were invited to participate by announcements in newspapers and locally. Study subjects had to meet the following criteria, which were checked both in a telephone interview and in a personal interview by the same trained nurse during the entire study period: 25–35 years of age; self-reported regular cycles (cycle length 22–38 days) within the previous three months; no use of hormonal contraceptives and no pregnancy or breastfeeding over the previous 6 months; no infertility, gynecological disorders, chronic disorders (i.e. diabetes, hypo-/hyperthyroidism) or abnormally high BMI (> 30 kg/m^2). The women participated in the study during an entire menstrual cycle, and all clinical procedures were conducted by trained nurses at the Department of Clinical Research, University Hospital of North Norway (UNN), Tromsø. All the participating women signed an informed consent form. The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

Figure 2. Creation of the study population in Paper II



3.2.2 Questionnaires - ascertainment of environmental factors

We used a general questionnaire (self-administered and by interview) to collect information on ethnicity, education, reproductive history, and past and current lifestyle including physical activity, use of hormonal contraceptives, tobacco and alcohol (Appendix B). To improve recall, the general questionnaire was supplied with a recall calendar as memory aid for the participants (Appendix B).

We asked about types of physical activities in the household, leisure time, work, and transport, the usual intensity of the activity (four levels), the usual time spent in each activity on each occasion, the frequency of each activity, and the number of months the activity was used in the past year. Total average energy expenditure in physical activities per week during the past year was estimated by multiplying the average number of hours per week spent at each activity by the energy cost of that particular activity expressed in metabolic equivalents (METs) (81).

Dietary data was collected for seven selected days in the menstrual cycle (day 3–6 and day 21–23). The women were asked to record the type and the portion of every food item consumed during 24 hours in a pre-coded food diary developed for the present study and we used a photographic booklet to illustrate the different portion sizes (Appendix B). Average daily intake of energy and nutrients were computed by using a food database and software system developed at the Institute for Nutrition Research, University of Oslo (82).

3.2.3 Clinical variables - ascertainment of metabolic profile

The participants met fasting on the first possible day after onset of the menstrual bleeding for clinical examinations. This clinical examination included height, weight and blood pressure measurement and blood sampling. The majority of the women met on day 1 or day 2 of their menstrual cycle, but some women had to wait until day 3 to 5 because the medical facilities were closed during holidays and weekends. The same instruments and procedures were used throughout the entire study period. Anthropometrical measures were taken with subjects wearing light clothing and no footwear: height was measured to the nearest centimeter and weight was measured to the nearest 0.1 kilogram on an electronic balance. BMI (kg/m^2) was used to estimate relative weight.

At a visit on day 7–12 of the menstrual cycle, we made a whole body scan by dual-energy X-ray absorptiometry (DEXA) to estimate the percentage of fat tissue in the trunk. In addition, mammograms were taken in order to examine parenchymal pattern of the breasts. Radiologist N. Bjurstam at the Department of Radiology, Centre of Breast Imaging, UNN, Tromsø, read all the mammograms. We used a modified Wolfe's classification of mammographic parenchymal density in our analysis (see Paper II for classification).

3.2.4 Serum and saliva samples - ascertainment of potential biomarkers

The fasting, venous blood sample on day 1–5 of the menstrual cycle was centrifuged and the serum was separated. The Department of Clinical Chemistry, UNN, Tromsø, measured concentrations of glucose, cholesterol, HDL-C, low-density lipoprotein cholesterol (LDL-C), triglycerides, testosterone, dehydroepiandrostendione sulfate (DHEA-SO_4), and SHBG in fresh sera. The Hormone Laboratory, Aker University Hospital, Oslo, measured concentrations of insulin, IGF-I, IGFBP-3 and leptin in sera that had been stored at –70°C until analysis.

The participants collected samples of their own saliva at home once a day, preferentially in the morning, for the complete menstrual cycle and recorded in a logbook the time and the date of the sample and whether they had menstrual bleeding in the previous 24 hours (Appendix B). Collection of saliva followed previously established protocols (83). Estradiol and progesterone concentrations in saliva were measured at the Department of Anthropology, Harvard University, Cambridge, MA, USA. Estradiol was assayed in saliva samples from 20 days (reverse cycle day –5 to –24) and progesterone was assayed in saliva samples from the last 14 days of each cycle (reverse cycle day –1 to –14). Methods for the serum and saliva analyses are presented in Paper II.

3.2.5 Statistical analyses

To study the relationship between salivary estradiol and progesterone concentrations throughout an entire menstrual cycle and metabolic profile, characterized by BMI and serum HDL-C, serum levels of androgens, insulin, IGF-I, and leptin, and mammographic breast density, we estimated some indices of ovarian function and performed a variety of statistical analyses. Alignment of the cycles for analysis of salivary estradiol and progesterone concentration was based on the identification of the day of the mid-cycle estradiol drop i.e. 'day 0'. Satisfactory identification of the mid-cycle estradiol drop could not be made for 8

women with too many missing days and for 6 women with either no drop or no rise in estradiol within the selected window, and their cycles were not aligned (Figure 2). The mid-luteal index was defined as the average of the hormone concentrations on day +5 to +9.

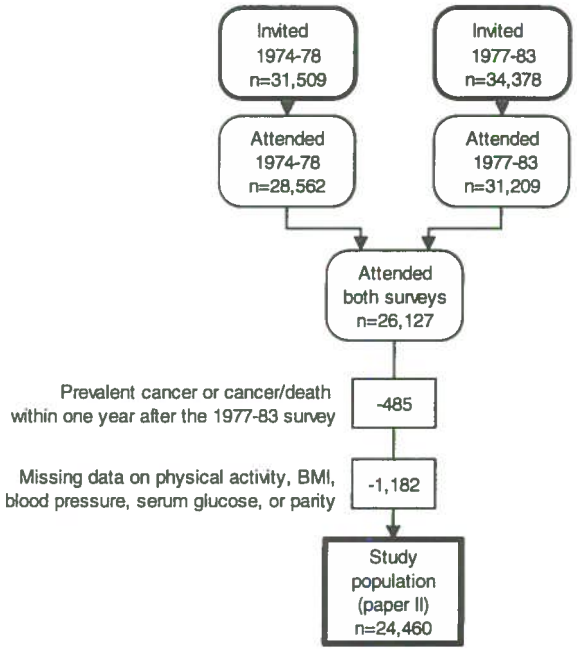
We used correlation analysis and regression models in analyses of single assessments of variables and indices. Additionally, we used a generalized linear regression model to compare average salivary estradiol concentrations by cycle day in subgroups of women and to control for dependencies between repeated observations in the same subject. We conducted post-hoc tests for multiple pair wise comparisons. Stratified and multivariate regression analyses were used to detect possible effect modification and to control for confounding variables. Plots of residuals were used to confirm that data fitted to the regression models. We considered results statistically significant when the two-sided p-value was < 0.05.

3.3 Paper III and IV – The cohort studies of lifestyle, metabolic profile and risk of endometrial and breast cancer

3.3.1 Study population

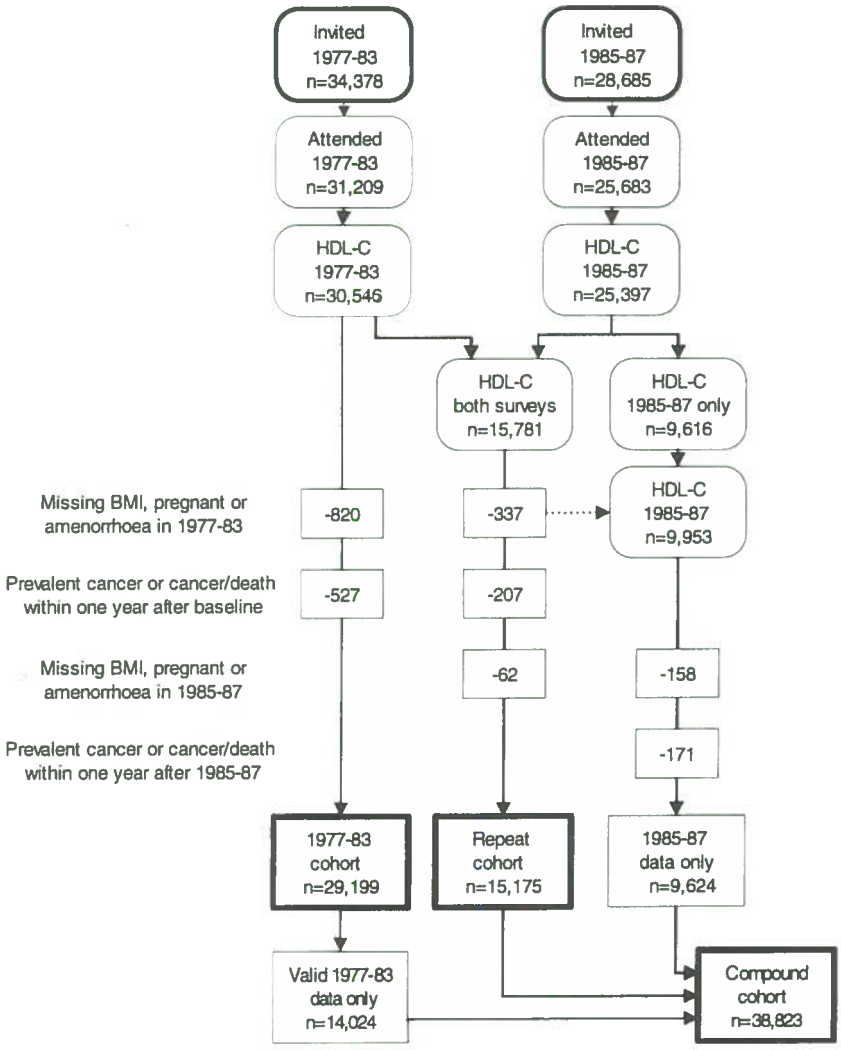
During 1974–78, 1977–83 and 1985–87 the National Health Screening Service screened the population in three counties of Norway (Finnmark, Oppland and Sogn og Fjordane), as part of a program to explore the association of lifestyle with chronic diseases (84,85). In 1974–78 all women between the ages of 35–49 years and a 10% random sample of women between the ages of 20–34 years were invited. In four municipalities of the county of Finnmark, all women in the youngest age group were asked to meet. Of 31,509 invited women, 28,562 (90.6%) attended. In 1977–83 those who registered at the first screening were re-invited, while a 5–11% random sample of women between the ages of 20–39 years (17–39 years in Sogn og Fjordane) were invited for the first time. Among the 34,378 women who were asked to participate, 31,209 (90.8%) women actually participated. A total of 26,127 women attended both the first and the second survey and were eligible for analysis in the cohort study of endometrial cancer (Paper III) (Figure 3). In the cohort study of endometrial cancer (Paper III), we referred to the different screening surveys using the dates when each survey was started in the three counties of Finnmark, Oppland and Sogn og Fjordane; the 1974–78 survey was started during 1974–76, and the 1977–83 survey was started during 1977–81.

Figure 3. Creation of the study population in Paper III



In all the three surveys, all attendees had a non-fasting blood sample drawn at the screening, but serum HDL-C was estimated only in the 1977–83 survey in every county and in the 1985–87 survey in Oppland and Sogn og Fjordane. In the third survey (1985–87) in Oppland and Sogn og Fjordane, all women who had been invited in the 1977–83 survey, and all women between the ages of 40–54 years, and random samples of women between the ages of 20–39 and 55–59 years were invited. Altogether 28,685 women were invited and 25,683 (89.5%) attended. In total, 16,028 of the women in Oppland and Sogn og Fjordane registered in both surveys. In the cohort study of breast cancer (Paper IV), only women who had serum HDL-C measured in one or both surveys were eligible for analysis and we studied three subgroups of women with different screening histories: women who attended the 1977–83 survey ("1977–83 cohort", Figure 4), women who attended the 1977–83 survey and/or the 1985–87 survey ("Compound cohort", Figure 4), and women who attended both the 1977–83 and the 1985–87 survey ("Repeat chohort", Figure 4). The study was approved by the Norwegian Data Inspectorate and the Norwegian Board of Health permitted access to medical record files.

Figure 4. Creation of the study population in Paper IV



3.3.2 Questionnaires and interviews - ascertainment of environmental factors

The screening procedures were almost identical in the three surveys and have been described in detail (84,85). The women received a written invitation with a one-page questionnaire on ethnicity, chronic diseases, smoking, alcohol (1985–87 survey only) and physical activity. They were asked to fill in the questionnaire at home and bring it to the screening examination. Each municipality was visited at the same time of the year in each of the three surveys and the same team of trained nurses conducted interviews with the participants at the screening to

confirm the information and to collect data on time since last meal, menopausal status, primary amenorrhoea, pregnancy, hysterectomy and use of oral contraceptives and hormone therapy. Hysterectomy and use of oral contraceptives and hormone therapy were collected only during the 1985–87 survey.

The women were asked to mark their usual level of physical activity in leisure time and during work hours on a four-grade scale, where each higher level of activity corresponded to higher energy expenditure (Appendix C–E).

A FFQ (Appendix F and G) was distributed at the screening in the second and third surveys and returned via mail by 25,892 women (83.0%) in the 1977–83 survey and by 22,799 (88.8%) in the 1985–87 survey. The semi-quantitative FFQ used in the 1977–83 survey included questions on 64 food items and focused on habitual use of fat in diet. The reproducibility and validity of the FFQ, and the method of estimating total energy intake have been described (86-88). The specification of types of fat and of the amount of milk per day was changed in the FFQ used in the 1985–87 survey; these data was converted to the old form to get comparable estimates of total fat and energy intake in both surveys (Paper IV). Questions about vegetables with the dinner and alcohol consumption were added in the 1985–87 survey and this data was not included in the estimation of total energy intake (Paper IV).

3.3.3 Clinical variables - ascertainment of metabolic profile

In all three surveys, the same team of trained nurses did a clinical examination. Height was measured to the nearest centimeter, and weight was measured to the nearest half kilogram with participants dressed in lightweight clothing and no footwear. BMI (kg/m^2) was used to estimate relative weight. In the cohort study of breast cancer (Paper IV), we tried to minimize misclassification of BMI due to errors in the registration of height among women with non-missing weight data, using information from all three surveys to produce the most consistent dataset for the statistical analyses. If height of an individual had been registered in two or more surveys and every pair of registrations differed by more than 5 cm, height was set to missing; this produced, for example a missing height in the 1977–83 survey for 125 of the 30,546 observations with information on serum HDL-C (difference in height registrations: median = 9 cm; maximum = 30 cm). If height had been registered in all three surveys and there was a difference of more than 5 cm between any pair of registrations, the most outlying value was set to the average of the two other registrations (difference less than 5 cm); for

example, we redefined the height in the 1977–83 survey for 84 of the 30,546 observations with information on serum HDL-C (difference in height registrations: median = 10 cm; maximum = 18 cm). If an individual had met in all three surveys and height was missing in only one of the surveys, this height was set to the average of the two other registrations if these differed by less than 5 cm; for example, height in the 1977–83 survey was calculated by this method for 4 of the 30,546 observations with information on serum HDL-C.

In the first and the second survey, a mercury sphygmomanometer (Erca) was used to measure systolic and diastolic blood pressure; after minimum 4 minutes' rest, two recordings were made at 1-minute intervals with the participant seated. In the third survey blood pressure was measured by an automatic oscillometric device (Dinamap 845 XT, Tampa, Florida, USA) and three recordings were taken for each subject. Diastolic blood pressure registered by this automatic method was 4 mmHg lower than the diastolic blood pressure registered manually, while there was almost no difference in the registration of systolic blood pressure between the methods (89). The deviations were not uniform throughout the diastolic blood pressure distributions, and no correction formula has been developed. The lowest systolic and diastolic blood pressure in the two first surveys and the lowest systolic and diastolic blood pressure of the second and third recordings in the last survey were used in the analyses.

3.3.4 Blood samples - ascertainment of possible biomarkers

In each survey, a non-fasting blood sample was drawn from an antecubital vein with the subject seated. The blood was centrifuged, and the serum collected, chilled and transported to the laboratory, where it was analyzed within two weeks or it was frozen until analysis. Serum triglycerides and serum cholesterol were assayed in fresh sera by the Central Laboratory at Ullevål Hospital, Oslo, in every survey (85).

Non-fasting serum glucose was assayed in fresh sera by the Central Laboratory at Ullevål Hospital, Oslo, according to the method described by Brown (90) in every sample in the first survey and in a sub-sample in the second survey (Finnmark, part of Oppland) (85), but not in the third survey.

Serum HDL-C in samples from Oppland and Sogn og Fjordane was assayed in fresh sera by the Central Laboratory at Ullevål Hospital, Oslo, in the two last surveys. Serum HDL-C in samples from Finnmark in the 1977–83 survey (n = 7,729) were assayed by the Institute of

Medical Biology at the University of Tromsø; the majority of these serum samples (n = 5,577; 72%) were kept frozen for 12 months until analysis. Serum HDL-C was assayed enzymatically after precipitation of lipoprotein with density <1·063 by the addition of heparin and $MnCl_2$ according to the method of Burstein et al. (91). An adjusted absolute mean difference of 0.12 mmol/l in HDL-C between the batches of fresh and frozen sera was added to the measured HDL-C levels obtained from frozen sera (92).

3.3.5 Follow-up and case identification

We used the women's national 11-digit personal identification number to assess data from the Central Population Register at Statistics Norway on reproductive history, emigration and death and data from the Cancer Registry of Norway on any cancer diagnosis throughout follow-up. Since 1952, clinicians and pathologists in Norway have been required to report all incident cancers. An accurate and complete registration is achieved through computerized matching with the data at Statistics Norway (93).

In the study of endometrial cancer in Paper III, women diagnosed with an endometrial carcinoma were defined as cases [Manual of tumor nomenclature and coding 1968 edition, American Cancer Society, Inc.: (the 3 first digits are given; the 4th digit varies between 3 and 9) 801, 814, 826, 856, 857 and ICD-7: (the 4 first digits are given; the 5th digit varies between 3 and 9) 7170, 8070, 8140, 8260, 8380, 8460, 8480, 8560, 8570].

In the study of breast cancer in Paper IV, women diagnosed with a malignant tumor of the breast were defined as cases [Manual of tumor nomenclature and coding 1968 edition, American Cancer Society, Inc.: (the 3 first digits are given; the 4th digit varies between 3 and 9) 801, 814, 821, 848, 850, 851, 852, 854 and ICD-7: (the 4 first digits are given; the 5th digit varies between 3 and 9) 7170, 7522, 7525, 8010, 8041, 8140, 8211, 8401, 8480, 8500, 8501, 8503, 8510, 8520, 8522, 8540, 8541, 8543, 8980, 9020].

3.3.6 Statistical analyses

To ensure that undiagnosed cancer or severe illness did not influence our estimates, women who died or were diagnosed with cancer within one year after participation in the 1977–83 survey were excluded in the cohort study of endometrial cancer (Paper III), whereas in the cohort study of breast cancer (Paper IV), women who died or were diagnosed with cancer

within one year after participation in one of the surveys were excluded from analysis with follow-up from that specific survey (Figure 3 and 4). In the cohort study of endometrial cancer (Paper III), 24,460 women with non-missing information on parity and repeated assessment of physical activity, BMI (height and weight) and blood pressure from both the 1974–78 survey and the 1977–83 survey and non-fasting serum glucose assessed in the 1974–78 survey were included in the analyses (Figure 3). In the cohort study of breast cancer (Paper IV), 38,823 women were included in the analyses who did not report to be pregnant at the screening or to have primary amenorrhoea and had data on BMI (height and weight) and serum HDL-C from one or both surveys (Figure 4).

In the cohort study of endometrial cancer (Paper III), the women were considered to be at risk from the date of the blood sample in the 1977–83 survey through 31 December 1996, or earlier on the occurrence of emigration, death or diagnosis of any cancer. In the cohort study of breast cancer (Paper IV), the women were followed from the date of the blood sample in either the 1977–83 or the 1985–87 survey (women with only 1985–87 data in the "compound cohort", Figure 4) to identify every incident case of cancer and every death and emigration through 31 December 1998.

We used Cox Proportional Hazards Modeling to estimate the associations between energy intake, physical activity, BMI, non-fasting serum glucose and blood pressure and the risk of endometrial cancer (Paper III) and to estimate the association between serum HDL-C and the risk of breast cancer (Paper IV). We included in the models as covariates plausible or potential risk factors for endometrial and breast cancer. In Paper IV, relative risks for pre- and postmenopausal breast cancer were estimated separately using the accumulated number of person-years in the pre- and postmenopausal periods and Cox models with time-dependent covariates were used to update the exposure status according to the most recent survey.

In the cohort study of endometrial cancer (Paper III), we used quartiles of energy intake and three-level variables for recreational and occupational physical activity (the two uppermost categories were combined due to few subjects in the highest category) in the models. In the study of endometrial cancer (Paper III), the WHO cut-offs for overweight (BMI $\geq$ 25 kg/m^2) and obesity (BMI $\geq$ 30 kg/m^2) were both used to define the heaviest women in different sub-sets of analyses, whereas in the study of breast cancer (Paper IV), only the cut-off for overweight was used. In the study of endometrial cancer (Paper III), we used the hypertension

criterion (≥ 140/90 mmHg) and quartiles of non-fasting serum glucose and in the study of breast cancer (Paper IV) we used quartiles of serum HDL-C for further categorization according to metabolic profile.

Data were adjusted for age and compared by analysis of covariance. Tests for linear trend were performed by assigning consecutive integers to different categories of energy intake, physical activity, BMI, blood pressure, non-fasting serum glucose and serum HDL-C, and testing whether the slope coefficient differed from zero using the Wald Chi-Square Test. Interaction effects were tested using a likelihood ratio test. All statistical tests were two-tailed and the level of statistical significance was set at 5 percent.

4. MAIN RESULTS

Paper I - The cross-sectional study of fish consumption as a potential source of organochlorines and exogenous sex steroid activity

Among the 47 women between the ages 40–42 who were included in the study, consumption of lean fish and fatty fish was high. Nevertheless, the measured plasma concentrations of organochlorines were in the range reported for the general female population of other Western countries where fish consumption can be presumed to be lower. There was no association between self-reported fish consumption and plasma levels of any organochlorine.

Seagull's eggs are considered traditionally to be a food source among people in coastal areas of North Norway. We observed a 31% [95% confidence interval (95%CI) = 7–60%, $p < 0.01$] increase in the plasma concentration of CB-153 (PCB congener 153) and a 27% (95%CI = 2–59, $p < 0.05$) increase in the plasma concentration of CB 138 (+CB-163) by each seagull's eggs consumed per year (calculated from Table 3 in Paper I). The statistically most significant association was observed between accumulated lactation time and the total concentration of all PCBs (ΣPCB); by each month of lactation the concentration of ΣPCB dropped by 1.4% [95%CI = –2.0%–(–0.7)%, $p < 0.001$; calculated from Table 3 in Paper I]. Additionally, accumulated lactation time was inversely related, whereas duration of residence in the study municipality and BMI were directly related to levels of most of the PCBs and pesticides.

Duration of residence and accumulated lactation time explained 34% of the variation in concentration of ΣPCB in a multivariate model ($p < 0.001$).

However a questionnaire on habitual diet during the past year is a rather imprecise method for dietary assessment. Furthermore, we studied a selected group of organochlorines and the study population was small, limiting the statistical power of the study.

Paper II - The cross-sectional study of HDL-C, metabolic syndrome, hormonal activity and breast density

Among women aged 25–35 years participating in the Norwegian EBBA-study (n = 206), serum HDL-C was inversely related to serum leptin, insulin, and DHEA-SO_4 ($p < 0.001$, $p < 0.01$ and $p < 0.05$, respectively). In women with BMI ≥ 23.6 kg/m^2, overall average salivary estradiol concentration dropped by 2.4 pmol/l (13.2% change in mean for the total population) by each 0.33 mmol/l (1-standard deviation) increase in serum HDL-C (age-adjusted analysis: 95% CI = –4.5–(–0.3) pmol/l, p = 0.03; p for interaction = 0.03). A subgroup of women characterized by both relatively high BMI (≥ 23.6 kg/m^2; Median split) and high serum LDL/HDL-cholesterol ratio (≥ 2.08; 75 percentile) had substantially higher levels of salivary estradiol by cycle day than other women (p = 0.001). BMI was the strongest predictor of overall average estradiol, increasing the concentration ($p < 0.001$). Serum DHEA-SO_4 was a predictor of average mid-luteal salivary estradiol concentration (p = 0.04). There was a direct relationship between breast density and healthy metabolic profiles (low BMI, high serum HDL-C; $p < 0.001$) and salivary progesterone concentration ($p < 0.05$).

We observed that low serum HDL-C is associated with increased levels of several breast mitogens and levels of free, biologically active estradiol, in particular. However, further studies are needed to test whether serum HDL-C might be a true biomarker of breast cancer risk and to study possible variation in susceptibility to low HDL-C and high levels of breast mitogens.

Paper III - The cohort study of lifestyle, metabolic profile and risk of endometrial cancer

During a mean follow-up period of 15.7 years, there were 130 incident cases of endometrial carcinoma diagnosed among 24,460 women. Obese women (BMI ≥ 30 kg/m^2) were at 2.6 times increased risk of endometrial cancer compared with normal weight women (BMI

< 25 kg/m^2) [relative risk (RR) = 2.57, 95% CI = 1.61–4.10]. Among overweight women (BMI ≥ 25 kg/m^2), non-fasting serum glucose in the upper quartile *vs.* in the lower quartile was associated with a 2.4 times increase in risk (RR = 2.41, 95%CI = 1.08–5.37, p for trend = 0.02, p for interaction = 0.92), whereas among obese women, blood pressure above 140/90 mmHg *vs.* below 140/90 mmHg in both surveys was associated with a 3.5 times increase in risk (RR = 3.47, 95%CI = 1.24–9.70, p for trend = 0.02, p for interaction = 0.04). Thus, relative hyperglycemia and hypertension were markers of increased endometrial cancer risk in our study.

Especially in women younger than 50 years, high energy intake (5,404–6,858 kJ/day) conferred high risk compared to low energy intake (< 4,571 kJ/day) (RR = 3.40, 95%CI = 1.52–7.60, p for interaction = 0.05). Among obese women with non-sedentary jobs at both screenings, RR declined to 0.18 (95%CI = 0.05–0.62) as the level of sustained occupational activity increased (p for trend = 0.03, p for interaction = 0.17). Increasing recreational activity tended to be protective.

Paper IV - The cohort study of metabolic profile and risk of breast cancer

We observed 708 cases of incident breast cancer (200 premenopausal and 508 postmenopausal) among 38,823 women during a median follow-up of 17.2 years. The risk of postmenopausal breast cancer decreased by each higher quartile of serum HDL-C in multivariate analysis (p for trend = 0.01). Among women with serum HDL-C above 1.64 mmol/l (highest quartile) *vs.* below 1.20 mmo/l (lowest quartile) a RR of 0.73 (95%CI = 0.55–0.95) was observed. When we divided the population into a normal weight (BMI < 25 kg/m^2) and an overweight and obese (BMI ≥ 25 kg/m^2) group, the effect of serum HDL-C was confined to the heavier subgroup with an observed 66% reduction in risk of postmenopausal breast cancer in women with serum HDL-C above 1.64 mmol/l *vs.* below 1.20 mmol/l (RR = 0.34, 95%CI = 0.19–0.59, p for trend < 0.001, p for interaction = 0.006). There was a suggested positive association between serum HDL-C and the risk of premenopausal breast cancer. Thus, serum HDL-C was a marker of increased postmenopausal breast cancer risk in our study.

5. DISCUSSION

In epidemiological studies of cancer causation we are not dealing with causes in the strict Hume's (1711–76) sense of a cause defining an effect E as a cause of a disease D if D follows all Es. Rather, with the prevention of cancer disease as our goal, we are interested in all kinds of exposure that might facilitate cancer development and that might be limited or eliminated by interventions. Cancer is in general a heterogeneous disease caused by multiple genetic and environmental factors. Furthermore, the influence of different environmental factors on cancer development may be dependent on timing in relation to age of the tissue (i.e. development and maturation of the breast and the endometrium) and timing in relation to stage of the disease process. Thus, Hume's concept of causation does not fit well with modern cancer epidemiology which needs a far less schematic view on causation in order to catch the fine network of factors that may lead to cancer.

Although, there is scepticism against the application of checklists alone to evaluate to what extent observed associations may reflect cause-effect relationships (94), common guidelines may facilitate a thorough and scientifically acceptable process of causal inference. The most widely used list of causal criteria is attributed to Hill (95) and focuses on strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence and analogy. The aims of this thesis will be discussed in light of these criteria wherever it seems relevant. Moreover, aspects of the studies that link the findings to what is thought to be the major underlying biological mechanisms of breast and endometrial carcinogenesis (i.e. sex steroid exposure) will be given special emphasis.

In the interpretation of epidemiological evidence it is important to consider to what extent the study could possibly tell us anything about the association of interest in the study population; how much of the variation in the distribution of exposure and outcome may have been due to error in design, conduct or analysis and how much of the variation is likely to have been real? A logical approach to this question is the discussion of two broad types of error in epidemiological studies; random error and systematic error. Random error in measurement, data processing, and calculation reduces the precision or reproducibility of estimates. Systematic error causes incorrect estimates. There are three categories of systematic error; selection bias, information bias and confounding, which may reduce the internal validity of

the results. Furthermore, bias in response and follow-up may reduce the external validity in studies that aim to draw inference about the association in the general population.

5.1 Methodological considerations

5.1.1 Subjects

Selection bias in a study results from the procedures used to select subjects and from factors that influence participation in the study. Due to selection bias, the associations between exposure and outcome may be different in the study population and in the general population if both exposures and outcome are distributed differently in the populations (96). Because the association between exposure and outcome among non-attendees is usually unknown, it is not possible to determine the magnitude of selection bias but the probable direction of bias may be inferred.

We did not have data of any kind on the people who did not participate in the population-based survey from which the participants in the cross-sectional study of fish consumption and organochlorines were recruited (Paper I). Thus, we were not able to make any inference about the magnitude or the direction of selection bias in our study. The overall attendance rate in the population-based survey among females in the selected municipality was fairly high, as was the proportion of women included in our analyses among the women invited to participate in our study, minimizing the selection-bias. Furthermore, our findings of inverse associations between lactation and internal dose of organochlorines as expected from previous studies in other populations (97-99), increase the external validity of our results.

The size of the study population in Paper I was small and one may argue that the power in the study was too low to detect any difference in plasma levels of organochlorines between groups of women with different consumption rates of fish in their diets. Power calculations were not included in the study protocol; rather the determined sample size and number of assays reflect financial constrains. However, we tried to increase size efficiency by selecting a study area in which we supposed that women would be eating large amounts of fish. We observed a wide range of habitual intake of both lean and fatty fish (147 to 1,765 g/week and 0 to 956 g/week, respectively), and 21% of the women did not eat any fatty fish fillet (Table 1 and 2, Paper I). This large variation in fish consumption may have increased the precision of

our estimates. Furthermore, interventions were taken to reduce measurement error due to responders, equipment, and observers.

Strictly, the results of Paper I apply only to women born in 1955–1957 who had been living in the coastal area for several years and who consumed large amounts of seafood. However, we doubt that geographical region is a modifying factor in the relationship between seafood consumption and levels of organochlorines. However, birth year may be a modifying factor of the association if the use of seafood during the past year correlates with past use, as long as organochlorines have long half-lives and decreasing trends in levels of organochlorines in marine organisms have been observed in some sub-Arctic waters (100).

In the EBBA-study (Paper II), the size of the study population corresponded to sample sizes found adequate to detect significant differences in indices of ovarian function between subgroups of women characterized by age (101), and level of recreational physical activity (102), among others. The chosen study design would allow for a difference of 60 pmol/l in overall average salivary progesterone concentration and for a difference of 2.2 pmol/l in overall average salivary estradiol concentration between two subgroups to be significant at the 5% level. Study efficiency was maximized by the use of strict inclusion criteria to limit confounding by age, hormonal contraceptive use, endocrine disorders, pregnancy and lactation and to control the distribution of BMI, a potential effect modifier. Furthermore, to limit potential season variation, women did not participate in sample collection during months with no daylight (December and January).

The study population in Paper II does not necessarily represent the general female population between 25 and 35 years, due to the methods of recruitment and the inclusion criteria. There may be an overrepresentation of women interested in having a mammogram and a clinical examination and who also may be sceptical about use of hormonal contraceptives, due either to breast cancer or other chronic diseases among relatives or to their own general health consciousness. Nonetheless, the precision in the estimates of the hypothesized associations and in the description of physiological processes (i.e. ovarian function) in our study signal relevance for breast cancer etiology in general. Furthermore, the associations between BMI and serum lipids were similar to observations done by our research group in a large prospective study of metabolic risk profiles among women of the same age and from the same geographical area (103). The associations between recognized risk factors for breast cancer

(i.e. parity, age at menarche) and breast density were in the expected direction and the direct relationships between healthy metabolic profiles and progesterone levels and breast density have been observed by others (104-108); these findings increase the external validity of our data.

Regarding the cohort studies on endometrial and breast cancer (Paper III and IV), the overall attendance rate was about 90% in the three counties in the 1974–78 and the 1977–83 surveys and in Oppland and Sogn og Fjordane in the 1985–87 survey. However, the attendance rate differed by county and age group. In these population-based three county surveys, the lowest attendance rates were reported for Finnmark, whereas the highest were reported for Sogn og Fjordane (1977–83: 86.4% and 93.1% respectively). Participation was less frequent in younger women; in the 1977–83 survey the overall attendance rate among women between 20–34 years was 76.9%. Thus, non-attendance may have influenced the external validity of our results if there was any selection bias. For example, the positive associations between BMI, hypertension, and serum glucose and endometrial cancer observed in Paper III may be weaker in the general population, if the metabolic parameters were relatively high and the incidence rate of endometrial cancer relatively low among non-responders. In contrast, the associations may have been underestimated in our study, if both the metabolic parameters and the incidence rate of endometrial cancer were high among non-responders.

We have no direct information on lifestyle and clinical variables among the non-responders in each survey (Paper III and IV). However, in a publication by the National Health Screening Service (85), mean serum cholesterol levels did not differ significantly between women who attended both the 1974–78 and the 1977–83 surveys and women who attended only one of the surveys, while mean number of cigarettes and mean infarct risk score (serum cholesterol, blood pressure, and smoking) were higher in the latter group of women. Tverdal combined data on the 1974–78 three county survey and data on similar surveys in two cities of Norway (Oslo and Tromsø) and observed higher death rates from several cancers, including breast cancer, among women who did not attend the surveys as compared to women who attended (109). Thus, the prevalence of common risk factors for chronic diseases and the relative risk of death from chronic diseases tend to be higher among Norwegian women who do not attend screening surveys as compared to women who attend the surveys. Most likely, selection bias may therefore have underestimated the true associations between metabolic parameters and

the risk of breast and endometrial cancer in the general population or it may not have influenced the associations.

In the cohort study of endometrial cancer (Paper III), we restricted our analyses to women who had participated in both surveys and had complete information on selected lifestyle and clinical variables; this might have enhanced the selection of healthy individuals and resulted in a further decrease of the external validity of our results. In the cohort study of breast cancer (Paper IV), we restricted the study population to women with certain characteristics (i.e. no pregnancy, primary amenorrhoea, or prevalent cancer) and data on BMI and serum HDL-C but we have no indication that this introduced a selection bias.

5.1.2 Exposure variables

Information bias results from systematically incorrect measurements or responses. Due to information bias, subjects may be misclassified for either exposure or outcome. Differential misclassification occurs when either the misclassification of the exposure differs by the outcome status or the misclassification of the outcome differs by the exposure status. If either the misclassification of the exposure or the outcome is independent of the status of the other, the misclassification is nondifferential. Differential misclassification can either exaggerate or underestimate an association, while nondifferential misclassification tends to dilute an association (110).

The prospective nature of the cohort studies of breast and endometrial cancer reduces information bias both in the collection of histories of exposure and the use of clinical measures of exposure (Paper III and IV). Misclassification of exposure is generally non-differential because it is unrelated to the cancer disease and produces estimates of associations between exposure and disease that are diluted. However, pre-clinical or undiagnosed cancer or serious illness influencing levels of lifestyle or clinical parameters is always a concern. For example, reduced levels of serum HDL-C has been found in cancer patients (111); thus, when follow-up time is short, it cannot be excluded that an inverse association between serum HDL-C and cancer is due to a lipid-lowering effect of the cancer itself, rather than an indication of serum HDL-C being a biomarker of cancer risk. In the cohort studies (Paper III and IV), we excluded all cancer cases and deaths within the first year of follow-up after an assessment, and this reduced potential differential misclassification of exposure.

Timing of exposure in relation to disease outcome is also problematic if the time period between exposure and cancer diagnosis is too long; then there may be increasing non-differential misclassification of exposure due to variation in exposure over time. In paper III and IV, we tried to minimize misclassification of exposures by using the information from two surveys (i.e. repeated assessments). In the cohort study of endometrial cancer (Paper III), optimal information on level of physical activity and blood pressure were focused by excluding women with missing data on any of these parameters in one or both surveys and combining the data from both surveys to get categories of women with consistently high, moderate or consistently low exposure levels. This restriction of the analyses to those who participated twice and had non-missing data on certain variables may however, have introduced a selection bias, as discussed above. In the cohort study of breast cancer (Paper IV), we used Cox models including only exposure information at baseline and Cox models with time-dependent covariates including repeated exposure information. This gave very similar results, even when we restricted the analysis with time-dependent covariates to women who had participated twice.

5.1.2.1 Lifestyle and diet

The reproducibility of the self-administered questionnaire used in the cross-sectional study of fish consumption and organochlorines (Paper I) has not been studied. However, even with a low reproducibility, a questionnaire may be reliable if the categorization of subjects is stable. In a validation study of the questions about seafood, there was a positive correlation between estimated intake of ω-3 fatty acids from fish and serum phospholipid ω-3 fatty acids, and this supports the validity of the reported use of seafood in our study population (79). The validity of the information on lactation is supported by the strong inverse relationship between lactation and plasma organochlorine levels (Paper I), which is well known from other studies (97-99). In the cross-sectional study of fish consumption and organochlorines (Paper I), we used self-reported height and weight to calculate BMI. Generally, people tend to underreport their weight and overreport their height slightly (112). As a consequence, our BMI data in Paper I might have been biased downward. In the study in Vestvågøy (Paper I), the women were encouraged to fill in the questionnaire at the study centre where we were ready to assist them in order to reduce the rate of responder mistakes.

In the EBBA-study (Paper II), we used a comprehensive and updated food diary made primarily for another study (82) but further developed for our study population by nutritionists

at the Institute for Nutrition Research, University of Oslo. The Institute for Nutrition Research computed daily intake of energy and nutrients by using a well-developed food database and software system and they also did quality controls of the data according to routine procedures (82). To minimize any information bias by day of the week or by cycle day, dietary data was collected for seven specially sampled days representing each day of the week and part of each cycle phase (follicular and luteal). We tried to increase the precision and validity of the dietary data by using a photographic booklet describing alternative portion sizes of a variety of food items. The participants were encouraged to consecutively write down what they were eating throughout the day, and the nurse made phone calls to each woman to remind her of the diary and to help her with any related problems. However, there might have been a general underreporting of energy intake in our study (113). Moreover, studies have shown that there is an increased frequency of women who are obese or have a desire for weight loss among underreporters of energy intake in dietary surveys (113), yet some of the variation in the rates of underreporting of energy intake between subgroups may be explained by real differences in energy expenditure due to differences in physical activity and smoking habits. Thus, BMI and level of dietary consciousness may have biased our estimates of energy intake.

The reproducibility and validity of the general questionnaire used in the EBBA-study (Paper II) have not been studied. Regarding physical activity in the past year, the majority of the questions, the design and the methods of data collection were largely derived from other questionnaires that have been validated and used in larger studies (46,51,114). Current literature suggests that data on occupational physical activity, high-intensity activities, and recent activities in general have the highest reproducibility (112). We exemplified intensity levels by describing common activities and usual increases in sweating, heart rate and breathing caused by the activities. Furthermore, we used the Compendium of Physical Activities Tracking Guide (81) including specification of type and intensity of a wide variety of activities, to assign METs to each activity reported by the participants, and the methods for computing METs from the physical activity questions were discussed with an expert (Barbara E. Ainsworth, personal communication, 2002). Data on age at menarche, parity and lactation had high reproducibility in other studies using re-interviewing (115,116). We supplied the general questionnaire with a life events calendar to improve recall. Finally, on returning the material at the end of the study, the participants were interviewed by the nurse, doing a check-up of the information that was given in the food diary, the general questionnaire, and the daily log.

The FFQ used to collect dietary data in the cohort studies of endometrial and breast cancer (Paper III and IV), was easy to answer and focused on fatty food items; thereby, a high response rate and a high completeness of dietary data were achieved. We excluded women with an estimated daily energy intake below 2,250 kJ or less than two-thirds of selected questions answered in analyses involving energy and fat intake (Paper III and IV) to reduce information bias due to possible misinterpretation or carelessness. The FFQ did not include the total diet and is merely suitable for categorization; Løken et al. reported that the FFQ's ability to categorize subjects according to dietary exposure was satisfactory (117). The validity and reproducibility of the FFQ, have been studied (86,87). The median overall reproducibility of the FFQ was 81% using a repeated assessment after one month (87). Solvoll compared data from the FFQ with those from a 24-hours recall and found an acceptable validity for food items in everyday use (i.e. bread, milk, coffee) (86). Furthermore, the validity of the questions about fat in diet is strengthened by the correlation between self-reported changes in fat intake and measured changes in serum cholesterol, which has been observed among subjects who participated in two of the screening surveys (118). Estimated energy intake has been directly related to level of physical activity, which may further increase the validity of the FFQ (46).

The information on usual level of recreational physical activity used in the cohort studies (Paper III and IV) has been validated; a dose-response relationship between levels of physical activity and serum lipid levels and BMI was found by Thune et al. (103). Aires et al. recently confirmed this relationship using data from women aged 40-42 years who had attended the screening surveys run by the National Health Screening Survey in Norway during 1974 to 1999 (119). Moreover, the validation study by Thune et al. also documented a direct relationship between self-reported levels of recreational physical activity and physical fitness (103) and this finding has been supported by others (120,121). We observed that sedentary women had lower serum HDL-C and higher BMI, serum LDL/HDL-cholesterol ratio, and serum triglycerides as compared with women who were active in their leisure time (Paper III and IV), further enhancing the validity of our physical activity data.

In the EBBA-study (Paper II) and in the cohort studies (Paper III and IV), we included in our analyses information on use of hormonal contraceptives, hormone therapy, smoking and alcohol. The reproducibility of hormonal contraceptive histories and the validity of hormone composition were high among women in the Nurses' Health Study II (122). In a population-

based study among women between 25 to 64 years of age in Finland, the validity of self-reported smoking was high, and most of the few self-reported non-smokers who had cotinine in their serum had only low or moderate levels (123).

However, the questionnaire instrument is in general subjective and imprecise. In our studies, few of the participants knew their blood pressure (Paper III), serum glucose (Paper III) or serum HDL-C (Paper II and IV) and none of the participants knew their plasma levels of organochlorines (Paper I) and serum and salivary levels of hormones (Paper II). On filling in the questionnaires, the women were not aware of any of the hypothesized associations (Paper I–IV). Thus, the misclassification of subjects, though probably considerable, is likely to be nondifferential with regard to the associations under study (Paper I–IV).

5.1.2.2 Serum variables

In all the studies included in the thesis, trained nurses drew optimal quality and quantity of blood samples from the subjects (Paper I,III,IV: nurses in the National Health Screening Service; Paper II: nurses at the Clinical Research Unit, UNN). All the subjects were sitting and the use of tourniquet was less than one minute to avoid any dilution or concentration of the blood that might influence the lipid content.

In the EBBA-study (Paper II), high reproducibility and validity of the serum concentrations measured at the laboratories at UNN and Aker University Hospital, were ensured through the use of well-developed protocols and continuous quality controls including use of internal standards and inter-laboratory comparisons. The serum testosterone immunoassay was changed in December 2001 to improve the measurement of testosterone values in the lowest range (from Immuno 1 to Elecsys 2010); 53 observations in the EBBA-study were conducted using the old method. The correlation coefficient was 0.97 for all samples run in parallel assays (regression equation: Elecsys 2010 = 0.859 X Immuno 1 – 0.432), but 0.45 for samples with the lowest serum testosterone concentrations (< 6.0 nmol/l). We did not correct for this change of assay and a nondifferential misclassification of our serum testosterone data may have been introduced. There was no drift in any other serum variable during the study period at any of the laboratories. Sera were stored at –70°C for up to three years until insulin, IGF-1, IGFBP-3, and leptin could be analysed. The Hormone Laboratory at Aker University Hospital, observed no degradation of these hormones and the binding protein in serum that

had been kept frozen at –70°C for several years (Peter A. Torjesen, personal communication, 2004).

As described in the methods section of the endometrial cancer study (Paper III), the Central Laboratory at Ullevål Hospital, Oslo, measured non-fasting serum glucose in women from all three counties in the 1974–78 survey. Bjartveit et al. described the validity of the glucose measurement; the serum glucose values obtained were 0.8–1.1 mmol/l higher than the true concentration defined as the value observed with a specific enzymatic method (84). Also the reproducibility of the glucose measurement was described by a coefficient of variation of about 3%; this corresponds to a standard deviation of about 0.2 for duplicate analyses, assuming a mean value of 5.7 mmol/l. During a short time period (April–June 1974) the laboratory measured systematically (0.25 mmol/l) lower glucose concentrations than during the remaining period of the study. As most of this variation was probably not due to real differences between sera in the different time periods, nondifferential misclassification may have produced a slightly weaker estimate of the association between serum glucose and endometrial cancer risk than was true for the study population (Paper III).

As described in the methods section of the breast cancer study (Paper IV), the Central Laboratory at Ullevål Hospital, Oslo, measured HDL-C in fresh sera from Oppland and Sogn og Fjordane in both the 1977–83 and the 1985–87 surveys, whereas the Institute of Medical Biology at the University of Tromsø measured HDL-C in sera from Finnmark and most of these sera where kept frozen for 12 months before analysis. Both laboratories used exactly the same method for estimating serum HDL-C, and the Central Laboratory at Ullevål Hospital, participated continuously in an international lipid standardization program within WHO, strengthening the validity of the serum HDL-C measurements. The coefficient of variation for replicated measurements of serum HDL-C by the Institute of Medical Biology was about 3% (92), which is similar to the reported reproducibility of lipid measurements by the Central Laboratory, Ullevål Hospital (84). Concentration of HDL-C in frozen sera was systematically lower than in fresh sera, and a constant estimated by Thelle et al. (92) was added to the measured HDL-C levels obtained from frozen sera. However, these differences between fresh and frozen samples may be due to factors other than those related to storage and later assessment. They may be due to demographic differences between the populations; in this case, our correction may have introduced a different bias toward the null. However, when we

excluded women with HDL-C measured in frozen serum, we observed only minor changes of the risk estimates (Paper IV).

5.1.2.3 Anthropometrical measures

The reproducibility and validity of height and weight measurements are high (124) and among the most precise biological measurements. In the cohort studies of endometrial and breast cancer (Paper III and IV), BMI cut-offs were used to define overweight and obesity. The validity of BMI as a measure of obesity is generally high. Among the participants in the EBBA-study, described in Paper II, the correlation coefficient between BMI and total body fat percentage measured by DEXA was 0.83. However, BMI is most correctly a measure of absolute fat mass adjusted for height and higher correlations (0.82 to 0.91) between BMI and absolute fat mass adjusted for height have been found (125).

As the participants in all our studies were not elderly women, any systematically different correlation between BMI and fat mass between different age groups is unlikely. However, the correlation between BMI and absolute fat mass differs across ethnic groups and ethnic specific BMI definitions of overweight and obesity have been suggested. When we excluded Sami women from our analyses on overweight/obesity and risk of endometrial cancer (Paper III) and breast cancer (Paper IV), we observed only minor changes in the results.

DEXA has gained acceptance as a reference method for analyzing body composition for both sexes, for all ages, and for both obese and non-obese individuals, and the validity of data on percentage fat tissue in the trunk obtained by DEXA is generally high (126,127). As the hydration of fat-free mass may vary throughout the menstrual cycle, all DEXA scans were taken within a narrow time period of the cycle (Paper II). Furthermore, theoretical and empirical studies have shown that the level and variability in hydration of the fat-free mass is not a major factor affecting fat percentages estimated by DEXA (128,129).

5.1.2.4 Blood pressure

In the cohort study of endometrial cancer (Paper III), hypertension was defined from systolic and diastolic blood pressure registered in the 1974–78 and the 1977–83 surveys. Blood pressure was measured manually by the same method in both surveys. The measurement was repeated after one minute in each individual, which increased the precision of the blood pressure values. Bjartveit et al. described the validity of the blood pressure measurement in

the 1974–78 survey (84); there was a statistically significant difference in mean values of diastolic blood pressure recordings made by one out of 18 nurses compared to the others. Some of this discrepancy may be due to true differences in mean diastolic blood pressure between the subgroups of women that were examined by different nurses.

5.1.3 Biomarkers, intermediate endpoints, diagnosis and follow-up

5.1.3.1 Organochlorines

In the cross-sectional study of fish consumption and organochlorines (Paper I), one person was responsible for processing of the blood and for transport and storage of the plasma samples. Neither the anticoagulant of the EDTA-glasses (EDTA calcium chelation) nor any component of the pre-cleaned tubes for storage has been reported to interact with any organochlorine in plasma. All samples were analysed for organochlorines within 6 months, and due to their long half-lives, any degradation of organochlorines during storage was low. Plasma concentrations of organochlorines were measured by highly sensitive high-resolution gas chromatography mass spectrometry. The laboratory procedures involve effective sample clean-up and extraction techniques. NILU ensured good quality control of the measurements by detailed in-house protocols and inter-laboratory testing exercises within AMAP (Paper I). Even though we did not have information on eventual drift in measurements during the laboratory work, we find that any information bias due to equipment, observers and procedures is unlikely to have influenced the validity of the organochlorine measurements. Furthermore, the observed pattern of plasma concentrations of different organochlorines in our study reflects their known half-lives (Figure 1, Paper I); this strengthens the validity of our organochlorine data.

5.1.3.2 Ovarian hormones

Concentration of sex steroids in saliva is regarded as a valid estimate of the free biologically active fraction of hormones in blood, unbound to SHBG and albumin (130). In the EBBA-study (Paper II), saliva sampling and salivary estradiol and progesterone measurements followed previously established protocols (83,131). For a minor number of cycles (n = 29; 14%) salivary estradiol measurements were made by an assay that was replaced by a new method for the majority of cycles. In a parallel run of the estradiol assays, the observed correlation was comparable to what the laboratory would have expected if cycles were assayed twice using the same system; therefore, we did not make any corrections of the

measured salivary estradiol concentrations. However, this change of assays may have introduced a non-differential misclassification of our salivary estradiol data. The impact of variation in hydration status on salivary estradiol and progesterone concentrations is small (130). Moreover, we tried to minimize the influence of possible diurnal variation in steroid levels by instructing the women to do the salvia sampling in the morning. Even though some sampled systematically at other times of the day, this may have caused only a negligible misclassification of the estradiol and progesterone data (Peter T. Ellison, personal communication, 2002). It has been shown that steroid levels remain stable in saliva samples stored at room temperature for several months (83). The curves describing the ovarian function in the study population (Figure 1, Paper IV) resemble those observed in other populations (132) and correspond with the established physiology of the female reproductive system (133); this strengthens the validity of our data.

5.1.3.3 Mammograms

In the EBBA-study (Paper II), mammograms were taken within the same narrow time frame of the menstrual cycle in all participants due to the suggested influence of cycle phases on parenchymal breast density (134). N. Bjurstam, an experienced radiologist, read all the mammograms without any knowledge about their metabolic or hormonal status. In a blinded rereading of mammograms in 41 postmenopausal women by N. Bjurstam there was nearly perfect agreement for selection of high-risk vs. low-risk parenchymal patterns (intra-observer kappa coefficient = 0.92) (Yngve Bremnes, personal communication, 2004). Classification of mammographic breast densities is a valid surrogate measure of breast cancer risk (135). Wolfe's classification was originally used in postmenopausal women and is less adequate for differentiation of mammographic patterns among premenopausal women as some of the features characterizing the upper categories (i.e. fibroadenomatosis) are infrequent among younger women (Nils Bjurstam, personal communication, 2003). Therefore, a modified Wolfe's classification was used. Additional classifications were performed in our study population but analyses, including different classifications are left for future publications by the group.

5.1.3.4 Cancer diagnosis and follow-up

In the cohort studies (Paper III and IV), cases of endometrial and breast cancer in the study population were identified in the Cancer Registry by use of specific codes for localization and histology. We do not know the validity of the endometrial and breast cancer diagnosis in the

database. However, Harvei et al. have described the validity of the cancer prostate diagnosis in a large study of the database; errors were observed in 0.5% of the controlled data elements (93).

The reproducibility of a cancer diagnosis depends on uniformity in diagnosing by each pathologist and between the pathologists. In a study among US pathologists, there was nearly perfect agreement for selection of benign *vs.* malignant categories of breast lesions (inter-observer kappa coefficient = 0.95), while there was less agreement for the categories of noninvasive malignant and benign with atypia (kappa coefficient = 0.59 and 0.22, respectively) (136), and similar reproducibility of breast lesion diagnosis has been found by others (137). In a study among US pathologists of the reproducibility of the diagnosis of proliferative lesions of the endometrium, there was strong agreement for endometrioid carcinoma (kappa coefficient = 0.83) (138). We do not have data on the reproducibility of breast and endometrial cancer diagnosis among pathologists in Norway. However, high uniformity is likely as they have been trained in only a few laboratories and participate in national and international slide seminars.

An almost complete registration of all incident cancer cases in Norway is obtained by a system including independent reporting of cancer cases from multiple sources (1). Based on studies of a large number of records, Harvei et al. have suggested a 99% completeness in the reporting of all cancer cases to the Cancer Registry (93). Thus, there is minimal bias due to inadequate reporting of cancer cases in our studies.

In the cohort studies (Paper III and IV), emigration and deaths in the study population throughout follow-up were identified by linkage to the Central Population Register and there was minimal, if any loss to follow-up.

We did not have any exact information on age at menopause. If a woman had not reported to be postmenopausal in survey at a younger age, we defined her as postmenopausal from age 50 given no contradictory information on her status at that age or later (Paper IV). We considered age 50 as an appropriate average age at menopause in the study population as average age at menopause has been 51 years in international studies (139), whereas it was 47.7 years in a large Norwegian study (140). Furthermore, age 50 has been used as the estimated average age at menopause in other studies in Norway (46,141). However, this procedure may have

introduced a nondifferential misclassification of person-years in pre- and postmenopausal periods and a possible underestimation of the association between serum HDL-C and postmenopausal breast cancer (Paper IV).

We did not have data on hysterectomies in the cohort study of endometrial cancer (Paper III). This might have introduced a biased follow-up if subgroups of women characterized by a specific lifestyle or metabolic profile were more likely to have a hysterectomy. However, we do not have any information indicating such bias and the estimated prevalence of extirpated corpora uteri among women aged 15 years or more in Norway in the three-year period 1988–1990 was 198 per 100,000 women (142); of an order of magnitude that makes any major influence of hysterectomy on our results unlikely.

One may argue that overweight and obese women with metabolic disturbances, seek medical assistance and have clinical examinations more often than other women; this might produce a biased follow-up and a differential misclassification of breast and endometrial cancer in Paper III and IV, if women with metabolic disturbances are more likely to have their cancer diagnosed than women without metabolic disturbances. However, when we excluded women with self-reported hypertension from the analysis in Paper III, the association between measured hypertension and endometrial cancer risk was strengthened.

The screening surveys were run in the three different counties consecutively and not in parallel. This means that the possible length of follow-up differed by region. As there are considerable differences in height and weight among women in different counties of Norway (143), there may have been a selection bias in follow-up period. Due to this potential bias, geographical region was put in the strata statement in the Cox models in both the endometrial cancer and the breast cancer study.

5.1.3 Confounding and effect modification

A confounder is defined as a variable associated with the exposure in the population, associated with the outcome conditional on the exposure, and not in the causal pathway between the exposure and the outcome (96). Confounding may over or underestimate the association under study, and may even change the direction of the association (110). To minimize bias due to confounding, stratified analysis or multivariate analysis, when

confounding by several variables simultaneously, may be used. Effect modification is distinct from confounding (or selection or information bias) in that it does not represent a bias, which should be removed or controlled, but rather a real difference in the effect of exposure in various subgroups that may be of considerable interest (144).

In the cross-sectional study of fish consumption and organochlorines (Paper I), we used multivariate models to adjust for confounding. The well-known impact of lactation on internal dose of organochlorines suggests that stratification on lactation experience might have been a useful approach, if the number of women in the "never lactating" group had been higher. Potential confounders that we did not have information on have been discussed (i.e., use of tobacco and alcohol, Paper I) and these might have been especially important if they affected the metabolism of organochlorines. As plasma levels of organochlorines generally correlate with concentrations of lipids in blood (145), which reflect dietary intake of fat, in particular, missing data on serum lipids in our study decrease the internal validity of the observed associations.

In the EBBA-study (Paper II), we used inclusion criteria to limit confounding by age, endocrine disorders, hormonal contraceptive use, pregnancy and lactation and included several potential confounding factors as covariates in the regression models. However, residual confounding might have influenced our estimates. A particular concern is possible individual differences in metabolic and hormonal effects of smoking and reproductive history due to acquired or inherited susceptibility (146,147).

In the cohort studies of endometrial and breast cancer (Paper III and IV), we restricted the study populations to women with certain characteristics (i.e. no pregnancy, primary amenorrhoea, or prevalent cancer) in the surveys and with complete information on selected variables to limit confounding. As mentioned, county was put in the strata statement in the Cox models (Paper III and IV); in this way, we adjusted for potential influence of geographical region on the relationship between an exposure or a biomarker and breast and endometrial cancer incidence. Furthermore, several potential confounders were included in the Cox models, while others that were lacking in the datasets were discussed (Paper III and IV). A further elaboration of the topic is given below to ascertain that inappropriate adjustment for confounders was not of any major importance for our results.

Both exogenous estrogens and progestin influence on serum HDL-C level (148), and use of estrogens and progestin in combination has been associated with a small increase in blood pressure (1.3–1.8 mmHg in diastolic blood pressure) (149). Moreover, hormone therapy has been less frequent among the heaviest women (140). Use of estrogen-progestin combination type of oral contraceptives has been inversely related to endometrial cancer risk (150). Postmenopausal estrogen therapy is an established risk factor for endometrial cancer, while combined estrogen-progestin therapy has generally been associated with a reduced risk of endometrial cancer or with no risk changes (150). The risk of breast cancer has been slightly increased among users of oral contraceptives (151) and hormone therapy has been directly related to breast cancer risk (152). The effect of exogenous estrogen and progestin use on endometrial and breast cancer risk is generally stronger the more recent and the longer the period of use. In the cohort study of endometrial cancer (Paper III) we did not have information on use of oral contraceptives and hormone therapy in any of the surveys, whereas in the cohort study of breast cancer (Paper IV) these data were available from the 1985–87 survey only. Nevertheless, we find that confounding by exogenous estrogen and progestin use is an unlikely explanation for the observed associations between metabolic parameters and risk of endometrial and breast cancer in our studies, due mainly, to the limited use of high-dose estrogen contraceptives (153) and hormone therapy among Norwegian women especially in the oldest birth cohorts (154), as observed in the cohort study of breast cancer (Paper IV).

The associations between dietary factors, physical activity, use of alcohol and tobacco and metabolic profile (BMI, blood pressure, serum glucose, serum lipids) are well known from prevention programs in cardiovascular disease. The role of dietary fat in influencing the risk of endometrial and breast cancer is unclear (155). Epidemiological evidence confirms a protective effect of physical activity in breast cancer, and supports a protective effect of physical activity in endometrial cancer (46,50,51). Alcohol is an established risk factor for breast cancer (156), and active smoking was associated with increased breast cancer risk in a recent large prospective study (157). In contrast, active smoking has been inversely related to endometrial cancer risk (158), and there is probably only a weak if any association between alcohol and endometrial cancer risk (159). Even though, dietary fat, physical activity, and use of alcohol and tobacco were included as covariates together with age at first birth and parity in the Cox models in the cohort studies of endometrial cancer and breast cancer (Paper III and IV), we can not rule out possible residual confounding due to individual differences in the effects of these exposures on metabolic profile and endometrial and mammary epithelial cells

caused in particular, by genetic polymorphisms (i.e. common gene variants with a minor allele frequency of more than 1%).

In the cohort study of endometrial cancer (Paper III), we used non-fasting serum glucose. As there is a physiological increase in postprandial serum glucose, variation in time since eating or drinking before the blood sample, may have caused considerable variation in the non-fasting serum glucose variable. However, adjustment for time since the last meal did not alter our risk estimates (Paper III).

Cohort effects reflect changes that affect the risk of a specific cancer in a given birth cohort throughout their lifetime. When speaking about breast and endometrial cancer, such changes could be living conditions in particular, in uterus and childhood and during puberty, adolescence and childbearing. Each of the surveys used in the cohort studies (Paper III and IV) was run in 3 to 6-year periods; this means that the women of a given age at measurement belong to 3 to 6 different birth cohorts. Studies have suggested that the lifetime risk of breast cancer in different birth cohorts of Norwegian women varies due to differences in exposure to energetic factors (i.e. energy intake and physical activity) in sensitive periods of life with regard to breast cancer development (13,160) and there is a strong cohort effect on BMI and metabolic profile (161). Nevertheless, the influence of birth cohort on our results is probably small as women born within a 3 to 6-year interval have had nearly the same living conditions, except for women who were born or grew up during World War II (162).

We did not include socio-economic status (i.e. marital status, education, professional experience and income) in our analyses (Paper I–IV), as we consider these data merely as a proxy correlating with other variables, which probably exert the effect on the outcome. Education was associated with age ($p < 0.05$), parity ($p < 0.001$), age at first birth ($p < 0.001$), use of hormonal contraceptives ($p < 0.01$), tobacco ($p < 0.01$) and alcohol ($p < 0.05$) in the Norwegian EBBA-data, supporting our position. BMI and physical activity influences age at menarche (163). Thus, age at menarche is plausibly on the causal pathway between BMI and related metabolic abnormalities and endometrial and breast cancer, and should not be considered as a confounder in Paper III and IV.

From statistical tests and physiological and clinical knowledge about coexisting phenomena (i.e. metabolic syndrome) we found that analyses of hypertension (Paper III), serum glucose

(Paper III) and serum HDL-C (Paper II and IV) should be stratified by BMI. Likewise, due to the shift in endogenous hormones at menopause, we stratified by age at exposure (younger or older than 50) in the analyses of BMI, energy intake and physical activity in Paper III. Other effect modifiers were not identified by tests of interaction (i.e. age at menarche, height, parity, physical activity, energy and fat intake, use of hormonal contraceptives, tobacco and alcohol) (Paper II-IV); nevertheless, we cannot rule out the existence of additional effect modifiers among environmental factors that were not considered.

Even though, we observed that lifestyle and metabolic profile influence the risk of breast and endometrial cancer in multivariate and stratified statistical models, we may not have been able to give the full picture. For example, recent studies found that a functional polymorphism in the promoter of the progesterone receptor gene was associated with the risk of breast (164) and endometrial cancer (165) and that the risk was even greater in obese and overweight women carriers, respectively. Furthermore, possible polymorphisms of genes encoding for enzymes involved in the metabolism of sex steroids and carcinogens (i.e. organochlorines) in particular, represent highly plausible effect modifiers in our studies. However, genetic information was not available in any of the study populations at the time we did the presented analyses.

One may argue that the cohort studies (Paper III and IV) were restricted in their age range and thus may not provide the full picture if cancers at specific ages are determined differently, i.e. if there is an interaction between exposure and age at diagnosis, or between metabolic markers and age at diagnosis. In the study of breast cancer in Paper IV, we performed separate analyses for pre- and postmenopausal breast cancer, due to the well known cross-over in breast cancer risk factors at about 50 years of age (166,167). Furthermore, the results were not changed by the inclusion of age at diagnosis as a covariate in the presented Cox models (Paper III and IV) or by the use of Cox models expressing the hazards as a function of age (Paper IV).

5.2 Considerations of appropriateness of biomarkers and causality

5.2.1 Strength of the association

Cross-sectional studies are not capable of establishing or refuting a causal relationship between a given exposure and disease. They do, however, provide mechanistic insight and

may yield useful information on relationships between biomarkers and the events they represent (168).

As marine fat is regarded as the main source of human exposure to organochlorines, we registered a wide variety of types and rates of seafood in diet and measured plasma concentrations of PCBs and pesticides/metabolites known to be present in the Arctic ecosystem (Paper I). The study population had a habitual intake of large amounts of seafood, especially lean fish filet, and the selected organochlorines, especially those with the longest half-lives, were present in the plasma samples. However, we did not observe any association between self-reported consumption of any fish or fish product (frequency and estimated average net amount per time unit) and measured plasma levels of any PCB or pesticide/metabolite. Thus, the negative results suggest that consumption of, in particular, lean fish from Norwegian waters is not a major source of exposure to organochlorines.

Consumption of seagulls' eggs was directly related to the levels of two major PCB congeners and ΣPCB. However, these findings may be due to chance because only 13% of the study population reported use of seagulls' eggs in their diet.

Concentrations of PCBs and pesticides/metabolites were strongly and positively correlated. This may make it difficult to draw valid conclusions about possible causal relationships between the body burden of individual organochlorines and breast and endometrial cancer in epidemiological studies. Furthermore, while BMI, duration of residence and accumulated lactation time were statistically significant predictors of plasma levels of several organochlorines, they were unrelated to the concentration of others. This inconsistency indicates that the mixture of organochlorines should not be treated as a homogenous group of compounds in exposure assessment, even though they are strongly correlated.

In the EBBA-study (Paper II), we observed a statistically significant drop in overall average salivary estradiol that equalled a 13.2% change in mean for the total population by each 0.33 mmol/l (1-standard deviation) increase in serum HDL-C among the heaviest women (BMI ≥ 23.6 kg/m^2) and a test of interaction was statistically significant. The association between serum LDL/HDL-cholesterol ratio and overall average salivary estradiol concentration in the heaviest women (BMI ≥ 23.6 kg/m^2) remained statistically significant after adjustment for age and BMI in a continuous term. Additionally, we observed a highly significant difference in

salivary estradiol levels by cycle day between women with serum LDL/HDL-cholesterol ratio in the highest quartile and BMI above median and other women ($p = 0.001$) as compared to the rest of the study population. There were statistically significant inverse associations between serum HDL-C and serum concentrations of leptin, insulin and DHEA-SO_4 and serum DHEA-SO_4 was a predictor of average mid-luteal salivary estradiol concentration. The inverse relationships between breast density and adiposity, serum total/HDL-cholesterol ratio, LDL/HDL-cholesterol ratio, insulin, and leptin, and the direct relationships between breast density and levels of HDL-C in serum and of progesterone in saliva were statistically significant after adjustments for potential confounders.

In cohort studies, a statistically robust association between an exposure and the risk of a specific malignancy, after adjustment for potentially confounding variables, is considered to support a causal relationship. In the cohort study of endometrial cancer (Paper III), the estimated 95% confidence intervals of the relative risk estimates were wide due to a limited number of endometrial cancer cases available for analysis. Nevertheless, the association between BMI and risk of endometrial cancer was statistically robust; the strongest association was observed for obesity, which was associated with a 2.6 times increase in risk of endometrial cancer compared to normal weight. Moreover, high energy intake was associated with a more than threefold increase in the risk of endometrial cancer among women younger than 50 years in analysis adjusted for BMI and physical activity. There was a statistically significant reduction in the risk of endometrial cancer by higher levels of sustained occupational physical activity in analysis adjusted for BMI. Furthermore, both the more than threefold increase in the risk of endometrial cancer associated with prolonged hypertension among obese women and the more than doubled increase in the risk of endometrial cancer associated with high non-fasting serum glucose among overweight women were statistically significant and independent of variation in BMI, physical activity, and other covariates considered, within the subgroups. The interaction between BMI (cut-off, 30 kg/m^2) and the categorical hypertension variable was statistically significant.

In cohort studies aimed at evaluating the association between a biomarker and the risk of a specific malignancy, a statistically robust association may give clues to the usefulness of the biomarker and to the biological mechanisms underlying cancer development. In the cohort study of breast cancer (Paper IV), the association between serum HDL-C and the risk of postmenopausal breast cancer was statistically significant after adjustment for several

potential confounders, including BMI and physical activity. The interaction between BMI (cut-off, 25 kg/m^2) and serum HDL-C was highly significant; among overweight women, high serum HDL-C was associated with a statistically significant 66% reduction in risk of postmenopausal breast cancer and the association was not distorted in analysis adjusted for BMI (continuous term). Furthermore, the robustness of the association is underscored by the finding of nearly the same results in Cox models that expressed hazards as a function of age.

5.2.2 Biological gradient: dose-response relationship

According to common biological principles, a monotonic relationship between a variable and the outcome under study is often considered to support the notion that an exposure is causal or that a hypothesized biomarker is appropriate. However, this pattern may not always be the optimal description of how an exposure or a biomarker is related to a disease process; epidemiological research may provide evidence for thresholds in the dose-response relationships between an exposure or a biomarker and a specific malignancy. Such thresholds may be copied into clinical guidelines to identify individuals at increased risk who may be candidates for interventions.

In the EBBA-study (Paper II), serum HDL-C was associated with the level of several hormones (i.e. free estradiol, DHEA-SO_4, insulin, leptin) in a dose-related manner. We observed that each 0.33 mmol/l (1-SD) increase in serum HDL-C produced a significant drop of 1.5 pmol/l ($p = 0.02$) in overall average estradiol concentration, which equals an 8.2% change in mean overall average estradiol concentration in the study population. Furthermore, our results were suggestive of thresholds in the relation between serum LDL/HDL-cholesterol ratio and BMI and levels of free estradiol at a ratio about 2.1 and a BMI about 24 kg/m^2.

In the cohort study of endometrial cancer (Paper III), the association between sustained occupational physical activity and risk of endometrial cancer was underscored by a test for trend that was nearly statistically significant. Furthermore, increasing levels of BMI at baseline (i.e. quartiles and WHO-categories) and increasing levels of non-fasting serum glucose in the 1974–78 survey (i.e. quartiles) produced higher endometrial cancer incidence in a statistically significant dose-related manner, while there was no association between the continuous non-fasting serum glucose variable and the risk of endometrial cancer. Moreover, our results suggest that there may be thresholds in the dose-response relation between BMI and the risk of endometrial cancer at a BMI close to overweight (25 kg/m^2), as well as

between non-fasting serum glucose and the risk of endometrial cancer at a non-fasting serum glucose concentration about 5.6 mmol/l. This may imply that variations in BMI and non-fasting serum glucose below these thresholds do not influence endometrial cancer risk to any material degree. There was also a statistically significant linear trend for increased endometrial cancer risk by increasing duration of hypertension (blood pressure ≥ 140/90 mmHg) among obese women, while there were no associations between the continuous systolic and diastolic blood pressure variables and endometrial cancer risk in the total population. This is consistent with the existence of a possible threshold in the relationship between blood pressure and the risk of endometrial cancer among obese women close to the cut-off for hypertension (140/90 mmHg).

In the cohort study of breast cancer (Paper IV), there was a statistically significant dose-response relationship between serum HDL-C and risk of postmenopausal breast cancer in the total population and the relationship was particularly strong among overweight women. There was no evidence of any threshold in the dose-response relationship between serum HDL-C and postmenopausal breast cancer risk.

5.2.3 Temporality

A major strength of cohort studies is the measurement of exposure before the cancer diagnosis. Misclassification of exposure due to too short or too long time period between exposure and cancer diagnosis has been discussed. An ideal study design would involve exposure assessment at several points in time to examine the influence of change in exposure level over time and the influence of exposure level in certain time periods of life.

We estimated the relative risks of endometrial cancer associated with continuous exposure levels (Paper III); we used the pooled information from two surveys on physical activity and on blood pressure, and we used the information from one survey on energy intake, BMI and non-fasting serum glucose. We examined the influence of age at exposure on the observed associations; our results suggest that overweight and obesity increase the risk of endometrial cancer mainly among the youngest women (< 50 years). As discussed in Paper III, this may point to the importance of the relative progesterone deficiency during the luteal phase of the cycle experienced by premenopausal women with high BMI as a result of a higher frequency of anovulatory cycles, amenorrhoea, and irregular menstrual periods (150). In postmenopausal women, a high BMI may increase estrogen exposure through increased conversion of

androgens to estrogens in adipose tissue. Our results are consistent with the hypothesis that the endometrial tissue is especially vulnerable to loss of the secretory transforming action of progesterone in premenopausal years. Moreover, our results suggest that energy intake and occupational physical activity are associated with risk among women younger than 50, while recreational physical activity is associated with risk among women older than 50. Thus, the carcinogenic effect of the increased mitotic activity in the endometrial tissue brought about by a positive energy balance in premenopausal women may be enhanced by reduced DNA-repair, increased oxidative damage to DNA and increased oncogene expression caused by excessive energy intake and low energy expenditure. Nevertheless, it seems likely that changes in physical activity level after the menopause may slow down the promotion of tumors in the endometrium. However, we should interpret our results with caution as they were based on a small number of cases in each stratum and formal tests of interaction were not significant. Furthermore, sensitive periods and changes in the association between BMI and sex steroid levels by menopausal status may only partly explain our findings; for example positive energy balance may represent diverse exposures with diverse effects on endometrial cancer incidence according to birth years as dietary habits and habitual physical activity associated with work and chores of daily living have changed markedly across the time periods when subgroups of the cohort (i.e. younger than 50 *vs.* older than 50 at baseline) might have been most susceptible to the hormonal changes caused by positive energy balance (13).

In the analysis of breast cancer risk among women who had participated in two surveys (Paper IV), we estimated the RRs associated with the exposure levels in two different time periods (i.e. between surveys and from the last survey until the end of follow-up). Serum HDL-C was associated with postmenopausal breast cancer risk, but not with premenopausal breast cancer risk. This crossover in breast cancer risk factors at about 50 years of age is a well-known phenomenon, which was initially discussed in relation to the observation of "Clemmesen's hook" in the age-specific incidence curve of breast cancer about this age (169) and has led to hypothesis about pre- and postmenopausal breast cancer as two separate malignancies with different aetiology. However, it might be that the hormonal changes associated with low serum HDL-C affect only the last steps in breast cancer development; i.e. tumor promotion. Furthermore, as the aromatisation of androgens is the dominant source of estrogens in postmenopausal women, and androgens are the major determinants of serum HDL-C level, serum HDL-C may turn out to be a biomarker predominantly for

postmenopausal breast cancer risk. An alternative explanation to our finding is that the induction time between the underlying etiological factor and breast cancer may be too long to produce an increase in breast cancer incidence before the menopause in the study population with an average age at assessment of 44 years.

5.2.4 Biological plausibility, specificity and consistency

The observed plasma levels of organochlorines in Paper I were similar to levels observed among the general female population in other European countries (145,170), and the distribution of different organochlorines reflected well-known variation in the half-lives of the compounds.

Also Rylander et al. did not observe any association between fish consumption and PCB concentration in plasma from fishermen's wives in Sweden (99). In several reports on positive associations between fish consumption and levels of organochlorines in blood in females (171,172), the fish was harvested from contaminated waters. Furthermore, comparison between studies is complicated by differences in methods of quantification of fish consumption. It is biologically plausible that there were no associations between fish consumption and plasma levels of organochlorines in our study, as organochlorines accumulate in fat tissue of living organisms and muscle of lean fish constituted most of the fish consumption in the study population.

The observed inverse associations between duration of lactation and plasma levels of PCBs and pesticides/metabolites in our study are in agreement with other studies (97-99). Because of the high lipid content of breast milk, organochlorines are mobilized from body stores and the maternal body burden of organochlorines is decreased during breast feeding (173). Studies have demonstrated that organochlorines acquired from breast milk elevate a child's body burden of these contaminants for several years, and pre- and postnatal exposures to organochlorines have been associated with developmental deficits in early childhood (174). Thus, our results justify concern about possible health hazards from organochlorines transferred to the infant through breast milk.

In accordance with our results, Glynn et al. observed a positive association between BMI and serum concentration of CB-105 and β-HCH (175), whereas other studies found no association between BMI and total PCB (171,176) and *p,p'*-DDE in blood (177,178). In contrast, others

have reported negative associations between BMI and total PCB and CB-138 (177,178), and a positive association between BMI and *p,p'*-DDE (175,179). In our study, BMI was also directly related to plasma concentrations of CB-153 and total chordane. Associations between BMI and circulating levels of organochlorines may reflect BMI-related alterations in toxicokinetics of the compounds (i.e. slower turnover by increasing BMI), and our findings indicate that the possible modulating effects of BMI may be compound-specific. Alternatively, a positive association between prolonged high consumption of organochlorine-rich fatty foods and BMI could also be a physiologically plausible mechanism explaining the increase in plasma levels of some organochlorines by increasing BMI. Our results indicate that there may be marked disparities in circulating levels of organochlorines between women due to differences in BMI and lactation experience; these interindividual variations may not be proportional over time. Thus, although a single assessment of the body burden of organochlorines may reflect lifetime exposure of the highly persistent compounds, it may not reflect the body burden of organochlorines at a time that is relevant to breast and endometrial cancer development.

Based on current knowledge, our results support the contention that the contribution of dietary organochlorine exposure to breast and endometrial cancer causation among Norwegian women is reassuring low. The first study reporting an association between circulating organochlorine levels and breast cancer was published in 1993; serum *p,p'*-DDE was significantly higher among breast cancer cases than among controls (180). The more than 30 population-based studies published on organochlorines (mainly PCBs and *p,p'*-DDE) and breast cancer since 1993 have been mostly negative overall (181), with positive results often limited to subgroups (30,182-185). However, a recent study observed an increased risk of breast cancer associated with high PCB levels in a subgroup of women with a certain variant of the *CYP1A1* gene (i.e. polymorphism) (186). To our knowledge, to date only two studies have addressed the association between organochlorines and endometrial cancer (187,188) and the results were negative in both.

Finally, plausible reasons for the many null epidemiological results have been reviewed (189) and include poor historical exposure measurement, restriction to a small number of organochlorines, failure to study organochlorines in current use, low statistical power to detect modest effects, and failure to take into account genetic susceptibility and life-cycle effects. Thus, although the potency of organochlorines is typically much lower than the

potency of endogenous estrogens, there is still a concern about a possible role of long-term low-dose exposure to organochlorines through dietary intake in breast and endometrial cancer. And, there is particular concern about the exposures that take place when levels of endogenous hormones are very low, such as in utero or during prepubertal, or postmenopausal time periods.

In the EBBA-study (Paper II), we reported for the first time that serum HDL-C is inversely related to level of free estradiol throughout one entire menstrual cycle in the heaviest premenopausal women (BMI ≥ 23.6 kg/m^2). Others have reported on the association between serum HDL-C and estradiol concentrations in blood and the sample sizes have been small; both a direct relationship (190,191) and no relationship (192-194) have been reported. The use of salivary estradiol assays in our study is a major advantage as this results in better estimates of the level of free biologically active estradiol as compared to measurements in blood (130). Our study is strengthened by the estimation of daily estradiol and progesterone concentrations in saliva using well-developed and validated methods and assays to characterize the women's exposure to ovarian steroid exposure, and the comparison of levels by aligned cycle days in the large majority of the population (132). This is a great advantage, given the large intra-cycle fluctuations in levels of ovarian hormones and the wide inter-individual variation in cycle length in menstruating women. Furthermore, as low serum HDL-C is an important aspect of metabolic syndrome, specific analysis of the relationships between serum HDL-C and levels of endogenous hormones among women in different categories of BMI may be needed to give the most relevant information, as in our study. We also observed an inverse association between serum HDL-C and serum DHEA-SO_4, which is in agreement with others (192-194). Furthermore, we observed a direct relationship between serum DHEA-SO_4 and average mid-luteal estradiol concentration. We did not observe any relationship between serum HDL-C and salivary progesterone levels and this null association is supported by several studies (195-197).

We found that mammographic breast density was specifically related to salivary progesterone levels and not to salivary estradiol levels, as also reported by others (Paper II) (107). As mammographic density is an independent predictor of breast cancer risk, with increase in risk by increasing density (135,198), this underlines the role of progesterone in breast carcinogenesis (8). We found that breast density decreased by increasing adiposity and by decreasing serum HDL-C, as in former studies (104-106,108). Interestingly, Sala et al. have

suggested that this negative confounding of potential markers of increased breast cancer risk (high BMI, low serum HDL-C) may mean that the effect of parenchymal patterns on risk will tend to be underestimated unless adjusted for metabolic profile (BMI, serum HDL-C) and vice versa (108).

The observed associations between serum HDL-C and DHEA-SO_4 and salivary estradiol in our study are biologically plausible as sex steroids are physiological regulators of plasma lipids (199). More specifically, androgens are major determinants of serum HDL-C, lowering the level by modulating the activity of hepatic lipase (200,201). High androgen levels may increase the level of free estradiol mainly through an increased conversion of androgens to estrogens in adipose tissue and trough an increased displacement of estrogens from SHBG due to the binding protein's higher affinity for androgens. Our results suggest that relative hyperinsulinemia among the heaviest women (BMI $\geq$ 23.6 kg/m^2), may further increase the level of free estradiol; insulin stimulates the ovarian and adrenal production of androgens (202).

Prior to the cross-sectional study of serum HDL-C, metabolic syndrome, endogenous hormone levels, and breast density (Paper II), we observed that serum HDL-C was associated with postmenopausal breast cancer risk, especially among overweight women (BMI $\geq$ 25 kg/m^2), in a large prospective study (Paper IV). Thus, by analysing the associations between metabolic profile and levels of free estradiol in the cross-sectional data we had the possibility to identify hypothesized physiological mechanisms that may link overweight and dyslipidemia to breast cancer risk in women. As excessive exposure to estrogens is a major mitotic stimulus in breast and endometrial tissue, our results support that low serum HDL-C is a true biomarker of breast cancer risk and also of endometrial cancer risk.

Several studies have reported lower levels of serum HDL-C in breast cancer cases *vs.* controls (111,203-205). Prospective data on serum HDL-C and breast cancer risk has been limited and inconsistent (141,206,207) and none of the studies examined the association between serum HDL-C and breast cancer risk among women in different BMI categories.

Both the cross-sectional (Paper II) and the prospective (Paper IV) data indicated an interaction with BMI, which suggest that serum HDL-C may be useful as a biomarker of breast cancer risk, especially in overweight and obese women. Despite the observed interactions and

thresholds, we should, however, be careful in limiting the possible value of our findings to specific subgroups; in a recent publication lack of obesity was associated with delayed onset of breast cancer among carriers of high-penetrance genes (i.e. *BRCA1* and *BRCA2*) (208). Thus, obesity-related biomarkers may be useful in the medical surveillance of these high-risk women.

In our study of endometrial cancer (Paper III), obesity was associated with a 2.6 times increase in the risk of endometrial cancer. This is in agreement with a recent report from an international expert panel saying that there is convincing evidence from epidemiological studies that obesity is associated with a two- to threefold increase in endometrial cancer risk in both pre- and postmenopausal (50).

We observed a considerable protective effect of occupational physical activity and a suggested protective effect of recreational physical activity on the risk of endometrial cancer. To our knowledge, Moradi et al. (209) are the only other group that have examined the association between occupational physical activity and endometrial cancer risk prospectively and the results were in accordance with ours. Several case-control studies support a protective effect of occupational physical activity (210-214). Similarly, we know of only one other cohort study of recreational physical activity and endometrial cancer risk (215) and a stronger protective effect was observed than in our data. Most retrospective studies of recreational physical activity support our finding (210,211,216), yet some do not (214). A recent cohort study with relatively short follow-up, did not observe any dose-response relationships with either total or vigorous activity (all types of physical activity), but there was a non-significant reduction in risk of endometrial cancer associated with the higher four quintiles of total physical activity compared to the lowest (217).

We observed a direct relationship between energy intake and endometrial cancer risk. There are few other studies on dietary energy intake and endometrial cancer risk and to our knowledge, none with a prospective design. Some case-control studies have found an increased risk of endometrial cancer by increasing energy intake as in our study (218,219), while others did not observe any association (43-45). Besides the prospective design of our study, our results are strengthened by the adjustments for occupational and recreational physical activity and for measured height and weight.

Hypertension was directly related to the risk of endometrial cancer among obese women in our study population. Findings in retrospective studies of hypertension and endometrial cancer have been inconclusive (220-225). However, a relatively recent, large case-control study observed an effect of hypertension on endometrial cancer risk confined to obese women (226), which is in agreement with our results. To our knowledge, our study is unique in its prospective design and in the assessment of hypertension by repeated measurements of arterial blood pressure.

We observed an increased risk of endometrial cancer associated with relative hyperglycemia in overweight women. Increased fasting serum glucose has been observed among endometrial cancer cases in small retrospective studies (227,228), but we do not know about any other prospective study on serum glucose. Several epidemiological studies have found a direct association between self-reported diabetes and endometrial cancer risk (226,229-234), including a prospective study (229), and the association has been confined to overweight and obese women in large studies (229,230,234) supporting our findings.

As outlined in previous sections, obesity and physical inactivity are associated with excessive estrogen exposure and relative progesterone deficiency due to a higher frequency of anovulatory cycles, increased production of estrogens in adipose tissue and decreased production of SHBG. This excessive estrogen stimulation unopposed by progesterone strongly predisposes to endometrial cancer. However, chronic hyperinsulinemia may be a major physiological link between obesity, high energy intake, physical inactivity, hypertension, and hyperglycemia and endometrial cancer development. In addition to insulin, IGF-I may be an important factor in endometrial cancer development. The proliferative action of estrogens in the endometrium is mediated through an increased local production of IGF-I, which is the major mitogenic stimulus. Progesterone opposes proliferation by a simultaneous stimulation of IGF-binding protein production (235). Insulin increases levels of free IGF-I, by increasing the production of the hormone and inhibiting the production of its binding proteins (75), and this may be a key mechanism for the carcinogenic effect of insulin in the endometrium. We found that the risk of endometrial cancer associated with hypertension and hyperglycemia was increased among women in whom these phenomena coexisted with other metabolic abnormalities (i.e. overweight/obesity); this suggests that the hormonal changes related to coexisting metabolic abnormalities might interact to enhance the carcinogenic process.

Even though statistical tests of interaction and biological knowledge may justify the chosen cut-offs for BMI and blood pressure in our studies and the use of these in clinical guidelines, we should be careful about regarding values below the cut-offs as "normal". From studies of isolated communities with a hunter-gatherer lifestyle typical of the Stone Age, it has been estimated that the current averages in BMI and blood pressure in Western populations are high in relation to the prehistoric values (236); today's average levels of BMI and blood pressure are not typical of values throughout human evolution and increasing disparity is observed by increased age. Furthermore, the levels of BMI and related metabolic variables in Norwegian women have changed most markedly during the last decades (161) and a continued rise is likely. Thus, as the "normal" BMI and blood pressure values are creeping upwards one should be especially aware of not focusing only on the established criteria, but struggle to catch possible increases in the risk of chronic diseases across all levels of the variables. Furthermore, it might be most appropriate to use specific cut-offs in different age groups.

In theory, randomised controlled clinical trials provide data that are superior to what we achieve in cross-sectional studies and cohort studies. Randomised controlled clinical trial refers to a study in which participants are recruited, screened for eligibility and interest, randomly assigned to one or more interventions or to one or more control groups, and followed forward in time for the development of end-points (i.e. cancer diagnosis or biomarker of cancer risk). Whereas randomised trials in relation to cancer incidence are impossible due to the difficulty of maintaining informative contrasts in exposure among large populations for several years, randomised trials of effect of environmental exposures and metabolic profiles on biomarkers can provide insight into the biological effects of interventions.

6. IMPLICATIONS AND FURTHER RESEARCH

Compared to the impact of lifestyle and genetic factors on breast and endometrial cancer development, organochlorines are likely to play a minor role. However, organochlorines are still in use. Additionally, modern and more persistent pesticides and new industrial chemicals and by-products are continuously being introduced, and due to long-range transport, organochlorines are spreading worldwide. Thus, they represent a potential preventable cause

of breast and endometrial cancer and other chronic diseases and exposure to organochlorines in the highly sensitive developing foetus and breast-fed infant is still a concern. This allows for further studies of body burden of organochlorines in selected populations of the Arctic and sub-Arctic areas. For example, blood samples from the EBBA-study might be used to assess the body burden of a broad spectrum of the "traditional" organochlorines and other relevant contaminants in a younger female population in North Norway and to evaluate potential interactions by the mixture of compounds, by various diets and lifestyle factors, and by maternal factors and genetic polymorphisms.

The importance of ovarian steroid hormones in breast and endometrial cancer development is well established. Studies of variation in levels of estradiol and progesterone within the Norwegian EBBA-population and between the Polish and Norwegian EBBA-populations may give further clues to reasons behind the observed national (across counties of Norway) and international variations in breast and endometrial cancer incidence. In addition to the current data, future studies should include analyses of DNA in frozen whole blood samples to evaluate whether genetic polymorphisms, especially gene variants changing the action of enzymes involved in the metabolism of sex steroids, may modify the associations between lifestyle factors and metabolic abnormalities and ovarian function. When sufficiently rapid, inexpensive, and automated methods for genetic analyses become available, possible interactions between genetic polymorphisms and lifestyle and metabolic abnormalities should be studied in larger cohorts of breast and endometrial cancer.

Breast cancer is etiologically and clinically a heterogeneous disease. As overweight/obesity and physical inactivity are thought to influence breast cancer risk mainly through alterations in sex steroid levels, it has been hypothesized that these lifestyle factors may act more strongly in the development or growth of tumors that are estrogen and progesterone receptor positive (237,238). According to this, prospective studies of overweight/obesity and related metabolic abnormalities (i.e. low serum HDL-C) in breast cancer should consider the estrogen and progesterone receptor status of the tumor in stratified analysis; in this way, different disease pathways may be identified and we may get a better understanding of the biological mechanisms which underlie the observed associations.

As outlined for breast cancer in particular, there are probably critical windows of time during which regulatory genes respond to environmental exposures. Susceptibility to environmental

exposures is a function of the rate of cell division. When exposures occur may be equally important to the levels of exposures. Thus, prospective studies of lifestyle factors and biomarkers in breast and endometrial cancer should include repeated assessments in different periods of life to learn more about possible phases of increased susceptibility during development and maturation of the breast and the endometrium and during the life cycle. Such data may provide further evidence for the hypothesized disease pathways and may suggest useful strategies for the prevention of the diseases.

7. CONCLUSIONS

In summary, our studies show that environmental factors (i.e. energy intake and physical activity) and metabolic profile are related to hormonal levels among women and influence the risk of breast and endometrial cancer.

Our results indicate that regular consumption of fish (mostly lean species) from Norwegian waters is not associated with an increased body burden of organochlorines (i.e. of importance to breast and endometrial cancer development), although they confirm that lactation is the most important elimination route of these contaminants in women.

Our cross-sectional findings support the hypothesis that low serum HDL-C may reflect an unfavourable hormonal profile with increased levels of endogenous hormones, and estrogens in particular, and suggest that serum HDL-C may be a true and useful biomarker of breast cancer risk especially in overweight and obese women. Furthermore, progesterone level was a predictor of mammographic density, which is suggestive of progesterone playing an important role in mammary tumorigenesis. We suggest further studies of parenchymal breast density among premenopausal women to clarify how breast cancer risk evaluation in the reading of mammograms should best avoid serious negative confounding of overweight/obesity and low serum HDL-C.

We found further support for serum HDL-C as a true and useful biomarker of breast cancer risk in a large prospective study; our results indicate that low serum HDL-C in young and middle-aged women, is a potential marker of increased postmenopausal breast cancer risk particularly among women with positive energy balance (i.e. overweight/obese).

Our results suggest that relative hyperglycemia and hypertension in young and middle aged women are significant markers of endometrial cancer risk especially among the heaviest women and that positive energy balance reflected by obesity, physical inactivity or high energy intake in this period of life is important in the etiology of the disease.

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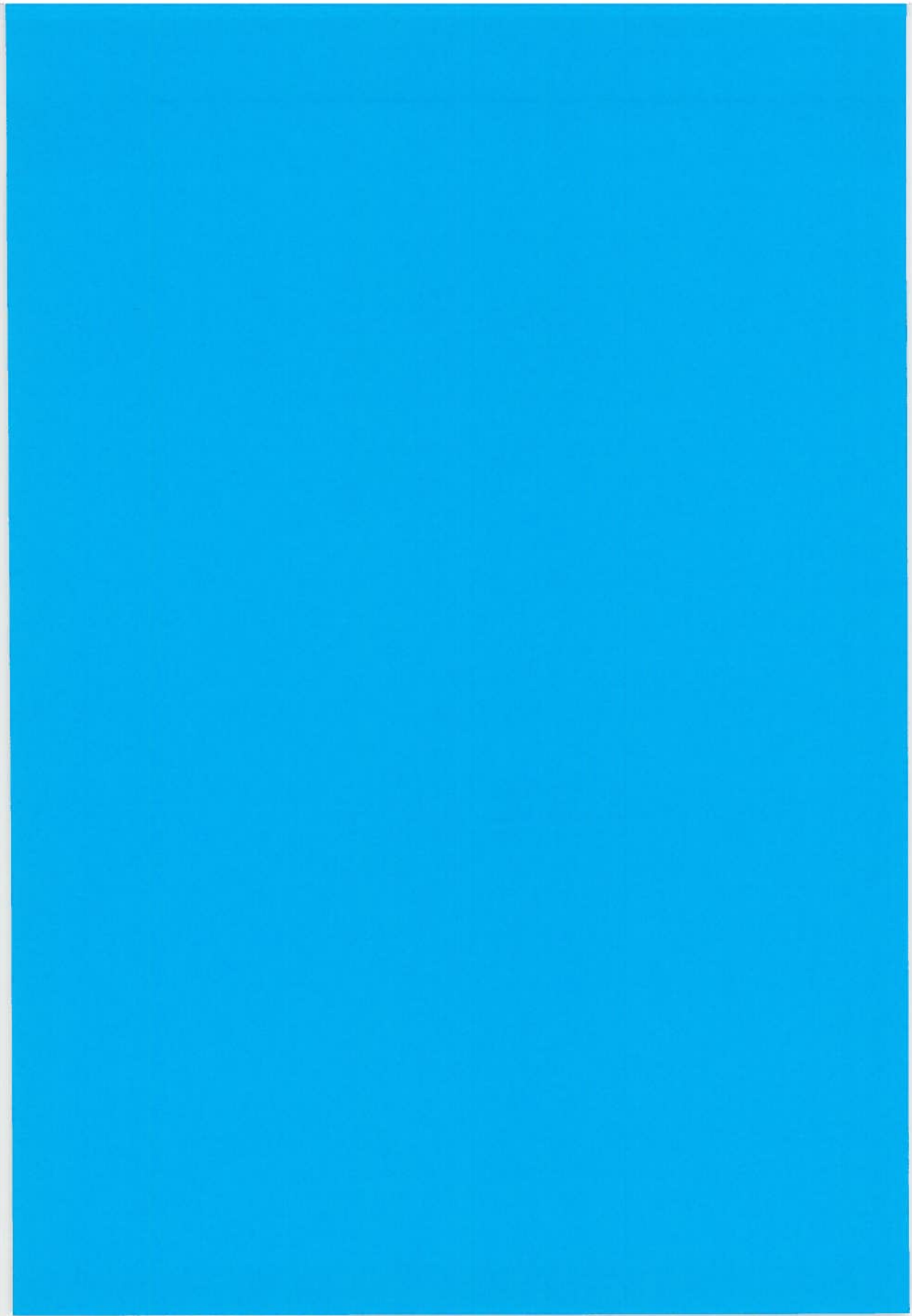
Paper I



Fish consumption and plasma levels of organochlorines in a female population in Northern Norway

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Increased cancer incidence and mortality have been found among humans exposed to high levels of organochlorines (OCs), either accidentally or as industrial workers. In order to assess levels of OCs in Norwegian women north of the Arctic Circle and validate self-reported fish consumption as a surrogate measure of organochlorine body burden, concentrations of seven polychlorinated biphenyl (PCB) congeners [IUPAC Nos. CB-105, CB-118, CB-138 (+ CB-163), CB-153, CB-180, CB-183, CB-187], β-hexachlorocyclohexane (β-HCH), 2,2′-bis(*p*-chlorophenyl)-1,1-dichloroethylene (*p,p*′-DDE) and *cis*- and *trans*-chlordane (*c*-CD and *t*-CD) were examined in plasma samples of middle-aged women attending for health screening. Altogether, 47 of those invited (81%) completed a questionnaire and donated a suitable blood sample. The ability of questionnaire data to predict plasma levels of OCs was tested in linear and logistic regression analyses. Measured plasma concentrations were in the range reported for the general female population of other Western countries and the relative amounts of PCBs were similar to the circumpolar pattern. Intake of seagulls' eggs was a predictor of PCB congeners CB-138 (+CB-163) ($p<0.05$) and CB-153 ($p<0.01$). No other food category was positively associated with any compound. In contrast, duration of residence in the study municipality, body mass index (BMI) and lifetime lactation (months) were the best univariate predictors. There was an increase in β-HCH, *p,p*′-DDE and most of the PCBs ($p<0.05$ for all) with increasing length of time a subject had lived in the municipality. BMI was a positive predictor for β-HCH (OR = 3.10, 95% CI 1.50–6.43, per 5 kg m^{-2}), chlordane (OR = 2.13, 95% CI 1.12–4.05, per 5 kg m^{-2}) and CB-105 and CB-153 ($p<0.05$ for both). Lactation was negatively associated with all OCs ($p<0.05$), except chlordane and two of the PCB congeners. Time living in the municipality and lactation explained 34% of the variance in concentration of total PCB in a multivariate model ($p<0.001$). The results indicate that regular consumption of fish (mostly lean species) from the Norwegian waters is not associated with an increased body burden of OCs (*e.g.*, of importance to cancer development), although they confirm that lactation is the most important elimination route of these contaminants in women.

Introduction

Sea food is rich in health-promoting nutrients, such as ω-3 fatty acids, vitamins and trace elements, and is protective against cardiovascular disease[1] and probably against cancer.[2] Concerns about environmental contaminants in marine organisms and their transmission to humans through the diet have prompted further studies in order to clarify the net health effect of sea food. Among the most relevant pollutants are organochlorines (OCs), which because of high fat solubility and high resistance to biodegradation, accumulate in living organisms and magnify in food chains. OCs originate from industry or use of pesticides and are spread worldwide by atmospheric and oceanic streams. In the northern hemisphere interaction of these factors, in particular, brings a burden to the Arctic ecosystem.[3] Despite bans and restrictions in the use of several OCs during the last 30 years, concentrations of these contaminants in fish from sub-Arctic waters have not changed significantly over the last 15–20 years.[4]

In animal studies, many OCs are genotoxic or tumor promoters.[5–9] Increased cancer incidence and mortality have been found among humans exposed to high levels of OCs either accidentally or as industrial workers.[10,11] The International Agency for Research on Cancer (IARC) has classified the most toxic organochlorine TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) as carcinogenic to humans, whereas others are considered as possible human carcinogens.[12] OCs with estrogenic or *anti*-estrogenic properties in human cell cultures have been linked to hypotheses about hormone-dependent cancer causation.[13,14] With regard to the potential role for these compounds in breast cancer etiology, epidemiological studies are inconsistent.[15–20]

Uncertainties about exposure and the effect of OCs in populations consuming sea food from Norwegian waters have the potential to discredit numerous related products incorrectly, thereby indirectly depriving people of a source of important nutrients. Thus, the association between consumption of fish from Norwegian waters and the body burden of OCs is an important issue to be clarified, both from a health perspective and from a socio-economic point of view.

We conducted a study among women in Lofoten, Norway, at a latitude of 63°N, in order to assess the concentration of 13 different OCs in plasma and through a questionnaire to evaluate dietary and lifestyle factors as predictors of plasma organochlorine concentration.

Experimental

Study population

The study was conducted in the municipality of Vestvågøy, which is part of the Lofoten Islands on the north-west coast of

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Norway. The Lofoten Islands are well known for their fishing fleet, with a peak season in winter, when mature cod have come south from the Barents Sea to spawn. In November 1997 all women living in Vestvågøy who were born in 1955–57 were invited to participate in a health screening program organized by the Norwegian National Health Screening Service. Of the total women invited 71.6% attended. We started to include participants in our study in parallel with this screening and finished when 61 women in total had attended. All but three were invited to participate in the validation study. After receiving written information about the project, 54 of those 58 who were eligible (93%) agreed to take part. Altogether, 47 of the 58 invited women (81%) were included; four women who had incomplete questionnaire data and three whose vials containing the plasma samples were broken had to be excluded. Informed consent was obtained from all participants and the design of the study was approved by the Regional Committee for Medical Research Ethics.

Food frequency questionnaire

The semi-quantitative dietary questionnaire was restricted to the three fat-containing food categories: fish, meat and milk. In all 67 different food items were included. Thirty-four questions on habitual intake of sea food listed traditional Norwegian fish dishes. Lean fish fillets and dishes that contained mostly lean fish which was mixed with other ingredients before being cooked into fish balls, fish cakes, *etc.* (referred to as fish dishes in our material) were the most common fish meals in coastal areas of Norway. However, in January–March fatty liver of cod and in July–August fatty liver of saithe were served along with the lean fish fillets or as a separate dish. The sea food items were categorized into lean fish (cod, pollack, saithe, haddock), fatty fish (salmon, trout, redfish, head of redfish, herring, wolffish, plaice, halibut, mackerel), fish liver, roe, shellfish, whale meat, seal meat and seagulls' eggs. We asked about the consumption of lean and fatty fish fillets by season.

The questionnaire was designed to be self-instructive although assistance was offered if needed. The form was either completed at the screening center or taken home together with a stamped, addressed envelope. Reminders were not sent to those who did not return the questionnaire ($n=4$; 7%).

The women were asked to record how often, on average, they had consumed each food item during the last year and to indicate the usual amount consumed on each occasion. Suggested portion sizes were given in natural or household units. With regard to fish liver, this was in terms of the number of tablespoonfuls per meal. Weights of the portions were derived from a Norwegian weights and measures table.[21] Multiplication of the frequency of consumption by portion size and the standard portion weight gave an estimated average net weight intake of single food items per unit of time. The percentage milk fat of different dairy products given in the national table was entered as an additional factor in calculating total milk fat intake. Frequency of consumption and estimated amount eaten per unit of time were calculated both in singles and in groups of food items.

Other questionnaire variables

Apart from the main dietary section, the questionnaire secured information about age, place of birth, time living in the study municipality, body weight and height, reproductive health, breast-feeding and occupation. The women were asked to give their present weight in kilograms and height in centimeters. We obtained a body mass index (BMI) estimate for each participant by dividing the body weight in kilograms by the squared height in meters (kg m^{-2}).

Blood sample analyses

Non-fasting blood samples were drawn from a cubital vein into two 7 ml Vacutainer Hemogard ethylenediaminetetraacetic acid (EDTA) glasses (Becton Dickinson, Sweden) by trained nurses. Plasma was separated by centrifugation at 2000 rev min^{-1} for 10 min (Model 2010 centrifuge, Kubota, Tokyo, Japan) and transferred within 2 h of drawing the blood into pre-cleaned vials, which were coded and kept frozen (−20 °C) until analysis. To check for possible contamination of the glass vials, three field blanks were made from the SupraSolv solvent cyclohexane and these were fractionated, purified and analyzed in the same way as the plasma sample hexane extracts.

Selection of contaminants to be analyzed conformed with the practice used in the Arctic Monitoring and Assessment Program (AMAP).[22]

The OCs measured in plasma from 47 women were seven PCB congeners [IUPAC Nos. 105, 118, 138 (+163), 153, 180, 183, 187], β-hexachlorocyclohexane (β-HCH), 2,2′-bis(*p*-chlorophenyl)-1,1-dichloroethylene (*p,p′*-DDE), *cis*- and *trans*-chlordane (*c*-CD and *t*-CD) and the toxaphenes Parlar 26 and 50. The plasma samples were extracted using liquid–liquid extraction with the sample, ethanol, de-ionized water saturated with ammonium sulfate and hexane. Internal standards were added before the first extraction. Specifically, 4 ml of plasma, to which 4 ml of ethanol and 4 ml of the de-ionized water saturated with ammonium sulfate were added, were extracted twice with 12 ml of hexane in a small glass tube. After this extraction, 90% of the lipids were removed using a gel permeation chromatography (GPC) column (105 cm × 1.0 cm id) purchased from LATEK (Eppelheim, Germany) and packed with 35 g of Biobeads S-X3. The remaining lipids were removed using small silica columns of 1.0 cm id. The silica columns were conditioned with 10 ml of hexane just before the sample was added. The following solvent combination was used as eluent for the OCs: 10 ml of hexane, 10 ml of hexane–dichloromethane (9+1), 10 ml of hexane–dichloromethane (4+6), 10 ml of dichloromethane–ethyl acetate (1+1). The combined fractions were evaporated to 0.5 ml using a Zymark (Hopkinton, MA, USA) Turbovap 500 closed cell concentrator, followed by a gentle flow of nitrogen for reduction to 100 µl. Gas chromatography (GC) was performed using a Fisons (Milan, Italy) 8060 Mega gas chromatograph. A 30 m × 0.25 mm id DB-5 MS column (0.25 µm film thickness) (J&W Scientific, Folsom, CA, USA) and a deactivated guard column (2.5 m × 0.53 mm id) (J&W Scientific) were used for all analyses. The gas chromatograph was further connected to a low-resolution Fisons MD 800 mass spectrometer. The internal standards, used for quantification, were C-13-labeled PCB 77, 101, 118, 144 and 178. Octachloronaphthalene (OCN) was added to calculate the recovery. The volume injected on to the GC column was 2 µl. Quantification was done using both negative chemical ionization (NCI) and positive electron ionization (EI+), both in the selected ion monitoring (SIM) mode. The different compounds were identified from their SIM masses and retention times. Peaks with differences in isotopic ratio >20% compared with the quantification standard were rejected and not quantified. For every 10 samples, a blank was analyzed to assess laboratory-derived sample contamination.

The limit of detection (LOD) was calculated using three times the area of the noise or, if peaks were found in the blanks, three times the area of the blank. The limit of quantification was set as 10 times the area of the noise or, if peaks were found in the blanks, 10 times the area of the blank.

The analytical method used in this study is based on accredited methods from the laboratory. The method was further developed in order to screen a large number of samples for a wide range of compounds while still being rapid and cost efficient. As part of the quality assurance system, the

laboratory also participates in the AMAP's Human Health Inter-comparison Program for human blood samples.

Statistical analyses

The relationship between intake of fatty fish and the plasma concentration of OCs was studied by dividing the study population into three subgroups: 'non-consumers' who never ate fillets of fatty fish and 'moderate consumers' and 'high consumers' who had an estimated mean monthly consumption of about one and six meals of fatty fish fillets, respectively. The total PCB (ΣPCB) concentration was estimated by adding the concentration of the individual PCB congeners, whereas the sum of *c*-CD and *t*-CD gave total chlordanes (Σchlordane). Plasma concentrations below the limit of detection (LOD) were set to half the value of the LOD while observations for which the concentration of a specific compound was not determined due to interference were treated as missing in the statistical analyses. We performed correlation analyses including the generation of Pearson correlation coefficients for any association of variables suspected of interacting.

Frequency distribution patterns of the outcome variable determined the approach to analyses of variance. The normally distributed plasma concentrations of *p,p'*-DDE allowed linear regression models. Left-skewed plasma levels of the PCB congeners (Fig. 1) required logarithmic transformation of the dependent variables before statistical treatment. Analyses of variance were repeated with ranked independent variables, divided into tertiles. In the multiple linear regression analysis, we tested for the effect of sea food consumption after evaluating the effect of eight background variables, namely age, time living in the study municipality, height, BMI, number of children (parity), lifetime lactation, consumption of meat and consumption of milk fat. Non-significant background variables were deleted from the initial model one at a time, except for age, which we found appropriate to force into the model. The adjusted effects of intake of fish, liver, roe, shellfish and seagulls' eggs were then estimated by adding these consumption variables to the model. Residual analyses confirmed the assumptions in the model. As a result of a substantial number of observations, with plasma levels below the detection limits for β-HCH, *c*-CD and *t*-CD, these outcomes were analyzed using the cumulative ordinal logit model. With respect to logistic regression, we categorized β-HCH, *c*-CD and *t*-CD in thirds. The bottom third contained all observations with non-detectable plasma levels, while the remaining observations were split into two groups by their median. Results of the logistic regression analysis are reported as odds ratios which can be interpreted as the effect of the predictor variables on the odds of being in one higher category of plasma concentration. The toxaphenes were excluded from statistical analyses because most of the observations were below the detection limits.

An association was accepted when the 95% CI of the regression coefficient in the linear model did not include 0 or the 95% CI of the OR in the logistic model did not include 1. The calculations and statistical analyses were done with the SAS software package (SAS Institute, Version 6.12, 1996).

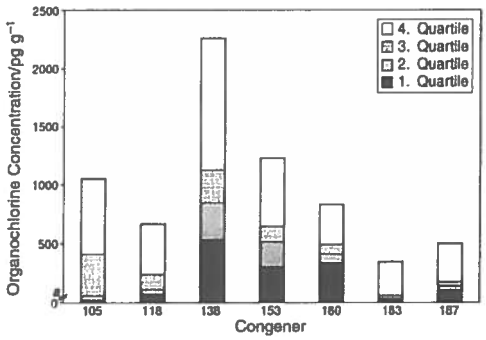

Fig. 1 Profile of plasma concentrations of seven different PCB congeners among 47 women in Lofoten, Northern Norway. Subgroups may not total to 47 due to missing values. [a]Minimum plasma concentration (pg g^{-1}): CB-105 = 11, CB-118 = 11, CB-138 (+CB-163) = 241, CB-153 = 171, CB-180 = 134, CB-183 = 18, CB-187 = 51.

Results

Population characteristics

The characteristics of the study population are given in Table 1. All 47 women were born in Norway, of whom 27 (57%) were born in Vestvågøy and four (9%) in neighboring municipalities. Seventeen women (38%) had always lived in Vestvågøy and none had lived there for less than 8 years. Eight women (17%) had never given birth. Among the mothers, the mean parity was 2.9 and mean total lactation time throughout life was 21.7 months. Parity and lactation were strongly correlated ($r=0.81$, $p<0.001$). Self-reported weight and height from 43 study objects placed 26 women (61%) in the normal weight category (BMI = 18.5–24.9 kg m^{-2}) and the rest in the overweight or obese class (BMI > 25 kg m^{-2}), using the criteria of the WHO (results not shown).

All participants regularly ate fish. Fish dishes were the most common meal, eaten on average 12 times a month by every woman. The mean frequency of a fish fillet meal was 11 per month, with lean and fatty fish fillets served 8.5 and 2.5 times per month, respectively. Among 10 women (21%) who never ate fatty fish fillet, five (11%) did not eat any fatty fish at all. Two women (4%) never ate fillets from white fish. The average consumption of bread with fish was 4.5 slices per week, although five participants (11%) did not eat fish in this way. Altogether 44 women (94%) ate the liver of cod or saithe served alone or with fillets, on average 3.7 times per year and a maximum of 9.1 times per year. An equal proportion of the population were whale meat eaters, with corresponding figures of 6.8 and 13 times per year. Shellfish was in the diet of 37 women (79%) and six (13%) ate two seagulls' eggs each per year.

Average consumption of meat was 18 meals per month, in addition to a slice of bread with meat daily. Every woman consumed dairy products. In fact 39 women (83%) drank milk,

Table 1 Selected characteristics among women in the Lofoten cross-sectional study, Northern Norway ($n=47$)[a]

Characteristic	Mean	Median	Range
Age/years	40.7	41	40–42
Lifetime living at Vestvågøy/years	30.7	36	8–42
Height/cm	166	167	153–176
Body mass index/kg m^{-2}	25.1	24.0	19–38
Parity (number of deliveries)	2.4	2.4	0–5
Lifetime lactation/months	18.0	16.0	0–70
Food consumption			
All sea food[b]/g $week^{-1}$	938	809	281–2829
Fatty fish/g $week^{-1}$	177	95	0–956
Lean fish/g $week^{-1}$	681	593	147–1765
Cod and saithe liver/g $week^{-1}$	2.8	1.3	0–13.1
Fish roe and caviar/g $week^{-1}$	46	25	0–350
Shellfish/$week^{-1}$	8.8	3.8	0–50
Whale meat/g $week^{-1}$	21	19	0–56
Seagulls' eggs/$year^{-1}$	0.26	0	0–2
Milk fat/g $week^{-1}$	111	92	17–261
Meat/g $week^{-1}$	795	733	150–2150

[a]Subgroups may not total to 47 due to missing values. [b]Includes fish, fish products, shellfish, whale meat and seal meat.

with the population average being one glass per day (1.5 dl) and a maximum of five glasses. Cheese was on average eaten with two slices of bread daily. Hen's eggs were eaten by 43 women (92%), with a population mean intake of 1.5 eggs per week (results not shown).

Plasma organochlorine concentrations

All 13 selected OCs were present in plasma samples from the study population (Table 2). The maximum concentration of a single compound was found for *p,p'*-DDE, with one observation above 5000 picograms per gram (pg g^{-1}) of plasma wet weight; another woman had plasma *p,p'*-DDE below the detection limit. Median *p,p'*-DDE was 936 pg g^{-1} wet weight, which was on the same scale as the median of the most prominent PCB congeners. For the total number of observations, ΣPCB was the dominant organochlorine. Interference hindered the determination of the plasma concentration of the PCB congeners CB-105, CB-118, CB-180 and CB-183 in two (4%), one (2%), one (2%) and three (6%) samples, respectively. Apart from that, all the congeners were detected in all women. The relative amounts of different congeners measured by median plasma concentrations decreased in the order CB-138(+CB-163) > 153 > 180 > 187 > 118 > 183 ≈ 105, with a left-skewed pattern (Fig. 1). For β-HCH, *c*-CD, *t*-CD and Parlar 26 and 50, multiple observations had plasma levels below the detection limits (54, 56, 32, 79 and 81% of observations, respectively). The order of magnitude of the remaining observations was 10–30 times smaller than the median value of *p,p'*-DDE or most PCBs (results not shown).

All PCBs were positively correlated with other congeners. The strongest associations were between CB-138 (+CB-163) and CB-153 ($r=0.86$), CB-183 and CB-187 ($r=0.83$) and between CB-180 and CB-187 ($r=0.79$). CB-180, CB-183 and CB-187 were related to all other congeners. CB-153 had the strongest correlation with ΣPCB ($r=0.89$). Intra-family correlation was also observed between the chlordanes ($r=0.81$; $p=0.0001$ for all the noted correlation coefficients). Concentrations of *p,p'*-DDE, β-HCH, *c*-CD and *t*-CD were all inter-family correlated with ΣPCB ($r=0.58$, $r=0.44$, $r=0.36$ and $r=0.43$, respectively; $p<0.0001$ for *p,p'*-DDE and $p=0.05$ for others) as well as with single congeners (results not shown).

For mean levels of OCs in the fatty fish consumption subgroups, there were no significant differences (*t*-test). Categorization of the study population by estimated net weight of the fatty fish fillets consumed per unit of time gave a very similar picture (results of *t*-test and alternative categorization are not shown).

Linear regression

In the univariate linear regression analysis, the regression coefficient corresponding to the age-adjusted change in *p,p'*-DDE level or log-transformed PCB level in picograms per gram of plasma by one unit change of the explanatory variable was examined (Table 3). The number of years lived in the municipality of Vestvågøy was a positive predictor for plasma *p,p'*-DDE ($p=0.02$), although the number of births ($p=0.03$) and lifetime lactation ($p=0.02$) were associated with a reduced body burden of this OC. No consumption variable reached significance with variations in *p,p'*-DDE level. The time lived in the municipality was a significant predictor for the internal dose of ΣPCB and all single congeners ($p<0.05$) except CB-105, CB-118 and CB-183; similarly, lifetime lactation explained variations in plasma levels of all congeners ($p<0.05$) except CB-105 and CB-118. BMI was positively associated with

Table 2 Plasma organochlorine concentration (pg g^{-1})[a] among the study group ($n=47$)[b]

				Fatty fish fillet intake[c]					
	Total population ($n=47$)			None ($n=10$)		Moderate ($n=19$)		High ($n=18$)	
Characteristic	Mean	Median	Range	Mean	Range	Mean	Range	Mean	Range
ΣPCB[d]	2344	2377	772–4782	2945	1883–4782	2068	772–3336	2375	1152–4571
p,p'-DDE	1204	936	150[e]–5075	1221	443–3836	1335	366–5075	1063	150[e]–2355
β-HCH	75	50[e]	50[e]–358	79	50[e]–238	72	50[e]–200	77	50[e]–358
ΣTox[e]	128	65[e]	65[e]–729	148	65[e]–523	151	65[e]–729	94	65[e]–450
ΣChlordane[f]	120	46	25[e]–747	195	25[e]–747	123	25[e]–644	84	25[e]–422

[a]The conversion factor to alter weight of plasma to volume of plasma is 0.9747.[51] [b]Subgroups may not total to 47 owing to missing values. [c]Divided into subgroups according to fatty fish fillet consumption during the last year: None, no consumption of fatty fish fillets; Moderate, less than two meals of fatty fish fillets per month; High, two or more meals of fatty fish fillets per month. [d]Includes the PCB congeners CB-105, CB-118, CB-138 (+CB-163), CB-153, CB-180, CB-183, CB-187. [e]Includes toxaphenes Parlar26 and 50. [f]Includes *cis*-chlordane (*c*-CD) and *trans*-chlordane (*t*-CD). [g]The value is limit of detection (LOD).

Table 3 Results of univariate linear regression. The presented estimates are $\beta \times 10^3$ with 95% CI ($n=47$)[a]

Predictor variable[b]	lnΣPCB[c]/pg g^{-1}[d]		lnCB-138 (+CB-163)/pg g^{-1}[d]		lnCB-153/ pg g^{-1}[d]		*p,p'*-DDE/(pg g^{-1})[d]	
Lifetime living at Vestvågøy/years	16.3	(5.7, 26.6)[f]	15.3	(1.9, 28.8)[e]	19.4	(7.3, 31.5)[f]	30.3	(5.5, 55.1)[e]
Height/cm	3.2	(−22.1, 28.5)	−0.54	(−28.4, 27.3)	13.8	(−11.6, 39.2)	33.6	(−14.6, 81.8)
Body mass index/kg m^{-2}	18.6	(−8.7, 45.9)	29.4	(−2.2, 60.9)	31.7	(3.0, 60.4)[e]	38.7	(−21.2, 98.6)
Parity (number of deliveries)	−101.6	(−189.1, −14.1)[e]	−69.8	(−181.7, 42.2)	−72.8	(−176.2, 30.6)	−217.0	(−411.7, −22.3)[e]
Lifetime lactation/months	−13.9	(−20.5, −7.3)[g]	−13.7	(−22.6, −4.8)[f]	−13.2	(−21.4, −5.0)[f]	−20.0	(−36.7, −3.2)[e]
Food consumption								
Fatty fish/g $week^{-1}$	0.081	(−0.519, 0.680)	−0.015	(−0.750, 0.720)	0.091	(−0.590, 0.773)	−0.29	(−1.6, 1.0)
Lean fish/g $week^{-1}$	0.022	(−0.322, 0.366)	−0.033	(−0.440, 0.374)	0.003	(−0.004, 0.004)	−0.04	(−0.78, 0.69)
Cod and saithe liver/g $year^{-1}$	−0.096	(−0.946, 0.754)	−0.094	(−1.110, 0.922)	−0.007	(−0.950, 0.937)	−0.53	(−2.3, 1.3)
Seagulls' eggs/$year^{-1}$	195.0	(0.23, 390.0)[e]	238.0	(15.4, 460.6)[e]	269.6	(68.3, 470.8)[f]	145.3	(−269.4, 560.1)
Milk fat/g $week^{-1}$	−1.8	(−3.8, 0.2)	−2.2	(−4.7, 0.15)	−1.8	(−4.0, 0.5)	−1.9	(−6.4, 2.7)
Meat/g $week^{-1}$	−0.11	(−0.48, 0.25)	−0.20	(−0.63, 0.22)	−0.064	(−0.458, 0.331)	−0.11	(−0.87, 0.65)

[a]Some estimates may be based on fewer observations, because subjects with missing information for the actual dependent or independent variable were excluded. [b]Variables were age-adjusted. [c]Includes the PCB congeners CB-105, CB-118, CB-138 (+CB-163), CB-153, CB-180, CB-183, CB-187. [d]The conversion factor to alter weight of plasma to volume of plasma is 0.9747.[51] [e]$p<0.05$. [f]$p<0.01$. [g]$p<0.001$.

CB-153 ($p<0.05$) and CB-105 ($p<0.05$), whereas parity was negatively associated with ΣPCB ($p<0.05$) and CB-187 ($p<0.05$; results for other than ΣPCB, CB-138 (+CB-163) and CB-153 not shown). The number of seagulls' eggs eaten per year was the only food category that explained differences in plasma concentration of PCBs. Levels of CB-138 (+ CB-163) ($p<0.05$), CB-153 ($p<0.01$) and ΣPCB ($p<0.05$) increased with intake of eggs. With regard to the PCB congeners not included in the table, none except those mentioned above was significantly dependent on any predicting variable. Furthermore, analysis of variance with ranked independent variables, divided into tertiles, did not reveal any additional relationships.

In the multiple linear regression analysis with ΣPCB as the outcome variable, we obtained a model using lifetime residence and lactation, which explained 34% ($p<0.001$) of the variation in plasma concentrations (results not shown). Adding age to the model did not change the estimates extensively. The model was not improved when consumption variables were added. As a result of the high correlation between parity and lactation, the effect of parity was no longer apparent in the multivariate model that included lactation.

Logistic regression

Table 4 provides the results of the logistic regression analysis with β-HCH, *c*-CD and *t*-CD as dependent variables; it gives the odds ratios (ORs) for being in one higher plasma concentration category per change in explanatory variables. We found a 63% increase in the odds of having a detectable β-HCH level in plasma for every 5 years of residence in the municipality (OR = 1.63, 95% CI: 1.17–2.28). Odds of being in one higher plasma concentration category increased, with OR = 3.10 (95% CI: 1.50–6.43) and OR = 2.13 (95% CI: 1.12–4.05) for β-HCH and Σchlordane, respectively, for every 5-unit increase in BMI. Separate analyses of the variation in concentration of the two chlordane compounds revealed a dependence on the changes in BMI; this was of the same order of magnitude as for the summary variable (results not shown). For each additional 6 months of lactation, the women reduced their odds of having a plasma concentration above the detection limits of β-HCH by 33% (OR = 0.67, 95% CI: 0.50–0.90).

Discussion

In this survey from the sub-Arctic area of Norway, all the selected OCs were present in plasma samples from the study population and every woman had measurable levels of the contaminants in her blood. Fish intake did not predict the plasma level of any of the measured OCs, however lean fish was one of the main dietary components. Consumption of seagulls' eggs was associated with an increased concentration of the PCB congeners, CB-138 (+ CB-163) and CB-153. The time spent living in this coastal area of Norway and the BMI had a positive association, whereas accumulated lactation time had a negative association, with the levels of most of the PCBs and pesticides.

Table 4 Logistic regression model for plasma β-HCH, *c*-CD and *t*-CD. Odds ratios with 95% CI for being in a higher category of plasma organochlorines ($n=47$)[a]

Predictor variable	β-HCH		ΣChlordane[b]	
Lifetime living at Vestvågøy/5 years	1.63	(1.17, 2.28)[d]	1.14	(0.88, 1.47)
Body mass index/5 kg m^{-2}	3.10	(1.50, 6.43)[d]	2.13	(1.12, 4.05)[c]
Lifetime lactation/6 months	0.67	(0.50, 0.90)[d]	1.03	(0.84, 1.25)
Food consumption				
Fatty fish/50 g week^{-1}	1.08	(0.95, 1.23)	0.90	(0.78, 1.03)
Lean fish/50 g week^{-1}	1.02	(0.95, 1.10)	0.99	(0.92, 1.06)
Seagulls' eggs/1 egg year^{-1}	1.83	(0.81, 4.13)	1.31	(0.55, 3.12)
Milk fat/20 g week^{-1}	0.87	(0.72, 1.06)	0.91	(0.76, 1.08)

[a]Some estimates may be based on fewer observations, because subjects with missing information for the actual dependent or independent variable were excluded. [b]Includes *cis*-chlordane (c-CD) and *trans*-chlordane (*t*-CD). [c]$p<0.05$. [d]$p<0.01$.

All of the OCs in our study have been detected in Arctic abiotic and biotic samples.[22] They have been selected for AMAP assessment because they would be expected to have biological effects on the Arctic biota if the exposures were similar to those in more polluted environments further south. According to this, the OCs determined were expected to be present in the plasma of the study population who lived close to the Arctic. Compared with the ranges of PCB concentrations in blood plasma of the samples collected from 50 wives of fishermen in Sweden in the mid-1990s, in our study the range for the congener CB-153 was lower (360–3960 *versus* 171–1232 pg g^{-1} wet weight), whereas the range for CB-138 (+CB-163) was similar (210–2490 *versus* 241–2256 pg g^{-1} wet weight).[23] In order to make sound comparisons with other studies, levels of CB-118, CB-138 (+CB-163), CB-153 and CB-180 should perhaps be emphasized, because they in general appear to be the four congeners with the highest concentrations. The median sum of these congeners in this study was 1875 pg g^{-1} wet weight (result not shown), which is fairly close to the median sum of the same congeners measured in 206 Dutch women during the last month of pregnancy (2040 pg ml^{-1}) from 1990 to 1992.[24,25] In blood drawn from a group of 240 American women around 1990, the plasma concentration of DDE ranged from 140 to 39 440 pg ml^{-1}, with a mean of 7090 pg ml^{-1}, which is about six times the mean plasma *p,p'*-DDE concentration in our study.[26]

In the plasma samples of our study the level of CB-153 was strongly related to ΣPCB ($r=0.89$); in fact, most specific congeners were inter-related. In the Swedish study mentioned above, there was a high correlation between the plasma concentration of the sum of PCBs and CB-153, a major and very stable congener ($r=0.99$).[23] This correlation was also found in an assessment of PCBs in the breast milk of 28 mothers in Oslo, Norway in 1991.[27] Among groups of American women, DeVoto *et al.*[28] found that blood levels of specific congeners were, in general, highly correlated. These findings support the use of CB-153 as an indicator substance when monitoring total PCB exposure and justifies measurement of a select group, rather than a large panel, of congeners in order to improve the cost-effectiveness and enhance uniformity of studies.

PCBs and *p,p'*-DDE comprise the bulk of OC residues found in humans, owing to their much longer half-lives in relation to other chlorinated contaminants.[29] The pattern of plasma concentrations found in our study clearly reflects these well-known variations in the efficiency of metabolism and excretion of different OCs. The left-skewed distribution of the PCBs in the 47 samples is a typical feature[22] further enhancing the external validity of our findings.

In our study, the BMI was related to plasma concentrations of the most prominent PCB congeners and all the pesticides except *p,p'*-DDE. The observed associations are physiologically plausible since OCs are lipophilic compounds which enter the body through ingestion of foods with a high fat content and become stored in adipose tissue. Regarding the PCBs, similar findings have been reported by others,[20] yet for *p,p'*-DDE both positive[30] and negative[20] correlations with BMI have been found in previous studies. In a study in Germany, it was found that a high post-pregnancy BMI increased the likelihood of having a high β-HCH level and decreased the likelihood of having high PCB levels in the nursing women's milk.[31] These findings indicate that the BMI may affect circulating levels of OCs and should also be considered as a potentially important modifying factor for exposure to lipophilic substances.

Lactation is the most important method of eliminating body stores of OCs.[32] PCB levels in breast milk were inversely related to the duration of lactation in another Norwegian study in the

early 1980s.[33] It is reassuring that data from our study clearly reflect an inverse association between lactation and OC body burden which is well known.[15,33,34] This justifies concern about the transmission of OCs to the breast-fed infant and about advice to pregnant and nursing women regarding the intake of potentially highly contaminated food.

It has been shown that the primary source of dietary exposure to PCBs varies with the level of food contamination and with dietary practices.[5] Consumption of fatty fish from the Baltic Sea and the Great Lakes is clearly reflected in internal human OC doses, because of the relatively high contamination levels in aquatic organisms in these water systems.[26,35–37] In certain circumpolar populations, fish, seal and beluga are the major sources of exposure.[22] The observed positive association between lifetime residence in Vestvågøy and the compounds that had the longest half-lives: most of the PCBs, *p,p'*-DDE and β-HCH, might thus reflect long-time OC exposure and accumulation either through relatively high levels of PCBs and pesticides in locally harvested food or through specific dietary habits in Vestvågøy.

There are few published studies comparing food intake directly with plasma levels of OCs, with the exception of the evaluation of contaminated fish intake. In a German study, only modest positive correlations were observed between consumption of beef and lamb and PCBs, DDT (dichlorodiphenyltrichloroethane) and β-HCH in plasma, whereas consumption of saltwater fish had a positive correlation with PCBs.[38] However, plasma levels of DDE and PCBs among 240 American women were not associated with intake of meat, dairy or poultry, although consumption of fish with dark meat and eggs from two specific geographical regions were positive predictors of PCBs.[26]

In our study, consumption of seagulls' eggs was a strong positive predictor for CB-138 (+CB-163) and CB-153, suggesting that eggs collected regionally in Lofoten, Northern Norway, may be an ongoing source of exposure to PCBs. Fish-eating birds are near the top of the food chain and tend to accumulate greater concentrations of contaminants.[39] In eggs collected from seabirds in Northern Norway in 1993, concentrations of the PCB congeners, CB-138 and CB-153 in particular, were high and similar to those in cod liver.[40] In a dietary survey in Northern Norway in 1998 more than a third of the population ate seagulls' eggs and the average consumption in Lofoten was 8–10 eggs per year.[41] It may be that the relatively long time lapsed since the last seagulls' eggs season (*e.g.*, May–June) contributed to a suggested underestimation by the women in our study. Consumption of seabirds' eggs among fishermen in the St. Lawrence Gulf, Canada, has indeed been shown to be strongly associated with plasma concentration of PCBs (Pearson correlation coefficient 0.27, $p=0.01$).[39] Our results justify the established dietary guidelines from the Norwegian Food Control Authority (SNT), which warns against an annual intake of more than 5–10 seagulls' eggs.[41]

We did not observe positive associations between plasma levels of OCs and intake of fish, meat and dairy products. There are a number of possible explanations for this lack of dietary predictors, other than seabirds' eggs, for the body burden of OCs in our study. The reported levels of environmental contaminants in fish caught in the coastal waters of Northern Norway and the Barents Sea in the 1990s are generally low. With regard to PCBs, the concentrations are lowest in shrimps, roe and the muscle of lean fish, somewhat higher in muscle of half-fatty fish (redfish, wolf-fish, halibut) and fatty fish (herring, salmon) and highest in cod liver.[42] Our study population ate a fish-rich diet. Nevertheless, we did not observe an association between levels of either PCBs or pesticides and intake of fish. This observation supports the questionnaire conclusion that lean fish was the major sea food consumed in this population.

Apart from fish, other fat-containing animal foodstuffs on the Norwegian food market also have low levels of PCBs.[43] Furthermore, the estimated exposure through diet was substantially lower in 1997 than in 1992, indicating a general decline in levels of OCs in the food supply over the last decade.[32] It has been suggested that the actual levels and/or the bioavailability of OCs in foods other than fish might generally be too low to be detected in plasma.[26]

In addition, as a result of the long half-lives of PCBs and *p,p'*-DDE, changes in diet over the years before exposure assessment might have masked our ability to observe dietary predictors. As a result of the high number of years that the women had lived in this coastal area and the stable availability and use of sea food in this region, however, great shifts in dietary pattern over the last few decades are not likely. A limitation of our study is the relatively small sample size, which may reduce our ability to detect weak dietary associations.

Sea food is a major contributor to the intake of ω-3 fatty acids. When the questions about sea food consumption used in this study were converted to intake of ω-3 fatty acids in a previous validation study, a significant correlation of the order of 0.55 was found with serum phospholipid ω-3 fatty acids.[44] Moreover, in a recent study in Greenland, plasma ω-3 fatty acids were strongly correlated with plasma levels of persistent organic pollutants, including 14 PCB congeners and four toxaphenes.[45] Hence the food frequency questionnaire can serve as a suitable instrument for predicting plasma levels of OCs.

Most of the participants reported eating more than one meal with fish or meat every day. This is consistent with dietary habits found in sociological studies among residents of the coastal line of Northern Norway (S. H. Eriksen, personal communication, 2001). Further, the high number of individuals classified in the upper BMI group is suggestive of the interpretation that a substantial proportion of the study population had a high daily intake of food.

The questionnaire did not cover the use of tobacco and alcohol. In a Norwegian study, there seemed to be a tendency towards higher levels of PCBs and DDE in milk samples from mothers who were smokers.[33] Smoking has a positive relationship with blood OC concentration in some studies.[45] However, Grimvall *et al.*[23] did not find any association between smoking habits and plasma levels of PCBs among 50 Swedish women and DeVoto *et al.*[38] found that β-HCH had a negative relationship with smoking in elderly Germans. A recent assessment of OCs in tobacco products showed that tobacco and cigarette smoke are a minor source of human exposure, in contrast to earlier studies.[46] An independent effect of alcohol consumption on OC body burden has been suggested in some studies,[45,47] which might reflect the adverse effect of alcohol on the liver's ability to metabolize OCs. Nevertheless, it is hard to believe that information about these stimulants in our study would have changed the overall results substantially.

Trained nurses ensured that samples were collected, handled and stored according to protocol. The use of field blanks controlled for inadvertent contamination of plasma samples. The blood sample collection was not uniform with regard to time of day and time since last meal, but any major variations resulting from this procedure are doubtful. One study of 31 healthy women suggested that temporal changes in OC levels within a 1–3-month period are minimal and that a single measure for estimating exposure is highly reliable for DDE and PCB.[48] Furthermore, Longnecker *et al.*[49] found that post-prandial and fasting OC blood levels were highly correlated in 39 individuals from the general population.

As a result of the biochemical properties of OCs, plasma levels of these compounds generally correlate with the lipid profile.[23,35] The present study did not include blood lipid analyses, which circumvented expression of the results on a lipid weight basis. This limited comparisons with some published studies. Nevertheless, the work of Kuwabara *et al.*[50]

indicates that increased concentrations of PCBs in the blood after a meal of heavily contaminated food are not associated with a corresponding change in serum lipids.

Conclusions

The study population of regular lean fish eaters appears not to be at special risk from organochlorine exposure and accumulation. The relatively low concentrations of plasma OCs observed and the lack of an association with consumption of fish indicate that worry about these contaminants should not be a deterrent for consumption of sea food from the coastal waters of Northern Norway. Similarly, our results also support the contention that the contribution of dietary OC exposure to hormone-dependent cancer causation in Norwegian women is reassuring low. However, a specific dietary habit, intake of seagulls' eggs, was strongly associated with the body burden of certain PCBs. Our results confirm that lactation is the most important elimination route for OCs in women.

The present data support the notion that the general Norwegian diet uniformly contains low levels of OCs and illustrate that in future national studies of cancer we shall have to strengthen the methods when categorizing female consumers with respect to OC exposure by use of the food frequency questionnaire alone.

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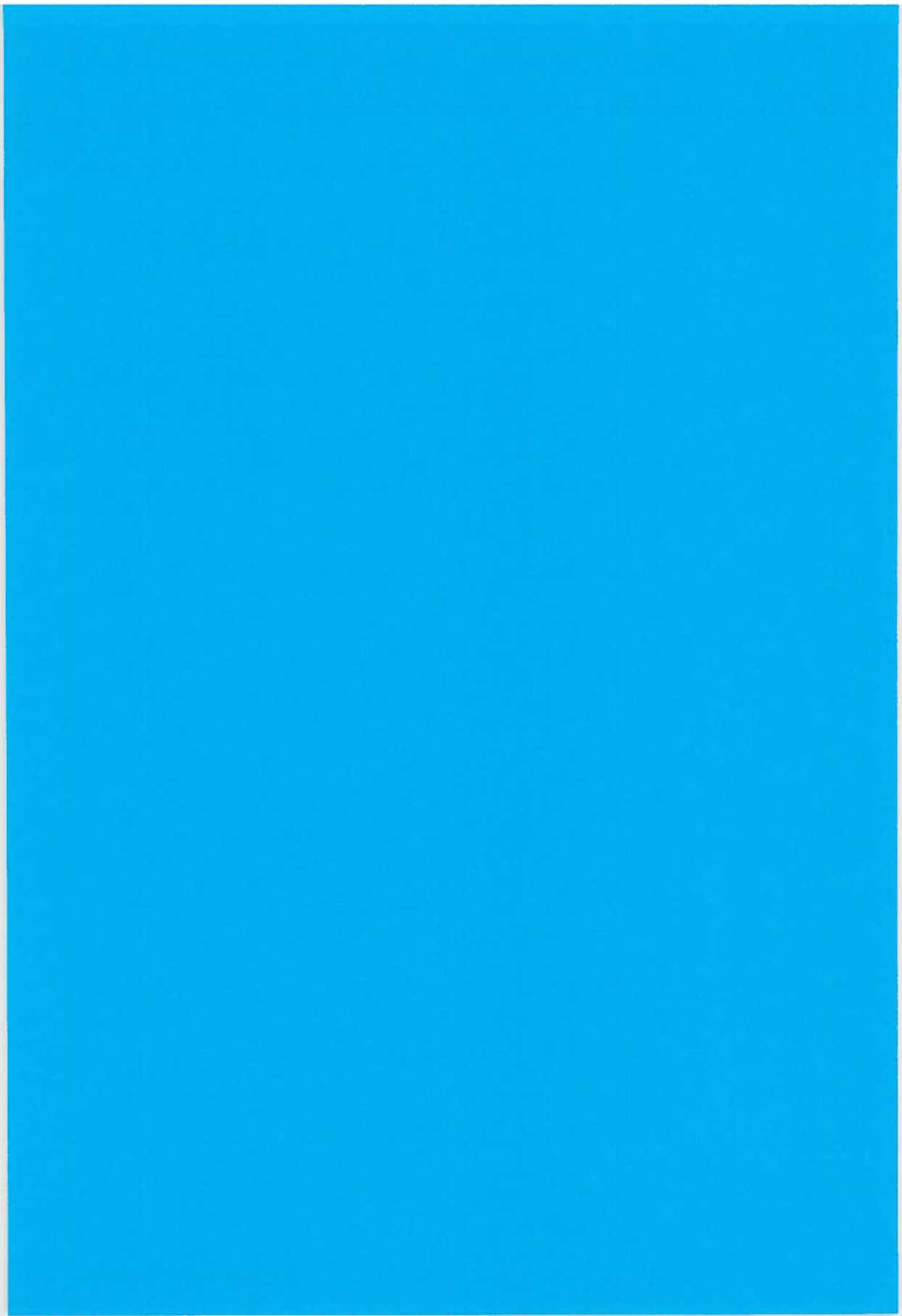
Paper II



Metabolic syndrome and hormonal profile – serum high-density lipoprotein cholesterol as a plausible biomarker of breast cancer risk. The Norwegian EBBA-study.

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Running title: HDL-C, metabolic profile, ovarian hormones, breast cancer risk

Abstract

Low serum high-density lipoprotein cholesterol (HDL-C) is an important aspect of the metabolic syndrome and has been related to increased breast cancer risk in overweight and obese women. As low serum HDL-C might be associated with an unfavourable hormonal profile with, in particular, increased levels of estrogens, serum HDL-C might be a biologically sound marker of breast cancer risk. We used cross-sectional data among 206 healthy women aged 25–35 years who participated in the Norwegian EBBA-study. We included salivary ovarian steroid concentrations assessed by daily samples throughout one entire menstrual cycle, metabolic profile with measures of adiposity (BMI, truncal fat percentage), serum concentrations of lipids and hormones (insulin, leptin, testosterone, dehydroepiandrostendione sulfate, insulin-like growth factor-I and its principal binding protein), and mammographic parenchymal pattern. We examined how aspects of the metabolic syndrome, including low serum HDL-C, were related to levels of hormones, and free estradiol concentration in particular, and studied predictors of mammographic parenchymal patterns using correlation analysis and regression models. Stratified and multivariate regression analyses were used to detect possible effect modification and to control for confounding variables. In women with BMI ≥ 23.6 kg/m^2 overall average salivary estradiol concentration dropped by 2.4 pmol/l (13.2% change in mean for the total population) by each 0.33 mmol/l (1-standard deviation) increase in serum HDL-C ($P = 0.03$; $P_{interaction} = 0.03$). A subgroup of women characterized by both relatively high BMI (≥ 23.6 kg/m^2) and high serum LDL/HDL-cholesterol ratio (≥ 2.08; 75 percentile) had substantially higher levels of salivary estradiol by cycle day than other women ($P = 0.001$). BMI was the strongest predictor of overall average estradiol with a direct relationship ($P < 0.001$). Serum HDL-C was inversely related to serum leptin, insulin, and dehydroepiandrostendione sulfate ($P < 0.001$, $P < 0.01$ and $P < 0.05$, respectively). There was a direct relationship between breast density and healthy metabolic profiles (low BMI, high serum HDL-C; $P < 0.001$) and salivary progesterone concentrations ($P < 0.05$). Our findings support the hypothesis that low serum HDL-C might reflect an unfavourable hormonal profile with, in particular, increased levels of estrogens and gives further clues to biomarkers of breast cancer risk especially in overweight and obese women.

Introduction

The prevalence of obesity (BMI ≥ 30 kg/m^2)[2] is increasing worldwide, and obese women and women with adult weight gain appear to be at increased risk of breast cancer (1). Moreover, obese women, are susceptible to the metabolic syndrome (i.e. glucose intolerance, dyslipidemia, hypertension), and this, in turn, seems to put women at an even higher risk of breast cancer (2-4).[3] In a prospective study in Norway,[3] we recently observed that serum HDL-C was inversely related to risk of postmenopausal breast cancer especially in overweight (BMI = 25–30 kg/m^2) and obese women. Thus, we hypothesized that low serum HDL-C might reflect an unfavourable hormonal profile with increased levels of breast mitogens, mainly of estrogens, but also of androgens, insulin and IGF-I.[3]

This allows for studies to verify whether the different aspects of the metabolic syndrome (i.e. serum lipids) are associated with levels of endogenous hormones, a major physiological link between obesity and risk of breast cancer (5), and with breast parenchymal density, a surrogate measure of breast cancer risk (6). Evidence from population-based studies might suggest reliable biomarkers of breast cancer risk among conventional clinical parameters, as serum lipids, that could provide a strategy for identifying high-risk individuals who might benefit from disease prevention interventions. As lack of obesity has been associated with delayed onset of breast cancer among carriers of high-penetrance genes (i.e. *BRCA1* and *BRCA2*) (7), obesity-related biomarkers may be useful in the medical surveillance of these women. Furthermore, as metabolic profile has also been related to endometrial cancer risk in epidemiological studies (8,9), including a study from our group (10), learning about obesity-related biomarkers may not be limited to breast cancer.

Therefore, the aim of the present study was to test whether aspects of the metabolic syndrome including low serum HDL-C, are associated with significantly higher levels of hormones, and free estradiol concentration, in particular, and further are related to mammographic parenchymal patterns in premenopausal women. We examined daily concentrations of estradiol and progesterone during one entire menstrual cycle using a salivary radioimmunoassay, serum concentrations of lipids, glucose, insulin, leptin, androgens, SHBG, IGF-I and IGFBP-3, and measures of adiposity (BMI, truncal fat percentage), and mammographic parenchymal patterns in 206 healthy Norwegian women aged 25–35 years.

Material and Methods

Subjects and study design

Subjects for the present study participated in the Norwegian EBBA study. A detailed description of the study is given elsewhere.[4] A total of 206 women living in North Norway entered the study from 2000 to 2002 and participated during one menstrual cycle. The women were invited to participate by announcements in newspapers and locally. Study subjects had to meet the following criteria, which were checked both in a telephone interview and in a personal interview by the same trained nurse during the entire study period: 25–35 years of age; self-reported regular cycles (cycle length 22–38 days) within the previous three months; no use of hormonal contraceptives and no pregnancy or breastfeeding over the previous 6 months; no infertility, gynecological disorders, chronic disorders (i.e. diabetes, hypo-/hyperthyroidism) or abnormally high BMI (> 30 kg/m^2). All clinical procedures were conducted by trained nurses at the Department of Clinical Research, UNN, Tromsø, Norway. All the participating women signed an informed consent form. The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

Questionnaires

We used a general questionnaire (self-administered and by interview) to collect information on ethnicity, education, reproductive history, and past and current lifestyle including physical activity, use of hormonal contraceptives, tobacco and alcohol. To improve recall, the general questionnaire was supplied with a recall calendar as memory aid for the participants. We asked about types of physical activities in the household, leisure time, work, and transport, the usual intensity of the activity (four levels), the usual time spent in each activity on each occasion, the frequency of each activity, and the number of months the activity was used in the past year. Total average energy expenditure per week during the past year was estimated by multiplying the average number of hours per week spent at each activity by the energy cost of that particular activity expressed in METs (11).

The women were asked to record the type and the portion of every food item consumed during 24 hours in a pre-coded food diary developed for the present study and we used a photographic booklet to illustrate the different portion sizes. Dietary data was collected for seven selected days in the menstrual cycle (day 3–6 and day 21–23). Average daily intake of energy and nutrients were computed by using a food database and software system developed at the Institute for Nutrition Research, University of Oslo, Norway (12).

Clinical parameters and mammogram

The participants met fasting on the first possible day after onset of the menstrual bleeding for clinical examinations. This clinical examination included height, weight and blood pressure measurement and blood sampling. The majority of the women met on day 1 or day 2 of their menstrual cycle, but some women had to wait until day 3 to 5 because the medical facilities were closed during holidays and weekends. The same instruments and procedures were used throughout the whole study period. Anthropometrical measures were taken with subjects wearing light clothing and no footwear: height was measured to the nearest centimeter and weight was measured to the nearest 0.1 kilogram on an electronic scale. BMI (kg/m^2) was used to estimate relative weight.

The women met once during mid-cycle (day 7–12) for whole body scan and mammography. Whole body scan was obtained by DEXA (DPX-L 2288, Lunar Radiation Corporation, Madison, WI, USA) operated by the nurse and percentage of fat tissue in the trunk was estimated by Lunar software. Mammograms were taken with Siemens Mammomat 3000 at the Centre of Breast Imaging, UNN. The mammographic parenchymal pattern in bilateral craniocaudal and mediolateral oblique projections was categorized by radiologist N. Bjurstam using a modified Wolfe's classification (6) with four categories: I = essentially normal breast tissue with parenchyma composed primarily of fat; II = prominent ductal pattern in up to one fourth of the breast volume; III = prominent ductal pattern in more than one fourth of the breast volume; and IV = extremely dense parenchyma, which usually denotes connective tissue hyperplasia.

Serum and saliva samples

Fasting blood samples were drawn from an ante-cubital vein. The blood was centrifuged and the serum was separated. Serum concentrations of glucose, triglycerides, total cholesterol, HDL-C, testosterone, DHEA-SO_4, and SHBG were measured in fresh sera at the Department of Clinical Chemistry, UNN, Tromsø. Serum glucose was measured enzymatically by the hexokinase method. Serum triglycerides were assayed by enzymatic hydrolysis with lipase. Serum cholesterol was determined enzymatically using cholesterol esterase and cholesterol oxidase. HDL-C was quantified by a direct assay using PEG-modified enzymes and dextran sulfat. Serum LDL-C was estimated according to Friedewalds formulae (total cholesterol – HDL-C – 0.46 X triglycerides). Serum testosterone was measured by an electrochemiluminescence immunoassay, serum DHEA-SO_4 was measured by a competitive chemiluminescent enzyme immunoassay, and serum SHBG was measured by an

immunometric method. Serum glucose, lipids and testosterone were measured by kits from Roche Diagnostics GmbH, Mannheim, Germany, and serum DHEA-SO_4 and SHBG were measured by kits from Diagnostic Products Corporation (DPC)-Bierman GmbH, Bad Nauheim, Germany. Serum concentrations of insulin, leptin, IGF-I and IGFBP-3 were measured at the Hormone Laboratory, Aker University Hospital, Oslo, in serum that were stored at –70°C for up to 3 years until analysis. Serum insulin and leptin were measured by RIA using kits from Linco Research Inc, St. Charles, MO, USA. The levels of IGF-I and IGFBP-3 were determined by ILMA using Immulite 2000 from Diagnostic Products Corporation (DPC), Los Angeles, CA, USA.

The participants collected samples of their own saliva at home once a day, preferentially in the morning, for the complete menstrual cycle and recorded in a logbook the time and the date of the sample and whether they had menstrual bleeding in the previous 24 hours. Collection of saliva followed previously established protocols from the laboratory at the Department of Anthropology, Harvard University, Cambridge, MA, USA, which analyzed the saliva samples (13). Estradiol was assayed in saliva samples from 20 days (reverse cycle day –5 to –24) and progesterone was assayed in saliva samples from the last 14 days of each cycle (reverse cycle day –1 to –14). For the great majority of cycles (n = 177, 86%) salivary estradiol measurements were made using a I-125 based RIA kit (#39100, Diagnostic Systems Laboratories, Webster, TX, USA) following modifications to the manufacturer's protocol described by Shirtcliff et al. (14). For the remaining cycles (the first 29 cycles in the study) salivary estradiol measurements were made using a tritium based assay (15). In a parallel run of the estradiol assays, the observed correlation was comparable to what the laboratory would have expected if cycles were assayed twice using the same system; therefore, we did not make any corrections of the measured salivary estradiol concentrations. Salivary progesterone measurements were made using an I-125 based RIA kit (#3400, Diagnostic Systems Laboratories, Webster, TX, USA) with the following modifications to the manufacturer's protocol to shift the location of the standard curve: Standards were prepared in assay buffer and run in six concentrations between 2 and 200 pg/ml in 200 µl amounts. First antibody was diluted 1:4. First antibody and labelled steroid were added to each reaction tube in 100 µl amounts. Samples were added in 100 µl amounts together with 100 µl of assay buffer. After overnight incubation at 4°C, 500 µl of second antibody was added to each reaction tube. Reaction tubes were centrifuged for 45 mins and decanted.

Statistical analyses

To test whether aspects of the metabolic syndrome including low serum HDL-C, are associated with significantly higher levels of hormones, and free estradiol concentration in particular, and further are related to mammographic parenchymal patterns in premenopausal women, we estimated some indices of ovarian function and performed a variety of statistical analyses by SAS statistical package version 8.2.

Alignment of the cycles for analysis was based on the identification of the day of the mid-cycle estradiol drop. The day of the mid-cycle estradiol drop provides a good estimate of the day of ovulation (15) and was designated as 'day 0'. Satisfactory identification of the mid-cycle estradiol drop could not be made for 8 women with too many missing days and for 6 women with either no drop or no rise in estradiol within the selected window, and their cycles were not aligned. Overall average salivary estradiol and progesterone were calculated for all the women while additional indices of hormone concentration were calculated for the 192 women with aligned cycles. We selected for presentation the overall average concentrations and a mid-luteal index defined as the average of the hormone concentrations on day +5 to +9, because the mid-luteal index corresponds to the period of maximal progesterone secretion by the corpus luteum and a relatively high (i.e. in comparison with the follicular phase) and stable production of estradiol. Besides, several of the predictors included in our study were associated with the mid-luteal index.

We calculated Pearson's correlation coefficients to examine the associations between different measures of metabolic profile (BMI, truncal fat percentage, serum lipids, glucose, and hormones). We used linear regression modeling to study the associations between measures of metabolic profile and average salivary estradiol and progesterone levels (overall and mid-luteal) throughout one entire menstrual cycle and adjusted for potential confounding factors in multivariate models.

We used a generalized linear model to compare average salivary estradiol concentrations by cycle day in the interval from day −10 to +9 in subgroups of women defined by both BMI and serum lipids: group A = BMI < 23.6 kg/m^2 (Median) and serum LDL/HDL-cholesterol ratio < 2.08 (75 percentile); group B = BMI ≥ 23.6 kg/m^2 and serum LDL/HDL-cholesterol ratio < 2.08; group C = BMI < 23.6 kg/m^2 and serum LDL/HDL-cholesterol ratio ≥ 2.08; group D = BMI ≥ 23.6 kg/m^2 and serum LDL/HDL-cholesterol ratio ≥ 2.08. We controlled for dependencies between repeated observations in the same subject (MIXED procedure) and used the model with the best fit to our data (Toeplitz covariance structure). We included age as a covariate in the model and we performed post-hoc tests for

multiple pair wise comparisons by Dunnett's method. There were no missing observations in the selected interval (day –10 to +9) among women with aligned cycles. Differences in means of serum hormones in subgroups of women defined by both BMI and serum LDL/HDL-cholesterol ratio (group A–D) were tested for statistical significance in multiple linear regression models and post-hoc tests for multiple pair wise comparisons were performed by Bonferroni's method.

Differences in means and proportions of selected characteristics in subgroups of women with different mammographic parenchymal patterns were tested for statistical significance in linear regression models and by chi-square tests (women with non-missing mammogram, n = 205). We used ordinal logistic regression models to estimate the age-adjusted ORs, with 95% CI, of being in one higher category of breast density associated with an increase of 1-SD in measures of metabolic profile and indices of ovarian hormones. To examine whether each of the statistically significant predictors were independent of known or potential determinants of parenchymal patterns, we used multivariate ordinal logistic regression models.

We evaluated possible interactions between each measure of metabolic profile (measures of adiposity, serum lipids, serum hormones) and categories (Median split for all continuous variables) of age at menarche (<13 years, ≥ 13 years), age at entry (<30.7 years, ≥ 30.7 years), parity (nullipara, 1+ children), BMI (< 23.6 kg/m^2, ≥ 23.6 kg/m^2), truncal fat percentage (< 33.0 %, ≥ 33.0 %), energy intake (< 8,016 g/day, ≥ 8,016 g/day), fat intake (< 75 g/day, ≥ 75 g/day), total physical activity (< 216 MET-hours/week, ≥ 216 MET-hours/week), current use of alcohol (yes, no) and tobacco (yes, no), and ever use of hormonal contraceptives (yes, no) by including multiplicative interaction terms between the explanatory variables and the category-variables in the linear and logistic regression models. Plots of residuals were used to confirm that data fitted to the regression models. We considered results statistically significant when the two-sided p-value was < 0.05.

Results

The 206 women included in our study were in average 30.7 years and had mean age at menarche of 13.1 years (Table 1). Mean height was 167 cm and mean BMI was 24.4 kg/m^2. Nearly half the population reported to have had a full-term pregnancy and mean age at first birth was 24.5 years. Average length of menstrual cycle in the study was 28.3 days (range = 20–47 days), mean overall average salivary estradiol concentration was 18.2 pmol/l, and mean

overall average salivary progesterone concentration was 131.1 pmol/l. The great majority of the women (83.0%) reported to use alcohol regularly, while 22.3% were smokers. Altogether, 80.6% of the women had previously used hormonal contraceptives, and average duration of previous use up to 6 months before entry into the study was 5.0 years.

Table 2 shows the correlations between BMI, truncal fat percentage, serum concentrations of glucose, lipids and hormones. Serum HDL-C was inversely related to measures of adiposity, serum leptin and DHEA-SO_4 ($P < 0.05$ for DHEA-SO_4; $P < 0.001$ for others), whereas serum LDL-C was directly related to these variables ($P < 0.05$ for leptin and DHEA-SO_4; $P < 0.001$ for BMI and truncal fat percentage). The above associations were strongest for serum HDL-C compared to the other serum lipids, and serum HDL-C was also inversely related to serum insulin ($P < 0.01$). Both BMI and truncal fat percentage were directly related to serum insulin and leptin ($P < 0.001$), and BMI was also directly related to serum DHEA-SO_4 level ($P < 0.05$).

Table 1 Means (SD) and proportions of selected characteristics in the study population. The Norwegian EBBA-study (N = 206[a]).

Age, years	30.7	(3.1)
Education, total years	16.1	(3.0)
Ethnic minority, Sami, %	7.8	
Clinical measures		
Height, cm	167	(7)
Weight, kg	68.1	(11.7)
BMI, kg/m^2	24.4	(3.8)
Systolic blood pressure, mmHg	113	(11)
Diastolic blood pressure, mmHg	71	(8)
Heart rate, per minute	69	(11)
Menstrual and reproductive characteristics		
Age at menarche, years	13.1	(1.4)
Ever had a full-term pregnancy, %	48.5	
Age at first full-term pregnancy, years	24.5	(3.8)
Cycle length	28.3	(3.4)
Salivary hormone concentration, pmol/l		
Overall average estradiol	18.2	(9.4)
Average mid-luteal estradiol	19.9	(11.1)
Overall average progesterone	131.1	(68.7)
Average mid-luteal progesterone	163.4	(87.7)
Dietary intake		
Energy, kJ/day	8,097	(1,891)
Fat, g/day	77	(24)
Physical activity, MET-hours/week		
Occupational physical activity	104	(79)
Household activities	80	(77)
Recreational physical activity	52	(36)
Alcohol consumption		
Teetotaller, %	17.0	
Average use among alcohol consumers, units/week	3.5	(3.4)
Smoking		
Ever smokers, %	45.6	
Current smokers, %	22.3	
Average number of cigarettes among smokers	10.1	(5.1)
Previous use of hormonal contraceptives		
Ever users, %	80.6	
Total duration of use among ever users, years	5.0	(3.5)

[a]Number may vary due to missing information
SD, standard deviation.

Table 2 Correlation between different measures of metabolic profile at day 1 to day 5 after onset of the menstrual cycle among women with non-missing serum variables. The Norwegian EBBA-study (N = 202).

		Serum levels										
	Truncal fat percentage	Glucose	Triglycerides	Total cholesterol	LDL-C	HDL-C	Insulin	IGF-I	IGFBP-3	Leptin	Testosterone	DHEA-SO_4
BMI	0.807	0.262	0.166	0.180	0.257	-0.390	0.318	0.019	0.096	0.722	0.040	0.151
Truncal fat percentage		0.242	0.136	0.137	0.239	-0.424	0.297	0.010	0.033	0.739	-0.035	0.064
Serum levels: Glucose			0.021	0.092	0.114	-0.091	0.090	-0.033	0.066	0.206	-0.063	0.027
Serum levels: Triglycerides				0.110	0.057	-0.121	0.117	-0.047	0.018	0.040	-0.037	-0.019
Serum levels: Total cholesterol					0.869	0.201	-0.011	0.008	0.140	0.136	0.006	0.128
Serum levels: LDL-C						-0.179	0.0001	-0.018	0.091	0.164	0.020	0.143
Serum levels: HDL-C							-0.224	0.032	0.023	-0.280	-0.108	-0.138
Serum levels: Insulin								0.074	0.039	0.386	0.035	0.016
Serum levels: IGF-I									0.559	0.173	0.131	0.084
Serum levels: IGFBP-3										0.218	0.144	0.164
Serum levels: Leptin											-0.033	0.018
Serum levels: Testosterone												0.652

Pearson correlation coefficients. Values > |0.137|, |0.179| and |0.227| are significant at $P < 0.05$, $P < 0.01$ and $P < 0.001$ respectively.
LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; IGF-I, insulin-like growth factor I; IGFBP-3, IGF-binding protein 3; DHEA-SO_4, dehydroepiandrostendione sulfate.

In age-adjusted linear regression analyses, HDL-C was the only serum lipid that was statistically significantly related to salivary estradiol concentration. By each 0.33 mmol/l (1-SD) increase in serum HDL-C overall average estradiol concentration dropped by 1.5 pmol/l ($P = 0.02$), which equals an 8.2% change in mean overall average estradiol concentration in the study population, and average mid-luteal estradiol concentration dropped by 1.6 pmol/l ($P = 0.04$), which equals an 8.0 % change in mean mid-luteal estradiol concentration in the study population (Table 3). We observed even stronger relationships between the ratio of serum total/HDL-cholesterol and serum LDL/HDL-cholesterol and salivary estradiol concentration ($P < 0.01$, for overall average and mid-luteal estradiol). Both BMI and truncal fat percentage were positively associated with overall average and mid-luteal salivary estradiol concentration. BMI was the strongest predictor of overall average estradiol; by each 3.8 kg/m^2 (1-SD) increase in BMI the overall average estradiol concentration increased by 2.2 pmol/l, which equals a 12.1% change in mean overall average estradiol concentration in the study population ($P < 0.001$). Moreover, serum DHEA-SO_4 was a predictor of average mid-luteal salivary estradiol concentration ($P = 0.04$), whereas serum insulin and leptin tended to predict overall average salivary estradiol concentration ($P = 0.11$ and $P = 0.06$, respectively). Age was negatively related to overall average salivary progesterone concentration ($P = 0.02$), while serum variables and measures of adiposity were unrelated to salivary progesterone levels. When we added age at menarche, parity, energy intake, total physical activity, average use of alcohol, current smoking status (yes/no), and accumulated number of years on hormonal contraceptives to the linear regression models, we observed only small

modifications of the relations between serum HDL-C, BMI, serum DHEA-SO_4 and salivary estradiol concentration and the associations remained statistically significant (results not shown).

Table 3 Estimated changes in salivary estradiol and progesterone concentrations (pmol/l) with 95% CI by 1-SD increase in explanatory variables. Age-adjusted linear regression analysis. The Norwegian EBBA-study.

Explanatory variables[a]	Mean ± SD	Overall average estradiol (N = 206)[b]	Average mid-luteal estradiol (N = 192)[b,c]	Overall average progesterone (N = 206)[b]	Average mid-luteal progesterone (N = 192)[b,c]
Age	30.7 ± 3.1	-0.5 (-1.8, 0.8)	-1.6 (-3.2, 0.01)	-11.4 (-20.8, -1.9)	-12.5 (-25.2, 0.2)
Measures of adiposity					
BMI, kg/m^2	24.4 ± 3.8	2.2 (0.9, 3.5)	2.2 (0.6, 3.8)	-2.9 (-12.4, 6.6)	-7.1 (-19.5, 5.4)
Truncal fat percentage	32.5 ± 7.6	1.7 (0.4, 3.0)	1.6 (0.1, 3.2)	-3.4 (-12.8, 5.9)	-8.2 (-20.5, 4.1)
Fasting serum lipids					
Triglycerides, mmol/l	0.86 ± 1.04	1.2 (-0.1, 2.5)	1.4 (-0.2, 2.9)	6.2 (-3.2, 15.6)	5.3 (-6.8, 17.5)
Total cholesterol, mmol/l	4.43 ± 0.79	0.8 (-0.6, 2.1)	1.1 (-0.6, 2.7)	2.5 (-7.1, 12.1)	4.0 (-8.8, 16.8)
LDL-C, mmol/l	2.52 ± 0.71	1.2 (-0.1, 2.6)	1.6 (-0.03, 3.2)	1.8 (-7.7, 11.3)	1.7 (-11.0, 14.4)
HDL-C, mmol/l	1.54 ± 0.33	-1.5 (-2.8, -0.2)	-1.6 (-3.2, -0.1)	3.4 (-5.8, 12.7)	9.1 (-3.3, 21.5)
Total/HDL-cholesterol ratio	3.00 ± 0.81	2.1 (0.8, 3.4)	2.3 (0.7, 3.9)	-1.2 (-10.8, 8.3)	-5.6 (-18.2, 7.1)
LDL/HDL-cholesterol ratio	1.74 ± 0.70	2.0 (0.7, 3.3)	2.2 (0.7, 3.8)	-0.5 (-10.1, 9.0)	-4.2 (-16.8, 8.5)
Fasting serum hormones					
Insulin, pmol/l	85 ± 59	1.1 (-0.2, 2.4)	1.0 (-0.6, 2.5)	-2.3 (-11.7, 7.1)	-3.1 (-15.5, 9.2)
IGF-I, nmol/l	25.0 ± 6.3	-0.6 (-2.0, 0.7)	-0.3 (-1.9, 1.4)	-6.9 (-16.6, 2.8)	-9.7 (-22.4, 3.1)
Leptin, pmol/l	856 ± 560	1.2 (-0.1, 2.5)	1.3 (-0.3, 2.9)	-4.3 (-13.7, 5.1)	-7.1 (-19.5, 5.4)
Testosterone, nmol/l	1.5 ± 0.5	0.1 (-1.2, 1.4)	0.8 (-0.7, 2.3)	4.1 (-4.9, 13.2)	2.3 (-9.6, 14.2)
DHEA-SO_4, nmol/l	4.6 ± 2.1	0.7 (-0.6, 2.1)	1.7 (0.1, 3.3)	6.9 (-2.7, 16.5)	9.3 (-3.3, 22.0)

[a]Age at entry and measurements at day 1 to day 5 after onset of the menstrual cycle.
[b]Numbers may vary due to missing serum values.
[c]Includes women with aligned cycles only. Aligned cycle day +5 to +9.
95% CI, 95% confidence interval; SD, standard deviation; LDL-cholesterol, low-density lipoprotein cholesterol; HDL-cholesterol, high-density lipoprotein cholesterol; IGF-I, insulin-like growth factor I; DHEA-SO_4, dehydroepiandrostendione sulfate.

Table 4 Estimated changes in salivary overall average estradiol concentration (pmol/l) with 95% CI by 1-SD increase in serum lipids according to BMI category. Age-adjusted linear regression analysis. The Norwegian EBBA-study (N = 203).

Serum lipids	Mean ± SD	BMI < 23.6 kg/m^2 †	BMI ≥ 23.6 kg/m^2 †	BMI ≥ 23.6 kg/m^2 ‡	*P* for interaction
LDL-C, mmol/l	2.52 ± 0.71	-0.3 (-1.9, 1.3)	1.7 (-0.5, 3.9)	1.5 (-0.6, 3.7)	0.13
HDL-C, mmol/l	1.54 ± 0.33	0.6 (-1.0, 2.2)	-2.4 (-4.5, -0.3)	-2.0 (-4.2, 0.3)	0.03
Total/HDL-cholesterol ratio	3.00 ± 0.81	-0.3 (-2.4, 1.8)	2.3 (0.4, 4.3)	2.0 (-0.1, 4.0)	0.08
LDL/HDL-cholesterol ratio	1.74 ± 0.70	-0.5 (-2.5, 1.5)	2.4 (0.4, 4.4)	2.1 (0.1, 4.1)	0.05

† Adjusted for age
‡ Adjusted for age and BMI in a continuous term
95% CI, 95% confidence interval; SD, standard deviation; LDL-cholesterol, low-density lipoprotein cholesterol; HDL-cholesterol, high-density lipoprotein cholesterol.

In age-adjusted analysis of overall average salivary estradiol concentration, there was a statistically significant interaction between BMI (Median split: < 23.6 kg/m^2, ≥ 23.6 kg/m^2) and serum HDL-C ($P_{interaction}$ = 0.03) (Table 4). Among women with BMI above 23.6 kg/m^2, overall average estradiol concentration dropped by 2.4 pmol/l (P = 0.03) by each 0.33 mmol/l (1-SD) increase in serum HDL-C. The other indices of HDL-C level, serum total/HDL-cholesterol ratio and serum LDL/HDL-cholesterol ratio, were positively associated with overall average estradiol concentration among the heaviest women (P = 0.02 for both), but

tests of interaction were not statistically significant. In analysis adjusted for BMI (continuous term), the association between serum LDL/HDL-cholesterol ratio and overall average estradiol concentration in women with BMI above 23.6 kg/m^2 remained statistically significant (P = 0.04). There was a statistically significant interaction between the dichotomised BMI variable and quartiles of serum total/HDL-cholesterol ratio ($P_{interaction}$ = 0.02) and quartiles of serum LDL/HDL-cholesterol ratio ($P_{interaction}$ = 0.007).

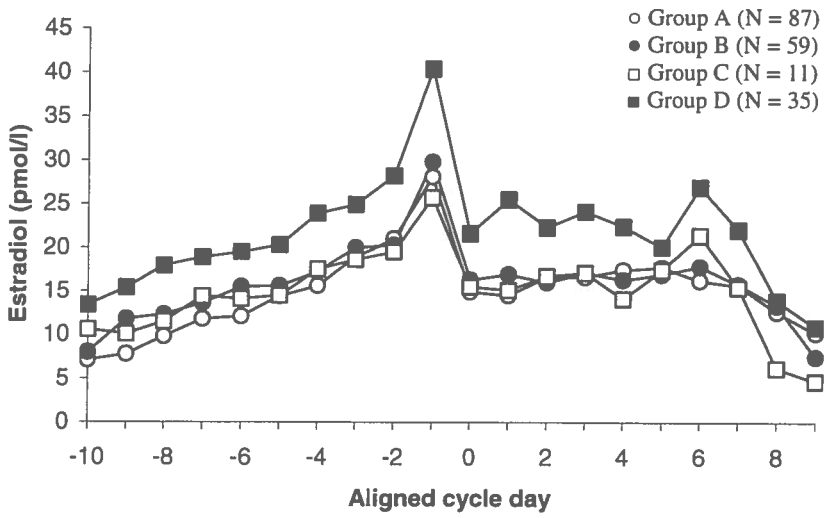

Figure 1.

Average salivary estradiol concentration by cycle day in cycles of women categorized by BMI and serum LDL/HDL-cholesterol ratio. The Norwegian EBBA-study (192 aligned cycles). P = 0.001 for difference in average estradiol concentration by cycle day between cycles of women characterized by BMI ≥ 23.6 kg/m^2 and LDL/HDL-cholesterol ratio ≥ 2.08 (group D) and cycles of women in the other categories (group A–C). Confidence intervals were omitted for clarity. BMI = body mass index. LDL/HDL-cholesterol ratio = low-density lipoprotein/high-density lipoprotein cholesterol ratio.

○ Group A: BMI < 23.6 kg/m^2 and LDL/HDL-cholesterol ratio < 2.08
● Group B: BMI ≥ 23.6 kg/m^2 and LDL/HDL-cholesterol ratio < 2.08
□ Group C: BMI < 23.6 kg/m^2 and LDL/HDL-cholesterol ratio ≥ 2.08
■ Group D: BMI ≥ 23.6 kg/m^2 and LDL/HDL-cholesterol ratio ≥ 2.08

Women characterized by both relatively high BMI (≥ 23.6 kg/m^2; Median split) and high serum LDL/HDL-cholesterol ratio (≥ 2.08; 75 percentile) had markedly higher average salivary estradiol levels by cycle day than the rest of the study population from a graphical illustration (Figure 1) and by generalized linear regression analysis ($P = 0.001$, age-adjusted). We examined how the average estradiol levels by cycle day in women with both high BMI and high serum LDL/HDL-cholesterol ratio (group D) differed from the levels in each of the other groups of women described in Figure 1 and observed statistically significant differences for all comparisons (group A: $P = 0.002$; group B: $P = 0.02$; group C: $P = 0.03$). Among women with high serum LDL/HDL-cholesterol ratio (group C and D), there was no statistically significant difference in mean serum LDL/HDL-cholesterol ratio by BMI category (Median split, 23.6 kg/m^2; $P = 0.07$).

Women characterized by having the highest salivary estradiol levels, a relatively high BMI and an unfavourable LDL/HDL-cholesterol ratio (high) (group D) had the highest levels of serum insulin, leptin and DHEA-SO_4 compared to the rest of the study population (group A–C, Figure 2). However, in statistical analysis, women in this high score group (group D) did not differ in mean serum insulin and leptin levels from the group of women with BMI above the same cut-off and lower serum LDL/HDL-cholesterol ratio (group B, Figure 2). Furthermore, they did not differ in mean serum DHEA-SO_4 level from women with serum LDL/HDL-cholesterol ratio above the same cut-off and lower BMI (group C, Figure 2). The remaining comparisons of mean serum insulin, leptin and DHEA-SO_4 levels among group D women versus women in the other groups were statistically significant (results not shown).

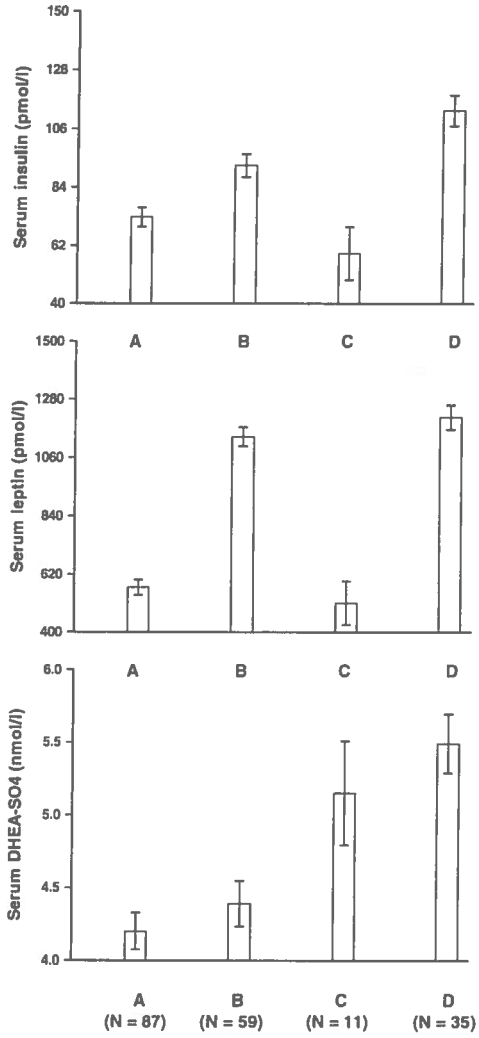

Figure 2.

Age-adjusted values of mean serum insulin, leptin and DHEA-SO_4 (± SE) in women categorized by BMI and serum LDL/HDL-cholesterol ratio. Women with aligned cycles, the Norwegian EBBA-study (N = 192). DHEA-SO_4, dehydroepiandrostendione sulfate; SE, standard error; BMI, body mass index; LDL/HDL-cholesterol ratio, low-density lipoprotein/high-density lipoprotein cholesterol ratio.

Group A: BMI < 23.6 kg/m^2 and LDL/HDL-cholesterol ratio < 2.08
Group B: BMI ≥ 23.6 kg/m^2 and LDL/HDL-cholesterol ratio < 2.08
Group C: BMI < 23.6 kg/m^2 and LDL/HDL-cholesterol ratio ≥ 2.08
Group D: BMI ≥ 23.6 kg/m^2 and LDL/HDL-cholesterol ratio ≥ 2.08

Table 5 describes the associations between established risk factors for breast cancer, metabolic variables, and hormones and mammographic parenchymal pattern. Breast density was directly related to serum HDL-C ($P_{equality} < 0.001$ and $P_{trend} < 0.001$) and salivary progesterone concentration (overall average progesterone, $P_{equality} = 0.05$ and $P_{trend} = 0.01$; mid-luteal progesterone, $P_{equality} = 0.04$ and $P_{trend} = 0.009$) and inversely related to measures of adiposity, serum total/HDL-cholesterol ratio, LDL/HDL-cholesterol ratio, insulin and leptin (insulin, $P_{equality} = 0.01$ and $P_{trend} = 0.005$; all others, $P_{equality}$ and $P_{trend} < 0.001$). There was no difference in means of salivary estradiol concentration between the subgroups of women with different parenchymal breast density.

Table 5 Means and proportions of selected characteristics according to mammographic parenchymal pattern (Modified Wolfe's classification). The Norwegian EBBA-study (N = 205)[a].

Characteristic	Lowest density I N=23[a]	II N=47[a]	III N=82[a]	Highest density IV N=53[a]	*P* for equality	*P* for trend
Age, years	31.9	31.1	30.7	30.0	0.07	0.009
Menstrual and reproductive history						
Age at menarche, years	12.4	12.9	13.3	13.2	0.02	0.01
Ever had a full-term pregnancy, %	73.9	66.0	47.6	24.5	<0.001	<0.001
Age at first full-term pregnancy, years	23.1	24.6	24.9	24.7	0.42	0.19
Ever use of hormonal contraceptives, %	100.0	83.0	79.3	71.7	0.04	0.006
Measures of adiposity						
BMI, kg/m^2	28.1	26.3	23.6	22.4	<0.001	<0.001
Truncal fat percentage	38.8	37.0	31.2	28.1	<0.001	<0.001
Fasting serum variables						
Triglycerides, mmol/l	1.10	1.02	0.84	0.65	0.22	0.04
Cholesterol, mmol/l	4.69	4.47	4.36	4.39	0.36	0.15
LDL-C, mmol/l	2.80	2.60	2.48	2.43	0.14	0.03
HDL-C, mmol/l	1.36	1.44	1.55	1.66	<0.001	<0.001
Total/HDL-cholesterol ratio	3.60	3.22	2.91	2.72	<0.001	<0.001
LDL/HDL-cholesterol ratio	2.18	1.91	1.68	1.53	<0.001	<0.001
Fasting serum hormones						
Insulin, pmol/l	122	89	78	78	0.01	0.005
IGF-I, nmol/l	23.6	25.6	25.1	24.8	0.64	0.77
Leptin, pmol/l	1,202	1,088	750	671	<0.001	<0.001
Testosterone, nmol/l	1.3	1.5	1.5	1.5	0.72	0.45
DHEA-SO_4, nmol/l	4.4	4.5	4.7	4.5	0.94	0.92
Salivary hormones, pmol/l						
Overall average estradiol	21.4	17.0	17.2	19.7	0.14	0.92
Average mid-luteal estradiol	23.2	19.4	18.9	20.5	0.43	0.54
Overall average progesterone	119.2	119.4	127.7	153.1	0.05	0.01
Average mid-luteal progesterone	146.5	144.7	161.8	191.2	0.04	0.009

[a]Number may vary due to missing or invalid information.
LDL-cholesterol, low-density lipoprotein cholesterol; HDL-cholesterol, high-density lipoprotein cholesterol; IGF-I, insulin-like growth factor I; DHEA-SO_4, dehydroepiandrostendione sulfate.

In multiple logistic regression analyses adjusted for age, age at menarche, parity (nulliparous, parous), and past use of hormonal contraceptives (ever, never) (Table 6), a 3.8 kg/m^2 (1-SD) increase in BMI was associated with a decrease of 64% (OR = 0.36; 95% CI = 0.26–0.49) in the odds of having breasts with density in one higher category, a 0.33 mmol/l

(1-SD) increase in serum HDL-C was associated with an increase of 63% (OR = 1.63; 95% CI = 1.24–2.14) in the odds of having breasts with density in one higher category, and a 87.6 pmol/l (1-SD) increase in average mid-luteal salivary progesterone concentration was associated with an increase of 36% (OR = 1.36; 95% CI = 1.03–1.81) in the odds of having breasts with density in one higher category. We did not observe any associations between salivary estradiol levels and mammographic breast density (results not shown).

Table 6 Measures of adiposity, metabolic variables and hormones in relation to mammographic parenchymal pattern. ORs (95% CI) for being in one higher category of breast density (Modified Wolfe's classification) by 1-SD increase in explanatory variables estimated by sequential logistic regression analysis. The Norwegian EBBA-study (N = 205)[a].

	Mean ± SD	OR[b]	95% CI	OR[c]	95% CI
Measures of adiposity					
BMI	24.4 ± 3.8	0.34	(0.25, 0.46)	0.36	(0.26, 0.49)
Truncal fat percentage	32.6 ± 7.6	0.35	(0.26, 0.47)	0.38	(0.28, 0.51)
Fasting serum variables					
HDL-cholesterol, mmol/l	1.53 ± 0.33	1.77	(1.36, 2.32)	1.63	(1.24, 2.14)
Total/HDL-cholesterol ratio	3.01 ± 0.80	0.54	(0.41, 0.70)	0.57	(0.43, 0.74)
LDL/HDL-cholesterol ratio	1.75 ± 0.70	0.60	(0.46, 0.78)	0.64	(0.49, 0.83)
Insulin, pmol/l	85 ± 59	0.66	(0.50, 0.87)	0.68	(0.52, 0.89)
Leptin, pmol/l	858 ± 561	0.49	(0.37, 0.64)	0.52	(0.39, 0.69)
Salivary hormones, pmol/l					
Overall progesterone	131.4 ± 68.7	1.33	(1.02, 1.73)	1.32	(1.01, 1.73)
Mid-luteal progesterone	164.0 ± 87.6	1.41	(1.07, 1.86)	1.36	(1.03, 1.81)

[a]Number may vary due to missing information.
ORs shown are for each measure of adiposity, serum variable and salivary hormone after the following adjustments:
[b]Adjusted for age.
[c]Adjusted for age, age at menarche, parity (nullipara, parous), and past use of hormonal contraceptives (ever, never).
OR, odds ratio; 95% CI, 95% confidence interval; SD, standard deviation; HDL-cholesterol, high-density lipoprotein cholesterol; LDL-cholesterol, low-density lipoprotein cholesterol.

We did not observe any statistically significant interactions apart from the described influence of BMI category on the associations between serum HDL-C and indices of serum HDL-C and salivary estradiol concentration. Regression analyses including the binding proteins (SHBG and IGFBP-3) did not give any additional information.

Discussion

This is the first report to our knowledge showing that a metabolic profile with low serum HDL-C in premenopausal women is related to increased levels of free, biologically active estradiol throughout one entire menstrual cycle. Moreover, we observed that women with both a relatively high BMI (≥ 23.6 kg/m^2; Median split) and a relatively high serum LDL/HDL-cholesterol ratio (≥ 2.08; 75 percentile) were exposed to far higher levels of free estradiol than other women. Apart from serum HDL-C and indices of serum HDL-C level,

other serum lipids were not associated with level of free estradiol. Recently, we documented an increased risk of postmenopausal breast cancer by decreasing serum HDL-C in a large prospective study and the risk was especially high among overweight women.[3] Thus, by analysing the associations between metabolic profile and levels of free estradiol in the present cross-sectional data we had the possibility to identify hypothesized physiological mechanisms that may link overweight and dyslipidemia to breast cancer risk in women. As excessive exposure to estrogens is a major stimulus of breast carcinogenesis, we suggest that low serum HDL-C is a true biomarker of breast cancer risk that may be most useful among overweight and obese women.

Apart from our study on serum HDL-C and breast cancer risk,[3] results from prospective studies are limited and not specified by BMI categories (16-18). However, several studies have reported lower levels of serum HDL-C in breast cancer patients versus controls (19-21).

Circulating estrogen and progesterone during the pre-menopause are thought to play a major role in breast carcinogenesis as the risk of breast cancer increases by early menarche and by late menopause (5). Bilateral oophorectomy before the age of 35 reduces the lifetime risk of breast cancer in a woman by nearly 75% (22). A reanalysis of nine prospective studies observed a 2.6 times increase in the risk of postmenopausal breast cancer among women with free serum estradiol in the highest quintile as compared to women with free serum estradiol in the lowest quintile (23). Results from epidemiological studies of premenopausal breast cancer are less conclusive and are complicated by the cyclic hormonal variation occurring during the menstrual cycle. An increased risk of breast cancer in premenopausal women with relatively high levels of estradiol has been suggested (24-26). Furthermore, migrant studies have shown that the lifestyle of Western societies is associated with increased breast cancer incidence (5) and Falk et al. (27) observed that among premenopausal Asian-American women, those least westernised had the lowest levels of plasma estradiol. The mechanisms by which estrogens cause breast cancer have not been firmly established but the prevailing theory proposes that estrogens increase the rate of cell proliferation by stimulating estrogen receptor-mediated transcription and thereby the number of errors occurring during DNA replication (28,29).

Previous studies have examined estradiol levels in blood and sample sizes have been small. Thomson et al. (30) (n = 24; 21 samples during one cycle), Shelley et al. (31) (n = 363; one sample in early follicular phase), and Semmers et al. (32) (n= 36; one sample) did not observe any association between serum HDL-C and estradiol. In contrast, Gorbach et al. (33) (n = 24; one sample in follicular phase) and Lyons Wall et al. (34) (n = 12; 20 samples during

one cycle) observed a positive association between serum HDL-C and estradiol. Increased serum HDL-C levels are also found in women using exogenous estrogens for contraception or hormone therapy (35,36).

Interestingly, there was a linear increase in salivary estradiol concentration related to increasing BMI and truncal fat percentage in our study. These findings have been discussed in more detail elsewhere.[4] Studies have generally found relatively stable and uniform estradiol levels among normal and overweight women, while obesity has been associated with impaired ovarian function and a decrease in serum estradiol (37-39). However, Kirschner et al. (40) and Leenen et al. (41) found that free estradiol levels in women with abdominal obesity were higher than in subjects with lower-body (gluteal) obesity.

One explanation for the difference in findings between studies of both serum HDL-C and BMI and levels of estradiol may be the use of different estimates of endogenous estradiol exposure; salivary estradiol concentration is probably superior to total serum estradiol as a predictor of free, biologically active estradiol level (42). Furthermore, the association between estradiol and serum HDL-C may be dependent on metabolic profile (i.e. overweight/obesity) and the presence of other hormones (i.e. insulin); thus, stratified analysis may be most appropriate. Besides, our work is based on relatively young birth cohorts who have experienced a more modern combination of sedentary lifestyle and abundance of tasty food and thereby developed other metabolic profiles throughout their lives than older women. Numerous studies have reported various patterns of cyclic fluctuations in serum HDL-C as a function of the phase of the menstrual cycle (34,43); however Reed et al. (44) found that the intraindividual variability for serum HDL-C in premenopausal women was similar to that found in men and postmenopausal women and differences between studies in timing of serum HDL-C assessment according to cycle phase are not likely to have influenced our results.

Our study shows that serum HDL-C is inversely related to level of serum DHEA-SO_4 and is in agreement with others (30-32). Serum HDL-C was not statistically significantly related to salivary progesterone concentration in our study population. This is in accordance with several studies that observed unchanged levels of serum HDL-C across the menstrual cycle, despite large fluctuations in progesterone levels (45-47). However, decreasing levels of serum HDL-C have been observed by increasing dosage of progestin treatment (48,49).

The observed associations between serum HDL-C and salivary estradiol and serum DHEA-SO_4 are biologically plausible as sex steroids are physiological regulators of serum lipids (50). The changes in serum HDL-C levels induced by sex steroids appear to be mediated, in part, by the lipolytic enzyme, hepatic lipase; the activity of this enzyme is

regulated by sex steroids (51). The study of sex differences in cardiovascular disease has revealed that androgens are the key modulators of serum lipid levels and in particular, of serum HDL-C levels (52). In parallel with a rise in testosterone levels during sexual maturation in males serum HDL-C drops (53). Women with relative androgen excess, i.e. polycystic ovary syndrome, have lower levels of serum HDL-C than women with normal ovarian function (52). In the present study, serum DHEA-SO_4 was directly related to average mid-luteal estradiol concentration; this supports that the conversion of androgens to estrogens in adipose tissue might be an underlying mechanism for the increased risk of breast cancer by low HDL-C, as hypothesized.[3] The present study also suggests that other hormonal changes, particularly hyperinsulinemia, in the heaviest women (BMI $\geq$ 23.6 kg/m^2) may be of importance; insulin enhances the ovarian function and lowers the level of SHBG (54).

In this cross-sectional study, serum LDL/HDL-cholesterol ratio was the index of HDL-C level that was the strongest predictor of salivary estradiol concentration and this ratio may be a more sensitive marker of breast cancer risk than serum HDL-C alone. Higher levels of serum LDL-C among breast cancer patients have been observed in retrospective studies (20,55), but not in prospective studies (16,17). Serum LDL/HDL-cholesterol ratio may reflect aspects of the serum lipid profile that are especially strongly influenced by sex steroid levels. LDL-C particle size could be interesting in this context; serum triglycerides/HDL-C ratio has been proposed as a valid indicator of atherogenic particles (i.e. small LDL-C particles) in studies of atherosclerotic disease among individuals with metabolic syndrome (56). However, in our study, serum triglycerides/HDL-C ratio was not related to levels of free estradiol among the heaviest women (BMI $\geq$ 23.6 kg/m^2) (result not shown).

The observed increase in levels of estradiol associated with potential markers of increased breast cancer risk (high BMI, low HDL-C, high LDL/HDL-cholesterol ratio) was not accompanied by an increase in progesterone levels. This suggests that the markers may also be relevant for endometrial cancer as the balance of estrogens and progesterone largely influences endometrial cancer risk (10).

Our finding of a direct relationship between salivary progesterone levels and breast density is in accordance with studies of serum progesterone (57). This supports the role of progesterone in breast carcinogenesis, as mammographic density is an independent predictor of breast cancer risk, with increase in risk by increasing density (58,59). The fact that estrogen plus progestin use increases both mammographic breast density and the incidence rate of breast cancer versus estrogen alone or placebo (60,61) underscores the biological significance

of our result. Salivary estradiol concentration was not associated with breast density in our study as also reported by others (57).

In our study, measures of adiposity were inversely related to breast density and this was reflected in associations for metabolic variables strongly correlated with adiposity (serum HDL-C, insulin, leptin). The impact of fat mass on breast density is well known from several studies in both premenopausal and postmenopausal women (62-64). A direct relationship between serum HDL-C and mammographic dysplasia was also observed by Boyd et al. independently of percentage body fat (65). Thus, studies indicate that potential markers of breast cancer risk (high BMI, low serum HDL-C and high serum LDL/HDL-cholesterol ratio) are negatively associated with high-risk mammographic parenchymal patterns. This negative confounding of potential markers of increased breast cancer risk may mean that the effect of parenchymal patterns on risk will tend to be underestimated unless adjusted for metabolic profile (BMI, serum HDL-C) and vice versa, as suggested by Sala et al. (64).

There will always be some degree of uncertainty and subjectivity in the evaluation of mammograms of premenopausal women and there may have been some nondifferential misclassification of the mammographic density readings that would have biased the results towards null. However, we think any such misclassification is likely to have been minimal, given the strong associations between mammographic parenchymal pattern and established risk factors for breast cancer and the stable work by one expert reader. Wolfe's classification was originally used in postmenopausal women and is less adequate for differentiation of mammographic patterns among premenopausal women. Therefore, a modified Wolfe's classification was used in our study. Additional classifications were performed in our study population but analyses, including different classifications are left for future publications by the group.

Our study is strengthened by the estimation of daily estradiol and progesterone concentrations in saliva using well-developed and validated methods and assays to characterize the women's exposure to free, biologically active ovarian steroids, and the comparison of levels by aligned cycle days in the large majority of the population (13,15). This is a great advantage, given the large intra-cycle fluctuations in levels of ovarian hormones and the wide inter-individual variation in cycle length in menstruating women. Furthermore, salivary levels of estradiol and progesterone are quite stable within subjects over time (42). The use of one clinical research department at a university hospital with specially trained nurses enhances the quality of our data. We registered all clinical variables, including mammogram, within the same narrow frame of the cycle in each participant by uniform

procedures. Thus, any influence of cycle phases on parenchymal breast density, in particular, was minimized (66). The same radiologist read all mammograms without knowledge about the women's metabolic profile. To limit potential influence of season, women were not participating during months with no daylight (December and January). Associations between BMI and serum lipids were comparable with observations in a large prospective study of metabolic risk profiles among women of the same age and from the same geographical area (67). We adjusted for potential confounders as age, age at menarche, parity, energy intake, physical activity, use of alcohol, tobacco and hormonal contraceptives in statistical analyses and evaluated possible effect modification.

In our recent prospective study,[3] from which the study hypothesis originated, the increased risk of postmenopausal breast cancer associated with low serum HDL-C was found particularly among overweight and obese women (BMI $\geq$ 25 kg/m^2). In this cross-sectional study we used another BMI cut-off ($\geq$ 23.6 kg/m^2) to define the heaviest women; the women were in average 13 years younger than in the follow-up study and there is a physiologic increase in BMI by increasing age at least up to age 60 years in females (1,68). Thus, it is reasonable that associations observed for younger women in lower BMI categories may be translated to older women in higher BMI categories.

In conclusion, our results support that low serum HDL-C in overweight and obese women is associated with higher levels of breast mitogens and estrogens, in particular. This supports that HDL-C is a biologically sound marker of breast cancer risk that may primarily be used to identify high risk individuals that may be candidates for intervention, but also to improve the medical surveillance of women with *BRCA1* and *BRCA2* mutations, and to estimate future breast cancer burden associated with the obesity epidemic.

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[2]The abbreviations used are: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; IGF-I, insulin-like growth factor I; SHBG, sex-hormone binding globulin; IGFBP-3, IGF-binding protein 3; EBBA study, Energy Balance and Breast Cancer Aspects study; UNN, University Hospital of North Norway; MET, metabolic equivalent; DEXA, dual-energy X-ray absorptiometry; DHEA-SO_4, dehydroepiandrostendione sulfate; PEG, polyethylene glycol; LDL-C, low-density lipoprotein cholesterol; RIA, radioimmunoassay; ILMA immunoluminometric assay; OR, odds ratio; CI, confidence interval; SD, standard deviation.

[3]Furberg A-S, Veierød MB, Wilsgaard T, Bernstein L, Thune I. Serum high-density lipoprotein cholesterol, metabolic syndrome, and breast cancer risk. *Submitted.*

[4]Thune I, Furberg A-S, Hjartåker A, Brill I, Jacobsen H, Emaus A, Jasienska G, Ellison PT. Body composition (height, weight, BMI, WHR, fat percentage) influences estradiol and progesterone levels throughout a menstrual cycle among women aged 25-35 years. The Norwegian EBBA-study. *In manuscript*

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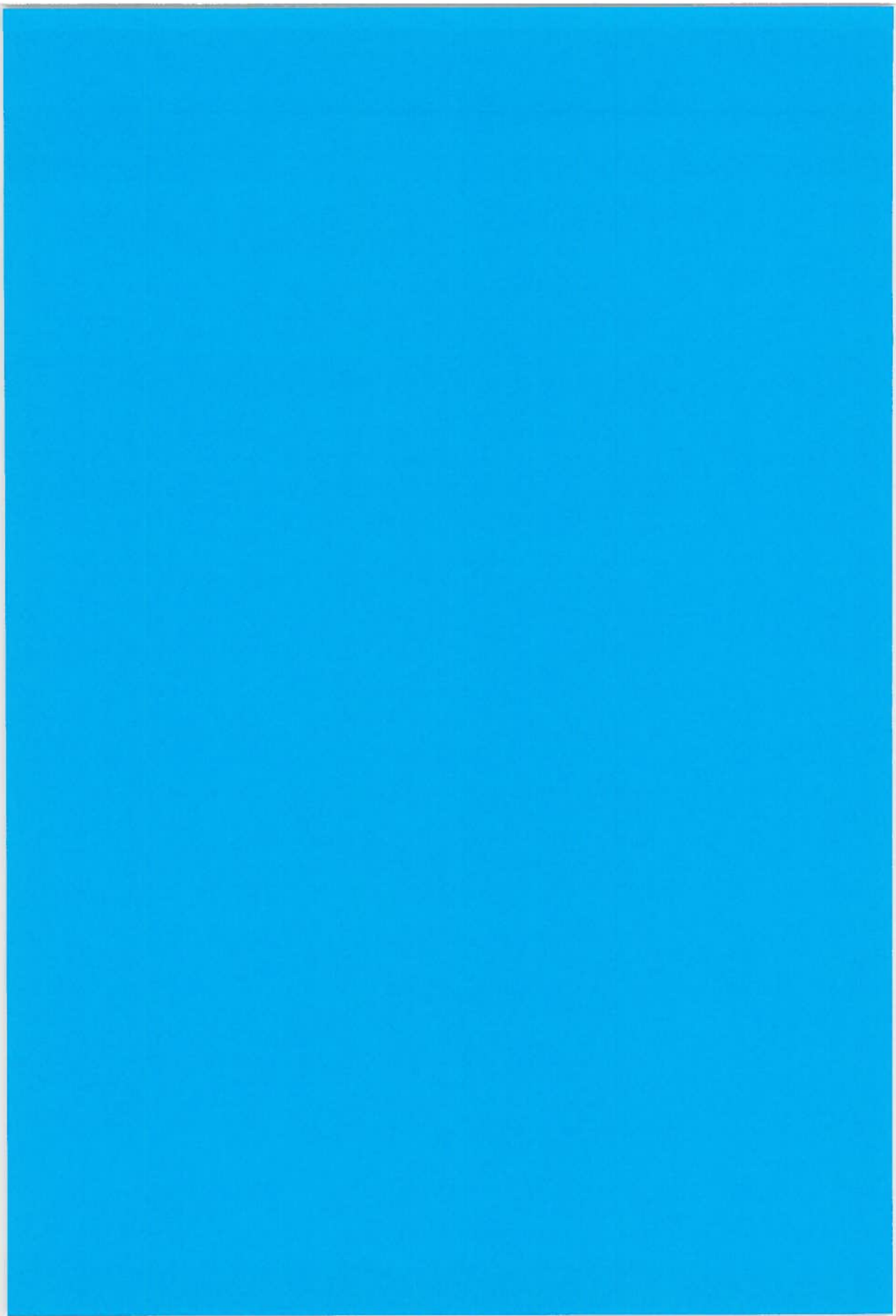
Paper III



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FAST TRACK

METABOLIC ABNORMALITIES (HYPERTENSION, HYPERGLYCEMIA AND OVERWEIGHT), LIFESTYLE (HIGH ENERGY INTAKE AND PHYSICAL INACTIVITY) AND ENDOMETRIAL CANCER RISK IN A NORWEGIAN COHORT

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Since high energy intake, inactivity, hypertension and diabetes are linked to obesity and an unfavorable hormonal profile, we wanted to test whether energy intake, physical activity, blood pressure and serum glucose are related to the risk of endometrial cancer independent of the body mass index (BMI). A cohort of 24,460 women, aged 20–49 years, attended a Norwegian health screening twice during 1974–1981; they answered questions about diet, physical activity and chronic diseases, and their height, weight, blood pressure and non-fasting serum glucose were measured. By the end of 1996, during 15.7 years of follow-up, 130 cases of endometrial carcinomas were identified. The relative risks (RRs) for endometrial cancer were estimated in proportional hazards models including potentially confounding factors. Obese women (BMI ≥ 30 kg/m^2) were at 2.6 times increased risk of endometrial cancer compared to normal weight women (BMI < 25 kg/m^2) (RR = 2.57, 95%CI = 1.61–4.10). Among overweight women (BMI ≥ 25 kg/m^2), non-fasting serum glucose in the upper quartile *vs.* in the lower quartile was associated with a 2.4 times increase in risk (RR = 2.41, 95%CI = 1.08–5.37), whereas among obese women, blood pressure above 140/90 mmHg *vs.* below 140/90 mmHg in both surveys was associated with a 3.5 times increase in risk (RR = 3.47, 95%CI = 1.24–9.70). Especially in women younger than 50 years, high energy intake (5,044–6,401 kJ/day) conferred higher risk compared to low energy intake (< 4266 kJ/day) (RR = 3.40, 95%CI = 1.52–7.60). Increasing recreational activity tended to be protective. Among obese women with non-sedentary jobs at both screenings, RR declined to 0.18 (95%CI = 0.05–0.62) as the level of sustained occupational activity increased (p_{trend} = 0.03). Our results suggest that inactivity and high energy intake are major risk factors for endometrial cancer independent of BMI, and that hypertension and relative hyperglycemia are significant markers of risk, especially among the heaviest women.

Key words: *endometrial cancer; metabolic abnormalities; lifestyle; Norwegian cohort*

The wide differences in incidence of endometrial cancer (type I-carcinoma) across countries and between urban and rural populations, as well as the changing disease incidence in migrants, indicate that environmental factors have a huge influence on the occurrence of the disease.[1] The etiology of endometrial cancer is unknown, yet it has been shown that malignant transformation, cancer cell proliferation, tumor invasion and tumor progression are enhanced by deficiency in progesterone and its action relative to estrogen in the glandular cells of the endometrium.[2,3] A shift in energy balance (*e.g.*, excessive energy intake relative to energy expenditure) might contribute to an unfavorable sex hormone profile in women.[2,4]

Epidemiological studies on the association between energy intake and the risk of endometrial cancer are inconclusive.[5–10] A chronically excessive intake of energy relative to requirements may lead to increased body weight. Although adult obesity has consistently been associated with an increased risk of endometrial cancer, the effect may be age and menopausal status dependent.[11] The energy expended during physical activity may represent between 15 and 50% of total energy expenditure, depending on the amount of physical activity performed and the body mass.[12] Epidemiological studies find that inactivity may be associated with an increased endometrial cancer risk.[13–18] However, some studies indicate that the effect may be dependent on type of activity (*i.e.*, during work and recreation).[19,20] We have previously reported on the effect of activity, energy intake and accurately measured body mass on the incidence of breast cancer[21] and similar studies on endometrial cancer are needed.[11]

Body mass and endogenous levels of estrogens have been associated with risk independently of each other,[22,23] suggesting that the unopposed estrogen/relative progesterone deficiency hypothesis is insufficient to explain endometrial cancer. It has been hypothesized that insulin, a growth factor known for its mitogenic activity,[24,25] plays a major role in endometrial carcinogenesis. Hypertension and diabetes are markers of insulin resistance/hyperinsulinemia.[26,27] Observations linking blood pressure, glucose metabolism and markers of insulin resistance to endometrial cancer come mostly from retrospective studies, which have provided less conclusive results because of self-reported disease history and anthropometry or an absence of adjustment for body mass.[1]

We analyzed data that included repeated assessments of variables from a cohort of 24,460 Norwegian women to elucidate whether energy intake, recreational and occupational activity, blood pressure and serum glucose concentration are associated with risk of endometrial cancer independent of body mass.

MATERIAL AND METHODS

Participants

The women included in our study participated in 2 population-based screening surveys started during 1974–1976 and 1977–1981 in 3 counties of Norway (Finnmark, Oppland and Sogn og Fjordane), as part of the Norwegian National Health Screening Service's program to explore the association of lifestyle with chronic diseases. In 1974–1976 all female residents, aged 35–49 years, and a 10% random sample, aged 20–34 years, received a written invitation to participate. In 4 municipalities of county of Finnmark, all women in the youngest age group were asked to meet. Of 31,509 invited women, 28,562 (90.6%) attended. In 1977–1981, those who registered at the first screening were re-invited, while a 5–11% random sample of women, aged 20–39 years, was invited for the first time. A total of 34,378 women were asked to partic-

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ipate and 31,209 (90.8%) actually did; 26,127 women attended both surveys. Detailed reports on the screenings have been published[28,29] and associations of dietary factors, physical activity and cancer have been found.[21,30–33]

Assessment of lifestyle parameters

The screening procedures were almost identical in the 2 surveys. The written invitation included a questionnaire on ethnicity, chronic diseases, smoking and physical activity. The women marked their usual level of recreational and occupational activity on a scale with the following 4 grades: Recreational activity: Grade 1, Reading, watching television or other sedentary activity; Grade 2, Walking, bicycling or other activity for at least 4 hr per week; Grade 3, Recreational athletics, heavy gardening or similar activities at least 4 hr per week; and Grade 4, Regular (several times a week) training or participation in athletic competitions. Occupational activity: Grade 1, Mostly sedentary work; Grade 2, A lot of walking; Grade 3, A lot of walking and lifting; and Grade 4, Heavy manual work. The same team of trained nurses conducted interviews with the participants at the screening center in both surveys to confirm the information given.

In the second survey, a food frequency questionnaire (FFQ) including questions on 64 explicit food items was also distributed at the screening and returned *via* mail by 25,892 women (83%) after one reminder. Special emphasis was given to habitual use of fat and fat-rich food items in the diet. The estimated energy intake per time unit was calculated according to the method developed by Gaard and colleagues.[21,34] The partly semi-quantitative FFQ has been described in detail and validated as a useful tool for categorizing individuals according to their intake of energy and fat.[35]

Assessment of clinical parameters

Body weight was measured to the nearest half kilogram with participants dressed in lightweight clothing. Height was measured in centimeters. As an estimate of relative weight, body mass index (BMI) was obtained by dividing the body weight in kilograms by the height in meters squared (kg/m^2). Specially trained nurses measured systolic and diastolic blood pressure by using a mercury sphygmomanometer. After the women had rested for a minimum of 4 min, 2 recordings were made at 1 min intervals with the individual sitting. The lowest blood pressure was used in the analyses. A non-fasting blood sample was drawn and analyzed at the Central Laboratory, Ullevål Hospital, Oslo. Details of the methods have been published.[28] Non-fasting serum glucose concentration was estimated according to the method described by Brown[36] in every sample in the first survey, while in the second survey this analysis was done on a sub-set only (in Finnmark, part of Oppland).

Follow-up and case identification

We restricted our study to women who were alive with no diagnosis of any malignant disease 1 year after participation in the second survey (1977–1981, $n = 25{,}642$). Only women with complete data from both surveys on parity, recreational and occupational activity, and the main clinical parameters [height, weight, blood pressure and non-fasting serum glucose (survey 1)] were included ($n = 24{,}460$). As the assessment of energy intake and the double assessments of other analytic variables were completed in the second survey only, we used this survey as the baseline.

Prevalence and incidence of cancer cases were identified through linkage to the Cancer Registry of Norway. Women with an incident, primary, histopathologically confirmed carcinoma of the endometrium were defined as cases. Since 1952, clinicians and pathologists in Norway have been required to report all new cancer cases. An accurate and complete database is achieved through matching with the Register of Deaths at Statistics Norway (SSB). Information about reproductive history, emigration and death was gathered by linkage to SSB. Women were considered to be at risk from the date of the blood sample in the 1977–1981 survey (baseline) through 31 December 1996, or earlier on the occurrence of emigration, death or diagnosis of any cancer. In total, 24,460 women were followed for 384,531 person-years.

Statistical analyses

To estimate relative risks (RRs) for endometrial cancer associated with high energy intake, overweight, physical inactivity, hypertension and relative hyperglycemia, we used Cox's proportional hazard regression model. The proportional hazard assumption was checked by evaluating the parallelism between graphs of the log-log survivor functions for different categories of the variables. Several models were used to fit, ranging from the simplest model (age at baseline) to the more complex ones, including the analytic variables and co-variates (county of residence, parity, height, alcohol and smoking status), one at a time or simultaneously. Based on substantial modification in RRs derived from inclusion of parity and BMI, and cause-and-effect decisions, we found it appropriate to present the results of equations including only age, as well as those including age, county of residence, parity, height, BMI, physical activity and smoking. Tests for trend were performed by the introduction of "semi-continuous" variables, which were obtained by assigning consecutive integers to levels of categorized variables. Interactions were evaluated by including appropriate product terms in the models.

Women were assigned to the overweight (BMI = 25–30 kg/m^2) or the obese class (BMI $\geq$ 30 kg/m^2) according to the World Health Organization (WHO) classification of adults by BMI. With regard to physical activity, the 2 uppermost levels were merged because only a few participants engaged in the most strenuous activities (grade 4 recreational: $n = 52$, 0.2% of included and grade 4 occupational: $n = 1{,}331$, 5.5% of included). Furthermore, for both recreational and occupational activity, a new variable was created containing information from both surveys. Women who reported sedentary activity (grade 1) in both surveys were characterized as "consistently sedentary." Those who reported minimum grade 2 level of activity in the first survey and minimum grade 3 in the next were characterized as "consistently active." The remaining women who were neither consistently sedentary nor consistently active were characterized as "moderately active."

Concerning systolic and diastolic blood pressure, we tested the WHO criteria for hypertension (140 and 90 mmHg, respectively) as relevant thresholds for endometrial cancer risk. Women with blood pressure below the 140/90 mmHg limit in both surveys were classified as "consistently normotensive" and women with blood pressure above the limit in both surveys were classified as "consistently hypertensive." Women who were neither consistently normotensive nor consistently hypertensive were classified as "hypertensive in one survey." With regard to non-fasting serum glucose concentration and energy intake, distribution-based cut-off points (*i.e.*, quartiles) were used. Dietary information was insufficient in observations if there was an estimated daily energy intake below 2,100 kJ and/or less than 20 adequate answers in the FFQ ($n = 4{,}370$, 17.9% of included); analyses were conducted on energy intake and fat intake after exclusion of these observations. All significance tests were 2-tailed and the level of significance was set at 5%. The analyses were performed with the SAS statistical package version 8e.

RESULTS

During a mean follow-up period of 15.7 years, there were 130 incident cases of endometrial carcinoma [127 adenocarcinomas (1 serous papillary adenocarcinoma = type II-carcinoma) and 3 unspecified carcinomas] diagnosed among 24,460 women. The mean age at diagnosis ($\bar{X}_{\text{age at diagnosis}}$) was 56.8 years (range 40.3–69.3). Women who developed endometrial cancer were somewhat older and had given birth to fewer children than those who did not (Table I). Baseline mean BMI, mean blood pressure and mean energy intake were higher, whereas mean serum cholesterol was lower in cases *vs.* non-cases. Those who developed cancer were

TABLE I – MEAN (STANDARD DEVIATION = SD) OR PROPORTIONS OF SELECTED BASELINE CHARACTERISTICS (1977–81 SURVEY) AMONG WOMEN IN A NORWEGIAN COHORT STUDY

	Total population (n = 24,460)[2]	Cases[1] (n = 130)[2]
	Mean (SD)	Mean (SD)
Age (years)	44.7 (6.7)	47.2 (4.5)
Parity[3]	2.6 (1.6)	2.3 (1.7)
Age at first birth (years)	23.9 (4.3)	23.6 (4.5)
Height (cm)	162.7 (6.0)	162.9 (6.2)
BMI (kg/m^2)	24.9 (4.1)	26.6 (5.8)
Diastolic blood pressure (mmHg)	82.3 (10.7)	83.9 (10.4)
Systolic blood pressure (mmHg)	131.4 (18.4)	134.1 (19.3)
Serum glucose (mmol/l)[4]	5.7 (1.0)	5.8 (0.8)
Serum cholesterol (mmol/l)	6.2 (1.2)	5.9 (1.3)
Serum HDL-cholesterol (mmol/l)	1.4 (0.4)	1.4 (0.3)
Serum triglycerides (mmol/l)	1.5 (0.9)	1.5 (0.9)
Energy intake (kJ/day)	5,374 (1,562)	5,458 (1,520)
Fat intake (g/day)	54.9 (19.4)	54.7 (18.1)
	Proportions (%)	Proportions (%)
Physically active in leisure time	82.9	78.5
Physically active at work	86.2	80.8
Daily smoking	35.3	29.7
Self-reported hypertension	6.5	8.6
Self-reported diabetes	0.6	0

[1]All variables except age were adjusted for age.–[2]Number may vary due to missing or insufficient information.–[3]Parity throughout follow-up.–[4]Non-fasting assessment in the 1974–76 survey.

TABLE II – RELATIVE RISKS (RR)[1] AND 95% CONFIDENCE INTERVAL (95%CI) OF ENDOMETRIAL CANCER ASSOCIATED WITH SELECTED BASELINE VARIABLES IN A NORWEGIAN COHORT STUDY

Variable (per change in variable)[2]	RR (95%CI)	Cases	All
Age (1 year)	1.08 (1.04, 1.11)	130	24,460
Parity (1 child)[3]	0.87 (0.77, 0.97)	130	24,460
Age at first birth (1 year)	0.98 (0.93, 1.03)	108	22,275
Height (6 cm)	1.06 (0.89, 1.27)	130	24,460
BMI (4.1 kg/m^2)	1.39 (1.21, 1.59)	130	24,460
Serum cholesterol (1.2 mmol/l)	0.77 (0.64, 0.93)	130	24,460
Serum HDL cholesterol (0.4 mmol/l)	0.83 (0.68, 1.02)	130	24,023
Serum triglycerides (0.9 mmol/l)	1.02 (0.86, 1.21)	130	24,458
Fat intake (19.4 g/day)	0.99 (0.82, 1.20)	110	20,090
Daily smoking (yes/no)	0.78 (0.53, 1.14)	130	24,460

[1]All variables except age were adjusted for age.–[2]Values are estimated RRs associated with one unit or one SD increase in exposure variable, except for smoking (yes *vs.* no).–[3]Parity throughout follow-up.

more likely to be sedentary in their leisure time and at work and to report hypertensive disease.

Age-adjusted survival analyses of selected background variables confirmed a protective effect of parity and serum cholesterol on endometrial cancer risk. In contrast, no association was observed between smoking and endometrial cancer risk (Table II). Furthermore, there was an overall positive association between BMI and risk of endometrial cancer in age-adjusted analysis [RR = 1.39, 95% confidence interval (95%CI) = 1.21–1.59, per 4.1 kg/m^2].

We observed an almost doubled risk of endometrial cancer among women in the third quartile of energy intake (5,044–6,401 kJ/day) compared to women in the bottom quartile (< 4,266 kJ/day) (RR = 1.87, 95%CI = 1.09–3.23; Table III). In stratified analyses, the association was confined to women below 50 years at baseline (RR = 2.94, 95%CI = 1.31–6.58 for the second; RR = 3.40, 95%CI = 1.52–7.60 for the third and RR = 1.91, 95%CI = 0.78–4.63 for the upper quartile, $p_{trend} = 0.17$; $p_{interaction} = 0.05$).

From the bottom (< 22.1 kg/m^2) to the top BMI-quartile (≥ 26.9 kg/m^2), the endometrial cancer risk increased by 126% (RR = 2.26, 95%CI 1.33–3.82, $p_{trend} = 0.002$, after adjustments; Table III). However, there was only a slight suggested increase in risk associated with BMI between 22.1 and 26.9 kg/m^2. To evaluate the possible modification of effect by changes in endocrine exposure around the menopause, we split the population by age; among women younger than 50 the heaviest quartile (≥ 26.9 kg/m^2) experienced almost 3 times the risk of the leanest (RR = 2.80, 95%CI = 1.47–5.34, $p_{trend} = 0.0008$). In contrast, among the older women the effect disappeared. However, a formal test of interaction was not significant ($p_{interaction} = 0.42$). In women younger than 50 with a BMI in the upper quartile, $\bar{X}_{age\ at\ diagnosis}$ was 55.3 years. As ethnicity may be a determinant of BMI, we repeated the analyses excluding the Lapp women (n = 1,243) but observed only minimal alterations in the risk estimates (results not shown).

We tested the WHO criteria for classification of adults by BMI. Data were consistent, with an increased risk among obese women (BMI ≥ 30 kg/m^2: RR = 2.57, 95%CI = 1.61–4.10), and suggestive of an increased risk among overweight women (BMI = 25–30 kg/m^2: RR = 1.43, 95%CI = 0.96–2.14, $p_{trend} = 0.0001$) *vs.* normal weight or lean women (Table III). However, among women younger than 50 at baseline, overweight was evidently associated with an increased risk (RR = 1.90, 95%CI = 1.17–3.09), and obesity conferred a higher risk than in older women (< 50 years: RR = 2.59, 95%CI = 1.39–4.83 *vs.* ≥ 50 years: RR = 2.28, 95%CI = 1.13–4.62; $p_{interaction} = 0.12$). In women younger than 50, $\bar{X}_{age\ at\ diagnosis}$ was 54.7 years in overweight and 56.7 years in obese individuals.

Recreational activity that corresponded to a minimum of 4 hr of walking per week (grades 2–4) at baseline or in both surveys tended to be protective against endometrial cancer even in multivariate analysis including BMI (Table IV). This was further supported by a significant 37% reduction in risk among women in the middle category of recreational activity (grade 2) in the 1974–1976 survey (RR = 0.63, 95%CI = 0.43–0.92, $p_{trend} = 0.12$; results not shown). We performed separate analyses for women

TABLE III – ADJUSTED RELATIVE RISKS (RR) AND 95% CONFIDENCE INTERVALS (95%CI) OF ENDOMETRIAL CANCER IN RELATION TO ENERGY INTAKE, BODY MASS INDEX (BMI) AND AGE AT BASELINE IN A NORWEGIAN COHORT STUDY

	All women		Age < 50 years		Age ≥ 50 years	
	Cases	RR (95%CI)	Cases	RR (95%CI)	Cases	RR (95%CI)
Energy intake[1] (kJ/day)						
< 4,266	21	1.00	8	1.00	13	1.00
4,266–5,043	31	1.54 (0.88, 2.68)	23	2.94 (1.31, 6.58)	8	0.64 (0.26, 1.55)
5,044–6,401	35	1.87 (1.09, 3.23)	24	3.40 (1.52, 7.60)	11	0.94 (0.42, 2.11)
≥ 6,402	23	1.36 (0.75, 2.48)	13	1.91 (0.78, 4.63)	10	1.01 (0.44, 2.34)
p for trend		0.21		0.17		0.83
BMI, Quartiles[2] (kg/m^2)						
< 22.1	21	1.00	14	1.00	7	1.00
22.1–24.0	27	1.22 (0.69, 2.17)	16	1.17 (0.57, 2.41)	11	1.19 (0.46, 3.07)
24.1–26.9	29	1.24 (0.70, 2.19)	18	1.34 (0.66, 2.72)	11	0.95 (0.36, 2.47)
≥ 26.9	53	2.26 (1.33, 3.82)	34	2.80 (1.47, 5.34)	19	1.41 (0.58, 3.43)
p for trend		0.002		0.0008		0.49
BMI, WHO criteria[2] (kg/m^2)						
< 25	56	1.00	35	1.00	21	1.00
25–30	45	1.43 (0.96, 2.14)	32	1.90 (1.17, 3.09)	13	0.82 (0.41, 1.65)
≥ 30	29	2.57 (1.61, 4.10)	15	2.59 (1.39, 4.83)	14	2.28 (1.13, 4.62)
p for trend		0.0001		0.0008		0.06

[1]*Energy intake:* Adjusted for age, geographical region, height, body mass index, recreational and occupational activity, and smoking at baseline and parity. Also considered blood pressure and serum glucose.–[2]*BMI:* Adjusted for age, geographical region, height, recreational and occupational activity, and smoking at baseline and parity. Also considered blood pressure and serum glucose.

TABLE IV – ADJUSTED RELATIVE RISKS (RR) AND 95% CONFIDENCE INTERVALS (95%CI) OF ENDOMETRIAL CANCER IN RELATION TO LEVEL OF ACTIVITY IN THE BASELINE SURVEY (1977–1981) AND COMBINED LEVEL OF ACTIVITY IN THE 1974–1976 SURVEY AND AT BASELINE IN A NORWEGIAN COHORT STUDY

	Cases	RR[1] (95%CI)	RR[2] (95%CI)
Recreational activity			
Baseline (1977–81)			
Grade 1 (lowest)	28	1.00	1.00
Grade 2	85	0.77 (0.50, 1.17)	0.81 (0.53, 1.25)
Grade 3 + 4 (highest)	17	0.69 (0.38, 1.27)	0.79 (0.43, 1.45)
p for trend		0.20	0.39
Both surveys			
Consistently sedentary	14	1.00	1.00
Moderately active	101	0.67 (0.38, 1.17)	0.72 (0.41, 1.27)
Consistently active	15	0.61 (0.30, 1.27)	0.71 (0.34, 1.49)
p for trend		0.23	0.40
Occupational activity			
Baseline (1977–81)			
Grade 1 (lowest)	24	1.00	1.00
Grade 2	76	0.68 (0.43, 1.07)	0.70 (0.44, 1.11)
Grade 3 + 4 (highest)	30	0.59 (0.34, 1.00)	0.61 (0.35, 1.05)
p for trend		0.07	0.09
Both surveys			
Consistently sedentary	16	1.00	1.00
Moderately active	85	0.55 (0.33, 0.95)	0.57 (0.33, 0.99)
Consistently active	29	0.47 (0.26, 0.87)	0.49 (0.26, 0.91)
p for trend		0.04	0.06

[1]Adjusted for age at baseline.–[2]Adjusted for age, geographical region, height, body mass index, recreational or occupational activity and smoking at baseline and parity. Also considered blood pressure and serum glucose.

aged younger and those older than 50 at baseline and data suggested that the oldest women profited most from having an active lifestyle in both surveys (≥ 50 years: $p_{trend} = 0.14$; $p_{interaction} = 0.30$; results not shown). Among consistently recreationally active women, $\bar{X}_{age\ at\ diagnosis}$ was 54.0 years in those younger than 50 and 60.4 years in older women. Stratification by BMI-categories did not reveal any further associations between recreational activity and endometrial cancer risk.

Increasing occupational activity was associated with a reduced risk of endometrial cancer (Table IV). Among women who reported having a job with a lot of walking at baseline, the RR for endometrial cancer was 0.70 (95%CI = 0.44–1.11) and, among those who reported lifting or heavy manual work, RR was 0.61 (95%CI = 0.35–1.05), compared to those who had sedentary work ($p_{trend} = 0.09$). By combining the assessments of occupational activity from the 2 surveys, we observed that moderately active and consistently active women had a 43% reduction (RR = 0.57, 95%CI = 0.33–0.99) and 51% reduction (RR = 0.49, 95%CI = 0.26–0.91) in the risk of endometrial cancer, respectively, compared to consistently sedentary women ($p_{trend} = 0.06$). Physical activity at work was especially protective in obese women (BMI ≥ 30 kg/m^2). In stratified analyses of occupational activity at baseline, and in both surveys combined, the RR decreased to 0.22 (95%CI = 0.08–0.66, $p_{trend} = 0.01$; $p_{interaction} = 0.07$) and 0.18 (95%CI = 0.05–0.62, $p_{trend} = 0.03$; $p_{interaction} = 0.17$; results not shown), respectively, as the level of activity increased among obese women. In separate analyses of the effect of occupational activity in women younger and older than 50 at baseline, active

work, in both surveys, tended to be most protective among the youngest women (age < 50 years, consistently active *vs.* consistently sedentary: RR = 0.44, 95%CI = 0.20–0.98, p_{trend} = 0.07; $p_{interaction}$ = 0.90; results not shown). Among consistently occupationally active women, $\bar{X}_{age\ at\ diagnosis}$ was 54.1 years in those younger than 50 and 61.9 years in older women.

Positive associations between measured blood pressure at baseline in a continuous scale and endometrial cancer risk were suggested in an age-adjusted analysis (RR = 1.14, 95%CI = 0.97–1.34 per 18.4 mmHg for systolic blood pressure and RR = 1.17, 95%CI = 0.98–1.39 per 10.7 mmHg for diastolic blood pressure; results not shown), but in models including BMI the associations disappeared. In analyses using quartiles of systolic and diastolic blood pressure, no associations with endometrial cancer risk were observed (results not shown).

We tested the relevance of the WHO criteria for hypertension (140/90 mmHg) with respect to endometrial cancer risk (Table V). Among obese women (BMI ≥ 30 kg/m^2) hypertension in both surveys was associated with a 3.5 times increase in risk of endometrial cancer compared to normotension in both surveys (RR = 3.47, 95%CI = 1.24–9.70, p_{trend} = 0.02; $p_{interaction}$ = 0.04). Furthermore, the association was not distorted by residual confounding in analysis adjusted for BMI (continuous term; RR = 3.06, 95%CI = 1.08–8.63; results not shown). Even though we observed 13 incident cases of endometrial cancer among women who reported being treated for high blood pressure at baseline (n = 1,594), hypertensive disease was not associated with risk in survival analysis. Moreover, when excluding women with self-reported hypertensive disease, the estimated RR associated with measured hypertension in both surveys increased to 5.25 (95%CI = 1.46–18.95, p_{trend} = 0.01) among obese women (results not shown).

Table VI shows that the RR of endometrial cancer increased to 2.12 (95%CI = 1.21–3.71) in the third quartile of non-fasting serum glucose compared to the bottom quartile (p_{trend} = 0.01). The risk associated with a non-fasting serum glucose ≥ 5.6 mmol/l was even higher in women who were overweight (BMI ≥ 25 kg/m^2; RR = 2.45, 95%CI = 1.11–5.42). In contrast, the effect of high serum glucose values was almost absent among women who had a BMI < 25 kg/m^2 ($p_{interaction}$ = 0.92). We did not observe any association between endometrial cancer risk and the continuous non-fasting serum glucose variable (results not shown). None of the women who reported having diabetes at baseline (n = 154) was diagnosed with endometrial cancer during follow-up.

The presence of a cluster of metabolic abnormalities, including self-reported or measured hypertension (diastolic blood pressure ≥ 90 mmHg or systolic blood pressure ≥ 140 mmHg), self-reported diabetes or level of non-fasting serum glucose in the upper quartile (≥ 6.1 mmol/l), level of triglycerides in the upper quartile (≥ 1.76 mmol/l) and level of high-density lipoprotein (HDL) in the lower quartile (< 1.20 mmol/l), was identified in 517 women at baseline. During follow-up, 6 of these women were diagnosed with endometrial cancer and in age-adjusted survival analysis the cluster was associated with a 1.9 times increase in risk (RR = 1.90, 95%CI = 0.84–4.34, results not shown).

DISCUSSION

Our study of 24,460 women followed for almost 16 years strongly suggests that a cluster of metabolic abnormalities, including hypertension and hyperglycemia, is a significant risk factor for the development of endometrial carcinoma, especially among overweight and obese women. Our results, from models that include energy expenditure (physical activity), body mass and energy intake, suggest that excessive energy intake increases the risk of this malignancy. Furthermore, to our knowledge, our study is the first prospective study to show the protective effect against endometrial cancer of both recreational and occupational activity controlling for measured height and weight (BMI) and other important risk factors.

Our results suggest that relatively high energy intake might be a co-factor in endometrial carcinogenesis, which is in agreement with several case-control studies published in the 1990s.[5–7] In contrast, recent case-control studies did not observe any association with total energy intake.[8–10] In this prospective study, we were able to study simultaneously the effect of energy intake and energy expenditure (physical activity), which is a major advantage considering the laws of thermodynamics. Observations on total energy intake and endometrial cancer from other cohort studies are, however, scarce.

The observed doubling of risk associated with the upper BMI categories was of the same magnitude as in other studies.[11] Interestingly, the WHO categories for classification of adults by BMI strongly predicted the risk of developing endometrial cancer. This supports the role of obesity in endometrial carcinogenesis; however a higher number of cases in the reference groups might have facilitated the detection of other significant thresholds (*i.e.*, quartiles). There was a higher proportion of current smokers among non-obese than among obese women (36.4% *vs.* 25.8%, age-adjusted) and smoking has been inversely related to the risk of endometrial cancer.[1,37] However, the effect of BMI was only minimaliy altered in the analysis stratified by smoking status (results not shown). The weakening of the associations observed in women older than 50 at baseline *vs.* younger women may reflect a physiological increase in body weight in post-menopausal women. A tendency among lean women towards more frequent use of hormone replacement therapy,[38] which was not allowed for in our analyses, may also have influenced our results.

The suggested slight reduction in the risk of endometrial cancer observed among women with sustained recreational activity is consistent with some observations,[13,14,20] but in contrast to others,[19] yet stronger associations have been reported.[15,16,18] In our study, there was a clustering of cases in the second level of the 4-point relative measurement scale of recreational physical activity (minimum 4 hr of walking per week). Non-differential misclassification between the second and third levels of activity is likely, and this might have contributed to the weak RR estimates. Furthermore, since ever use of exogenous hormones has been associated with higher social class[38] and more time spent in sport activities,[39] eventual adjustments for hormonal therapy or social class might have strengthened our results.

TABLE V – ADJUSTED RELATIVE RISKS (RR) AND 95% CONFIDENCE INTERVALS (95%CI) OF ENDOMETRIAL CANCER IN RELATION TO COMBINED LEVEL OF ARTERIAL BLOOD PRESSURE IN THE 1974–1976 SURVEY AND IN THE BASELINE SURVEY (1977–1981) IN A NORWEGIAN COHORT STUDY

Combined level of arterial blood pressure	All women		BMI < 30 kg/m^2		BMI ≥ 30 kg/m^2	
	Cases	RR[1] (95%CI)	Cases	RR[2] (95%CI)	Cases	RR[2] (95%CI)
Consistently normotensive[3]	85	1.00	75	1.00	10	1.00
Hypertensive in one survey[4]	25	1.11 (0.70, 1.77)	20	1.42 (0.86, 2.34)	5	0.77 (0.26, 2.27)
Consistently hypertensive[5]	20	1.24 (0.69, 2.25)	6	0.61 (0.24, 1.51)	14	3.47 (1.24, 9.70)
p for trend		0.24		0.68		0.02

[1]Adjusted for age, geographical region, height, body mass index (in a continuous scale), recreational and occupational activity, and smoking at baseline and parity.–[2]Adjusted for age, geographical region, height, recreational and occupational activity, and smoking at baseline and parity. Also considered serum glucose.–[3]Blood pressure < 140/90 mmHg in both surveys.–[4]Blood pressure ≥ 140/90 mmHg in one survey.–[5]Blood pressure ≥ 140/90 mmHg in both surveys.

TABLE VI – ADJUSTED RELATIVE RISKS (RR) AND 95% CONFIDENCE INTERVALS (95%CI) OF ENDOMETRIAL CANCER IN RELATION TO SERUM GLUCOSE IN THE 1974–76 SURVEY IN A NORWEGIAN COHORT STUDY

Serum glucose (mmol/l)	All women		BMI < 25 kg/m²		BMI ≥ 25 kg/m²	
	Cases	RR[1] (95%CI)	Cases	RR[2] (95%CI)	Cases	RR[2] (95%CI)
< 5.2	17	1.00	9	1.00	8	1.00
5.2–5.59	27	1.43 (0.78, 2.63)	12	1.36 (0.57, 3.24)	15	1.60 (0.68, 3.78)
5.6–6.09	45	2.12 (1.21, 3.71)	19	1.96 (0.89, 4.35)	26	2.45 (1.11, 5.42)
≥ 6.1	41	1.88 (1.07, 3.33)	16	1.55 (0.68, 3.51)	25	2.41 (1.08, 5.37)
p for trend		0.01		0.22		0.02

[1]Adjusted for age, geographical region, height, body mass index (in a continuous scale), recreational and occupational activity, and smoking at baseline and parity.–[2]Adjusted for age, geographical region, height, recreational and occupational activity, and smoking at baseline and parity. Also considered blood pressure.

Our finding of a 40–50% protective effect from increasing levels of occupational activity is in agreement with that observed in a Swedish cohort.[40] However, we found that occupational activity tended to be most protective among younger women (mean age at baseline = 42.0 years, $X_{\text{age at diagnosis}}$ = 54.6 years), whereas Moradi *et al.*[40] found that the effect of this activity was limited to women aged 50–69 years in analyses adjusted for attained age, calendar year of follow-up and place of residence. As we observed that women who reported sedentary jobs at baseline had fewer children, a lower BMI and were more sedentary in their leisure time, relative to those who were physically active at work ($p < 0.05$, age adjusted; results not shown), confounding may partly explain the discrepancy between studies. A number of retrospective studies[13,14,16,19,41] support an inverse relationship between occupational activity and risk of endometrial cancer, although in the case-control study by Moradi *et al.*,[16] the effect was confined to women who were not obese and smokers. In our study, the effect modification by weight was in favor of the obese women (BMI ≥ 30 kg/m²) and the protection experienced by sustained occupational activity tended to be confined to non-smokers (results not shown). Only in 1 case-control study, which was hampered by a low participation rate and limited sample size, was occupational activity not related to the risk of endometrial cancer.[20]

An innovation in the study of hypertensive disease and endometrial cancer is our equation, which includes information on 2 repeated measurements of blood pressure, measured height and weight (BMI), and other co-variates (county of residence, parity, smoking and physical activity) used to describe variation in endometrial cancer incidence during follow-up. The increase in risk by more than 3 times, observed among obese women with blood pressure ≥ 140/90 mmHg in 2 assessments at an interval of 3–5 years, is convincing and, similarly, Weiderpass *et al.*[42] found that self-reported hypertension was a risk factor only among obese women.

To our knowledge, ours is the first prospective study of the relationship between a marker of glucose metabolism and risk of endometrial cancer adjusted for BMI, physical activity and other potential co-variates. We found an overall positive association between non-fasting serum glucose concentration and risk of endometrial cancer, which was confined to overweight women (BMI ≥ 25 kg/m²). In a case-control study, mean fasting levels of glucose and insulin were higher in endometrial cancer patients than in healthy controls.[43] In another small study, the cancer patients ($n = 10$) had significantly higher fasting glucose and insulin levels and higher insulin responses after glucose administration than the normal women ($n = 10$), even though their glucose responses were similar.[44] However, Troisi *et al.*[45] found that adjustments for BMI and other risk factors eliminated an apparent positive association between fasting C-peptide levels and risk of endometrial cancer in a retrospective study. In our study, only non-fasting serum glucose levels were available. Nevertheless, the fact that adjustment for time since last meal did not affect the risk estimates strengthens our data (results not shown). The lack of any effect of serum glucose on the endometrial cancer incidence among normal weight women in our cohort is in agreement with a prospective study in which an increased risk of endometrial cancer associated with self-reported diabetes was confined to women with BMI ≥ 27.4 kg/m².[46] Likewise, most retrospective studies of this relationship have reported an increased risk among overweight (BMI ≥ 25 kg/m²)[47] or obese (BMI ≥ 30 kg/m², BMI ≥ 31.9 kg/m²)[17,48] women, while Weiderpass *et al.*[42] saw no difference in the effect of diabetes when comparing obese women with non-obese. In our study, it is likely that the majority of women who reported to have diabetes at baseline were type I diabetics and thus the absence of any association with endometrial cancer risk is in agreement with a suggested increase in risk confined to type 2 diabetes.[47]

In light of the observed effects of overweight/obesity, hypertension and relative hyperglycemia, we suggest that a metabolic syndrome with insulin resistance as a major feature is a risk factor for endometrial cancer as already hypothesized by Weiderpass *et al.*[42] In order to address this question in further detail, we analyzed the effect of a cluster of metabolic abnormalities (*e.g.*, high blood pressure, low levels of HDL and high levels of triglycerides and blood glucose) linked to insulin resistance[26] and newly introduced as a predictor of colorectal cancer mortality.[27] We found a suggested positive association in age-adjusted analysis between this cluster of metabolic abnormalities and the risk of endometrial cancer.

The mechanism of increased endometrial cancer risk linked to obesity and inactivity is unclear, but it is biologically plausible that changes in metabolism and hormonal activity may be implicated.[49] The normal menstrual cycle reflects the refined balance between the proliferative actions of estrogen and the antiestrogenic and secretory transforming actions of progesterone on the endometrium.[49] In our study, obesity conferred a higher risk of endometrial cancer in women younger than 50 years than in older women. This points to the importance of the progesterone insufficiency experienced by obese premenopausal women as a result of an increased number of anovulatory cycles[23,49] in the etiology of endometrial cancer. The smaller increase in risk observed among obese women aged 50 years or more might be the result of increased circulating levels of free estradiol associated with increased conversion of androgens to estrogens in the adipose tissue and lower levels of sex hormone-binding globulin (SHBG) in obese postmenopausal women.[23,49]

A proposed mechanism for the protective effect on risk of endometrial cancer by exercise is lowered body mass.[19] However, we found a significant effect of physical activity even after adjustment for BMI, and inactive women have been shown to have higher serum estrogen levels than active women independent of body weight.[50,51] Experimental and epidemiological evidence suggest that insulin-like growth factor (IGF)-I, a hormone with strong mitogenic and antiapoptotic actions, is important in endometrial carcinogenesis. While BMI and physical activity also appear to affect blood level of IGF-I, dietary energy intake seems to be the critical regulator even in obese subjects.[52] Thus, the observed increased risk associated with relatively high energy intake even after adjustments (BMI and physical activity) in our study may reflect an increased proliferative action of IGF-I in response to excessive energy intake. In the case of negative energy balance

(low energy intake relative to energy expenditure), which may be reflected in a low BMI, the body will experience energy restriction, which has been associated with decreased level of IGF-I.[52] Besides, energy restriction is known to enhance DNA repair, modulate oxidative damage to DNA and reduce oncogene expression.[53] Moreover, energy restriction also affects insulin metabolism,[53] while inactivity and obesity are associated with insulin resistance and the resultant hyperinsulinemia[54] and there is an established link between diabetes, a disease characterized by hyperinsulinemia when diagnosed as type 2 diabetes, and endometrial cancer.[1] There is increasing evidence that insulin is a growth factor for tumor formation.[24,25] The mechanisms underlying insulin-mediated neoplasia may include enhanced DNA synthesis with resultant tumor cell growth, inhibition of apoptosis and an altered sex hormone milieu.[54] In our study, high blood glucose levels and hypertension, which are associated with insulin resistance/hyperinsulinemia, were strong markers of endometrial cancer risk, in particular, in combination with high body weight. This suggests that in overweight and obese women, coexisting metabolic disturbances may act synergistically and facilitate malignant transformation of the endometrial glandular cells. In light of this, the observed protective effect from relative hypercholesterolemia, which is also generally associated with obesity, is interestingly odd and, to our knowledge, there is at present no well-founded hypothesis about the molecular events, which may explain this suggested antagonistic effect on endometrial carcinogenesis.

The high attendance rate in the population-based screenings, the almost complete follow-up for almost 16 years, the measurements at 2 different time points of height, weight and blood pressure by a constant team of trained nurses, the repeated assessments of self-reported recreational and occupational activity, the dietary data and the definition of cases based on a diagnosis of endometrial carcinoma by a pathologist strengthen our results and are clear advantages over previous studies published in this field. Moreover, the accuracy of the levels of recreational activity reported on the questionnaire has been validated and the level of recreational activity correlates positively with physical fitness.[55–57] The findings in our study that women who were sedentary in their leisure time had a higher BMI and a significant dyslipidemia relative to those who were active ($p < 0.05$ for higher BMI, serum LDL/HDL ratio and serum triglycerides in inactive *vs.* active, age adjusted; results not shown) strengthen the validity of our assessment.

The wide confidence intervals of our risk estimates are the result of the limited number of events available for analysis. Additionally, information about actual hysterectomy rates in the population was not accessible. However, the prevalence of extirpated corpora uteri among women aged 15 years or more in Norway in the 3-year period 1988–1990 was estimated to be 198 per 100,000 women[58] and hysterectomy is unlikely to be a real confounding factor in our study. Norwegian women were restrictive in their use of estrogens for peri- and post-menopausal symptoms (HRT) until the 1990s, when the rate of prescription started to increase, with combined estrogen-progestin hormone replacement being most frequently prescribed.[38] Likewise, use of oral contraceptives has been limited in Norway compared to neighboring countries, and the low-dose estrogen pills have been the predominant preparation since 1975,[59] making the missing information on exogenous hormone use of minor importance in this context.

In conclusion, our study advocates public health efforts aimed at reducing physical inactivity and excessive energy intake in order primarily to reduce the prevalence of obesity and metabolic syndrome and to have an additional effect on endometrial cancer morbidity. Furthermore, we find it reasonable that women with high body weight might benefit from regular measurements of serum glucose and blood pressure, and eventual treatment of established diabetes and hypertension, with respect to endometrial cancer morbidity through calorie restriction and exercise, among other standard measures.

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ERRATA

Furberg A-S, Thune I. Metabolic abnormalities (hypertension, hyperglycemia, overweight) and lifestyle (high energy intake, physical inactivity) and endometrial cancer risk in a Norwegian cohort. Int. J. Canc 2003; 104:669–676.

In reading the above referenced article, the following should be noted:

The correct values for daily energy intake in kJ are calculated by multiplying each written figure of energy intake by 1.0714 [in Abstract, Statistical analyses (paragraph 3), Results (paragraph 3), Table I (row 12) and Table III (column 1)]. The correct values for daily fat intake in g/day are calculated by multiplying each written figure of fat intake by 1.0714 [in Table I (row 13) and Table II (row 9)].

The authors regret the error.

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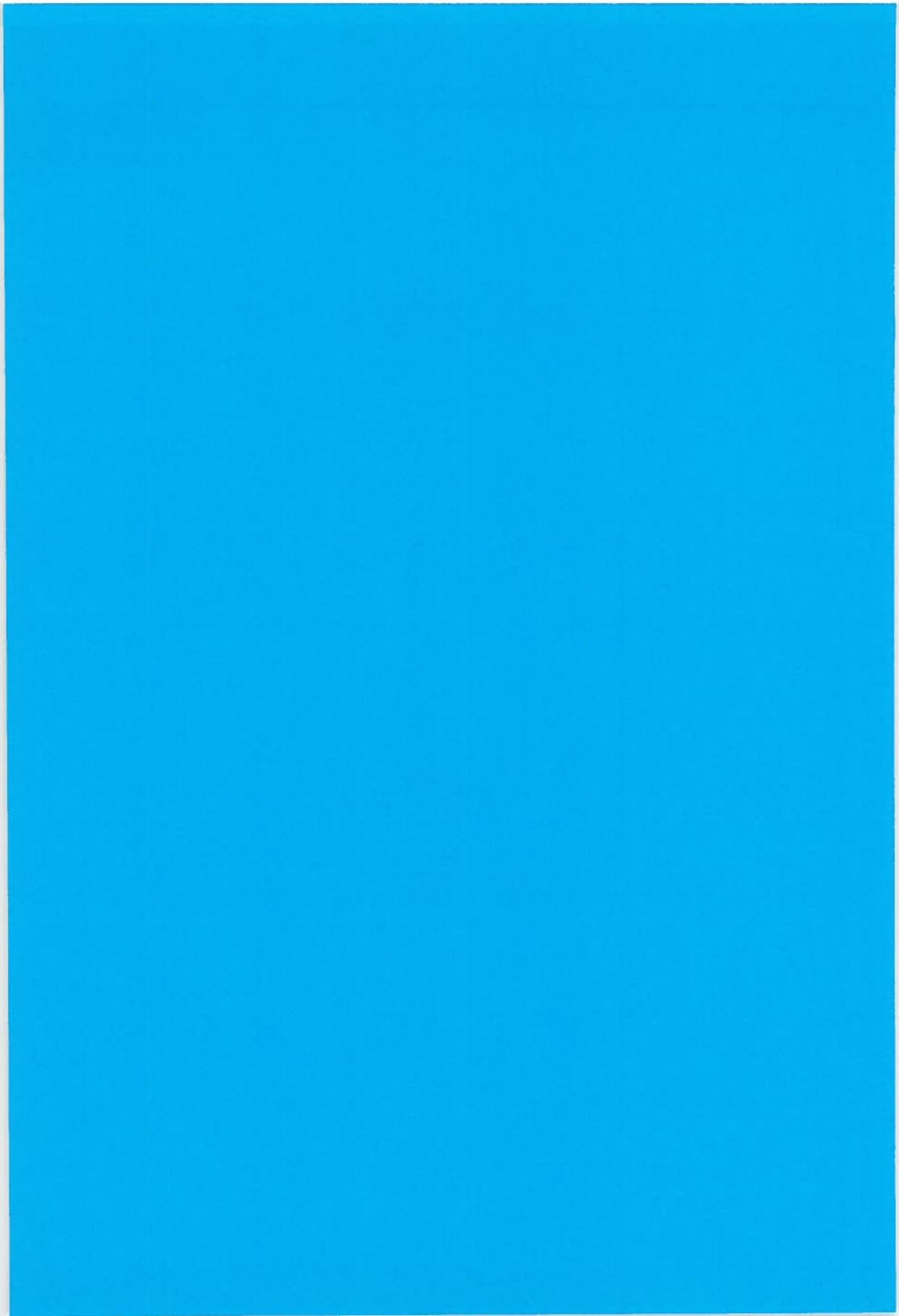
Paper IV



Serum high-density lipoprotein cholesterol, metabolic syndrome, and breast cancer risk

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ABSTRACT

Background: The metabolic syndrome (obesity, glucose intolerance, dyslipidemia, hypertension) has a high and increasing prevalence that runs in parallel with an increase in breast cancer incidence worldwide. High-density lipoprotein cholesterol (HDL-C) represents an important aspect of the syndrome, yet its role in breast cancer is still undefined.

Methods: In two population-based screening surveys during 1977–83 and 1985–88 serum HDL-C was assayed enzymatically among 38,823 Norwegian women aged 17–54 years at entry. Height, weight, blood pressure, serum lipids, fat and energy intake, physical activity, parity, and use of oral contraceptives, hormone therapy, alcohol and tobacco were assessed. We used Cox proportional hazards modeling to estimate the relative risk (RR) for breast cancer associated with serum HDL-C and to adjust for potential confounding variables and performed stratified analyses to evaluate effect modification by other risk factors.

Results: During a median follow-up of 17.2 years (maximum = 21.8 years), we identified 708 cases of invasive breast cancer. In multivariate analysis the risk of postmenopausal breast cancer decreased by each higher quartile of HDL-C (P_{trend} = .01). Among women with HDL-C above 1.64 mmol/l (highest quartile) vs. below 1.20 mmol/l (lowest quartile) a RR of 0.73 (95% confidence interval [CI] = 0.55 to 0.95) was observed. When we divided the population into a normal weight (BMI < 25 kg/m^2) and an overweight and obese (BMI ≥ 25 kg/m^2) group, the effect of HDL-C was confined to the heavier subgroup with an observed 66% reduction in risk of postmenopausal breast cancer in women with HDL-C above 1.64 mmol/l vs. below 1.20 mmol/l (RR = 0.34; 95% CI = 0.19 to 0.59; P_{trend} < .001; $P_{interaction}$ = .006).

Conclusions: Our study demonstrates that low HDL-C, as part of the metabolic syndrome, is a potential marker of increased postmenopausal breast cancer risk and might be used to facilitate identification of high-risk individuals and in disease prevention.

INTRODUCTION

The metabolic syndrome, characterized by visceral obesity, glucose intolerance, hypertension and dyslipidemia, has a high and increasing prevalence that runs in parallel with an increase in breast cancer incidence worldwide *(1,2)*. Studies support increased insulin and insulin-like growth factor I (IGF-I) in metabolic syndrome as a causal link to breast cancer *(3–6)*. However, specific examination of other biomarkers in metabolic syndrome is needed, i.e. the still undefined role of high-density lipoprotein cholesterol (HDL-C).

In vitro studies have shown that HDL-C stimulates the growth of human breast cancer cells *(7,8)* especially in hormone-independent cells *(9)*. In contrast, androgens lower HDL-C in women *(10)* and androgens have been positively associated with breast cancer risk *(11–13)*.

Previously we reported that physical activity and energy balance were associated with breast *(14)* and endometrial *(15)* cancer risk and that endometrial cancer risk was increased by hyperglycemia and hypertension in overweight and obese women *(15)* in a cohort of Norwegian women established in 1974–76. Interestingly, several studies have reported lower levels of HDL-C in breast cancer patients versus controls *(16–19)*. However, data from prospective studies are limited *(20–22)*.

On this background we hypothesize that HDL-C, as an important aspect of the metabolic syndrome, may influence the risk of breast cancer and that HDL-C may be an important clinical marker of breast cancer risk that may be more pronounced in women with positive energy balance (i.e. high body mass index) *(2)*. Our study was based on 21 years of follow-up in 38,823 women from the Norwegian cohort *(14,15,21,23)* with repeated assessments of serum lipids, measured height and weight, diet and lifestyle factors.

METHODS

Participants

The women in our study participated in two population-based screening surveys during 1977–83 and 1985–87 in three counties of Norway (Finnmark, Oppland and Sogn og Fjordane), as part of the Norwegian National Health Screening Service's program to explore the association of lifestyle with chronic diseases. The screening procedures were almost identical in the two surveys *(24,25)*. In the 1977–83 survey, we invited all women aged 35–52 years in Finnmark, all women aged 40–54 years in Oppland and Sogn og Fjordane, and a random sample of women aged 20–39 years in all counties (17–39 years in Sogn og Fjordane) to participate. A total of 34,378 women received a mailed invitation and 31,209 (90.8%) attended. All attendees in the 1977–83 survey had a non-fasting blood sample drawn at the screening and 30,546 (88.8% of invited) samples satisfied the technical requirements for estimation of HDL-C.

In 1985–87 a similar survey including blood samples, was carried out in all three counties, but the HDL-C assay was run in samples from Oppland and Sogn og Fjordane only. In these two counties, all women who had been invited in the 1977–83 survey, all aged 40–54 years, and random samples aged 20–39 and 55–59 years were invited. Altogether 28,685

women were invited and 25,683 (89.5%) attended, while 25,397 (88.5%) had serum HDL-C estimated. In total, 16,028 of the women in Oppland and Sogn og Fjordane registered in both surveys and out of these 15,781 had serum HDL-C assessed twice. The majority of the women in our study participated in a similar survey 3–5 years prior to the 1977–83 survey but HDL-C was not assessed *(14,15)*.

Clinical parameters and laboratory procedures

Body weight was measured to the nearest half kilogram with participants dressed in lightweight clothing. Height was measured in centimeters. Body mass index (BMI, kg/m^2) was used to estimate relative weight.

The serum lipid analyses were conducted within 2 weeks after sampling by the Central Laboratory, Ullevål University Hospital, Oslo, except for the determination of HDL-C in samples from Finnmark in the 1977–83 survey (n = 7,729). These were assayed by the Institute of Medical Biology, University of Tromsø; the majority of these serum samples (n = 5,577; 72%) were kept frozen for 12 months until analysis. HDL-C was assayed enzymatically after precipitation of lipoprotein with density <1·063 by the addition of heparin and $MnCl_2$ according to the method of Burstein et al. *(26)*. An adjusted absolute mean difference of 0.12 mmol/l in HDL-C between the batches of fresh and frozen sera was added to the measured HDL-C levels obtained from frozen sera *(27)*. The concentration of total cholesterol and triglycerides was estimated *(24)*.

Lifestyle parameters and diet

The written invitation included a questionnaire on ethnicity, chronic diseases, smoking, alcohol (1985–87 survey only) and usual level of physical activity during the past year *(14,25)*. The same team of trained nurses conducted interviews with the participants at the screening in both surveys to confirm the information and to collect data on time since last meal, menopausal status, primary amenorrhoea, hysterectomy and use of oral contraceptives (OCs) and hormone therapy (HT). Hysterectomy and use of OCs and HT were collected only during the 1985–87 survey.

A food frequency questionnaire (FFQ) was distributed at the screening and returned via mail by 25,892 women (83%) in the 1977–83 survey and by 22,799 (89%) in the 1985–87 survey. The semi-quantitative FFQ, its reproducibility and validity and the method of estimating total energy intake have been described *(23,28)*. Information was considered insufficient in observations if estimated daily energy intake was less than 2,250 kJ or less than

two-thirds of selected questions was answered (1977–83: 5,764 women [20% of included] and 1985–87: 3,371 women [14% of included]); analyses involving energy and fat intake excluded these women.

Menopausal status

Information on menopausal status from both surveys was used in the calculation of pre- and postmenopausal years. A woman was considered to be premenopausal when she reported that menstrual bleeding had not ceased or until the age of 50 years *(14)*.

Follow-up and case identification

The participants were followed by their national 11-digit personal identification number to identify every incident case of breast cancer reported to the Cancer Registry of Norway through the end of follow-up (31 December 1998). Among the 30,546 participants with HDL-C in the 1977–83 survey, we excluded women with missing BMI, pregnancy, primary amenorrhoea (n = 820) or prevalent cancer (n = 439; Figure 1). To ensure that undiagnosed cancer or severe illness did not influence our estimates we included in the "1977–83 cohort" only the 29,199 women who were cancer free and alive one year after participation in the 1977–83 survey. Among women in the 1977–83 cohort, 15,175 women had HDL-C and study data in the 1985–87 survey and were included in the "repeat cohort". In addition, there were 9,953 women with HDL-C in the 1985–87 survey. Among these, 158 women were excluded due to improper data in the 1985–87 survey (BMI, menstrual characteristics) and 171 were excluded due to cancer or death within one year after participation in the survey. Thus, there was a "compound cohort" of 38,823 women who met the inclusion criteria in one or both surveys.

Through linkage to the Central Population Register at Statistics Norway, we obtained information on death, emigration and reproductive history through end of follow-up. The study was approved by the Norwegian Data Inspectorate and the Norwegian Board of Health permitted access to medical record files.

Statistical Analyses

To estimate the relative risks (RRs) for breast cancer associated with serum HDL-C and covariates we used Cox proportional hazard regression models. Women were categorized according to their serum HDL-C concentration and the quartiles for the total population in the 1977–83 survey were used for categorization (<1.20, 1.20 to 1.40, 1.41 to 1.64, >1.64

mmol/l). The 1977–83 data were adjusted for age and compared by analysis of covariance. RRs for pre- and postmenopausal breast cancer were estimated separately using the accumulated number of person-years in the pre- and postmenopausal periods *(14)*.

Variables included in the models as covariates represent plausible or potential risk factors for breast cancer: age, height, BMI, serum cholesterol, recreational physical activity (sedentary, walking 4 hours/week, sports), occupational physical activity (sedentary, walking, lifting/heavy manual work) and menopausal status (menopausal, not menopausal, uncertain) in both surveys and parity at the end of follow-up. Covariates considered but not included in the final models were age at first birth, serum triglycerides, blood pressure, time since last meal, total fat, saturated fat and polyunsaturated fat in diet, smoking status, current alcohol use, current OC use and current HT use. These had no influence on the RR estimates.

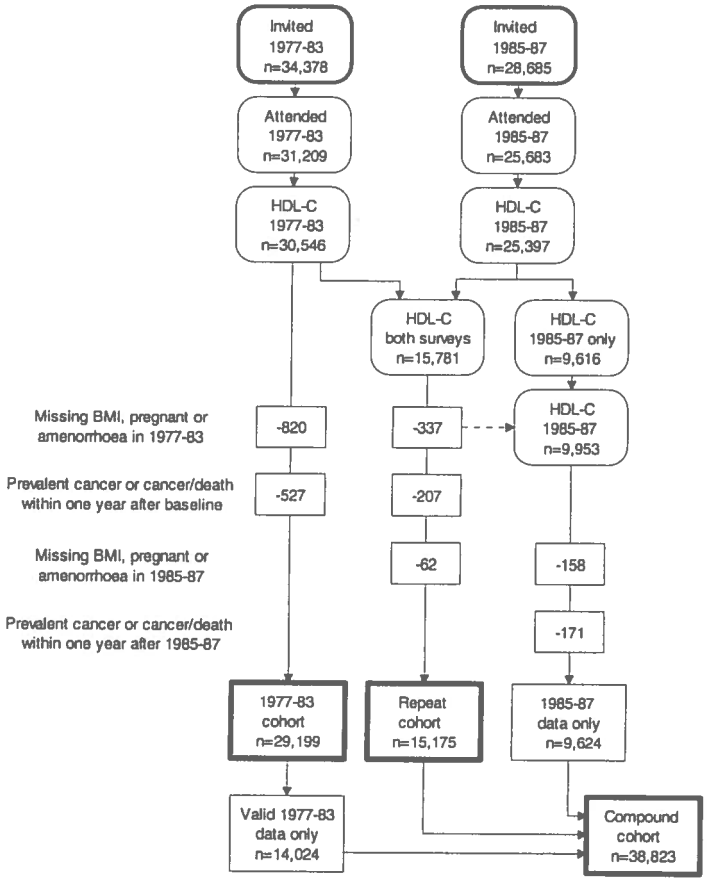

Figure 1. Creation of analytic cohorts. The Norwegian Cohort Study.

Tests for linear trend were performed by assigning consecutive integers to each quartile of serum HDL-C, and testing whether the slope coefficient differed from zero using the Wald chi-square test. Interaction effects were tested using a likelihood ratio test.

We performed separate analyses for subgroups defined by parity, height, BMI, recreational and occupational physical activity, energy intake and smoking to study potential effect modifiers. For BMI, we used quartiles based on the 1977–83 data: < 21.8, 21.8 to 23.7, 23.8 to 26.5, > 26.5 kg/m^2 and World Health Organization classification of adults by BMI: < 25 kg/m^2 = under/normal weight, ≥ 25 kg/m^2 = overweight/obese. All models included geographical region (county of residence) as a stratification variable.

In analyses of the "repeat" and the "compound" cohorts we used the Cox model with time-dependent covariates that were updated one year after the repeated (second) assessment.

We also used Cox models that expressed the hazards as a function of age and observed minimal alterations in the RRs. Thus we present the results of the analyses that used follow-up time as the scale of interest. All statistical tests were two-tailed and the level of statistical significance was set at 5%. The analyses were performed with SAS 8.02.

RESULTS

Among the 38,823 women in the "compound cohort", we observed 708 cases of incident breast cancer (200 premenopausal and 508 postmenopausal) during a median follow-up of 17.2 years (maximum = 21.8 years). Among the 29,199 women in the "1977–83 cohort", we observed 579 cases of incident breast cancer (135 premenopausal and 444 postmenopausal) during a median follow-up of 17.7 years.

Table 1 shows the characteristics among the women in the "1977–83 cohort" at entry. The age-adjusted mean HDL-C in the frozen sera from Finnmark was significantly higher than in the fresh sera. There was a tendency towards a lower BMI, a higher level of recreational physical activity and a lower rate of smoking with increasing level of serum HDL-C in the 1977–83 survey. In the 1985–87 survey, 7% of those asked (n = 9,606) confirmed use of HT.

In age-adjusted analyses of the 1977–83 data, height was positively, while parity and occupational activity were inversely related to the risk of both pre- and post-menopausal breast cancer. Among overweight and obese women (BMI ≥ 25 kg/m^2) the RR of premenopausal breast cancer was 0.67 (95% confidence interval [CI] = 0.45 to 1.01) as compared with underweight and normal weight women (BMI < 25 kg/m^2) and for

postmenopausal breast cancer the corresponding RR was 0.87 (95% CI = 0.72 to 1.06). The risk of postmenopausal breast cancer was lowered by childbirth at young ages and by an increase in total serum cholesterol (results not shown).

Table 1. Age-adjusted means (standard deviation) and proportions of characteristics among all women and women in each quartile of serum HDL-cholesterol in the 1977–83 survey. The Norwegian Cohort Study

	Total population	Quartiles of serum HDL-cholesterol (mmol/l)			
	n=29,199[1]	≤ 1.20 n=6,994[1]	1.20–1.40 n=7,264[1]	1.41–1.64 n=7,387[1]	> 1.64 n=7,554[1]
Age (years)	43.6 (8.1)	43.5 (8.4)	43.2 (8.3)	43.5 (8.0)	44.0 (7.6)
Reproductive history					
Parity[2]	2.6 (1.6)	2.7 (1.6)	2.6 (1.6)	2.6 (1.5)	2.6 (1.6)
Age at first birth (years)	23.1 (7.7)	22.7 (8.0)	22.9 (8.0)	23.2 (7.6)	23.5 (7.1)
Clinical parameters					
Height (cm)	163 (6)	163 (6)	163 (6)	163 (6)	163 (6)
Body mass index (BMI) (kg/m^2)	24.6 (4.1)	26.0 (4.8)	24.8 (4.2)	24.2 (3.8)	23.6 (3.3)
Diastolic blood pressure (mmHg)	82 (11)	83 (11)	82 (11)	81 (10)	81 (10)
Systolic blood pressure (mmHg)	130 (18)	132 (19)	130 (18)	129 (18)	130 (18)
Serum lipids (mmol/l)					
Triglycerides	1.41 (0.81)	1.95 (1.06)	1.43 (0.68)	1.24 (0.59)	1.05 (0.51)
Cholesterol	6.10 (1.23)	6.06 (1.31)	6.01 (1.24)	6.07 (1.19)	6.25 (1.17)
HDL-cholesterol	1.45 (0.35)	1.04 (0.12)	1.30 (0.06)	1.52 (0.07)	1.90 (0.26)
Fresh sera	1.43 (0.34)				
Sera frozen for 1 year	1.52 (0.36)				
Dietary factors					
Energy (10^3kJ/day)	5.5 (1.6)	5.4 (1.6)	5.5 (1.6)	5.6 (1.6)	5.6 (1.6)
Fat (g/day)	55 (20)	54 (20)	55 (20)	56 (20)	56 (20)
Saturated fat (g/day)	24 (9)	18 (9)	18 (9)	19 (10)	19 (10)
Monounsaturated fat (g/day)	18 (7)	23 (7)	24 (7)	24 (7)	24 (7)
Lifestyle habits (%)					
Physically active in leisure time	82.8	79.4	83.1	83.9	84.6
Physically active at work	85.1	85.1	85.0	84.9	85.5
Daily smoking	36.4	44.2	37.8	34.3	30.1
Disease history (%)					
Self-reported hypertension	5.8	9.2	6.2	4.7	3.4
Self-reported diabetes	0.6	0.8	0.4	0.4	0.8

[1]Number may vary due to missing.
[2]Parity throughout follow-up.

We observed no association between quartiles of serum HDL-C in the "1977–83 cohort" and the incidence of breast cancer during the premenopausal years (mean follow-up = 9.1 years) (Table 2). In contrast, we observed a significant trend of decreasing risk of postmenopausal breast cancer with increasing level of HDL-C (mean follow-up = 12.9 years). The risk of postmenopausal breast cancer was reduced by about 30% in women with HDL-C above 1.64 mmol/l as compared with women with HDL-C below 1.20 mmol/l (Table 2). In an analysis including fresh sera only, similar results were observed (results not shown).

Table 2. Adjusted relative risks (RRs) of premenopausal and postmenopausal breast cancer in relation to serum[1] HDL-cholesterol (HDL-C) in the 1977–83 survey and in the 1985–87 survey. The Norwegian Cohort Study

		Premenopausal				Postmenopausal			
HDL-C (mmol/l)		Cases	RR	(95% CI)[2]	RR (95% CI)[3]	Cases	RR	(95% CI)[2]	RR (95% CI)[3]
1977–83	< 1.20	23	1.00		1.00	128	1.00		1.00
cohort	1.20–1.40	39	1.56	(0.93, 2.62)	1.49 (0.88, 2.50)	103	0.76	(0.59, 0.99)	0.77 (0.59, 1.00)
	1.41–1.64	35	1.39	(0.82, 2.36)	1.32 (0.77, 2.25)	107	0.74	(0.58, 0.96)	0.76 (0.59, 0.99)
	> 1.64	38	1.54	(0.92, 2.58)	1.43 (0.83, 2.46)	106	0.68	(0.53, 0.88)	0.73 (0.55, 0.95)
	P for trend		0.19		0.33		0.005		0.03
Compound	< 1.20	25	1.00		1.00	109	1.00		1.00
cohort	1.20–1.40	43	1.20	(0.73, 1.96)	1.14 (0.69, 1.87)	122	0.90	(0.70, 1.17)	0.89 (0.69, 1.34)
(1977–83	1.41–1.64	56	1.33	(0.83, 2.13)	1.24 (0.77, 2.01)	132	0.84	(0.65, 1.08)	0.82 (0.64, 1.08)
+ 1985–87)	> 1.64	76	1.60	(1.02, 2.52)	1.46 (0.91, 2.32)	145	0.76	(0.59, 0.98)	0.75 (0.58, 0.97)
	P for trend		0.03		0.08		0.03		0.01

[1]Fresh and frozen samples.
[2]Adjusted for age.
[3]Adjusted for age, menopausal status, county, parity, height, body mass index, total serum cholesterol, recreational and occupational activity. Also considered blood pressure, age at first birth, time since last meal, smoking, dietary energy and fat intake in both surveys and oral contraceptives, hormone therapy (for postmenopausal cancer) and alcohol use in the 1985–87 survey.
Subjects for whom information concerning certain variables was missing are not included. CI denotes confidence interval.

In analyses of the "compound cohort" using time-dependent covariates, we observed a modest positive association between HDL-C and the risk of premenopausal breast cancer, while the negative association with postmenopausal breast cancer observed in the 1977–83 data was confirmed (Table 2). The results were not altered in analyses confined to women with HDL-C assayed in fresh sera in both surveys (results not shown).

When we divided the population into underweight or normal weight (BMI < 25 kg/m^2) and overweight or obese (BMI ≥ 25 kg/m^2) women, we observed no significant relationship between HDL-C (all sera or fresh batch separately) and premenopausal breast cancer in an analysis of the "1977–83 cohort" or of the "compound cohort" (Table 3).

In contrast, the observed association between HDL-C and the risk of postmenopausal cancer in the "1977–83 cohort" was confined to the overweight women and in this subgroup, relative to women in the reference group (fresh sera, HDL-C < 1.20 mmol/l), risk was reduced by 40% in women with HDL-C from 1.20 to 1.40 mmol/l (RR = 0.60; 95% CI = 0.40 to 0.89), by 50% in women with HDL-C from 1.41 to 1.64 mmol/l (RR = 0.50; 95% CI = 0.32 to 0.78), and by 66% in women with HDL-C above 1.64 mmol/l (RR = 0.34; 95% CI = 0.19 to 0.59, $P_{trend} < .001$) (Table 4). Among overweight women in the "compound cohort", the highest *vs.* the lowest HDL-C level was associated with a 57% decrease in risk in an analysis restricted to women with HDL-C assayed in fresh sera (RR = 0.43; 95% CI = 0.28 to 0.67; $P_{trend} < .001$) (Table 4). There was significant interaction between the dichotomized BMI variable (cut-off, 25 kg/m^2) and quartiles of serum HDL-C in both the "1977–83" and the "compound cohort" ($P_{interaction} = .006$ and $P_{interaction} = .001$, respectively). The association was not distorted in an

analysis adjusted for BMI (continuous term); when observations from the frozen batch were added, the association was slightly weakened (results not shown).

Table 3. Adjusted relative risks (RRs) of premenopausal breast cancer in relation to serum[1] HDL-cholesterol (HDL-C) and body mass index (BMI) in the 1977–83 survey and in the 1985–87 survey. The Norwegian cohort study

		BMI < 25kg/m²				BMI ≥ 25kg/m²				*P* for
HDL-C (mmol/l)		Cases	RR (95% CI)[2]	RR (95% CI)[3]		Cases	RR (95% CI)[2]	RR (95% CI)[3]		interaction[4]
	< 1.20	12	1.00	1.00		11	1.00	1.00		
	1.20–1.40	31	1.99 (1.02, 3.87)	1.99 (1.02, 3.88)		8	0.92 (0.37, 2.29)	0.91 (0.36, 2.27)		
1977–83	1.41–1.64	26	1.51 (0.76, 3.00)	1.52 (0.77, 3.04)	}	12	0.94 (0.42, 2.14)	0.99 (0.43, 2.28)		
cohort	> 1.64	35	1.92 (1.00, 3.70)	1.99 (1.02, 3.88)						
	P for trend		0.17	0.14			0.89	0.98		0.24
Compound	< 1.20	13	1.00	1.00		12	1.00	1.00		
cohort	1.20–1.40	32	1.42 (0.74, 2.70)	1.40 (0.74, 2.67)		11	0.83 (0.37, 1.89)	0.82 (0.36, 1.86)		
(1977–83	1.41–1.64	43	1.45 (0.78, 2.70)	1.45 (0.78, 2.69)		13	1.06 (0.48, 2.33)	1.06 (0.48, 2.34)		
+ 1985–87)	> 1.64	63	1.70 (0.93, 3.11)	1.66 (0.91, 3.04)		13	1.20 (0.55, 2.66)	1.27 (0.57, 2.81)		
	P for trend		0.09	0.11			0.53	0.45		0.76

[1]Fresh and frozen samples.
[2]Adjusted for age.
[3]Adjusted for age, menopausal status, county, parity, height, total serum cholesterol, recreational and occupational activity. Also considered blood pressure, BMI (continuous scale), age at first birth, time since last meal, smoking, dietary energy and fat intake in both surveys, and oral contraceptives and alcohol use in the 1985–87 survey.
[4]Multivariate model.
Subjects for whom information concerning certain variables was missing are not included. CI denotes confidence interval.

Table 4. Adjusted relative risks (RRs) of postmenopausal breast cancer in relation to serum[1] HDL-cholesterol (HDL-C) and body mass index (BMI) in the 1977–83 survey and in the 1985–87 survey. The Norwegian Cohort Study

			BMI < 25kg/m²			BMI ≥ 25kg/m²				*P* for
HDL-C (mmol/l)		Cases	RR (95% CI)[2]	RR (95% CI)[3]		Cases	RR (95% CI)[2]	RR (95% CI)[3]		interaction[4]
1977–83	< 1.20	41	1.00	1.00		74	1.00	1.00		
cohort	1.20–1.40	50	0.96 (0.63, 1.44)	1.01 (0.67, 1.53)		38	0.63 (0.42, 0.93)	0.60 (0.40, 0.89)		
	1.41–1.64	62	1.01 (0.68, 1.51)	1.07 (0.72, 1.60)		27	0.50 (0.32, 0.78)	0.50 (0.32, 0.78)		
	> 1.64	71	1.03 (0.70, 1.51)	1.17 (0.78, 1.74)		16	0.36 (0.21, 0.62)	0.34 (0.19, 0.59)		
	P for trend		0.80	0.39			<0.001	<0.001		0.006
Compound	< 1.20	26	1.00	1.00		70	1.00	1.00		
cohort	1.20–1.40	50	1.25 (0.78, 2.01)	1.27 (0.79, 2.06)		57	0.79 (0.55, 1.11)	0.76 (0.54, 1.08)		
(1977–83	1.41–1.64	75	1.39 (0.89, 2.18)	1.39 (0.89, 2.20)		39	0.55 (0.37, 0.81)	0.55 (0.37, 0.81)		
+ 1985–87)	> 1.64	98	1.31 (0.85, 2.02)	1.33 (0.86, 2.08)		28	0.43 (0.28, 0.67)	0.43 (0.28, 0.67)		
	P for trend		0.28	0.27			<0.001	<0.001		0.001

[1]Fresh samples.
[2]Adjusted for age.
[3]Adjusted for age, menopausal status, county, parity, height, total serum cholesterol, recreational and occupational activity. Also considered blood pressure, BMI (continuous scale), age at first birth, time since last meal, smoking, dietary energy and fat intake in both surveys, and oral contraceptives, hormone therapy and alcohol use in the 1985–87 survey.
[4]Multivariate model.
Subjects for whom information concerning certain variables was missing are not included. CI denotes confidence interval.

We also performed analyses of the association between HDL-C and the risk of breast cancer in subgroups defined by other BMI criteria (i.e. quartiles, BMI ≥ 30 kg/m^2) without finding other BMI thresholds for an interaction or stronger associations than those reported among overweight and obese postmenopausal women (results not shown).

The association between HDL-C and postmenopausal breast cancer among overweight and obese women was relatively robust across strata of potential effect modifiers; parity (0, 1 to 2, ≥ 3 live born children), height (< 163, 163 to 166, > 166 cm), energy intake (< 4,390, 4,390 to 5,195, > 5,195 kJ/day), recreational physical activity (sedentary, walking 4 hours/week, sports), occupational physical activity (sedentary, walking, lifting/heavy manual work) and smoking history (never, former, current) (Figure 2).

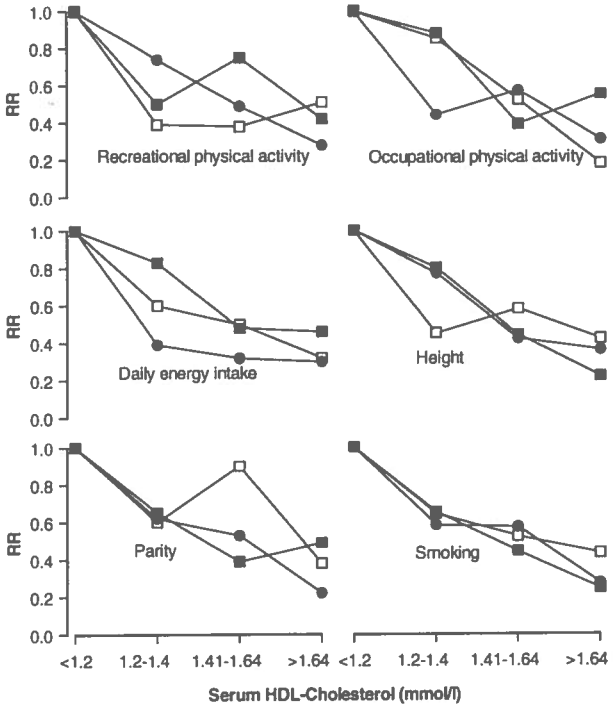

Figure 2. Age-adjusted relative risk (RR) of postmenopausal breast cancer among overweight and obese women (body mass index ≥ 25kg/m^2) by serum HDL-cholesterol level and categories of;
Recreational physical activity: □ = Sedentary, • = Walking, ■ = Sports.
Occupational physical activity: □ = Sedentary, • = Walking, ■ = Lifting/heavy manual work.
Daily energy intake: □ = < 4,390 kJ/day, • = 4,390–5,195 kJ/day, ■ = > 5,195 kJ/day.
Height: □ = < 163 cm, • = 163–166 cm, ■ = > 166 cm.
Parity: □ = Nullipara, • = 1–2 children, ■ = ≥ 3 live born children.
Smoking: □ = Never smoker, • = Former smoker, ■ = Current smoker.
Data in the 1977–83 survey and parity throughout follow-up. The Norwegian Cohort Study.

In the analysis restricted to women with HDL-C assessed in both surveys, the "repeat cohort" (n = 15,175; mean time between surveys = 5.1 years; range = 3.6 to 10.8 years), we observed associations with postmenopausal breast cancer similar to the results for the 1977–83 assessment only; HDL-C in the highest category *vs.* in the lowest category was associated with a 35% decrease in risk among all women (RR = 0.65; 95% CI = 0.43 to 0.99; P_{trend} = .03) and a 68% decrease in risk among overweight and obese women (RR = 0.32; 95% CI = 0.15 to 0.69; P_{trend} < .001; $P_{interaction}$ = .01).

To determine if recent alterations in metabolic risk profile influence the relationship between HDL-C and postmenopausal breast cancer risk we divided the women who participated in both surveys and were observed in their postmenopausal years (n = 13,607) according to whether they had a change in weight below or above the median weight change between surveys of 1.5 kg. Among women with weight gain below 1.5 kg, no association between HDL-C and risk of postmenopausal breast cancer was observed (95 cases). In contrast, among women with greater weight gain, we observed an inverse association between HDL-C and breast cancer risk (107 cases; Figure 3). Women in the category of HDL-C above 1.64 mmol/l had a 52% reduction in risk compared to those with HDL-C below 1.20 mmol/l (RR = 0.48; 95% CI = 0.28 to 0.85; P_{trend} = .01). However, a formal test of interaction was not statistically significant ($P_{interaction}$ = .98).

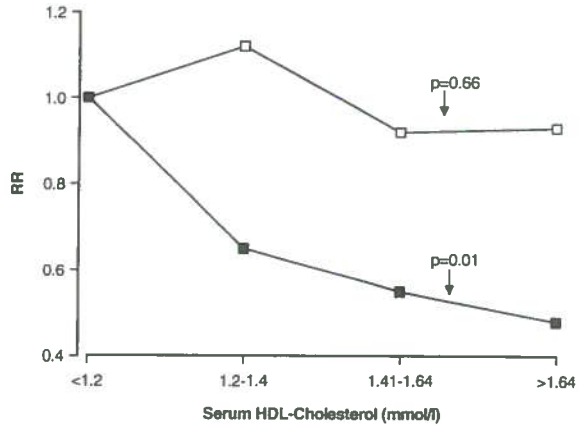

Figure 3. Adjusted relative risk (RR) of postmenopausal breast cancer by serum HDL-cholesterol level and change in weight between the 1977–83 survey and the 1985–87 survey; □ = < 1.5 kg, ■ = ≥ 1.5 kg change in weight between the surveys. The p values refer to test for linear trend. Adjusted for age, menopausal status, county, parity, height, body mass index, total serum cholesterol, recreational and occupational activity. The Norwegian Cohort Study.

In analysis of the total 1977–83 cohort, the association between total serum cholesterol and the risk of postmenopausal breast cancer was similar to the association observed for HDL-C with a 37% reduction in risk in women with total cholesterol above 6.82 mmol/l (highest quartile) *vs.* below 5.24 mmol/l (lowest quartile) (age-adjusted RR = 0.63; 95% CI = 0.48 to 0.82, P_{trend} = .005). However, the association between total serum cholesterol and the risk of postmenopausal breast cancer was absent in overweight and obese women and a test of interaction was not statistically significant ($P_{interaction}$ = 0.13)

DISCUSSION

Our study provides evidence that low serum HDL-C is an independent biomarker of increased postmenopausal breast cancer risk, particularly among women with positive energy balance (i.e. overweight/obese). We found that risk among overweight and obese women in the highest HDL-C quartile was one-third the risk of women in the lowest HDL-C quartile. The relationship between HDL-C and the risk of postmenopausal breast cancer was strongest among those who gained weight during follow-up independently of BMI in surveys. These findings suggest a synergism between metabolic disturbances (i.e. overweight/obesity and dyslipidemia) in postmenopausal breast carcinogenesis.

The 30% overall reduction in the risk of postmenopausal breast cancer among the women with the highest serum HDL-C levels in our study is in agreement with an expected reduction in the risk of postmenopausal breast cancer among women with a relative androgen deficit, as serum HDL-C may be a marker of androgen status in our study. After menopause, bioavailable estrogens formed in adipose tissue by the aromatisation of androgens is a major stimulus for breast carcinogensis *(29)*. Androgens are also the key modulators of serum lipid levels and in particular, of HDL-C levels *(10)*.

The modification by BMI of the relationship between HDL-C and postmenopausal breast cancer in our data may reflect a synergistic action of insulin, IGF-I and sex steroids in breast carcinogenesis among women with positive energy balance. Overweight or obesity, are major determinants of insulin resistance with increased insulin, IGF-I and free fraction of androgens *(30)* and both experimental and epidemiological studies support that these hormonal changes all have independent effects on breast cancer development *(4–6,13,31–33)*.

The suggested positive association between serum HDL-C and the risk of premenopausal breast cancer in our study is biologically plausible as low HDL-C may be a marker of decreased exposure to the female sex-steroids in premenopausal women and a

decreased risk of breast cancer in young ages. Low HDL-C is generally associated with decreased insulin sensitivity and hyperinsulinemia *(34)*. It has been observed that an up-regulated androgen production by insulin and IGF-I in the ovaries often coexists with subnormal production of estradiol and progesterone *(30)*. Our results support that the tumour promoting action of HDL-C observed in cell cultures *(7–9)* may not have an equivalent impact in vivo.

Our finding of an increased risk of postmenopausal breast among women with the lowest HDL-C is in agreement with a small (51 cases) Danish prospective study *(20)* which reported a RR of breast cancer of 0.3 for women in the highest quartile of HDL-C compared with the lowest quartile. However, in a nested case-control study *(22)*, a positive association between HDL-C in serum stored for more than 20 years and postmenopausal breast cancer risk and an inverse association for premenopausal breast cancer risk were observed. There was substantial degradation of the HDL-C during storage *(22)* and analyses were not stratified by BMI.

A prior report from a portion of our cohort with follow-up of women through 31 December 1990 *(21)*, showed no association between HDL-C and breast cancer risk overall or among postmenopausal women. One explanation may be that an increase in the prevalence of overweight and obesity among women in Norway mostly developed after 1990 *(35)*. Further, we have a longer follow-up period with increase in number of postmenopausal women, performed separate analyses of pre- and postmenopausal breast cancer using the accumulated number of person-years in each period *(14)*, excluded the frozen batch, used repeated measurements of HDL-C and covariates, and conducted stratum specific analyses among women with the least favourable metabolic profile (i.e. those who were overweight or obese).

Our findings are supported by observations of lower levels of HDL-C among postmenopausal breast cancer patients in retrospective studies *(16–19)*, but a lipid-lowering effect of the cancer itself may have influenced these results. Furthermore, in agreement with our prospective data, a tendency towards higher levels of HDL-C among premenopausal cases presenting a low BMI has been reported *(36)*.

As expected, we did not observe the same strong risk patterns for postmenopausal breast cancer associated with total serum cholesterol as with HDL-C which is highly influenced by androgen levels and has been recognized as a marker of metabolic status. This underlines the hypothesis about the biological mechanisms underlying the observed associations between HDL-C and postmenopausal breast cancer risk.

Assessments (blood draws and height and weight measurement) were conducted by the same team of trained nurses and during the same season in both surveys. We used consistent methods in both surveys within the same laboratory to obtain HDL-C levels in fresh sera *(24)*. The population-based approach, the high participation rate and the high rate of fresh serum HDL-C assessment in the surveys reduced selection and measurement bias. The high quality of the cancer registry data strengthens our results *(37)*. In our study all analyses were adjusted for major confounders and stratified analyses were conducted.

Information on exact age at menopause was not available and the definition of menopause at the age of 50 years may have biased our estimates. Estrogens increase HDL-C and more frequent use of HT among lean women has been observed *(38)*. Nevertheless, HT use in the 1985–87 survey did not influence our results and Norwegian women were restrictive in their use of HT until the 1990s *(38)*. It is unlikely that HT use is a significant effect modifier in our study as the prescription rates in Norway started to increase in the early 1990s and in our cohort, younger women were more likely to be users (1985–87 survey; mean age [standard deviation] = 49.5 [4.8] years and 51.4 [4.4] years among users and non-users, respectively). Furthermore, in Norway, HT has primarily been recommended to climacteric women and prophylactic use among the elderly has been limited *(38)*.

In conclusion, our study demonstrates that low serum HDL-C is an independent predictor of increased postmenopausal breast cancer risk, particularly among overweight and obese women. As low HDL-C is related to increased levels of several cancer promoting hormones (i.e. androgens, estrogens, insulin, IGF-I) the observed association may reflect the relative importance and mutual dependence of different disease pathways in malignant breast tumours after the menopause. Thus, HDL-C is a potential marker of postmenopausal breast cancer risk that could provide a means for identifying women at higher risk who may be candidates for intervention in the future.

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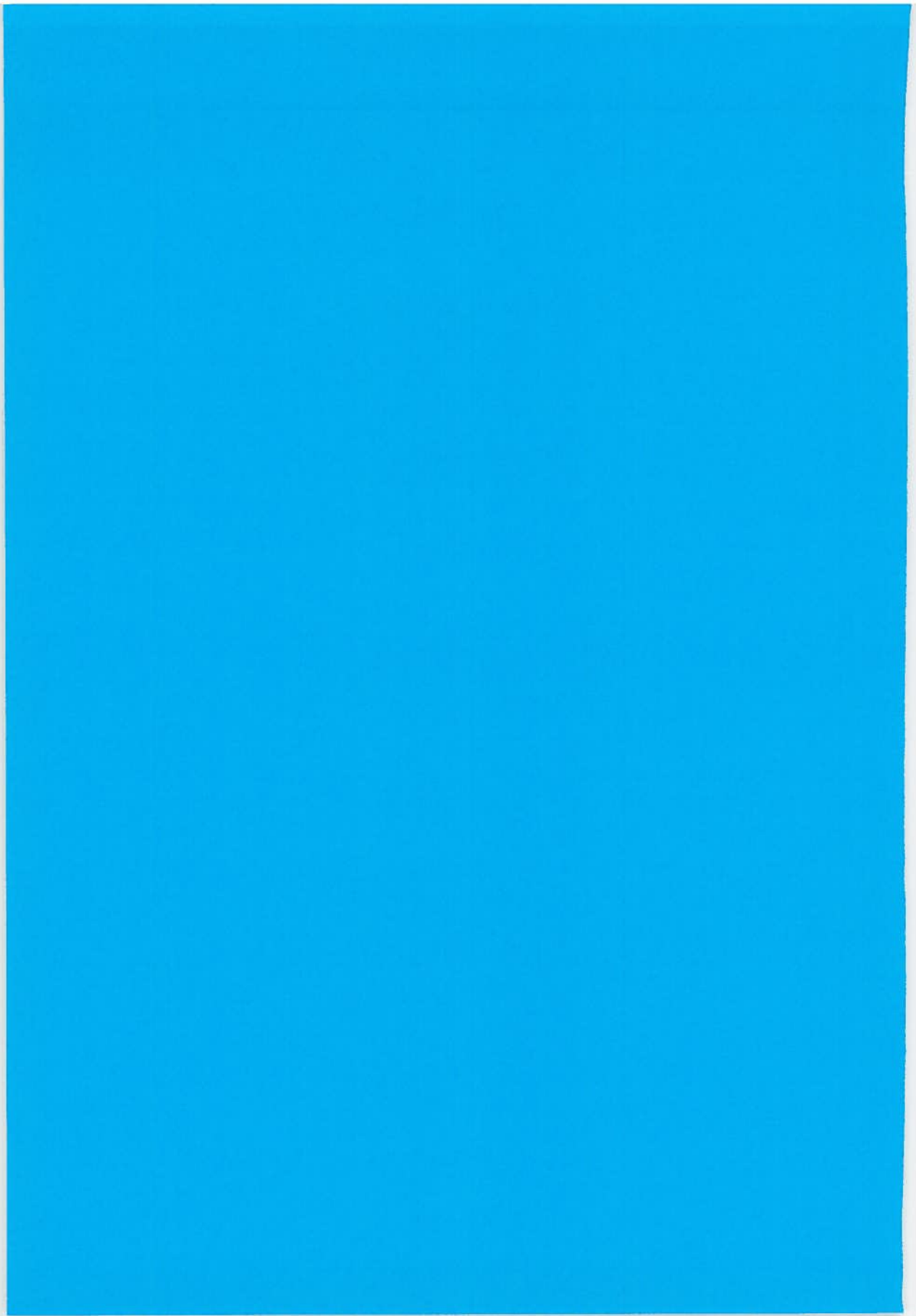
Appendix A

Questionnaire used in Vestvågøy, November 1997

English translation
Original questionnaire

Paper I



DIET AND PESTICIDES

English translation; Mrs. Anne Clancy

INSTRUCTIONS FOR FILLING IN THE QUESTIONNAIRE

We would like to know how your diet normally is. Give an average for the past year on how often you have used a particular foodstuff. Tick off for each question. Tick off in the appropriate box for foodstuffs you seldom or never use. Regarding foodstuffs you use, state also the amount you normally eat /drink each time.

If none of the given alternatives are relevant in your case, tick off for the most appropriate alternative.

Hormone-like substances are fat-soluble. For this reason we focus on intake of fish, meat and dairy produce in this dietary survey.

We request that you fill in the questionnaire as accurately as possible.

We would like to know how often you normally eat fish, and request that you answer the questions on fish consumption as accurately as possible.

The availability of fish can vary throughout the year. Please specify which particular season you eat the various types of fish.

	Seldom/Never	The same amount throughout the year	Winter	Spring	Summer	Autumn
Cod, coalfish, haddock, pollack						
Wolffish, flounder, Norway haddock						
Salmon, trout						
Mackerel						
Herring						

Regarding the period of the year that you eat fish, how often do you eat the following? (tick off once on each line)

	Seldom/ never	1 per mth.	2-3 per mth.	1 per wk.	2 per wk.	3 per wk	4+ per wk
Fresh cod, coalfish, haddock, pollack							
Frozen fillet of cod, coalfish							
Farmed salmon							
Farmed trout							
Wild salmon							
Wild trout							
Norway pollack							
Norway pollack fish heads							
Herring							
Wolffish							
Flounder							
Halibut							
Mackerel							
Cod roe							

If you eat fish, how many pieces do you normally eat each time? (1 piece = 150 grams) (Tick off once)

☐ 1 ☐ 2 ☐ 3 ☐ 4+

Did you eat fish for dinner yesterday? ☐ Yes ☐ No

How many fish dinners have you had in the last week? Number……..

How often do you eat the following fish products?
(Tick off once on each line)

	Seldom/ never	1 per mth.	2-3 per mth.	1 per wk.	2 per wk.	3 + per wk
Fish cakes, fish pudding						
Fish balls						
Flaked fish in white sauce, fish pie						
Fish in batter, fish fingers						
Fish soup						
Other fish dishes						

How many times a year do you eat "mølje"?
(Cod mølje comprises cod cutlets, cod liver and cod roe. Pollack "mølje" comprises pollack cutlets and pollack liver.) (Tick off once)

☐ 0 ☐ 1-3 ☐ 4-5 ☐ 6-8 ☐ 9-12 ☐ 13+

How many times a year do you eat fish liver other than in "mølje"? (Tick off once)

☐ 0 ☐ 1-3 ☐ 4-5 ☐ 6-8 ☐ 9-12 ☐ 13+

If you do eat fish liver, how many tablespoons do you normally eat each time? (Tick off once)

☐ 1 ☐ 2 ☐ 3-4 ☐ 5-6 ☐ 7+

How many seagulls' eggs do you eat yearly? (Tick off once)

☐ 0 ☐ 1-3 ☐ 4-5 ☐ 6-8 ☐ 9-12 ☐ 13+

How many times a year do you eat the following seafood products?
(Tick off once on each line)

	0	1-3	4-5	6-8	9-12	13+
Shrimps						
Crab						
Whale meat						
Seal meat						

How many times a year do you eat the following dishes?
(Tick off once for each dish)

	Seldom/ never	1 per mth.	2-3 per mth.	1 per wk.	2 per wk.	3 + per wk
Roast beef, pork or lamb						
Chops						
Steak						
Meat balls, hamburgers						
Sausages						
Frankfurters						
Casseroles, stews						
Pizza with meat topping						
Chicken						
Liver						
Reindeer meat in thin slices						
Game						
Other meat dishes						

If you eat a roast or chops, how much do you normally eat?
(Tick off once on each line)

Roast (slices) ☐ 1-2 ☐ 3-4 ☐ 5-6 ☐ 7+

Chops (no.) ☐ 1/2 ☐ 1 ☐ 1 ½ ☐ 2+

If you eat the following dishes, please specify the amount that you normally eat.
(Tick off once on each line)

- meat balls, hamburgers (no.) ☐ 1 ☐ 2 ☐ 3 ☐ 4+
- sausages (no.) ☐ 1 ☐ 2 ☐ 3+
- frankfurters (no.) ☐ 1 ☐ 2 ☐ 3 ☐ 4+
- casserole, stew (dl.) ☐ 1-2 ☐ 3-4 ☐ 5-6 ☐ 7+
- pizza with meat topping (1slice = 150 grams) ☐ 1 ☐ 2 ☐ 3 ☐ 4+

How many eggs do you normally eat weekly?
(fried, boiled, scrambled, omelette) (tick off once)

☐ 0 ☐ 1 ☐ 2 ☐ 3-4 ☐ 5-6 ☐ 7+

The following questions are about the use of different types of sandwich fillings and spreads. We ask about how many slices of bread you use with the below mentioned spreads and sandwich fillings. If you use these foodstuffs in other ways than with bread (with waffles, breakfast cereals, porridge) please take this into account when you answer the questions.

On how many slices of bread do you use the following?
(Tick off once on each line)

	0 per week	1-3 per week	4-6 week	1 per day	2-3 per day	4-5 per day	6 per day
Brown cheese, full fat							
Brown cheese, reduced fat							
Gouda, full fat							
Gouda, reduced fat							
Cheese spread							
Other full fat cheeses							
Cold meats							
Liver pâté							

The next questions refer to fish spreads and sandwich fillings.
During the past year, on how many slices of bread a week have you used the following?
(Tick off once on each line)

	0 per week	1per week	2-3 per week	4-6 per week	7-9 per week	10-14 per week	15+ per week
Mackerel in tomato sauce, smoked mackerel							
Sardines in oil or tomato							
Marinated herring, herring salad							
Caviar							
Tuna fish							
Salmon, smoked or marinated							
Other fish spreads or sandwich fillings							

Do you drink milk? Yes ☐ No ☐

If yes, tick off for how many glasses of the different types of milk you normally use?
(Tick off once on each line)

	Seldom/ Never	1-4 per week	5-6 per week	1 per day	2-3 per day	4 + per day
Full cream milk (ordinary type or curdled)	☐	☐	☐	☐	☐	☐
Light milk (ordinary type or curdled)	☐	☐	☐	☐	☐	☐
Skimmed milk (ordinary type or curdled)	☐	☐	☐	☐	☐	☐

How often do you eat yoghurt (1 pot)? (Tick off once)

☐ seldom or never ☐ 1-3 per mth. ☐ 1 per wk. ☐ 2-3 per wk.
☐ 4-5 per wk. ☐ 6-7 per wk. ☐ 8+ per wk.

How often do you eat rice porridge? (Tick off once)

☐ seldom/never ☐ 1 per mth. ☐ 2-3 per mth. ☐1+ per wk.

How often do you eat ice cream (for dessert, ice cream cone etc.)?
(Tick off once for how often you eat ice cream during the summer. Tick off once for the rest of the year.)

	seldom/ never	1-3 per month	1 per week	2-3 per week	4-5 per week	6+ per week
- during the summer	☐	☐	☐	☐	☐	☐
- the rest of the year	☐	☐	☐	☐	☐	☐

How much ice cream do you normally eat each time? (Tick off once)

☐1 dl. ☐2 dl. ☐3 dl. ☐ 4+ dl

How often do you eat cream cakes or desserts made with cream?
(cream cake, creamed rice, fromage, cloudberries in whipped cream)

☐ seldom/never ☐ 1-2 per mth. ☐ 3 per mth. ☐ 1 per wk. ☐ 2+ per wk.

How often do you eat chocolate? (Tick off once)

☐ seldom/never ☐ 1-3 per mth. ☐1 per wk.
☐ 2-3 per wk. ☐ 4-6 per wk. ☐ 1 +per day

If you eat chocolate, how much do you normally eat each time? Imagine the size of a Kit Kat bar and use that as a reference when you answer.

☐ 1/4 ☐ 1/2 ☐ 3/4 ☐ 1 ☐1,5 ☐ 2+

How often do you eat biscuits?
(Tick off once)

☐ seldom/never ☐ 1-3 per mth. ☐ 1 per wk.
☐ 2-3 per wk. ☐ 4-6 per wk. ☐ 1 + per day

If you eat biscuits, how many do you eat each time?

☐1 ☐ 2 ☐ 3-4 ☐ 5-6 ☐ 7+

Dietary supplements

How often do you take the following dietary supplements?
Regarding cod liver oil and cod liver oil capsules, please tick off once for the winter and once for the rest of the year; even if you use the supplement just as frequently throughout the year.

	Seldom/ never	1-3 per mth	1 per wk.	2-3 per wk.	4-6 per wk.	daily
Cod liver oil						
- during the winter	☐	☐	☐	☐	☐	☐
- the rest of the year	☐	☐	☐	☐	☐	☐
Cod liver oil capsules						
- during the winter	☐	☐	☐	☐	☐	☐
- the rest of the year	☐	☐	☐	☐	☐	☐
Fish oil capsules	☐	☐	☐	☐	☐	☐

If you take cod liver oil, how much do you take each time?

☐ 1 teaspoon ☐ ½ tablespoon ☐ 1+ tablespoon

To what extent do you think that your lifestyle influences your health?

☐ has little or no effect ☐ some effect ☐ a good deal ☐ a great deal

Pregnancy, birth and breastfeeding

Are you pregnant?
☐ Yes ☐ No

If yes, how many months pregnant are you? .....mths.

Are you breastfeeding at the moment?
☐ Yes ☐ No

Fill in information on year of birth and number of months the child was breastfed, including children who died. Please include year of birth for stillborn babies.

Child	Year of birth	Number of months breastfed
1		
2		
3		
4		
5		
6		

Personal information

Age……years Height……cm. Weight……..kg

Profession……..

Community of residence……

How long have you lived in the community?……years

In which community were you born?……..

Thank you for your help!

KOSTHOLD OG PLANTEVERNMIDLER

OM UTFYLLING AV SKJEMAET

Vi er interessert i å få kjennskap til hvordan kostholdet ditt er **vanligvis.** Kryss av for hvert spørsmål om hvor ofte du **i gjennomsnitt siste året** har brukt den aktuelle matvaren. Kryss av for matvarer du aldri eller sjelden bruker. For de matvarene du bruker, angi også hvor mye du pleier spise/drikke hver gang.

Dersom ingen av de oppgitte svaralternativene dekker din situasjon, sett kryss for det alternativet som ligger nærmest.

De hormonliknende stoffene er fettløselige. Derfor vektlegges inntak av fisk-, kjøtt- og melkeprodukter i kostholdsundersøkelsen.

Vi ber deg fylle ut skjemaet så nøye som mulig.

Vi vil gjerne vite hvor ofte du pleier å spise fisk, og ber deg fylle ut spørsmålene om fiskeforbruk så godt du kan.

Tilgangen på fisk kan variere gjennom året. Vær vennlig å markere i hvilke årstider du spiser de ulike fiskeslagene.

	aldri/ sjelden	like mye hele året	vinter	vår	sommer	høst
Torsk, sei, hyse, lyr						
Steinbit, flyndre, uer						
Laks, ørret						
Makrell						
Sild						

Med tanke på de periodene av året der du spiser fisk, hvor ofte pleier du spise følgende? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd	2-3 pr. mnd	1 pr. uke	2 pr. uke	3 pr. uke	4+ pr. uke
Fersk torsk, sei, hyse, lyr							
Frossen filet av torsk, sei							
Oppdrettslaks							
Oppdrettsrøye							
Villaks							
Villrøye							
Uer							
Uerhoder							
Sild							
Steinbit							
Flyndre							
Kvelte							
Makrell							
Torskerogn							

Dersom du spiser fisk, hvor mange stykker/skiver spiser du vanligvis pr. gang? (1 skive/stykke = 150 gram) (Sett ett kryss)

☐ 1 ☐ 2 ☐ 3 ☐ 4+

Spiste du fisk til middag i går? ☐ Ja ☐ Nei

Hvor mange fiskemiddager har du spist den siste uka?

Antall .....

Hvor ofte pleier du bruke følgende typer fiskemat? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd	2-3 pr. mnd	1 pr. uke	2 pr. uke	3+ pr. uke
Fiskekaker, fiskepudding						
Fiskeboller						
Plukkfisk, fiskegrateng						
Frityrfisk, fiskepinner						
Fiskesuppe						
Andre fiskeretter						

Hvor mange ganger pr. år spiser du mølje?
(Torskemølje = fisk, lever og rogn. Selmølje = fisk og lever) (Sett ett kryss)

☐ 0 ☐ 1-3 ☐ 4-5 ☐ 6-8 ☐ 9-12 ☐ 13+

Hvor mange ganger pr. år spiser du fiskelever utenom mølje?
(Sett ett kryss)

☐ 0 ☐ 1-3 ☐ 4-5 ☐ 6-8 ☐ 9-12 ☐ 13+

Dersom du spiser fiskelever, hvor mange spiseskjeer pleier du spise hver gang? (Sett ett kryss)

☐ 1 ☐ 2 ☐ 3-4 ☐ 5-6 ☐ 7+

Hvor mange måsegg spiser du pr. år? (Sett ett kryss)
☐ 0 ☐ 1-3 ☐ 4-5 ☐ 6-8 ☐ 9-12 ☐ 13+

Hvor mange ganger pr. år spiser du følgende typer sjømat? (Sett ett kryss pr. linje)

	0	1-3	4-5	6-8	9-12	13+
Reker						
Krabbe						
Hvalkjøtt						
Selkjøtt						

Hvor ofte pleier du bruke følgende kjøtt- og fjærkreretter? (Sett ett kryss for hver rett)

	aldri/ sjelden	1 pr. mnd	2-3 pr. mnd	1 pr. uke	2 pr. uke	3+ pr. uke
Steik (okse, svin, får)						
Koteletter						
Biff						
Kjøttkaker, karbonader						
Kjøttpølser						
Grillpølser						
Gryterett, lapskaus						
Pizza m/kjøtt						
Kylling						
Dyrelever						
Reinsdyrskav						
Vilt						
Andre kjøttretter						

Dersom du spiser steik eller koteletter, hvor mye pleier du å spise? (Sett ett kryss for hver linje)

Steik (skiver) ☐ 1-2 ☐ 3-4 ☐ 5-6 ☐ 7+
Koteletter (stk.) ☐ 1/2 ☐ 1 ☐ 1 1/2 ☐ 2+

Dersom du spiser følgende retter, oppgi mengden du vanligvis spiser: (Sett ett kryss for hver linje)

- kjøttkaker, karbonader (stk.) ☐ 1 ☐ 2 ☐ 3 ☐ 4+
- kjøttpølser (stk.) ☐ 1 ☐ 2 ☐ 3+
- grillpølser (stk.) ☐ 1 ☐ 2 ☐ 3 ☐ 4+
- gryterett, lapskaus (dl) ☐ 1-2 ☐ 3-4 ☐ 5-6 ☐ 7+
- pizza m/kjøtt (stykke à 100 g) ☐ 1 ☐ 2 ☐ 3 ☐ 4+

Hvor mange egg spiser du vanligvis i løpet av en uke (stekte, kokte, eggerøre, omelett)? (Sett ett kryss)

☐ 0 ☐ 1 ☐ 2 ☐ 3-4 ☐ 5-6 ☐ 7+

Nedenfor er det spørsmål om bruk av ulike påleggstyper. Vi spør om hvor mange brødskiver med det aktuelle pålegget du pleier å spise. Dersom du også bruker matvarene i andre sammenhenger enn til brød (f. eks. til vafler, frokstblandinger, grøt), ber vi om at du tar hensyn til dette når du besvarer spørsmålene.

På hvor mange brødskiver bruker du? (Sett ett kryss pr. linje)

	0 pr. uke	1-3 pr. uke	4-6 pr. uke	1 pr. dag	2-3 pr. dag	4-5 pr. dag	6+ pr. dag
Brun ost, helfet							
Brun ost, halvfet/mager							
Hvit ost, helfet							
Hvit ost, halvfet/mager							
Smøreost							
Andre fete oster							
Kjøttpålegg							
Leverpostei							

Videre kommer spørsmål om fiskepålegg.
På hvor mange brødskiver pr. uke har du i gjennomsnitt siste året spist? (Sett ett kryss pr. linje)

	0 Pr. uke	1 Pr. uke	2-3 Pr. uke	4-6 Pr. uke	7-9 Pr. uke	10-14 Pr. uke	15+ Pr. uke
Makrell i tomat, røkt makrell							
Sardin (olje, tomat)							
Sursild, sildesalat							
Kaviar							
Tunfisk							
Laks, røykt/gravet							
Annet fiskepålegg							

Drikker du melk? Ja ☐ Nei ☐
Hvis Ja, kryss av for hvor mange glass du vanligvis pleier å drikke av hver melketype. (Sett ett kryss pr. linje)

	aldri/ sjelden	1-4 pr. uke	5-6 pr. uke	1 pr. dag	2-3 pr. dag	4+ pr. dag
Helmelk (søt, sur)	☐	☐	☐	☐	☐	☐
Lettmelk (søt, sur)	☐	☐	☐	☐	☐	☐
Skummet (søl, sur)	☐	☐	☐	☐	☐	☐

Hvor ofte spiser du yoghurt (1 beger)? (Sett ett kryss)
☐ aldri/sjelden ☐ 1-3 pr. mnd ☐ 1 pr. uke ☐ 2-3 pr. uke
☐ 4-5 pr. uke ☐ 6-7 pr. uke ☐ 8+ pr. uke

Hvor ofte spiser du risengrynsgrøt? (Sett ett kryss)
☐ aldri/sjelden ☐ 1 pr. mnd ☐ 2-3 pr. mnd ☐ 1+ pr. uke

Hvor ofte spiser du iskrem (til dessert, krone-is osv.)?
(Sett ett kryss for hvor ofte du spiser iskrem om sommeren, og ett kryss for resten av året)

	aldri/ sjelden	1-3 pr mnd	1 pr. uke	2-3 pr. uke	4-5 pr. uke	6+pr. uke
– om sommeren	☐	☐	☐	☐	☐	☐
– resten av året	☐	☐	☐	☐	☐	☐

Hvor mye is spiser du vanligvis pr. gang? (Sett ett kryss)

☐ 1 dl ☐ 2 dl ☐ 3 dl ☐ 4+ dl

Hvor ofte spiser du kake eller dessert laget med krem,
(f. eks. bløtkake, riskrem, fromasj, multekrem)? (Sett ett kryss)

☐ aldri/sjelden ☐ 1-2 pr. mnd ☐ 3 pr. mnd
☐ 1 pr. uke ☐ 2+ pr. uke

Hvor ofte spiser du sjokolade?
(Sett ett kryss)

☐ aldri/sjelden ☐ 1-3 pr. mnd ☐ 1 pr. uke
☐ 2-3 pr. uke ☐ 4-6 pr. uke ☐ 1+ pr. dag

Dersom du spiser sjokolade, hvor mye pleier du vanligvis å spise hver gang? Tenk deg størrelsen på en Kvikk-Lunsj sjokolade, og oppgi hvor mye du spiser i forhold til den.
(Sett ett kryss)

☐ 1/4 ☐ 1/2 ☐ 3/4 ☐ 1 ☐ 1,5 ☐ 2+

Hvor ofte spiser du småkaker eller kjeks?
(Sett ett kryss)

☐ aldri/sjelden ☐ 1-3 pr. mnd ☐ 1 pr. uke
☐ 2-3 pr. uke ☐ 4-6 pr. uke ☐ 1+ pr. dag

Dersom du spiser småkaker/kjeks, hvor mange pleier du å spise hver gang?

☐ 1 ☐ 2 ☐ 3-4 ☐ 5-6 ☐ 7+

Kosttilskudd

Hvor ofte tar du følgende kosttilskudd? For tran og tranpiller vær vennlig å sette ett kryss for vinteren og ett kryss for resten av året; også om du bruker det like ofte gjennom hele året.

	aldri/ sjelden	1-3 pr. mnd	1 pr. uke	2-3 pr. uke	4-6 pr. uke	daglig
Tran,						
- om vinteren	☐	☐	☐	☐	☐	☐
- resten av året	☐	☐	☐	☐	☐	☐
Tranpiller,						
- om vinteren	☐	☐	☐	☐	☐	☐
- resten av året	☐	☐	☐	☐	☐	☐
Fiskeolje -kapsler	☐	☐	☐	☐	☐	☐

Dersom du tar tran, hvor mye pleier du ta hver gang?

☐ 1 ts ☐ 1/2 ss ☐ 1+ ss

I hvilken grad mener du kostholdet ditt har betydning for helsa?

☐ ingen/svært liten ☐ noen ☐ stor ☐ svært stor

Graviditeter, fødsler og amming

Er du gravid? ☐ Ja ☐ Nei
Hvis Ja, i hvilken svangerskapsmåned er du? .....mnd

Ammer du nå? ☐ Ja ☐ Nei

Fyll ut for hvert barn opplysninger om fødselsår og antall måneder du ammet barnet (fylles også ut for dødfødte eller for barn som er døde seinere i livet). Dersom du ikke har født barn, går du videre til neste spørsmål.

Barn	Fødselsår	Antall måneder med amming
1	.....	.....
2	.....	.....
3	.....	.....
4	.....	.....
5	.....	.....
6	.....	.....

Personalia

Alder ..... år Høyde .....cm Vekt .....kg

Yrke .....

Bostedskommune.....

Hvor lenge har du bodd i denne kommunen? .....år

I hvilken kommune ble du født? .....

Takk for hjelpen!

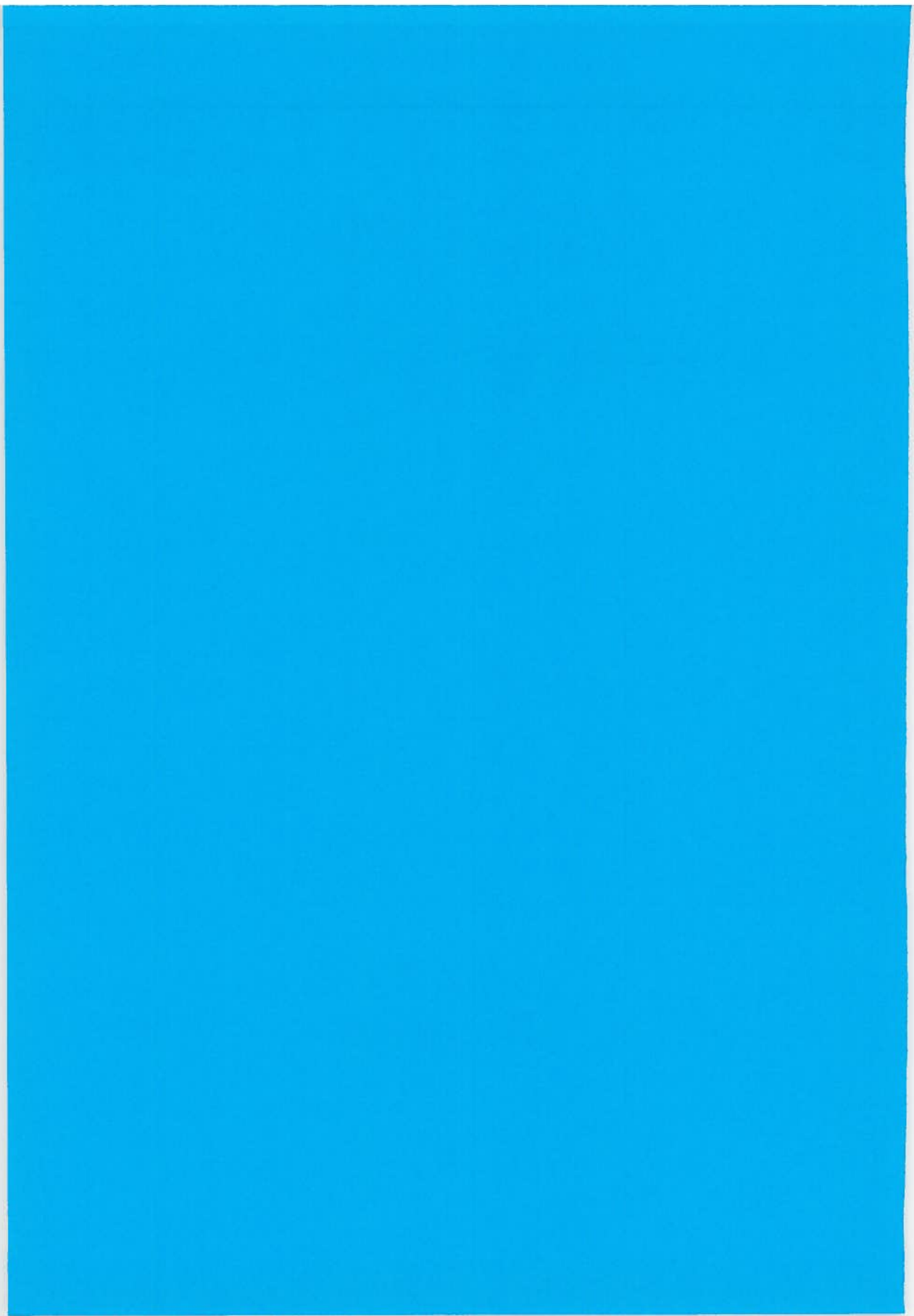
Appendix B

Questionnaires used in the Norwegian EBBA-study, 2000–2002:

General questionnaire
Questionnaire on use of hormonal contraceptives
Logbook for recording saliva samples and physical activity
Dietary diary and Picture booklet
Life events calendar
Flow chart for participants (original)

English translations
Original questionnaires

Paper II



THE EBBA SURVEY

English translation; Mrs. Anne Clancy and Mrs. Anniken Telnes Iversen

We know little about the direct causes of various types of cancer. For that reason it is uncertain what each one of us can do to reduce our risk of getting cancer. The main purpose of this survey is to improve our knowledge of these illnesses in order to prevent them. We would like you to answer questions about your lifestyle and health. You will be making an important contribution by providing us with good knowledge that can be put to practical use in helping to prevent these serious diseases.

The survey has been approved by the Regional Board of Research Ethics. The answers you give will be treated in strict confidence and will only be used for research purposes. The information may later be compared with information from other public health registers in accordance with the rules laid down by the Data Inspectorate and the Regional Board of Research Ethics.

Thank you in advance for helping us.

Yours sincerely,
Inger Thune , M.D.

CONFIDENTIAL

GENERAL INFORMATION

Municipality of birth _____
(If you were born outside Norway, give name of country instead of municipality.)

Marital status (tick the appropriate box)
- Single ☐
- Married/living together ☐
- Widow ☐
- Separated/divorced ☐
- Other ☐

How many years schooling/training have you had in total?
(Include everything from primary school upwards - middle/ secondary school, vocational training/higher education/university)

_____ years

How many years of your active working life have you mainly
done housework (including maternity leave)?
_____ years

been employed full time outside the home?
_____ years

been employed part time outside the home?
_____ years

Do you have brothers and/or sisters? ☐ Yes ☐ No

If yes, how many? Sisters? _____
Brothers?_____

How many children had your mother given birth to before you were born? _____

Which ethnic group do your ancestors belong to?
(Parents/grandparents) (Tick the most appropriate boxes)
- Norwegian ☐
- Sami ☐
- Other European ☐
- Finnish ☐
- Asian ☐
- Other; give details _____ ☐

HEIGHT/WEIGHT

You might not know your height and weight from childhood onwards. We would nevertheless like you to try to answer.

Birth:	Weight	____	grams	Height	____ cm
At age 18:	Weight	____	kg	Height	____ cm
Today:	Weight	____	kg	Height	____ cm

How would you describe your body compared to children your own age when you were growing up? (Tick one box for each age group)

	Much thinner	Thinner	Normal	Fatter	Much fatter
Pre-school	☐	☐	☐	☐	☐
Grades 1-6	☐	☐	☐	☐	☐
Grades 7-9 (13-16 years)	☐	☐	☐	☐	☐

MENSTRUATION/PREGNANCIES/BREAST-FEEDING

How old were you when you had your first menstrual period?
_____ years _____months

How long did it take before your periods became regular?
(Tick the most appropriate box)
- One year or less ☐
- More than 1 year ☐
- Never ☐
- Cannot remember ☐

How have your periods been? (Tick one box)
- Always regular ☐
- Usually regular ☐
- Irregular ☐

What was/is the usual number of days between periods?
(From day 1 of one period to day 1 of the next period)

_____ days

Have you had children? ❑ Yes ❑ No
If yes, have you ever been treated for nausea/ vomiting during pregnancy? ❑ Yes ❑ No

If you have had children, fill in year of birth and number of months you breast-fed each child (this should be completed also for children who died at birth or later in life).

Child no.	Year of birth	Number of months of breast-feeding

PHYSICAL ACTIVITY

HOUSEWORK

THE LAST 12 MONTHS
Imagine an average week of housework during the last 12 months (all types of work in the home, including caring for and dressing children/others in need of care). We have divided housework into 4 levels of activity. For each activity level, you should fill in the **number of days per week** and average **time per day** (in minutes) spent on such work.

Level of activity for housework is defined as	Days per week	Minutes per day
1 = Mostly sedentary work (sewing, writing)		
2 = Light work, carried out standing up, sitting down, or while walking slowly (e.g. cooking, dusting)		
3 = Fairly heavy work: You perspire a little and your heart beats a little faster; (e.g. doing laundry, vacuum cleaning, caring for/dressing others)		
4 = Heavy physical work: You perspire profusely and your heart beats quickly; (e.g. heavy cleaning)		

THROUGHOUT YOUR LIFE
Housework changes with age and circumstances. Using the same activity levels as above (1-4), we would like you to fill in for each age given: the average number of **days per week and hours per day** you carried out activities at each level.

Activity level:		Age 10-14 years	15-19 years	20-24 years	25-29 years	30-34 years
1=Sedentary work	Days per week					
	Hours per day					
2=Light work	Days per week					
	Hours per day					
3=Fairly heavy work	Days per week					
	Hours per day					
4=Heavy physical	Days per week					
	Hours per day					

LEISURE ACTIVITIES (EXERCISE, HIKING, SPORTS)
THE LAST 12 MONTHS
What kind of physical activity have you done in your leisure time in the last 12 months? If your activity level varies a lot, for instance between summer and winter, then give an average. (Tick only the most appropriate box.)

1= Reading, watching TV or doing other sedentary activities? ❑
2= Walking, riding a bicycle or other forms of exercise at least four hours a week? (Including walking or riding a bicycle to and from work, Sunday walks, etc.) ❑
3= Exercising, doing heavy gardening, etc.? (Note that the activity must take up **a minimum of four hours** a week.) ❑
4= Exercising intensively or doing competitive sports regularly several times a week? ❑

LEISURE ACTIVITIES AND CODES
Below is a list of various leisure activities. We would like you to note the activities you have participated in. In the form below please indicate how much time (number of sessions per month and time per session) you spent doing each activity. Using the four activity levels given for leisure activities below, tick the level that best fits each activity.

1. Reading books/watching TV
2. Walking to/from work/school, taking walks, walking with a pram
3. Hiking in the forest/mountains, hunting
4. Jogging/running
5. Riding a bicycle to/from work/school (including exercise bike)
6. Swimming (and diving/deep-sea diving)
7. Handball/basketball/ (ball-game similar to baseball or rounders)/football (soccer)
8. Volleyball
9. Tennis/badminton/squash
10. Golf/bowling/curling
11. Athletics: javelin, discus, shot-put/high and long jump
12. Gymnastics/aerobics/exercising/ dancing/ballet
13. Health studio/weight lifting
14. Skipping or similar
15. Skiing: cross-country – recreational/competitive
16. Downhill skiing/ Telemark ski-ing/snowboarding
17. Tobogganing/kick-sledging/skating (ice and roller skates)
18. Horse riding
19. Rowing/paddling/sailing
20. Picking berries/ mushrooms/fishing
21. Other

ACTIVITY LEVELS FOR LEISURE ACTIVITIES:
1 = Mainly sedentary.
2 = Light training: You do not sweat and your heart does not beat faster.
3 = Moderate training: You sweat a little and your heart beats a little faster.
4 = Hard/heavy training: You sweat profusely and your heart beats fast.

Activity Type of activity	Months per year	Average no. of sessions per month	Average time per session (minutes)	Activity level 1	2	3	4

THROUGHOUT YOUR LIFE

Look again at the list of various leisure activities. Please mark the activities you have participated in. Then give the age at which you participated in the activity, and indicate how often and for how long you participated (months per year, time per week and per session). Tick the **one** activity level that best fits each activity, using the four levels given for leisure activities above.

Activity and code	Age at start	Age at end	Months per year	Hours per week	Average time per session (minutes)	Activity level			
						1	2	3	4

WATCHING TV, SITTING, REST IN YOUR FREE TIME.

How many minutes or hours of your free time per 24 hours do you usually devote to the following activities? Calculate an average for the last 12 months.

	Number of hours	Number of minutes
Resting, sleeping	_____	_____
Listening to music/radio	_____	_____
Watching TV/videos	_____	_____
Meals, coffee/tea	_____	_____
Reading/writing	_____	_____
Conversation (incl. phone calls)	_____	_____
Handicrafts, hobbies	_____	_____

WORK/SCHOOL ACTIVITIES

THE LAST 12 MONTHS

Have you been in paid employment/a student during the last 12 months? ❑ Yes ❑ No

If yes:

Months working/studying in the last 12 months _____ months

Workdays per week _____ days

Working hours per day _____ hours

What level of physical activity do you normally have at work/school now? (Tick the box that you feel fits best)

1 = Mostly sedentary work
(e.g. office work) ❑

2 = Work that requires a lot of walking
You do not perspire and your heart does not beat faster (e.g. shop assistant, teacher, hairdresser) ❑

3 = Work that requires a lot of walking and lifting
You perspire a little and your heart might beat faster (e.g. nurse/assistant nurse, postman/woman) ❑

4 = Heavy manual labour.
You perspire quite a bit and your heart beats fast (e.g. heavy lifting, farming, heavy-duty care) ❑

Imagine an average week of work/school activity in the last 12 months. Here too we have divided the activities into the same 4 activity levels as above. For each activity level indicate the number of months per year, hours per week and average number of hours per day, which you dedicated to the activity.

Type of work Activity level	Months per year	Hours per week	Average per day
1=seated			
2=Standing and walking			
3=Walking and carrying			
4=Heavy			

TRAVEL TO/FROM WORK/SCHOOL

This question relates to travel between home and work in the last 12 months.

How do you usually get to/from work? Give an average for a month for the numbers of times you use:

Car _____
Bus/tram/train/boat _____
Bicycle _____
On foot _____

How long does it usually take you to get to/from work?
Add up the time you spend getting to work and back for each mode of transportation. If relevant, give the time it takes you to walk to/from car park/bus stop, etc.

Car _____ minutes
Bus/tram/train/boat _____ minutes
Bicycle _____ minutes
On foot _____ minutes

THROUGHOUT YOUR LIFE

We would first like you to indicate the schools you have attended/jobs you have had. If you have worked at home in a capacity other than as a housewife, e.g. farming, childminding, sewing, these should be given. You might have had several jobs in the same time period, e.g. while working part-time. Please fill in how old you were when you started and finished each job, and indicate how much time you usually spent/spend at various activity levels: number of months per year, days per week, and hours per day. Tick the activity level most appropriate for each job, using the 4 activity levels above. Remember exercise hours/breaks at school.

Jobs/ schools	Age at start	Age at end	Months per year	Days per week	Hours per day	Activity level			
						1	2	3	4

MEDICINES

Please tick **yes** for the medicines you have used occasionally (however little) and **no** for those you have never used. If you tick yes, try to remember what age you were the first time you used the medicine and the number of times per month you use it now.

	Yes	No	Age first time	No of times per month
Hypertensive drugs	❑	❑	_____	_____
Painkillers	❑	❑	_____	_____
Acetylsalicylic acid/Albyl E				
Antidepressants	❑	❑	_____	_____
If yes, which ones				
Others	❑	❑	_____	_____
If yes, which ones				

Please tick YES for those of the following medicines you use regularly (daily, almost daily)

	Yes
Sleeping pills	❑
Painkillers	❑
Hypertensive drugs	❑
Antidepressants	❑
Other medicines	❑
If yes, which ones	_____
Homoeopathic/herbal medicines	❑
If yes, which ones	_____

CANCER IN THE FAMILY

Have any of your close biological relatives had cancer? ❑ Yes ❑ No

If yes, which type of cancer has occurred in your maternal and paternal family?

Maternal family	*Type of cancer*	No	Don't know
Mother	_____	❑	❑
Mother's mother	_____	❑	❑
Mother's father	_____	❑	❑
Aunt	_____	❑	❑
Uncle	_____	❑	❑
Others,	_____		
indicate relationship	_____	❑	❑
Paternal family			
Father	_____	❑	❑
Father's father	_____	❑	❑
Father's mother	_____	❑	❑
Uncle	_____	❑	❑
Aunt	_____	❑	❑
Others,	_____		
indicate relationship	_____	❑	❑

LIFESTYLE

Have you ever smoked on a daily basis? ❑ Yes ❑ No

If yes, how many cigarettes did you smoke each day on average? (Tick one box for each age group.)

	Number of cigarettes per day						
	0	1-4	5-9	10-14	15-19	20-25	25 +
12-14 years	❑	❑	❑	❑	❑	❑	❑
15-19 years	❑	❑	❑	❑	❑	❑	❑
20-24 years	❑	❑	❑	❑	❑	❑	❑
25-34 years	❑	❑	❑	❑	❑	❑	❑

Do you smoke every day now? ❑ Yes ❑ No

If yes, how many cigarettes a day?

How many habitual smokers did you live with at the following ages? (Tick one box in each line.)

Number of persons :	None	1	2	3 or more	Don't know
Childhood	❑	❑	❑	❑	❑
15-19 years	❑	❑	❑	❑	❑
20-24 years	❑	❑	❑	❑	❑
25-34 years	❑	❑	❑	❑	❑

Do you currently live with someone who smokes? ❑ Yes ❑ No

If yes, how many cigarettes do they normally smoke per day when you are with them? __ cigarettes

Have you ever worked in smoke-filled workplaces? ❑ Yes ❑ No

If yes, for how long altogether? _____ years

Have you ever drunk alcohol? ❑ Yes ❑ No

If yes, how many glasses of wine, ½ litres of beer, or measures of spirits did you drink on average per month at the following ages? (Tick one box in each line.)

	Never/ rarely	1 pr. month	2-3 pr. month	1 pr. week	2-4 pr. week	5-6 pr. week	1+ pr. day
15-19 years	❑	❑	❑	❑	❑	❑	❑
20-24 years	❑	❑	❑	❑	❑	❑	❑
25-34 years	❑	❑	❑	❑	❑	❑	❑

Are you currently a teetotaller? ❑ Yes ❑ No

If no, how many glasses of wine, ½ litres of beer, or measures of spirits have you drunk on average per month or per week in the last 12 months? (Tick one box in each line.)

	Never rarely	1 pr. month	2-3 pr. month	1 pr. week	2-4 pr. week	5-6 pr. week	1+ day
Beer (1/2 litre)	❑	❑	❑	❑	❑	❑	❑
Wine (glasses)	❑	❑	❑	❑	❑	❑	❑
Fortified wine (0,4 dl)	❑	❑	❑	❑	❑	❑	❑
Spirits (measures)	❑	❑	❑	❑	❑	❑	❑

Your comments:

_____

_____

_____

May we have your permission to contact you again at a later stage to update this information?

❑ Yes ❑ No

Thank you for taking part in the survey!

THE EBBA SURVEY

English translation; Mrs. Anne Clancy

CONTRACEPTIVE PILLS/INJECTABLE CONTRACEPTION/HORMONE-RELEASING INTRAUTERINE DEVICE **Serial number**_____

	Yes	No
Have you ever used the pill, mini pill included?	☐	☐
Have you ever used injectable contraception?	☐	☐
Have you used a hormone-releasing intrauterine device ("coil")?	☐	☐
If you have given birth, did you use the pill, an injectable contraceptive or intrauterine device before you gave birth the first time?	☐	☐
Have you been given the pill, an injectable contraceptive or intrauterine device for reasons other than contraception?	☐	☐
Have you, for medical reasons, been recommended to discontinue use of the pill, injectable contraceptive or intrauterine device?	☐	☐

We would like more detailed information about your usage of the pill, injectable contraceptive or intrauterine device.

Can you remember which periods of your life you used the pill, injectable contraceptive or intrauterine device continuously?
How old were you when you started?
How old were you when you stopped?
Over how long a period did you use the same brand of the pill, injectable contraceptive or intrauterine device?
What was the name of the pill, injectable contraceptive or intrauterine device (see enclosed list of brand names and numbers)? If you cannot recall the brand, write "unsure" in the space provided for the brand.

Period	Age started	Age stopped	Continuously Year	Month	Contraceptive pill Number	Brand
First						
Second						
Third						
Fourth						
Fifth						
Sixth						
Seventh						

Brands of the pill, injectable contraception or intrauterine device?

Monophasic pills

Recommended use: 1 tablet daily for 21-22 days, then a break or placebo tablets for 6-7 days.

(1) **Follimin**

(2) **Microgynon**

(3) **Eugynon**

(4) **Marvelon**

(5) **Yasmin**

(6) **Diane**

(7) **Loette**

Multiphasic pills

Usual use: comes in calendar blister packs.

(8) **Synfase**

(9) **Trinordiol**

(10) **Trionetta**

Progestagen-only pills

(11) **Conludag**

(12) **Exlutona**

(13) **Microluton**

Injectable contraception

(14) **Depo-provera**

Hormone-releasing intrauterine device

(15) **Levonova**

Other

(16) Name the brand

Unsure

(17)

THE EBBA SURVEY

(Breast cancer and lifestyle)

English translation; Mrs. Anne Clancy

Logbook (diary) for recording saliva samples and physical activity

Instructions for filling in the logbook

Fill in the logbook daily

Serial no._____

-DATE Write down day, date, month and year, e.g.: Tuesday 16th October 2001

-SLEEP Write down the number of hours sleep you had in the last 24 hrs.

-TIME FOR SAMPLE indicates the time you took the saliva sample.
Use a 24-hour clock, e.g.: 07.30 for morning and 19.30 for the evening. If you happen to miss out on a sample, write, "missing".
The more accurately you record date and time for sample, the easier it will be to identify your samples reliably at a later date.

-MENSTRUAL BLEEDING points to menstruation during the past 24 hrs.
Answer yes or no.

-TYPE AND DURATION OF ACTIVITY
We wish to know how you got to and from work, the shops, leisure time activities etc. during the day. Fill in the means and duration of the transport you used.

-At work:
We wish to know all types of activities you took part in during your day at work. Choose the level of activity you think suits best for each work task performed. Fill in the duration of the activity.

-At home, indoors and outdoors:
We wish to know all the activities you were engaged in, other than those you have mentioned at work and at home. Choose the level of activity that suits best for each task performed. Fill in the duration of the activity. In addition, you can mention what the task was.

-Leisure time
We wish to know all types of activities you were engaged in, in addition to those at home and at work. Choose from the list of activities, or write down in your own words the activities you took part in during the day. Use the intensity scale from 1-4 to describe how much you exerted yourself during each activity. Remember to write down the duration of the activity.

-Additional information
It is possible for you to write comments here and if necessary other remarks that you did not have room for in the section on physical activity.

Day 1	Sample collection			Physical activity		
Date Day of the week	Sleep (no. of hours)	Time you woke up (use 24 hr. clock)	Menstrual bleeding (Yes/No)	Type of activity		Duration (hrs/mins)
				Transport	Car	
					Bus/train/tram	
					Bicycle	
					Walking	
					Jogging/running	
Additional information:				**Work**	Sitting still	
					Standing	
					Walking at a slow pace	
					Light manual work	
					Heavy manual work	
				At home in the house and outdoors	Sitting down (sewing)	
					Standing (preparing food)	
					Walking at a slow pace (dusting)	
					Moderately heavy work (vacuum cleaning)	
					Heavy work (washing floors)	

Leisure time	Type of activity	Duration (hrs/mins)	Intensity (1-4)

Different types of leisure time activity

1. Reading books/watching TV
2. Taking a walk/walking with a pram a p
3. Hiking in the forest/mountains
4. Picking berries/mushrooms
5. Jogging/running
6. Bicycling
7. Exercising/gymnastics/aerobics
8. Downhill skiing/telemark/snowboard
9. Cross country skiing
10. Tennis, badminton
11. Golf/bowling
12. Weight-lifting/body strengthening
13. Swimming
14. Skating
15. Other

Level of intensity

1 =Mainly sedentary
2 = Light exercise. You do not perspire and your heart does not beat faster.
3 = Moderate exercise. You perspire a little and your heart beats a little faster.
4 = Heavy exercise: You perspire profusely and your heart beats fast

ID. number:_____

THE EBBA SURVEY

(Breast cancer and lifestyle)
English translation; Mrs. Anne Clancy

DIETARY QUESTIONS

Day:_____ **Date:**_____ **Reg day:**_____

Was today a normal day, or an unusual one, considering what you ate and drank?

Normal day ☐ **Unusual day** ☐

The reason for it being an unusual day: _____

Where do I find the different foodstuffs in the dietary questions?

Cod-liver oil/dietary supplements

1 tea spoon = 5 ml

	Number	(Morning Midday afternoon evening) All together today
Cod-liver oil	tea-spoon	
Cod-liver capsules	No.	
Soluble multivitamins	tea-spoon	
(eg. biovit sanasol)	tea-spoon	
Multivitamin tablets (vitaplex, vitamineral)	no.	
Fluoride tablets	no	
Iron pills (9 mg)	no.	
Vitamin C tablets	no.	
Others - describe type and amount:		

Drinks

Use no. 1 and 2 in the photo series to estimate the size of cups and glasses
1/2 liter = 2,5 glasses

	Number	Morning	Midday	Afternoon	Evening
Water/sparkling water	glass				
Full cream milk (sweet/sour)	glass				
Semi-skimmed milk (sweet/sour)	glass				
Extra semi-skimmed milk	glass				
Skimmed milk (sweet/sour)	glass				
Drinking yogurt	glass				
Chocolate milk	glass				
Cocoa	cup				
Juice /nectar	glass				
Soft drink with sugar	glass				
Soft drink without sugar	glass				
Tea	cup				
Ice tea with sugar	glass				
Coffee	cup				
Artificial sweetener	No..				
Sugar for tea/coffee	tea spoon				
Milk for tea/coffee	soup spoon				
Beer	½ litter				
Wine	glass				
Spirits	shorts/ cocktails				
Others – describe type and amount:					

Yogurt

	Number	Morning	Midday	Afternoon	Evening
Natural yogurt plain	cup (175 ml)				
Fruit yogurt	cup (175 ml)				
Low fat yogurt	cup (150 ml)				
Yogurt and muesli	cup (with muesli)				
Others – describe type and amount:					

Bread

Use no.3 in the photo series to estimate bread thickness
1 slice of bread=1/2 bread roll

	Number	Morning	Midday	Afternoon	Evening
White bread/bread roll	of slices photo series 3				
Semi-wholemeal bread	of slices photo series 3				
Wholemeal bread	of slices photo series 3				
Baguette / Ciabatta	pcs.				
Crisp bread	pcs..				
Flat potato cake	pcs.				
Hamburger bread/Hot dog bread roll	pcs.				
Thin wafer crisp bread	pcs.				
Others – describe type and amount:					

What type of butter/margarine do you spread on your bread?

For the amount of butter/margarine on bread, use no. 4 in the photo series (chose A,B,C or D)
1 slice of bread = ½ roll = 2 biscuits

	Number	Morning	Midday	Afternoon	Evening
Butter	of slices:				
Soft margarine	of slices:				
Light margarine	of slices:				
Hard margarine	of slices:				
Others – describe type and amount:	of slices:				

Cereals and porridge

Use no. 5 and 6 in the photo series (chose A,B,C or D)

	Number of portions	Morning	Midday	Afternoon	Evening
Oatmeal porridge					
Oat flakes					
Muesli with added sugar					
Muesli (unsweetened)					
Cornflakes					
Frosties/ choco pops					
Others – describe type and amount:					

Milk/sugar/jam used with cereals and porridge

1 soup spoon = 3 teaspoons (15ml)

	Number	Morning	Midday	Afternoon	Evening
Full cream milk (sweet/sour)	dl				
Semi-skimmed milk (sweet/sour)	dl				
Skimmed milk (sweet/sour)	dl				
Jam, marmalade	teaspoons				
Jam, low sugar	teaspoons				
Sugar	teaspoons				
Others – describe type and amount:					

Sandwich fillings/spreads

Fill in the number of slices of bread. Indicate amount of fillings/spreads according to slices of bread. If you have two fillings on the same slice of bread, mention both. (eg. 1 White cheese, full cream and 1 ham). If you have eaten only the filling and not bread, please note how many slices of bread you could have used the filling on.
1 slice of bread = ½ roll = 1 crisp bread = 2 biscuits

	Number	Morning	Midday	Afternoon	Evening
Cheese					
White cheese, full cream (27% fat)	of slices				
White cheese, reduced fat (16% fat)	of slices				
Brown full fat cheese,	of slices				
Brown cheese, reduced fat	of slices				
Cream cheese (eg. Philadelphia)	of slices				
Cream cheese low fat (eg. Philadelphia light)	of slices				
Desert cheese (eg. Brie, Camembert)	of slices				
Sandwich meats/spreads					
Luncheon roll	of slices				
Ham, cured ham, low fat luncheon roll	of slices				
Salami, smoked sausage, mutton sausage	of slices				
Liver patè	of slices				
Liver patè, low fat	of slices				
Fish fillings/spreads					
Caviar	of slices				
Smoked salmon/trout	of slices				
Mackerel in tomato sauce	of slices				
Sardines, marinated herrings, anchovies	of slices				
Jam/other sweet spreads					
Jam, marmalade	of slices				
Jam, marmalade (low sugar)	of slices				
Honey	of slices				
Peanut butter	of slices				
Chocolate fillings/spreads	of slices				
Other sandwich fillings					
Egg, boiled/fried	of slices				
Salads with mayonnaise	of slices				
Salads with mayonnaise, low fat	of slices				
Tomatoes	of slices				
Bananas	of slices				
Mayonnaise	of slices				
Mayonnaise, low fat	of slices				
Others – describe type and amount:					

Meat and meat dishes

	Amount	Morning	Midday	Afternoon	Evening
Sausages					
Frankfurters	no.				
Frankfurters, low fat	no.				
Sausages, dinner type	no.				
Sausages, dinner type, low fat	no.				
Minced meat dishes / pasta / pizza					
Meat balls (made from minced beef)	pcs.				
Meat balls (made from minced pork)	pcs.				
Taco (with minced meat and salad)	filled taco				
Kebab / Pita bread (with meat and salad)	filled pita				
Minced meat sauce / tomato sauce with minced meat	photo series 12				
Pasta with tomato sauce (without meat)	photo series 7				
Pasta with white sauce	photo series 7				
Lasagna	piece (10 x 5 cm)				
Pizza, square slices	photo serie 14				
Pizza, triangular slices	photo serie 13				
Lean meat					
Beef /lam/ pork	pcs.				
Chops (beef, lam, pork)	pcs.				
Roast (beef, lam, pork)	slices				
Ham	slices				
Grilled chicken	1/4 chicken				
Chicken filet	no. of filets				
Bacon	slices				
Stew/ casserole dishes					
Rice dishes/risotto)	photo series 12				
Mutton and cabbage stew / mutton with white gravy sauce	photo series 12				
Norwegian stew (meat and vegetable stew)	photo series 12				
Other meat and vegetable stews	photo series 12				
Liver dishes	photo series 12				
Others – describe type and amount:					

Fish and fish dishes

	Number	Morning	Midday	Afternoon	Evening
Minced fish					
Fish balls	No.				
Fish cakes/fish loaf	No. / slices				
Fish					
Cod/coalfish/Norway haddock (boiled)	pcs.				
Cod/coalfish/Norway haddock (fried)	photo series 15				
Salmon/trout/halibut (boiled)	pcs.				
Salmon/trout/halibut (fried)	photo series 15				
Herring/mackerel (boiled)	pcs.				
Herring/mackerel (fried)	photo series 15				
Flounder/wolf fish (boiled)	pcs.				
Flounder/wolf fish (fried)	photo series 15				
Fish dishes/fish in batter					
Fish fingers	pcs.				
Fried fish (in batter)	pcs. (10x10 cm)				
Fish casserole/fish soup	dl				
Fish pie	dl				
Shrimps	dl				
Others – describe type and amount:					

Other hot dishes/salads

	Number	Morning	Midday	Afternoon	Evening
Rice porridge	photo series 6				
Pancakes	pcs.				
Meat soup	soup bowls				
Soup (eg. cauliflower soup, tomato soup)	soup bowls				
Egg, boiled, fried, omelette.	number of eggs				
Cheese pie/quiche	pcs.				
Mixed salad with cheese, meat or shrimps	photo series 11				
Salad with pasta and cheese, meat or shell fish	photo series 11				
Vegetarian dish – describe type and amount:					
Others – describe type and amount:					

Potatoes/rice/pasta

	Number	Morning	Midday	Afternoon	Evening
Boiled potatoes	No.				
Baked potatoes	no.				
Mashed potatoes	photo series 8				
French fries	photo series 9				
Fried potatoes	photo series 9				
Potato salad	tea-spoons				
Rice, boiled	photo series 7				
Pasta boiled (eg. spaghetti, macaroni, tagliatelle)	photo series 7				
Others – describe type and amount:					

Vegetables

	Number	Morning	Midday	Afternoon	Evening
Carrots	pcs.				
Turnips	slices				
Broccoli, cauliflower	dl				
Cabbage	dl				
Raw-grated vegetables (mix of several vegetables)	photo series 10				
Vegetable mix	photo series 10				
Mixed salad (eg. chinese leaves, corn, tomato, cucumber)	photo series 11				
Tomato/pepper/fried onion	slices				
Others – describe type and amount:					

Sauce/salad dressings

1 soup spoon = 3 tea spoons

	Number	Morning	Midday	Afternoon	Evening
White sauce	soup spoons				
Gravy	soup spoons				
Melted butter/margarine	soup spoons				
Tomato sauce (without meat)	soup spoons				
Béarnaise sauce	soup spoons				
Salad dressing (eg. Thousand Island)	soup spoons				
Salad dressing low fat (eg. Thousand Island light)	soup spoons				
Sour Cream 35 % fat	soup spoons				
Sour Cream 20 % fat	soup spoons				
Mayonnaise	soup spoons				
Mayonnaise low fat	soup spoons				
French dressing	soup spoons				
Others – describe type and amount:					

Ice cream/desserts

	Number	Morning	Midday	Afternoon	Evening
Ice cream (eg. crushed caramel, vanilla)	photo series 16				
Ice lolly/cone	no.				
Jelly	photo series 16				
Pudding (eg. Crème-Brule, chocolate pudding)	photo series 16				
Creamed rice, fromage, cloudberries in whipped cream	photo series 16				
Cream	soup spoons				
Whipped cream	soup spoons				
Chocolate sauce/caramel sauce	soup spoons				
Custard	dl				
Others – describe type and amount:					

Fruit/berries

	Number	Morning	Midday	Afternoon	Evening
Apple/pear	no.				
Banana	no.				
Orange	no.				
Mandarin oranges	no.				
Grapes	no.				
Peach/nectarine	no.				
Fresh/frozen berries	dl.				
Others – describe type and amount:					

Cakes/biscuits

	Number	Morning	Midday	Afternoon	Evening
Sweet buns	pcs.				
Danish pastries	pcs.				
Waffles	pcs.				
Apple pie/cut-cake	slices				
Chocolate cake	slices				
Cream cake	slices				
Macaroon cake, nut cake	slices				
Plain sweet biscuits (eg. Marietta)	pcs.				
Fancy biscuits (eg. Maryland Cookies)	pcs.				
Oat meal biscuits	pcs.				
Plain biscuits	pcs.				
Water biscuits	pcs.				
Biscuits with salt (Ritz)	pcs.				
Others – describe type and amount:					

Chocolate/Sweets

	Number	Morning	Midday	Afternoon	Evening
Milk chocolate	chocolate bar (100 g)				
Marzipan covered with chocolate	chocolate bar (65 gram)				
Assorted chocolates	pcs.				
Snickers, Mars bars (60 g)	chocolate bar				
Chocolate wafer biscuits (eg. Kit-kat, Twix)	Kit-Kat size				
Chocolate bar with marzipan jelly and nougat filling	chocolate bar				
Chocolate ("New Energy")	chocolate bar				
Sweets (eg. marshmallows, jelly, fudge, boiled sweets)	pcs.				
Others – describe type and amount:					

Snacks

	Number	Morning	Midday	Afternoon	Evening
Crisps (1 handful = 8 flakes)	handful				
Crisps low fat (1 handful = 8 flakes)	handful				
Cheese doodles (1 handful = 8 doodles)	handful				
Peanuts	bag (100 g)				
Dip (fx sour cream, cheese dip)	soup spoon				
Others – describe type and amount:					

Picture Booklet illustrating size of portions

English translation; Mrs. Anne Clancy

This photo illustrates plate sizes used in the booklet

1.Glasses

Picture A	Picture B
150 g	230 g

2.Cups

Picture A	Picture B	Picture C	Picture D
110 g	160 g	240 g	270 g

3. Thickness of slices of bread

A B C

4. Butter/margarine on bread

Picture A	Picture B	Picture C	Picture D
3 g	6 g	9 g	12 g

5. Cornflakes (Cereals)

Picture A	Picture B	Picture C	Picture D
10 g	30 g	57 g	86 g

6 Porridge

Picture A	Picture B	Picture C	Picture D
50 g	200 g	350 g	500 g

7. Spaghetti/pasta (rice)

Picture A	Picture B	Picture C	Picture D
34 g	68 g	160 g	250 g

8. Mashed potatoes

Picture A	Picture B	Picture C	Picture D
60 g	205 g	355 g	500 g

9. French fries

Picture A	Picture B	Picture C	Picture D
30 g	60 g	90 g	120 g

10. Mixed vegetables (raw grated vegetables)

Picture A	Picture B	Picture C	Picture D
40 g	80 g	120 g	160 g

11. Salad

Picture A	Picture B	Picture C	Picture D
33 g	52 g	100 g	175 g

12. Meat Stew

Picture A	Picture B	Picture C	Picture D
50 g	200 g	350 g	500 g

13. Pizza , triangular slices

Picture A	Picture B	Picture C	Picture D
56 g	114 g	165 g	270 g

14. Pizza, square slices

Picture A	Picture B	Picture C	Picture D
52 g	112 g	165 g	270 g

15. Filet of fish

Picture A	Picture B	Picture C	Picture D
36 g raw	*102 g raw*	*16 0 g raw*	*195 g raw*
27 g fried	84 g fried	134 g fried	166 g fried

16. Dessert (ice cream)

Picture A	Picture B	Picture C	Picture D
38 g	64 g	97 g	139 g

Some foods that we have mentioned, in the questionnaire, but that are not illustrated in the picture booklet.

Cereals (conversion factor from cornflakes to whole grain muesli cereal is 4,6)

Picture A	Picture B	Picture C	Picture D

46 g	138 g	262 g	396 g

Rice (conversion factor from spaghetti to rice is 1,3)

Picture A	Picture B	Picture C	Picture D
44 g	88 g	208 g	325 g

Fried potato (conversion factor from french fries to fried potatoes id is 1,33)

Picture A	Picture B	Picture C	Picture D
40 g	80 g	120 g	160 g

Raw grated vegetables (conversion factor from mixed vegetables to raw grated vegetables is 0,7)

Picture A	Picture B	Picture C	Picture D
28 g	56 g	84 g	112 g

Chocolate pudding (conversion factor from ice cream to chocolate pudding is 2)

Picture A	Picture B	Picture C	Picture D
76 g	128 g	194 g	278 g

Personal calendar of events in life

It can be difficult to remember what one has done previously, what one was occupied with during different periods of life and how physically active one has been. It may help to have a calendar in front of you and maybe even fill in events, before you attempt to answer the questionnaire.

Year	What happened?	Suggested events you can fill in.
1964		
1965		- Date of birth
1966		
1967		
1968		
1969		
1970		
1971		-Started primary school
1972		
1973		
1974		
1975		
1976		-Started secondary school
1977		
1978		-First menstrual period
1979		
1980		
1981		- Confirmation
1982		
1983		-Started other schools
1984		
1985		
1986		-Work
1987		
1988		-Gave birth, number of children
1989		
1990		-Other events
1991		Arrival of siblings
1992		Travels
1993		Wedding
1994		Family events (Mother's /father's 50th birthday etc.)
1995		
1996		
1997		
1998		
1999		
2000		
2001		
2002		

EBBA-STUDIEN

Sammenhengen mellom livsstil og brystkreft

Vi vet lite om de direkte årsakene til de ulike kreftsykdommene. Av den grunn er det uvisst hva hver enkelt av oss selv kan gjøre for å beskytte seg mot kreft. Hovedformålet med denne undersøkelsen er å skaffe ny kunnskap om disse sykdommene for å kunne forebygge dem. Vi ber deg svare på spørsmål om levevanene dine og helsen din. Din innsats vil være et viktig bidrag til god og praktisk anvendelig kunnskap om hvordan vi kan forebygge disse alvorlige sykdommene. Undersøkelsen er tilrådd av Regional komité for medisinsk forskningsetikk.

Svarene du gir behandles strengt fortrolig og brukes bare til forskning. Opplysningene kan senere bli sammenholdt med informasjon fra andre offentlige helseregistre etter de regler som Datatilsynet og Regional komite for medisinsk forskningsetikk gir.

På forhånd takk for hjelpen!

Med vennlig hilsen
Inger Thune dr.med.

KONFIDENSIELT

GENERELLE OPPLYSNINGER

Fødekommune_____
(Hvis du er født utenfor Norge, oppgi land i stedet)

Sivilstand (Sett kryss i den ruten som passer best)

- Enslig ☐
- Gift/samboer ☐
- Enke ☐
- Separert/skilt ☐
- Annet ☐

Hvor mange års skolegang har du i alt?
(F.o.m. folkeskole/grunnskole/yrkesutdanning/høgskole/-universitet) _____ år

Hvor mange år har du i yrkesaktiv alder hovedsakelig vært

- Hjemmearbeidende (inkl. sv. skapsperm.)? _____ år
- Heltidsarbeidende utenfor hjemmet? _____ år
- Deltidsarbeidende utenfor hjemmet? _____ år

	Ja	Nei
Har du søsken?	☐	☐

Hvis **Ja**, hvor mange ....Søstre? _____
Brødre? _____

Hvor mange barn hadde moren din født før du ble født? _____

Hvilken etnisk tilhørighet har dine forfedre?
(Foreldre/besteforeldre) (Sett kryss i de rutene som passer best)

- Norsk ☐
- Samisk ☐
- Annen europeisk ☐
- Finsk ☐
- Asiatisk ☐
- Annet; spesifiser _____

HØYDE/VEKT

Det kan være vanskelig å kjenne til høyde og vekt fra oppvekst og senere i livet. Likevel ber vi deg forsøke.

Fødsel:	Vekt _____ gram	Høyde _____ cm
18 år:	Vekt _____ kg	Høyde _____ cm
Dagens:	Vekt _____ kg	Høyde _____ cm

Hvordan mener du kroppen din var i forhold til jevnaldrende i oppveksten? (Sett ett kryss i hver aldersgruppe)

	Mye tynnere	Tynnere	Normal	Tykkere	Mye tykkere
Førskolealder	☐	☐	☐	☐	☐
1.-6. klasse	☐	☐	☐	☐	☐
7.-9. klasse (13-16 år)	☐	☐	☐	☐	☐

MENSTRUASJON/SVANGERSKAP/AMMING

Hvor gammel var du da du fikk din første menstruasjon? _____år ____måneder

Hvor lang tid tok det før menstruasjonen ble regelmessig? (Sett ett kryss i den ruten som passer best)

- Ett år eller mindre ☐
- Mer enn ett år ☐
- Aldri ☐
- Husker ikke ☐

Hvordan har menstruasjonen din vært ?
(Sett ett kryss)

- Alltid regelmessig ☐
- Oftest regelmessig ☐
- Uregelmessig ☐

Hva er gjennomsnittlig antall dager mellom hver menstruasjon? (fra 1. dag i en menstruasjon til 1. dag i neste menstruasjon) _____dager

	Ja	Nei
Har du født barn?	☐	☐
Hvis Ja, har du noen gang fått lege-behandling for kvalme i svangerskap?	☐	☐

Dersom du har født barn, fyll ut fødselsår og antall måneder du ammet hvert barn (fylles også ut for barn som er død senere i livet eller ved fødselen).

Barn nr	Fødselsår	Antall måneder med amming

FYSISK AKTIVITET

HUSARBEID

SISTE ÅRET

Tenk deg en gjennomsnittlig uke med husarbeid (arbeid i hjemmet, stell/påkledning av barn/pleietrengende) det siste året. Vi har delt husarbeid inn i 4 aktivitetsnivåer. Fyll inn for hvert aktivitetsnivå **antall dager pr uke** og gjennomsnittlig **tid pr dag (minutter)** du utførte arbeidet.

Aktivitetsnivå for husarbeid er definert som:	Dager pr uke	Min. pr dag
1 = **Overveiende stillesittende arbeid;** (f.eks. sy-,skrivearbeid)		
2 = **Lett arbeid, stående, sittende,** i sakte gange; (f.eks. matlaging, støvtørk)		
3 = **Middels tungt arbeid. Du svetter litt og hjertet slår litt fortere;** (f.eks. klesvask, støvsuging, stell/påkledning)		
4 = **Tungt arbeid. Du svetter mye og hjertet slår fort;** (f.eks. tung husvask)		

GJENNOM LIVET

Husarbeid endrer seg med livssituasjon og alder. Ved hjelp av de samme aktivitetsnivåer som over (1-4) ber vi deg i ulike aldre notere ned; **gjennomsnittlig antall dager pr uke og timer pr dag** hvert aktivitetsnivå ble utført.

Aktivitetsnivå:		Alder			
		10 -14 år	15-19 år	20-24 år	25-29 år
1 = Stille-sittende arbeid	Dager pr uke				
	Timer pr dag				
2 = Lett arbeid	Dager pr uke				
	Timer pr dag				
3 = Middels tungt arbeid	Dager pr uke				
	Timer pr dag				
4 = Tungt arbeid	Dager pr uke				
	Timer pr dag				

FRITIDSAKTIVITET (MOSJON, TURGÅING, IDRETT)

SISTE ÅRET

Hva slags aktivitet har du utført i din fritid det siste året? Dersom aktiviteten varierer mye, f.eks. mellom sommer og vinter, så tenk deg et gjennomsnitt. (Sett ett kryss i den ruten som passer best.)

1= Leser, ser på fjernsyn eller annen stillesittende aktivitet ..... ❑

2= Spaserer, sykler eller beveger deg på annen måte minst fire timer i uken (Her skal du også regne med gang eller sykling til arbeidssted, søndagsturer m.m.) ..... ❑

3= Driver mosjonsidrett, tyngre hagearbeid e.l. (Merk at aktiviteten skal vare i **minst fire timer** i uken.) ..... ❑

4= Trener hardt eller driver konkurranse idrett regelmessig og flere ganger i uken ..... ❑

FRITIDS AKTIVITETER OG KODER

Nedenfor ser du en liste med ulike fritidsaktiviteter. Vi ber deg finne de aktiviteter du har deltatt i. Oppgi i skjemaet nedenfor hvor lang tid (antall ganger pr måned og tid pr gang) du deltok i de ulike aktivitetene. Kryss av for det aktivitetsnivå som passer best for hver aktivitet ved hjelp av de 4 nivåer for fritidsaktivitet som er oppgitt nedenfor i aktivitetsnivå for fritidsaktiviteter.

1. Lese bøker/TV-titting
2. Gå til/ fra arbeid/ skole/ spaserturer/ trille barnevogn.
3. Gå i skogen/på fjellet/jakte
4. Jogge/løpe
5. Sykle til/fra arbeid/skole (også trimsykkel)
6. Svømme (også dykke/stupe)
7. Håndball/basketball/slåball/ fotball
8. Volleyball
9. Tennis/badminton/squash
10. Golf/bowling/curling
11. Friidrett kast/ høyde-lengde
12. Gymnastikk/aerobic/trim turning/dans/ballett
13. Styrketrening/vekttrening
14. Hoppe tau/strikk
15. Ski; langrenn - turgåing/ konkurranse
16. Kjøre slalåm/telemark/ snowboard
17. Akø/sparke/ gå på skøyter (også rulleskøyter)
18. Hesteridning
19. Ro/padle/seile
20. Plukke bær/sopp/fiske
21. Annet

AKTIVITETSNIVÅ FOR FRITIDSAKTIVITETER:

1 = Overveiende stillesittende.
2 = Lett trening. Du blir ikke svett og hjertet slår ikke fortere.
3 = Middels hard trening. Du svetter litt, og hjertet slår litt fortere.
4 = Hard trening. Du svetter mye, og hjertet slår fort.

Aktivitet Aktivitetstype	Mnd pr år	Gj.sn. ant. ggr. pr mnd.	Gj.sn. tid pr gang (min)	Aktivitetsnivå 1	2	3	4

GJENNOM LIVET

Se igjen på listen over de ulike fritidsaktiviteter. Vi ber deg finne de aktiviteter du har deltatt i. Deretter angi alder ved uført aktivitet og tiden du deltok (måneder pr år, tid pr uke og hver gang). Sett **ett** kryss for det aktivitetsnivået som passer best for hver aktivitet ved hjelp av de 4 nivåene oppgitt for fritidsaktivitet ovenfor.

Aktivitet og kode	Alder start	Alder slutt	Mnd pr år	Timer pr uke	Gj.sn tid pr gang (min)	Aktivitets-nivå			
						1	2	3	4

TV-TITTING, STILLESITTING, HVILE I FRITIDEN.

Hvor mange minutter eller timer av fritiden din pr døgn bruker du gjennomsnittelig på følgende aktiviteter? Ta et gjennomsnitt for siste året.

	Antall timer	Antall minutter
Hvile, sove	_____	_____
Lytte til musikk/radio	_____	_____
TV-/videotitting	_____	_____
Måltid, kaffe/te	_____	_____
Lese, skrive	_____	_____
Samtale, også pr telefon	_____	_____
Håndarbeid, hobby	_____	_____

ARBEIDS/SKOLE AKTIVITETER

SISTE ÅRET

Har du vært yrkesaktiv/student de siste 12 mnd?

Ja ❑ Nei ❑

Hvis Ja;

	Antall	
Arbeidsmåneder siste 12 mnd:	_____	mnd
Arbeidsdager pr uke:	_____	dager
Arbeidstimer pr dag:	_____	timer

Hva slags aktivitet har du vanligvis i arbeidet ditt / på skolen nå? (Sett **ett** kryss i den ruten som passer best)

1= For det meste stillesittende arbeid
(f.eks. kontorarbeid) ❑

2= Arbeid som krever at du går mye
Du blir ikke svett og hjertet slår ikke fortere
(f.eks. ekspeditør, lærer, frisør) ❑

3= Arbeid der du går og løfter mye.
Du svetter litt og hjertet kan slå raskere
(f.eks.syke-/hjelpepleier, postbetjent) ❑

4= Tungt kroppsarbeid.
Du svetter en del og hjertet slår raskt
(f.eks. tunge løft, landbruk, tungt omsorgsarbeid) ❑

Tenk deg en gjennomsnittlig uke med aktiviteter i arbeidet/på skolen i det siste året. Vi har også her delt aktivitetene inn i de samme 4 aktivitetsnivåer. Fyll inn for hvert aktivitetsnivå antall måneder pr år, timer pr uke og timer gjennomsnitt pr dag du utførte aktiviteten.

Type arbeids aktivitetsnivå	Måneder pr år	Timer pr uke	Gjennom-snitt pr dag
1= Stillesittende			
2= Står og går			
3= Går og bærer			
4= Tungt			

TRANSPORT TIL/FRA ARBEID/SKOLE

Spørsmålene gjelder transport mellom hjemmet og arbeidsplassen det siste året.

Hvordan kommer du deg vanligvis til/fra arbeid?

Ta et gjennomsnitt for en måned (Angi antall ggr du bruker de forskjellige transportmidlene.)

	Antall ggr. pr mnd
1.Bil	_____
2.Buss/trikk/tog/båt	_____
3.Sykkel	_____
4.Til fots	_____

Hvor lang tid tar vanligvis transporten til/fra arbeid?

Legg sammen tiden tur/retur for hvert transportmiddel. Oppgi «til fots» tiden du eventuelt går til/fra p-plass/ busstopp e.l.

1.Bil	_____min
2.Buss/trikk/tog/båt	_____min
3.Sykkel	_____min
4.Til fots	_____min

GJENNOM LIVET

Vi ber deg først skrive hvilke skoler/yrker du har/har hatt. Dersom du har hatt arbeidsplass i hjemmet som annet enn husmor, f.eks. gårdbruker, dagmamma, sydame, oppgi dette som yrker. Du kan ha hatt flere yrker i samme tidsrom, f.eks. ved deltidsarbeid. Fyll inn når du startet og sluttet i hvert yrke og hvor mye tid (antall måneder pr år, dager pr uke og timer pr dag) du vanligvis bruker/brukte. Kryss av for det aktivitetsnivået som passer best for hvert yrke ved hjelp av de 4 nivåene over.

Yrker/ skoler	Alder start	Alder slutt	Mnd pr år	Dager pr uke	Timer pr dag	Aktivitetsnivå			
						1	2	3	4

LEGEMIDLER

Vi ber deg krysse **Ja** for legemiddler du har brukt (uansett mengde) av og til og **Nei** for dem som du aldri har brukt. Dersom du krysser **Ja**, forsøk å huske alderen din første gangen du tok legemiddelet og antall ggr. pr måned du bruker det nå.

	Ja	Nei	Alder 1. gang	Ant. ggr. pr mnd
Blodtrykksmedisin	☐	☐		
Smertestillende (Acetylsalesylsyre/Albyl E)	☐	☐		
Midler mot depresjon	☐	☐		
Hvis Ja, hvilke				
Andre	☐	☐		
Hvis Ja, hvilke				

Vi ber deg krysse Ja for følgende legemidler du bruker fast (daglig, nesten daglig):

	Ja
Sovemedisin	☐
Smertestillende	☐
Blodtrykksmedisin	☐
Medisin mot depresjon	☐
Andre legemidler	☐
Hvis Ja, hvilke	
Naturmedisin	☐
Hvis Ja, hvilke	

KREFT I FAMILIEN

Har nære biologiske slektninger av deg hatt kreft? Ja ☐ Nei ☐

Hvis Ja, hvilken type kreft på mors- og farside;

Mors side	*Type kreft*	Nei	Vet ikke	*Fars side*	*Type kreft*	Nei	Vet ikke
Mor		☐	☐	Far		☐	☐
Mormor		☐	☐	Farfar		☐	☐
Morfar		☐	☐	Farmor		☐	☐
Tante		☐	☐	Onkel		☐	☐
Onkel		☐	☐	Tante		☐	☐
Andre		☐	☐	Andre		☐	☐
angi slektsskap				angi slektsskap			

LEVEVANER

Har du noen gang røykt daglig? Ja ☐ Nei ☐

Hvis Ja, hvor mange sigaretter røykte du gjennomsnittlig daglig? (Sett ett kryss i de ulike aldersgruppene)

	Antall sigaretter daglig						
	0	1-4	5-9	10-14	15-19	20-24	25+
12-14 år	☐	☐	☐	☐	☐	☐	☐
15-19 år	☐	☐	☐	☐	☐	☐	☐
20-24 år	☐	☐	☐	☐	☐	☐	☐
25-34 år	☐	☐	☐	☐	☐	☐	☐

Røyker du daglig nå? Ja ☐ Nei ☐

Hvis Ja, hvor mange sigaretter pr dag? _____stk

Hvor mange dagligrøykere bodde du sammen med i følgende aldre? (Sett ett kryss på hver linje.)

Antall personer:	Ingen	1	2	3 el. flere	Vet ikke
Barneårene	☐	☐	☐	☐	☐
15-19 år	☐	☐	☐	☐	☐
20-24 år	☐	☐	☐	☐	☐
25-34 år	☐	☐	☐	☐	☐

Bor du sammen med noen som røyker nå? Ja ☐ Nei ☐

Hvis Ja, hvor mange sigaretter røyker de i gjennomsnitt sammenlagt daglig når du er sammen med de? _____stk

Har du noen gang arbeidet på røykfulle arbeidsplasser? Ja ☐ Nei ☐

Hvis Ja, hvor lenge til sammen? _____ antall år

Har du noen gang drukket alkohol? Ja ☐ Nei ☐

Hvis Ja, hvor mange glass vin, 1/2 litere øl eller drinker brennevin drakk du i gjennomsnitt pr måned i følgende aldre? (Sett ett kryss på hver linje)

	aldri/ sjelden	1 pr mnd.	2-3 pr mnd.	1 pr uke	2-4 pr uke	5-6 pr uke	1+ pr dag
15-19 år	☐	☐	☐	☐	☐	☐	☐
20-24 år	☐	☐	☐	☐	☐	☐	☐
25-34 år	☐	☐	☐	☐	☐	☐	☐

Er du totalavholdskvinne nå? Ja ☐ Nei ☐

Hvis Nei, hvor mange glass vin, 1/2 litere øl eller drinker brennevin drakk du i gjennomsnitt pr måned eller pr uke siste året? (Sett ett kryss på hver linje).

	aldri/ sjelden	1 pr mnd.	2-3 pr mnd.	1 pr uke	2-4 pr uke	5-6 pr uke	1+ pr dag
Øl (1/2l)	☐	☐	☐	☐	☐	☐	☐
Vin (glass)	☐	☐	☐	☐	☐	☐	☐
Hetvin (0,4 dl)	☐	☐	☐	☐	☐	☐	☐
Brennevin (drinker)	☐	☐	☐	☐	☐	☐	☐

Dine kommentarer

_____

_____

_____

Vi ber om tillatelse til å kontakte deg på nytt ved et senere tidspunkt for å oppdatere opplysningene.

Ja ☐ Nei ☐

Takk for at du ville delta i undersøkelsen!

P-PILLER/P-SPRØYTE/HORMONSPIRAL Løpenr_____

	Ja	Nei
Har du noen gang brukt p-piller, minipiller inkludert?	☐	☐
Har du noen gang brukt p-sprøyte ?	☐	☐
Har du brukt hormonspiral?	☐	☐
Hvis du har født barn, brukte du p-piller/sprøyte/spiral før første fødsel?	☐	☐
Har du fått p-piller/sprøyte/spiral av andre årsaker enn prevensjon?	☐	☐
Har du blitt anbefalt å slutte med p-piller/sprøyte/spiral av medisinske årsaker?	☐	☐

Vi ønsker mer detaljert informasjon om p-pille/sprøyte/spiral bruk.

Kan du huske hvilke perioder du har brukt p-piller/sprøyte/spiral sammenhengende?

Hvor gammel var du da du startet?

Hvor gammel var du da du sluttet?

Hvor lenge brukte du det samme p-pille/sprøyte/spiral merket?

Hva var navnet på p-pillen/sprøyten/spiralen (se vedlagt liste over navn og nummer); dersom du ikke husker merket, skriv "usikker" i navnefeltet?

Periode	Alder start	Alder slutt	Sammenhengende		P-pille	
			År	Måneder	Nummer	Navn
Første						
Andre						
Tredje						
Fjerde						
Femte						
Sjette						
Syvende						

P-pille/sprøyte/spiral merker:

Enfase-piller

Vanlig bruk: 1 tablett daglig i 21-22 dager, deretter opphold (evnt placebotablett i 7-6 dager)

(1) **Follimin**

(2) **Microgynon**

(3) **Eugynon**

(4) **Marvelon**

(5) **Yasmin**

(6) **Diane**

(7) **Loette**

Sekvens-piller

Vanlig bruk: Leveres i datopakninger

(8) **Synfase**

(9) **Trinordiol**

(10) **Trionetta**

Minipiller

(11) **Conludag**

(12) **Exlutona**

(13) **Microluton**

P-sprøyte

(14) **Depo-provera**

Hormonspiral

(15) **Levonova**

Annet

(16) Angi hvilket

Usikker

(17)

EBBA-STUDIEN

Sammenhengen mellom livsstil og brystkreft

Daglig log-registrering av spyttprøver og fysisk aktivitet

INSTRUKSJONER FOR UTFYLLING Lpnr: _____

Fyll ut daglig log hver dag.

- **Dato** Skriv inn både dag og dato, for eksempel: tirsdag 16. Oktober 2001.
- **Søvn** Skriv inn antall timer du har sovet de siste 24 timer og tidspunkt du sto opp.

- **Tid prøve** betyr klokkeslett spytt prøver
  Bruk 24-timer angivelse. Eks: 7.30 om morgenen og 19.30 om kvelden. Dersom du mister en prøve en dag, skriv "Missing".
  Jo mer fullstendig du registrerer dato og klokkeslett for spytt prøven, jo større er sjansen for at alle dine prøver senere vil la seg identifisere korrekt.

- **Blødning** Indikerer om du har hatt menstruasjonsblødning i løpet av de siste 24 timene.
  JA dersom du har hatt blødning, NEI dersom du ikke har hatt det.

- **Aktivitetens type og varighet**
  Transport:
  Vi ønsker å vite hvordan du kom deg til og fra arbeid, butikk, fritidsarrangement etc i løpet av dagen. Velg type transport du har benyttet, og fyll inn varigheten.

  Jobb:
  Vi ønsker å vite alle typene aktiviteter du har drevet med i løpet av dagen på arbeid. Velg det nivået du synes passer best for hver arbeidsoppgave du har utført, og fyll inn varighet av aktiviteten.

  Arbeid i hjemmet inne og ute:
  Vi ønsker å vite alle arbeidsaktiviteter du har utført hjemme, enten inne eller ute, i løpet av dagen. Velg det nivået du synes passer best for hvert arbeid du har gjort, og fyll inn varighet av arbeidet. Du kan i tillegg skrive akkurat hva du har gjort.

  Fritid:
  Vi ønsker å vite alle typer aktiviteter du har drevet med utenom det du har oppgitt som arbeid i jobb eller hjemme. Velg aktiviteter fra listen eller skriv med egne ord hvilke aktiviteter du har drevet med i løpet av dagen. Bruk intensitetsskalaen 1-4 for å angi hvor mye du anstrengte deg ved hver aktivitet. Husk å angi varighet for hver aktivitetstype.

  Det er viktig å få med all fysisk aktivitet i løpet av døgnet.
  Enkelte sysler, som f. eks. shopping, hører ikke klart hjemme i noen av kategoriene over, men kan skrives i åpne felt under fritidsaktivitet eller tilleggsinformasjon.

- **Tilleggsinformasjon**-feltet kan benyttes til kommentarer og til aktiviteter som du ikke har skrevet andre steder.

Dag 1	Prøvetaking				Fysisk aktivitet		
Dato ukedag	Søvn (ant. timer)	Tid du våknet (klokkeslett)	Tid spytt prøve (kl.)	Blødningsdag (Ja/Nei)	Type aktivitet		Varighet (t/min)
					Transport	Bil	
Tilleggsinformasjon:						Buss/tog/trikk	
						Sykkel	
						Til fots: spasere	
						jogge/løpe	
					Jobb	Stillesittende	
						Stående	
						Sakte gange	
						Lett kroppsarbeid	
						Hardt kroppsarbeid	
					Arbeide i hjemmet inne og ute	Stillesittende (f.eks. sy)	
						Stående (f.eks. lage mat)	
						Sakte gange (f.eks. tørke støv)	
						Middels tungt (f.eks. støvsuge)	
						Tungt arbeid (f.eks. gulvvask)	

Ulike typer fritidsaktiviteter:		Fritid	Type aktivitet	Varighet (t/min)	Intensitet (1-4)
1. Lese bøker/TV-titting	8. Slalåm/telemark/snowboard				
2. Spasere/trille barnevogn	9. Ski (langrenn, turgåing)				
3. Gå i skogen/fjellet	10. Tennis, badminton				
4. Plukke bær/sopp	11. Golf/bowling				
5. Jogge/løpe	12. Styrke/vekt-trening				
6. Sykle	13. Svømming				
7. Trim/gymnastikk/aerobic	14. Ake/sparke/skøyter/rulleskøyter				
	15. Annet				
Intensitetsnivåer for fritidsakt.:					
1= Overveiende stillesittende	3= Middels hard aktivitet. Du svetter litt og hjertet slår litt fortere				
2= Lett aktivitet. Du blir ikke svett og hjertet slår ikke fortere	4= Hard trening. Du svetter mye og hjertet slår fort				

Dag 2	Prøvetaking				Fysisk aktivitet		
Dato ukedag	Søvn (ant. timer)	Tid du våknet (klokkeslett)	Tid spytt prøve (kl.)	Blødningsdag (Ja/Nei)	Type aktivitet		Varighet (t/min)
					Transport	Bil	
Tilleggsinformasjon:						Buss/tog/trikk	
						Sykkel	
						Til fots: spasere	
						jogge/løpe	
					Jobb	Stillesittende	
						Stående	
						Sakte gange	
						Lett kroppsarbeid	
						Hardt kroppsarbeid	
					Arbeide i hjemmet inne og ute	Stillesittende (f.eks. sy)	
						Stående (f.eks. lage mat)	
						Sakte gange (f.eks. tørke støv)	
						Middels tungt (f.eks. støvsuge)	
						Tungt arbeid (f.eks. gulvvask)	

Ulike typer fritidsaktiviteter:		Fritid	Type aktivitet	Varighet (t/min)	Intensitet (1-4)
1. Lese bøker/TV-titting	8. Slalåm/telemark/snowboard				
2. Spasere/trille barnevogn	9. Ski (langrenn, turgåing)				
3. Gå i skogen/fjellet	10. Tennis, badminton				
4. Plukke bær/sopp	11. Golf/bowling				
5. Jogge/løpe	12. Styrke/vekt-trening				
6. Sykle	13. Svømming				
7. Trim/gymnastikk/aerobic	14. Ake/sparke/skøyter/rulleskøyter				
	15. Annet				
Intensitetsnivåer for fritidsakt.:					
1= Overveiende stillesittende	3= Middels hard aktivitet. Du svetter litt og hjertet slår litt fortere				
2= Lett aktivitet. Du blir ikke svett og hjertet slår ikke fortere	4= Hard trening. Du svetter mye og hjertet slår fort				

EBBA-STUDIEN

Sammenhengen mellom livsstil og brystkreft

Kostdagbok

Dato:_____ Ukedag:_____ Reg. dag:_____

Var denne dagen en ganske vanlig dag eller en helt uvanlig dag med hensyn til hva du spiste og drakk?

Vanlig dag ❑ Uvanlig dag ❑

Hvis uvanlig dag angi årsak:

_____

Hvor finner jeg de forskjellige matvarene?

Tran/kosttilskudd

1 barneskje = 5 ml	Antall	Morgen	For-middag	Etter middag	Kveld
Tran	barneskje				
Trankapsler	stk				
Sanasol	barneskje				
Biovit	barneskje				
Multivitaminpille (eks. Vitaplex, Vitamineral)	stk				
Fluortabletter	stk				
Jerntabletter (9mg)	stk				
C-vitaminer (eks. Ester C)	stk				
Annet – beskriv type og mengde:					

Drikke

Bruk **Bildeserie 1 og 2** for å angi størrelsen på glassene og koppene

1/2 liter = 2,5 glass

	Antall	Morgen	For-middag	Etter middag	Kveld
Vann, usøtet mineralvann (eks. Farris)	glass				
Helmelk (søt/sur)	glass				
Lettmelk (søt/sur)	glass				
Ekstra Lett lettmelk	glass				
Skummet melk (søt/sur)	glass				
Drikkeyoghurt	glass				
Sjokolademelk (eks. O'Boy, Litago)	glass				
Kakao	kopp				
Juice, nektar	glass				
Brus, saft med sukker	glass				
Brus, saft uten sukker	glass				
Te	kopp				
Iste med sukker	glass				
Kaffe	kopp				
Suketter (eks. Natrena, Canderel)	stk				
Sukker til te, kaffe	teskje				
Melk til te, kaffe	spiseskje				
Øl	1/2 liter				
Vin	vinglass				
Brennevin	drink				
Annet – beskriv type og mengde:					

Yoghurt

	Antall	Morgen	For-middag	Etter middag	Kveld
Yoghurt naturell	beger (175 ml)				
Yoghurt med frukt	beger (175 ml)				
Lettyoghurt	beger (150 ml)				
Go'morgen yoghurt m/müsli	beger (inkludert müsli)				
Annet – beskriv type og mengde:					

Brød m.m.

Bruk **Bildeserie 3** for å angi tykkelse på brødet

1 skive = 1/2 rundstykke

	Antall	Morgen	For-middag	Etter middag	Kveld
Loff, fint rundstykke	skiver bildeserie 3				
Mellomgrovt brød (eks. kneip), - grovt rundstykke	skiver bildeserie 3				
Grovbrød	skiver bildesene 3				
Baguette, ciabatta	stk				
Knekkebrød	stk				
Lompe	stk				
Pølsebrød, hamburgerbrød	stk				
Flatbrød	stk				
Annet – beskriv type og mengde:					

Hva smurte du på brødet?

Angi hvor mye smør/margarin du har på brødet, se **bildeserie 4**

1 skive = 1/2 rundstykke = 2 kjeks

	Antall	Morgen	For-middag	Etter middag	Kveld
Meierismør	skiver				
Myk margarin (eks. Soya soft)	skiver				
Lett margarin (eks. Soft light)	skiver				
Hard margarin (eks. Per, Melange)	skiver				
Annet – beskriv type og mengde:	skiver				

Frokostgryn og grøt

	Antall	Morgen	For-middag	Etter middag	Kveld
Havregrøt	bildeserie 6				
Havregryn, firkorn	bildeserie 5				
Müsli søtet (eks. Crüsli, Solfrokost)	bildeserie 5				
Müsli usøtet (eks. Go'Dag, Gullfrokost)	bildeserie 5				
Cornflakes	bildeserie 5				
Frosties, chocofrokost, honnikorn	bildeserie 5				
Annet – beskriv type og mengde:					

Tilbehør til frokostgryn og grøt

1 spiseskje = 3 teskjeer

	Antall	Morgen	For-middag	Etter middag	Kveld
Helmelk (søt/sur)	dl				
Lettmelk (søt/sur)	dl				
Ekstra lett lettmelk	dl				
Skummet melk (søt/sur)	dl				
Syltetøy vanlig, gelé, marmelade	teskjeer				
Syltetøy lett, frysetøy	taskjeer				
Sukker	teskjeer				
Annet – beskriv type og mengde:					

Pålegg

Oppgi mengde pålegg i forhold til brødskiver.
Om du har spist to typer pålegg på samme brødskive, fører du opp begge. (Eks. 1 hvitost helfet og 1 skinke.)

Hvis du bare har spist pålegg og ikke brød, anslå til hvor mange skiver du kunne brukt dette pålegget.

1 skive = 1/2 rundstykke = 1 knekkebrød = 2 kjeks

	Antall	Morgen	For-middag	Etter middag	Kveld
Ost					
Hvitost helfet 27% fett (eks. Jarlsberg, Norvegia)	til antall skiver				
Hvitost halvfet 16% fett (eks.Norvegia lettere)	til antall skiver				
Brunost helfet (eks. Geitost G35, Fløtemysost)	til antall skiver				
Brunost halvfet, prim	til antall skiver				
Smøreost, vanlig (eks. Baconost, Snøfrisk)	til antall skiver				
Smøreost, mager (eks. mager skinkeost, mager prim)	til antall skiver				
Dessertoster (eks. Brie, Gräddost, Gourmet frukt)	til antall skiver				
Kjøttpålegg					
Servelat vanlig	til antall skiver				
Skinke, spekeskinke, lettservelat	til antall skiver				
Salami, spekepølse, fårepølse	til antall skiver				
Leverpostei vanlig	til antall skiver				
Leverpostei mager	til antall skiver				
Fiskepålegg					
Kaviar	til antall skiver				
Røkt laks, ørret	til antall skiver				
Makrell i tomat, røkt makrell	til antall skiver				
Sardiner, sursild, ansjos	til antall skiver				
Syltetøy, søtt pålegg					
Syltetøy vanlig, gelé, marmelade	til antall skiver				
Syltetøy lett, frysetøy	til antall skiver				
Honning	til antall skiver				
Peanøttsmør	til antall skiver				
Sjokolade, søtt pålegg	til antall skiver				
Annet pålegg					
Majonessalat (eks. italiensk salat, rekesalat)	til antall skiver				
Majonessalat lett	til antall skiver				
Tomat som pålegg	til antall skiver				
Banan som pålegg	til antall skiver				
Majones, remulade vanlig	til antall skiver				
Majones, remulade lett	til antall skiver				
Annet – beskriv type og mengde:					

Kjøtt og kjøttretter

	Antall	Morgen	For-middag	Etter middag	Kveld
Pølse					
Grillpølse, wienerpølse vanlig	stk				
Grillpølse, wienerpølse lett	stk				
Middagspølse, kjøttpølse, medisterpølse	kjøttpølse				
Middagspølse lett, kjøttpølse lett	kjøttpølse				
Kjøttdeigretter, pasta, pizza					
Kjøttkaker, karbonadekaker	stk				
Medisterkaker	stk				
Tacoskjell (med kjøttdeig og salat)	fylte skjell				
Kebab, pitabrød (med kjøtt og salat)	fylte pitabrød				
Kjøttdeigsaus, tomatsaus med kjøttdeig	bildeserie 12				
Pasta med tomatsaus uten kjøtt	bildeserie 7				
Pasta med hvit saus	bildeserie 7				
Lasagne	stykke (10 x 5 cm)				
Pizza, firkantete stykker	bildeserie 14				
Pizza, trekantete stykker	bildeserie 13				
Rent kjøtt					
Biff (okse, lam, svin)	stk				
Koteletter (svin, lam, okse)	stk				
Stek (svin, okse, lam)	skiver				

Kokt skinke	skiver				
Grillet kylling	1/4 kylling				
Kyllingfilet	filèer				
Bacon	skiver				

Gryteretter

Risotto, risretter	bildeserie 12				
Fårikål, frikasé	bildeserie 12				
Lapskaus	bildeserie 12				
Kjøttgryte (kjøtt og grønnsaker i samme gryte)	bildeserie 12				
Leverretter	bildeserie 12				
Annet – beskriv type og mengde:					

Fisk og fiskeretter

	Antall	Morgen	For-middag	Etter middag	Kveld
Fiskefarse, fiskemat					
Fiskeboller	stk				
Fiskekaker, fiskepudding	stk/skiver				
Ren fisk					
Torsk, sei, uer (kokt)	skiver				
Torsk, sei, uer (stekt)	bildeserie 15				
Laks, ørret, kveite (kokt)	ver				
Laks, ørret, kveite (stekt)	b eserie 15				
Sild, makrell (kokt)	sk ver				
Sild, makrell (stekt)	bildeserie 15				
Flyndre, steinbit (kokt)	skiver				
Flyndre, steinbit (stekt)	bildeserie 15				
Tillagede fiskeretter og fiskepinner					
Fiskepinner	stk				
Panert fisk	stk (10x10 cm)				
Fiskegryte, fiskesuppe	dl				
Fiskegratene, plukkfisk	dl				
Reker uten skall	dl				
Annet – beskriv type og mengde:					

Annen varm mat/salater

	Antall	Morgen	For-middag	Etter middag	Kveld
Risengrynsgrøt	bildeserie 6				
Pannekaker	stk				
Kjøttsuppe (eks. betasuppe med kjøtt)	tallerken				
Suppe (eks. blomkålsuppe, tomatsuppe)	tallerken				
Egg, kokt, stekt	antall egg				
Omelett	antall egg				
Ostepai, quiche	stykke (10 x 8 cm)				
Blandet salat med ost, kjøtt eller skalldyr	bildeserie 11				
Salat med pasta og ost, kjøtt eller skalldyr.	bildeserie 11				
Vegetarrett – beskriv type og mengde:					
Annet – beskriv type og mengde:					

Poteter/ris/pasta

	Antall	Morgen	For-middag	Etter middag	Kveld
Potet, kokt	stk				
Potet, bakt	stk				
Potetmos	bildeserie 8				
Pommes frites	bildeserie 9				
Stekt potet	bildeserie 9				
Potetsalat	spiseskjeer				
Ris, kokt	bildeserie 7				
Pasta kokt (eks. spaghetti, makaroni, tagliatelle)	bildeserie 7				
Annet – beskriv type og mengde:					

Grønnsaker

	Antall	Morgen	For-middag	Etter middag	Kveld
Gulrot	stk				
Kålrot	skive				
Brokkoli, blomkål	dl				
Hodekål	dl				
Råkost (blandet av flere grønnsaker)	bildeserie 10				
Grønnsaksblanding kokt	bildeserie 10				
Blandet salat (eks. kinakål, mais, tomat og agurk)	bildeserie 11				
Tomat, paprika, stekt løk	ringer				
Annet – beskriv type og mengde:					

Sauser/dressinger

1 spiseskje = 3 teskjeer

	Antall	Morgen	For-middag	Etter middag	Kveld
Hvit saus	spiseskjeer				
Brun saus	spiseskjeer				
Smeltet smør, margarin	spiseskjeer				

Tomatsaus (uten kjøtt)	spiseskjeer				
Bernaise saus	spiseskjeer				
Dressing vanlig (eks. Thousand Island)	spiseskjeer				
Dressing lett (eks. Thousand Island light)	spiseskjeer				
Seterrømme 35 % fett	spiseskjeer				
Lettrømme 20 % fett	spiseskjeer				
Majones, remulade vanlig	spiseskjeer				
Majones, remulade lett	spiseskjeer				
Oljedressing (eks. Fransk dressing)	spiseskjeer				
Annet – beskriv type og mengde:					

Is/dessert

	Antall	Morgen	For-middag	Etter middag	Kveld
Is (eks. vanilje, krokan)	bildeserie 16				
Ispinne, kremmerhus (eks. Gullpinne, Kroneis)	stk				
Gelé	bildeserie 16				
Pudding (eks. sjokoladepudding, karamellpudding)	bildeserie 16				
Riskrem, multekrem, fromasj	bildeserie 16				
Fløte	spiseskjeer				
Krem, pisket	spiseskjeer				
Sjokoladesaus, karamellsaus	spiseskjeer				
Vaniljesaus	dl				
Annet – beskriv type og mengde:					

Frukt/bær

	Antall	Morgen	For-middag	Etter middag	Kveld
Eple, pære	stk				
Banan	stk				
Appelsin	stk				
Mandarin, klementin	stk				
Druer	stk				
Fersken, nektarin	stk				
Friske, frosne bær	dl				
Annet – beskriv type og mengde:					

Kaker/kjeks

	Antall	Morgen	For-middag	Etter middag	Kveld
Boller, kringle, skolebrød	stk				
Wienerbrød	stk				
Vafler	hjerter				
Epiekake, formkake	stykke				
Sjokoladekake	stykke				
Bløtkake	stykke				
Fyrstekake, nøttekake	stykke				
Kjeks (eks. Mariekjeks, Gjende)	stk				
Fylte kjeks (eks. Ballerina, Maryland Cookies)	stk				
Havrekjeks (eks. Bixit, Sibas)	stk				
Smørbrødkjeks (eks. Kornmo, Golden Crisp)	stk				
Smørbrødkjeks (eks. Kaptein, Start)	stk				
Salte kjeks (eks. Ritz, Salinas)	stk				
Annet – beskriv type og mengde:					

Sjokolade/godterier

	Antall	Morgen	For-middag	Etter middag	Kveld
Melkesjokolade (eks. Melkesjokolade, Firkløver, Helnøtt)	sjokoladeplate (100 g)				
Marsipan med sjokolade (eks. Gullbrød)	stk (65 gram)				
Sjokoladebiter (eks. Twist, konfekt).	biter				
Snickers, Japp (vanlig 60 g)	stk				
Kjekssjokolade (eks. Kvikklunsj,Twix)	Kvikklunsj størrelse				
Troika	stk				
New Energy	stk				
Smågodt (eks. skumgodt, gelé, lakris, karamell, vingummi, drops)	stk				
Annet – beskriv type og mengde:					

Snacks

	Antall	Morgen	For-middag	Etter middag	Kveld
Potetgull vanlig (1 neve = 8 flak)	neve				
Potetgull lett , potetskruer (1 neve = 8 flak)	neve				
Ostepop (1 neve = 8 "ostebuer")	neve				
Peanøtter	pose (100 g)				
Dip (eks. rømme m/dipmix, cheese dip)	spiseskjeer				
Annet – beskriv type og mengde:					

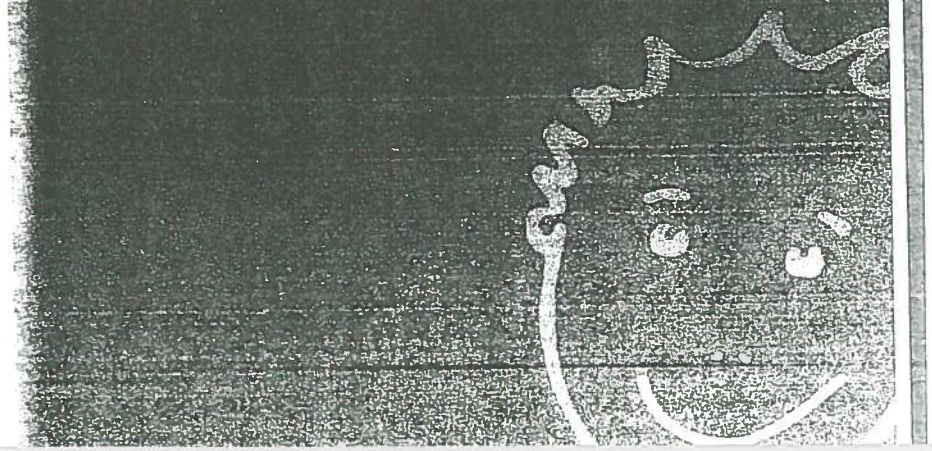
Takk for at du ville delta i undersøkelsen!

ID. nummer_____ . _____

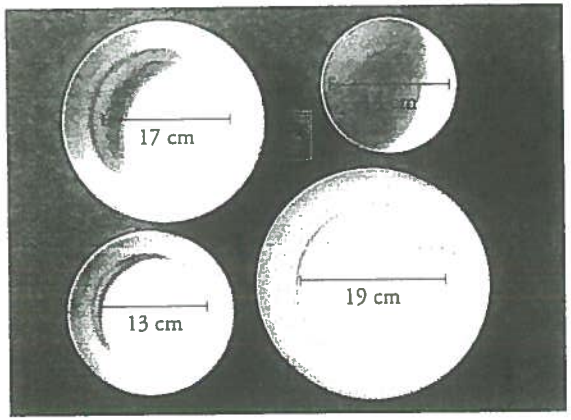
STATENS RÅD FOR ERNÆRING OG FYSISK AKTIVITET

SNT Statens næringsmiddeltilsyn

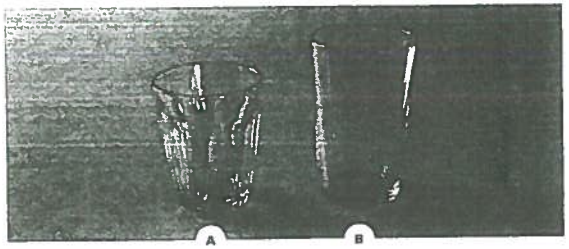
Bildehefte med porsjonsstørrelser



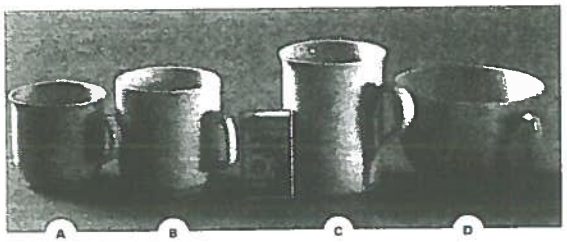
DETTE BILDET VISER STØRRELSEN PÅ TALLERKENENE SOM ER BRUKT I BILDEHEFTET



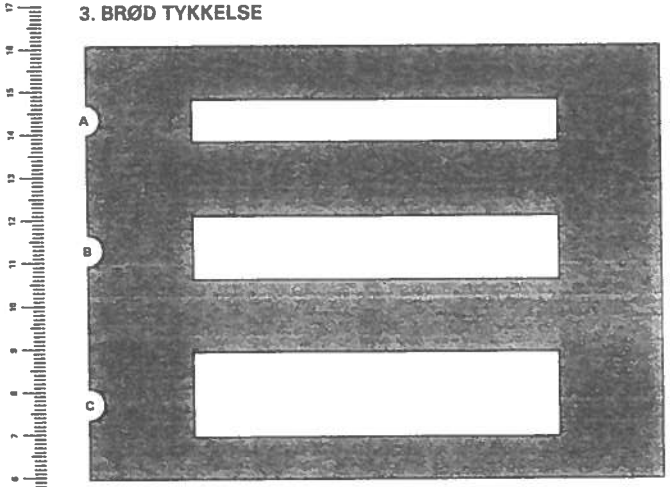
1. GLASS



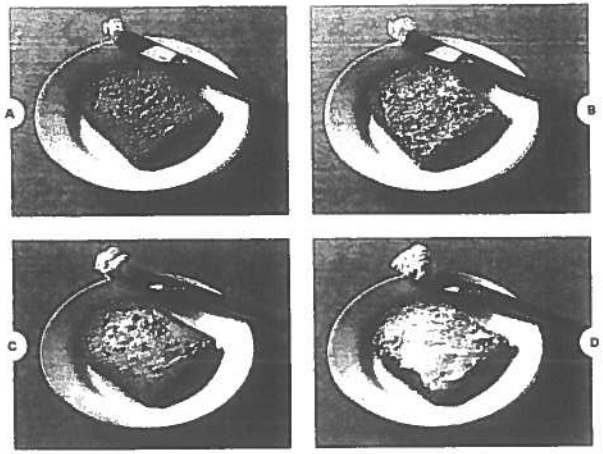
2. KOPPER



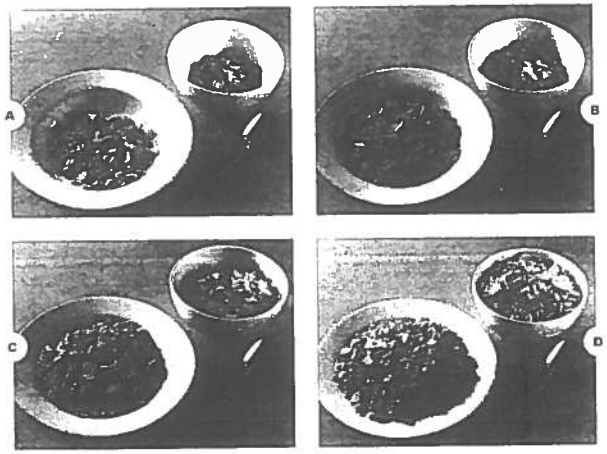
3. BRØD TYKKELSE



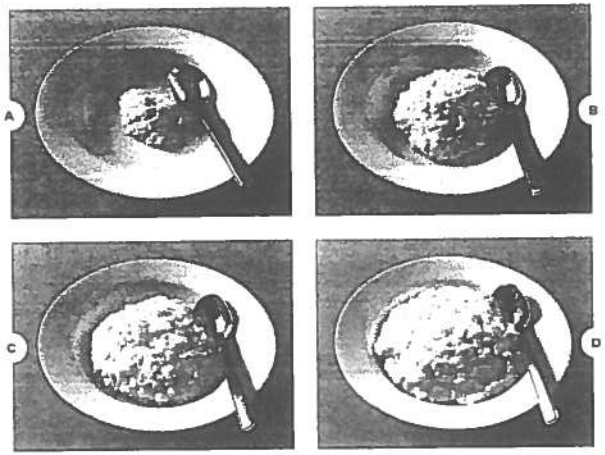
4. SMØR/MARGARIN PÅ BRØDET



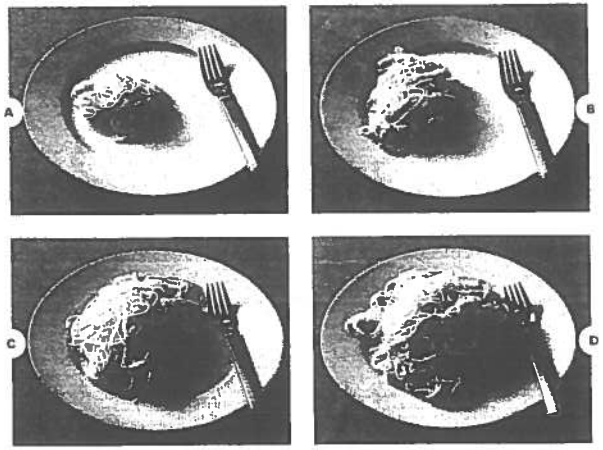
5. CORNFLAKES (FROKOSTBLANDING)



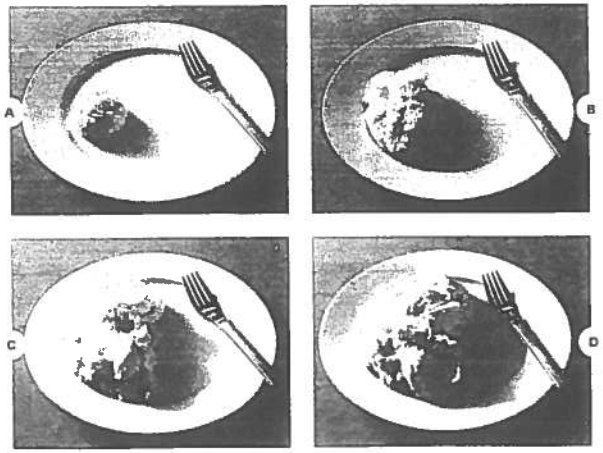
6. GRØT



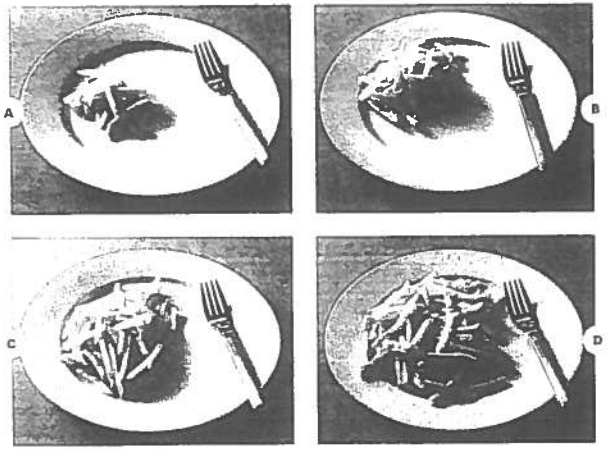
7. SPAGHETTI / PASTA (RIS)



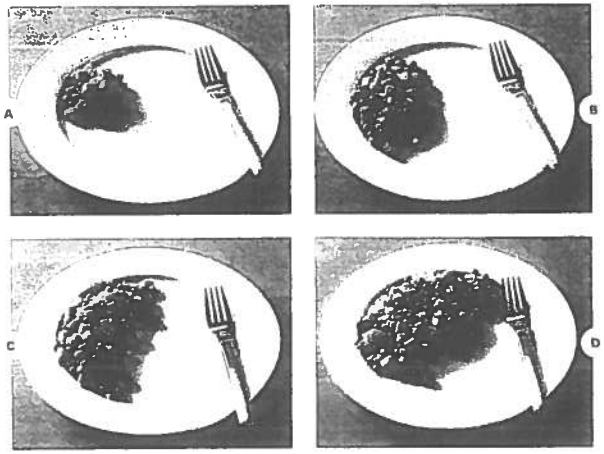
8. POTETMOS



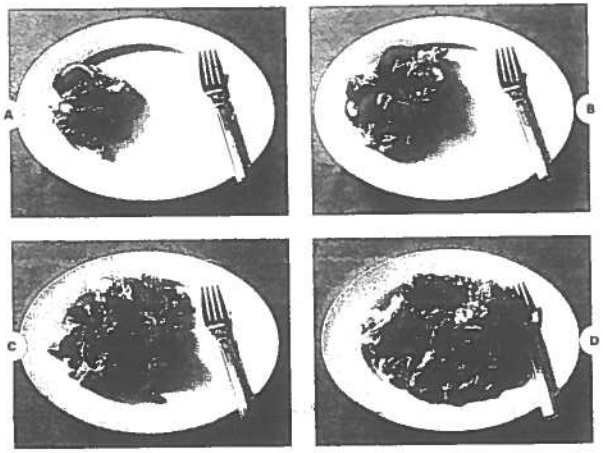
9. POMMES FRITES (STEKT POTET)



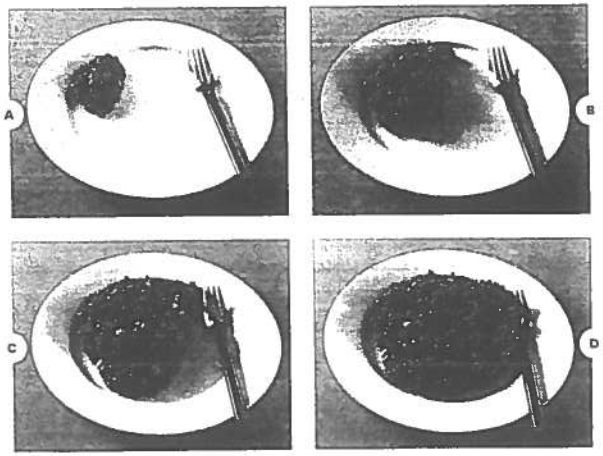
10. GRØNNSAKSBLANDING (RÅKOST)



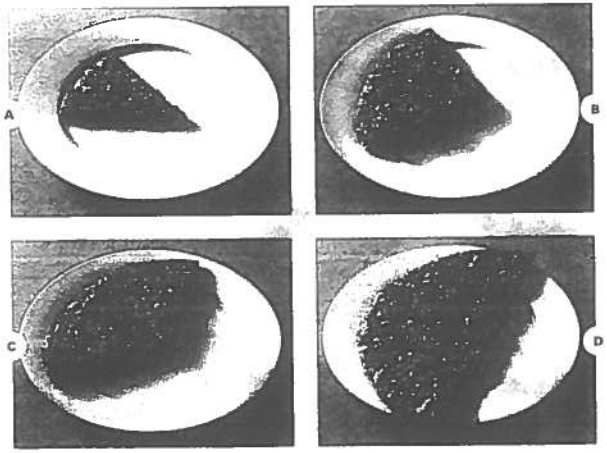
11. SALAT



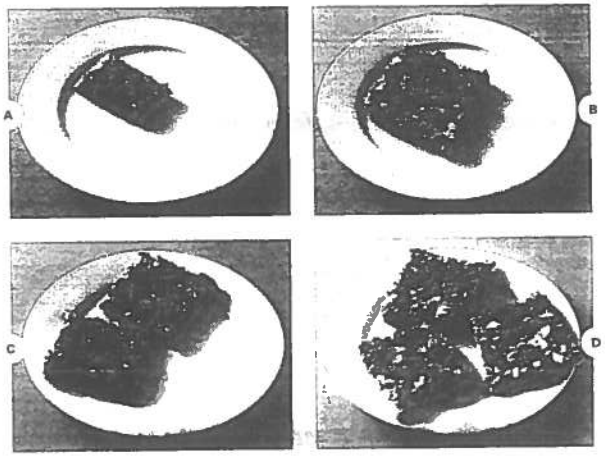
12. KJØTTSAUS (LAPSKAUS)



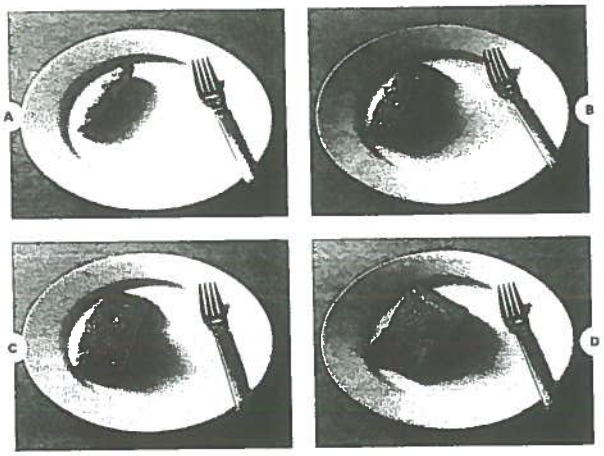
13. PIZZA, TREKANTSTYKKER



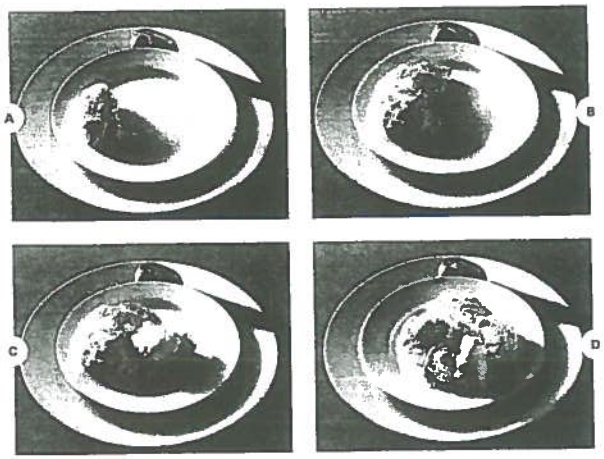
14. PIZZA, FIRKANTSTYKKER



15. FISKEFILET



16. IS (PUDDING)



Livskalender

Det kan være vanskelig å huske hva man har gjort tidligere, hva man drev på med i forskjellige perioder av livet og hvor fysisk aktiv man har vært. Kanskje kan det hjelpe å ha en slik livskalender framfor seg og eventuelt fylle den ut før du begynner å svare på spørreskjemaet.

År	Hva skjedde?	Forslag til hendelser du kan skrive inn:
1964		
1965		- Fødselsår
1966		
1967		
1968		
1969		
1970		
1971		- Start barneskole
1072		
1973		
1974		
1975		
1976		- Start ungdomsskole
1977		- Første menstruasjon
1978		
1979		
1980		- Evt konfirmasjon
1981		- Start evt andre skoler
1982		
1983		
1984		- Arbeid
1985		
1986		- Fødsel evt barn
1987		
1988		- Evt andre hendelser:
1989		Fikk søsken
1990		Reiser
1991		Bryllup
1992		Familiehendelser (mor/ far 50 år osv)
1993		
1994		
1995		
1996		
1997		
1998		
1999		
2000		
2001		
2002		

TIDSPLAN
DELTAKELSE I EBBA-STUDIEN

"MENS" SYKLUS	HJEMME	STUDIE SENTER
Dag 1	OBS!Spyttprøve 1 Start daglig log.	Ring sykepleier
Dag 2		Visitt 1: Dag 2 blodprøver målinger
Dag 3-6	Kostdagbok dag 3	
Dag 5	Kostdagbok dag 4	
	Kostdagbok dag 5	
	Kostdagbok dag 6	Sykepleier ringer
Dag 7-11/12		Mammografi/Dexa
Dag 12		Visitt 2: Dag 12 blodprøver
Dag 18	Avhengig av ukedag, start kost reg. dag 21-23	Sykepleier ringer
Dag 21-23	Kostdagbok dag 21	
	Kostdagbok dag 22	Visitt 3: Dag 21, blodprøver målinger
	Kostdagbok dag 23	
Dag 24		
		Innlevering skjema spyttprøve
Dag 25-36		

Daglig spyttprøve og loggføring av fysisk aktivitet

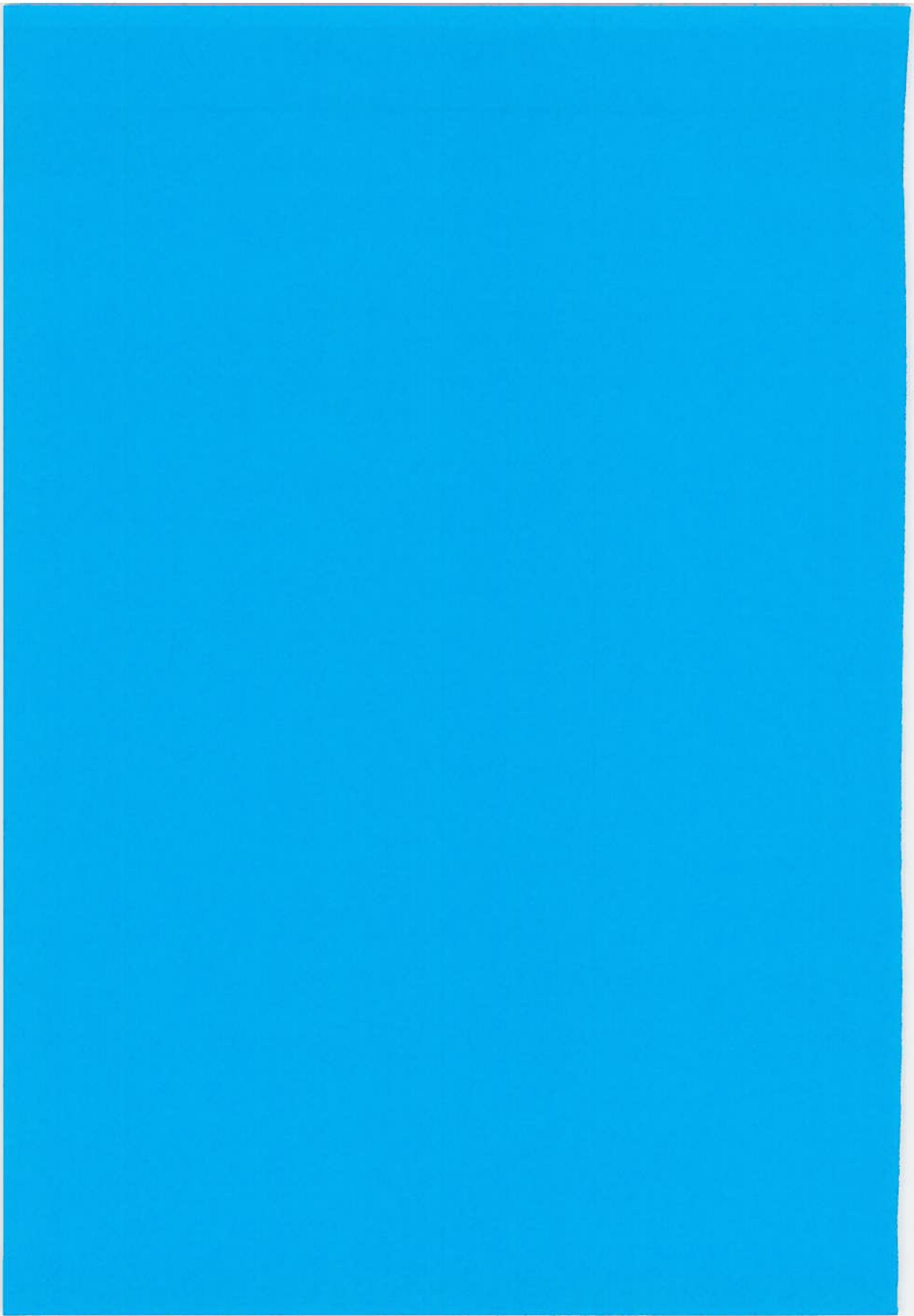
Appendix C

Questionnaire used in the cardiovascular disease studies in the counties of Finnmark, Oppland and Sogn og Fjordane:

Questionnaire, 1974–78 survey

English translation
Original questionnaire

Paper III



English translation of the questionnaire used in the cardiovascular disease study in Oslo* 1972-73, Norwegian counties 1974-78 (Finnmark, Oppland and Sogn og Fjordane) and Tromsø 1974.

English translation; Mr. Kevin McCafferty

Tick "yes/no" or "yes", as appropriate.

Part A

Have you, or have you had:
- a heart attack?
- angina pectoris (heart cramp)?
- any other heart disease?
- hardened arteries in the legs?
- a cerebral stroke?
- diabetes?

Are you being treated for:
- high blood pressure?

Do you use:
- nitroglycerine?

Part B

Do you have pain or discomfort in the chest when:
- walking up hills or stairs, or walking fast on level ground?
- walking at normal pace on level ground?

If you get pain or discomfort in the chest when walking, do you usually:
- (1) stop?
- (2) slow down?
- (3) carry on at the same pace?

If you stop or slow down, does the pain disappear:
- (1) within 10 minutes?
- (2) after more than 10 minutes?

Do you have pain in the calf while:
- walking?
- resting?

If you get pain in the calf, then:
- does the pain increase when you walk faster or uphill?
- does the pain disappear if you stop?

Do you usually have:
- cough in the morning?
- phlegm chest in the morning?

Part C

Exercise and physical exertion in *leisure time.* If your activity varies much, for example between summer and winter, then give an average. The questions refer only to the last twelve months.

Tick "YES" beside the description that fits best:
- (1) Reading, watching TV, or other sedentary activity?
- (2) Walking, cycling, or other forms of exercise at least 4 hours a week? (including walking or cycling to place of work, Sunday-walking, etc.)
- (3) Participation in recreational sports, heavy gardening, etc.? (note: duration of activity at least 4 hours a week).
- (4) Participation in hard training or sports competitions, regularly several times a week?

Part D*

Do you smoke daily at present?

If "Yes":
- Do you smoke cigarettes daily? (handrolled or factory made)

If you do not smoke cigarettes at present:
- Have you previously smoked cigarettes daily?

If "Yes", how long is it since you stopped?
- (1) Less than 3 months?
- (2) 3 months to 1 year?
- (3) 1 to 5 years?
- (4) More than 5 years?

For those who smoke or have smoked previously:

How many years altogether have you smoked daily? Number of years .....

How many cigarettes do you, or did you, smoke daily? Give number of cigarettes per day (handrolled + factory made)

Number of cigarettes .....

Do you smoke tobacco products other than cigarettes daily?
- cigars or cigarillos?
- a pipe?

If you smoke a pipe, how many packs of tobacco (50 grams) do you smoke per week?
Give average number of packs per week.

Number of tobacco packs .....

Part E

Do you usually work shifts or at night?
Can you usually come home from work:
- every day?
- every weekend?

Are there periods during which your working days are longer than usual? (e.g.: fishing season, harvest)

*In Oslo preset groups of cigarettes smoked per day and packs of pipe tobacco smoked per day (see original questionnaire)

During the last year, have you had: (Tick "YES" beside description that fits best):

(1) mostly sedentary work? (e.g., office work, watchmaker, light manual work)
(2) work that requires a lot of walking? (e.g., shop assistant, light industrial work, teaching)
(3) work that requires at lot of walking and lifting? (e.g., postman, heavy industrial work, construction)
(4) heavy manual labour? (e.g., forestry, heavy farmwork, heavy construction)

During the last 12 months, have you had to move house for work reasons?
Is housekeeping your main occupation?
Have you within the last 12 months received unemployment benefit?
Are you at present on sick leave, or receiving rehabilitation allowance?
Do you receive a complete or partial disability pension?

Part F (alternatives: yes, no, don't know)

Have one or more of your parents or sisters or brothers had a heart attack (heart wound) or angina pectoris (heart cramp)?

In Finnmark and Tromsø only:
Are two or more of your grandparents of Finnish origin?
Are two or more of your grandparents of Lapp origin?

MELDING OM SKJERMBILDEFOTOGRAFERING OG HJERTE-KARUNDERSØKELSE

(Gjelder bare den person brevet er adressert til)

Skjermbildefotograferingen kommer nå til Deres distrikt.

Tid og sted for Deres frammøte vil De finne nedenfor.

Denne gangen vil en del av befolkningen få tilbud om hjerte-karundersøkelse. De tilhører denne gruppe. En orientering om undersøkelsen er gitt i vedlagte brosjyre.

Vennligst fyll ut spørreskjemaet på baksiden og ta det med til undersøkelsen. Ta også med tuberkulinkort eller helsebok, om De har.

Fravær bes meldt på vedlagte seddel.

Med hilsen

TROMSØ HELSERÅD FYLKESLEGEN I TROMS
FAGOMRÅDET MEDISIN, UNIVERSITETET I TROMSØ
STATENS SKJERMBILDEFOTOGRAFERING

Født dato Personnr. Kommune Kretsnr.

Første bokstav

Kjønn

Møtested

A

Har De, eller har De hatt:

	JA	NEI
Hjerteinfarkt?		
Angina pectoris (hjertekrampe)?		
Annen hjertesykdom?		
Åreforkalkning i bena?		
Hjerneslag?		
Sukkersyke?		
Er De under behandling for:		
Høyt blodtrykk?		
Bruker De:		
Nitroglycerin?		

B

	JA	NEI
Får De smerter eller ubehag i brystet når De:		
Går i bakker, trapper eller fort på flat mark?		
Går i vanlig takt på flat mark?		
Hvis De får smerter eller ubehag i brystet ved gange, pleier De da å:		
1 Stanse?		
2 Saktne farten?		
3 Fortsette i samme takt?		
Hvis De stanser eller saktner farten, forsvinner smertene da:		
1 Etter mindre enn 10 minutter?		
2 Etter mer enn 10 minutter?		
Får De smerter i tykkleggen når De:		
Går?		
Er i ro?		
Hvis De får leggsmerter, besvar da:		
Forverres smertene ved raskere tempo eller i bakker?		
Gir smertene seg når De stopper?		
Har De vanligvis:		
Hoste om morgenen?		
Oppspytt fra brystet om morgenen?		

C

	JA
Bevegelse og kroppslig anstrengelse i Deres fritid. Hvis aktiviteten varierer meget f.eks. mellom sommer og vinter så ta et gjennomsnitt. Spørsmålet gjelder bare det siste året. Sett kryss i den ruten hvor „JA" passer best.	
1 Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse?	
2 Spaserer, sykler eller beveger Dem på annen måte minst 4 timer i uken? (Heri medregnes også gang eller sykling til arbeidsstedet, søndagsturer m.m.)	
3 Driver mosjonsidrett, tyngre hagearbeid e.l.? (Merk at yirksomheten skal være minst 4 timer i uken.	
4 Trener hardt eller driver konkurransedidrett, regelmessig og flere ganger i uken?	

D

	JA	NEI
Røyker De daglig for tiden?		
Hvis svaret var „JA" på forrige spørsmål, besvar da:		
Røyker De sigaretter daglig? (håndrullede eller fabrikkframstilte)		
Hvis De ikke røyker sigaretter nå, besvar da:		
Har De røykt sigaretter daglig tidligere?		
Hvis De svarte „JA", hvor lenge er det siden De sluttet?		
1 Mindre enn 3 måneder?		
2 3 måneder - 1 år?		
3 1 - 5 år?		
4 Mer enn 5 år?		
Besvares av dem som røyker nå eller har røykt tidligere:		
Hvor mange år tilsammen har De røykt daglig?	Antall år:	
Hvor mange sigaretter røyker eller røykte De daglig? Oppgi antall pr. dag (håndrullede + fabrikkframstilte)	Ant. sigaretter:	
Røyker De noe annet enn sigaretter daglig?		
Sigarer eller sørutter/cigarillos?		
Pipe?		
Hvis De røyker pipe, hvor mange pakker tobakk (50 gram) bruker De i pipa pr. uke?		
Oppgi gjennomsnittlig antall pakker pr. uke.	Ant. tobakk:	

E

	JA	NEI
Har De vanligvis skiftarbeid eller nattarbeid?		
Kan De vanligvis komme hjem fra arbeidet:		
Hver dag?		
Hver helg?		
Har De i perioder lengre arbeidsdager enn vanlig? (f.eks. under sesongfiske, onnearbeid)		
Har De i løpet av siste året hatt:		
Sett kryss i den ruten hvor „JA" passer best.		
1 Overveiende stillesittende arbeid? (f.eks. skrivebordsarb., urmakerarb., montering)		
2 Arbeid som krever at De går mye? (f.eks. ekspeditørarb., lett industriarb., undervisn.)		
3 Arbeid hvor De går og løfter mye? (f.eks. postbud, tyngre industriarb., byggingsarb.)		
4 Tungt kroppsarbeid? (f.eks. skogsarbeid, tungt jordbruksarb., tungt byggingsarb.)		
Har De i løpet av de siste 12 mnd måttet flytte fra hjemstedet på grunn av forandring i arbeidssituasjonen?		
Er husmorarbeid Deres hovedyrke?		
Har De i løpet av de siste 12 mnd fått arbeidsledighetstrygd?		
Er De for tiden sykmeldt, eller får De attføringspenger?		
Har De full eller delvis uførepensjon?		

F

	JA	NEI
Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)?		
Er to eller flere av Deres besteforeldre av finsk ætt?		
Er to eller flere av Deres besteforeldre av samisk ætt?		

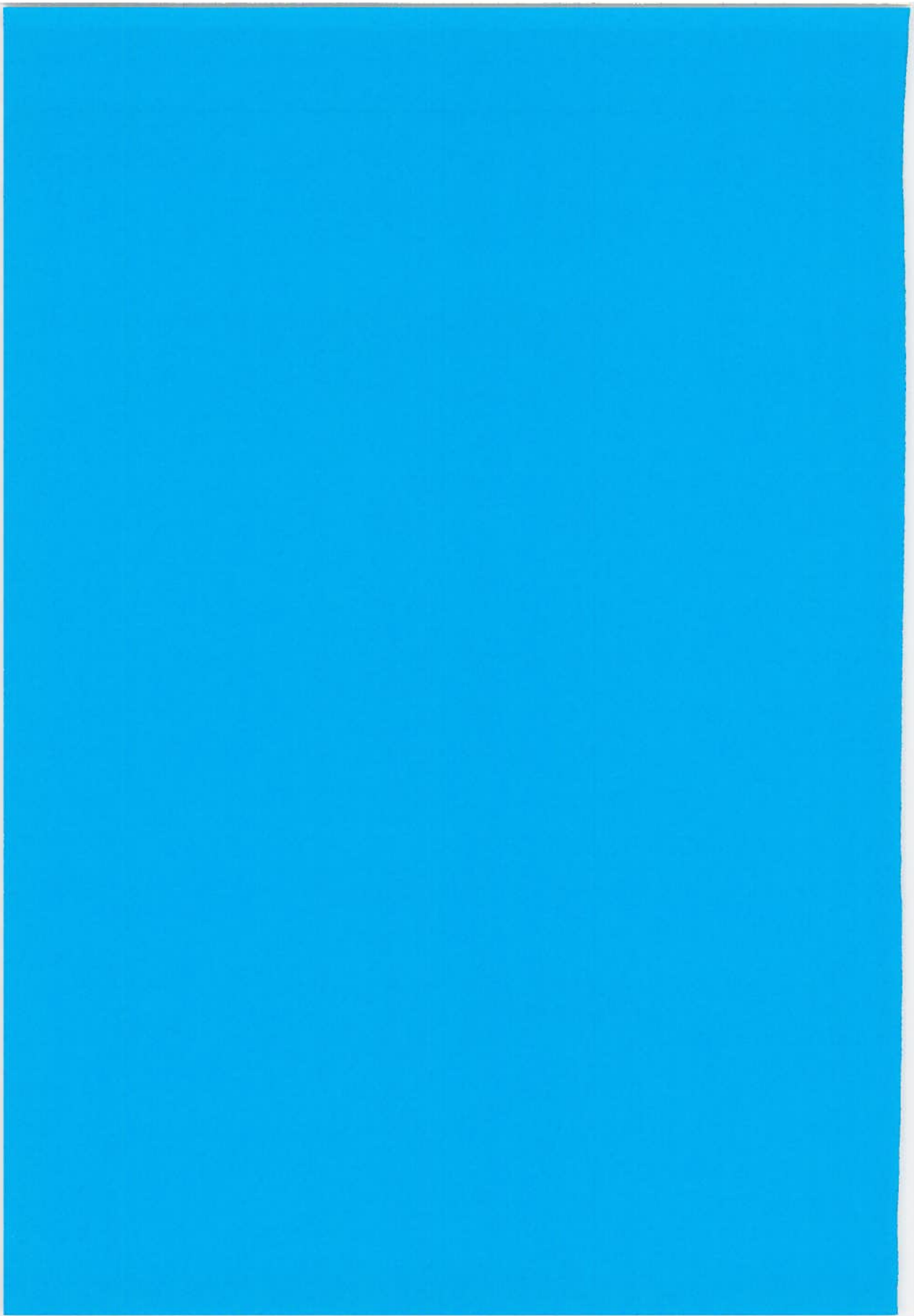
Appendix D

Questionnaire used in the cardiovascular disease studies in the counties of Finnmark, Oppland and Sogn og Fjordane:

Questionnaire, 1977–83 survey

English translation
Original questionnaire

Paper III and IV



English translation of the questionnaire used in the cardiovascular disease study in Norwegian counties 1977-83 (Finnmark, Sogn og Fjordane, Oppland) and Tromsø 1979-80

English translation; Mrs. Anne Clancy and Mr. Kevin McCafferty

Tick "yes/no" or "yes", as appropriate.

Part A

Have you, or have you had:
- a heart attack?
- angina pectoris (heart cramp)?
- any other heart disease?
- arteriosclerosis of the legs?
- a cerebral stroke?
- diabetes?

Are you being treated for:
- high blood pressure?

Do you use:
- nitroglycerine?

Part B

Do you have pain or discomfort in the chest when:
- walking up hills or stairs, or walking fast on level ground?
- walking at normal pace on level ground?

If you get pain or discomfort in the chest when walking, do you usually:
- (1) stop?
- (2) slow down?
- (3) carry on at the same pace?

If you stop or slow down, does the pain disappear:
- (1) within 10 minutes?
- (2) after more than 10 minutes?

Do you have pain in the calf while:
- walking?
- resting?

If you get pain in the calf, then:
- does the pain increase when you walk faster or uphill?
- does the pain disappear if you stop?

Do you usually have:
- cough in the morning?
- phlegm chest in the morning?

Part C

Exercise and physical exertion in *leisure time*. If your activity varies much, for example between summer and winter, then give an average. The questions refer only to the last twelve months.

Tick "YES" beside the description that fits best:
- (1) Reading, watching TV, or other sedentary activity?
- (2) Walking, cycling, or other forms of exercise at least 4 hours a week? (including walking or cycling to place of work, Sunday-walking, etc.)
- (3) Participation in recreational sports, heavy gardening, etc.? (note: duration of activity at least 4 hours a week).
- (4) Participation in hard training or sports competitions, regularly several times a week?

Part D

Do you smoke daily at present?

If "Yes":

Do you smoke cigarettes daily? (handrolled or factory made)

If you do not smoke cigarettes at present:

Have you previously smoked cigarettes daily?

If "Yes", how long is it since you stopped?
- (1) Less than 3 months?
- (2) 3 months to 1 year?
- (3) 1 to 5 years?
- (4) More than 5 years?

For those who smoke or have smoked previously:

How many years altogether have you smoked daily? *Number of years* .....

How many cigarettes do you, or did you, smoke daily? Give number of cigarettes per day (handrolled + factory made)

Number of cigarettes .....

Do you smoke tobacco products other than cigarettes daily?
- cigars or cigarillos?
- a pipe?

If you smoke a pipe, how many packs of tobacco (50 grams) do you smoke per week? Give average number of packs per week.

Number of tobacco packs .....

Part E

Do you usually work shifts or at night?
Can you usually come home from work:
- every day?
- every weekend?

Are there periods during which your working days are longer than usual? (e.g.: fishing season, harvest)

During the last year, have you had: (Tick "YES" beside description that fits best):
(1) mostly sedentary work? (e.g., office work, watchmaker, light manual work)
(2) work that requires a lot of walking? (e.g., shop assistant, light industrial work, teaching)
(3) work that requires at lot of walking and lifting? (e.g., postman, heavy industrial work, construction)
(4) heavy manual labour? (e.g., forestry, heavy farmwork, heavy construction)

During the last 12 months, have you had to move house for work reasons?
Is housekeeping your main occupation?
Have you within the last 12 months received unemployment benefit?
Are you at present on sick leave, or receiving rehabilitation allowance?
Do you receive a complete or partial disability pension?

Part F (alternatives: yes, no, don't know)

Have one or more of your parents or sisters or brothers had a heart attack (heart wound) or angina pectoris (heart cramp)?

In Finnmark and Tromsø only:
Are two or more of your grandparents of Finnish origin?
Are two or more of your grandparents of Lapp origin?

Part G

Has anyone in your household (other than yourself), been called in to a doctor for further medical examination after the previous cardiovascular disease survey?

MELDING OM SKJERMBILDEFOTOGRAFERING OG HJERTE-KARUNDERSØKELSE

(Gjelder bare den person brevet er adressert til)

Skjermbildefotograferingen kommer nå til Deres distrikt.

Tid og sted for Deres frammøte vil De finne nedenfor.

Også denne gangen vil en del av befolkningen få tilbud om hjerte-karundersøkelse. De tilhører denne gruppe. En orientering om undersøkelsen er gitt i vedlagte brosjyre.

Vennligst fyll ut spørreskjemaet på baksiden og ta det med til undersøkelsen. Ta også med tuberkulinkort eller helsebok, om De har.

Fravær bes eventuelt meldt på vedlagte seddel.

Med hilsen

HELSERÅDET FYLKESLEGEN
STATENS SKJERMBILDEFOTOGRAFERING

Født dato | Personnr. | Kommune | Kretsnr.

Møtested | Kjønn | Første bokstav etternavn | Dag og dato | Klokkeslett

SKRIV IKKE HER!

T. S. M.: | M: | / | / |

A

Har De, eller har De hatt:

	JA	NEI
Hjerteinfarkt? 33		
Angina pectoris (hjertekrampe)? 34		
Annen hjertesykdom? 35		
Åreforkalkning i bena? 36		
Hjerneslag? 37		
Sukkersyke? 38		
Er De under behandling for:		
Høyt blodtrykk? 39		
Bruker De:		
Nitroglycerin? 40		

B

Får De smerter eller ubehag i brystet når De:

	JA	NEI
Går i bakker, trapper eller fort på flat mark? 41		
Går i vanlig takt på flat mark? 42		
Hvis De får smerter eller ubehag i brystet ved gange, pleier De da å:		
1 Stanse? 43		
2 Saktne farten?		
3 Fortsette i samme takt?		
Hvis De stanser eller saktner farten, forsvinner smertene da:		
1 Etter mindre enn 10 minutter? 44		
2 Etter mer enn 10 minutter?		
Får De smerter i tykkleggen når De:		
Går? 45		
Er i ro? 46		
Hvis De får leggsmerter, besvar da:		
Forverres smertene ved raskere tempo eller i bakker? 47		
Gir smertene seg når De stopper? 48		
Har De vanligvis:		
Hoste om morgenen? 49		
Oppspytt fra brystet om morgenen? 50		

C

Bevegelse og kroppslig anstrengelse i Deres **fritid**.
Hvis aktiviteten varierer meget f.eks. mellom sommer og vinter så ta et gjennomsnitt.

Spørsmålet gjelder bare det siste året.

Sett kryss i den ruten hvor „JA" passer best.

	JA
1 Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse? 51	
2 Spaserer, sykler eller beveger Dem på annen måte minst 4 timer i uken? (Heri medregnes også gang eller sykling til arbeidsstedet, søndagsturer m.m.)	
3 Driver mosjonsidrett, tyngre hagearbeid e.l.? (Merk at yrksomheten skal vare minst 4 timer i uken.	
4 Trener hardt eller driver konkurranseidrett, regelmessig og flere ganger i uken?	

G

	JA	NEI
Har noen i Deres husstand (utenom Dem selv) vært innkalt til nærmere undersøkelse hos distriktslegen etter forrige hjerte-kar undersøkelse? 80		

D

	JA	NEI
Røyker De daglig for tiden? 52		
Hvis svaret var „JA" på forrige spørsmål, besvar da:		
Røyker De sigaretter daglig? (håndrullede eller fabrikkframstilte) 53		
Hvis De ikke røyker sigaretter nå, besvar da:		
Har De røykt sigaretter daglig tidligere? 54		
Hvis De svarte „JA", hvor lenge er det siden De sluttet?		
1 Mindre enn 3 måneder? 55		
2 3 måneder - 1 år?		
3 1 - 5 år?		
4 Mer enn 5 år?		
Besvares av dem som røyker nå eller har røykt tidligere:		
Hvor mange år tilsammen har De røykt daglig? 56-57 — Antall år:		
Hvor mange sigaretter røyker eller røykte De daglig? Oppgi antall pr. dag 58-60 (håndrullede + fabrikkframstilte) — Ant. sigaretter:		
Røyker De noe annet enn sigaretter daglig?		
Sigarer eller serutter/cigarillos? 62		
Pipe? 63		
Hvis De røyker pipe, hvor mange pakker tobakk (50 gram) bruker De i pipa pr. uke?		
Oppgi gjennomsnittlig antall pakker pr. uke. 64-66 — Ant. tobakkp.:		

E

	JA	NEI
Har De vanligvis skiftarbeid eller nattarbeid? 67		
Kan De vanligvis komme hjem fra arbeidet:		
Hver dag? 68		
Hver helg? 69		
Har De i perioder lengre arbeidsdager enn vanlig? (f.eks. under sesongfiske, onnearbeid) 70		
Har De i løpet av siste året hatt:		
Sett kryss i den ruten hvor „JA" passer best.		
1 Overveiende stillesittende arbeid? (f.eks. skrivebordsarb., urmakerarb., montering) 71		
2 Arbeid som krever at De går mye? (f.eks. ekspeditørarb, lett industriarb., undervisn.)		
3 Arbeid hvor De går og løfter mye? (f.eks. postbud, tyngre industriarb, bygningsarb)		
4 Tungt kroppsarbeid? (f.eks skogsarbeid, tungt jordbruksarb tungt bygningsarb)		
Har De i løpet av de siste 12 mnd måttet flytte fra hjemstedet på grunn av forandring i arbeidssituasjonen? 72		
Er husmorarbeid Deres hovedyrke? 73		
Har De i løpet av de siste 12 mnd fått arbeidsledighetstrygd? 74		
Er De for tiden sykmeldt, eller får De attføringspenger? 75		
Har De full eller delvis uførepensjon? 76		

F

	JA	NEI	Vet ikke
Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)? 77			
Er to eller flere av Deres besteforeldre av finsk ætt? 78			
Er to eller flere av Deres besteforeldre av samisk ætt? 79			

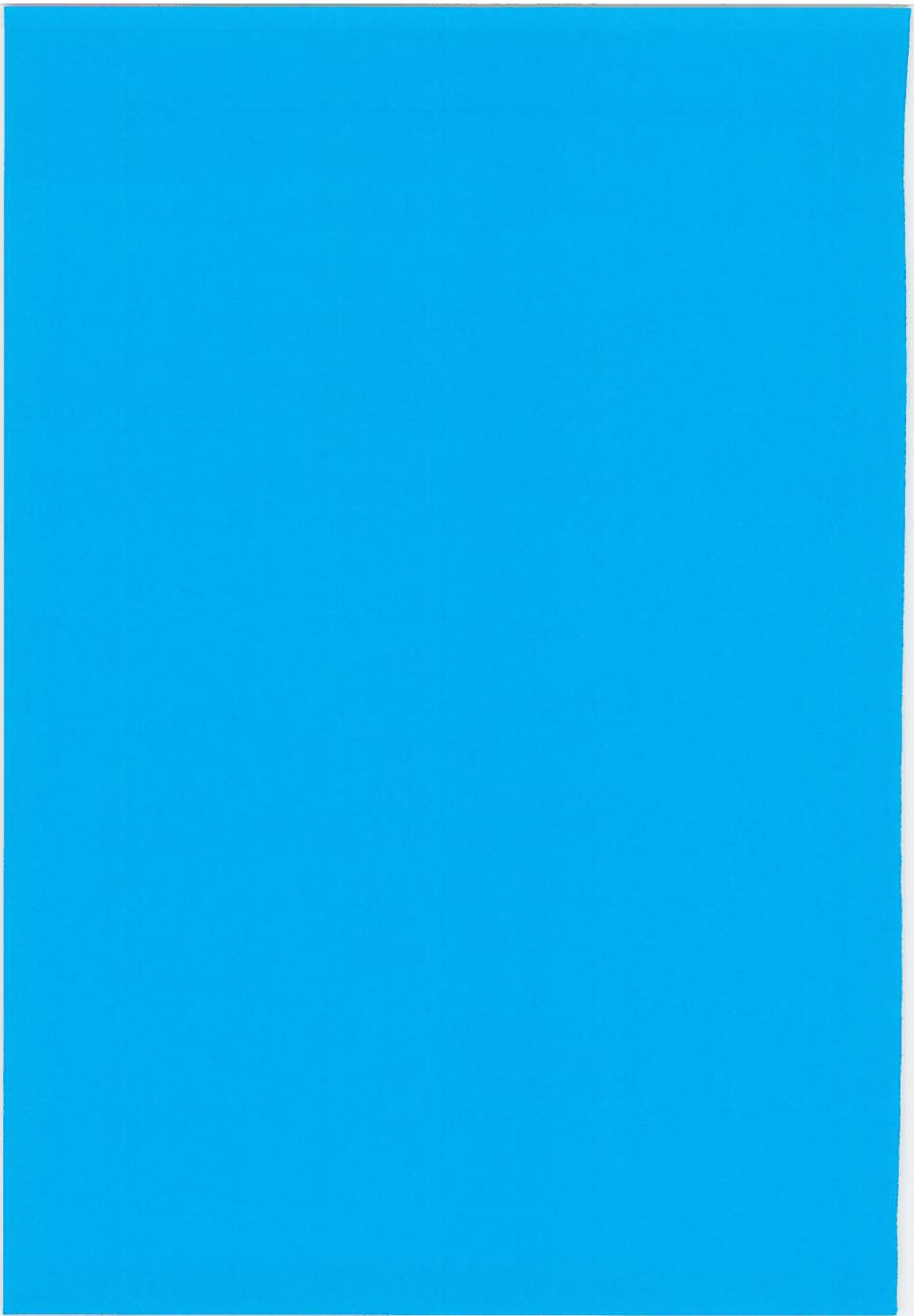
Appendix E

Questionnaire used in the cardiovascular disease studies in the counties of Oppland and Sogn og Fjordane:

Questionnaire, 1985–87 survey

Original questionnaire

Paper IV



MELDING OM HJERTE- KARUNDERSØKELSE

(Gjelder bare den person som brevet er adressert til.)

Hjerte- karundersøkelsen kommer nå til Deres distrikt.

Tid og sted for frammøte vil De finne nedenfor.

De finner en orientering om undersøkelsen i den vedlagte brosjyren.

Vi ber Dem vennligst fylle ut spørreskjemaet på baksiden og ta dette med til undersøkelsen.

Vi ber Dem eventuelt melde fra om fraværet på den vedlagte fraværsmeldingen.

Med hilsen

KOMMUNEHELSETJENESTEN FYLKESLEGEN
STATENS HELSEUNDERSØKELSER

Født dato Personnr. Kommune Kretsnr.

Møtested Kjønn Første bokstav i ettternavn Dag og dato Klokkeslett

A FAMILIE

Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)? 12

B EGEN SYKDOM

Har De, eller har De hatt:

Hjerteinfarkt? 13
Angina pectoris (hjertekrampe)? 14
Hjerneslag? 15
Sukkersyke? 16

Er De under behandling for:

Høyt blodtrykk? 17

Bruker De:

Nitroglycerin? 18

C SYMPTOMER

Får De smerter eller ubehag i brystet når De:

Går i bakker, trapper eller fort på flat mark? 19
Går i vanlig takt på flat mark? 20

Dersom De får smerter eller vondt i brystet ved gange, pleier De da:

Stoppe? 21
Saktne farten? 1
Fortsette i samme takt? 2
3

Dersom De stopper eller saktner farten, går da smertene bort:

Etter mindre enn 10 minutter? 22
Etter mer enn 10 minutter? 1
2

Har De vanligvis:

Hoste om morgenen? 23
Oppspytt fra brystet om morgenen? 24

D MOSJON

Bevegelse og kroppslig aktivitet i Deres fritid. Dersom aktiviteten varierer mye, f.eks. mellom sommer og vinter, så ta ett gjennomsnitt. Spørsmålet gjelder bare det siste året.

Sett kryss i den ruten som passer best.

Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse? ..... 25 — 1

Spaserer, sykler eller beveger Dem på annen måte minst 4 timer i uken? 2
(Her skal De også regne med gang eller sykling til arbeidssted, søndagsturer m.m.)

Driver mosjonsidrett, tyngre hagearbeid e.l.? .. 3
(Merk at aktiviteten skal vare i minst 4 timer i uken.)

Trener hardt eller driver konkurransoidrett regelmessig og flere ganger i uken? 4

E SALT/FETT

Hvor ofte bruker De salt kjøtt eller salt fisk til middag?

Sett kryss i den ruten som passer best.

Aldri eller sjeldnere enn en gang i måneden ..... 26 — 1
Inntil en gang i uken 2
Inntil to ganger i uken 3
Mer enn to ganger i uken 4

Hvor ofte pleier De å strø ekstra salt på middagsmaten?

Sett kryss i den ruten som passer best.

Sjelden eller aldri ..... 27 — 1
Av og til eller ofte 2
Alltid eller nesten alltid 3

Hva slags margarin eller smør bruker De vanligvis på brødet?

Sett kryss i den ruten som passer best.

Bruker ikke smør eller margarin på brød ..... 28 — 1
Smør 2
Hard margarin 3
Myk (Soft) margarin 4
Smør/margarin blanding 5

Hva slags fett blir vanligvis brukt til matlaging i husholdningen Deres?

Sett kryss i den ruten som passer best.

Smør eller hard margarin ..... 29 — 1
Myk (Soft) margarin eller olje 2
Smør/margarin blanding 3

F RØYKING

Røyker De daglig for tida? ..... 30 — JA / NEI

Dersom svaret er «JA», svar da på dette:

Røyker De sigaretter daglig? 31
(håndrullede eller fabrikkframstilte)

Dersom De ikke røyker sigaretter nå, svar da på dette:

Har De røykt sigaretter daglig tidligere? 32

Dersom De svarte «JA», hvor lenge er det da siden De sluttet?

Mindre enn 3 måneder? ..... 33 — 1
3 måneder – 1 år? 2
1–5 år? 3
Mer enn 5 år? 4

Skal besvares av de som røyker nå eller som har røykt tidligere:

Hvor mange år til sammen har De røykt daglig? ..... 34 — År

Hvor mange sigaretter røyker eller røykte De daglig?
Gi opp antallet sigaretter daglig ..... 36 — Sigaretter
(håndrullede + fabrikkframstilte)

Røyker De noe annet enn sigaretter daglig?

Sigarer eller serutter/sigarillos? 40
Pipe? 41

Dersom De røyker pipe, hvor mange pakker tobakk (50 gram) bruker De i pipen på en uke?

Gi opp gjennomsnittlig tall på pakker i uken ..... 42 — Tobakkspk.

G KAFFE

Hvor mange kopper kaffe drikker De vanligvis hver dag?

Sett kryss i den ruten som passer best.

Drikker ikke kaffe, eller mindre enn en kopp ..... 45 — 1
1 – 4 kopper 2
5 – 8 kopper 3
9 eller flere kopper 4

Hva slags kaffe drikker De vanligvis hver dag?

Kokekaffe 46
Filterkaffe 47
Pulverkaffe 48
Koffeinfri kaffe 49
Drikker ikke kaffe 50

H ARBEID

Har De i do siste 12 månedene fått arbeidsledighetstrygd? ..... 51 — JA / NEI
Er De for tiden sykemeldt, eller får De attføringspenger? 52
Har De full eller delvis uførepensjon? 53
Har De vanligvis skiftarbeid eller nattarbeid 54

Har De i det siste året hatt:

Sett kryss i den ruten som passer best.

For det meste stillesittende arbeid? ..... 55 — 1
(f.eks. skrivebordsarb., urmakerarb., montering)
Arbeide som krever at De går mye? 2
(f.eks. ekspeditørarb., lett industriarb., undervisn.)
Arbeide der De går og løfter mye? 3
(f.eks. postbud, tyngre industriarb., bygningsarb.)
Tungt kroppsarbeid? 4
(f.eks. skogsarb., tungt jordbruksarb., tungt bygningsarb.)

Er husmorarbeid hovedyrket Deres? ..... 56 — JA / NEI

I ETTERUNDERSØKELSE

Har noen i husstanden Deres (utenom Dem selv) vært innkalt til nærmere undersøkelse hos lege etter den siste hjerte-karundersøkelsen? ..... 57 — JA / NEI / VET IKKE

Er to eller flere av Deres besteforeldre av finsk ætt? 58
Er to eller flere av Deres besteforeldre av samisk ætt? 59

Dersom denne helseundersøkelsen viser at De bør undersøkes nærmere: Hvilken almenpraktiserende lege ønsker De da å bli henvist til?

Skriv navnet på legen her →

..... 60

Ingen spesiell lege 03

Ikke skriv her

Ikke skriv her

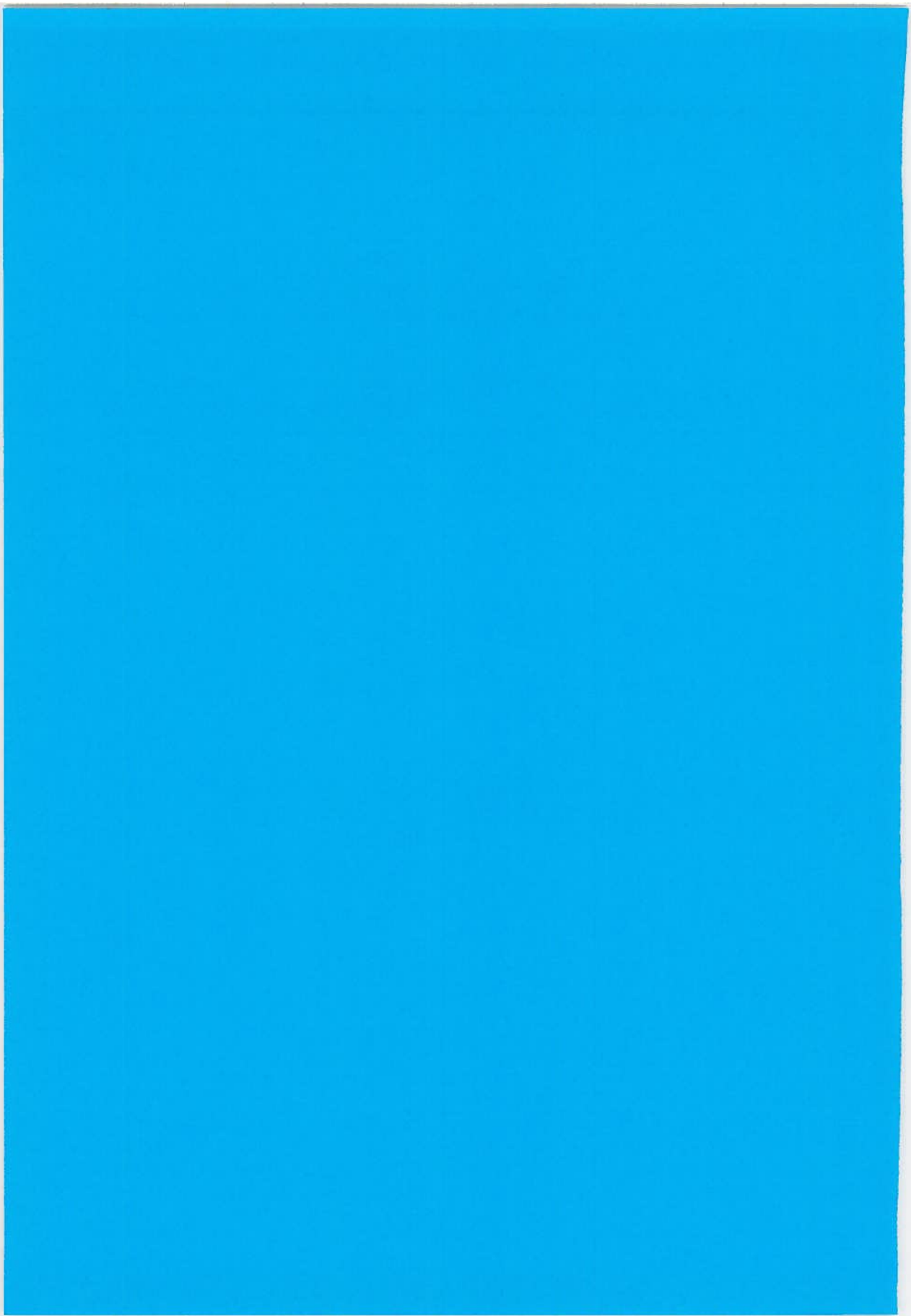
Appendix F

Food frequency questionnaire
used in the cardiovascular disease studies
in the counties of Finnmark, Oppland and Sogn og Fjordane:

Questionnaire, 1977–83 survey

English translation
Original questionnaire

Paper III and IV



Food frequency questionnaire

Prepared by the Section for Dietary Research

University of Oslo

English version in: Gaard M. *Nutritional aspects of cancer of the breast and colon*
An epidemiological study. Thesis Oslo, 1997

Questionnaire

In connection with the present examination, we would like to ask some questions about your dietary habits.
Please, fill inn the questionnaire and return it in the envelope provided. The postage is paid by the recipient.
If several in your household have received a questionnaire, each one is asked to fill it in.
All information that you give will be regarded as strictly confidential.

With regards

The Board of Health *County Medical Officer of Health*

Section for Dietary Research
University of Oslo

National Health Screening Service

Guidance

Answer each question by checking the most appropriate box.
If it is difficult to give an accurate answer, then answer in accordance with your best judgement. Perhaps there will be questions which you cannot answer at all. Leave these questions, and answer as many as possible of the other questions.

14 Do you live on a diet?
1 ☐ Yes 2 ☐ No
If you are on a regimen, try to fill in the questionnaire, nevertheless.

15 How many slices of bread do you usually eat daily?
1 ☐ Less than 2 slices a day
2 ☐ 2-4 slices a day
3 ☐ 5-6 slices a day
4 ☐ 7-8 slices a day
5 ☐ 9-12 slices a day
6 ☐ 13 or more slices a day

16 What type of bread do you eat most frequently?
1 ☐ Factory made
2 ☐ Home made

17 If factory made bread, what type do you eat most often?
1 ☐ White bread
2 ☐ Medium brown bread
3 ☐ Brown bread

18 If home made bread, how much whole meal flour is used?

1 ☐ Do not use whole meal flour
2 ☐ Less than 1/4 whole meal flour
3 ☐ 1/4-1/2 whole meal flour
4 ☐ More than 1/2 whole meal flour

19 What type of fat do you usually spread on bread?

1 ☐ Nothing
2 ☐ Butter
3 ☐ Margarine

20 If you spread margarine on your bread, what brand do you usually use?

.....

21 Check the appropriate package

1 ☐ Packet
2 ☐ Beaker

22 Which sandwich spreads do you usually use? Check all the appropriate boxes.

22 ☐ White cheese
23 ☐ Whey cheese
24 ☐ Honey, syrup, sugar
25 ☐ Jam, marmalade
26 ☐ Other sweet spreads
27 ☐ Mayonnaise, salads
28 ☐ Liver paste
29 ☐ Cold cuts, bologna
30 ☐ Sardines, pickled herring

31 How many glasses/cups of milk do you usually during daily?

1 ☐ Do not drink milk, or drink less than 1 glass/cup a day
2 ☐ 1 glass/cup a day
3 ☐ 2 glasses/cups a day
4 ☐ 3 glasses/cups a day
5 ☐ 4 glasses/cups a day
6 ☐ 5 or more glasses/cups a day

32 What type of milk do you usually drink?

1 ☐ Do not drink milk
2 ☐ Whole milk, sweet or sour
3 ☐ Skim milk, sweet or sour
4 ☐ Hand-skimmed milk
5 ☐ Both whole and skimmed milk

33 How many cups of coffee do you usually drink daily?

1 ☐ Do not drink coffee or less than 1 cup a day
2 ☐ 1-2 cups a day
3 ☐ 3-4 cups a day
4 ☐ 5-6 cups a day
5 ☐ 7-8 cups a day
6 ☐ 9 or more cups a day

34 How much sugar do you use with/in your coffee?

1 ☐ Do not drink coffee
2 ☐ Do not use sugar
3 ☐ 1-2 lumps per cup
4 ☐ 3-4 lumps per cup
5 ☐ 5-6 lumps per cup
6 ☐ 7 lumps per cup

35 How many eggs (boiled, fried) do you usually eat during a week?

1 ☐ Do not eat, or less than 1 egg a week
2 ☐ 1 egg a week
3 ☐ 2 eggs a week
4 ☐ 3-4 eggs a week
5 ☐ 5-6 eggs a week
6 ☐ 7 or more eggs a week

36 How many oranges do you usually eat during a week?

1 ☐ Do not eat, or less than 1 orange a week
2 ☐ 1 orange a week
3 ☐ 2 oranges a week
4 ☐ 3-4 oranges a week
5 ☐ 5-6 oranges a week
6 ☐ 7 or more oranges a week

37 How often do your main meal contain fish?

1 ☐ Less than once a week
2 ☐ 1-2 times a week
3 ☐ 3-4 times a week
4 ☐ 5-6 times a week
5 ☐ 7 times a week

38 How often do your main meal contain meat (dishes with blood and/or offal included)?

1 ☐ Less than once a week
2 ☐ 1-2 times a week
3 ☐ 3-4 times a week
4 ☐ 5-6 times a week
5 ☐ 7 times a week

39 How often do your main meal contain other dishes like porridge, pancakes etc.?

1 ☐ Less than once a week
2 ☐ 1-2 times a week
3 ☐ 3-4 times a week
4 ☐ 5 or more times a week

40 How often do you use melted fat (butter, margarine, bacon fat etc.) on or with meat dishes?

1 ☐ Never, or less than once a week
2 ☐ 1-2 times a week
3 ☐ 3-4 times a week
4 ☐ 5 or more times a week

41 How often do you use melted fat (butter, margarine, bacon fat etc.) on or with fish dishes?

1 ☐ Never, or less than once a week
2 ☐ 1-2 times a week
3 ☐ 3-4 times a week
4 ☐ 5 or more times a week

42 How often do you eat fish liver (when fish liver is available)?

1 ☐ Never, or less than once a week
2 ☐ 1-2 times a week
3 ☐ 3-4 times a week
4 ☐ 5 or more times a week

43 How often do you eat potatoes with your main meal in the course of an ordinary week?

1 ☐ Less than 3 times a week
2 ☐ 3-5 times a week
3 ☐ 6-7 times a week

44 How many potatoes do you usually eat per dinner?

1 ☐ Less than one per meal
2 ☐ 1 potato per meal
3 ☐ 2 potatoes per meal
4 ☐ 3-4 potatoes per meal
5 ☐ 5 or more per meal

45 How often do you drink soft drinks during an ordinary week?

1 ☐ Never, or less than once a week
2 ☐ 1-2 times a week
3 ☐ 3-4 times a week
4 ☐ 5-6 times a week
5 ☐ 7 or more times a week

46 How often do you eat cakes, cookies etc. during an ordinary week?

1 ☐ Never, or less than once a week
2 ☐ 1-2 times a week
3 ☐ 3-4 times a week
4 ☐ 5-6 times a week
5 ☐ 7 or more times a week

47 Do you use some of these products during an ordinary week? Check the appropriate boxes.

47 ☐ Potato chips
48 ☐ Chocolate, candy
49 ☐ Wine, liquor
50 ☐ Beer
51 ☐ Cod liver oil
52 ☐ Vitamin supplements

HOW MANY TIMES PER MONTH DO YOU USE ANY OF THE FOLLOWING TYPES OF DISHES WITH YOUR MAIN MEAL?

53 Poached or fried sausages etc.?

1 ☐ Never, or less than once a month
2 ☐ 1-2 times a month
3 ☐ 3-4 times a month
4 ☐ 5-8 times a month
5 ☐ More than 8 times a month

54 Meat balls, hamburgers, rissoles etc.

1 ☐ Never, or less than once a month
2 ☐ 1-2 times a month
3 ☐ 3-4 times a month
4 ☐ 5-8 times a month
5 ☐ More than 8 times a month

55 Meat stews?

1 ☐ Never, or less than once a month
2 ☐ 1-2 times a month
3 ☐ 3-4 times a month
4 ☐ 5-8 times a month
5 ☐ More than 8 times a month

56 Fried or roast meat?

1 ☐ Never, or less than once a month
2 ☐ 1-2 times a month
3 ☐ 3-4 times a month
4 ☐ 5-8 times a month
5 ☐ 9-16 times a month
6 ☐ More than 16 times a month

57 Poached fish?
- 1 ☐ Never, or less than once a month
- 2 ☐ 1-2 times a month
- 3 ☐ 3-4 times a month
- 4 ☐ 5-8 times a month
- 5 ☐ 9-12 times a month
- 6 ☐ 13-16 times a month
- 7 ☐ More than 16 times a month

58 Fish cakes, fish balls, processed fish?
- 1 ☐ Never, or less than once a month
- 2 ☐ 1-2 times a month
- 3 ☐ 3-4 times a month
- 4 ☐ 5-8 times a month
- 5 ☐ More than 8 times a month

59 Fried fish?
- 1 ☐ Never, or less than once a month
- 2 ☐ 1-2 times a month
- 3 ☐ 3-4 times a month
- 4 ☐ 5-8 times a month
- 5 ☐ 9-12 times a month
- 6 ☐ 13-16 times a month
- 7 ☐ More than 16 times a month

60 Fruit soups, stewed fruit?
- 1 ☐ Never, or less than once a month
- 2 ☐ 1-2 times a month
- 3 ☐ 3-4 times a month
- 4 ☐ 5-8 times a month
- 5 ☐ 9-12 times a month
- 6 ☐ 13-16 times a month
- 7 ☐ More than 16 times a month

61 How many times do you usually eat per day? (Include coffee breaks)
- 1 ☐ 2 times per day
- 2 ☐ 3 times per day
- 3 ☐ 4 times per day
- 4 ☐ 5 times per day
- 5 ☐ 6 or more times per day

62 At what time do you eat or drink for the first time in the morning?
- 1 ☐ Before 6 a.m.
- 2 ☐ Between 6 a.m. and 8 a.m.
- 3 ☐ Between 8 a.m. and 10 a.m.
- 4 ☐ At 10 a.m. or later

63 How many bread meals do you usually have per day?
- 1 ☐ Do not eat bread
- 2 ☐ Once a day
- 3 ☐ 2-3 times a day
- 4 ☐ 4 or more times a day

64 Do you have a household on your own or with others?
- 1 ☐ Private household alone
- 2 ☐ Private household with other adults
- 3 ☐ Private household with adults and children
- 4 ☐ Usually eat in a canteen

65 The drawings below show cubes of butter or margarine in a true scale. *
Mark the cube with which best resembles the amount you spread on a slice of bread. If in doubt, try buttering a slice.
* (see original questionnaire)

1 ☐ Do not use
2 ☐ 3 grammes
3 ☐ 5 grammes
4 ☐ 8 grammes
5 ☐ 12 grammes

66 Do you make any attempts to change your body weight?

1 ☐ Yes 2 ☐ No

I forbindelse med den undersøkelsen De er med på, vil vi stille Dem noen spørsmål om Deres kosthold og endringer av dette de siste 3 årene.
Vi vil også spørre om endringer av den fysiske aktivitet i fritiden og av røykevaner.

Vennligst fyll ut dette spørreskjemaet og returner det i den vedlagte svarkonvolutt. Portoen vil bli betalt av mottakeren.

Om det skulle være flere i Deres husstand som har fått spørreskjema, ber vi om at hver enkelt fyller det ut.

Opplysningene De gir vil bli behandlet strengt fortrolig.

Med hilsen

Helserådet — Fylkeslegen

Avdeling for kostholdsforskning
Universitetet i Oslo

Statens skjermbildefotografering

VEILEDNING FOR UTFYLLING AV SPØRRESKJEMAET.

Besvar de enkelte spørsmål ved å sette kryss i den ☐ som passer.
Hvis De ikke kan gi et helt nøyaktig svar, vennligst svar da etter beste skjønn.
Det kan forekomme spørsmål som De finner at De i det hele tatt ikke er i stand til å besvare. La disse spørsmål stå åpne, og besvar så mange som mulig av de øvrige.

14 Er De på diett (spesiell kost) nå?

1 ☐ Ja 2 ☐ Nei

Om De er på diett, så prøv likevel å fylle ut skjemaet.

15 Hvor mange brødskiver spiser De vanligvis pr. dag?

1 ☐ Mindre enn 2 skiver pr. dag
2 ☐ 2 - 4 skiver pr. dag
3 ☐ 5 - 6 skiver pr. dag
☐ 7 - 8 skiver pr. dag
5 ☐ 9 - 12 skiver pr. dag
6 ☐ 13 eller flere skiver pr. dag

16 Hva slags brød spiser De oftest?

1 ☐ Kjøpt
2 ☐ Hjemmebakt

17 Hvis kjøpt brød, hva slags oftest?

1 ☐ Loff
2 ☐ Fint (lyst) brød
3 ☐ Grovt (mørkt) brød

18 Hvis hjemmebakt brød, hvor stor andel av melet er grovt (mørkt)?

1 ☐ Bruker ikke grovt mel
2 ☐ Mindre enn 1/4 grovt mel
3 ☐ 1/4 - 1/2 grovt mel
4 ☐ Mer enn 1/2 grovt mel

19 Hva pleier De vanligvis å smøre på brødet?

1 ☐ Bruker ikke noe
2 ☐ Smør (meierismør)
3 ☐ Margarin

20 Hvis De bruker margarin på brødet, hvilket merke bruker De vanligvis?

.....

21 Kryss av for den aktuelle pakning.

1 ☐ Pakke
2 ☐ Bordpakning (beger)

22 Hvilke påleggslag bruker De vanligvis?
30 Kryss av i alle ruter som er aktuelle.

22 ☐ Hvit (gul) ost
23 ☐ Brun ost
24 ☐ Honning, sirup, sukker (på brød)
25 ☐ Syltetøy, marmelade
26 ☐ Andre søte påleggslag (sunda, sjokade, banos, nøtte m.v.)
27 ☐ Majones, salater
28 ☐ Leverpostei
29 ☐ Spekepølse (salt pølse) og annet kjøttpålegg
30 ☐ Sardiner, sursild, speket fisk og annet fiskepålegg

31 Hvor mange glass eller kopper melk drikker De vanligvis pr. dag?

1 ☐ Drikker ikke, eller mindre enn 1 glass eller kopp pr. dag
2 ☐ 1 glass eller kopp pr. dag
3 ☐ 2 glass eller kopper pr. dag
4 ☐ 3 glass eller kopper pr. dag
5 ☐ 4 glass eller kopper pr. dag
6 ☐ 5 eller flere glass eller kopper pr. dag

32 Hva slags melk drikker De vanligvis?

1 ☐ Drikker ikke melk
2 ☐ Melk (helmelk), søt, sur
3 ☐ Skummet melk, søt, sur
4 ☐ Håndskummet melk
5 ☐ Både helmelk og skummet melk

33 Hvor mange kopper kaffe drikker De vanligvis pr. dag?

1 ☐ Drikker ikke, eller mindre enn 1 kopp pr. dag
2 ☐ 1 - 2 kopper pr. dag
3 ☐ 3 - 4 kopper pr. dag
4 ☐ 5 - 6 kopper pr. dag
5 ☐ 7 - 8 kopper pr. dag
6 ☐ 9 eller flere kopper pr. dag

34 Hvor mye sukker bruker De vanligvis til eller i kaffen?

1 ☐ Drikker ikke kaffe
2 ☐ Bruker ikke sukker til/i kaffen
3 ☐ 1 - 2 biter/teskjeer pr. kopp
4 ☐ 3 - 4 biter/teskjeer pr. kopp
5 ☐ 5 - 6 biter/teskjeer pr. kopp
6 ☐ 7 eller flere biter eller teskjeer pr. kopp

35 Hvor mange egg (kokte eller stekte) spiser De vanligvis i uken?

1 ☐ Spiser ikke, eller mindre enn 1 egg i uken
2 ☐ 1 egg i uken
3 ☐ 2 egg i uken
4 ☐ 3 - 4 egg i uken
5 ☐ 5 - 6 egg i uken
6 ☐ 7 eller flere egg i uken

36 Hvor mange appelsiner spiser De vanligvis i uken?

1 ☐ Spiser ikke, eller mindre enn 1 appelsin i uken
2 ☐ 1 appelsin i uken
3 ☐ 2 appelsiner i uken
4 ☐ 3 - 4 appelsiner i uken
5 ☐ 5 - 6 appelsiner i uken
6 ☐ 7 eller flere appelsiner i uken

37 Hvor ofte består middagsmåltidet av fisk eller retter med fisk?

1 ☐ Sjeldnere enn én gang i uken
2 ☐ 1 - 2 ganger i uken
3 ☐ 3 - 4 ganger i uken
4 ☐ 5 - 6 ganger i uken
5 ☐ 7 ganger i uken

38 Hvor ofte består middagsmåltidet av kjøtt eller retter med kjøtt (også retter med blod og innmat)?

1 ☐ Sjeldnere enn én gang i uken
2 ☐ 1 - 2 ganger i uken
3 ☐ 3 - 4 ganger i uken
4 ☐ 5 - 6 ganger i uken
5 ☐ 7 ganger i uken

39 Hvor ofte består middagsmåltidet av a typer retter, som grøt, pannekaker m.

1 ☐ Sjeldnere enn én gang i uken
2 ☐ 1 - 2 ganger i uken
3 ☐ 3 - 4 ganger i uken
4 ☐ 5 eller flere ganger i uken

40 Hvor ofte bruker De fett (smør, margar kjøttfett eller fleskefett) til eller på kjøtt?

1 ☐ Aldri eller sjeldnere enn én g i uken
2 ☐ 1 - 2 ganger i uken
3 ☐ 3 - 4 ganger i uken
4 ☐ 5 eller flere ganger i uken

41 Hvor ofte bruker De fett (smør, margar kjøttfett eller fleskefett) til eller på fisk?

1 ☐ Aldri eller sjeldnere enn én ga i uken
2 ☐ 1 - 2 ganger i uken
3 ☐ 3 - 4 ganger i uken
4 ☐ 5 eller flere ganger i uken

42 Hvor ofte spiser De fiskelever (i perioder fiskelever er å få)?

1 ☐ Aldri eller sjeldnere enn én ga i uken
2 ☐ 1 - 2 ganger i uken
3 ☐ 3 - 4 ganger i uken
4 ☐ 5 eller flere ganger i uken

43 Hvor ofte spiser De poteter til middag løpet av en vanlig uke?

1 ☐ Sjeldnere enn 3 ganger i uken
2 ☐ 3 - 5 ganger i uken
3 ☐ 6 - 7 ganger i uken

44 Hvor mange poteter spiser De vanligvis til middag?

1 ☐ Mindre enn én potet pr. mål
2 ☐ 1 potet pr. måltid
3 ☐ 2 poteter pr. måltid
4 ☐ 3 - 4 poteter pr. måltid
5 ☐ 5 eller flere poteter pr. måltid

45 Hvor ofte drikker De saft, brus eller andre søte drikker i løpet av en vanlig uke?

1 ☐ Aldri eller sjeldnere enn én gang i uken
2 ☐ 1 - 2 ganger i uken
3 ☐ 3 - 4 ganger i uken
4 ☐ 5 - 6 ganger i uken
5 ☐ 7 eller flere ganger i uken

46 Hvor ofte spiser De kaker, kjeks, vafle eller lefser i løpet av en vanlig uke?

1 ☐ Aldri eller sjeldnere enn én gang i uken
2 ☐ 1 - 2 ganger i uken
3 ☐ 3 - 4 ganger i uken
4 ☐ 5 - 6 ganger i uken
5 ☐ 7 eller flere ganger i uken

47 Bruker De noe av de følgende varer i
52 løpet av en vanlig uke?
Kryss av i alle ruter som er aktuelle.

47 ☐ Potetgull (potetchips)
48 ☐ Sjokolade, konfekt, drops eller pastiller
49 ☐ Vin, brennevin
50 ☐ Øl (uansett type)
51 ☐ Tran
52 ☐ Vitaminpiller eller vitaminpreparat

HVOR MANGE GANGER I MÅNEDEN SPISER DE NOEN AV DE FØLGENDE RETTER TIL MIDDAG?
Gjelder spørsmålene 53-60.

53 Kokte eller stekte pølser

1 ☐ Aldri eller sjeldnere enn én gang i måneden
2 ☐ 1 - 2 ganger i måneden
3 ☐ 3 - 4 ganger i måneden (inntil én gang i uken)
4 ☐ 5 - 8 ganger i måneden (inntil 2 ganger i uken)
5 ☐ Mer enn 8 ganger i måneden (mer enn 2 ganger i uken)

54 Kjøttkaker, karbonader og lignende

1 ☐ Aldri eller sjeldnere enn én gang i måneden
2 ☐ 1 - 2 ganger i måneden
3 ☐ 3 - 4 ganger i måneden
4 ☐ 5 - 8 ganger i måneden
5 ☐ Mer enn 8 ganger i måneden

55 Kokt kjøtt, fårikål, kjøttsuppe, lapskaus

1 ☐ Aldri eller sjeldnere enn én gang i måneden
2 ☐ 1 - 2 ganger i måneden
3 ☐ 3 - 4 ganger i måneden
4 ☐ 5 - 8 ganger i måneden
5 ☐ Mer enn 8 ganger i måneden

56 Stekte kjøttretter (koteletter, småstek m.v.)

1 ☐ Aldri eller sjeldnere enn én gang i måneden
2 ☐ 1 - 2 ganger i måneden
3 ☐ 3 - 4 ganger i måneden
4 ☐ 5 - 8 ganger i måneden
5 ☐ 9 - 16 ganger i måneden
6 ☐ Mer enn 16 ganger i måneden

57 Kokt fisk

1 ☐ Aldri eller sjeldnere enn én gang i måneden
2 ☐ 1 - 2 ganger i måneden
3 ☐ 3 - 4 ganger i måneden
4 ☐ 5 - 8 ganger i måneden
5 ☐ 9 - 12 ganger i måneden
6 ☐ 13 - 15 ganger i måneden
7 ☐ Mer enn 16 ganger i måneden

58 Fiskekaker, fiskepudding, fiskeboller

1 ☐ Aldri eller sjeldnere enn én gang i måneden
2 ☐ 1 - 2 ganger i måneden
3 ☐ 3 - 4 ganger i måneden
4 ☐ 5 - 8 ganger i måneden
5 ☐ Mer enn 8 ganger i måneden

59 Stekt fisk

1 ☐ Aldri eller sjeldnere enn én gang i måneden
2 ☐ 1 - 2 ganger i måneden
3 ☐ 3 - 4 ganger i måneden
4 ☐ 5 - 8 ganger i måneden
5 ☐ 9 - 12 ganger i måneden
6 ☐ 13 - 15 ganger i måneden
7 ☐ Mer enn 16 ganger i måneden

60 Søtsuppe, fruktsuppe, fruktgrøt, kompot

1 ☐ Aldri eller sjeldnere enn én gang i måneden
2 ☐ 1 - 2 ganger i måneden
3 ☐ 3 - 4 ganger i måneden
4 ☐ 5 - 8 ganger i måneden
5 ☐ 9 - 12 ganger i måneden
6 ☐ 13 - 16 ganger i måneden
7 ☐ Mer enn 16 ganger i måneden

61 Hvor mange ganger spiser De vanligvis pr. dag (tell også med kaffemåltider)?

1 ☐ 2 ganger pr. dag
2 ☐ 3 ganger pr. dag
3 ☐ 4 ganger pr. dag
4 ☐ 5 ganger pr. dag
5 ☐ 6 eller flere ganger pr. dag

62 Når spiser eller drikker De første gang om morgenen?

1 ☐ Før kl. 0600
2 ☐ Mellom kl. 0600 og kl. 0800
3 ☐ Mellom kl. 0800 og kl. 1000
4 ☐ Kl. 1000 eller senere

63 Hvor mange ganger om dagen spiser De brødmat?

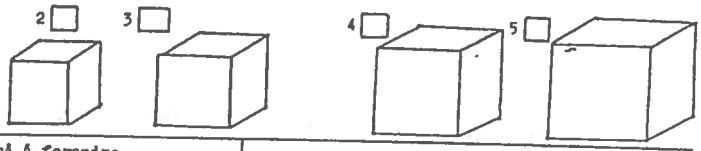
1 ☐ Spiser ikke brød
2 ☐ 1 gang pr. dag
3 ☐ 2 - 3 ganger pr. dag
4 ☐ 4 eller flere ganger pr. dag

64 Har De husholdning alene eller sammen med andre?

1 ☐ Har privat husholdning alene
2 ☐ Har privat husholdning sammen med voksne
3 ☐ Har privat husholdning sammen med voksne og barn
4 ☐ Spiser hovedsaklig i messe, kantine (storhusholdning)

65 Nedenstående tegninger forestiller terninger av smør eller margarin i naturlig størrelse. Kryss av for den terning som likner mest på den mengde De bruker til en skive brød. Er De i tvil, forsøk å prøvesmøre en skive.

1 ☐ Bruker ikke 2 ☐ 3 ☐ 4 ☐ 5 ☐



66 Gjør De noe forsøk på å forandre kroppsvekten Deres?

1 ☐ Ja 2 ☐ Nei

Dette spørreskjemaet er utarbeidet av Avdeling for kostholdsforskning, Universitetet i Oslo for bruk i Statens Skjermbildefotograferings hjerte- kar-undersøkelser. For bruk i Finnmark II ble skjemaet også oversatt til samisk.
Siden skjemaet belyser spesielle sider av kostholdet er det ikke uten videre egnet til å gi en generell beskrivelse. Vi ber om at andre grupper som måtte være interessert i å bruke skjemaet eller deler av det, først kontakter oss, og at det blir gitt kilde-henvisning.

Avdeling for kostholdsforskning
Universitetet i Oslo

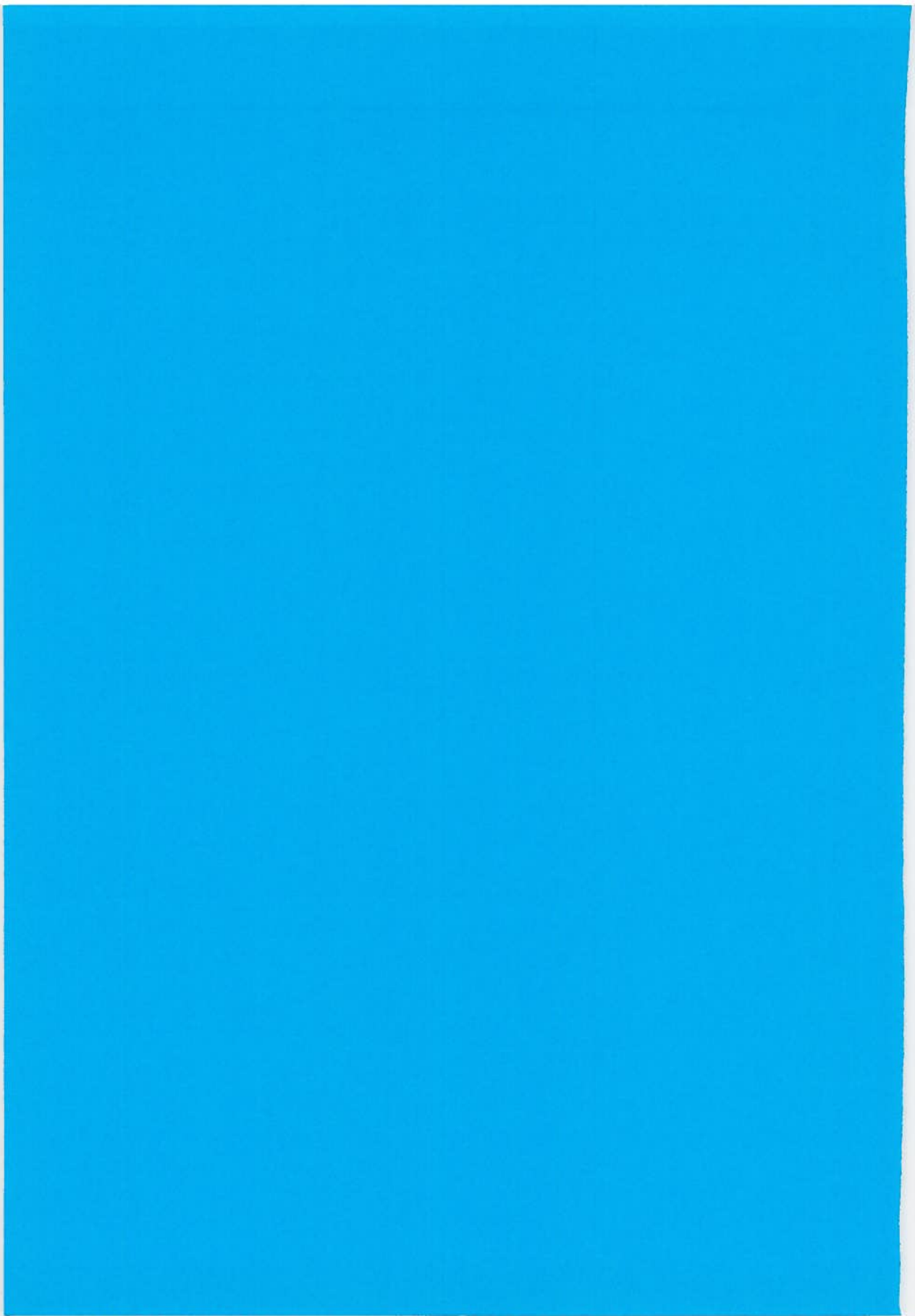
Appendix G

Food frequency questionnaires
used in the cardiovascular disease studies
in the counties of Oppland and Sogn og Fjordane:

Questionnaire Oppland, 1985–87 survey
Questionnaire Sogn og Fjordane, 1985–87 survey

Original questionnaires

Paper IV



OPPLAND

I samband med undersøkinga De er med på, vil vi stille nokre spørsmål om kosthaldet Dykkar. Ver venleg og fyll ut dette spørjeskjemaet og send det attende til oss i den vedlagte svar-konvolutten.

Har fleire i huslyden fått spørjeskjema, ber vi om at kvar enkelt fyller det ut.

Mottakaren betalar portoen.

Opplysningane De gjev, vil bli handsama strengt konfidensielt.

Med helsing

Helserådet

Fylkesiækjaren

Avdeling for kostholdsforskning
Universitetet i Oslo

Statens helseundersøkelser

RETTLEIING

Svar på kvart enkelt spørsmål ved å setja kryss i den ☐ som passar best. Er det vanskeleg å gje nøyaktig svar, så svar etter beste skjønn. Det kan finnast spørsmål som De ikkje kan svare på. La slike spørsmål stå opne, men svar på så mange av dei andre som råd er.

12 Held De diett (spesiell kost) no?

1 ☐ Ja
2 ☐ Nei

Om De held diett, så prøv likevel å fylle ut skjemaet.

13 Kor mange gonger et De vanlegvis om dagen (rekne og med kaffimåltid)?

1 ☐ 2 gonger om dagen
2 ☐ 3 gonger om dagen
3 ☐ 4 gonger om dagen
4 ☐ 5 gonger om dagen
5 ☐ 6 eller fleire gonger om dagen

14 Fyrste gongen De et eller drikk noko om morgonen, kva tid er det?

1 ☐ Før kl 0600
2 ☐ Mellom kl 0600 og kl 0800
3 ☐ Mellom kl 0800 og kl 1000
4 ☐ Kl 1000 og seinare

15 Kor mange gonger et De brødmat om dagen?

1 ☐ Et ikkje brød
2 ☐ 1 gong om dagen
3 ☐ 2 gonger om dagen
4 ☐ 3 gonger om dagen
5 ☐ 4 eller fleire gonger om dagen

16 Kor ofte et De middag?

1 ☐ Kvar dag
2 ☐ 5-6 gonger i veka
3 ☐ 4 gonger eller mindre i veka

17 Kor mange skiver brød et De vanlegvis om dagen?

1 ☐ Mindre enn 2 skiver om dagen
2 ☐ 2-4 skiver om dagen
3 ☐ 5-6 skiver om dagen
4 ☐ 7-8 skiver om dagen
5 ☐ 9-12 skiver om dagen
6 ☐ 13 eller fleire skiver om dagen

18 Kva slag brød brukar De vanlegvis?

1 ☐ Kjøpt
2 ☐ Heimebakt

19 Dersom kjøpt brød, kva slag oftast?

1 ☐ Loff
2 ☐ Fint (lyst) brød
3 ☐ Grovt (mørkt) brød

20 Dersom heimebakt brød, kor stor del av mjølet et grovt?

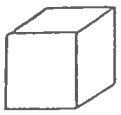
1 ☐ Brukar ikkje grovt mjøl
2 ☐ Mindre enn 1/4 grovt mjøl
3 ☐ 1/4 - 1/2 grovt mjøl
4 ☐ Meir enn 1/2 grovt mjøl

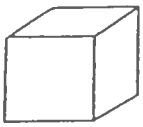
21 Kva brukar De vanlegvis å smørje på brødet?

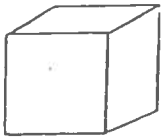
1 ☐ Brukar ikkje noko
2 ☐ Smør (meierismør)
3 ☐ Fast (vanleg) margarin (Per, Melange)
4 ☐ Mjuk (soft, soya) margarin
5 ☐ Bremykt
6 ☐ Smøregod
7 ☐ Lettmargarin(Minarin, Minett)
8 ☐ Annan margarin

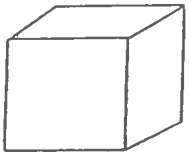
22 Desse figurane viser smør- eller margarinterningar i naturleg storleik.
Kryss av for den terningen som liknar mest på den mengden De brukar til ei skive brød.
Er De i tvil, prøv å smørje ei skive.

1 ☐ Brukar ikkje

2 ☐ 

3 ☐ 

4 ☐ 

5 ☐ 

Kva for pålegg brukar De vanlegvis?

	Ja	Nei	
23	☐	☐	Kvit (gul) ost
24	☐	☐	Brun ost
25	☐	☐	Honning, sirup, sukker (på brød)
26	☐	☐	Syltetøy, marmelade
27	☐	☐	Andre søte påleggslag (sunda, sjokade, banos, nøtte m v)
28	☐	☐	Majones, majonessalat
29	☐	☐	Leverpostei
30	☐	☐	Spekepølse (salt pølse) og anna kjøtpålegg
31	☐	☐	Sardiner, sursild, speka fisk og anna fiskepålegg

32 Kor mange glas mjølk drikk De vanlegvis om dagen?

1	☐	Drikk ikkje eller mindre enn 1 glas om dagen
2	☐	1 glas om dagen
3	☐	2 glas om dagen
4	☐	3 glas om dagen
5	☐	4 glas om dagen
6	☐	5 glas om dagen
7	☐	6 eller fleire glas om dagen

33 Kva slag mjølk drikk De vanlegvis?

1	☐	Drikk ikkje mjølk
2	☐	Mjølk (heilmjølk) søt, sur
3	☐	Skumma mjølk, søt, sur
4	☐	Lettmjølk
5	☐	Heilmjølk og skumma/lettmjølk

34 Kor mange koppar kaffi drikk De vanlegvis om dagen?

1	☐	Drikk ikkje eller mindre enn 1 kopp om dagen
2	☐	1-2 koppar om dagen
3	☐	3-4 koppar om dagen
4	☐	5-6 koppar om dagen
5	☐	7-8 koppar om dagen
6	☐	9-10 koppar om dagen
7	☐	11 eller fleire koppar om dagen

35 Kor mykje sukker brukar De vanlegvis til eller i kaffien?

1	☐	Drikk ikkje kaffi
2	☐	Brukar ikkje sukker til/i kaffi
3	☐	1-2 bitar per kopp
4	☐	3-4 bitar per kopp
5	☐	5-6 bitar per kopp
6	☐	7 eller fleire bitar per kopp

KOR MYKJE/KOR MANGE GONGER I VEKA BRUKAR DE NOKRE AV DEI FØLGJANDE VARENE/RETTENE ?

36 Egg (kokte eller steikte)

1	☐	Et ikkje eller mindre enn 1 egg i veka
2	☐	1 egg i veka
3	☐	2 egg i veka
4	☐	3-4 egg i veka
5	☐	5-6 egg i veka
6	☐	7 eller fleire egg i veka

37 Appelsiner

1	☐	Et ikkje eller mindre enn 1 appelsin i veka
2	☐	1 appelsin i veka
3	☐	2 appelsiner i veka
4	☐	3-4 appelsiner i veka
5	☐	5-6 appelsiner i veka
6	☐	7 eller fleire appelsiner i veka

38 Epler/pærer

1	☐	Et ikkje eller mindre enn 1 eple/pære i veka
2	☐	1-2 epler/pærer i veka
3	☐	3-4 epler/pærer i veka
4	☐	5-6 epler/pærer i veka
5	☐	7 eller fleire epler/pærer i veka

39 Saft, brus eller andre søte drikker

1	☐	Aldri eller sjeldnare enn ein gong i veka
2	☐	1-2 gonger i veka
3	☐	3-4 gonger i veka
4	☐	5-6 gonger i veka
5	☐	7 eller fleire gonger i veka

40 Kaker, kjeks, vafler eller lefser

1	☐	Aldri eller sjeldnare enn ein gong i veka
2	☐	1-2 gonger i veka
3	☐	3-4 gonger i veka
4	☐	5-6 gonger i veka
5	☐	7 eller fleire gonger i veka

41 Kjøt eller retter med kjøt til middag, (også retter med blod og innmat)

1 ☐ Sjeldnare enn ein gong i veka
2 ☐ 1-2 gonger i veka
3 ☐ 3-4 gonger i veka
4 ☐ 5-6 gonger i veka
5 ☐ 7 gonger i veka

42 Fisk eller retter med fisk til middag

1 ☐ Sjeldnare enn ein gong i veka
2 ☐ 1-2 gonger i veka
3 ☐ 3-4 gonger i veka
4 ☐ 5-6 gonger i veka
5 ☐ 7 gonger i veka

43 Andre typer retter som graut, pannekaker, raspeball, pizza, m v til middag

1 ☐ Sjeldnare enn ein gong i veka
2 ☐ 1-2 gonger i veka
3 ☐ 3-4 gonger i veka
4 ☐ 5 eller fleire gonger i veka

44 Feitt (smør, margarin, kjøtfeitt eller fleskefeitt) til eller på kjøt

1 ☐ Aldri eller sjeldnare enn ein gong i veka
2 ☐ 1-2 gonger i veka
3 ☐ 3-4 gonger i veka
4 ☐ 5 eller fleire gonger i veka

45 Feitt (smør, margarin, kjøtfeitt eller fleskefeitt) til eller på fisk

1 ☐ Aldri eller sjeldnare enn ein gong i veka
2 ☐ 1-2 gonger i veka
3 ☐ 3-4 gonger i veka
4 ☐ 5 eller fleire gonger i veka

46 Fiskelever (i periodar fiskelever er å få)

1 ☐ Aldri eller sjeldnare enn ein gong i veka
2 ☐ 1-2 gonger i veka
3 ☐ 3-4 gonger i veka
4 ☐ 5 eller fleire gonger i veka

47 Poteter til middag i ei vanleg veke

1 ☐ Sjeldnare enn 3 gonger i veka
2 ☐ 3-5 gonger i veka
3 ☐ 6-7 gonger i veka

48 Kor mange poteter et De vanlegvis til middag?

1 ☐ Mindre enn ei potet per måltid
2 ☐ 1 potet per måltid
3 ☐ 2 poteter per måltid
4 ☐ 3-4 poteter per måltid
5 ☐ 5 eller fleire poteter per måltid

KOR MANGE GONGER I MÅNADEN BRUKAR DE NOKRE AV DEI FØLGJANDE RETTENE TIL MIDDAG?

49 Kokte eller steikte pølser

1 ☐ Aldri eller sjeldnare enn ein gong i månaden
2 ☐ 1-2 gonger i månaden
3 ☐ 3-4 gonger i månaden (opptil ein gong i veka)
4 ☐ 5-8 gonger i månaden (opptil 2 gonger i veka)
5 ☐ Meir enn 8 gonger i månaden (meir enn 2 gonger i veka)

50 Kjøtkaker, karbonader og liknande

1 ☐ Aldri eller sjeldnare enn ein gong i månaden
2 ☐ 1-2 gonger i månaden
3 ☐ 3-4 gonger i månaden
4 ☐ 5-8 gonger i månaden
5 ☐ Meir enn 8 gonger i månaden

51 Kokt kjøt, sausekjøt, fårikål, betasuppe, lapskaus m v

1 ☐ Aldri eller sjeldnare enn ein gong i månaden
2 ☐ 1-2 gonger i månaden
3 ☐ 3-4 gonger i månaden
4 ☐ 5-8 gonger i månaden
5 ☐ Meir enn 8 gonger i månaden

52 Steikte kjøtretter (koteletter, stelk m v)

1 ☐ Aldri eller sjeldnare enn ein gong i månaden
2 ☐ 1-2 gonger i månaden
3 ☐ 3-4 gonger i månaden
4 ☐ 5-8 gonger i månaden
5 ☐ 9-16 gonger i månaden
6 ☐ Meir enn 16 gonger i månaden

53 Kokt fisk

1 ☐ Aldri eller sjeldnare enn ein gong i månaden
2 ☐ 1-2 gonger i månaden
3 ☐ 3-4 gonger i månaden
4 ☐ 5-8 gonger i månaden
5 ☐ 9-12 gonger i månaden
6 ☐ 13-16 gonger i månaden
7 ☐ Meir enn 16 gonger i månaden

54 Fiskekaker, fiskepudding, fiskebollar

1 ☐ Aldri eller sjeldnare enn ein gong i månaden
2 ☐ 1-2 gonger i månaden
3 ☐ 3-4 gonger i månaden
4 ☐ 5-8 gonger i månaden
5 ☐ Meir enn 8 gonger i månaden

55 Steikt fisk

1 ☐ Aldri eller sjeldnare enn ein gong i månaden
2 ☐ 1-2 gonger i månaden
3 ☐ 3-4 gonger i månaden
4 ☐ 5-8 gonger i månaden
5 ☐ 9-12 gonger i månaden
6 ☐ 13-16 gonger i månaden
7 ☐ Meir enn 16 gonger i månaden

56 Kor ofte brukar De vanlegvis grønsaker til/ved sida av kjøt/retter med kjøt?

1 ☐ Aldri eller sjeldan
2 ☐ Av og til
3 ☐ Ofte
4 ☐ Alltid eller mest alltid

57 Kor ofte brukar De vanlegvis grønsaker til/ved sida av fisk/retter med fisk?

1 ☐ Aldri eller sjeldan
2 ☐ Av og til
3 ☐ Ofte
4 ☐ Alltid eller mest alltid

58 Kor ofte brukar De gulrot (rå, kokt, stua, i lapskaus m v) til retter med kjøt og fisk?

1 ☐ Aldri eller sjeldnare enn ein gong i månaden
2 ☐ 1-2 gonger i månaden
3 ☐ 3-4 gonger i månaden
4 ☐ 5-8 gonger i månaden
5 ☐ 9-16 gonger i månaden
6 ☐ Meir enn 16 gonger i månaden

59 Kor ofte brukar De hovudkål (rå, kokt, stua, i fårikål m v), surkål til retter med kjøt og fisk?

1 ☐ Aldri eller sjeldnare enn ein gong i månaden
2 ☐ 1-2 gonger i månaden
3 ☐ 3-4 gonger i månaden
4 ☐ 5-8 gonger i månaden
5 ☐ 9-16 gonger i månaden
6 ☐ Meir enn 16 gonger i månaden

60 Fruktgraut, kompott, fruktsuppe, søtsuppe?

1 ☐ Aldri eller sjeldnare enn ein gong i månaden
2 ☐ 1-2 gonger i månaden
3 ☐ 3-4 gonger i månaden
4 ☐ 5-8 gonger i månaden
5 ☐ 9-12 gonger i månaden
6 ☐ 13-16 gonger i månaden
7 ☐ Meir enn 16 gonger i månaden

61 Kva slag feitt brukar De vanlegvis til matlaging?

1 ☐ Smør (meierismør)
2 ☐ Fast (vanleg)margarin (Per, Melange)
3 ☐ Mjuk (soft, soya) margarin
4 ☐ Annan margarin
5 ☐ Olje
6 ☐ Anna feitt

BRUKAR DE NOKON AV DESSE VARENE I LØPET AV EI VANLEG VEKE?

	Ja	Nei	
62	☐	☐	Potetgull (potetchips)
63	☐	☐	Sjokolade, konfekt, drops, pastiller
64	☐	☐	Tran
65	☐	☐	Vitaminpiller eller vitaminpreparat

66 Brukar De nokon gong alkoholhaldige drikkar?

1 ☐ Nei, er totalavhalden
2 ☐ Ja

67 Har De drukke øl siste veke?

1 ☐ Har ikkje drukke øl siste veke
2 ☐ 1 gong siste veke
3 ☐ 2-3 gonger siste veke
4 ☐ 4 eller fleire gonger siste veke

68 Har De drukke vin siste veke?

1 ☐ Har ikkje drukke vin siste veke
2 ☐ 1 gong siste veke
3 ☐ 2-3 gonger siste veke
4 ☐ 4 eller fleire gonger siste veke

69 Har De drukke brennevin siste veke?

1 ☐ Har ikkje drukke brennevin siste veke
2 ☐ 1 gong siste veke
3 ☐ 2-3 gonger siste veke
4 ☐ 4 eller fleire gonger siste veke

ANDRE SPØRSMÅL

70 Gjer De noko forsøk på å endre kroppsvekta Dykkar?

1 ☐ Ja
2 ☐ Nei

71 Dersom ja, kvifor?

1 ☐ Vil gå ned i vekt
2 ☐ Vil auke i vekt

72 Har De gått inn for å endre mengda av den fysiske aktiviteten i fritida dei siste 5 åra?

1 ☐ Har større fysisk aktivitet no enn før
2 ☐ Har same fysiske aktivitet som før
3 ☐ Har mindre fysisk aktivitet no enn før

73 Har De hushald åleine eller saman med andre?

1 ☐ Har privat hushald aleine
2 ☐ Har privat hushald saman med vaksne
3 ☐ Har privat hushald saman med vaksne og born
4 ☐ Et for det meste i messe, kantine (storhushald)

SOGN OG FJORDANE

I samband med undersøkinga De er med på, vi vi stille nokre spørsmål om kosthaldet Dykkar. Ver venleg og fyll ut dette spørjeskjemaet og send det attende til oss i den vedlagte svar-konvolutten.

Har fleire i huslyden fått spørjeskjema, ber vi om at kvar enkelt fyller det ut.

Mottakaren betalar portoen.

Opplysningane De gjev, vil bli handsama strengt konfidensielt.

Med helsing

Helserådet — Fylkeslækjar

Avdeling for kostholdsforskning
Universitetet i Oslo

Statens Skjermbildefotografering

RETTLEIING

Svar på kvart enkelt spørsmål ved å setja kryss i den ☐ som passar best. Er det vanskeleg å gje nøyaktig svar, så svar etter beste skjønn. Det kan finnast spørsmål som De ikkje kan svare på. La slike spørsmål stå opne, men svar på så mange av dei andre som råd er.

12 Held De diett (spesiell kost) no?

1 ☐ Ja
2 ☐ Nei

Om De held diett, så prøv likevel å fylle ut skjemaet.

13 Kor mange gonger et De vanlegvis om dagen (rekne og med kaffimåltid)?

1 ☐ 2 gonger om dagen
2 ☐ 3 gonger om dagen
3 ☐ 4 gonger om dagen
4 ☐ 5 gonger om dagen
5 ☐ 6 eller fleire gonger om dagen

14 Fyrste gongen De et eller drikk noko om morgonen, kva tid er det?

1 ☐ Før kl 0600
2 ☐ Mellom kl 0600 og kl 0800
3 ☐ Mellom kl 0800 og kl 1000
4 ☐ Kl 1000 og seinare

15 Kor mange gonger et De brødmat om dagen?

1 ☐ Et ikkje brød
2 ☐ 1 gong om dagen
3 ☐ 2 gonger om dagen
4 ☐ 3 gonger om dagen
5 ☐ 4 eller fleire gonger om dagen

16 Kor ofte et De middag?

1 ☐ Kvar dag
2 ☐ 5-6 gonger i veka
3 ☐ 4 gonger eller mindre i veka

17 Kor mange skiver brød et De vanlegvis om dagen?

1 ☐ Mindre enn 2 skiver om dagen
2 ☐ 2-4 skiver om dagen
3 ☐ 5-6 skiver om dagen
4 ☐ 7-8 skiver om dagen
5 ☐ 9-12 skiver om dagen
6 ☐ 13 eller fleire skiver om dagen

18 Kva slag brød brukar De vanlegvis?

1 ☐ Kjøpt
2 ☐ Heimebakt

19 Dersom kjøpt brød, kva slag oftast?

1 ☐ Loff
2 ☐ Fint (lyst) brød
3 ☐ Grovt (mørkt) brød

20 Dersom heimebakt brød, kor stor del av mjølet er grovt?

1 ☐ Brukar ikkje grovt mjøl
2 ☐ Mindre enn 1/4 grovt mjøl
3 ☐ 1/4 - 1/2 grovt mjøl
4 ☐ Meir enn 1/2 grovt mjøl

21 Kva brukar De vanlegvis å smørje på brødet?

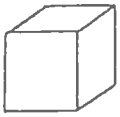
1 ☐ Brukar ikkje noko
2 ☐ Smør (meierismør)
3 ☐ Margarin

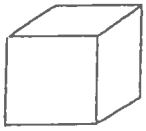
22 Dersom De brukar margarin på brødet, kva merke brukar De vanlegvis?

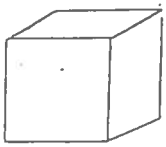
.....

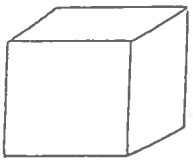
terningar i naturleg storleik.
Kryss av for den terningen som liknar mest på den mengden De brukar til ei skive brød. Er De i tvil, prøv å smørje ei skive.

1 ☐ Brukar ikkje

2 ☐ 

3 ☐ 

4 ☐ 

5 ☐ 

Kva for pålegg brukar De vanlegvis?

	Ja	Nei	
24	☐	☐	Kvit (gul) ost
25	☐	☐	Brun ost
26	☐	☐	Honning, sirup, sukker (på brød)
27	☐	☐	Syltetøy, marmelade
28	☐	☐	Andre søte påleggslag (sunda, sjokade, banos, nøtte m v)
29	☐	☐	Majones, majonessalat
30	☐	☐	Leverpostei
31	☐	☐	Spekepølse (salt pølse) og anna kjøtpålegg
32	☐	☐	Sardiner, sursild, speka fisk og anna fiskepålegg

33 Kor mange glas mjølk drikk De vanlegvis om dagen?

1 ☐ Drikk ikkje eller mindre enn 1 glas om dagen
2 ☐ 1 glas om dagen
3 ☐ 2 glas om dagen
4 ☐ 3 glas om dagen
5 ☐ 4 glas om dagen
6 ☐ 5 glas om dagen
7 ☐ 6 eller fleire glas om dagen

34 Kva slag mjølk drikk De vanlegvis?

1 ☐ Drikk ikkje mjølk
2 ☐ Mjølk (heilmjølk) søt, sur
3 ☐ Skumma mjølk, søt, sur
4 ☐ Lettmjølk
5 ☐ Heilmjølk og skumma/lettmjølk

om dagen?

1 ☐ Drikk ikkje eller mindre enn 1 kopp om dagen
2 ☐ 1-2 koppar om dagen
3 ☐ 3-4 koppar om dagen
4 ☐ 5-6 koppar om dagen
5 ☐ 7-8 koppar om dagen
6 ☐ 9-10 koppar om dagen
7 ☐ 11 eller fleire koppar om dagen

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4 ☐ 3-4 bitar per kopp
5 ☐ 5-6 bitar per kopp
6 ☐ 7 eller fleire bitar per kopp

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3 ☐ 3-4 gonger i veka
4 ☐ 5-6 gonger i veka
5 ☐ 7 eller fleire gonger i veka

1 ☐ Sjeldnare enn ein gong i veka
2 ☐ 1-2 gonger i veka
3 ☐ 3-4 gonger i veka
4 ☐ 5-6 gonger i veka
5 ☐ 7 gonger i veka

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3 ☐ 3-4 gonger i veka
4 ☐ 5 eller fleire gonger i veka

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1 ☐ Aldri eller sjeldnare enn ein gong i veka
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4 ☐ 5 eller fleire gonger i veka

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TIL MIDDAG!

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2 ☐ 1-2 gonger i månaden
3 ☐ 3-4 gonger i månaden
4 ☐ 5-8 gonger i månaden
5 ☐ Meir enn 8 gonger i månaden

1 ☐ Aldri eller sjeldnare enn ein gong i månaden
2 ☐ 1-2 gonger i månaden
3 ☐ 3-4 gonger i månaden
4 ☐ 5-8 gonger i månaden
5 ☐ 9-12 gonger i månaden
6 ☐ 13-16 gonger i månaden
7 ☐ Meir enn 16 gonger i månaden

57 Kor ofte brukar De vanlegvis grønsaker til/ved sida av kjøt/retter med kjøt?

1 ☐ Aldri eller sjeldan
2 ☐ Av og til
3 ☐ Ofte
4 ☐ Alltid eller mest alltid

58 Kor ofte brukar De vanlegvis grønsaker til/ved sida av fisk/retter med fisk?

1 ☐ Aldri eller sjeldan
2 ☐ Av og til
3 ☐ Ofte
4 ☐ Alltid eller mest alltid

59 Kor ofte brukar De gulrot (rå, kokt, stua, i lapskaus m v) til retter med kjøt og fisk?

1 ☐ Aldri eller sjeldnare enn ein gong i månaden
2 ☐ 1-2 gonger i månaden
3 ☐ 3-4 gonger i månaden
4 ☐ 5-8 gonger i månaden
5 ☐ 9-16 gonger i månaden
6 ☐ Meir enn 16 gonger i månaden

60 Kor ofte brukar De hovudkål (rå, kokt, stua, i fårikål m v), surkål til retter med kjøt og fisk?

1 ☐ Aldri eller sjeldnare enn ein gong i månaden
2 ☐ 1-2 gonger i månaden
3 ☐ 3-4 gonger i månaden
4 ☐ 5-8 gonger i månaden
5 ☐ 9-16 gonger i månaden
6 ☐ Meir enn 16 gonger i månaden

61 Fruktgraut, kompott, fruktsuppe, søtsuppe?

1 ☐ Aldri eller sjeldnare enn ein gong i månaden
2 ☐ 1-2 gonger i månaden
3 ☐ 3-4 gonger i månaden
4 ☐ 5-8 gonger i månaden
5 ☐ 9-12 gonger i månaden
6 ☐ 13-16 gonger i månaden
7 ☐ Meir enn 16 gonger i månaden

62 Kva slag feitt brukar De vanlegvis til matlaging?

1 ☐ Smør (meierismør)
2 ☐ Margarin
3 ☐ Olje
4 ☐ Anna feitt

63 Dersom De til vanleg brukar margarin til matlaging, kva merke brukar De da?

	Ja	Nei	
64	☐	☐	Potetgull (potetchips)
65	☐	☐	Sjokolade, konfekt, drops, pastiller
66	☐	☐	Tran
67	☐	☐	Vitaminpiller eller vitaminpreparat

68 Brukar De nokon gong alkoholhaldige drikka

1 ☐ Nei, er totalavhalden
2 ☐ Ja

69 Har De drukke øl siste veke?

1 ☐ Har ikkje drukke øl siste veke
2 ☐ 1 gong siste veke
3 ☐ 2-3 gonger siste veke
4 ☐ 4 eller fleire gonger siste veke

70 Har De drukke vin siste veke?

1 ☐ Har ikkje drukke vin siste veke
2 ☐ 1 gong siste veke
3 ☐ 2-3 gonger siste veke
4 ☐ 4 eller fleire gonger siste veke

71 Har De drukke brennevin siste veke?

1 ☐ Har ikkje drukke brennevin siste veke
2 ☐ 1 gong siste veke
3 ☐ 2-3 gonger siste veke
4 ☐ 4 eller fleire gonger siste veke

72 Gjer De noko forsøk på å endre kroppsvekta Dykkar?

1 ☐ Ja
2 ☐ Nei

73 Dersom ja, kvifor?

1 ☐ Vil gå ned i vekt
2 ☐ Vil auke i vekt

74 Har De gått inn for å endre mengda av den fysiske aktiviteten i fritida dei siste 5 åra?

1 ☐ Har større fysisk aktivitet no enn før
2 ☐ Har same fysiske aktivitet som før
3 ☐ Har mindre fysisk aktivitet no enn før

75 Har De hushald åleine eller saman med andre?

1 ☐ Har privat hushald aleine
2 ☐ Har privat hushald saman med vaksne
3 ☐ Har privat hushald saman med vaksne og born
4 ☐ Et for det meste i messe, kantine (storhushald)

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