Faculty of Health Sciences, Department of Community Medicine

**Lifestyle factors and colorectal cancer**

The Norwegian Women and Cancer Study

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A dissertation for the degree of Philosophiae Doctor .... november 2019
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Department of Community Medicine
Faculty of Health Sciences
UiT-The Arctic University of Norway

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“God gave us life, and we added style onto it. That’s what gave us our lifestyle…”
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Summary
Colorectal cancer (CRC) is a major global disease. In Norway, it is the most common cancer to affect both sexes, and the incidence rate among Norwegian women is currently the highest in the world. Lifestyle factors have substantial influence on CRC susceptibility. However, it is unclear whether these factors are responsible for the high incidence in Norwegian women, bearing in mind the steep increase in the incidence rate in the past 50 years. It is also unclear whether these factors play a role in CRC survival. The aim of this doctoral thesis was to evaluate the association between physical activity (PA) patterns and CRC incidence in Norwegian women (Paper I); to determine whether the geographical distribution of lifestyle factors explain the geographical variations in CRC incidence (Paper II); and to investigate the association between pre-diagnostic lifestyle factors and CRC survival (Paper III).

We used data from the Norwegian Women and Cancer (NOWAC) Study, a prospective cohort study which started in 1991 and has more than 172,000 participants from all counties of Norway. The participants answered questionnaires regarding their health, lifestyle, and diet. Data on cancer incidence, emigration, and cause-specific mortality were obtained through record linkage to Cancer Registry of Norway, Statistics Norway, and Norwegian Institute of Public Health. In Paper I, we used multivariable Cox proportional hazards models to estimate hazard ratios with 95% confidence intervals for CRC risk by PA level. In Paper II, we used Cox proportional hazards models and Karlson, Holm, and Breen method of decomposition to examine the extent to which the lifestyle risk factors accounted for geographical differences in CRC incidence. In Paper III, we performed multivariable competing mortality risks analyses to assess associations between pre-diagnostic lifestyle factors and CRC survival.

In Paper I, we found no association between PA levels and the risk of CRC. In Paper II, height; being a former smoker who smoked ≥10 years; or being a current smoker who has smoked for ≥10 years, were associated with increased CRC risk. A duration of education of >12 years, and a fruit and vegetable intake of >300 g/day were associated with reduced CRC risk. However, these factors combined, did not account for the geographical differences in CRC risk. In Paper III, a pre-diagnostic vitamin D intake of >10 μg/day was associated with 25% reduction in CRC death. No evidence of an association was found between other pre-diagnostic lifestyle factors and CRC survival.
In conclusion, our data suggest that women may need to look further than PA in order to reduce their CRC risk. Even though height, smoking status, duration of education, and fruit and vegetable intake were significantly related to CRC risk, they did not explain geographical variations in CRC incidence in Norwegian women. Our data suggest that pre-diagnostic vitamin D intake could improve CRC survival.
Sammendrag

Tarmkreft (tykk- og endetarmskreft) er en økende sykdom globalt. I Norge er det den vanligste kreftformen blant både kvinner og menn, og forekomsten blant norske kvinner er for tiden den høyeste i verden. Livsstilsfaktorer har betydelig innflytelse på risikoen for å få tarmkreft. Det er imidlertid ukjent om disse faktorene er ansvarlige for den høye forekomsten blant norske kvinner, med tanke på den bratte økningen i forekomsten de siste 50 årene. Det er også ukjent om disse faktorene spiller en rolle for overlevelse av tarmkreft. Målet med denne doktoravhandlingen var å evaluere sammenhengen mellom fysisk aktivitetsmønster og forekomst av tarmkreft hos norske kvinner (artikkel I); å undersøke om den geografiske fordelingen av livsstilsfaktorer forklarer de geografiske variasjonene i tarmkreftforekomst (artikkel II); og å undersøke sammenhengen mellom pre-diagnostiske livsstilsfaktorer og overlevelse av tarmkreft (artikkel III).

Vi brukte data fra den norske Kvinner og Kreft-studien, en prospektiv kohortstudie som startet i 1991 og har mer enn 172 000 deltakere fra alle fylker i Norge. Deltakerne svarte på spørreskjemaer angående helse, livsstil og kosthold. Data om kreftforekomst, utvandring og årsaksspesifikk død ble innhentet gjennom kobling til Kreftregisteret, Statistisk Sentralbyrå og Folkehelseinstituttet. I artikkel I brukte vi multivariable Cox proporsjonale hasardmodeller (95% konfidensintervaller) for å estimere risiko for tarmkreft og fysisk aktivitetsnivå. I artikkel II brukte vi Cox proporsjonale hasardmodeller og Karlson, Holm og Breenes metode for beregning av indirekte effekter for å undersøke i hvilken grad livsstilsfaktorene utgjorde geografiske forskjeller i forekomst av tarmkreft. I artikkel III utførte vi multivariable dødelighetsrisikoanalyser hvor vi tok høyde for død av andre årsaker for å vurdere assosiasjoner mellom pre-diagnostiske livsstilsfaktorer og overlevelse av tarmkreft.

I artikkel I fant vi ingen sammenheng mellom fysisk aktivitetsnivåer og risikoen for tarmkreft. I artikkel II fant vi at høyde, å være en tidligere røyker som røykte ≥10 år, eller å være en nåværende røyker som har røukt i ≥10 år, var forbundet med økt risiko for tarmkreft. En utdanningsvarighet på >12 år og inntak av frukt- og grønnsaker på >300 g/dag var forbundet med redusert risiko for tarmkreft. Disse faktorene tilsammen utgjorde imidlertid ikke de geografiske forskjellene i tarmkreftrisiko. I artikkel III var pre-diagnostisk D-vitamininntak på >10 μg/dag assosiert med 25% reduksjon i død av tarmkreft. Vi fant ingen assosiasjon mellom andre pre-diagnostiske livsstilsfaktorer og overlevelse av tarmkreft.
Avslutningsvis antyder dataene våre at fysisk aktivitetsnivå ikke reduserer risiko for tarmkreft, mens andre livsstilsfaktorer som høyde, røykestatus, utdanningsvarighet og inntak av frukt og grønnsaker var betydelig relatert til økt risiko for tarmkreft. Til tross for dette, forklarte de ikke geografiske variasjoner i forekomst av tarmkreft hos norske kvinner. Våre data antyder at inntak av pre-diagnostisk vitamin D kan forbedre overlevelsen av tarmkreft.
List of papers
This thesis is based on the following papers, hereafter referred to as Papers I, II, and III

Paper I

Paper II

Paper III
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AFAP</td>
<td>Attenuated familial adenomatous polyposis</td>
</tr>
<tr>
<td>AICR</td>
<td>American Institute of Cancer Research</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CRC</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>FAP</td>
<td>Familial adenomatous polyposis</td>
</tr>
<tr>
<td>EPIC</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
</tr>
<tr>
<td>FFQ</td>
<td>Food frequency questionnaires</td>
</tr>
<tr>
<td>HPP</td>
<td>Hyperplastic polyposis</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Statistical Classification of Diseases and Related Health Problems, 10th Revision</td>
</tr>
<tr>
<td>KHB</td>
<td>Karlson, Holm, and Breen</td>
</tr>
<tr>
<td>LS</td>
<td>Lynch syndrome</td>
</tr>
<tr>
<td>MAP</td>
<td>MUTYH-associated polyposis</td>
</tr>
<tr>
<td>MAR</td>
<td>Missing at random</td>
</tr>
<tr>
<td>MCAR</td>
<td>Missing completely at random</td>
</tr>
<tr>
<td>MNAR</td>
<td>Missing not at random</td>
</tr>
<tr>
<td>MUTYH</td>
<td>mutY homolog</td>
</tr>
<tr>
<td>NOWAC</td>
<td>Norwegian Women and Cancer</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>PA</td>
<td>Physical activity</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SES</td>
<td>Socioeconomic status</td>
</tr>
<tr>
<td>WCRF</td>
<td>World Cancer Research Fund</td>
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1 Introduction
This thesis and the accompanying articles focus on colorectal cancer (CRC). Specifically, this thesis investigates the relation between lifestyle and dietary factors, and CRC incidence and survival in women.

1.1 Colorectal cancer
CRC, sometimes referred to as bowel cancer, is the development of cancer in the main parts of the large intestine, which are the colon and rectum [Figure 1].

Figure 1 - Overview of the colon and rectum in the human body
Source: Reprinted with permission, copyright 2014 WebMD.

1.1.1 Historic perspective
The existence of cancer dates back to antiquity. Evidence from the remains of dinosaurs indicates that cancer may have been around since the dawn of time (1, 2). Evidence of cancer in humans has been uncovered in inscriptions, paleo-pathological specimens, and primordial medical records of the ancient Egyptians (1, 3, 4). There are indications that the prevalence of cancer may have been lower in ancient times (3). The rarity of soft tissue cancer in the ancient population has been theorised to be partly due to their relatively short life span, which may
have precluded the development of cancer; their different lifestyle and diet; and the presence of fewer oncogenic substances in the environment (1, 3). However, technological difficulties may have limited the detection of neoplastic lesions in previously examined mummified tissues (4, 5).

To-date, histological examinations have been carried out on 18 soft tissue tumours from mummified human remains (4): 13 were found to be benign tumours, while five were identified as cancers. Of the five cancers identified, three were CRC (4). These three cases included a rectal cancer from an Egyptian mummy from the Roman Period (200 CE-400 CE) (3, 4); a CRC in the mummy of Ferrante of Aragon, King of Naples (1424-1494) (4); and a colon cancer from the mummy of Luigi Carafa, Prince of Stigliano (1511-1576) (4). This may be a crude indication of the relative prevalence of CRC among the presumably few cancers in the pre-modern era.

1.1.2 Modern perspective
The prevalence of cancer has increased substantially over the past centuries, and this increase has been cautiously connected to the aging of modern populations (5, 6). Indeed, over time, the human lifespan has increased steadily from about 30-40 years to about 70-80 years (3, 5). Cancer prevalence generally increases with age, from less than 5% in those aged less than 50 years to about 30% in those aged 70 years or older (7). In Norway, when the incidence rate of all cancers combined in the most recent 5-year period (2013-2017) was compared with the previous one (2008-2012), an overall increase of 0.9% and 5.5% was observed among men and women, respectively (8).

Likewise, global CRC incidence has increased in the modern era, accounting for about 10% of all incident cancers (9). The modern patterns and trends in the occurrence of CRC reflect human development levels, and the incremental changes suggest that there may be a link with the adoption of Western lifestyles and civilisation (10). Indeed, it has been reported that migrants who move from developing countries with low CRC incidence to developed countries, tend to acquire the higher risk of CRC of their host countries, and this becomes more obvious in later generations (11, 12).

1.2 Epidemiology of colorectal cancer
CRC is a major global disease, with over 1.8 million new cases recorded in 2018 (9). It is the third most common cancer in men and the second most common in women worldwide (9),
and incidence rates are considerably higher in men than in women (9, 13, 14). CRC is more common in high-income countries than in low- and middle-income countries; however, the incidence rates in many low- and middle-income countries are rapidly increasing (10). The rates are steadily declining in the United States (15) and are stabilising in some Western and Northern European countries, while they are still showing a considerable upsurge in several Eastern European nations (10).

The Nordic countries have experienced an overall increase in the trend of CRC incidence in the last 60 years (16, 17). Norway has shown the most rapid increase in incidence rates since the late 1950s (16, 17), and its CRC incidence now ranks among the highest in the world (9, 10). The trends in Finland, Denmark, and Sweden have been similar, but Finland has consistently had the lowest rates of all the Nordic countries. The rates have been consistently high in Denmark, whereas Sweden has experienced only a weak increase in CRC incidence rates over the same period (16, 17) [Figure 2]. The reasons for the steeper increase in incidence in Norway have yet to be unravelled (18, 19).

![Figure 2 - Colorectal cancer incidence in the Nordic countries (females aged 0-85 years)](image)

Source: Reprinted from the Association of Nordic Cancer registries (NORDCAN), copyright 2019 (16).
In Norway, CRC is the second most common cancer after prostate cancer in men and after breast cancer in women (8), making it the most common cancer among both sexes combined. A total of 4,332 new cases of CRC were diagnosed in 2017; 2,253 in men and 2,079 in women (8). A comparison of incidence rates between the most recent 5-year period (2013-2017) and the previous one (2008-2012) reveal that rates of colon cancer increased by 2.3% in men and 6.6% in women, whereas the rates for rectal cancer remained relatively stable in both sexes (for the last 3 decades) (8). In Norway today, about 5% (1 in 20) of all men and 4% (1 in 25) of all women will develop CRC by the age of 75 years (8).

1.3 Anatomy and anatomical distribution of colorectal cancer
The colon is located largely within the abdominal cavity, while the rectum resides within the pelvis (20). The colon and the rectum are the last part of the digestive system and are sometimes collectively referred to as the large intestine or bowel. The colon is an inverted U-shaped part of the large intestine [Figure 1]. It starts as a pouch-like caecum (and appendix) joined to the end of the small intestine. It extends into the ascending colon, which continues up the abdomen until it turns under the right lobe of the liver (hepatic flexure) and then travels across the width of the abdominal cavity as the transverse colon. It then turns downward (splenic flexure) near the tail of the pancreas and below the inferior end of the spleen as the descending colon. After entering the pelvis, it continues as the S-shaped sigmoid colon and extends to the midline, where it becomes the rectum. The caecum, ascending, hepatic flexure, and transverse colon are the proximal colon, and embryologically they originate from the midgut (20, 21). The splenic flexure, descending, and sigmoid colon make up the distal colon, and, together with the rectum, they originate from the hindgut (20, 21). Cancers arising from the proximal colon are referred to as right-sided colon cancers, while those from the distal colon are referred to as left-sided colon cancers (22, 23).

About two-thirds of all CRC are colon cancers, while the other one-third are rectal cancers (8). Almost half (47%) of all colon cancers are located in the proximal colon (right-sided colon cancers), while the other 53% are located in the distal colon (left-sided colon cancers) (22). However, there has been a relative increase in the proportion of right-sided colon cancers (the so-called left to right shifting) (17). The sigmoid colon alone houses most left-sided colon cancers, and more than 40% of all colon cancers (22). With respect to anatomical site and screening importance, this makes sigmoid colon the most frequent colon cancer site (22). Right-sided colon cancers are more predominant (55%) in women, while left-sided colon cancers are more frequent (54%) in men (22).
1.4 Pathogenesis and biology of colorectal cancer

The pathogenesis of CRC refers to the mechanism underlying the development of the disease. CRC arises from the epithelial cells that line the colon and rectum. A large proportion of CRC develops from pre-existing adenomas (24), which are well-demarcated lumps of dysplastic epithelium. Adenomas can be found in all segments of the large bowel, and their occurrence increases with age (24). The transformation of a normal colonic or rectal cell into a malignant cell happens through multistep, multifactorial disease process that is the result of an accumulation of genetic and epigenetic changes (24, 25). These changes can, for instance, transform normal glandular epithelial cells into invasive adenocarcinoma (25). Adenocarcinoma is the most common type of CRC, representing about 95% of the disease occurrence (26).

The sequence of “normal mucosa - small adenoma - large adenoma - carcinoma” is a well-established CRC developmental process (24, 26), which is driven by factors including, but not limited to, gene mutations, epigenetic alterations, and local inflammatory changes (25). Studies have demonstrated that the “adenoma to CRC” sequence is heterogeneous and comprises of different pathways leading to CRC (25). However, the cancer progression sequence, as proposed by Fearon and Vogelstein, summarily involves three main phases: a phase initiating the formation of benign neoplasms (such as tubular adenomas and serrated polyps); followed by a phase promoting the progression to an advanced form; and a phase transforming the neoplasm into invasive carcinoma [Figure 3] (25, 27).

Figure 3 - Model of normal colonic mucosal development into adenoma and colorectal cancer

Source: Adapted and reprinted with permission, copyright 2014 Springer Nature (25).
However, this does not imply that all adenomas evolve into invasive carcinoma (24). Indeed, only few adenomas eventually transform into cancer (28, 29). Even so, the possibility of CRC carcinogenesis "de novo", from apparently flat colonic mucosa, does exist (24).

Insight from biological findings highlights the different possible pathogenic pathways leading to CRC at the molecular level (30). The accumulation of genetic errors leads to genomic and epigenomic instability, which cause dysfunctional regulation of the molecular pathways controlling cell migration, differentiation, apoptosis, and proliferation (12). This “genetic instability” resulting from the accumulation of genetic errors within the cell has been considered as a necessary pre-condition for neoplastic development (29).

Several types of genomic or epigenomic instability have been defined in CRC. These include:

(a) Chromosomal instability, seen in about 85% of CRC. This instability is due to a loss or gain of whole or large portions of chromosomes (25). These chromosomal structural changes result in a complex process of inactivation of tumour suppressor genes, and activation of oncogenes by mutation (or other mechanisms), which eventually cause the formation of adenomas and finally CRC (12, 24).

(b) DNA microsatellite instability is found in about 15% of CRC. This instability is due to an underlying defect in the DNA mismatch repair system (25), which manifests in the failure to repair mismatches that arise during DNA synthesis (12, 30).

(c) CpG Island Methylator Phenotype is a form of epigenetic instability in CRC. This manifests as an abnormal hypermethylation of loci containing cytosine and guanine dinucleotides (aka CpG islands). It could also manifest as global DNA hypomethylation. All CRC has some proportion of aberrant DNA methylation (25).

Another possible pathway is the inflammatory pathway, in which chronic inflammation is considered an essential component of CRC initiation and progression. This is demonstrable by the association between inflammatory bowel disease and CRC (31), and the protective effect of prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs) in CRC (32). It has been postulated that CRC could develop from one or more of these different pathways.

1.5 Risk factors for colorectal cancer
Primarily, CRC is regarded as both a genetic and lifestyle disease. Lifestyle diseases include those associated with the way one lives one’s life. Indeed, about 70% of all CRC are sporadic,
that is, they occur in people with no apparent genetic predisposition (33-35). This implies that lifestyle or environmental factors contribute substantially to the aetiology of CRC (12, 36).

1.5.1 Genetic factors
About 30% of all CRC are attributable to inheritable genetic predispositions (33-35), which is one of the largest proportions among all common familial cancers (33, 34). However, only about 5% of these genetically-attributable cases can be identified as resulting from well-defined specific genetic conditions (33-35). Others are referred to as common familial CRC (35).

1.5.1.1 Specific genetic conditions
Lynch syndrome (LS, or hereditary non-polyposis CRC) is an autosomal dominant syndrome, which makes affected individuals highly susceptible to CRC and other cancers, such as endometrial and gastric cancers. LS is the most common of the hereditary CRC syndromes, and accounts for about 3% of CRC (14, 33) [Figure 4].

Familial adenomatous polyposis (FAP) is the second most common hereditary CRC syndrome, and accounts for less than 1% of CRC. Affected individuals develop hundreds to thousands of colonic adenomas; 7% develop CRC by age 21 and 95% by age 50. Inheritance occurs through autosomal dominance (33, 37).

MUTYH-associated polyposis (MAP) is an autosomal recessive syndrome characterised by colonic and rectal adenomatous polyposis, and an increased risk of CRC (33). MAP is caused by bi-allelic mutations in the repair gene mutY homolog (MUTYH) (14, 33).

Other specific genetic conditions that confer an increased risk of CRC are relatively uncommon, such as hamartomatous polyposis conditions (such as in Peutz-Jeghers syndrome and juvenile polyposis syndrome) and hyperplastic polyposis (HPP).

1.5.1.2 Common familial colorectal cancer
The genetic basis of common familial CRC is not as well understood, but includes several different, less-penetrant, and potentially more common forms of susceptibility based on family history and population studies (33, 35). About 25% of individuals with CRC have one or more first- to third-degree relatives with a history of CRC (35). The above-described inheritable syndromes (Lynch, FAP, etc.) are associated with a lifetime risk of developing CRC of up to 70-95%, whereas common familial CRC is associated with a 2-3 fold increase in the risk of CRC (33, 35). However, having one first-degree relative diagnosed with CRC,
or two first-degree relatives diagnosed with CRC before the age of 45 years, increases the risk by about 3- to 6-fold, respectively, compared with the general population (35).

Figure 4 - The model of colon cancer risk susceptibility
Source: Adapted with permission, copyright 2010 Elsevier (33).

1.5.2 Lifestyle factors
Lifestyle refers to one’s manner of living, or the typical way of life of a person, group, or culture, which include interests, customs, dietary behaviours, and behavioural orientations (38). Most lifestyle factors are largely modifiable. Thus, a high proportion of CRC cases are potentially preventable (36). However, some risk factors that may also influence lifestyle are not modifiable; an individual cannot modify factors such as age, sex, height, or race.

1.5.2.1 Non-modifiable risk factors
Age
Cancer prevalence generally increases with age, and CRC is not an exception (7, 39). CRC becomes more common after the age of 50 years, when over 90% of CRC occur in the population (7, 40). However, recent studies indicate that CRC is becoming increasingly common among individuals under 50 years of age (41). This is currently of public health
concern, and the main drivers of increased CRC incidence in the younger generation have yet to be unravelled (41).

Sex
The incidence rate of CRC is higher among men than women (13, 42). This sex difference is more apparent in high-incidence populations, such as Australia and Norway, than in the low-incidence populations, such as Thailand (43). Studies in migrants have also indicated that when people migrate from low- to high-incidence areas, the CRC incidence among men increases faster than it does in women. This may indicate that the observed sex differences are more attributable to environmental factors (43, 44). It has been suggested that the higher susceptibility observed in men is due to both biological and sex-related behavioural factors (13). Men are thought to have a greater propensity for exposure to factors associated with increased risk of CRC (13), and these are mostly modifiable lifestyle and dietary factors.

Height
There is a convincing body of evidence supporting the association between adult attained height and risk of CRC (45, 46). It has been suggested that attained height may not directly influence the risk of CRC, but rather that it may be a marker for genetic, hormonal, environmental, and nutritional growth factors that affect growth from conception to the end of linear body growth (45-47). Some authors have posited a possible causal association between adult attained height and the risk of CRC (45).

1.5.2.2 Modifiable lifestyle factors
Physical activity
The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR), a leading authority on cancer prevention research related to diet, physical activity (PA), and nutrition, classified PA as a convincing risk reduction factor for CRC (47). Substantial observational data have demonstrated that regular PA, be it occupational, household, transport, or recreational, reduces the risk of CRC (36, 47-51). A recent meta-analysis found an overall protective association between PA and the risk of CRC (48), while another reported an overall risk reduction of almost 25% through participation in PA (49).

The actual underlying mechanism for the apparent protective effect of PA is unknown (14, 52). However, there are several plausible hypothetical explanatory biological mechanisms (52, 53), including the involvement of PA in the reduction of intestinal faecal transit time;
increased production of motility-inducing prostaglandin F2α; improved immune function; reduction in insulin resistance and hyperinsulineamia; changes in free radical generation; and changes in body fat (36, 52, 53). It is possible that no single mechanism is responsible for the observed risk reduction, it may instead be that a combination of some of these mechanisms and other factors are required (52).

Even though the WCRF/AICR concluded that all domains of PA reduce the risk of CRC (47), consistent results for this conclusion have been found mostly in men. Similar studies in women have rendered inconsistent results (54, 55). Some prospective studies reported statistically significant inverse associations between PA and CRC among women (50, 51, 56-59), similar to findings in men; however, many other studies reported no association (54, 60-67). It has been suggested that this discrepancy might be due to sex differences in the physiobiological response to PA (67-69). Other studies have suggested that regular PA may also offer men greater protection against cancer in other parts of the body (70, 71).

The sex differences in reported findings may have stemmed from methodological differences in the studies, especially regarding the methods of assessment of PA (72). Indeed, most epidemiological questionnaires are constructed to explore the PA habits of men rather than women (71). Questions do not usually cover areas of caring for children and aged relatives, household chores, and the more multidimensional nature of women’s lives (72). Women generally show more positive health behaviours than men, but when it comes to PA, epidemiological studies generally report lower PA among women (73). This could be due to the inability of typical PA questionnaires to properly and adequately assess PA in women, especially in regard to the risk of CRC. The mostly equivocal findings in the association between PA in women and the risk of CRC requires more study.

**Obesity**

Obesity is a compelling risk factor for CRC (36, 47, 74) and is commonly assessed in epidemiological studies by body mass index (BMI), waist circumference, and waist-to-hip ratio. Although, lack of PA could lead to obesity, however, obesity has been deemed an independent risk factor for CRC (75). Findings from a meta-analysis suggested that weight gained between early adulthood and midlife was associated with a higher risk of CRC compared to weight gained between midlife and older adulthood. Those in the highest weight categories bear the highest risk (74, 76).
The association between obesity and risk of CRC is generally weaker in women than men (77). This has been suggested to be the result of modification by menopausal status in women (77-79), as the association is stronger in premenopausal women and weaker or null in postmenopausal women (77-80).

Smoking
There is a convincing association between cigarette smoking and CRC incidence (81). Likewise, smoking has been identified as a risk factor for the development and aggressiveness of adenomas, the precursor of CRC (82). Cigarette smoke contains numerous compounds that are mutagens, such as polycyclic aromatic hydrocarbons and nitrosamines, in addition to other promoters, which together constitute complete carcinogens (that is, the combination of cancer initiators and promoters) (83). A meta-analysis of 106 observational studies reported an almost 20% increased risk of CRC in smokers over those who never smoked (81). The report from the United States Surgeon General concluded that the evidence is sufficient to infer a causal relationship between smoking and CRC (84).

Alcohol intake
The WCRF/AICR classified alcohol intake as a convincing risk factor for CRC (47). A meta-analysis of observational 61 studies provided evidence of an association between alcohol intake and CRC (85). A moderate alcohol intake (of 2-3 drinks/day, where 1 drink=12.5 g of ethanol) was associated with an increased risk of CRC of about 20%, while heavy alcohol intake (of ≥4 drinks/day) was associated with an increased risk of more than 50% (85). The metabolism of alcohol leads to the production of acetaldehyde and free radicals. Accumulated evidence shows that acetaldehyde may be predominantly responsible for alcohol-associated carcinogenesis (86). Other possible mechanisms include the stimulation of cytochrome P-4502E1, which is associated with an increased production of free radicals (86).

Dietary factors
Diet is one of the principal modifiable CRC risk factors. When healthy dietary habits and other lifestyle factors are combined, up to 70% of CRC cases could theoretically be prevented (87, 88). The WCRF/AICR report concluded that there was convincing evidence of an association between consumption of processed meat and CRC incidence, while that of red meat was probable (47). High-temperature cooking produces polycyclic aromatic hydrocarbons, heterocyclic amines, and other carcinogens in meat, and this cooking practice
has also been implicated in the development of CRC (89). Fish intake, or omega 3 fatty acids which are mainly found in oily fish, has been associated with reduced CRC incidence (14). A meta-analysis of 22 observational studies reported an overall lower CRC incidence among individuals with the highest compared to the lowest fish intake (90).

The reported association between fibre intake and risk of CRC has been inconsistent. While large epidemiological studies have reported a reduced risk of CRC with high fibre intake (91-93), some other studies reported no association (94, 95). However, a meta-analysis supported by the WCRF found that for every 10 g/day increase in dietary fibre intake, the risk of CRC reduces by 10% (96). There are suggestions that the risk of CRC is mediated by the interaction between dietary fibre and intestinal microbiota, especially *Fusobacterium nucleatum* (14, 97). On the other hand, many epidemiological studies have shown that a diet high in fruits and vegetables offers protection against CRC (98-100), although, the results of other studies conflict with this assertion (101, 102).

Intake of dairy products, such as milk, has been associated with a reduced risk of CRC. Dairy products are thought to protect against CRC because of their high calcium content. Studies have demonstrated that calcium lowers the risk of colorectal adenoma recurrence (103) and the risk of CRC (104, 105).

*Socioeconomic status*

Socioeconomic status (SES) is regarded as an important predictor of health and wellbeing. It is often quantified by rating and combining individuals’ occupational status, income, and education level (106). People with high SES are likely to have higher education, earn higher salaries, and work in high-status, influential positions than individuals with low SES. Low SES is associated with an increased risk of CRC. A study involving half a million adults found an increased risk of CRC of about 30% in the lowest SES quintile when compared to the highest quintile (107). Modifiable factors such as physical inactivity, obesity, smoking, unhealthy diet, and relatively lower rates of CRC screening, are thought to be responsible for the high risk of CRC among people with low SES (88, 107, 108).

*Medications, supplements, and exogenous hormones*

There is a considerable body of evidence to suggest that NSAIDs, such as aspirin, protect against the development of adenomas and CRC (32). This is also the case for calcium supplements and hormone replacement therapy in women. A meta-analysis of three
randomised controlled trials found that calcium supplements prevented recurrent colorectal adenomas (103). However, a conclusive, direct, protective effect of calcium supplements on CRC has yet to be proven (14).

Observational studies have shown that poor vitamin D status increases the risk of CRC (109), and is linked with the risk of several other cancers (110). However, according to the World Health Organisation, poor vitamin D status has the strongest association with colon cancer when compared to all other cancers (110). This may be due to the possible inhibitory influence of vitamin D on CRC initiation and progression (111).

The use of oral contraceptives in premenopausal women and hormone replacement therapy in postmenopausal women have been linked to a reduced risk of CRC. However, oral contraceptives and hormone replacement therapy are not used for CRC prevention, because of the concurrent increased risk of breast and other cancers with their use (112, 113). Nevertheless, the use of hormone replacement therapy has been found to vary geographically, as it is more likely to be used by women living in the urban areas than those living in the rural areas (114).

1.5.3 Geographical differences in the risk of colorectal cancer

There is an over 10-fold variation in CRC incidence worldwide, with the highest incidence rates in Australia and New Zealand, Europe, and North America, and the lowest in Africa and South-Central Asia (14, 115). These variations are apparently attributable to differences in exposure to environmental, lifestyle, and dietary risk factors, with background genetic and epigenetic susceptibility (14, 116, 117). Probably for similar reasons, there is also geographical variation in the distribution of CRC within many countries, including Norway (8, 18). The incidence rate of CRC, especially in Norwegian women, currently ranks among the highest in the world (118). However, the rates vary within the country, with a difference of more than 20 per 100,000 person-years between areas of high and low incidence (8). The factors responsible for this geographical heterogeneity in Norway have yet to be determined, and the knowledge of these factors could be useful in guiding national screening strategies and health policy.

1.6 Colorectal cancer survival

CRC survival is principally a function of the stage of the disease at diagnosis (119): the earlier the stage at diagnosis, the better the survival. CRC stage describes where the disease is
located (e.g., still within the colon walls, as in early CRC stage); if or where it has spread (e.g., through colon walls into nearby tissues); and whether it has affected other parts of the body (e.g., spread to liver or lungs, as in late CRC stage). Generally, the 5-year survival rate of CRC diagnosed at an early stage is about 90%, whereas the rate for cases diagnosed at a late stage is about 13% (47). CRC survival at all stages has improved substantially in the past few decades, especially in nations with a high life expectancy and good access to modern CRC management, such as Norway (119, 120). Access to appropriate, modern, specialised healthcare is an important factor that contributes to improved survival (119).

1.6.1 Lifestyle factors and colorectal cancer survival
There is considerable variability in the survival outcome of individuals with the same stage of CRC who receive same treatment. This variability is thought to be due to lifestyle and dietary factors (121). The relationship between lifestyle factors and CRC survival has not yet been studied as much as the relationship with CRC incidence. CRC survivors are usually asked to follow recommended guidelines for CRC prevention. It is unclear whether or which of these recommendations would improve survival (122), thus necessitating more studies in this area.
2 Aim of the thesis

The overall aim of this doctoral thesis was to explore the association between lifestyle and dietary factors in relation to CRC incidence and survival, in a large population-based cohort: The Norwegian Women and Cancer (NOWAC) Study.

The specific objectives were:

1. To examine the relationship between PA patterns and the risk of CRC in Norwegian women.
2. To determine whether the geographical distribution of lifestyle-related CRC risk factors explains the geographical differences in CRC incidence in Norwegian women.
3. To evaluate the association between pre-diagnostic lifestyle factors and CRC survival.
3 Material and methods

3.1 The Norwegian Women and Cancer Study
This thesis utilised data from the NOWAC Study (in Norwegian, Kvinner og Krefstudien), a population-based, prospective cohort study, which was initiated in 1991 (123). Details of this study, including the design, cohort profile, and scientific rationale have been published previously (123, 124). In brief, samples of Norwegian women between the ages of 30 and 70 years were randomly selected from the Norwegian Central Population Register and invited to participate. Participants were recruited in three different waves: 1991-92, 1995-97, and 2003-07 [Figure 5].

The original aim of the NOWAC Study was to examine the association between oral contraceptive use and the risk of breast cancer. This aim was expanded later to include other risk factors and outcomes. A food frequency questionnaire (FFQ) was added during the second wave of recruitment in 1996-97. More than 172,000 women from all over Norway agreed to participate, gave written informed consent, and completed a questionnaire that collected information on their lifestyle, health status, reproductive status, and dietary habits. The participants received follow-up questionnaires 5 to 10 years after completing the baseline questionnaire.

3.1.1 Study sample
In Papers I-III, we used information from questionnaires of women who were recruited in 1991-92, 1996-97, and 2003-04, and completed FFQs in 1998, 1996-97, and 2003-04, respectively. The women recruited in 1991-92 completed a FFQ in 1998 because a FFQ was not included in the 1991-92 questionnaire. Therefore, we used the 1998 information as the baseline for women recruited in 1991-92. Our follow-up information was extracted from questionnaires returned in 2004-05, 2002-03, and 2011-14, respectively, which was about 5-10 year after the baseline questionnaire [see Figure 5].
Figure 5 - Cohort enrolment and follow-up in the Norwegian Women and Cancer Study
3.1.1.1 Study sample for Paper I - Physical activity patterns and the risk of colorectal cancer
In this study, 101,321 women were eligible for inclusion. We excluded 18 women who emigrated or died before the start of follow-up. We also excluded 4,429 women with prevalent cancer other than non-melanoma skin cancer and 9,210 women with missing information on PA level at baseline. We further excluded 8,480 women due to lack of information on other covariates at baseline, such as height and weight (used in calculating BMI), duration of education, alcohol intake, and smoking status. Thus, our final analytical sample in Paper I was 79,184 women [see Figures 1 and 2 in Paper I]. We used information extracted from follow-up questionnaires returned in 2002-14 for repeated measurements on PA level, BMI, and smoking status.

3.1.1.2 Study sample for Paper II - Geographical differences in the incidence of colorectal cancer
An initial NOWAC cohort of 101,321 women was eligible for inclusion in this study (similar to Paper I). These participants completed a baseline questionnaire with dietary information between 1996 and 2004, and a follow-up questionnaire between 2002 and 2014. We subsequently excluded 14 women who died or emigrated prior to the start of follow-up, and 4,414 women with prevalent cancer except non-melanoma skin cancer. The final analytical sample in Paper II included 96,893 women. Follow-up information on PA level, BMI, alcohol intake, smoking history, hormone replacement therapy use, and all dietary intakes was available for 68,626 (70.8%) women.

3.1.1.3 Study sample for Paper III - Pre-diagnostic lifestyle and dietary factors in colorectal cancer survival
Using the same eligibility criteria in Papers I and II, we included 101,316 participants (five participants withdrew their consent) who completed a FFQ between 1996 and 2004. We excluded 4,427 women who emigrated, died, or had prevalent cancer by the time of the return of the questionnaire. Out of the 96,889 remaining women, 13,487 developed cancer during follow-up, of which 1,875 was CRC. We excluded eight women with no follow-up time (because CRC was diagnosed at autopsy), three who had cancer with unknown stage, and another three with an undocumented cause of death. Thus, the analytical sample in Paper III included 1,861 women who developed CRC between the time of recruitment and the end of follow-up [see Figure 1 in Paper III].
3.2 Ascertainment of cancer, death, and emigration
With the aid of the unique 11-digit personal identification number assigned to every Norwegian at birth, record linkage was done with national registries. Complete follow-up on cancer incidence, date of cancer diagnosis, cancer site, and cancer stage was possible through linkage to the Cancer Registry of Norway. Causes and dates of death were taken from the Cause of Death Register, and information on emigration was taken from the National Population Register. Annual updates for all the participants were performed to confirm their status. We used the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) codes C18 and C19-20 to identify colon cancer and rectal cancer, respectively (125, 126).

3.3 Estimation of dietary intakes in the Norwegian Women and Cancer Study
The dietary intakes were extracted from the NOWAC Study FFQ. The participants were requested to report the average consumption of foods items and beverages in the last year by selecting provided options, with the corresponding frequencies in the questionnaire. The participants reported quantity (portion size) of food items consumed in household measures or natural unit, such as in tablespoons, slices (of bread), decilitre, and so on. The consumption of each food item was then estimated by multiplying the quantity (portion size) by the midpoint if the frequency was an interval. In the estimation, the lowest value in the uppermost category was used in the calculation. That is, food frequency option of "4+" was treated as "4" in the estimation. Missing quantities (portion sizes) were treated as the smallest portion unit, while missing frequencies were recorded as no consumption or lowest frequency. The subsequent estimation in grams was based on the Norwegian Weight and Measurement Table (127). Daily intakes were estimated based on the Norwegian Food Composition Table and the nutrient contents of all the food items were added up (128). Furthermore, use of supplements were not included in the estimation, except liquid cod liver oil.

The FFQ was based on knowledge of common food items and beverages, and probable frequency options of consumption in Norway. The FFQs were mostly the same in the baseline and follow-up questionnaires, aside for few improvements on the questions, new food items in the market, or new research questions. The Institute of Community Medicine, UiT-The Arctic University of Norway developed a program in SAS software to estimate the daily intake of food items and nutrients for each NOWAC Study participant.
3.4 Assessment of lifestyle and dietary factors in Paper I-III

In Paper I, PA level was the principal lifestyle factor of focus. The baseline and follow-up questionnaires contained the same question regarding PA level. Participants were asked, “By physical activity we mean activity both at work and outside work, at home, as well as training/exercise and other physical activity, such as walking, etc. Please mark the number that best describes your level of physical activity; 1 being very low and 10 being very high”. The scale reflects the total amount of PA, including all domains (occupational, household, transport, and recreational) combined into one global score. We grouped the 10 PA levels into five categories: 1-2, 3-4, 5-6, 7-8, and 9-10.

In a separate analysis, we used changes in PA level as the exposure variable, by categorising PA levels into "inactive" (PA level 1-4), "moderately active" (PA level 5-6), and "active" (PA level 7-10). We then used the follow-up data on PA level to categorise participants as "consistently active" (PA level 7-10 at baseline and follow-up), "consistently moderately active" (PA level 5-6 at baseline and follow-up), "consistently inactive" (PA level 1-4 at baseline and follow-up), "increased PA" (increased PA level between baseline and follow-up), and "decreased PA" (decreased PA level between baseline and follow-up).

We adjusted for the following covariates: height (continuous, in metres); BMI calculated from weight divided by the square of the height (<25.0, 25.0-29.9, ≥30.0 kg/m²); and duration of education (<10, 10-12, ≥13 years, which correspond to primary and lower secondary school, upper secondary school, and higher education, respectively). We also adjusted for alcohol intake (0, ≤3, >3 g/day); smoking status (never, former, current); red meat intake (0, ≤15, >15 g/day); processed meat intake (0, ≤30, >30 g/day); dietary calcium (<700, ≥700 mg/day) and dietary fibre (<21, ≥21 g/day). The final models included only those covariates associated with a change of ≥10% in the regression coefficient of any of the PA level groups. This criterion excluded hormone replacement therapy use, household income, and red meat intake. However, we added red meat intake to the models because of its reported association in the carcinogenesis of colorectal tissues (129).

In Paper II, the aim of the study warranted the inclusion of more covariates. Therefore, we included all the covariates in Paper I in addition to the county of residence of the participants. At the time of the data collection, there were 19 counties in Norway. We used percentiles of CRC incidence rate [Table 1] to categorise the counties into four groups. The purpose was to
compare the lowest 10% to the highest 10% to detect possible disparities in lifestyle-related CRC risk factors. However, we increased the cut-off for low-incidence counties to the 15th percentile to allow for more cases of CRC in this group. Thus, counties from 0-15th percentile were categorised as low-incidence counties (Oppland, Sør Trøndelag, and Telemark); 16-50th percentile as mid-low-incidence counties (Hedmark, Hordaland, Oslo, Møre and Romsdal, Nord-Trøndelag, Vest-Agder, and Buskerud); 51-90th percentile as mid-high-incidence counties (Rogaland, Akershus, Aust-Agder, Vestfold, Østfold, Finnmark, and Troms); and 91-100th percentile as high-incidence counties (Nordland, Sogn and Fjordane).

Table 1 - Grouping of 19 counties into four categories by percentiles of CRC incidence in the Norwegian Women and Cancer Study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>1-15th percentile</th>
<th>16-50th percentile</th>
<th>51-90th Percentile</th>
<th>91-100th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence categories</td>
<td>Low incidence</td>
<td>Mid-low incidence</td>
<td>Mid-high incidence</td>
<td>High incidence</td>
</tr>
<tr>
<td>County groups</td>
<td>Oppland, Sør-Trøndelag, Telemark</td>
<td>Hedmark, Hordaland, Oslo, Møre and Romsdal, Nord-Trøndelag, Vest-Agder, Buskerud</td>
<td>Rogaland, Akershus, Aust-Agder, Vestfold, Østfold, Troms, Finnmark</td>
<td>Nordland, Sogn and Fjordane</td>
</tr>
<tr>
<td>Population in each county group</td>
<td>11,563</td>
<td>34,454</td>
<td>37,544</td>
<td>13,332</td>
</tr>
</tbody>
</table>

In addition, we combined smoking status and smoking intensity (in pack years) into one, more detailed variable of smoking history, which was categorised as never smoker, former smoker of <10 years, former smoker of ≥10 years, current smoker of <10 years, and current smoker of ≥10 years. We also included household income (low income: <300,000; medium income: 300,000-600,000; high income: >600,000 Norwegian krone per annum); oral contraceptive use (never/every), and hormone replacement therapy use (never, former, current). In addition to the dietary variables used in Paper I, we included fish intake (0-90, >90g/day), fruit and vegetable intake (0-300, >300g/day), and vitamin D intake (0-6, >6μg/day). Whenever possible, we used the median values (50th percentile) to split the variables into categories, as median values are more robust and undistorted by outliers (130).

In Paper III, we combined red meat and processed meat and categorised this intake as ≤70g/day and >70g/day. This cut-off was taken from the recommendations of the WCRF/AICR, which recommends a red meat intake of not more than 50-70g/day, and little or
no processed meat intake (131). Average daily fish intake was categorised as ≤130g/day and >130g/day, using the 75th percentile of fish intake in the dataset. Daily fruit and vegetable intake was combined into one variable and categorised as ≤300g/day and >300g/day. Average daily vitamin D intake was categorised as ≤10.0μg/day and >10μg/day using the Nordic daily nutrition recommendation of 10μg (132). Finally, we added the self-reported medical history of diabetes mellitus (yes/no) and cardiovascular disease (yes/no), which was available in the questionnaire.

3.5 Statistical analysis
All analyses were conducted using Stata for Windows version 15.0 (StataCorp, College Station, Texas, USA). In addition, some analyses in Paper III were conducted using R version 3.5.3 (R Foundation for Statistical Computing 2019). All statistical tests were two-sided and conducted at the 0.05 significance level.

3.5.1 Statistical analysis in Paper I - Physical activity patterns and the risk of colorectal cancer
In Paper I, we used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between PA levels and risk of CRC. We used age as the time scale. We ran three main analyses, with (1) baseline data only, (2) baseline and follow-up data, and (3) change in PA level.

In the first main analysis, we applied baseline information on PA level and covariates until information on emigration, death, diagnosis of any incident cancer, or the end of the study period (31 December 2015), whichever occurred first.

The second main analysis was a repeated measurements analysis, in which we used baseline information until the point when follow-up data (repeated measurement) on PA level was available. We used baseline values for those missing on follow-up (last value carried forward). We also used the follow-up data on BMI and smoking status. This is because of the changes in BMI and smoking status over time. For instance, almost a quarter of the study sample had stopped smoking at the time of the follow-up questionnaire. Thus, follow-up information on PA level, BMI, and smoking status was applied (that is, treating them as time-dependent covariates) until emigration, death, diagnosis of any incident cancer, or the end of the study period, whichever occurred first.
In the third main analysis, we used change in PA level between baseline and follow-up as the exposure variable. We adjusted for the time interval between the two measurements and covariates. We considered participants to be at risk from the date of the follow-up measurement until emigration, death, CRC diagnosis, or the end of the study period, whichever came first.

3.5.2 Statistical analysis in Paper II - Geographical differences in lifestyle factors and incidence of colorectal cancer

In Paper II, we used Cox proportional hazard regression models with age as the time scale, to estimate HRs and 95% CIs of the associations between the county groups (low-, mid-low-, mid-high-, and high-incidence counties), CRC risk factors, and CRC incidence. Follow-up time was defined as the period in years between age at baseline and age at diagnosis of incident cancer, death, emigration, or age at the end of follow-up (31 December 2016), whichever came first.

We also carried out a repeated measurements analysis, in which we used baseline information until the point when follow-up information was available on PA, BMI, alcohol intake, smoking history, hormone replacement therapy use, and all the dietary intakes. We used multiple imputation to handle missing data at baseline and follow-up. We then used the follow-up information until death, emigration or the end of the study, whichever occurred first.

To examine the extent to which the CRC risk factors (mediating variables) account for the observed differences in CRC incidence between individual counties, and between county groups, we used the Karlson, Holm, and Breen (KHB) method of mediation analysis (133).

3.5.2.1 Mediation analysis using the Karlson, Holm, and Breen method of decomposition

The KHB method decomposes the total effects of county groups on CRC incidence into direct and indirect effects (133). The basic outputs from the KHB method consist of three models: the reduced model, the full model, and the difference (model). The reduced model expresses the estimated effect of the counties with no mediating variables in the model (total effect). The full model expresses the estimated effect of counties with all mediating variables in the model (direct effect). The difference between these two models represents the indirect effect, which is interpreted as the mediation effect.

We used a logistic regression model with the KHB method. The KHB method is versatile in that it works well with standard Stata estimation commands, such as -regress-, -logit-,
-probit-, and so on. However, the use of estimation commands such as -stcox- in the KHB method were still experimental at the time of the analysis of Paper II and submission of this thesis (133).

The KHB method assumes a normal distribution of the indirect effect, and this assumption has been shown to be valid in large samples such as the NOWAC Study (134). We fitted the KHB models using baseline data, and subsequently used multiply imputed data.

3.5.2.2 Multiple imputation

In Papers II and III, under the assumption that data was missing at random, we performed multiple imputation by chained equations to deal with missing data (135). The missing values were replaced by imputed values from 20 duplicate datasets (50 in Paper III), which were based on the observed data. We created these duplicate datasets from the imputation simulation to reduce sampling variability (136). We included all the CRC risk factors used in the analyses (at baseline and follow-up) along with the Nelson-Aalen cumulative hazard estimator as predictors in the imputation model (137, 138).

We used linear regression to impute continuous variables when a linear model was proper (such as for height and weight), otherwise we used predictive mean matching with the 100 closest individual observations (nearest neighbours), from which imputed values were drawn to impute continuous variables. We used logistic regression, ordinal logistic regression, and multinomial logistic regression to impute binary, ordinal, and nominal variables, respectively. We used Rubin’s rules to combine the estimates from the imputed datasets, which were then utilised to estimate the HRs and corresponding 95% CIs (139).

3.5.3 Statistical analysis in Paper III - Pre-diagnostic lifestyle and dietary factors in colorectal cancer survival

In Paper III, following multiple imputation, we used competing risks analysis to investigate lifestyle and dietary factors in relation to CRC survival. The rationale behind this was the fact that CRC is predominantly a disease that occurs in middle and old age. Mortality rises rapidly with age after the age of 35 years, especially in developed countries (140); thus CRC survivors are also at risk of dying from causes other than CRC. Hence, our choice of a competing mortality risks analysis.

3.5.3.1 Competing mortality risks analysis

We extended the standard Cox proportional hazards model, normally used when there is no competing event, to model cause-specific hazards as suggested by Prentice et al (141). The
proportional hazards model was applied to the event of interest and the competing event, respectively. The event of interest was death due to CRC, hereafter referred to as CRC death, and the competing event was death due to any other causes, hereafter referred to as non-CRC death. We censored the competing event while estimating the association between lifestyle factors and the risk of CRC death; and likewise censored the event of interest while estimating the association between lifestyle factors and the risk of non-CRC death. This is the preferred method when investigating aetiological questions (factors associated with CRC death), in the presence of competing risks (142-145).

In addition to the cause-specific hazards model, we used the sub-distribution hazard model approach proposed by Fine and Gray (146). This is because of the hypothetical nature of a cause-specific hazards model in which the “competing event is removed” (censored). This implies that hazards estimations are calculated as if CRC survivors could not die of any other cause aside from CRC. In contrast, sub-distribution hazard estimations in the Fine and Gray approach are calculated in the “presence of competing events”, thereby eliminating the hypothetical nature of the cause-specific hazards model. This is achieved by modelling hazards on the basis of the cumulative incidence function (143). The fundamental difference between the two approaches lies in the risk sets. The cause-specific approach excludes competing events from its risk set, while the Fine and Gray approach includes competing events in the risk set (143, 144). Similarly, we applied the sub-distribution hazard model to the event of interest and the competing event, respectively.

We used the two statistical approaches to gain complete understanding of the association between lifestyle and dietary factors, and CRC survival, as recommended by Latouche et al (147).

3.5.4 Statistical assessments common to Papers I-III
We assessed the proportional hazards assumption in all three studies. In Paper I, this was done by testing an interaction variable between PA levels and the logarithmic transformation of the age of the participants. In Papers II and III, we used Schoenfeld residuals. In Paper III, we had to run all models stratified by CRC stage in order to keep the assumption in the two competing risks approaches.

We tested for collinearity between calcium and milk intake, calcium and vitamin D intake; red meat and processed meat intake; and between fibre and fruit and vegetable intake. We
excluded milk from the final analyses because of its collinearity with calcium. In Paper III, we assessed collinearity between the variables fish intake and vitamin D intake.

In Paper I, we tested for linear trend across PA levels by using the original 10-level PA scale modelled as a continuous variable, while in Paper III, we modelled all the lifestyle and dietary factors as continuous variables, except smoking status, diabetes, and cardiovascular disease. We also tested for possible interactions between PA level and BMI, duration of education, alcohol intake, and smoking status, respectively. We also investigated the possible relationship between PA levels and CRC stratified by BMI category, given that obesity is considered a convincing risk factor for the development of CRC (74, 148). In Paper II, we also assessed for interaction effects between duration of education and BMI, smoking history, alcohol intake, and dietary factors, respectively. In Paper III, we tested for pre-defined interactions between PA level and BMI; PA level and vitamin D intake; duration of education and annual household income; and fish intake and vitamin D intake.

We assessed reverse causation by excluding women who received a cancer diagnosis within the first 2 years of follow-up in Papers I and II, and within the first 1 year of follow-up in Paper III, due to the relatively smaller sample size. We further conducted sensitivity analysis in Paper I, by recategorising PA levels into three groups (1-4, 5-6, and 7-10) and re-running the main analysis. In Paper II, sensitivity analyses consisted of running the KHB method using the 19 counties individually (instead of in country groups as was done in the main analysis), using the region of residence, and using the area of residence (rural/urban), respectively. In Paper III, we limited the analysis to CRC diagnosed within 10 years of enrolment, in order to minimise the impact of changes in lifestyle during follow-up. In yet another sensitivity analysis, we restricted the analysis to incident cases of CRC diagnosed by 31 December 2014, and subsequently followed participants until the end of follow-up (31 December 2016).

3.6 Ethics
The Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate approved the NOWAC Study. In addition, the Norwegian Directory of Health exempted the NOWAC Study from duty of confidentiality by giving permission to link participants’ record to the Cancer Registry of Norway, Cause of Death Registry, and other national registries. The
women were informed about subsequent linkages of their information to national registries. The women gave written informed consent along with their completed questionnaires.
4 Results - summary of the papers

4.1 Paper I - Physical activity patterns and the risk of colorectal cancer in the Norwegian Women and Cancer Study: a population-based prospective study

The objective of this study was to examine the association between PA patterns and the risk of CRC among participants in the NOWAC study.

Among the 79,184 women followed up for an average of 14.6 years, 1,311 cases of CRC were diagnosed (885 [68%] colon cancers and 426 [32%] rectal cancers).

There was no association between PA level and the risk of CRC in baseline or repeated measurements analyses. Comparing women with PA level 1-2 to those with PA level 5-6 (reference) at baseline rendered an HR for colon cancer of 0.90 (95% CI 0.66-1.23) and of 0.78 (95% CI 0.55-1.10) with repeated measurements. Comparing PA level 9–10 to the reference level at baseline rendered HR of 0.80 (95% CI 0.56–1.12) and of 0.82 (5% CI 0.58–1.16) with repeated measurements. Similarly, we found no association between PA level and the risk of rectal cancer when comparing PA level 1-2 to the reference level (baseline: HR=1.40, 95% CI 0.94-2.10; repeated measurements: HR=1.40, 95% CI 0.93-2.09), and PA level 9-10 to the reference level (baseline: HR=1.18, 95% CI 0.77-1.82; repeated measurements: HR=1.22, 95% CI 0.78-1.89).

Women who showed “increased PA” between baseline and follow-up had a reduced risk of colon cancer compared to those who remained “consistently moderately active” (HR=0.69, 95% CI 0.50-0.95). Women who were “consistently active”, “consistently inactive”, or those with “decreased PA” displayed no association when similarly compared.

We found no evidence of violation of the proportional hazards assumption. None of the interactions assessed reached statistical significance. Exclusion of cases diagnosed in the first 2 years of follow-up did not substantially change the findings.

This study did not support an association between total PA or consistent participation in PA over time and a reduced risk of CRC in women.
4.2 Paper II - Exploring geographical differences in the incidence of colorectal cancer in the Norwegian Women and Cancer Study: a population-based prospective study

The aim of this study was to determine whether the geographical distribution of lifestyle-related CRC risk factors explains geographical differences in CRC incidence in Norwegian women.

Analyses included 96,893 women from 19 counties of Norway, who were followed for an average of 15.5 years. During this time, 1,875 CRC cases (1,276 [68%] colon cancers and 599 [32%] rectal cancers) were identified. The county with the lowest crude incidence rate was Oppland, while the highest rate was observed in Sogn and Fjordane.

At baseline, the low-incidence county group had a higher proportion of physically active women compared to high-incidence county group (46 vs 41%). Similarly, the low-incidence county group had a higher proportion of women with a longer duration of education (38 vs 25%), never smokers (38 vs 34%), high annual household income (12 vs 5%), hormone replacement therapy use (34 vs 30%), and oral contraceptive use (53 vs 43%), compared to the high-incidence county group. Conversely, the high-incidence county group had a higher proportion of women who were overweight (33 vs 31%), obese (10 vs 9.6%), ever smokers (64 vs 60%), and had low annual household income (48 vs 36%), compared to the low-incidence county group.

The high-incidence county group had a HR of 1.37 (95% CI 1.13-1.66) relative to the low-incidence county group, which was similar to the unadjusted estimate. Risk of CRC was associated with height (HR=1.12, 95% CI 1.08-1.17 per 5 cm increase), being a former smoker of at least 10 years (HR=1.34, 95% CI 1.15-1.57), or a current smoker who had been smoking for at least 10 years (HR=1.28, 95% CI 1.12-1.46), compared to never smokers. Duration of education >12 years (HR=0.78, 95% CI 0.69-0.87) compared to ≤12 years, and daily fruit and vegetable intake >300g (HR=0.90, 95% CI 0.80-0.99) compared to ≤300g, were associated with decreased risk of CRC. Other lifestyle factors (such as PA, BMI, and intake of: alcohol, red meat, processed meat, fibre, calcium, and vitamin D) showed no evidence of association with the risk of CRC.

In the KHB analysis, the combined effects of the investigated CRC risk factors did not significantly mediate the difference in CRC incidence between the low- and high-incidence
county groups ($b=0.02$, 95% CI -0.02, 0.06, $p=0.26$). A parallel KHB analysis using the 19 counties separately also showed that the combined effects of the risk factors did not significantly mediate the variations in CRC incidence across counties.

Overall, the study revealed that the investigated CRC risk factors did not account for the risk differences between areas of low and high CRC incidence.

4.3 Paper III - A competing mortality risks analysis of pre-diagnostic lifestyle and dietary factors in colorectal cancer survival: the Norwegian Women and Cancer Study

The aim of this study was to evaluate the association between pre-diagnostic lifestyle and dietary factors and CRC survival in the presence of competing mortality risks.

Out of the 1,861 cases of CRC diagnosed within the cohort between 1996 and 2016, 1,201 (65%) were alive and 660 (35%) had died by the end of follow-up. There were 550 (83%) CRC deaths and 110 (17%) non-CRC deaths. The average follow-up duration was 5.0 years. This average was lower in the group of CRC deaths (2.1 years) compared to the group of non-CRC deaths (5.3 years).

The results of the multivariable-adjusted, cause-specific Cox analysis revealed that a pre-diagnostic vitamin D intake of $>10\mu g/day$ compared to $\leq10\mu g/day$ was associated with better CRC survival ($HR=0.75$, 95% CI 0.61-0.92; $p$-trend <0.001). Other pre-diagnostic lifestyle and dietary factors (such as PA, BMI, household income, and intake of: alcohol, red meat, processed meat, fish, vegetable and fruit) showed no evidence of association with CRC survival. The corresponding results obtained from Fine-Gray regressions were similar.

The use of Schoenfeld residuals to check the proportional hazards assumption in the two competing risks approaches, and with the two competing events, did not indicate any violation of the proportional hazards assumption. However, this was only after we stratified by CRC stage. Thus, all models were stratified by CRC stage in order to uphold the assumption. None of the pre-defined interaction terms tested were statistically significant in any of the outcomes investigated.

In conclusion, we found that pre-diagnostic vitamin D intake could improve CRC survival.
5 Discussion of methodology

Most epidemiological studies are designed to provide essential information regarding the general population. Different study phases are accompanied by various methodological challenges that could affect the validity of the conclusions drawn. Issues regarding validity in the studies’ methodological approaches shall be discussed here before the discussion of the results. The validity of a study refers to whether its findings can be considered an accurate representation of the true situation (149). Study validity can be divided into two types: internal and external validity.

5.1 Internal validity

Internal validity implies whether the study results are valid for the original study population (150, 151). It reflects the manner in which a study was designed, conducted, and analysed, and whether all these stages permit valid study results (152, 153). For the study results to be valid, the study should avoid biases or systematic errors. This is an essential prerequisite of any good epidemiological study (149, 150). Variables obtained from participants need to be the true measure of what they intend to measure. A research study should avoid errors in order to make accurate inferences from the study participants (154). The main factors that can generally undermine the validity of study findings are selection bias, information bias, confounding factors, and erroneous use of statistical methods.

5.1.1 Selection bias - Papers I-III

Selection bias occurs when there is a systematic difference between those participating in a study and those who are not, such that the association between exposure and outcome differ for those who participate and those who do not participate in the study (155). In such a case, the study sample does not accurately reflect the source population.

In the NOWAC Study, the participants were women aged between 30 and 70 years and randomly sampled from the Norwegian Central Population Register (124). However, participants who chose to respond and those who did not are not necessarily random. A possible scenario is the healthy volunteer effect, whereby those who volunteer to respond to a health survey might have healthier attributes than those who do not respond (156). This may inevitably create clear systematic differences between responders and non-responders, especially if the response rate is very low.
About 57% of the invited women responded to the NOWAC baseline questionnaire (124). Participations were not uniform across age groups. The response rate decreased with increasing age, with the rate in the age groups 30-35 to 55-59 years at about 60%, while that of age group 65-70 years dropped to about 45%. The women in Northern Norway had a higher response rate than those in the rest of the country, whereas women born outside the Nordic countries had lower response rates (124). Validation through linkage to national education registers revealed that responders were better educated, as a higher proportion of responders had more than 12 years of education when compared with the source population (124).

CRC is strongly associated with age and inversely related to duration of education. Thus, a lower proportion of elderly women, and a higher proportion of educated women among responders could yield an underestimation of the effect of age, and an overestimation of the inverse effect of duration of education on CRC, when compared to the source population. In addition, we used the eight-page questionnaire series in all three papers, which included the FFQ. The two-page and four-page questionnaire series did not include the FFQ. The effect of the length of the questionnaires was inconsistent in the NOWAC Study. Even though the response rate was highest for the shortest questionnaires, the questionnaires with the highest number of pages (eight pages) did not have the lowest response rates (124, 157). In spite of all this, the results of validity studies conducted in the NOWAC Study indicated no selection bias between responders and non-responders (124). In a postal survey conducted among non-responders in the NOWAC Study, where the non-responders were asked for reasons for not participating and at the same time asked questions on oral contraceptive use, parity, and years of education. No significant difference was found between the non-responders and responders from the same subcohort in the self-reported oral contraceptive use, parity, or years of education (124). Reasons for non-participation were apparently not due to the healthy volunteer effect, but included lack of time, worries about confidentiality, and simply forgetting about the questionnaire (124). Furthermore, data from the Cancer Registry of Norway showed age-specific cumulative incidence rates that were almost identical to those observed in the NOWAC Study, for all cancer sites combined, breast cancer (123), as well as for CRC [Figure 6].
Additionally, it has also been shown that the distribution of risk factors was independent of response rate and design of questionnaires in the NOWAC Study (157).

In prospective cohort studies, selection bias is generally less likely to occur because at recruitment, the study outcome of interest has yet to happen (154). However, selection bias could be introduced inadvertently if participants with one risk category are less likely to be followed up than those with another, and if the explanations for loss to follow-up are associated with the outcome of interest (154). For instance, if smokers are less likely than non-smokers to be followed, and the reasons for loss to follow-up are associated with CRC (the outcome of interest in this case). The use of the individually unique national identification number and linkage to national registries, including Cancer Registry of Norway, allowed participants to be passively, but almost completely followed up for the outcome of interest (123, 124).

**In Papers I and II**, we used NOWAC follow-up information for repeated measurements of exposure of interest. All participants who completed the NOWAC baseline questionnaire received an invitation to complete a follow-up questionnaire (first NOWAC follow-up) and the response rate after adjusting for death and emigration was 81% (123). These participants were then compared with the respondents of the NOWAC baseline questionnaire regarding
information given at enrolment. Almost no differences were found, except that those who responded to the follow-up questionnaire were slightly younger and slightly more educated (123). This implies that the decision to combine data from the NOWAC baseline questionnaire and the first NOWAC follow-up questionnaire to form the baseline data in Papers I-III did not lead to subject selection [baseline data are in blue circles in Figure 5].

Exclusion of participants with missing information could lead to item non-response bias if those with missing information were substantially different from those with complete information. In Paper I, we excluded participants with missing information on PA and other covariates at baseline. One method to examine whether this decision introduced bias into the study was to compare the characteristics of included participants to those of eligible participants [Table 2]. The results suggested there were no substantial differences between the two populations.

Table 2 - Characteristics of eligible vs included participants in Paper I

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Eligible for analyses</th>
<th>Parameters</th>
<th>Included in study</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (in years)</td>
<td>96,874</td>
<td>52.1 (6.7)</td>
<td>79,184</td>
<td>51.5 (6.3)</td>
</tr>
<tr>
<td>Mean follow-up duration (in years)</td>
<td>96,874</td>
<td>14.6 (4.0)</td>
<td>79,184</td>
<td>14.6 (4.0)</td>
</tr>
<tr>
<td>Mean physical activity (1-10 scale)</td>
<td>87,664</td>
<td>5.55 (1.8)</td>
<td>79,184</td>
<td>5.56 (1.8)</td>
</tr>
<tr>
<td>Mean height (in metres)</td>
<td>96,284</td>
<td>166.1 (5.7)</td>
<td>79,184</td>
<td>166.3 (5.7)</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>94,675</td>
<td>24.8 (4.0)</td>
<td>79,184</td>
<td>24.7 (3.9)</td>
</tr>
<tr>
<td>Mean duration of education (years)</td>
<td>91,275</td>
<td>12.0 (3.5)</td>
<td>79,184</td>
<td>12.3 (3.5)</td>
</tr>
<tr>
<td>Mean alcohol intake (g/day)</td>
<td>94,916</td>
<td>3.34 (4.21)</td>
<td>79,184</td>
<td>3.51 (4.29)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Never</td>
<td>35,578</td>
<td>37.5%</td>
<td>29,292</td>
<td>37.0%</td>
</tr>
<tr>
<td>- Former</td>
<td>31,092</td>
<td>32.7%</td>
<td>26,387</td>
<td>33.3%</td>
</tr>
<tr>
<td>- Current</td>
<td>28,335</td>
<td>29.8%</td>
<td>23,505</td>
<td>29.7%</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>1,704</td>
<td>100%</td>
<td>1,311</td>
<td></td>
</tr>
<tr>
<td>- Colon cancer</td>
<td>1,151</td>
<td>67.5%</td>
<td>885</td>
<td>67.5%</td>
</tr>
<tr>
<td>- Rectal cancer</td>
<td>553</td>
<td>32.5%</td>
<td>426</td>
<td>32.5%</td>
</tr>
</tbody>
</table>

BMI: body mass index.

In Papers II and III, participants were not excluded based on missing data. Instead, missing data was handled using multiple imputation at baseline and follow-up, under the assumption that data was missing at random (135). Subsequent comparisons between the imputed and the complete-case datasets in Papers II and III revealed there were no substantial changes in the characteristics of the study samples in each paper [Tables 3 and 4, respectively].
### Table 3 - Comparison of characteristics of the complete-case and imputed datasets in Paper II

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Missing, n (%)</th>
<th>Complete-case dataset, mean (SD) or %</th>
<th>Imputed datasets, mean (SD) or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>County of residence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-incidence (%)</td>
<td>0 (0)</td>
<td>11.9</td>
<td>11.9</td>
</tr>
<tr>
<td>Mid-low-incidence (%)</td>
<td></td>
<td>35.6</td>
<td>35.6</td>
</tr>
<tr>
<td>Mid-high-incidence (%)</td>
<td></td>
<td>38.7</td>
<td>38.7</td>
</tr>
<tr>
<td>High-incidence (%)</td>
<td></td>
<td>13.8</td>
<td>13.8</td>
</tr>
<tr>
<td>Age at study onset</td>
<td>0 (0)</td>
<td>52.1 (6.7)</td>
<td>52.1 (6.7)</td>
</tr>
<tr>
<td>Physical activity (SD)</td>
<td>9,214 (9.5)</td>
<td>5.6 (1.8)</td>
<td>5.5 (1.8)</td>
</tr>
<tr>
<td>Adult attained height (SD)</td>
<td>561 (0.6)</td>
<td>166.1 (5.7)</td>
<td>166.1 (5.7)</td>
</tr>
<tr>
<td>Body mass index (SD)</td>
<td>2,187 (2.3)</td>
<td>24.8 (4.0)</td>
<td>24.8 (4.0)</td>
</tr>
<tr>
<td>Duration of education (SD)</td>
<td>5,601 (5.8)</td>
<td>12.1 (3.5)</td>
<td>12.0 (3.5)</td>
</tr>
<tr>
<td>Alcohol intake (SD)</td>
<td>1,958 (2.0)</td>
<td>3.6 (4.5)</td>
<td>3.5 (4.5)</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td>1,869 (1.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never (%)</td>
<td></td>
<td>37.4</td>
<td>37.6</td>
</tr>
<tr>
<td>Ex (%)</td>
<td></td>
<td>32.7</td>
<td>32.7</td>
</tr>
<tr>
<td>Current (%)</td>
<td></td>
<td>29.8</td>
<td>29.7</td>
</tr>
<tr>
<td>Pack years (SD)</td>
<td>6 (0.01)</td>
<td>6.3 (8.5)</td>
<td>6.3 (8.5)</td>
</tr>
<tr>
<td>Household income</td>
<td>7,054 (7.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (%)</td>
<td></td>
<td>39.1</td>
<td>39.1</td>
</tr>
<tr>
<td>Medium (%)</td>
<td></td>
<td>47.1</td>
<td>47.1</td>
</tr>
<tr>
<td>High (%)</td>
<td></td>
<td>13.8</td>
<td>13.8</td>
</tr>
<tr>
<td>Hormone replacement therapy use</td>
<td>2,793 (2.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never (%)</td>
<td></td>
<td>65.5</td>
<td>65.8</td>
</tr>
<tr>
<td>Ever (%)</td>
<td></td>
<td>34.5</td>
<td>34.2</td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td>3,695 (3.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never (%)</td>
<td></td>
<td>53.7</td>
<td>53.3</td>
</tr>
<tr>
<td>Ever (%)</td>
<td></td>
<td>46.3</td>
<td>46.7</td>
</tr>
</tbody>
</table>

SD: standard deviation.
Table 4 - Comparison of characteristics of the complete-case and imputed datasets in Paper III

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Missing n (%)</th>
<th>Complete-case dataset mean (SD), or %</th>
<th>Imputed datasets mean (SD), or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis of CRC</td>
<td>0 (0)</td>
<td>66.4 (8.7)</td>
<td>66.4 (8.7)</td>
</tr>
<tr>
<td>Physical activity</td>
<td>250 (13.4)</td>
<td>5.5 (1.9)</td>
<td>5.5 (1.9)</td>
</tr>
<tr>
<td>Body mass index (SD)</td>
<td>48 (2.6)</td>
<td>25.2 (4.1)</td>
<td>25.2 (4.1)</td>
</tr>
<tr>
<td>Duration of education (SD)</td>
<td>140 (7.5)</td>
<td>11.1 (3.4)</td>
<td>11.0 (3.4)</td>
</tr>
<tr>
<td>Annual household income</td>
<td>169 (9.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low (%)</td>
<td>50.6%</td>
<td>50.6%</td>
</tr>
<tr>
<td></td>
<td>Medium (%)</td>
<td>40.7%</td>
<td>40.7%</td>
</tr>
<tr>
<td></td>
<td>High (%)</td>
<td>8.7%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Alcohol intake (SD)</td>
<td>143 (7.7)</td>
<td>3.1 (4.5)</td>
<td>3.1 (4.5)</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td>30 (1.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Never (%)</td>
<td>34.2%</td>
<td>34.6%</td>
</tr>
<tr>
<td></td>
<td>Ex (%)</td>
<td>36.4%</td>
<td>36.2%</td>
</tr>
<tr>
<td></td>
<td>Current (%)</td>
<td>29.4%</td>
<td>29.2%</td>
</tr>
<tr>
<td>Red and processed meat intake</td>
<td>0 (0)</td>
<td>45.9 (26.9)</td>
<td>45.9 (26.9)</td>
</tr>
<tr>
<td>Fish intake</td>
<td>0 (0)</td>
<td>102.8 (63.5)</td>
<td>102.8 (63.5)</td>
</tr>
<tr>
<td>Fruit and vegetable intake</td>
<td>0 (0)</td>
<td>321.0 (201.7)</td>
<td>321.0 (201.7)</td>
</tr>
<tr>
<td>Vitamin D intake</td>
<td>0 (0)</td>
<td>9.0 (7.8)</td>
<td>9.0 (7.8)</td>
</tr>
</tbody>
</table>

SD: standard deviation.

Finally, in Paper III, we looked into CRC survival following diagnosis, and restricted the analyses to CRC survivors diagnosed within the baseline cohort used in Papers I and II. Analyses restricted to cancer survivors are subject to methodological concerns of possible selection bias (158). Indeed, restricting analyses to women with a CRC diagnosis may constitute conditioning on this diagnosis, which is affected by exposures (such as PA level, BMI, smoking, and dietary factors) that also share common aetiological relationships with the outcome, CRC death. Conditioning on CRC diagnosis could potentially produce a type of selection bias called collider stratification bias (159). This bias is liable to attenuate risk estimates toward the null among women with CRC, unless one adjusts for all common causes of CRC incidence and CRC death (158). In Paper III, we adjusted for variables available in the NOWAC Study database, which included most of these common associated exposures. Even then, selection bias could still come from the presence of unmeasured confounders (such as inherited susceptibility) that could influence both the risk of CRC and the probability of CRC death (158).
5.1.2 Information bias - Papers I-III
Information bias is a blanket term used for a number of subtypes of bias. This bias occurs when the information used in a study is either inaccurately measured or recorded, consequently producing erroneous results or conclusions that are systematically different from the truth (160). The inaccurate information could be in the measurement of exposures (and potential confounders), and/or in the outcome of interest (160). Inaccuracy in measurement can introduce two types of misclassification. Non-differential misclassification occurs when the measurement error in the exposure is independent of the study outcome. An ambiguous questionnaire could introduce this type of misclassification. Differential misclassification occurs when the measurement error is systematically different between those with a disease or outcome and those without a disease or outcome of interest (149).

The NOWAC Study used self-reporting instruments in the form of self-administered questionnaires to assess exposures and potential confounders (123). Self-reported information has the merit of being pragmatic when sampling large numbers of individuals, as data can be gathered rapidly, easily, and at low cost (161). However, this method can also lead to self-reporting bias and thus misclassification. Participants may provide incorrect information either deliberately due to denial, or just to provide socially desirable answers (e.g., smokers declaring they are non-smokers). Participants may also under-report (e.g., under-estimation of body weight), over-report (e.g., over-estimation of height), misunderstand questions, or simply have difficulties in giving reasonable averages of behaviours that they do not perform regularly (such as PA, alcohol intake, and dietary habits) (160).

One of the key strategies to unmasking information bias is to validate the self-reporting instrument. The main exposure in Paper I was PA. A validation study has been carried out on the PA question included the NOWAC Study questionnaire, and the 10-point PA scale was found to be valid in ranking the participants, but not in quantifying the intensity, frequency, duration, or type of PA (162). The authors found a moderate, but significant Spearman’s rank correlation coefficient between the PA scale and the outcomes from the measurements of a combined sensor monitoring heart rate and movement (range: 0.36-0.46; \( p <0.001 \)) (162). This scale matches up to the International Physical Activity Questionnaire, with reported criterion validity by Spearman correlation of a median of 0.30 in a validation study across 12 countries (163).

In Paper I, we adjusted for other lifestyle and dietary factors. These factors included BMI, duration of education, smoking status, alcohol intake, and dietary factors; while in Papers II
and III, we used these factors as predictors. Thus, it is also important to assess these factors for information bias. Diet is discussed in the next section (5.1.2.1). BMI was used as a measure of obesity and was calculated from the self-reported height and weight of the participants. A validation study showed that self-reported BMI in the NOWAC cohort tended to be under-reported among overweight and obese women. However, the discrepancies between self-reported and directly measured BMI were small, and the agreement between the two values was substantial (164). Likewise, validation studies have demonstrated that duration of education, hormone replacement therapy use, as well as history of diabetes mellitus, are all reliable variables in the NOWAC Study (124, 164-167).

While some data may be static (such as adult attained height), most information is dynamic and may change over time (such as diet). We used repeated measurements in Papers I and II to accommodate such changes in some of the variables. Thus, in Paper I, we updated information on PA level, BMI, and smoking status, while in Paper II, we updated information on PA, BMI, alcohol intake, smoking history, hormone replacement therapy use, and dietary intake. These variables were treated as time-dependent covariates in the respective analysis, such that their values changed over time.

Some fairly sensitive aspects of the NOWAC questionnaire could be prone to social desirability bias. Such aspects may include smoking status and intensity (pack years), alcohol intake, and household income. Self-reported data could be influenced by prejudice caused by social desirability or approval, especially if the participants have doubts regarding the assurance of anonymity and confidentiality at the time of data collection (168). Consequently, in Papers I and II, we attempted to correct possible inconsistencies in the data. Such inconsistencies included participants who had current or former smoking status at baseline, and reported to be never smokers in the follow-up questionnaire. Similar inconsistencies were corrected in hormone replacement therapy use. Nevertheless, social desirability bias could have influenced some of these factors enough to cause some level of misclassification (168). However, any misclassification in our studies is likely non-differential, as the data was collected long before the outcome of interest ever occurred. Consequently, the observed effect estimates of the association between lifestyle and dietary factors and risk of CRC or CRC survival might have been attenuated towards the null.

5.1.2.1 Challenges in assessment of dietary variables
The assessment of diet is one of the most challenging tasks in nutrition epidemiology (169), and no method is entirely the best (170). A 24-hour dietary recall conducted by a dietician...
could give accurate and quantitative information, but does not represent the usual intake of the participants. Food diary or interview of participants could provide a complete food history but could be time consuming and expensive (170, 171). FFQ has the advantage of providing better estimates of the usual diet of participants, but gives less quantitative information. FFQ is saddled with problems of recall and seasonality, however, it could provide a better prediction of diet-chronic disease association (170). FFQ is cost-effective and pragmatic, and these advantages are important in population-based study such as NOWAC Study with large numbers of participants (172). However, there is need to verify the degree to which the FFQ measures the aspect of diet it was intended to measure in validity studies (170, 172).

The NOWAC FFQ has been validated by 24-hour dietary recall study. The ability of the FFQ to rank participants was good for frequently eaten food items, and weak for macronutrients, as the FFQ did not cover entire diet (173). A test-retest reproducibility study of the NOWAC FFQ assessed habitual diet over the past year. The study found Pearson's correlation coefficients and Spearman's rank correlation coefficients for food groups and nutrients to range from 0.5 to 0.8 (174). In total, the relative validity of NOWAC FFQ is comparable to other FFQs used in other large cohorts (175, 176).

5.1.2.2 Misclassification of outcome of interest

The outcome of interest in Paper I and II is CRC. The likelihood of misclassification of CRC is rather minimal. This is because linkage of the NOWAC data to the Cancer Registry of Norway ensured the high quality of outcome data. The Cancer Registry of Norway is deemed to be reasonably accurate and almost 100% complete (124, 177), which means that the outcome assessed in Papers I and II, and the cohorts used in Paper III, are largely valid.

Data on emigration, death, and cause of death of participants was obtained through linkage to the National Population Register and the Cause of Death Register. These data are regarded to be of high quality; however, misclassification of the primary cause of death, which was used in Paper III, is a possibility we cannot completely rule out (178). The Cause of Death Register uses death certificates as their main source of information on the primary cause of death (178). In a previous study in Norway, information on cause of death in over 90% of cases was taken from death certificates. Autopsy, which is a medical investigation to ascertain the underlying cause of death, is only performed in few cases (178). In the study, autopsy findings revealed a slight underestimation of cancer as the underlying cause of death, with the proportion of deaths caused by cancer shifting from 23% to 25% after an autopsy was performed (178). The proportion of agreement between death certificates and autopsy reports

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was highest for cancer death, compared to other causes of death (178). Other international studies on the extent of agreement between death certificates and autopsy reports found that cancer as the underlying cause of death was the most accurately diagnosed when compared to other causes of death (179, 180). Therefore, we expect that any misclassification of CRC death in Paper III would have been minimal. Both cancer and cause of death statistics were classified according to the World Health Organisation’s ICD-10.

5.1.3 Confounding factors
In Paper I, where the aim was to find the association between PA and CRC incidence, we adjusted for confounders. A confounder (or confounding factor) is a factor that influences both the study exposure and the outcome of interest, thereby causing a distorted association when one fails to adjust for it. The confounder should not be in the intermediate pathway of causation between the exposure and outcome. In Paper I, we used a backward stepwise approach to build the multivariable model by including a potential confounder in the final model if its removal led to a change of at least 10% in the regression coefficients in any of the groups of PA levels. Nevertheless, in the presence of measurement errors in variables, this 10% change-in-coefficient approach can still fail to identify some confounders (181, 182).

We lacked information on family history of CRC, and use of aspirin and other NSAIDs. Participants who know that they have a familial susceptibility to CRC or other cancers, may be more health conscious and indulge in regular PA more often than others. Likewise, it has been shown that regular use of aspirin or other NSAIDs, which may also interact with PA, could protect against CRC. These could have introduced residual confounding in Paper I.

In Paper II, we evaluated whether the geographical distribution of lifestyle-related CRC risk factors could explain the geographical differences in CRC incidence in Norwegian women. Thus, we used the existing literature-backed risk factors available in the NOWAC database as covariates in the study. Lack of information on family history of CRC could be an important confounding factor in this study. However, hereditary CRC is generally more common in a slightly younger age group when compared to sporadic CRC (183).

Contrary to Paper II, in which we combined smoking status and pack years into one variable to reflect smoking intensity, this was not possible in Paper III, because of the smaller sample size. There could have been some residual confounding secondary to smoking and intensity.

Lastly, incorrect modelling of continuous variables (such as dichotomisation) could lead to inadequate adjustment in our analysis, especially if the relationship between the variable and
the outcome was incorrectly assumed to be linear. For instance, if the relationship between the variable and outcome is U- or J-shaped. Possible inadequate adjustment could be a source of residual confounding (184). The impact of the incorrect assumption vis-à-vis residual confounding depends on the extent of departure from linearity (184).

5.1.4 Validity of statistical analyses
We used the Cox proportional hazards regressions with repeated measurements in Papers I and II, and competing mortality risks analysis in Paper III. In addition, we used the KHB method of decomposition in Paper II, and multiple imputation in Papers II and III. Under the circumstances, we consider these statistical methods suitable investigative approaches to answer the different research questions in the three papers. In summary, the statistical analyses used in Papers I-III were:
Paper I - Cox proportional hazards including repeated measurements
Paper II - Cox proportional hazards, multiple imputation, with repeated measurements
Paper III - Competing risks analysis and multiple imputation

5.1.4.1 Proportional hazards assumption
Common and central to the three papers was the proportional hazards assumption. The HR is the ratio of the hazard of an event in the exposed group to the hazard of an event in the unexposed group. The hazards of an event can fluctuate over time in the exposed and unexposed groups. It can be construed at each time point as the instantaneous risk of having the event at that time point, provided that a participant is still at risk of the event at that time point (144). The proportional hazards assumption presupposes that the HR between the exposed and unexposed groups is constant over time. That is, the assumption presumes that the HR for different strata of a given covariate remains constant over time. Violation of this assumption could lead to unreliable and deceptive conclusions (143). It was therefore necessary to check the proportionality assumption in all three papers.

In Paper I, we checked this assumption by testing the interaction between the PA levels and the logarithmic transformation of the age of the participants, while in Papers II and III, the assumption was checked by testing Schoenfeld’s residuals. In Papers I and II, there was no evidence of violation of the assumption. In Paper III, we had to stratify by cancer stage in order to keep the assumption valid.

5.1.4.2 Missing information and multiple imputation
Missing information is unavoidable in epidemiological studies, especially when it is prospective over several years. Researchers have the option of including only participants
who have no missing information for any of the necessary variables in the analytic sample. These are the complete cases, and we used such participants in the analysis in Paper I. However, the use of complete cases comes with the risk of excluding a large part of the original sample, loss of power, and possible bias (136). The possibility of bias due to missing information depends on why the information is missing (136). Indeed, a complete-case analysis could be valid depending on the type of missing data. There are three kinds of missing data: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR).

In MCAR, the difference between the missing values and observed values are not systematic in nature. The reason for a missing value does not depend on the observed or unobserved information. Data is just missing, and there is no logic in the missingness. This means there are no systematic differences between participants with missing data and those with complete data. If a complete-case analysis is used in this situation, the missing data will lower the analytical sample population and the statistical power of the study, but it will not introduce bias (185).

In MAR, the difference between the missing values and observed values is systematic in nature and can be explained by differences in the observed data (136). There is a systematic connection between the tendency of missing values and the observed values. This tendency of missing values can be predicted by the observed values or by other aspects of the dataset. The missing data are not connected to the unobserved data, given the observed data. In this case, a complete-case analysis may or may not result in bias. If bias exists, proper adjustment in the analysis for the known, observed factors can give unbiased results (185).

In MNAR, the missing data is systematically connected to the unobserved data. That is, the missingness is connected to factors unmeasured in the data collection. A complete-case analysis using MNAR data may or may not result in bias. However, if bias exists, adjustment cannot be made in the analysis, because the reasons for the missing data are themselves unmeasured, and the estimate of effect will likely be biased (185). Complete-case analysis of MNAR data does not necessarily result in biased estimates. It will be unbiased (due to missing data) if the missingness is independent of the outcome under study, and this is a possibility that could exist whether the data is MAR or MNAR (185). However, if the missingness is not independent of the outcome, one can only make proper adjustments in the analysis if the missingness is MAR. This illustrates the important difference between MAR and MNAR (185). The challenge lies in the impossibility to differentiate between MAR and
MNAR using observed data. Therefore, the bias arising from MNAR can be tackled only by sensitivity analyses (136).

Multiple imputation implies imputing data several times, that is, creating several different replicate (imputed) datasets in order to allow for uncertainty about the missing data. Multiple imputation will yield unbiased estimates in both MCAR and MAR (136). Methods have also been proposed that could be used with multiple imputation in the presence of MAR predictors, to deal with MNAR outcomes to produce unbiased estimates (186).

Under the assumption that data was MAR, we used multiple imputation with chained equations in Papers II and III. This method creates imputations based on a series of imputation regression models (138). The regression model used for each variable depends on the type of variable to be imputed (as described in section 3.5.2.2).

Some authors have recommended the creation of 20 imputed replicate datasets when about 10-20% of the information is missing, and 40 imputed replicate datasets when about 50% is missing, or simply the creation of a number of imputed replicates datasets that is similar to the percentage of missing data (138, 187). The more replicate datasets one requires, the more computing time one needs, especially with large datasets and many variables, such as in the NOWAC Study.

Following multiple imputation, the results from the different imputed replicate datasets (20 in Paper II, and 50 in Paper III) are appropriately coalesced using Rubin’s rules to yield estimates with the corresponding standard errors. A comparison between the complete-case dataset and imputed datasets in Papers II and III revealed similar characteristics in the two corresponding groups of datasets (Tables 3 and 4, respectively). In addition, the estimates of effect computed from the complete-case and the imputed datasets were similar in both Papers II and III.

5.1.4.3 Karlson, Holm, and Breen method of decomposition
In Paper II, we used the KHB method to decompose the total effects of counties on CRC incidence into direct and indirect effects (133, 188).

In the linear regression model setting, let there be a model such that,

\[ Y = \alpha_F + \beta_F X + \gamma_F Z + \delta_F C + \epsilon \]  

(full model)  

- - - - - equation 1

where \(X\) is the variable whose effect is to be decomposed, and \(Z\) is the mediating variable. It is hypothesised that \(X\) operates partly through \(Z\) (133). \(C\) is a concomitant (control) variable in
the decomposition, while \( \epsilon \) is an error term. The regression coefficient \( \beta_F \) is called the direct effect (equation 1).

The total effect of \( X \) is illustrated by the coefficient \( \beta_R \) of a reduced model, which excludes the mediating variable \( Z \) (equation 2):

\[
Y = \alpha_R + \beta_R X + \delta_R C + \epsilon \quad \text{(reduced model)} \quad - - - - - \text{equation 2}
\]

The difference between the total effect and the direct effect is called the indirect effect (equation 3):

\[
\beta_I = \beta_R - \beta_F \quad \text{(indirect effect)} \quad - - - - - \text{equation 3}
\]

The indirect effect is interpreted as the mediation effect. There are no statistical challenges even when variables of type \( X, Z, \) and \( C \) are multiple in equations 1 and 2 (133).

The KHB method is a general decomposition method that expands the decomposability attributes of linear models to non-linear models (189). It is also capable of decomposing effects of both discrete and continuous variables, and it is not influenced by the rescaling bias that usually occurs in cross-model comparisons in non-linear models (133, 190). This means that the coefficients presented in Paper II are measured on the same scale (133, 189, 190). In our analysis in Paper II, CRC represented \( Y \), and the predictors (PA level, smoking status, diet, etc.) represented \( Z \), while the county groups represent \( X \), and subcohorts in the NOWAC Study represented \( C \). Thus, we used the method to show the extent to which the mediating variables (predictors) account for the difference in CRC incidence between the low-incidence county group (reference) and the other county groups.

The user-written program khb in Stata implements the KHB method. The method works well with the standard Stata estimation commands. In Paper II, we used the method with the -logit- command instead of -stcox- command. This was because implementation of the KHB method with the command -stcox- was still experimental at the time of the analysis in Paper II (133). A note in the output indicated this: “Note: stcox not supported. Output is experimental”.

Nevertheless, results from the use of -stcox- command were similar to that obtained from the use of -logit-, and did not alter the inference.

5.1.4.4 Competing mortality risk

The competing mortality risks analysis is the main analysis in Paper III. A competing risk is an event whose occurrence prevents the occurrence of the event of interest (191). In Paper III
for instance, CRC death was the event of interest, while non-CRC death was the competing event. For instance, someone who died from a cardiovascular event would no longer be at risk of CRC death. Competing risks methodology is considered valid and may be essential in the statistical analysis of cancer mortality (143-145, 192, 193). The general age bracket of CRC patients requires competing risks techniques, which incorporate the likelihood of non-CRC death. The impact of disregarding the risk of death from competing events on the results of the analysis is determined by the incidence of the competing event, in relation to the event of interest (194, 195).

We used two methods for the competing risk analysis in Paper III. First, we used cause-specific Cox regression, which is an extension of the standard Cox proportional hazard model. The cause-specific hazard refers to the instantaneous rate of failure due to one of the causes (194). The cause-specific hazards of CRC death and non-CRC death were estimated separately, by censoring failures due to causes other than the one being considered. In each of the models, and while censoring the other event, we estimated the effects of lifestyle factors on the risk of CRC death and non-CRC death, respectively. Ideally, the cause-specific hazard provide estimates of the rates observable in the absence of competing causes of death. This happens only when the independence assumption between the competing risks is kept. This is an unverifiable concept that does not exist in reality, because the independence assumption is generally untestable by data (196, 197). However, Andersen et al posited that the independence of competing events is not needed to obtain valid hazard estimates from the cause-specific approach (142).

The second method we used for the competing risk analysis was the Fine and Gray sub-distribution hazard approach (146). The sub-distribution hazard is the instantaneous risk of failure due to a cause, provided the person has not failed from that cause (194). This method resolves the main drawback of the cause-specific hazards model, that is, the hypothetical setting of “absence of competing event”. The estimates from the Fine and Gray approach are calculated in the “presence of competing events”. The hypothetical setting is removed by modelling hazards on the basis of the cumulative incidence function (143). The risk set for the sub-distribution hazard includes those who have already failed due to other causes. This means that someone who died of the other cause remains in the risk set. This is not so in the risk set for cause-specific Cox regression, where such a person would be censored from the risk set (194). A cause-specific model is considered more appropriate when investigating aetiological research questions, such as in this study (143-145).
The results obtained from cause-specific Cox and Fine and Gray methods results usually differ (194), but in our study they were numerically similar due to the relatively small number of competing events (non-CRC death).

5.2 External validity
External validity refers to the generalisability of the study results to another population or to a wider population outside the study population (150, 151). Internal validity is generally a precondition for external validity (151). If a study is already affected by bias (poor internal validity), generalising its results may be worthless and perhaps even dangerous (149).

The concept of generalisability may also relate to sampling theory (198). For instance, generalisability may be poor for studies with sociodemographic restrictions, that is, when a certain group of people are excluded from the study (152). The participants in the NOWAC Study were drawn randomly from the target age groups of the female population, using the country's population registry. Previous studies found the NOWAC cohort to be representative of the corresponding age groups of the female population in Norway (123, 124). Moreover, a comparison of the cumulative, age-specific CRC incidence rates in the NOWAC cohort and in the Cancer Registry of Norway were almost identical for all cancer sites combined, as well as for CRC [Figure 6]. This indicates that the participants of the NOWAC Study are representative of the general Norwegian female population, and that our results can thus be generalised to that population.

The generalisability of study results can also relate to separating the relevant and irrelevant facts of the study, and then conveying an implication or extrapolation of the relevant facts (153); that is, the value of the study results to other populations (150). For instance, even though our results from Paper III were from a female cohort with CRC, we believe the results could be generalised to men with CRC. The fact that our cohort consisted only of women may not be relevant to generalisability in terms of gender.
6 Discussion of main results

6.1 Physical activity patterns and the risk of colorectal cancer in women

Paper I examined the relationship between PA level and the risk of CRC in women. We did not find an association between PA level and the risk of CRC in our female cohort. Although we found a reduced risk in those who increased their PA from a lower level to a higher level during follow-up, our main results were inconsistent with the more common findings in men that PA reduces the risk of CRC.

There is the possibility that men and women have different physiological responses to PA that place women at a disadvantage regarding the risk of CRC, or that PA interacts with sex-specific factors that influence these physiological responses (68, 69).

In their 2017 publication, the WCRF/AICR concluded that all domains of PA (recreation, occupational, transport, and household) reduce the risk of CRC (47). However, most of the prospective cohort studies that found significant inverse associations between PA and CRC were conducted in men. Only a few prospective cohort studies found similar results in women (50, 51, 56-59). In these few studies, the effect sizes found in women were usually less than those found in men. Nevertheless, more prospective cohort studies conducted in women, or that contained sex-specific findings, obtained results similar to ours (54, 60-66, 199-203). The results obtained from the National Institutes of Health-American Association of Retired Persons Diet and Health Study revealed an inverse association between PA and the risk of CRC in men, whereas no association was found in the participating women (54). The Japan Public Health Center-based Prospective Study also found an inverse association between PA and the risk of CRC in men, but none in women from the same study (66). Similarly, the Framingham Study (201) and the Breast Cancer Detection Demonstration Project (60) observed an association only in men, but not women (60, 201). All these aforementioned studies used a global PA assessment similar to that used in the NOWAC Study. A recent Norwegian study using the HUNT cohort found an inverse association between PA and the risk of CRC in men, whereas no association was found in women (55).

The explanation for these conflicting results between the sexes may lie in the measurement of PA, as PA could be a challenging parameter to measure in women, especially in a population-based study. Generally, women perform more family care and household PA. A recent
Australian study investigated domain-specific PA and the risk of CRC, and found an inverse association with recreational PA, and a non-significant inverse association with occupational PA. No such association was observed with transport or household PA domains (204).

Recreational, occupational, and transport PA may be relatively easier to remember and document, while family care and household PA tend to be underrated and are often difficult to quantify appropriately. This makes women more liable than men to misclassification errors in PA level. This is also the case when the PA instrument is designed to measure a global PA score, like the one used in the NOWAC Study (162). More often than not, a PA instrument measures other domains of PA, such as recreational or occupational PA, and completely excludes household PA. Most studies that reported a similar inverse relationship between PA and the risk of CRC among women and men made use of either recreational (50, 51, 56) or occupational PA (56, 58, 59), and effectively excluded household PA. This may partly explain the possible sex bias in the appraisal of PA in epidemiological studies (73).

Bearing in mind the existence of important PA-related public health concerns, such as cardiovascular protection, the recommendation of regular PA takes precedence.

6.2 Geographical differences in lifestyle factors and incidence of colorectal cancer

Paper II aimed to determine whether geographical distribution of lifestyle-related CRC risk factors explains the geographical differences in CRC incidence in Norwegian women. We found that differences in lifestyle-related CRC risk factors did not explain county-level differences in CRC incidence. CRC risk factors such as body height, smoking history, duration of education, and fruit and vegetable intake were significantly associated with CRC incidence. However, these factors, together with other CRC risk factors, did not significantly explain the differences in the CRC incidence between the counties. This suggests that there are other important, unmeasured risk factors that account for the differences in CRC incidence between Norwegian counties.

Previous studies have ascribed variations in CRC incidence in different geographical areas of a country to different contributory factors. These factors include rural-urban disparities, SES, ease of access to health care, unique social and lifestyle risk factors, differences in exposure to risk factors such as dietary customs and ethnic variations in food preparation, and different exposures to unknown risk factors (107, 116, 117, 205). Some studies found an increased risk
of CRC in rural areas (206, 207), and suggested this could be due to screening behaviours, whereas others found a higher risk in urban areas (208-210).

One of the indices of rural-urban disparities is SES. Previous studies regarding SES have been inconsistent. A recent review indicated that individuals with low SES have a higher CRC incidence compared to those with high SES in North America, whereas it is largely the opposite in Europe (205). Education and household income, which are often used together as a proxy measure of SES, were examined separately in our analysis. While we found an association between higher education and low CRC incidence, no such association was found with household income. Studies suggested that education could be a better predictor of a healthy lifestyle than income (211, 212).

Our results revealed that, aside from an increased risk of CRC among current smokers, the risk remains even among former smokers. This is in conformity with results from a previous study in NOWAC cohort (213) and other Norwegian cohorts (214). This finding was also in agreement with a meta-analysis of 106 observational studies, which concluded that ever smokers have a higher risk of developing CRC than never smokers (81). Other studies revealed that living in an urban area could be a determinant of both smoking and severity of current smoking (215), and that smoking is inversely associated with SES (216).

We neither found association between red meat intake nor processed meat intake and CRC incidence. There were indications that red meat and processed meat could have been under-reported, while dishes with meat over-reported in the FFQ, compared to the 24-hour diet recall (217). In a study conducted in NOWAC cohort, where processed meat (meatballs, hamburgers, sausages and sandwich meats, liver pâté) was separated from dishes with meat (casseroles stew, pizza with meat and other meat dishes), an association was found between red meat and CRC incidence while no association was found between dishes with meat and CRC incidence (217). We probably did not find similar results because we had dishes with meat in our processed meat variable. Therefore, findings may be partly dependent on what one includes as processed meat. We found a significant, lower risk of CRC with fruit and vegetable intake. There are indications that vegetarian diets are associated with a lower incidence of CRC (100). This is consistent with results from the European Prospective Investigation into Cancer and Nutrition (EPIC) study (218).

In our study sample, women in the low-incidence county group were more physically active, had a longer duration of education, were more often never smokers, and had a higher fruit and
vegetable intake. Nevertheless, these factors fall short of explaining the difference in CRC incidence between the low- and high-incidence county groups. If established risk factors do not address these differences in the risk of CRC across county groups, then one needs to contemplate the unmeasured risk factors. In a large Scandinavian study where cohorts of twins from Sweden, Denmark, and Finland were merged, it was revealed that inheritable genetic factors accounted for 35% (95% CI 10-48%) of CRC cases (219). The well-described, highly penetrant inherited syndromes only accounted for about 3-5% of inherited cases of CRC, while the remainder of inherited cases apparently come from less penetrant factors (220).

Thus, family history of CRC could be especially central when deciding on suitable preventive screening strategies in areas of high incidence.

6.3 Pre-diagnostic lifestyle and dietary factors in relation to colorectal cancer survival

Paper III aimed to evaluate which pre-diagnostic lifestyle and dietary factors are associated with CRC survival. We found that a pre-diagnostic vitamin D intake of >10 µg/day was associated with 25% lower risk of CRC death. We did not find any evidence of an association between other pre-diagnostic lifestyle and dietary factors and CRC survival.

The two methods we used for the competing mortality risks analysis produced similar results. The results could have been different, because the two methods made use of different risk sets (194). However, similar results were produced because the competing event, that is, non-CRC death, represented relatively few persons.

Our results regarding pre-diagnostic vitamin D intake and decreased risk of CRC death is consistent with results from the EPIC study (221). However, the EPIC study estimated vitamin D level directly in the blood of participants by measuring circulating 25-hydroxyvitamin D [25(OH)D] levels, the most physiologically active molecular form of vitamin D. A 31% lower risk of CRC death was found in the highest quintile compared to the lowest quintile of 25(OH)D levels (221). Moreover, a recent updated systematic review and meta-analysis concluded that sufficient vitamin D intake offers better CRC survival when comparing the highest to lowest categories of blood 25(OH)D levels (222).

Our null findings regarding the association between pre-diagnostic fruit and vegetable intake, and CRC survival were similar to the results of the Cancer Prevention Study-II Nutrition
Cohort (223). Moreover, and similar to our findings, the Cancer Prevention Study-II Nutrition Cohort did not find any association between pre-diagnostic red and processed meat intake, and CRC survival (223). This finding is also consistent with the results from the EPIC study (224).

Similar to most previous studies (225-227), we did not find an association between pre-diagnostic alcohol intake and CRC survival. Smoking has been implicated in overall mortality (228-230), but we did not find any association between pre-diagnostic smoking status and CRC survival. However, we observed a 98% increased risk of non-CRC death in CRC survivors who were pre-diagnostic current smokers. This is probably because smoking increases the incidence of several other diseases and indirectly increases the risk of non-CRC death. In line with our findings, a recent meta-analysis of 14 prospective cohort studies did not find an association between pre-diagnostic smoking status and CRC survival (230). In Paper II, we found that duration of education was significantly and inversely associated with CRC incidence (231). However, we did not find any association between duration of education and CRC survival.
7 Conclusion and future perspective

7.1 Main conclusions
There was no association between PA and the risk of CRC in women. Thus, women may need to look beyond PA in order to reduce their risk of CRC. Nevertheless, the recommendation of regular PA supersedes this fact, due to other, important PA-related health benefits, such as cardiovascular protection.

Even though height, duration of education, smoking status, and fruit and vegetable intake were significantly associated with CRC incidence, they did not account for the geographical differences in CRC incidence in Norwegian women.

A pre-diagnostic vitamin D intake of >10μg/day could lower CRC death by 25%. The results from reviews and meta-analyses strengthen the evidence for the relationship between pre-diagnostic vitamin D intake and enhanced CRC survival.

7.2 Future perspectives
There is a need for more studies to clarify the reasons for sex differences in the association between PA and the risk of CRC, as PA apparently confers more advantages on men than women. More prospective studies are also required to pin-point the actual factors responsible for the high CRC incidence in Norway, specifically in some counties (or areas) where CRC incidence has been high for decades.

Of the approximately 30% of CRC that is regarded to have some genetic origin (familial CRC), only about 5% is attributable to specific inherited syndromic conditions. Further investigations on the remaining 25% of cases with a positive family history of CRC are needed to find the possible genetic factors or genetic-lifestyle factor interactions responsible for their CRC. A novel discovery could provide the opportunity for future genetic appraisal and CRC risk assessment outside the known inherited syndromic conditions.

Pre-diagnostic recommendations for CRC survival are important, but more importantly, and of public health interest, is to institute more prospective research on what can be done to improve survival once CRC is diagnosed. This would involve the investigation of post-diagnostic lifestyle factors and changes in these factors, and their effect on CRC survival.
There is currently a paucity of relevant data in this area, and merging of different databases may be necessary.

Our findings regarding pre-diagnostic vitamin D intake may have significant public health implications, and randomised clinical trials are warranted to certify this protective association.
References

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Van Der Pas S, Nelissen R, Fiocco M. Different competing risks models for different questions may give similar results in arthroplasty registers in the presence of few events. Acta Orthop. 2018;89(2):145-51.


Erratum

Paper II, in Figure 2:

The HR and 95% CI for processed meat intake “≤70.0g/day vs Never” should be 0.92 (0.71-1.20) and *not* 0.92 (1.00-1.24).
Oyeyemi SO, Braaten T, Licaj I, Lund E, Borch KB.


Pubmed: PMID: 30514263
Physical activity patterns and the risk of colorectal cancer in the Norwegian Women and Cancer study: a population-based prospective study

Sunday Oluwafemi Oyeyemi1*, Tonje Braaten1, Idlir Licaj1,2, Eiliv Lund1 and Kristin Benjaminsen Borch1

Abstract

Introduction: Colorectal cancer (CRC) remains the second most common cancer in women worldwide. Physical activity (PA) has been associated with reduced risk of CRC; however, this has been demonstrated more consistently in men, while results of studies in women have been largely equivocal. We aimed to further examine the relationship between PA patterns and the risk of CRC in women, using repeated measurements.

Methods: We followed participants of the Norwegian Women and Cancer (NOWAC) Study - a nationally representative cohort. Baseline information was available for 79,184 women, and we used this information in addition to follow-up information collected 6–8 years later, for repeated measurement analysis. At enrollment, participants were cancer-free and aged 30–70 years, with a median age of 51 years. We used Cox proportional hazards regression to compute hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: During an average of 14.6 years of follow-up and 1.16 million person-years, 885 cases of colon and 426 cases of rectal cancer were identified through linkage to the Norwegian Cancer Registry (median age at diagnosis: 65 years). We found no association between PA level and the risk of colon cancer in baseline or repeated measurements analyses when comparing women with PA level 1–2 to those with PA level 5–6 (reference) (baseline: HR = 0.90, 95% CI 0.66–1.23, p-trend = 0.76; repeated measurements: HR = 0.78, 95% CI 0.55–1.10, p-trend = 0.27). Results were the same when comparing PA level 9–10 to the reference level (baseline: HR = 0.80, 95% CI 0.56–1.12, p-trend = 0.76; repeated measurements: HR = 0.82, 95% CI 0.58–1.16, p-trend = 0.27). Similarly, we found no association between PA levels and the risk of rectal cancer.

Conclusions: Women may need to look beyond PA in order to reduce their risk of CRC.

Keywords: Physical activity, Colon cancer, Rectal cancer, Colorectal cancer, Women, NOWAC

Background

Colorectal cancer (CRC) remains the second most common cancer in women worldwide [1]. This is also true in Norway, where CRC is the second most common cancer in women [2]. In 2018, it was estimated that Norway had the highest incident rate of CRC in women worldwide, at 39.3 per 100,000, compared to 24.2 per 100,000 in the rest of Europe (World age-standardised rate) [1, 3]. The average annual number of new cases in women in Norway has been on the increase in the past few years, with 1706 in 2002–06; 1833 in 2007–11; and 2049 in 2012–16 [2].

There is convincing epidemiological evidence suggesting that a healthy lifestyle, body weight, and diet could substantially prevent the development of CRC [4], and several epidemiological studies have demonstrated a risk-reducing association between physical activity (PA) and CRC [5–8]. The Continuous Update Project on colorectal cancer by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) published in September 2017 concluded that all domains of PA (occupational, household, transport, and recreational) reduce the risk of CRC [9]. However, this has
only been demonstrated consistently in men, while results of such studies in women have been largely equivocal [10, 11]. Considering only prospective studies that either included women alone or presented sex-specific findings, 13 studies reported no associations between PA and CRC among women with relative risks ranging from 0.69 to 1.15 [10–22]. Six studies reported statistically significant inverse associations among women with relative risks ranging from 0.54 to 0.90 [6–8, 23–25], which were consistent with the findings of most studies in men. However, the associations in women were weaker than those in men, and some of the significant observations in women were only present in sub-analyses [11, 26].

These discrepancies may have stemmed from methodological differences, such as relatively small sample sizes, deficient or poor assessment methods for PA, or assessment of different domains of PA by methods of unknown validity or reproducibility. It may be that the assessment of PA in women has more intricacies than that in men, as inclusion of household PA in women may be under- (or over-) rated [27]. It is also plausible that a sex difference exists in the physio-biological response to PA [28, 29].

The aim of the present study was to further examine the relationship between PA patterns and the risk of CRC in women, using a validated, single-item, self-administered questionnaire and repeated measurements, in a nationally representative cohort of Norwegian women.

Methods

The Norwegian women and Cancer study

The Norwegian Women and Cancer (NOWAC) Study is a nationally representative, prospective cohort study which started in 1991. The details of the cohort are fully described elsewhere [30, 31]. In summary, invitations to participate in the NOWAC Study were sent to a sample of women aged 30–70 years, who were randomly selected from the Norwegian Central Population Register. The participants were recruited in three waves: 1991–92, 1996–97, and 2003–04. More than 172,000 women agreed to participate and completed questionnaires regarding their lifestyle and health status. All participating women gave written informed consent, and the overall response rate was 52.7%. The NOWAC Study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

Study sample

In these analyses, we used information from 101,321 women who were recruited in 1991–92, 1996–97, and 2003–04, and completed food frequency questionnaires in 1998, 1996–97 and 2003–04, respectively (baseline); and follow-up questionnaires 6–8 years after baseline questionnaire (repeated measurement). We excluded women who emigrated or died before the start of follow-up (n = 18), those with prevalent cancer other than non-melanoma skin cancer at baseline (n = 4429), those with missing information on PA level at baseline (n = 9210), and those with missing information on any of the covariates at baseline (height and weight (used to calculate body mass index), duration of education, alcohol consumption, smoking status, and intake of red meat, processed meat, dietary calcium and dietary fibre) (n = 8480). Thus the final analytical sample consisted of 79,184 women (Fig. 1). In the repeated measurement analysis, we used measurements from baseline (first measurements) and follow-up information (second measurements) of PA, BMI, and smoking status. Thereafter follow-up information was applied until emigration, death, cancer diagnosis, or the end of the study period, whichever occurred first.

We also carried out separate analyses where we used change in PA level between baseline and follow-up as the exposure variable. These analyses consisted of 44,498 women who had both baseline and follow-up information on PA level, after exclusion of those who died (n = 3), emigrated (n = 24), or had cancer (n = 1884) before the follow-up measurement took place (Fig. 2).

Assessment of physical activity level and covariates

Information on PA level was taken from the NOWAC questionnaires. The baseline and follow-up questionnaires contained the same question on PA level. The participants were asked, “By physical activity we mean activity both at work and outside work, at home, as well as training/exercise and other physical activity, such as walking, etc. Please mark the number that best describes your level of physical activity; 1 being very low and 10 being very high”.

The PA scale used in this study reflects the total amount of PA, which includes the domains (occupational, household, transport, and recreational), in one global score. This PA scale has been validated to rank PA levels in the Norwegian female population, and a moderate, but significant Spearman’s rank correlation coefficient was found (range: 0.36–0.46; p < 0.001) between the PA scale and the outcomes from the measurements of a combined sensor monitoring heart rate and movement [32].

Information on initial covariates obtained through the NOWAC questionnaires at baseline included age, height, BMI, duration of education, household income, alcohol consumption, smoking status, use of hormone replacement therapy, intake of red meat, processed meat, dietary calcium, and dietary fibre. The choice of these covariates was based on documented risk factors in the literature and in previous similar studies [10–12, 26].
Cancer incidence, emigration, and death
NOWAC participants diagnosed with primary CRC using the International Statistical Classification of Diseases and Related Health Problems, Tenth Edition (ICD-10 code C18 or C19–20), were identified through linkage to the Cancer Registry of Norway with the aid of the unique national identity number. The Cancer Registry of Norway has been judged to be more than 98% complete [33]. Information on date of emigration and death in the cohort was obtained through linkage to the Norwegian Central Population Register.

Fig. 1 Flowchart for study sample

Fig. 2 Flowchart for sub-cohort (used for additional analyses of change in PA)
Statistical methods

Analyses using baseline data

We used Cox proportional hazards models, with age as the time scale, to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for the associations between PA levels and risk of CRC. PA levels at baseline were divided into five groups [1–10], which was used as the reference group. We used similar models to estimate multivariable-adjusted HRs with 95% CIs. We stratified the data by recruitment sub-cohort (1991–92, 1996–97, and 2003–04) to control for potential differences in the three recruitment waves. In the Cox models, follow-up time was defined as the interval between age at baseline and age at emigration, death, diagnosis of any incident cancer, or age at the end of the study period (31 December 2015), whichever occurred first.

We checked the proportional hazards assumption by testing an interaction variable between the groups of PA levels and the logarithm of the age of the participants. We carried out an initial analysis on the baseline data to select the covariates to adjust for in the final models. This initial analysis included: height (continuous, in metres); body mass index calculated from weight divided by the square of the height (BMI, \(< 25.0, 25.0–29.9, \geq 30.0 \text{ kg/m}^2\)); duration of education (\(< 10, 10–12, \geq 13\) years, corresponding to primary and lower secondary school, upper secondary school, and higher education, respectively); household income (\(< 300,000, 300,000–600,000, > 600,000 \text{ Norwegian krone per annum}, \text{ corresponding to low, medium and high income}\)); alcohol consumption (0, \(\leq 3, > 3 \text{ g/day}\)); smoking status (never, former, current); hormone replacement therapy (never, former, current); red meat intake (0, \(\leq 15, > 15 \text{ g/day}\)); processed meat intake (0, \(\leq 30, > 30 \text{ g/day}\)); dietary calcium (\(< 700, \geq 700 \text{ mg/day}\)) and dietary fibre (\(< 21, > 21 \text{ g/day}\)). Only covariates associated with a change of at least 10% in the regression coefficient of any of the groups of the PA levels were included in final models. All the above covariates met this criterion except hormone replacement therapy, household income, and red meat intake. However, the latter was still added to the models because of its reported association in the carcinogenesis of colorectal tissues [34].

We assessed possible interactions between PA and BMI, duration of education, alcohol consumption, and smoking status, respectively. We further explored the relationship between PA levels and CRC stratified by BMI categories, as obesity has been deemed as a convincing factor in the development of CRC [35, 36]. We tested for linear trend by using the original 10-level PA scale modelled as a continuous variable. We conducted sensitivity analyses by re-categorising the PA levels into three groups [1–10], and using the baseline information. We also repeated baseline analyses after excluding cancers diagnosed during the first 2 years of the follow-up in order to control for possible reverse causality.

Analyses using repeated measurements of physical activity level

We used baseline information on PA level until follow-up information became available. Subsequently, we applied follow-up information until emigration, death, cancer diagnosis, or the end of the study period (31 December 2015), whichever came first. Follow-up information on BMI and smoking status was also applied once available.

Analyses according to change in physical activity level

We grouped the 10 PA levels into three categories at baseline: ‘inactive’ (PA level 1–4), ‘moderately active’ (PA level 5–6), and ‘active’ (PA level 7–10). We then used the follow-up data on PA level to categorize participants as ‘consistently active’ (PA level 7–10 at baseline and follow-up), ‘consistently moderately active’ (PA level 5–6 at baseline and follow-up), ‘consistently inactive’ (PA level 1–4 at baseline and follow-up), ‘increased PA’ (increased PA level between baseline and follow-up), and ‘decreased PA’ (decreased PA level between baseline and follow-up).

We then used this change in PA level as the exposure variable and adjusted for the time period between the two measurements. Thus, we considered participants to be at risk from the date of the follow-up measurement until emigration, death, CRC diagnosis, or the end of the study period (31 December 2015), whichever came first. All statistical tests were two-sided, and all statistical analyses were conducted using Stata for Windows version 15.0 (StataCorp, College Station, Texas, USA). All p values were considered statistically significant at a level of < 0.05.

Results

During an average of 14.6 years of follow-up and 1.16 million person-years, 885 cases of colon cancer and 426 cases of rectal cancer were diagnosed. The median age of the cohort at baseline was 51 years, while the median age at diagnosis was 65 years, ranging from 43 to 87 years.

At baseline, 43% of the cohort reported PA levels 5–6, and 74% reported a PA level of 5 or higher (Table 1). Compared to participants with PA levels 1–4, women with PA levels 5–10 had a lower mean BMI (24.3 vs 26.0 \text{ kg/m}^2), similar mean age (51.3 vs 52.2 years), similar mean duration of education (12.4 vs 12.0 years), and same daily alcohol consumption (3.5 vs 3.5 \text{ g/day}). Furthermore, women with PA levels 5–10 were more often never smokers (38% vs 36%), less often current smokers (29% vs 33%), consumed slightly less red meat (15.3 vs 16.0 \text{ g/day}), less processed meat (33.3 vs 34.8 \text{ g/day}), more dietary calcium (763 vs 717 \text{ mg/day}), and more dietary fibre (22.0 vs 20.0 \text{ g/day}), than women with PA levels 1–4.
In the multivariable baseline analyses, we found no statistical significant association between PA level and the risk of CRC when women with PA level 9–10 were compared to those with PA level 5–6 (colon: HR = 0.80, 95% CI 0.56–1.12, p-trend = 0.76; rectal: HR = 1.40, 95% CI 0.94–2.10, p-trend = 0.87) (Table 2). This null relationship did not change after excluding those who were diagnosed with cancer in the first 2 years of follow-up (data not shown). We explored the outcome of re-categorising the PA levels into three groups: 1–4, 5–6, and 7–10, with 5–6 as the reference group and using the baseline information. This does not change the effects, p-trend nor the overall findings (data not shown). Furthermore, interaction terms between PA levels and categories of BMI, duration of education, alcohol consumption, and smoking status were not significant. In analyses stratified by BMI, we found no association between PA level and CRC (data not shown).

In multivariable repeated PA measurement analyses, after adjustment for repeated measurements of BMI and smoking status, the corresponding risks obtained were similarly not statistically significant (colon: HR = 0.82, 95% CI 0.58–1.16, p-trend = 0.27; rectal: HR = 1.40, 95% CI 0.93–2.09, p-trend = 0.74) (Table 3).

In analyses of the influence of changes in PA level on the risk of CRC, a statistically significant reduction in the risk of colon cancer was observed in those with “increased PA” when compared to those who remained “consistently moderately active” (HR = 0.69, 95% CI 0.50–0.95). We did not observe any significant association between women who were “consistently active”, “consistently inactive”, or those with “decreased PA” when compared to women who were “consistently moderately active” (Table 4).

Intriguingly, those who were “consistently active” were at an increased risk of rectal cancer when compared to women who were “consistently moderately active” (HR = 1.57, 95% CI 1.02–2.42) (Table 4).

| Table 1 | Characteristics of participants in NOWAC Study by physical activity level at baseline (n = 79,184) |

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Physical activity level at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population (N = 79,184)</td>
<td>3616 (4.6%) 17,360 (21.9%) 34,208 (43.2%) 20,029 (25.3%) 3971 (5.0%)</td>
</tr>
<tr>
<td>Mean age (±SE)</td>
<td>52.91 (0.11) 52.00 (0.05) 51.38 (0.03) 51.11 (0.04) 51.65 (0.10)</td>
</tr>
<tr>
<td>Person-years at risk a</td>
<td>51,685 255,773 503,850 289,189 57,422</td>
</tr>
<tr>
<td>Average follow-up time (SD) b</td>
<td>14.29 years (4.62) 14.73 years (4.10) 14.73 year (3.93) 14.44 years (3.88) 14.46 years (3.92)</td>
</tr>
<tr>
<td>Colon cancer (885)</td>
<td>45 (1.25%) 203 (1.17%) 393 (1.15%) 208 (1.04%) 36 (0.91%)</td>
</tr>
<tr>
<td>Rectal cancer (426)</td>
<td>24 (0.66%) 100 (0.58%) 175 (0.51%) 99 (0.49%) 28 (0.71%)</td>
</tr>
<tr>
<td>Colorectal cancer (1311)</td>
<td>69 (1.91%) 303 (1.75%) 568 (1.66%) 307 (1.53%) 64 (1.61%)</td>
</tr>
<tr>
<td>Mean height in cm (±SE)</td>
<td>165.9 (0.10) 166.1 (0.04) 166.3 (0.03) 166.5 (0.04) 166.1 (0.09)</td>
</tr>
<tr>
<td>Mean BMI in kg/m² (±SE)</td>
<td>26.92 (0.09) 25.81 (0.03) 24.61 (0.02) 23.83 (0.02) 23.58 (0.05)</td>
</tr>
<tr>
<td>Mean duration of education in years (±SE)</td>
<td>11.46 (0.06) 12.15 (0.03) 12.28 (0.02) 12.62 (0.03) 11.85 (0.06)</td>
</tr>
<tr>
<td>Mean alcohol consumption, grams (±SE)</td>
<td>3.25 (0.08) 3.51 (0.03) 3.48 (0.02) 3.64 (0.03) 3.25 (0.07)</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td>29,292 (37.0%) 1081 (29.9%) 6370 (36.7%) 12,871 (37.6%) 7564 (37.8%)</td>
</tr>
<tr>
<td>Former 26,387 (33.3%)</td>
<td>1104 (30.5%) 5475 (31.5%) 11,335 (33.1%) 7128 (35.6%) 1345 (33.9%)</td>
</tr>
<tr>
<td>Current 23,505 (29.7%)</td>
<td>1431 (39.6%) 5515 (31.8%) 10,002 (29.2%) 5337 (26.7%) 1220 (30.7%)</td>
</tr>
<tr>
<td>Mean daily intakes in grams</td>
<td>16.45 (0.22) 15.86 (0.09) 15.31 (0.06) 15.19 (0.08) 15.39 (0.20)</td>
</tr>
<tr>
<td>Red meat (±SE)</td>
<td>35.57 (0.41) 34.69 (0.17) 33.92 (0.12) 32.44 (0.15) 32.72 (0.38)</td>
</tr>
<tr>
<td>Processed meat (±SE)</td>
<td>698.16 (5.46) 720.64 (2.29) 748.91 (1.64) 779.19 (2.24) 807.32 (5.67)</td>
</tr>
<tr>
<td>Dietary calcium (±SE)</td>
<td>18.85 (0.12) 20.20 (0.05) 21.45 (0.04) 22.58 (0.05) 23.53 (0.12)</td>
</tr>
<tr>
<td>Dietary fibre (±SE)</td>
<td>18.85 (0.12) 20.20 (0.05) 21.45 (0.04) 22.58 (0.05) 23.53 (0.12)</td>
</tr>
</tbody>
</table>

aTotal person years = 1,157,919
bAverage follow-up time = 14.62 years (SD = 3.99, SE = 0.01)
Table 2 Hazard ratios (95% CI) of colon, rectal, and colorectal cancers by physical activity level at baseline (n = 79,184) in the NOWAC Study

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Models</th>
<th>Physical activity level at baseline</th>
<th>Hazard ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>Age-adjusted</td>
<td>1–2</td>
<td>0.98 (0.72–1.33)</td>
</tr>
<tr>
<td></td>
<td>N of cases: 885</td>
<td>45</td>
<td>0.94 (0.80–1.12)</td>
</tr>
<tr>
<td></td>
<td>Multivariable 1</td>
<td>45</td>
<td>1.00 (0.82–1.15)</td>
</tr>
<tr>
<td></td>
<td>N of cases: 885</td>
<td>45</td>
<td>0.97 (0.70–1.28)</td>
</tr>
<tr>
<td></td>
<td>Multivariable 2</td>
<td>45</td>
<td>0.92 (0.77–1.09)</td>
</tr>
<tr>
<td></td>
<td>N of cases: 885</td>
<td>45</td>
<td>1.00 (0.84–1.18)</td>
</tr>
<tr>
<td></td>
<td>Multivariable 2</td>
<td>45</td>
<td>0.91 (0.77–1.09)</td>
</tr>
<tr>
<td></td>
<td>N of cases: 885</td>
<td>45</td>
<td>1.00 (0.85–1.19)</td>
</tr>
<tr>
<td>Rectal</td>
<td>Age-adjusted</td>
<td>1.22 (0.80–1.87)</td>
<td>1.01 (0.79–1.29)</td>
</tr>
<tr>
<td></td>
<td>N of cases: 426</td>
<td>1.09 (0.85–1.39)</td>
<td>1.01 (0.79–1.29)</td>
</tr>
<tr>
<td></td>
<td>Multivariable 1</td>
<td>1.08 (0.84–1.39)</td>
<td>1.02 (0.79–1.30)</td>
</tr>
<tr>
<td></td>
<td>N of cases: 426</td>
<td>1.07 (0.83–1.37)</td>
<td>1.03 (0.80–1.32)</td>
</tr>
<tr>
<td></td>
<td>Multivariable 2</td>
<td>1.07 (0.83–1.37)</td>
<td>1.03 (0.80–1.32)</td>
</tr>
<tr>
<td></td>
<td>N of cases: 426</td>
<td>1.07 (0.83–1.37)</td>
<td>1.03 (0.80–1.32)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Age-adjusted</td>
<td>1.05 (0.82–1.35)</td>
<td>1.00 (0.86–1.13)</td>
</tr>
<tr>
<td></td>
<td>N of cases: 1311</td>
<td>0.99 (0.86–1.13)</td>
<td>0.98 (0.86–1.13)</td>
</tr>
<tr>
<td></td>
<td>Multivariable 1</td>
<td>1.08 (0.84–1.39)</td>
<td>1.02 (0.79–1.30)</td>
</tr>
<tr>
<td></td>
<td>N of cases: 1311</td>
<td>1.07 (0.83–1.37)</td>
<td>1.03 (0.80–1.32)</td>
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<tr>
<td></td>
<td>Multivariable 2</td>
<td>1.07 (0.83–1.37)</td>
<td>1.03 (0.80–1.32)</td>
</tr>
<tr>
<td></td>
<td>N of cases: 1311</td>
<td>1.07 (0.83–1.37)</td>
<td>1.03 (0.80–1.32)</td>
</tr>
</tbody>
</table>

Multivariable 1 = adjusted for age, height, body mass index, duration of education, alcohol consumption, and smoking status
Multivariable 2 = additionally adjusted for intake of red meat, processed meat, dietary calcium, and dietary fibre

that those who increased their PA from baseline to follow-up had a lower risk of colon cancer.

There is an established inverse relationship between PA and the risk of CRC, and several plausible explanatory biological mechanisms and hypotheses have been proposed [37, 38]. These mechanisms are not completely clear, however, the existing plausible hypotheses include the involvement of PA in the reduction of intestinal fecal transit time; increase production of motility-inducing prostaglandin F2α; alterations in sex hormones;

Table 3 Hazard ratios (95% CI) of colon, rectal, and colorectal cancers by physical activity level at baseline and follow-up (n = 79,184) in the NOWAC Study

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Models</th>
<th>Physical activity level at baseline/follow-up</th>
<th>Hazard ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>Age-adjusted</td>
<td>1–2</td>
<td>0.85 (0.61–1.19)</td>
</tr>
<tr>
<td></td>
<td>N of cases: 833</td>
<td>37</td>
<td>0.96 (0.81–1.14)</td>
</tr>
<tr>
<td></td>
<td>Multivariable 1</td>
<td>36</td>
<td>0.94 (0.79–1.25)</td>
</tr>
<tr>
<td></td>
<td>N of cases: 818</td>
<td>36</td>
<td>0.94 (0.79–1.12)</td>
</tr>
<tr>
<td></td>
<td>Multivariable 2</td>
<td>36</td>
<td>0.94 (0.79–1.12)</td>
</tr>
<tr>
<td></td>
<td>N of cases: 818</td>
<td>36</td>
<td>0.94 (0.79–1.12)</td>
</tr>
<tr>
<td>Rectal</td>
<td>Age-adjusted</td>
<td>1.22 (0.79–1.88)</td>
<td>0.90 (0.69–1.17)</td>
</tr>
<tr>
<td></td>
<td>N of cases: 398</td>
<td>23</td>
<td>0.90 (0.69–1.17)</td>
</tr>
<tr>
<td></td>
<td>Multivariable 1</td>
<td>23</td>
<td>0.90 (0.69–1.17)</td>
</tr>
<tr>
<td></td>
<td>N of cases: 390</td>
<td>23</td>
<td>0.90 (0.69–1.17)</td>
</tr>
<tr>
<td></td>
<td>Multivariable 2</td>
<td>23</td>
<td>0.88 (0.67–1.15)</td>
</tr>
<tr>
<td></td>
<td>N of cases: 390</td>
<td>23</td>
<td>0.88 (0.67–1.15)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Age-adjusted</td>
<td>0.96 (0.74–1.26)</td>
<td>0.94 (0.81–1.09)</td>
</tr>
<tr>
<td></td>
<td>N of cases: 1231</td>
<td>60</td>
<td>0.94 (0.81–1.09)</td>
</tr>
<tr>
<td></td>
<td>Multivariable 1</td>
<td>59</td>
<td>0.93 (0.80–1.08)</td>
</tr>
<tr>
<td></td>
<td>N of cases: 1208</td>
<td>59</td>
<td>0.93 (0.80–1.08)</td>
</tr>
<tr>
<td></td>
<td>Multivariable 2</td>
<td>59</td>
<td>0.92 (0.80–1.09)</td>
</tr>
<tr>
<td></td>
<td>N of cases: 1208</td>
<td>59</td>
<td>0.92 (0.80–1.09)</td>
</tr>
</tbody>
</table>

Multivariable 1 = adjusted for age, height, body mass index, duration of education, alcohol consumption, and smoking status
Multivariable 2 = additionally adjusted for intake of red meat, processed meat, dietary calcium, and dietary fibre
Confidence intervals in bold have p-values less than 0.05
As the exposure of interest, PA may be an intricate relationship that responds to several variables. For instance, PA, including all the domains in one total score, we can compare our study to others that utilized the Continuous Update Project on CRC by the WCRF/AICR recently inferred that PA of all types reduces the risk of CRC [9]. However, most of the epidemiological studies that corroborate this relationship have been conducted in men [11]. Results of studies in women have been largely inconsistent and less conclusive [10, 11, 14, 24].

As the exposure of interest, PA may be an intricate and difficult parameter to measure, especially in population-based studies. Inconsistencies may be associated with variations in PA instruments (assessment methods), the use of different domains of PA (occupational, household, transport, and recreational) with the frequency, duration, and intensity of PA in the investigation of the relationship. Nevertheless, the same heterogeneity in the assessment of PA in women also exist in the studies of the PA-CRC relationship in men; whereas the findings in men have been more consistent and largely conclusive [11, 13, 14, 24].

Our findings of no association between PA and the risk of CRC in women may be an accurate reflection of a true lack of association, which is consistent with findings from many previous prospective studies among women [10–22]. From the available prospective studies that included only women or gave sex-specific results, we identified 21 studies [6–8, 10–26, 39]. Thirteen of these studies found no association between PA and risk of CRC [10–22], six observed a statistically significant association [6–8, 23–25], while two reported both [26, 39]. The last two studies further underscore the discrepancies in the findings of PA-CRC relationship in women [26, 39].

Out of the 13 prospective studies that found no association, none of them used the same PA instrument we used in our study. Nevertheless, since our PA scale corresponds to total PA, including all the domains in one global score, we can compare our study to others that utilized total PA. For example, the questionnaire used in the National Institutes of Health-American Association of Retired Persons Diet and Health (NIH-AARP Diet and Health) Study [11] assessed participants’ detailed routine throughout the day, at home and work (daily routine activity), and sporting activities. Daily routine activity and sporting activity were analysed separately and neither were statistically significant (HR = 0.84, 95%CI 0.50–1.42, p-trend = 0.714 and HR = 0.87, 95%CI 0.71–1.06, p-trend = 0.536, respectively) in women. Interestingly, the same analyses were statistically significant in the participating men (HR = 0.86, 95%CI 0.66–1.12, p-trend = 0.007 and

Table 4 Hazard ratios (95% CI) of colon, rectal and colorectal cancers by changes in physical activity level between enrollment and follow-up (n = 44,498) in the NOWAC Study

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Models</th>
<th>Consistently active (PA 7–10) [n = 9417]</th>
<th>Consistently moderately active (PA 5–6) [n = 13,189]</th>
<th>Increased PA [n = 7869]</th>
<th>Decreased PA [n = 6317]</th>
<th>Consistently inactive (PA 1–4) [n = 7706]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>Age-adjusted</td>
<td>0.83 (0.62–1.11) 69 134 0.70 (0.51–0.97) 0.85 (0.62–1.16) 0.91 (0.69–1.20)</td>
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<tr>
<td></td>
<td>N of cases: 393</td>
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<tr>
<td></td>
<td>Multivariable 1</td>
<td>0.86 (0.64–1.15) 69 134 0.69 (0.50–0.96) 0.82 (0.60–1.11) 0.86 (0.65–1.14)</td>
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<tr>
<td></td>
<td>N of cases: 393</td>
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<tr>
<td></td>
<td>Multivariable 2</td>
<td>0.87 (0.65–1.16) 69 134 0.69 (0.50–0.95) 0.81 (0.60–1.11) 0.86 (0.65–1.14)</td>
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<td></td>
<td>N of cases: 393</td>
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<tr>
<td>Rectal</td>
<td>Age-adjusted</td>
<td>1.57 (1.03–2.41) 43 42 1.36 (0.86–2.16) 1.16 (0.70–1.91) 1.02 (0.63–1.66)</td>
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<tr>
<td></td>
<td>N of cases: 168</td>
<td></td>
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<tr>
<td></td>
<td>Multivariable 1</td>
<td>1.54 (1.01–2.37) 43 42 1.34 (0.84–2.12) 1.11 (0.67–1.84) 1.02 (0.62–1.66)</td>
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<td></td>
<td>N of cases: 168</td>
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<td></td>
<td>Multivariable 2</td>
<td>1.57 (1.02–2.42) 43 42 1.32 (0.83–2.10) 1.11 (0.67–2.84) 1.00 (0.61–1.63)</td>
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<td></td>
<td>N of cases: 168</td>
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<tr>
<td>Colorectal</td>
<td>Age-adjusted</td>
<td>1.01 (0.80–1.28) 112 176 0.86 (0.67–1.12) 0.92 (0.71–1.20) 0.94 (0.74–1.20)</td>
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<tr>
<td></td>
<td>N of cases: 561</td>
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<tr>
<td></td>
<td>Multivariable 1</td>
<td>1.03 (0.81–1.31) 112 176 0.85 (0.65–1.10) 0.89 (0.68–1.15) 0.90 (0.71–1.15)</td>
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<td>N of cases: 561</td>
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<tr>
<td></td>
<td>Multivariable 2</td>
<td>1.04 (0.82–1.32) 112 176 0.84 (0.65–1.10) 0.88 (0.68–1.15) 0.90 (0.70–1.15)</td>
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<tr>
<td></td>
<td>N of cases: 561</td>
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</tbody>
</table>

**Table 4** Hazard ratios (95% CI) of colon, rectal and colorectal cancers by changes in physical activity level between enrollment and follow-up (n = 44,498) in the NOWAC Study

Multivariable 1 = additionally adjusted for intake of red meat, processed meat, dietary calcium, and dietary fibre

Confidence intervals in bold have p-values less than 0.05

- Reduction in insulin resistance and hyperinsulinaemia; improved immune function; changes in free radical generation; and changes in body fat [37, 38]. There could be sex-specific differences in the physiological responses in some of these mechanisms that may place women at a disadvantage, or PA may also interact with other sex-specific factors influencing the responses [28, 29]. The Continuous Update Project on CRC by the WCRF/AICR recently inferred that PA of all types reduces the risk of CRC [9]. However, most of the epidemiological studies that corroborate this relationship have been conducted in men [11]. Results of studies in women have been largely inconsistent and less conclusive [10, 11, 14, 24].

- As the exposure of interest, PA may be an intricate and difficult parameter to measure, especially in population-based studies. Inconsistencies may be associated with variations in PA instruments (assessment methods), the use of different domains of PA ( occupational, household, transport, and recreational) with the frequency, duration, and intensity of PA in the investigation of the relationship. Nevertheless, the same heterogeneity in the assessment of PA in women also exist in the studies of the PA-CRC relationship in men; whereas the findings in men have been more consistent and largely conclusive [11, 13, 14, 24].

- Our findings of no association between PA and the risk of CRC in women may be an accurate reflection of a true lack of association, which is consistent with findings from many previous prospective studies among women [10–22]. From the available prospective studies that included only women or gave sex-specific results, we identified 21 studies [6–8, 10–26, 39]. Thirteen of these studies found no association between PA and risk of CRC [10–22], six observed a statistically significant association [6–8, 23–25], while two reported both [26, 39]. The last two studies further underscore the discrepancies in the findings of PA-CRC relationship in women [26, 39].
HR = 0.82, 95%CI 0.71–0.95, p-trend = 0.013, respectively). The Japan Public Health Center-based Prospective Study also found no relationship between total daily PA and CRC in women (HR = 0.82, 95%CI 0.56–1.21, p-trend = 0.198 for colon cancer; HR = 1.79, 95%CI 0.99–3.23, p-trend = 0.077 for rectal cancer) [20]. Corresponding analyses in the participating men from that study were statistically significant for colon cancer (HR = 0.58, 95%CI 0.48–0.79, p-trend < 0.001), but not for rectal cancer (HR = 0.88, 95%CI 0.57–1.36, p-trend = 0.464). The Framingham Study used the summary PA index of daily activity, which also relates to total daily PA. The authors observed no association between total daily PA and large bowel cancer (p-trend 0.89) among women, but they did report an association among men (p-trend 0.06) [18]. Likewise, the Breast Cancer Detection Demonstration Project (BCDDP), which used a PA instrument similar to that of Framingham Study, observed no association between total PA and the risk of colon cancer (HR = 1.15, 95%CI 0.76–1.75, p-trend = 0.77) [10].

The other nine prospective studies, which found no association between PA and CRC in women used various PA instruments and assessed different domains of PA. These ranged from recreational and non-recreational, with HR = 1.60, 95%CI 0.70–3.50 (inactivity-CRC relation) [17]; recreational and occupational, with HR = 0.86, 95%CI 0.77–1.03 [12]; recreational only, with HR = 0.77, 95%CI 0.43–1.38, p-trend = 0.27 [14], HR = 0.90, 95%CI 0.56–1.46, p-trend = 0.68 [15], HR = 0.89, 95%CI 0.50–1.60 [16], HR = 0.95, 95%CI 0.68–1.39, p-trend = 0.75 [22]; non-recreational only, with HR = 0.94, 95%CI 0.40–2.21 [21], amount of time spent walking, with HR = 1.02, 95%CI 0.60–1.75, p-trend = 0.91 [19]; to metabolic equivalent (MET) hours per day, with HR = 1.16, 95%CI 0.76–1.77, p-trend = 0.569 [13]. However, some of these studies observed statistically significant associations among men from the same studies [13, 14, 16, 19].

On the other hand, six prospective studies reported a significant association between PA and colon cancer or CRC [6–8, 23–25]. The Nurses’ Health Study found significant inverse association between recreational PA and incidence of colon cancer in women (HR = 0.54, 95%CI 0.33–0.90, p-trend = 0.03) consistent with results found in men [6]. The Nord-Trøndelag Health Study conducted in Norway also found a significant association among women who reported high recreational PA versus no PA (HR = 0.77, 95%CI 0.53–0.98, p-trend = 0.03). No linear association was found for rectal cancer risk (p-trend = 0.74) [7]. Another population-based cohort study in women in Norway found recreational PA to be associated with decreased risk of colon cancer (HR = 0.62, 95% CI 0.40–0.97, p-trend = 0.25) [8]. However, the California Teachers Study found that lifetime recreational PA reduces colon cancer risk among postmenopausal women who had never taken hormone therapy (HR = 0.51, 95% CI 0.31–0.85, p-trend = 0.02), but not in postmenopausal women with history of hormone therapy use (HR = 0.98, 95% CI 0.66–1.44 p-trend = 0.49) [23]. One thing is conspicuously common to these studies: they all utilized the single domains of either recreational [6–8, 23] or occupational [8, 24, 25] PA. This may have effectively excluded the household (domestic or family care) PA domain, which is mostly important for the female population [27]. This could partly account for the gender bias in the appraisal of PA in epidemiological studies [40]. On the other hand, it may be relatively easy to remember and thus simpler to appraise recreational and occupational PA compared to total PA.

According to our findings, those who increased their PA from baseline to follow-up had a lower risk of colon cancer, thus this lower risk may very well be a marker of a generally healthy lifestyle. However, we found no association between those who were consistently active and the risk of colon cancer. This further portrays that both short and consistent PA over a period of time may not confer protection against colon cancer in women. The association between long-term PA and a reduced risk of colon cancer (consistently active vs consistently inactive) is more often seen in men [39, 41], and even then it is inconsistent [42]. Intriguingly, women who were consistently active were at an increased risk of rectal cancer when compared to those who were consistently moderately active. This result must be interpreted with caution as it could be a spurious finding, which is probably due to another associated factor. This is because the finding on its own has no plausible physio-biological explanations.

The present study has some limitations. Our PA measurement may not have been sensitive enough to detect perhaps small effect of PA on CRC among women. The PA level in our study was self-reported through questionnaires and thus is inevitably susceptible to measurement error [43]. Unfortunately, in large population-based studies, one may not be able to use more accurate PA assessment methods, such as the accelerometer and gyroscope. Furthermore, although the PA assessment used in our study gave a total PA score, this score lacks quantification and distinguishability of the domains involved, the frequencies, durations, and intensities of the PA [32]. The ordinal scale measures self-perceived PA, which is subjected to individual frame of reference, which may differ widely [28]. Thus, one should be cautious of this limitation while interpreting the results. Notwithstanding, the PA instrument we used has been validated, and the results show that the scale is sufficient to differentiate between levels of the total amount of PA. The Spearman correlation coefficient was found
to be moderate at 0.36–0.46 with *p*-value less than 0.001 [32]. This compares well with the International Physical Activity Questionnaire, which reported criterion validity by Spearman correlation of a median of 0.30 in a validation study across 12 countries [44]. The covariates in our study were also self-reported and are therefore prone to the errors inherent to self-reporting. Indeed, self-reporting leads to a tendency for people to overstate desirable behaviours, such as PA, dietary habits, and alcohol consumption habits, thereby introducing some level of misclassification error [45]. We used only one measure of the dietary intakes, taken at enrollment. These intakes likely change over time and may be invalid over the length of the study period [46]; thus, residual confounding cannot be excluded. Nevertheless, the information in the NOWAC Study on PA, BMI, dietary habits, and alcohol consumption habits have been validated with satisfactory results [32, 47–49]. The self-reported duration of education has been compared to the relevant national registries and no statistical differences were found [30]. Accordingly, this self-reporting method is judged to be adequate and pragmatic, especially considering the large sample size of the NOWAC Study. Our study lacked information on family history of CRC. Women who have a familial predisposition to developing CRC may be more health conscious than others, which may cause residual confounding. Likewise, we lacked information on use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) by our participants. Regular use of aspirin and other NSAIDs are suggestive of protection against colon adenoma and cancer [50]. This may also be a source of confounding.

Our study has several strengths. These include the prospective and population-based design, the large sample size, the long follow-up time, information on important confounding factors, and the use of a high-quality national cancer registry to identify cases of CRC [31]. The NOWAC cohort consists of participants who were randomly recruited from the general population and is representative of the Norwegian female population aged 30 to 70 years [32]. The external validity of the NOWAC cohort has been found to be acceptable [30]. We used repeated measurements of PA level, BMI, and smoking status in order to account for changes in these variables over time and to attenuate the risk of measurement error. The availability of data on PA level at two different time points also allowed us to investigate changes in PA levels, which is a vital strength of this study. The self-reported BMI and the food frequency questionnaire in the NOWAC Study have been validated [47–49]. There is a substantial agreement between the self-reported and measured BMI values [49], while 24-h dietary recall studies found the food frequency questionnaire to be reliable [47, 48].

Conclusions

Our data do not support the hypothesis that total physical activity, nor consistent participation in PA over a period of time, is associated with a reduced risk of CRC in women. Thus, women may need to look beyond PA in order to reduce their risk of CRC.

Abbreviations


Acknowledgements

We thank all the participants in the Norwegian Women and Cancer Study for their time and efforts at advancing science. Many thanks to Marko Lukic, Runa Borgund Barnung, and Marisa da Silva for good discussions during the work on this paper. We acknowledge Trudy Perdrix-Thoma of Professional Standards Editing for language review and editing. Some of the data in this article came from the Cancer Registry of Norway, but they are not responsible for the analysis or interpretation of the data presented.

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Availability of data and materials

To access the data supporting the presented findings, kindly contact the person responsible in the NOWAC Study - https://site.uit.no/nowac/contact-information/

Authors’ contributions

SOO carried out the statistical analyses and drafted the manuscript. TB prepared the data, participated in the statistical analyses, and critical revision of the manuscript. IL contributed to the statistical analyses and critical revision of the manuscript. EL is the principal investigator of the NOWAC Study and contributed with critical revision of the manuscript. KBB contributed to the statistical analyses, drafting, and critical revision of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Norwegian Women and Cancer Study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate (P REK NORD 141/2008). All the participants gave written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

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References


Paper II

Oyeyemi SO, Braaten T, Botteri E, Berstad P, Borch KB.


Clinical Epidemiology 2019;11:669-82.

Pubmed: PMID: 31496822
Exploring geographical differences in the incidence of colorectal cancer in the Norwegian Women and Cancer Study: a population-based prospective study

Purpose: Norway has experienced an unexplained, steep increase in colorectal cancer (CRC) incidence in the last half-century, with large differences across its counties. We aimed to determine whether geographical distribution of lifestyle-related CRC risk factors can explain these geographical differences in CRC incidence in Norwegian women.

Methods: We followed a nationally representative cohort of 96,898 women with self-reported information on lifestyle-related CRC risk factors at baseline and at follow-up 6–8 years later in the Norwegian Women and Cancer Study. We categorized Norwegian counties into four county groups according to CRC incidence and used Cox proportional hazard models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for risk factors. We used the Karlson, Holm, and Breen (KHB) method of mediation analysis to investigate the extent to which the risk factors accounted for the observed differences in CRC incidence between counties.

Results: During an average of 15.5 years of follow-up, 1875 CRC cases were diagnosed. Height (HR=1.12; 95% CI 1.08, 1.17 per 5 cm increase); being a former smoker who smoked ≥10 years (HR=1.34; 95% CI 1.15, 1.57); or being a current smoker who has smoked for ≥10 years (HR=1.28; 95% CI 1.12, 1.46) relative to never smokers was associated with increased CRC risk. Duration of education >12 years (HR=0.78; 95% CI 0.69, 0.87) vs ≤12 years, and intake of vegetables and fruits >300 g (HR=0.90; 95% CI 0.80, 0.99) vs ≤300 g per day were associated with reduced CRC risk. However, these risk factors did not account for the differences in CRC risk between geographical areas of low and high CRC incidence. This was further confirmed by the KHB method using baseline and follow-up measurements (b=0.02, 95% CI −0.02, 0.06, p=0.26).

Conclusion: Lifestyle-related CRC risk factors did not explain the geographical variations in CRC incidence among Norwegian women. Possible residual explanations may lie in heritable factors.

Keywords: lifestyle, diet, risk factors, colorectal cancer, women, NOWAC study

Introduction

Colorectal cancer (CRC) is the second most common malignancy in women globally,¹ and the second leading cause of cancer-related death in high-income countries.² Norway has experienced an unexplained, steep increase in the incidence of CRC in both men and women in the last half-century.³,⁴ From 1957–61 to 2012–16, incidence rates among Norwegian women increased from 21 to 54 per 100,000 person-years for colon cancer, and from 9 to 20 per 100,000 person-years for rectal cancer.⁵ The CRC incidence rates among women in Norway are currently among the highest in the world,⁶ having almost tripled from 1957–61 to 2012–16, and surpassing the rates in...
other Nordic countries with apparently similar lifestyles. So far, the reasons for this steep increase have been elusive. Moreover, differences in CRC incidence vary over 10-fold across countries,\(^7\) which may be ascribed to variations in dietary and environmental exposures, coupled with genetic susceptibility.\(^8\) CRC incidence also varies within Norway, with a more than 20 per 100,000 person-years difference between areas of high and low CRC incidence.\(^9,10\) The factors responsible for this geographical heterogeneity are yet to be determined, and knowledge of these factors could be useful to guide screening strategies and health policy.

Therefore, this study aimed to determine whether the geographical distribution of lifestyle-related CRC risk factors can explain the geographical differences in CRC incidence, using the Norwegian Women and Cancer (NOWAC) Study.

**Materials and methods**

The NOWAC Study is a nationwide, representative prospective cohort study which started in 1991.\(^11\) The full detail of the cohort profile has been described previously.\(^11,12\) Summarily, the study consists of over 172,000 women who were recruited over three different time periods: 1991–92, 1996–97, and 2003–04. Potential participants aged 30–70 years were randomly selected from the Norwegian Central Population Register (Statistics Norway) and received a questionnaire by mail that collected information on their lifestyle and health status at enrollment (baseline questionnaire). Similar follow-up questionnaires were sent to the same women about 6–8 years later. All women who agreed to participate completed and returned the questionnaires with written informed consent. The NOWAC Study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.\(^11\)

NOWAC participants who were enrolled in 1991–92, 1996–97, and 2003–04 and completed a food frequency questionnaire (FFQ) in 1998, 1996–97, and 2003–04, respectively, were eligible for inclusion in the present study. Those who were enrolled in 1991–92 completed an FFQ in 1998 because an FFQ was not included in the 1991–92 questionnaire. Thus, we used the 1998 information as baseline for the participants enrolled in 1991–92. This represented 101,321 participants who completed a baseline questionnaire with dietary information between 1996 and 2004. We subsequently excluded women who died or emigrated (n=14) prior to the start of follow-up, and all cases of prevalent cancer except non-melanoma skin cancer (n=4,414). This resulted in a final study sample of 96,893 women. Follow-up information was available for 68,626 (70.8%) of these women.

**Assessment of CRC risk factors**

Information on age, physical activity, height, weight, duration of education, alcohol intake, smoking status and intensity (pack-years), annual household income, hormone replacement therapy use, oral contraceptive use, and dietary habits (daily intake of red meat, processed meat, fish, fruits and vegetables, fiber, calcium, vitamin D, and milk) were taken from the NOWAC questionnaire. Physical activity was reported on a validated 10-point scale, on which 1 was “very low” and 10 was “very high”. This is a global (ie, all-inclusive) physical activity score that has been found valid to rank the physical activity of women in the NOWAC Study.\(^13\) The validated, self-reported height and weight measurements from the questionnaires were used to compute body mass index (BMI).\(^14\) Information on the duration of education and alcohol intake was obtained from the questionnaire, while information on smoking status and smoking intensity (pack-years) were combined into one variable of smoking history. Information on annual household income, hormone replacement therapy use, and oral contraceptive use were also extracted from the NOWAC questionnaire. The FFQ includes foods that are common in Norway and has been validated.\(^15,16\)

The choice of these CRC risk factors was based on the literature, previous similar studies,\(^8,17\) and the availability of information in the NOWAC Study.

**Assessment of county of residence and creation of county groups by CRC incidence**

County of residence at baseline was accessed through linkage to the Norwegian Central Population Register (Statistics Norway). There were 19 counties in Norway at the time of data collection (Figure 1). We used percentiles of CRC incidence rate (Table 1) to categorize the counties into four groups. The intent was to compare the lowest 10% to the highest 10% to discern possible differences in lifestyle-related CRC risk factors. However, we raised the limit of the low-incidence counties to the 15th percentile to allow for more cases of CRC in this group. Thus, we grouped counties from 0 to 15th percentile as low-incidence counties (Oppland, Sør Trøndelag, and Telemark); 15–50th as mid-low-incidence counties (Hedmark, Hordaland, Oslo, More and Romsdal,
Nord-Trøndelag, Vest-Agder, and Buskerud); 50–90th as mid-high-incidence counties (Rogaland, Akershus, Aust-Agder, Vestfold, Østfold, Finnmark, and Troms); and 90–100th as high-incidence counties (Nordland, Sogn and Fjordane).

We also conducted sensitivity analyses in which, we grouped participants by region of residence (Oslo, East, South, West, Middle, and North)\(^\text{18}\) and by rural/urban area of residence. Urban residence was defined as living in a “dense area” with a maximum distance of 50 m between houses, except for public areas or natural barriers, and inhabited by at least 200 persons.\(^\text{19}\)

**CRC incidence, emigration, and death**

Participants diagnosed with primary colon or rectal cancer were ascertained through linkage to the Cancer Registry of Norway. We used the International Statistical Classification of Diseases and Related Health Problems, Tenth Edition (ICD-10), which uses code C18 for colon and C19-20 for rectal cancer.

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\(^\text{18}\) Oeyemi et al. Clinical Epidemiology 2019:11

\(^\text{19}\) Oeyemi et al. Clinical Epidemiology 2019:11

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**Figure 1** Map of Norway showing the 19 counties and regions.
rectal cancer. The county of residence, date of emigration, and date of death were ascertained via linkage to the Norwegian Central Population Register (Statistics Norway).

Analytic variables
We carried out an initial analysis using the baseline data to assess the CRC risk factors for multi-collinearity. This initial analysis included height (continuous, in meters); physical activity (dichotomized into inactive (1–5) and active (6–10)); BMI (<20.0, 20.0–24.9, 25.0–29.9, and ≥30.0 kg/m²); duration of education (≤12 and >12 years); alcohol intake (0, ≤3.0, >3.0–10.0, and >10.0 g/day); smoking history (never, former smoker of <10 years, former smoker of ≥10 years, current smoker of <10 years, current smoker of ≥10 years); annual household income in Norwegian kroner (NOK) (low: <300,000 NOK, medium: 300–600,000 NOK, and high: >600,000 NOK); hormone replacement therapy use (never/ever); and oral contraceptive use (never/ever). All the dietary variables were dichotomized along their median values: red meat intake (0, ≤15, >15 g/day); processed meat intake (0, ≤70, >70 g/day); fish intake (0–90, >90 g/day); fruit and vegetable intake (0–300, >300 g/day); fiber (0–21, >21 g/day); calcium intake from food (0–700, >700 mg/day); vitamin D intake (0–6, >6 µg/day); and milk intake (0, ≤170, >170 g/day). Where possible, we used the median values (50th percentile) to split the variables into categories, as the median values are more robust and undistorted by outliers.20

Statistical methods
We present descriptive statistics at baseline as mean values (± standard errors, SEs) or percentages. We used Cox proportional hazard regression models with age as the time scale to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between the county groups (low-, mid-low-, mid-high-, and high-incidence counties), risk factors, and CRC incidence. Follow-up time was defined as the period in years between age at baseline and age at diagnosis of incident cancer, death, emigration, or age at the end of follow-up (31 December 2016), whichever came first.

We assessed predefined possible interaction effects between physical activity versus BMI, smoking history, alcohol intake, and dietary factors, respectively. We also checked for interaction effects between duration of education and BMI, smoking history, alcohol intake, and dietary

<table>
<thead>
<tr>
<th>Counties</th>
<th>Sample population per county</th>
<th>Number of CRC cases</th>
<th>Incidence proportion of CRC (%)</th>
<th>Crude incidence rate per 100,000</th>
<th>Average follow-up time in years</th>
<th>Person-years at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Østfold</td>
<td>4836</td>
<td>106</td>
<td>2.2</td>
<td>146</td>
<td>15.0</td>
<td>72,563</td>
</tr>
<tr>
<td>Akershus</td>
<td>9661</td>
<td>177</td>
<td>1.8</td>
<td>121</td>
<td>15.1</td>
<td>146,259</td>
</tr>
<tr>
<td>Oslo</td>
<td>8439</td>
<td>142</td>
<td>1.7</td>
<td>111</td>
<td>15.1</td>
<td>127,573</td>
</tr>
<tr>
<td>Hedmark</td>
<td>3808</td>
<td>62</td>
<td>1.6</td>
<td>108</td>
<td>15.2</td>
<td>57,671</td>
</tr>
<tr>
<td>Oppland 4</td>
<td>3544</td>
<td>47</td>
<td>1.3</td>
<td>88</td>
<td>15.0</td>
<td>53,315</td>
</tr>
<tr>
<td>Buskerud</td>
<td>4496</td>
<td>78</td>
<td>1.7</td>
<td>115</td>
<td>15.1</td>
<td>67,970</td>
</tr>
<tr>
<td>Vestfold</td>
<td>4267</td>
<td>81</td>
<td>1.9</td>
<td>125</td>
<td>15.2</td>
<td>64,808</td>
</tr>
<tr>
<td>Telemark</td>
<td>3137</td>
<td>45</td>
<td>1.4</td>
<td>96</td>
<td>15.0</td>
<td>46,975</td>
</tr>
<tr>
<td>Aust-Agder</td>
<td>1827</td>
<td>34</td>
<td>1.9</td>
<td>123</td>
<td>15.1</td>
<td>27,640</td>
</tr>
<tr>
<td>Vest-Agder</td>
<td>2715</td>
<td>47</td>
<td>1.7</td>
<td>114</td>
<td>15.1</td>
<td>41,088</td>
</tr>
<tr>
<td>Rogaland</td>
<td>6503</td>
<td>117</td>
<td>1.8</td>
<td>119</td>
<td>15.2</td>
<td>98,500</td>
</tr>
<tr>
<td>Hordaland</td>
<td>7736</td>
<td>130</td>
<td>1.7</td>
<td>110</td>
<td>15.2</td>
<td>117,863</td>
</tr>
<tr>
<td>Sogn og Fjordane 4</td>
<td>1889</td>
<td>49</td>
<td>2.6</td>
<td>171</td>
<td>15.2</td>
<td>28,655</td>
</tr>
<tr>
<td>Møre og Romsdal</td>
<td>4653</td>
<td>80</td>
<td>1.7</td>
<td>112</td>
<td>15.3</td>
<td>71,354</td>
</tr>
<tr>
<td>Sør-Trøndelag</td>
<td>4882</td>
<td>67</td>
<td>1.4</td>
<td>114</td>
<td>15.1</td>
<td>73,835</td>
</tr>
<tr>
<td>Nord-Trøndelag</td>
<td>2607</td>
<td>45</td>
<td>1.7</td>
<td>114</td>
<td>15.2</td>
<td>39,530</td>
</tr>
<tr>
<td>Nordland</td>
<td>11,443</td>
<td>322</td>
<td>2.8</td>
<td>169</td>
<td>16.7</td>
<td>190,621</td>
</tr>
<tr>
<td>Troms</td>
<td>7264</td>
<td>176</td>
<td>2.4</td>
<td>146</td>
<td>16.6</td>
<td>120,723</td>
</tr>
<tr>
<td>Finnmark</td>
<td>3186</td>
<td>70</td>
<td>2.2</td>
<td>132</td>
<td>16.7</td>
<td>53,171</td>
</tr>
<tr>
<td>Total</td>
<td>96,893</td>
<td>1,875</td>
<td>1.9</td>
<td>125</td>
<td>15.5</td>
<td>1,500,112</td>
</tr>
</tbody>
</table>

Notes: aCounty with lowest CRC incidence. bCounty with highest CRC incidence.
Abbreviation: CRC, colorectal cancer.
Mediation analysis using Karlson, Holm, and Breen (KHB) method of decomposition

We used the KHB method of mediation analysis to investigate the extent to which the CRC risk factors (mediating variables) account for the observed difference in CRC incidence between individual counties. The KHB method provides decomposition of the total effects of counties on CRC incidence into direct and indirect effects. The basic outputs from the KHB method include three models: the reduced model, the full model, and the difference (model). The reduced model describes the estimated effect of the counties with no mediating variables in the model (total effect). The full model describes the estimated effect of counties with all mediating variables in the model (direct effect). The difference between these two models represents the indirect effect. The indirect effect is interpreted as the mediation effect. The KHB method assumes a normal distribution of the indirect effect, and this assumption has been shown to be legitimate in large samples such as the NOWAC Study. We fitted the KHB models using the data collected at baseline and then used the multiply imputed data.

Multiple imputation and repeated measurements analyses

Multiple imputation using chained equations was used to handle missing data, under the assumption that this data was missing at random. The missing values were replaced by multiply imputed values from 20 duplicate datasets. We created 20 duplicates datasets from the imputation simulation to reduce sampling variability. We included all the CRC risk factors used in the analyses and the Nelson–Aalen cumulative hazard estimator as predictors in the imputation model. We used Rubin’s rules to combine the estimates from the 20 imputed datasets to estimate HRs and corresponding 95% CIs. The KHB method also computes the total, direct, and indirect effects for each imputed dataset and combines the estimates using Rubin’s rules.

We used baseline information up to the point when follow-up information was available on physical activity, BMI, alcohol intake, smoking history, hormone replacement therapy use, and all dietary intakes. We then used the follow-up information until death, emigration, or the end of the study, whichever occurred first.

All the analyses and multiple imputations were done in Stata version 15.0 (StataCorp, College Station, TX, USA). Figure 1 is produced using GraphPad Prism 8 (GraphPad Software, San Diego, CA). All statistical analyses were two-sided, and p-values were considered statistically significant at a level of <0.05.

Results

During an average of 15.5 years of follow-up and 1.5 million person-years, 1875 CRC cases (1276 [68%] colon cancers and 599 [32%] rectal cancers) were diagnosed in the study sample. The counties of lowest and highest crude incidence rates were Oppland, and Sogn and Fjordane, respectively (Table 1).

The median age at baseline was 51 years, while the median age at diagnosis of CRC was 66 years (range 43–89). When looking at county groups, low-incidence counties had a higher proportion of physically active women compared to high-incidence counties (46% vs 41%) at baseline. Similarly, the low-incidence counties had a higher proportion of women with a longer duration of education (38% vs 25%), never smokers (38% vs 34%), high annual household income (12% vs 5%), hormone replacement therapy use (34% vs 30%), and oral contraceptive use (53% vs 43%), compared to high-incidence counties. Conversely, high-incidence counties had higher proportion of women with overweight (33% vs 31%), obese (10% vs 9.6%), ever smokers (64% vs 60%), and low annual household income (48% vs 36%), compared to low-incidence counties (Table 2).

The variables with the highest proportion of missing values at baseline were physical activity (9.5%), annual household income (7.3%), and duration of education (5.8%). At follow-up, 38% of the women had missing values on physical activity, and approximately 30% had missing information on BMI, alcohol intake, smoking history, hormone replacement therapy use, and dietary intakes. There was no substantial change in the
Table 2: Selected participant characteristics by county group at study enrollment (baseline) in the Norwegian Women and Cancer Study

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>11,563</td>
<td>34,454</td>
<td>37,544</td>
<td>13,332</td>
</tr>
<tr>
<td>Colorectal cancer, n (% in the area)</td>
<td>159 (1.4)</td>
<td>584 (1.7)</td>
<td>761 (2.0)</td>
<td>371 (2.8)</td>
</tr>
<tr>
<td>Crude incidence rate per 100,000</td>
<td>91</td>
<td>112</td>
<td>130</td>
<td>169</td>
</tr>
<tr>
<td>Mean age at baseline in years</td>
<td>51.6</td>
<td>51.6</td>
<td>52.1</td>
<td>53.7</td>
</tr>
<tr>
<td>Physical activity (% active, 6–10)</td>
<td>46</td>
<td>46</td>
<td>44</td>
<td>41</td>
</tr>
<tr>
<td>Mean height in cm (SE)</td>
<td>166 (0.05)</td>
<td>167 (0.03)</td>
<td>166 (0.03)</td>
<td>165 (0.05)</td>
</tr>
<tr>
<td>Mean body mass index (SE)</td>
<td>24.9 (0.04)</td>
<td>24.6 (0.02)</td>
<td>24.8 (0.02)</td>
<td>25.1 (0.03)</td>
</tr>
<tr>
<td>Mean duration of education in years</td>
<td>12.2 (0.03)</td>
<td>12.5 (0.02)</td>
<td>12.0 (0.02)</td>
<td>10.9 (0.03)</td>
</tr>
<tr>
<td>Mean alcohol intake in g/day (SE)</td>
<td>3.5 (0.04)</td>
<td>3.9 (0.03)</td>
<td>3.6 (0.02)</td>
<td>2.6 (0.03)</td>
</tr>
<tr>
<td>Smoking history, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Never</td>
<td>38</td>
<td>38</td>
<td>37</td>
<td>34</td>
</tr>
<tr>
<td>• Former</td>
<td>31</td>
<td>32</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>• Current</td>
<td>29</td>
<td>28</td>
<td>30</td>
<td>32</td>
</tr>
<tr>
<td>• (% of ever smokers)</td>
<td>(60)</td>
<td>(60)</td>
<td>(62)</td>
<td>(64)</td>
</tr>
<tr>
<td>Annual household income, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Low (&lt;300,000 NOK)</td>
<td>36</td>
<td>33</td>
<td>35</td>
<td>48</td>
</tr>
<tr>
<td>• Medium (300,000–600,000 NOK)</td>
<td>45</td>
<td>45</td>
<td>443.6</td>
<td>38</td>
</tr>
<tr>
<td>• High (&gt;600,000 NOK)</td>
<td>12</td>
<td>15</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Hormone therapy use (% of ever users)</td>
<td>34</td>
<td>35</td>
<td>33</td>
<td>30</td>
</tr>
<tr>
<td>Oral contraceptive use (% of ever users)</td>
<td>53</td>
<td>55</td>
<td>52</td>
<td>43</td>
</tr>
<tr>
<td>Dietary factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean red meat intake in g/day (SE)</td>
<td>14.3 (0.10)</td>
<td>14.8 (0.06)</td>
<td>15.4 (0.06)</td>
<td>15.0 (0.10)</td>
</tr>
<tr>
<td>Mean processed meat in g/day (SE)</td>
<td>68.9 (0.38)</td>
<td>69.1 (0.23)</td>
<td>68.6 (0.21)</td>
<td>60.8 (0.33)</td>
</tr>
<tr>
<td>Mean fish intake in g/day (SE)</td>
<td>87.2 (0.50)</td>
<td>92.4 (0.30)</td>
<td>96.9 (0.31)</td>
<td>121.0 (0.60)</td>
</tr>
<tr>
<td>Fruit and vegetables intake in g/day (SE)</td>
<td>337 (1.9)</td>
<td>349 (1.11)</td>
<td>333 (1.0)</td>
<td>292 (1.6)</td>
</tr>
<tr>
<td>Mean fiber intake in g/day (SE)</td>
<td>21.2 (0.08)</td>
<td>21.5 (0.04)</td>
<td>20.9 (0.04)</td>
<td>20.6 (0.06)</td>
</tr>
<tr>
<td>Calcium intake in mg/day (SE)</td>
<td>745 (3.4)</td>
<td>740 (1.6)</td>
<td>744 (1.7)</td>
<td>730 (2.7)</td>
</tr>
<tr>
<td>Vitamin D in μg/day (SE)</td>
<td>8.56 (0.08)</td>
<td>8.65 (0.04)</td>
<td>9.10 (0.04)</td>
<td>9.36 (0.07)</td>
</tr>
</tbody>
</table>

Abbreviation: SE, standard error.
characteristic features of the study sample between the imputed and the complete-case dataset (Table S1).

The multivariable-adjusted model of repeated measurements showed that the high-incidence county group had an HR of 1.37 (95% CI 1.13–1.66) relative to the low-incidence county group (Figure 2), which was similar to the unadjusted estimate (Table S2). Height (HR=1.12; 95% CI 1.08, 1.17 per 5 cm increase), being a former smoker who smoked ≥10 years (HR=1.34; 95% CI 1.15, 1.57), or a current smoker who had been smoking ≥10 years (HR=1.28; 95% CI 1.12, 1.46), compared to never smokers, were significantly associated with a higher CRC risk. Duration of education >12 years (HR=0.78; 95% CI 0.69, 0.87) compared to ≤12 years, and daily fruit and vegetable intake >300 g (HR=0.90; 95% CI 0.80, 0.99) compared to ≤300 g, were associated with decreased CRC risk (Figure 2).

Figure 2 Multivariable hazard ratios (HRs) and 95% confidence intervals (CIs) of factors associated with colorectal cancer (CRC) incidence at baseline and follow-up with chained multiple imputations, in the Norwegian Women and Cancer study.
No substantial difference was seen after excluding those who were diagnosed with CRC during the first 2 years of follow-up (data not shown). Sensitivity analyses by region showed no differences in the HR estimates for CRC risk factors, nor were any statistically significant differences seen in the HR estimates for the regions before and after multivariable adjustment. This was also the case in sensitivity analyses that used rural/urban area of residence (Table S2).

The KHB analysis showed the extent to which the mediating variables (CRC risk factors) account for the difference in CRC incidence between the low-incidence county group (reference) and that of other county groups. At baseline, the log odds of having CRC in the high-incidence county group were 0.41 higher than those in the low-incidence county group (Table 3). After adjusting for mediators, the effect of living in the high-incidence county group reduced to 0.39, leaving an indirect effect of 0.02 ($b=0.02$; 95% CI $-0.02$, 0.06, $p=0.26$). This shows that the differences in CRC incidence between the low- and high-incidence county groups are not significantly mediated by the combined effects of the investigated CRC risk factors (Table 3). The mediation analysis results in the imputed dataset were similar to the baseline results. We conducted a sensitivity analysis using the 19 counties individually (without grouping), which also showed that the combined effects of the risk factors did not significantly mediate the variations in CRC incidence across counties (data not shown).

**Discussion**

In this large cohort of Norwegian women, we found that county-level differences in CRC incidence were not explained by differences in lifestyle-related CRC risk factors. This was demonstrated by two different approaches: Cox proportional hazards models and the relatively new KHB method of decomposition.

The lifestyle-related CRC risk factors significantly associated with CRC incidence in our cohort of women included height, smoking history, duration of education, and fruit and vegetable intake. Our results showed that these factors, together with other CRC risk factors, did not significantly explain the differences in the CRC incidence between the counties. CRC risk in county groups remained statistically the same before and after adjusting for risk factors. These results remained consistent when using baseline data, as well as when using repeated measurements with multiple imputation. Our findings suggest that there are other important or unmeasured risk factors that are responsible for the differences in CRC incidence between Norwegian counties.

Previous international studies have rationalized that variations in CRC incidence in different areas of a country are due to different, but overlapping, contributory factors, such as geographic, cultural, and economic differences. Our study, however, suggests that these variations are not significantly explained by lifestyle-related factors alone. This highlights the need for further research to identify other underlying factors that contribute to the differences in CRC incidence across counties.

### Table 3

Decomposition of total effects of county groups into direct and indirect effects using the Karlson, Holm, and Breen method at baseline and follow-up in the Norwegian Women and Cancer Study

<table>
<thead>
<tr>
<th>County groups</th>
<th>Baseline data Coefficient (95% CI)</th>
<th>p-value</th>
<th>Imputed data Coefficient (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low incidence</td>
<td>(base outcome)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mid-low incidence</td>
<td>Reduced model</td>
<td>0.252 (0.040, 0.463)</td>
<td>0.020</td>
<td>0.198 (0.021, 0.375)</td>
</tr>
<tr>
<td></td>
<td>Full model</td>
<td>0.253 (0.041, 0.465)</td>
<td>0.019</td>
<td>0.205 (0.028, 0.383)</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>−0.001 (−0.018, 0.016)</td>
<td>0.880</td>
<td>−0.007 (−0.022, 0.007)</td>
</tr>
<tr>
<td>Mid-high incidence</td>
<td>Reduced model</td>
<td>0.317 (0.109, 0.526)</td>
<td>0.003</td>
<td>0.268 (0.095, 0.442)</td>
</tr>
<tr>
<td></td>
<td>Full model</td>
<td>0.321 (0.113, 0.530)</td>
<td>0.003</td>
<td>0.277 (0.103, 0.451)</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>−0.004 (−0.024, 0.016)</td>
<td>0.690</td>
<td>−0.009 (−0.026, 0.008)</td>
</tr>
<tr>
<td>High incidence</td>
<td>Reduced model</td>
<td>0.409 (0.175, 0.642)</td>
<td>0.001</td>
<td>0.342 (0.150, 0.535)</td>
</tr>
<tr>
<td></td>
<td>Full model</td>
<td>0.388 (0.152, 0.624)</td>
<td>0.001</td>
<td>0.323 (0.129, 0.518)</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>0.021 (−0.016, 0.057)</td>
<td>0.263</td>
<td>0.019 (−0.013, 0.048)</td>
</tr>
</tbody>
</table>

**Abbreviation:** CI, confidence interval.
as rural–urban disparities, socioeconomic status (SES), ease of access to health care, public health campaigns, unique social and lifestyle risk factors, differences in exposure to risk factors, such as in dietary customs and ethnic variations in food preparation, and different exposures to unknown risk factors. Some studies have indicated that rural–urban disparities confer an increased risk of CRC in rural areas, and suggested that the relationship may be mediated through screening behavior. Other studies have reported that the increased risk may simply reflect the socioeconomic differences between rural and urban communities. Other studies found a higher risk of CRC in urban areas. These findings differ by country and time period of assessment, and differences in the definition of rural/urban areas may mask the relationship between this variable and CRC risk. There is currently no national CRC screening program in Norway, which could expound on some of the geographical differences in the present population.

Education and household income are often used as proxy indicators of SES. We found a significant inverse association between duration of education and CRC risk, while we found no such association with annual household income. Results of previous similar studies regarding SES have been inconsistent. A recent review showed that, in the United States and Canada, low SES groups have a higher CRC incidence than high SES groups (RR from 1.0 to 1.5), while these findings were mostly reversed (RR from 0.3 to 0.9) in Europe. Nonetheless, education, and not necessarily income, may be a better predictor of a healthy lifestyle.

Cigarette smoking has been associated with increased incidence of CRC, and our data further suggest that the risk remains even among former smokers. A meta-analysis of 106 observational studies concluded that smokers have an increased risk of developing CRC compared to never smokers (RR 1.18, 95% CI 1.11–1.25). Height was also associated with increased CRC risk in our study sample. This finding is in agreement with two recent systematic reviews of prospective studies, which posited a potential causal association of adult attained height with the risk of CRC. Our study found a significant inverse association between fruit and vegetable intake and CRC risk, which is in concurrence with the findings in the European Prospective Investigation into Cancer and Nutrition (EPIC) study.

In our study, participants in the low-incidence county group were more physically active, had a longer duration of education, were more often never smokers, and had a higher fruit and vegetable intake. These are markers of a generally healthy lifestyle, and the reduced CRC risk observed in this county group may be a reflection of this lifestyle. Notwithstanding, these factors failed to account for the risk differences between low- and high-incidence county groups.

Occurrence of exposure to established risk factors for cancer has been reported to vary geographically within some countries. For instance, the prevalence of obesity varies within Finland, while the use of hormone replacement therapy is more likely in women living in urban areas of Denmark. Therefore, it is plausible that the risk of CRC could vary in different counties or areas due to different prevalences of exposure to established CRC risk factors. However, since these established risk factors did not account for the observed risk differences in CRC between the counties in the present study, considerable uncertainty remains about what is responsible for these differences. This may be a partial reflection of the incomplete understanding of the carcinogenesis of CRC, although the unexplained risk differences could also come from unmeasured risk factors. A large Scandinavian study, which combined cohorts of twins from Sweden, Denmark, and Finland, demonstrated that genetically inheritable factors account for 35% of the CRC cases, while non-shared environmental factors account for 60%, and shared environmental factors the remaining 5%. Thus, a possible explanation for our observed differences in risk between high- and low-incidence county groups probably lies more in genetically inherited factors. The well-described CRC-related inheritable syndromes (such as hereditary nonpolyposis colon cancer (HNPCC) and familial adenomatous polyposis (FAP)), where inheritance is highly penetrant, only account for about 3–5% of the inherited cases of CRC.

The main limitations of this study are the unmeasured established CRC risk factors. This includes family history of CRC and its precursors (such as adenomatous polyps), as genetically inherited factors can increase the likelihood of CRC oncogenesis. Our study lacks information on the use of aspirin and other non-steroidal anti-inflammatory drugs, the regular use of which has been associated with reduced CRC risk. The lack of information on these factors may have confounded our study. The county of residency used in this study was captured only at baseline; thus, some of the participants could have changed their county of residence in the course of the study. However, most women at the age of our cohort would have settled down at a county
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on a long-term basis. We lack the power to explore the CRC risk in each county or in each county group separately. Most variables in our study are self-reported and therefore are saddled with the errors inherent with self-reported measurements. However, most of these variables, such as physical activity, duration of education, BMI, alcohol intake, and dietary habits, have been validated with good results.12–16

The strengths of our study include the prospective and population-based design, with a large sample size of participants who were randomly recruited and are representative of Norwegian women between 30 and 70 years at recruitment,12 information on important risk factors, and the high quality of the national cancer registry with almost 100% completeness.49 The NOWAC Study has been shown to have almost the same observed cumulative incidence rates for all cancer sites as that of the national figures.11,12 We used repeated measurements of variables to account for changes in these variables over time in order to lower the risk of measurement error. We used chained multiple imputation to deal with missing data, and thus maximize the number of participants, and by extension, the number of CRC cases included in the analyses.

Conclusion
The lifestyle-related CRC risk factors that we investigated did not account for the risk differences between the areas of low and high incidence of CRC. A possible explanation lies in inheritable factors. Thus, the family history of CRC cases may be especially important in determining the appropriate preventive screening strategy in areas of high incidence.

Abbreviations
CRC, colorectal cancer; NOWAC, Norwegian Women and Cancer Study; FFQ, Food frequency questionnaire; BMI, body mass index; NOK, Norwegian kroner; KHB method, Karlson, Holm, and Breen method.

Ethical approval and informed consent
The Norwegian Women and Cancer Study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate (P REK NORD 141/2008). All participants gave written informed consent.

Data availability
To access the data supporting the findings presented, kindly contact the person in charge of the NOWAC Study - https://site.uit.no/nowac/contact-information/.

Acknowledgments
We thank the staff and participants in the Norwegian Women and Cancer Study for the time and effort they put forth to advancing medical science. Many thanks to Rolf Wynn, Dolley Charles, Runa Borgund Barmung, and Jan Håkon Rudolfesen for their constructive critiques during the work on this study. The publication of this manuscript was funded by the publication fund of UiT-The Arctic University of Norway. The funder had no role in the study design, data analysis, preparation of the manuscript, and decision to publish.

Author contributions
SOO and KBB conceived the study idea. All authors contributed to the data analysis. SOO organised the writing and wrote the initial draft. All authors contributed toward drafting and critically revising the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Disclosure
The authors report no conflicts of interest in this work.

References


## Supplementary materials

### Table S1 Comparison of the complete-case and imputed dataset, the Norwegian Women and Cancer study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Missing n (%)</th>
<th>Complete-case mean (SD), or %</th>
<th>Multiply imputed mean (SD), or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>County of residence</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Low incidence (%)</td>
<td>0 (0)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Mid-low incidence (%)</td>
<td></td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Mid-high incidence (%)</td>
<td></td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>High incidence (%)</td>
<td></td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Age at baseline (SD)</td>
<td>0 (0)</td>
<td>52.1 (6.7)</td>
<td>52.1 (6.7)</td>
</tr>
<tr>
<td>Physical activity (SD)</td>
<td>9,214 (9.5)</td>
<td>5.6 (1.8)</td>
<td>5.5 (1.8)</td>
</tr>
<tr>
<td>Height (SD)</td>
<td>561 (0.6)</td>
<td>166.1 (5.7)</td>
<td>166.1 (5.7)</td>
</tr>
<tr>
<td>Body mass index (SD)</td>
<td>2,187 (2.3)</td>
<td>24.8 (4.0)</td>
<td>24.8 (4.0)</td>
</tr>
<tr>
<td>Duration of education (SD)</td>
<td>5,601 (5.8)</td>
<td>12.1 (3.5)</td>
<td>12.0 (3.5)</td>
</tr>
<tr>
<td>Alcohol intake (SD)</td>
<td>1,958 (2.0)</td>
<td>3.6 (4.5)</td>
<td>3.5 (4.5)</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Never (%)</td>
<td>1,869 (1.9)</td>
<td>37</td>
<td>37</td>
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<tr>
<td>Ex (%)</td>
<td></td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Current (%)</td>
<td></td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Pack years (SD)</td>
<td>6 (0.01)</td>
<td>6.3 (8.5)</td>
<td>6.3 (8.5)</td>
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<tr>
<td>Annual household income</td>
<td></td>
<td></td>
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<tr>
<td>Low (%)</td>
<td>7,054 (7.3)</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>Medium (%)</td>
<td></td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>High (%)</td>
<td></td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Hormone replacement therapy use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never (%)</td>
<td>2,793 (2.9)</td>
<td>66</td>
<td>66</td>
</tr>
<tr>
<td>Ever (%)</td>
<td></td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never (%)</td>
<td>3,695 (3.8)</td>
<td>54</td>
<td>53</td>
</tr>
<tr>
<td>Ever (%)</td>
<td></td>
<td>46</td>
<td>47</td>
</tr>
</tbody>
</table>

**Abbreviation:** SD, standard deviation.
Table S2 Hazard ratios (HRs) and 95% confidence intervals (CIs) before and after multivariable risk adjustment at baseline (complete-case analysis) in the Norwegian Women and Cancer study

<table>
<thead>
<tr>
<th>Groupings by</th>
<th>Baseline (complete-case analysis)</th>
<th>Baseline and follow-up (with chained multiple imputation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude (unadjusted)</td>
<td>Multivariable adjusted</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>CRC incidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Mid-low</td>
<td>1.29 (1.04–1.59)</td>
<td>1.29 (1.05–1.59)</td>
</tr>
<tr>
<td>Mid-high</td>
<td>1.37 (1.12–1.69)</td>
<td>1.39 (1.13–1.71)</td>
</tr>
<tr>
<td>High</td>
<td>1.51 (1.20–1.89)</td>
<td>1.52 (1.20–1.92)</td>
</tr>
<tr>
<td>Regions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oslo</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>East</td>
<td>1.03 (0.84–1.26)</td>
<td>1.05 (1.85–1.29)</td>
</tr>
<tr>
<td>South</td>
<td>1.08 (0.79–1.48)</td>
<td>1.10 (0.80–1.51)</td>
</tr>
<tr>
<td>West</td>
<td>1.12 (0.90–1.40)</td>
<td>1.18 (0.94–1.48)</td>
</tr>
<tr>
<td>Middle</td>
<td>0.83 (0.62–1.11)</td>
<td>0.85 (0.64–1.14)</td>
</tr>
<tr>
<td>North</td>
<td>1.04 (0.84–1.28)</td>
<td>1.05 (0.84–1.32)</td>
</tr>
<tr>
<td>Rural–urban area of residence</td>
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<td></td>
</tr>
<tr>
<td>Rural</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Rural</td>
<td>1.04 (0.94–1.16)</td>
<td>1.05 (0.94–1.17)</td>
</tr>
</tbody>
</table>

Notes: aUnadjusted except for age (age was used as the time scale). bAdjusted for age, physical activity, height, body mass index, duration of education, alcohol intake, smoking history, hormone replacement therapy use, oral contraceptive use, annual household income, and dietary factors.
Paper III

Oyeyemi SO, Braaten T, Skeie G, Borch KB.

A competing mortality risks analysis of pre-diagnostic lifestyle and dietary factors in colorectal cancer survival: the Norwegian Women and Cancer Study.

Competing mortality risks analysis of prediagnostic lifestyle and dietary factors in colorectal cancer survival: the Norwegian Women and Cancer Study

Sunday Oluwafemi Oyeyemi, Tonje Braaten, Guri Skeie, Kristin Benjaminsen Borch

ABSTRACT

Background It remains unclear whether or which prediagnostic lifestyle and dietary factors influence colorectal cancer (CRC) survival following diagnosis. This study used competing mortality risks analysis to evaluate the association between these factors and CRC survival.

Methods A total of 96 889 cancer-free participants of the Norwegian Women and Cancer Study completed the study’s baseline questionnaire on lifestyle and dietary factors between 1996 and 2004. Of the 1861 women who subsequently developed CRC, 550 had CRC as the cause of death, while 110 had a non-CRC cause of death. We used multiple imputation to handle missing data. We performed multivariable competing mortality risks analyses to determine the associations between prediagnostic lifestyle and dietary factors and CRC survival. Cause-specific HRs were estimated by Cox regression and subdistribution HRs were estimated by the Fine-Gray regression with corresponding 95% CIs.

Results Following multivariable adjustment, a prediagnostic vitamin D intake of >10 μg/day compared with ≤10 μg/day was associated with better CRC survival (HR=0.75, 95% CI 0.61 to 0.92). Other prediagnostic lifestyle and dietary factors showed no association with CRC survival. The corresponding results obtained from cause-specific Cox and Fine-Gray regressions were similar.

Conclusion Our study shows that prediagnostic vitamin D intake could improve CRC survival.

INTRODUCTION

Colorectal cancer (CRC) is the fourth leading cause of cancer-related death worldwide and the second leading cause in high-income countries. CRC is an important public health concern in that it imposes a considerable medical and economic burden, and temporal and demographic projections predict that this burden will increase by about 60% by 2030.1–4 CRC incidence is increasing globally, and the combination of this high incidence and improved CRC management is giving rise to a relatively large population of CRC survivors, especially in countries such as Norway, where incidence is still on the rise and mortality continues to decrease.

Primarily, CRC is considered both a genetic and lifestyle disease. The relationship between CRC incidence and factors like adult-attained height, physical activity, obesity, socioeconomic status, alcohol consumption, smoking status, and certain dietary factors has been investigated extensively, with some clearly established associations. However, the relationship between CRC survival and these same factors has yet to be expansively researched. This knowledge gap has been attributed to a comparative lack of relevant data.

The primary predictor of CRC survival is the stage of the disease at the time of diagnosis. However, there is still variability in the survival among people with similar stages of CRC and similar access to healthcare, which may be due to variations in lifestyle and dietary habits before and/or after CRC diagnosis. For instance, vitamin D status as much as three decades prior to diagnosis has
been shown to be related to survival among patients with some organ-specific cancers. A recent review of the literature concluded that both prediagnostic and postdiagnostic lifestyle factors, including physical activity, obesity, and dietary habits, may play a critical role in improving CRC survival.

The Norwegian Women and Cancer (NOWAC) Study offers the opportunity to study prediagnostic lifestyle and dietary factors and subsequent CRC survival following diagnosis. This study used competing mortality risks analysis to evaluate the association between these factors and CRC survival.

**METHODS**

The NOWAC Study is a prospective population-based cohort study that was initiated in 1991 and has been described in detail elsewhere. In brief, Norwegian women between the ages of 30 and 70 years were randomly selected from the Norwegian Central Population Register (Statistics Norway) and invited to participate. More than 172 000 women, recruited at different time periods, gave written informed consent and completed a questionnaire that collected information on lifestyle factors, health status, and dietary habits.

**Study sample**

In this study, we included 101 316 eligible participants who completed a baseline questionnaire, which included a food frequency questionnaire (FFQ), between 1996 and 2004. We excluded those who emigrated, died, or had prevalent cancer (n=4427) before the start of study recruitment. Of the 96 889 remaining participants, 13 487 developed cancer during follow-up, of whom 1875 were diagnosed with CRC. Women diagnosed at autopsy (n=8), as well as those with unknown cancer stage (n=3) or an undocumented cause of death (n=3), were excluded, leaving a final analytical sample of 1861 women with a CRC diagnosis (figure 1).

**Ascertainment of cancer diagnosis in the study sample**

The 1861 women included in our study sample had primary incident CRC (International Classification of Diseases, 10th Revision (ICD-10) codes C18–C20) diagnosed between study recruitment and 31 December 2016. CRC diagnosis, dates of diagnosis, and cancer stage were obtained through record linkage to the Cancer Registry of Norway (CRN), which has been acknowledged to be more than 98% complete. The CRN uses the pathological tumour, node, and metastasis staging system, which is considered the most accurate and reliable staging system.

**Assessment of emigration, death, and cause of death**

Information on dates of emigration and death was obtained through record linkage to the Norwegian Population Registry, while information on cause of death was obtained from the Cause of Death Registry. Primary causes of death were then categorised into death due to CRC (ICD-10 codes C18–C20), hereafter referred to as CRC death, and death due to any other causes, hereafter

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**Figure 1** Flowchart of the study sample of colorectal cancer survivors in the Norwegian Women and Cancer Study.
referred to as non-CRC death. Follow-up time was defined as the period in days between the date of CRC diagnosis and the date of emigration, death, or the end of follow-up (31 December 2016), whichever occurred first.

Assessment of prediagnostic lifestyle and dietary factors

The choice of prediagnostic lifestyle and dietary factors considered in this analysis was based on the literature, previous similar studies,6–9 16 and availability in the NOWAC Study database. Information on prediagnostic physical activity, height, weight, duration of education, annual household income, alcohol intake, smoking habits, dietary habits, and self-reported medical conditions was extracted from the NOWAC questionnaire.

Physical activity was reported on a 10-point scale, where 1 was ‘very low’ and 10 was ‘very high’. This is a validated scale,17 which implicitly included recreational, occupational, transportation, and domestic physical activities in a global format. We categorised this into 1–2 (least active), 3–4, 5–6, 7–8, and 9–10 (most active). Height and body weight were self-reported and were used to compute the body mass index (BMI) as the weight in kilogram divided by the square of the height in metre. We categorised BMI into underweight (<20.0 kg/m²), normal weight (20.0–24.9 kg/m²), overweight (25.0–29.9 kg/m²), and obese (≥30.0 kg/m²). We used <20.0 kg/m² as the cut-off point for the underweight category because few women had a BMI of <18.5 kg/m². Duration of education was categorised into low (0–9 years), medium (10–12 years), and high (>12 years). These categories correspond to primary and lower secondary schools, upper secondary school, and higher education, respectively. Annual household income in Norwegian kroner (NOK) was categorised into low (<300 000 NOK), medium (300–600 000 NOK), and high (>600 000 NOK). Alcohol intake was categorised as none, ≤3.0 g/day, >3.0–10.0 g/day, and >10.0 g/day; and smoking status was categorised as never, former, or current.

The validated FFQ in the baseline questionnaire included foods that are common in Norway.18 We used either hypothesis-driven or data-driven percentiles to categorise average daily dietary intake into groups. Hypothesis-driven cut-offs were based on nutritional recommendations and/or knowledge of diet–disease associations; while data-driven cut-offs were based on the 50th or 75th percentile values of the study sample. We combined red meat and processed meat and created two categories of consumption: ≤70 and >70 g/day. The World Cancer Research Fund/American Institute for Cancer Research recommend a red meat intake of not more than 50–70 g/day, and little or no processed meat intake.19 Fish intake was categorised into ≤130 and >130 g/day, fruit and vegetable intake into ≤300 and >300 g/day, and vitamin D intake into ≤10.0 and >10 µg/day, as 10 µg/day is the Nordic nutrition recommendation.20 Participants were categorised as having or not having (yes or no) the prediagnostic comorbidities of diabetes mellitus and cardiovascular disease (CVD). CVD included self-reported medical conditions such as hypertension, angina pectoris, infarction, and stroke.

Statistical methods

Competing mortality risks analysis

CRC survivors are also at risk of dying from causes other than CRC. Indeed, CRC is predominantly a disease of the middle-aged and the elderly, bearing in mind that mortality increases exponentially with age after the age of 35 years, especially in high-income countries.21 Thus, we chose to use competing risks analysis.

We extended the standard Cox proportional hazard model, normally used when there are no competing events, to model cause-specific hazards as proposed by Prentice et al.22 We applied the model to cause-specific hazards of (1) CRC death and (2) non-CRC death, respectively. In each model, we censored the competing event while estimating the effects of lifestyle and dietary factors on the risk of death. This is the method of choice when focusing on epidemiological questions of aetiology (such as factors associated with CRC death), rather than the probability of CRC death, both in the presence of competing risks.23–26

In addition, we used the subdistribution hazard model approach proposed by Fine and Gray.27 This is because of the inherent hypothetical setting of a cause-specific hazard model in which the ‘competing event is removed’ (censored). The estimations from the Fine and Gray approach is in the ‘presence of competing events’, thereby removing the hypothetical setting by modelling hazards on the basis of the cumulative incidence function.23 We used these two statistical methods to gain complete understanding of the effects of lifestyle and dietary factors on competing risk endpoints, as recommended by Latouche et al.28 We used these methods to estimate HRs and subdistribution HRs (SHRs), with 95% CIs for the associations between lifestyle and dietary factors, and CRC death and non-CRC death, respectively. CRC death was the event of interest, while non-CRC death was the competing event.

We used Schoenfeld residuals to check the proportional hazards assumption in the two approaches and with the two competing events, respectively. In order to keep the proportional hazards assumption, we had to run all models stratified by CRC stage. We used the Breslow approximation method to handle tied failures. We adjusted for prediagnostic follow-up duration, which is the period between the date of NOWAC recruitment and CRC diagnosis, in all models. We tested for linear trend by using variables originally in continuous scale as continuous variables in the model. We assessed collinearity between the prediagnostic variables fish intake and vitamin D intake, and predefined interactions between physical activity and BMI, physical activity and vitamin D intake, duration of education and annual household income, and fish intake and vitamin D intake, respectively. The final prediagnostic variables included in all analyses were age at diagnosis of CRC; physical activity;
BMI; duration of education; annual household income; alcohol intake; smoking status; red and processed meat intake, fish intake, and fruit and vegetable intake; and vitamin D intake. We also included diabetes mellitus status and CVD status.

**Multiple imputation**

We used multiple imputation to handle missing data under the assumption that data were missing at random.\(^{29}\) We replaced missing values by computed estimates of 50 replicate datasets from multiple imputations using chained equations. We created 50 replicates to minimise variability\(^ {30}\) and used Rubin’s rules to coalesce the values from the 50 imputed replicates to estimate HRs and SHRs with corresponding 95% CIs.\(^ {31,32}\)

In order to rule out the effects of latent disease conditions, we conducted sensitivity analyses excluding those who died less than 1 year after recruitment and those who died less than 1 year after CRC diagnosis, respectively. We also assessed reverse causation by excluding women who had CRC diagnosis less than 1 year after recruitment. To minimise the impact of changes in lifestyle and dietary habits during follow-up, we conducted further analysis restricted to women who received a CRC diagnosis within 10 years of recruitment. Finally, we ran a sensitivity analysis in which we did not include CRC cases diagnosed after 31 December 2014 to allow for a longer follow-up time.

Analyses were performed using STATA V.15.0 and R V.3.5.3 (R Foundation for Statistical Computing 2019). All statistical analyses were two-sided, and p values were considered statistically significant at a level of <0.05.

**RESULTS**

Of the 1861 women with CRC in our study sample, 65% (1201/1861) were alive, and 35% (660/1861) had died by the end of follow-up (31 December 2016). Of these deaths, 83% (550/660) were CRC deaths and 17% (110/660) were non-CRC deaths. The mean age was 67.6 years at CRC death and 75.9 years at non-CRC death. The average duration of follow-up was 5 years. This was lower among CRC deaths (2.1 years) compared with non-CRC deaths (5.3 years) (table 1). Other cancer types (41.8%) and CVD (30.0%) were the most common causes of non-CRC death.

Most CRC survivors (92%, 1107/1201) who were alive at the end of follow-up had been diagnosed with early-stage CRC (localised or regional spread), whereas more than half (60%, 330/550) of CRC deaths had been diagnosed with advanced-stage CRC (remote metastases). Non-CRC death (88%, 97/110) was more common in those who were diagnosed with early-stage CRC (localised or regional spread). Few CRC survivors reported comorbidities at recruitment, with less than 3% (48/1861) having diabetes mellitus and less than 20% (358/1861) having CVD (table 1).

The prediagnostic variables with the highest proportion of missing values were physical activity (13.4%), annual household income (9.1%), alcohol intake (7.7%), and duration of education (7.5%) (online supplementary table 1). After multiple imputation, there was no substantial change in the characteristic features of the study sample between the complete-case and the imputed datasets (online supplementary table 2).

**Competing risks mortality analyses**

We present the multivariable competing risk regressions of the imputed datasets in table 2, with the estimated HRs, SHRs, and the corresponding 95% CIs. We observed a 5% increase in the cause-specific hazard of CRC death (HR=1.05, 95% CI 1.03 to 1.06) for each 1-year increase in age at diagnosis; the corresponding increase for non-CRC death was 12% (HR=1.12, 95% CI 1.08 to 1.16). Similarly, each 1-year increase in age at diagnosis raised the cumulative incidence of CRC death by 4% (SHR=1.04, 95% CI 1.03 to 1.06) and that of non-CRC death by 9% (SHR=1.09, 95% CI 1.06 to 1.13) (table 2).

Participants with a prediagnostic physical activity level of 1–2 (compared with 5–6) had a small and non-significant lower cause-specific hazard of CRC death (HR=0.95, 95% CI 0.62 to 1.44), whereas the corresponding cause-specific hazard of non-CRC death was more than 100% higher (HR=2.14, 95% CI 1.05 to 4.37). The cause-specific HRs for the two competing events went in opposite directions. This same phenomenon was also demonstrated by prediagnostic CVD (table 2). Similar results were observed in corresponding cumulative incidence estimates. Prediagnostic current smoking was important only in non-CRC deaths (HR=1.98, 95% CI 1.21 to 3.23).

Our results revealed that participants with a prediagnostic vitamin D intake of ≥10 µg/day, compared with those with an intake of ≤10.0 µg/day, had a 25% lower cause-specific hazard of CRC death (HR=0.75, 95% CI 0.61 to 0.92, p trend=0.001) and a 23% lower cumulative incidence of CRC death (SHR=0.77, 95% CI 0.62 to 0.96, p trend=0.001). In both cause-specific and cumulative incidence approaches, our data did not show any association between prediagnostic BMI and CRC death. Similarly, no association was observed between other prediagnostic variables, such as duration of education, annual household income, alcohol intake, fish intake, and diabetes mellitus status, and CRC death.

Sensitivity analyses excluding those who died less than 1 year after recruitment and another excluding those who died less than 1 year after diagnosis did not change our findings in either of the competing risks approaches. When women diagnosed with CRC less than 1 year after recruitment were excluded to test for reverse causation, the analysis yielded similar estimates. We also conducted analyses that considered only incident CRC diagnosed before 31 December 2014, in order to allow for more follow-up time. However, for both of the aforementioned analyses, the associations and estimates of other variables remained essentially the same. None of the predefined
Table 1  Prediagnostic demographic, lifestyle, and dietary characteristics of the study sample at recruitment and during follow-up: the Norwegian Women and Cancer Study (N=1861)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Categories or parameters</th>
<th>Numbers (%)</th>
<th>Alive</th>
<th>Died of CRC</th>
<th>Died of other causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cohort, n (%)</td>
<td>1861</td>
<td>1201 (64.5)</td>
<td>550 (29.6)</td>
<td>110 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Mean age at enrolment</td>
<td>Years (SD) (range)</td>
<td>55.8 (7.3) (41–75)</td>
<td>55.0 (6.9) (41–75)</td>
<td>56.6 (7.5) (41–74)</td>
<td>61.2 (7.4) (41–75)</td>
</tr>
<tr>
<td>Mean age at diagnosis</td>
<td>Years (SD) (range)</td>
<td>66.4 (8.7) (43–89)</td>
<td>66.4 (8.3) (43–89)</td>
<td>65.5 (9.4) (43–87)</td>
<td>70.6 (8.6) (43–86)</td>
</tr>
<tr>
<td>Mean age at death</td>
<td>Years (SD) (range)</td>
<td>69.0 (47–89)</td>
<td>67.6 (9.1) (47–88)</td>
<td>75.9 (8.6) (50–86)</td>
<td></td>
</tr>
<tr>
<td>Mean prediagnostic follow-up duration</td>
<td>Years (SD)</td>
<td>10.5 (5.4)</td>
<td>11.3 (5.3)</td>
<td>8.8 (5.2)</td>
<td>9.3 (4.7)</td>
</tr>
<tr>
<td>Mean postdiagnosis survival duration</td>
<td>Years (SD)</td>
<td>5.0 (4.7)</td>
<td>6.4 (5.0)</td>
<td>2.1 (2.3)</td>
<td>5.3 (4.3)</td>
</tr>
<tr>
<td>CRC stage, n (%)</td>
<td>Localised</td>
<td>452 (24.3)</td>
<td>377 (31.4)</td>
<td>32 (5.8)</td>
<td>43 (39.1)</td>
</tr>
<tr>
<td></td>
<td>Regional spread</td>
<td>972 (52.2)</td>
<td>730 (60.8)</td>
<td>188 (34.2)</td>
<td>54 (49.1)</td>
</tr>
<tr>
<td></td>
<td>Remote metastases</td>
<td>437 (23.5)</td>
<td>94 (7.8)</td>
<td>330 (60.0)</td>
<td>13 (11.8)</td>
</tr>
<tr>
<td>Physical activity</td>
<td>1–2 (least active)</td>
<td>83 (5.2)</td>
<td>46 (4.4)</td>
<td>26 (5.4)</td>
<td>11 (12.4)</td>
</tr>
<tr>
<td></td>
<td>3–4</td>
<td>366 (22.7)</td>
<td>236 (22.7)</td>
<td>112 (23.3)</td>
<td>18 (20.2)</td>
</tr>
<tr>
<td></td>
<td>5–6</td>
<td>687 (42.6)</td>
<td>458 (43.9)</td>
<td>198 (41.3)</td>
<td>31 (34.8)</td>
</tr>
<tr>
<td></td>
<td>7–8</td>
<td>385 (23.9)</td>
<td>248 (23.8)</td>
<td>116 (24.2)</td>
<td>21 (23.6)</td>
</tr>
<tr>
<td></td>
<td>9–10 (most active)</td>
<td>90 (5.6)</td>
<td>54 (5.2)</td>
<td>28 (5.8)</td>
<td>8 (9.0)</td>
</tr>
<tr>
<td>Body mass index, n (%)</td>
<td>Underweight (&lt;20.0)</td>
<td>100 (5.5)</td>
<td>52 (4.4)</td>
<td>41 (7.7)</td>
<td>7 (6.6)</td>
</tr>
<tr>
<td></td>
<td>Normal (20.0–24.9)</td>
<td>883 (48.7)</td>
<td>583 (49.6)</td>
<td>253 (47.6)</td>
<td>47 (44.4)</td>
</tr>
<tr>
<td></td>
<td>Overweight (25.0–29.9)</td>
<td>640 (35.3)</td>
<td>417 (35.5)</td>
<td>188 (35.3)</td>
<td>35 (3.0)</td>
</tr>
<tr>
<td></td>
<td>Obese ≥30.0</td>
<td>190 (10.5)</td>
<td>123 (10.5)</td>
<td>50 (9.4)</td>
<td>17 (16.0)</td>
</tr>
<tr>
<td>Duration of education</td>
<td>&lt;10 years</td>
<td>658 (38.2)</td>
<td>413 (36.9)</td>
<td>197 (39.2)</td>
<td>48 (48.0)</td>
</tr>
<tr>
<td></td>
<td>10–12 years</td>
<td>583 (33.9)</td>
<td>383 (34.2)</td>
<td>171 (34.1)</td>
<td>29 (29.0)</td>
</tr>
<tr>
<td></td>
<td>&gt;12 years</td>
<td>480 (27.9)</td>
<td>323 (28.9)</td>
<td>134 (26.7)</td>
<td>23 (23.0)</td>
</tr>
<tr>
<td>Annual household income</td>
<td>&lt;300 000 NOK</td>
<td>857 (50.7)</td>
<td>515 (46.7)</td>
<td>274 (55.8)</td>
<td>68 (70.1)</td>
</tr>
<tr>
<td></td>
<td>301 000–600 000 NOK</td>
<td>688 (40.6)</td>
<td>483 (43.7)</td>
<td>178 (36.3)</td>
<td>27 (27.8)</td>
</tr>
<tr>
<td></td>
<td>&gt;600 000 NOK</td>
<td>147 (8.7)</td>
<td>106 (9.6)</td>
<td>39 (7.9)</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Alcohol intake (g/day)</td>
<td>None</td>
<td>472 (27.5)</td>
<td>315 (28.3)</td>
<td>119 (23.5)</td>
<td>38 (38.4)</td>
</tr>
<tr>
<td></td>
<td>≤3.0 g</td>
<td>720 (41.9)</td>
<td>447 (40.2)</td>
<td>231 (45.5)</td>
<td>42 (42.4)</td>
</tr>
<tr>
<td></td>
<td>&gt;3.0–10.0 g</td>
<td>395 (23.0)</td>
<td>259 (23.3)</td>
<td>121 (23.9)</td>
<td>15 (15.2)</td>
</tr>
<tr>
<td></td>
<td>&gt;10.0 g</td>
<td>131 (7.6)</td>
<td>91 (8.2)</td>
<td>36 (7.1)</td>
<td>4 (4.0)</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Never smoker</td>
<td>627 (34.2)</td>
<td>410 (34.7)</td>
<td>173 (31.9)</td>
<td>44 (40.7)</td>
</tr>
<tr>
<td></td>
<td>Former smoker</td>
<td>666 (36.4)</td>
<td>437 (37.0)</td>
<td>202 (37.3)</td>
<td>27 (25.0)</td>
</tr>
<tr>
<td></td>
<td>Current smoker</td>
<td>538 (29.4)</td>
<td>334 (28.3)</td>
<td>167 (30.8)</td>
<td>37 (34.3)</td>
</tr>
<tr>
<td>Red and processed meat intake combined (g/day)</td>
<td>≤70.0 g</td>
<td>1523 (81.8)</td>
<td>986 (82.1)</td>
<td>444 (80.7)</td>
<td>93 (84.6)</td>
</tr>
<tr>
<td></td>
<td>&gt;70.0 g</td>
<td>338 (18.2)</td>
<td>215 (17.9)</td>
<td>106 (19.3)</td>
<td>17 (15.4)</td>
</tr>
<tr>
<td>Fish intake (g/day)</td>
<td>≤130 g</td>
<td>1364 (73.3)</td>
<td>890 (74.1)</td>
<td>401 (72.9)</td>
<td>73 (66.4)</td>
</tr>
<tr>
<td></td>
<td>&gt;130 g</td>
<td>497 (26.7)</td>
<td>311 (25.9)</td>
<td>149 (27.1)</td>
<td>37 (33.6)</td>
</tr>
<tr>
<td>Fruit and vegetable intake (g/day)</td>
<td>≤300 g</td>
<td>1002 (53.8)</td>
<td>629 (52.4)</td>
<td>296 (53.8)</td>
<td>77 (70.0)</td>
</tr>
<tr>
<td></td>
<td>&gt;300 g</td>
<td>859 (46.2)</td>
<td>572 (47.6)</td>
<td>254 (46.2)</td>
<td>33 (30.0)</td>
</tr>
<tr>
<td>Vitamin D intake (µg/day)</td>
<td>≤10.0 µg</td>
<td>1340 (72.0)</td>
<td>851 (70.9)</td>
<td>411 (74.7)</td>
<td>78 (70.9)</td>
</tr>
<tr>
<td></td>
<td>&gt;10.0 µg</td>
<td>521 (28.0)</td>
<td>350 (29.1)</td>
<td>139 (25.3)</td>
<td>32 (29.1)</td>
</tr>
</tbody>
</table>

Continued
interaction terms tested were statistically significant in any of the outcomes investigated.

The Arctic Circle divides Norway into approximately two equal parts. As a complementary analysis for vitamin D status through sunlight exposure, we conducted a parallel multivariable-adjusted analysis in which we compared CRC survival in participants living above and below the Arctic Circle. Those living above the Arctic Circle (North Norway) were at a non-significant higher risk of CRC death (HR=1.10, 95% CI 0.90 to 1.35) compared with the rest of Norway.

**DISCUSSION**

We found a lower risk of CRC death associated with a prediagnostic vitamin D intake of >10 µg/day, with evidence of a monotonic relationship between the intake and the risk of CRC death, using competing mortality risks approach and chained multiple imputation. The results were consistent with those of the complete-case analysis. The lower risk of death associated with prediagnostic fruit and vegetable intake and the increased risk of death associated with prediagnostic current smoking were both more pronounced and statistically significant only for non-CRC death. The apparent reduction in the risk of CRC death in those with CVD that we observed could be explained via the effects of the variable on the competing cause of death (non-CRC death). The same phenomenon was also seen among participants with the lowest prediagnostic physical activity level. We did not find any evidence of association between prediagnostic BMI, annual household income, alcohol intake, red and processed meat intake, fish intake, and diabetes mellitus status, and CRC survival.

Our results regarding prediagnostic vitamin D intake and decreased risk of CRC death are consistent with findings from the European Prospective Investigation into Cancer and Nutrition (EPIC) study, in which prediagnostic vitamin D level was estimated directly by measuring circulating 25-hydroxyvitamin D (25(OH) D) levels in the blood. The EPIC study reported a 31% lowered risk of death in those within the highest quintile compared with the lowest quintile of 25(OH)D (adjusted HR=0.69, 95% CI 0.50 to 0.93). Some other studies found similar results, while others found no association. However, a recent updated systematic review and meta-analysis compared the highest and lowest categories of blood 25(OH)D and concluded that sufficient vitamin D offers better survival in patients with CRC (pooled HR=0.67, 95% CI 0.57 to 0.78). Physiologically, the most active molecular form of vitamin D, 1α,25-dihydroxyvitamin D₃, has the capacity to inhibit cell proliferation, angiogenesis, and metastatic potential. It also induces differentiation and apoptosis in the cells of organs such as the large intestine.

Few studies have investigated the association between prediagnostic fruit and vegetable intake and CRC-specific mortality, but the comparable studies that do exist found results similar to ours. A study using data from the Cancer Prevention Study-II (CPS-II) Nutrition Cohort did not find any association. That study used prediagnostic dietary patterns, characterised mainly by a high intake of fruits and vegetables (termed the prudent dietary pattern), and the American Cancer Society (ACS) Guidelines on Nutrition and Physical Activity for Cancer Prevention to score participants. The ACS score is based on the intake of at least five servings per day of a variety of mainly fruits and vegetables. Neither the prudent dietary pattern nor the ACS score-based dietary pattern was associated with CRC-specific mortality (HR=0.85, 95% CI 0.64 to 1.13, and HR=0.74, 95% CI 0.54 to 1.03, respectively). In contrast to CRC incidence, we did not find an association between prediagnostic combined red and processed meat intake and CRC survival. This is consistent with results from the EPIC study and the Western dietary pattern described in the CPS-II Nutrition Cohort study, which was characterised by a high intake of red and processed meats. A recent, large, pooled analysis of CRC survivors also did not find any association between the highest prediagnostic red or processed meat intake and CRC survival when compared with the lowest intake. However, consistently high prediagnosis and postdiagnosis red and processed meat intake has been associated with an increased risk of CRC death (HR=1.79, 95% CI 1.11 to 2.89). Similar to our findings, most previous studies found no evidence of an association between prediagnostic alcohol intake and CRC death. Interestingly, some studies posited that prediagnostic wine intake may favour CRC survival.

Smoking is a well-known risk factor for many cancers, including CRC, and it has also been associated with overall mortality. Our study did not find any association between prediagnostic smoking status and CRC

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**Table 1 Continued**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Categories or parameters</th>
<th>Numbers (%)</th>
<th>Alive</th>
<th>Died of CRC</th>
<th>Died of other causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>No</td>
<td>1813 (97.4)</td>
<td>1175 (97.8)</td>
<td>532 (96.7)</td>
<td>106 (96.4)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>48 (2.6)</td>
<td>26 (2.2)</td>
<td>18 (3.3)</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>No</td>
<td>1503 (80.8)</td>
<td>981 (81.7)</td>
<td>450 (81.8)</td>
<td>72 (65.4)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>358 (19.2)</td>
<td>220 (18.3)</td>
<td>100 (18.2)</td>
<td>38 (34.6)</td>
</tr>
</tbody>
</table>

CRC, colorectal cancer; NOK, Norwegian kroner; SD, standard deviation.
Table 2  Multivariable cause-specific and subdistribution HRs, and 95% CIs of CRC and non-CRC deaths, with chained multiple imputation (N=1861)

<table>
<thead>
<tr>
<th>Prediagnostic variables</th>
<th>Categories</th>
<th>Cause-specific hazard model*</th>
<th>Subdistribution hazard model (Fine and Gray regression)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CRC death</td>
<td>P trend</td>
</tr>
<tr>
<td>Age at diagnosis of CRC</td>
<td>Per year increase</td>
<td>1.05 (1.03 to 1.06)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Physical activity</td>
<td>1–2 (least active)</td>
<td>0.95 (0.62 to 1.44)</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>3–4</td>
<td>0.92 (0.73 to 1.18)</td>
<td>0.98 (0.54 to 1.78)</td>
</tr>
<tr>
<td></td>
<td>5–6</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>7–8</td>
<td>0.97 (0.77 to 1.23)</td>
<td>1.19 (0.67 to 2.11)</td>
</tr>
<tr>
<td></td>
<td>9–10 (most active)</td>
<td>1.01 (0.67 to 1.53)</td>
<td>2.00 (0.89 to 4.48)</td>
</tr>
<tr>
<td>Body mass index (kg/m^2)</td>
<td>Underweight (&lt;20.0)</td>
<td>1.09 (0.77 to 1.53)</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>Normal (20.0–24.9)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Overweight (25.0–29.9)</td>
<td>0.97 (0.80 to 1.18)</td>
<td>0.84 (0.53 to 1.32)</td>
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<tr>
<td></td>
<td>Obese (≥30.0)</td>
<td>0.91 (0.66 to 1.26)</td>
<td>1.44 (0.77 to 2.68)</td>
</tr>
<tr>
<td>Duration of education (years)</td>
<td>&lt;10</td>
<td>1.00</td>
<td>0.52</td>
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<tr>
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<td>10–12</td>
<td>0.99 (0.79 to 1.24)</td>
<td>1.21 (0.74 to 1.98)</td>
</tr>
<tr>
<td></td>
<td>&gt;12</td>
<td>0.96 (0.74 to 1.24)</td>
<td>1.79 (1.02 to 3.15)</td>
</tr>
<tr>
<td>Annual household income</td>
<td>Low (&lt;300 000 NOK)</td>
<td>1.00</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>Middle (300–600 000 NOK)</td>
<td>0.93 (0.75 to 1.14)</td>
<td>0.97 (0.58 to 1.64)</td>
</tr>
<tr>
<td></td>
<td>High (&gt;600 000 NOK)</td>
<td>0.93 (0.64 to 1.35)</td>
<td>0.53 (0.12 to 2.32)</td>
</tr>
<tr>
<td>Alcohol intake (g/day)</td>
<td>None</td>
<td>1.00</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>≤3.0 g</td>
<td>1.17 (0.92 to 1.47)</td>
<td>0.89 (0.57 to 1.40)</td>
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<tr>
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<td>&gt;3.0–10.0 g</td>
<td>1.02 (0.78 to 1.34)</td>
<td>0.75 (0.39 to 1.42)</td>
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<tr>
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<td>&gt;10.0 g</td>
<td>1.01 (0.68 to 1.48)</td>
<td>0.55 (0.19 to 1.62)</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Never</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Former</td>
<td>1.09 (0.88 to 1.34)</td>
<td>0.89 (0.54 to 1.47)</td>
</tr>
<tr>
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<td>Current</td>
<td>1.16 (0.92 to 1.46)</td>
<td>1.98 (1.21 to 3.23)</td>
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<tr>
<td>Red and processed meat (g/day)</td>
<td>≤70 g</td>
<td>1.00</td>
<td>0.69</td>
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</table>

Continued
## Table 2 Continued

<table>
<thead>
<tr>
<th>Prediagnostic variables</th>
<th>Categories</th>
<th>Cause-specific hazard model*</th>
<th>Subdistribution hazard model (Fine and Gray regression)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CRC death P trend</td>
<td>Non-CRC death P trend</td>
</tr>
<tr>
<td>Fish intake (g/day)</td>
<td>≤130 g</td>
<td>1.00 (0.04)</td>
<td>0.96 (0.56 to 1.64)</td>
</tr>
<tr>
<td></td>
<td>&gt;130 g</td>
<td>1.01 (0.82 to 1.23)</td>
<td>1.05 (0.68 to 1.62)</td>
</tr>
<tr>
<td>Vegetable and fruit intake (g/day)</td>
<td>≤300 g</td>
<td>1.00 (0.53)</td>
<td>1.00 (0.06)</td>
</tr>
<tr>
<td></td>
<td>&gt;300 g</td>
<td>0.89 (0.74 to 1.07)</td>
<td>0.61 (0.39 to 0.93)</td>
</tr>
<tr>
<td>Vitamin D intake (μg/day)</td>
<td>≤10.0 μg</td>
<td>1.00 (0.001)</td>
<td>1.00 (0.80)</td>
</tr>
<tr>
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<td>&gt;10.0 μg</td>
<td>0.75 (0.61 to 0.92)</td>
<td>0.91 (0.58 to 1.43)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>No</td>
<td>1.00 (–)</td>
<td>1.00 (–)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1.19 (0.73 to 1.94)</td>
<td>1.36 (0.48 to 3.84)</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>No</td>
<td>1.00 (–)</td>
<td>1.00 (–)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>0.98 (0.77 to 1.23)</td>
<td>1.80 (1.17 to 2.77)</td>
</tr>
</tbody>
</table>

Boldfaced values are statistically significant.

*Stratified by CRC stages and adjusted for prediagnostic follow-up duration.

CRC, colorectal cancer; NOK, Norwegian kroner; SHR, subdistribution HR.
survival, although we observed an almost 100% increased risk of non-CRC death among participants who were current smokers prior to CRC diagnosis compared with never smokers. The lack of an association between prediagnostic smoking status and CRC death, and the presence of an association between this variable and non-CRC death could be attributed to the fact that smoking increases the incidence of several diseases and thus could indirectly increase the risk of non-CRC death. Nevertheless, a study using data from the CPS-II Nutrition Cohort found an association with prediagnostic current smoking but not former smoking. However, our findings are in agreement with the results of a recent meta-analysis of 14 prospective cohort studies on prediagnostic smoking status and CRC survival. The authors found no association between prediagnostic former smoking (pooled HR=1.00, 95% CI 0.91 to 1.09) or current smoking (pooled HR=1.15, 95% CI 0.95 to 1.41) and CRC survival, but they did find an association with overall survival. While higher education has been noted as a predictor of healthy lifestyle and is inversely related to CRC incidence in the NOWAC cohort, we found no association between duration of education and CRC survival. The cause-specific HRs for the two competing events (CRC death and non-CRC death) in our study apparently went in opposite directions in the least physically active and those with CVD, which is consistent with the SHR of cumulative incidence. This ‘opposite directions’ phenomenon was previously reported by Latouche et al. and Austin et al. This demonstrates that a variable could reduce the occurrence of the event of interest (CRC death) by increasing the occurrence of the competing event (non-CRC death). However, the variable does not necessarily affect the causal mechanism that produces the event of interest (CRC death). Nonetheless, patients with comorbidities such as diabetes mellitus and CVD are known to have lower odds of receiving treatment with a curative intent and to be at a greater risk of death than those without any comorbidity. Competing risks imply that a subject can experience a competing event that prevents the occurrence of the outcome of interest. The two approaches we used for handling the competing mortality risk data rendered similar results. These approaches could give different results because the composition of the risk sets in the two approaches differs, and especially if the competing event occurs early in follow-up and is frequent. In our study, the corresponding HRs and SHR were similar numerically because the competing event (non-CRC death) was relatively infrequent. The interpretation of these findings is subject to some limitations. One main limitation is that the prediagnostic lifestyle and dietary information we used was collected at recruitment, and only once before CRC diagnosis. Lifestyle and dietary habits could have changed before or after diagnosis and may have affected CRC survival. A repeat measurement of prediagnostic lifestyle and dietary factors could mitigate the impact of such changes. To minimise the impact of such changes during follow-up, we conducted sensitivity analyses restricted to CRC diagnosed within 10 years of recruitment. Even though we observed some changes, the estimates and associations (or lack thereof) remained essentially the same. Nonetheless, in a previous study of the NOWAC cohort, where prediagnosis and postdiagnosis assessments in CRC survivors were made, results showed only substantial changes in vegetable intake, BMI, and smoking status. Notably, over 50% of the participants quit smoking after their CRC diagnosis, compared with 20% in the cancer-free women. This may create a healthy ripple effect, leading to fewer comorbidities and an improved quality of life among CRC survivors. Second, we do not have access to the details of CRC treatment, and thus we were unable to evaluate treatment as an outcome modifier. CRC stage at diagnosis correlates with treatment options, but this will not completely assuage the limitation. Third, measurement errors and misclassification of variables are inherent in self-reported assessments of lifestyle and dietary habits (including overestimation or underestimation of social desirable behaviours), and unmeasured potential confounding factors may have influenced our estimates. For instance, vitamin D intake estimation was based on dietary intake and cod liver oil supplement intake; thus, intake of other vitamin D supplements or outdoor exposure to the solar radiation may have confounded these estimates. Moreover, we did not have data on family history of CRC and its precursors (such as colonic adenomas). Fourth, the relatively small size of some of the subgroups in our sample (for instance, in the most physically active participants) may have limited our analysis from detecting valid associations. Finally, we obtained information on cause of death from the Cause of Death Registry, and misclassification of the primary cause of death is a possibility we cannot completely rule out.

The strengths of this study include its prospective nature, the large sample size, prediagnostic information on several important lifestyle and dietary factors, and the high quality of data in the CRN that was used to identify CRC cases. The use of chained multiple imputation to handle missing data maximises the number of CRC survivors in the analyses. Most lifestyle and dietary factors in the NOWAC Study have been validated previously.

CONCLUSION
While we found no evidence of an association between CRC survival and prediagnostic physical activity, BMI, education, alcohol, or red and processed meat intake, our study showed that prediagnostic vitamin D intake could improve CRC survival. However, prediagnostic repeat measurements and/or postdiagnostic measurements would be desirable to draw a firmer conclusion.

Acknowledgements We are grateful to the participants in the Norwegian Women and Cancer Study for their time and efforts in providing the data. Many thanks to Therese Haugdahl Nest and Jan Håkon Rudolfsen for good discussions regarding...
R. We acknowledge Trudy Perdrix-Thoma of Professional Standards Editing for language review and editing. Some of the data in this article came from the Cancer Registry of Norway and Cause of Death Registry, but they are not responsible for the analysis or interpretation of the data presented.

Contributors S00 and KBB conceived the initial study idea. S00 carried out the statistical analyses and drafted the manuscript. TB prepared the data and participated in the statistical analyses and critical revision of the manuscript. GS contributed to the statistical analyses and critical revision of the manuscript. All authors approved the final manuscript version to be published and agreed to be accountable for all aspects of the work.

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Data availability statement Data are available upon reasonable request.

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2. Reminder to first questionnaire (series 35).
3. Questionnaire sample (series 35).
4. Letter of invitation and information to the NOWAC study second questionnaire (series 26).
5. Questionnaire sample (series 26).
6. English consent to be contacted again (series 26).
7. English summary of information to participants.
KVINNER OG KREFT

Institutt for samfunnsmedisin ved Universitetet i Tromsø gjennomfører en spørreundersøkelse om levesett og kreft blant norske kvinner. En slik undersøkelse gir et verdifullt grunnlag for å studere mulige sammenhenger mellom f.eks. kosthold, barnefødsler, p-pills, solvaner og utviklingen av kreft. Resultatet vil bli publisert i dagspressen og i internasjonale fagtidsskrifter.

Ansvarlig for undersøkelsen er professor Eiliv Lund.

Du forespørs hermed om å delta i undersøkelsen. Alle som blir forespurt er trukket ut tilfeldig. Statistisk Sentralbyrå har trukket utvalget og står for utsendning av spørreskjemaene.


Hvis du vil delta i undersøkelsen, ber vi deg om å besvare det vedlagte spørreskjemaet så riktig som mulig. Dersom ingen av de oppgitte svaralternativer dekker din situasjon, sett kryss for det alternativet som ligger nærmest. Du behøver ikke svare på alle spørsmål.


Ditt bidrag til undersøkelsen vil være å svare på spørsmålene i spørreskjemaet. For spørsmål om hormoner og p-pille bruk finner du bilder i denne brosjyren som skal være et hjelpemiddel til å svare riktig (brosjyren skal ikke returneres). Spørreskjemaet returneres i vedlagte konvolutt med betalt svarporto.

Med vennlig hilsen

Eiliv Lund
professor dr.med.

Bente A. Augdal
prosjektmedarbeider
Undersøkelsen
“KVINNER OG KREFT”

Vi minner om at vi nylig har sendt deg et spørreskjema som vi håper du tar deg tid til å svare på. Ditt svar er et viktig bidrag for oss, fordi slutningene vi kan trekke ut fra undersøkelsen vil være mer pålitelige dersom mange har svart.

Vi ønsker at resultatene fra undersøkelsen skal komme deg og andre kvinner til gode. Du velger likevel selv om du vil delta i undersøkelsen.

Hvis du nylig har returnert skjemaet, ber vi deg se bort fra denne hendvendelsen. Vi takker for verdifull bistand.

Alle opplysninger fra undersøkelsen behandles konfidensielt og etter Datatilsynets regler.

Har du spørsmål om undersøkelsen, eller trenger du et nytt spørreskjema, kan du kontakte Institutt for samfunnsmedisin, Universitetet i Tromsø, 9037 Tromsø,
Bente A. Augdal tlf. 77 64 66 38

Med vennlig hilsen

Eiliv Lund
professor dr.med.
KVINNEN OG KREFT

HVIS DU SAMTYKKER I Å VÆRE MED, SETT KRYSS FOR JA I RUTEN VED Siden AV. DERSOM DU IKKE ÖNSKER Å DELTA KAN DU UNNGÅ PURRING VED Å SETTE KRYSS FOR NEI OG RETURNERE SKJEMAET I VEDLAGTE SVARKONVOLUTT. VI BER DEG FYLLE UT SPØRRESKJEMAET SÅ NØYE SOM MULIG.


Med vennlig hilsen
Eiliv Lund
Professor dr. med

Forhold i oppveksten

I hvilken kommune har du bodd lengre enn et år?

Kommune:
Alder

1. Fødested: Fra år til år
2. Fra år til år
3. Fra år til år
4. Fra år til år
5. Fra år til år
6. Fra år til år
7. Fra år til år

Kroppstype i 1. klasse. (Sett ett kryss)

√ veldig tynn √ tynn √ normal √ tykk √ veldig tykk

Menstruasjonsforhold

Hvor gammel var du da du fikk menstruasjon første gang?

Hvor mange år tok det før menstruasjonen ble regelmessig?

√ Ett år eller mindre √ Mer enn ett år
√ Aldri √ Husker ikke

Har du regelmessig menstruasjon fremdeles?

√ Ja √ Har uregelmessig menstruasjon
√ Vet ikke (menstruasjon uteblitt pga. sykdom o.l.)
√ Bruk av hormonpreparat med østrogen
√ Nei

HVIS NEI;

har den stoppet av seg selv? √ operert vekk eggstokkene? √ operert vekk livmoren? √ annet?

Alder da menstruasjonen opphørte?

Graviditeter, fødsler og amming

Har du noen gang vært gravid?

Ja Nei

HVIS JA; fyll ut for hvert barn du har født opplysninger om fødselsår og antall måneder du ammet (fylles også ut for dødfødte eller for barn som er døde senere i livet). Dersom du ikke har født barn, fortsetter du ved neste spørsmål.

Barn Fødselsår Antall måneder med amming Barn Fødselsår Antall måneder med amming
1 2 3 4 5 6 7 8

Bruk av hormonpreparater med østrogen i overgangsalderen

Har du noen gang brukt østrogen-tabletter/plaster?

Ja Nei

HVIS NEI;

har den stoppet av seg selv? √ operert vekk eggstokkene? √ operert vekk livmoren? √ annet?

Bruker du soyapreparater mot plaget i overgangsalderen?

Ja Nei

Bruk av hormonpreparater med østrogen i overgangsalderen

Hvis Ja; hvor mange år har du brukt østrogen-tabletter/plaster i alt?

Hvor gammel var du første gang du brukte østrogen-tabletter/plaster?

√ Ja √ Har uregelmessig menstruasjon √ har den stoppet av seg selv? √ operert vekk eggstokkene? √ operert vekk livmoren? √ annet?

Litel pålitelig Pålitelig Meget pålitelig Vet ikke/ usikkert

Allmenpraktiserende lege √ √ √ √
Gynekolog √ √ √ √
Apotek √ √ √ √
Radio/TV √ √ √ √
Ukeblader/aviser √ √ √ √
Slekt/venninner √ √ √ √

Eiliv Lund
Professor dr. med
UTFYLLENDE SPØRSMÅL TIL ALLE SOM HAR BRUKT ELLER BRUKER PREPARATER MED ØSTROGEN I FORM AV TABLETTER ELLER PLASTER.


### Hormonspiral

Har du noen gang brukt hormonspiral (Levonova)?
- [ ] Ja
- [ ] Nei

Hvis Ja; hvor mange hele år har du brukt hormonspiral i alt?

Hvor gammel var du første gang du fikk insatt hormonspiral?

Bruker du hormonspiral nå?
- [ ] Ja
- [ ] Nei

### Østrogenpreparat til lokal bruk i skjeden

Har du noen gang brukt østrogen-krem/stikkpille?
- [ ] Ja
- [ ] Nei

Hvis Ja; bruker du krem/stikkpille nå?

### Andre legemidler

Bruker du noen av disse legemidlene daglig nå?

- [ ] Fontex, Fluoxetin
- [ ] Cipramil, Citalopram
- [ ] Seroxat, Paroxetin
- [ ] Zoloft
- [ ] Fevarin
- [ ] Cipralex

Hvis Ja; hvor lenge har du brukt dette legemidlet sammenhengende?

Har du benyttet noen av disse legemidlene tidligere?

Hvis Ja; hvor lenge har du benyttet disse legemidlene i alt?

### Sykdom

Har du eller har du hatt noen av følgende sykdommer?

- [ ] Kreft
- [ ] Høyt blodtrykk
- [ ] Hjertesvikt/hjertekrampe
- [ ] Hjerteinfarkt
- [ ] Slag
- [ ] Sukkersyke (diabetes)
- [ ] Depresjon (oppsøkt lege)

Kvinner og Kreft 35, Høst 2003 O-032161

2
Selvopplevd helse

Oppfatter du din egen helse som; (Sett ett kryss)
Meget god ☐ God ☐ Dårlig ☐ Meget dårlig ☐

Røykevaner

Har du i løpet av livet røukt mer enn 100 sigaretter til sammen? Ja ☐ Nei ☐

Hvor gammel var du da du tok din første sigaret?

Hvis Ja, ber vi deg om å fylle ut for hver aldersgruppe i livet hvor mange sigaretter du i gjennomsnitt røykte pr. dag i den perioden.

Antall sigaretter hver dag

<table>
<thead>
<tr>
<th>Alder</th>
<th>0</th>
<th>1-4</th>
<th>5-9</th>
<th>10-14</th>
<th>15-19</th>
<th>20-24</th>
<th>25+</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-14</td>
<td>☐</td>
<td>☐</td>
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<td>20-29</td>
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<td>30-39</td>
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<td>40-49</td>
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<td>50+</td>
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</tbody>
</table>

Røyker du daglig nå?

Røykte noen av dine foreldre når du var barn?

Hvis Ja, hvor mange sigaretter røykte de til sammen pr. dag?

Brystkreft i nærmeste familie

Har noen nære slektnings hatt brystkreft?

<table>
<thead>
<tr>
<th>Datter</th>
<th>☐</th>
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<tr>
<td>Søster</td>
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</table>

Mammografiundersøkelse

Har du vært til undersøkelse av brystene med mammografi?

Hvis Ja; hvor gammel var du første gangen? (hele år)

Hvor mange ganger har du vært undersøkt?

- etter invitasjon fra Mammografiprogrammet
- etter henvisning fra lege
- uten henvisning fra lege

Har du silikoninnlegg i brystene? Ja ☐ Nei ☐

Hvis Ja; hvor mange år har du hatt det?

Har du hatt silikoninnlegg tidligere? Ja ☐ Nei ☐

Fysisk aktivitet


<table>
<thead>
<tr>
<th>Alder</th>
<th>Svært lite</th>
<th>Svært mye</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 år</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
<tr>
<td>30 år</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
<tr>
<td>I dag</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
</tbody>
</table>

Hvor mange timer pr. dag i gjennomsnitt går eller spaserer du utendørs?

<table>
<thead>
<tr>
<th>sjelden</th>
<th>mindre enn 1/2 time</th>
<th>1/2-1 time</th>
<th>1-2 timer</th>
<th>mer enn 2 timer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinter</td>
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<td>☐ □ □ □ □ □ □ □ □</td>
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<tr>
<td>Vår</td>
<td>☐ □ □ □ □ □ □ □ □</td>
<td>☐ □ □ □ □ □ □ □ □</td>
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<td>Høst</td>
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For hver av følgende aktiviteter du deltar i, ber vi deg oppgi hvor mange minutter pr. dag du bruker i gjennomsnitt til hver av aktivitetene.

Høyde og vekt

Hvor høy er du? (i hele cm.)

Hvor mye veide du da du var 18 år? (i hele kg.)

Hvor mye veier du i dag? (i hele kg.)

3
Kosthold

Påvirker noen av følgende forhold kostholdet ditt? (sett gjerne flere kryss)

- Er vegetarianer/veganer
- Spiser ikke norsk kost til daglig
- Har allergi/intoleranse
- Kronisk sykdom
- Har anoreksi
- Har bulimi
- Prøver å gå ned i vekt

Vi er interessert i å få kjennebok til hvordan kostholdet ditt er vanligvis. Kryss av for hvert spørsmål om hvor ofte du i gjennomsnitt siste året har brukt den aktuelle matvaren, og hvor mye du pleier å spise/drikke hver gang.

Hvor mange glass melk drikker du vanligvis av hver type? (Sett et kryss pr. linje)

<table>
<thead>
<tr>
<th>Helmelk (søt, sur)</th>
<th>Lettmelk (søt, sur)</th>
<th>Ekstra lettmelk</th>
<th>Skummet (søt, sur)</th>
<th>Makrell i tomat</th>
<th>Røkt makrell</th>
<th>Kaviar</th>
<th>Sild/ansjos</th>
<th>Laks (gravet/røkt)</th>
<th>Annet fiskepålegg</th>
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</table>

Hvor mange kopper kaffe/te drikker du vanligvis av hver sort? (Sett et kryss for hver linje)

<table>
<thead>
<tr>
<th>Helmelk (søt, sur)</th>
<th>Lettmelk (søt, sur)</th>
<th>Ekstra lettmelk</th>
<th>Skummet (søt, sur)</th>
<th>Kokekaffe</th>
<th>Traktekaffe</th>
<th>Pulverkaffe</th>
<th>Espresso o.l.</th>
<th>Svart te</th>
<th>Grønn te</th>
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</table>

Hvor mange glass vann drikker du vanligvis? (Sett et kryss for hver linje)

<table>
<thead>
<tr>
<th>Springvann</th>
<th>Flaskevann u/kullsyre</th>
<th>Flaskevann m/kullsyre</th>
</tr>
</thead>
<tbody>
<tr>
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Hvor mange glass appelsinjuice, saft og brus drikker du vanligvis? (Sett et kryss for hver linje)

<table>
<thead>
<tr>
<th>Appelsinjuice</th>
<th>Saft/brus med sukker</th>
<th>Saft/brus sukkerfri</th>
</tr>
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</table>

Hvor ofte spiser du yoghurt (1 beger)? (Sett et kryss)

- Aldri/sjelden: 1 pr. uke
- 2-3 pr. uke
- 4+ pr. uke

Hvor ofte spiser du kornblanding, havregryn eller müsli? (Sett et kryss)

- Aldri/sjelden: 1-3 pr. uke
- 4-6 pr. uke
- 1 pr. dag

Hvor mange skiver brød/rundstykker og knekkebrød/skonrokker spiser du vanligvis? (1/2 rundstykke = 1 brødskive) (Sett et kryss for hver linje)

<table>
<thead>
<tr>
<th>Grovt brød</th>
<th>Kneipp/halvfint</th>
<th>Fint brød</th>
<th>Knekkebrød o.l.</th>
</tr>
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På hvor mange brødskiver bruker du? (Sett et kryss pr. linje)

<table>
<thead>
<tr>
<th>0 pr. uke</th>
<th>1-3 pr. uke</th>
<th>4-6 pr. uke</th>
<th>1 pr. dag</th>
<th>2-3 pr. dag</th>
<th>4+ pr. dag</th>
</tr>
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</table>

På hvor mange brødskiver pr. uke har du i gjennomsnitt siste året spist? (Sett et kryss pr. linje)

<table>
<thead>
<tr>
<th>Syltetøy</th>
<th>Brun øst, helfet</th>
<th>Brunost, halvfet/mager</th>
<th>Hvitøst, helfet</th>
<th>Hvitøst, halvfet/mager</th>
<th>Kjøtpålegg, Leverpostei</th>
<th>Rekesalat, italiensk o.l.</th>
</tr>
</thead>
<tbody>
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</tr>
</tbody>
</table>

Hvor ofte spiser du kornblanding, havregryn eller musli? (Sett et kryss)

<table>
<thead>
<tr>
<th>0 pr. uke</th>
<th>1-3 pr. uke</th>
<th>4-6 pr. uke</th>
<th>1 pr. dag</th>
<th>2-3 pr. dag</th>
<th>4+ pr. dag</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
</tbody>
</table>

Hva slags fett bruker du vanligvis på brødet? (Sett gjerne flere kryss)

- Bruker ikke fett på brødet
- Smør
- Hard margarin (f. eks. Per, Melange)
- Myk margarin (f. eks. Soft, Vita, Solisikke)
- Smørblandet margarin (f. eks. Bremyk)
- Brelett
- Lettmargarin (f. eks. Soft light, Letta)
- Middels lett margarin (f. eks. Olivero, Omega)

Dersom du bruker fett på brødet, hvor tykt lag pleier du smøre på? (En kuvertpakke med margarin veier 12 gram) (Sett et kryss)

<table>
<thead>
<tr>
<th>Skrapet (3 g)</th>
<th>Tynt lag (5 g)</th>
<th>Godt dekket (8 g)</th>
<th>Tykt lag (12 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Kvinner og Kreft 35, Høst 2003 O-032161

4
**Hvor ofte spiser du frukt?** (Sett ett kryss pr. linje)

<table>
<thead>
<tr>
<th></th>
<th>aldri/</th>
<th>sjelden</th>
<th>1-3 pr.mnd.</th>
<th>1 pr.uke</th>
<th>2-4 pr.uke</th>
<th>5-6 pr.uke</th>
<th>1 pr. dag</th>
<th>2+ pr. dag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epler/pærer</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Appelsiner o.l.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bananer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annen frukt</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Hvor ofte spiser du ulike typer grønnsaker?**

(Sett ett kryss pr. linje)

<table>
<thead>
<tr>
<th></th>
<th>aldri/</th>
<th>sjelden</th>
<th>1-3 pr.mnd.</th>
<th>1 pr.uke</th>
<th>2 pr.uke</th>
<th>3 pr.uke</th>
<th>4-5 pr.uke</th>
<th>6-7 pr. uke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gulrøtter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kål</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Kårot</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brokkoli/blomkål</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blandet salat</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Tomat</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Grønnsakblanding (frossen)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andre grønnsaker</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Fisk**


<table>
<thead>
<tr>
<th></th>
<th>aldri/</th>
<th>sjelden</th>
<th>like mye</th>
<th>heile året</th>
<th>vintrer</th>
<th>vår</th>
<th>sommer</th>
<th>høst</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torsk, sei, hyse, lyr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steinbit, flyndre, uer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laks, ørret</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Makrell</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sild</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Annen fisk</td>
<td></td>
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</tr>
</tbody>
</table>

**Med tanke på de periodene av året der du spiser fisk, hvor ofte pleier du å spise følgende?**

(Sett ett kryss pr. linje)

<table>
<thead>
<tr>
<th></th>
<th>aldri/</th>
<th>sjelden</th>
<th>1 pr. mond</th>
<th>2-3 pr. mond</th>
<th>1 pr. uke</th>
<th>2+ pr. uke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Køkt torsk, sei, hyse, lyr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stekt torsk, sei, hyse, lyr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steinbit, flyndre, uer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laks, ørret</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Makrell</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sild</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annen fisk</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Dersom du spiser fisk, hvor mye spiser du vanligvis pr. gang?** (1 skive/stykke = 150 gram)

<table>
<thead>
<tr>
<th></th>
<th>aldri/</th>
<th>sjelden</th>
<th>1</th>
<th>1,5</th>
<th>2</th>
<th>3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kokt fisk (skive)</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td>1,5</td>
<td>2</td>
</tr>
<tr>
<td>Stekt fisk (stykke)</td>
<td></td>
<td></td>
<td>1</td>
<td>1,5</td>
<td>2</td>
<td>3+</td>
</tr>
</tbody>
</table>

**Hvor mange poteter spiser du vanligvis (kokte, stekte, mos)?**

(Sett et kryss for hver sort)

<table>
<thead>
<tr>
<th></th>
<th>aldri/</th>
<th>sjelden</th>
<th>1-4 pr. uke</th>
<th>5-6 pr. uke</th>
<th>1 pr. dag</th>
<th>2 pr. dag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rogn</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiskelever</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hvor mange ganger pr. år spiser du fiskeinnmat?**

(Sett et kryss pr. linje)

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1-3</th>
<th>4-6</th>
<th>7-9</th>
<th>10+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rogn</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiskelever</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Dersom du spiser fiskelever, hvor mange spise-skjær pleier du å spise hver gang?** (Sett et kryss)

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3-4</th>
<th>5-6</th>
<th>7+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rogn</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiskelever</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Hvor ofte bruker du følgende typer fiskemat?**

(Sett et kryss pr. linje)

<table>
<thead>
<tr>
<th></th>
<th>aldri/</th>
<th>sjelden</th>
<th>1 pr. mond</th>
<th>2-3 pr. mond</th>
<th>1 pr. uke</th>
<th>2+ pr. uke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risengrynsgrot</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annen grøt (havre o.l.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hvor ofte spiser du grot?** (Sett ett kryss)

<table>
<thead>
<tr>
<th></th>
<th>aldri/</th>
<th>sjelden</th>
<th>1 pr. mond</th>
<th>2-3 pr. mond</th>
<th>1 pr. uke</th>
<th>2-6 pr. uke</th>
<th>1+ pr. dag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risengrynsgrot</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annen grøt (havre o.l.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
I tillegg til informasjon om fiskeforbruk er det viktig å få kartlagt hvilket tilbehør som blir servert til fisk.

**Hvor ofte bruker du følgende til fisk?**

(Sett ett kryss pr. linje)

<table>
<thead>
<tr>
<th>Aldri/sjelden</th>
<th>1 pr. mnd.</th>
<th>2-3 pr. mnd.</th>
<th>1 pr. uke</th>
<th>2+ pr. uke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smetet smør</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smetet eller fast margarin/fett</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seterrømme (35%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lettrømme (20%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saus med fett (hvit/brun)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saus uten fett (hvit/brun)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

For de ulike typene tilbehør du bruker til fisk, vær vennlig å kryss av for hvor mye du vanligvis pleier å spise.

<table>
<thead>
<tr>
<th>Aldri/sjelden</th>
<th>1 pr. mnd.</th>
<th>2-3 pr. mnd.</th>
<th>1 pr. uke</th>
<th>2+ pr. uke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smetet smør</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smetet margasin/fett</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seterrømme (ss)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lettrømme (ss)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saus med fett (dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saus uten fett (dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hvor ofte spiser du skalldyr** (f. eks. reker, krabbe og skjell)? (Sett ett kryss)

| Aldri/sjelden | 1 pr. mnd. | 2-3 pr. mnd. | 1+ pr. uke |
|---------------|-------------|--------------|------------|-------------|
| Gjær bakst (boller) |             |              |           |             |
| Wienerbørd, kringle |             |              |           |             |
| Kaker (bløtkaker) |             |              |           |             |
| Pannekaker |             |              |           |             |
| Vafler |             |              |           |             |
| Småkaker, kjeks |             |              |           |             |

**Dersom du spiser følgende retter, oppgi mengden du vanligvis spiser:**

<table>
<thead>
<tr>
<th>Aldri/sjelden</th>
<th>1 pr. mnd.</th>
<th>2-3 pr. mnd.</th>
<th>1 pr. uke</th>
<th>2+ pr. uke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steik (skiver)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koteletter (stk.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kjøttkaker, karbonader (stk.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pølser (stk. à 150g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gryterett, lapskua (dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pizza m/kjøtt (stykke à 100 g)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Hvor mange egg spiser du vanligvis i løpet av en uke?** (Sett ett kryss pr. linje)

<table>
<thead>
<tr>
<th>Aldri/sjelden</th>
<th>1-3 pr.</th>
<th>2-3 pr. mnd.</th>
<th>1 pr. uke</th>
<th>2+ pr. uke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pudding sjokolade/karamell</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riskrem, fromasj</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kompott, fruktgrøt, hermelsk frukt</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jordbær (friske, frosne)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andre bær (friske, frosne)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hvor ofte spiser du sjokolade?**

(Sett ett kryss)

<table>
<thead>
<tr>
<th>Aldri/sjelden</th>
<th>1-3 pr.</th>
<th>1 pr.</th>
<th>2-3 pr pr.</th>
<th>4-6 pr.</th>
<th>1+ pr. dag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mørk sjokolade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lys sjokolade</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Andre matvarer**

**Hvor ofte spiser du reinkjøtt?**

<table>
<thead>
<tr>
<th>Aldri/sjelden</th>
<th>1 pr. mnd.</th>
<th>2-3 pr. mnd.</th>
<th>1 pr. uke</th>
<th>4+ pr. uke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steik (okse, svin, får)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koteletter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biff</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kjøttkaker, karbonader</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pølser</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gryterett, lapskua</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pizza med kjøtt</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kylling</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andre kjøttretter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 1/4 | 1/2 | 3/4 | 1 | 1,5 | 2+ |

Hvor ofte spiser du snacks? (Sett ett kryss)  

<table>
<thead>
<tr>
<th>Potetchips</th>
<th>sjelden</th>
<th>1-3 pr. uke</th>
<th>1 pr. pr. uke</th>
<th>2-3 pr. uke</th>
<th>4-6 pr. uke</th>
<th>7+ pr. uke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanøtter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andre nøtter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annen snacks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hvor mange personer er det i ditt hushold? 

<table>
<thead>
<tr>
<th>gift</th>
<th>samboer</th>
<th>ugift</th>
<th>skilt</th>
<th>enke</th>
</tr>
</thead>
</table>

Kosttilskudd

Hvor ofte bruker du kosttilskudd?  

<table>
<thead>
<tr>
<th>Navn på vitamin/mineraltilskudd:</th>
<th>aldri/ sjelden</th>
<th>1-3 pr. mond</th>
<th>1 pr. uke</th>
<th>2-3 pr. uke</th>
<th>4-6 pr. uke</th>
<th>7+ pr. uke</th>
</tr>
</thead>
</table>

Alkohol

Er du totalavholdskvinne? Ja [ ] Nei [ ]

Hvis Nei, hvor ofte og hvor mye drakk du i gjennomsnitt siste året? (Sett ett kryss for hver linje)  

<table>
<thead>
<tr>
<th>Øl (1/2 l.)</th>
<th>Aldri</th>
<th>1-3 pr. dag</th>
<th>1 pr. dag</th>
<th>2-6 pr. dag</th>
<th>7+ pr. dag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vint (glass)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brennevin (drank)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Likør/Hetvin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sosiale forhold

Er du: (Sett ett kryss)

<table>
<thead>
<tr>
<th>gift</th>
<th>samboer</th>
<th>ugift</th>
<th>skilt</th>
<th>enke</th>
</tr>
</thead>
</table>

Hvor mange års skolegang/yrkesutdannelse har du i alt, ta med folkeskole og ungdomsskole? 

<table>
<thead>
<tr>
<th>Alkohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varm mat</td>
</tr>
</tbody>
</table>

Hvor mye tran pleier du å ta hver gang?  

<table>
<thead>
<tr>
<th>1 ts.</th>
<th>1/2 ss.</th>
<th>1+ ss.</th>
</tr>
</thead>
</table>

Bruker du tran (flytende)? Ja [ ] Nei [ ]

Hvis ja; hvor ofte tar du tran?

<table>
<thead>
<tr>
<th>Aldri/ sjelden</th>
<th>1-3 pr. pr. uke</th>
<th>1 pr. pr. uke</th>
<th>2-3 pr. pr. uke</th>
<th>4-6 pr. pr. uke</th>
<th>7+ pr. pr. uke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Om vinteren</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resten av året</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bruker du tranpiller/kapsler? Ja [ ] Nei [ ]

Hvis ja; hvor ofte tar du tranpiller/kapsler?

<table>
<thead>
<tr>
<th>Aldri/ sjelden</th>
<th>1-3 pr. pr. uke</th>
<th>1 pr. pr. uke</th>
<th>2-6 pr. pr. uke</th>
<th>daglig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Om vinteren</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resten av året</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hvordan var de økonomiske forhold i oppveksten?

<table>
<thead>
<tr>
<th>Hver høy er bruttoinntekten i husholdet pr. år?</th>
</tr>
</thead>
<tbody>
<tr>
<td>under 150.000 kr.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hva er din arbeidssituasjon? (sett kryss)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arbeider heltid</td>
</tr>
<tr>
<td>Hjemmearbeidende</td>
</tr>
<tr>
<td>Under attføring</td>
</tr>
</tbody>
</table>

Yrke:  

Hvordan var de økonomiske forhold i oppveksten?

<table>
<thead>
<tr>
<th>Meget gode</th>
<th>Gode</th>
<th>Dårlige</th>
<th>Meget dårlige</th>
</tr>
</thead>
</table>

Arbeider du utendørs i yrkessammenheng? Ja [ ] Nei [ ]

Hvis Ja;  

hvor mange timer pr. uke?  

<table>
<thead>
<tr>
<th>Sommer</th>
<th>vinter</th>
</tr>
</thead>
</table>

Kvinner og Kreft 35, Høst 2003 O-032161 7
Hvor ofte bruker du følgende hudpleiemidler? (Sett ett kryss pr. linje)

- Ansiktskrem
- Håndkrem
- Body lotion
- Parfyme

Hvor ofte har du solt deg i solarium? (Alder: Aldri, Sjelden, 1 gang pr. måned, 2 ganger pr. måned, 3-4 ganger pr. måned, oftere enn 1 gang pr. måned)

- Aldri
- Sjelden
- 1 gang pr. måned
- 2 ganger pr. måned
- 3-4 ganger pr. måned
- Oftere enn 1 gang pr. måned

Hvor ofte dusjer eller bader du? (Sett ett kryss pr. linje)

- mer enn 1 gang / dag.
- 1 gang / dag.
- 4-6 ganger / pr. uke.
- 2-3 ganger / pr. uke.
- 1 ganger / pr. uke.
- 2-3 ganger / pr. uke.
- sjelden / aldi.

Når bruker du krem med solfaktor? (Sett et eller flere kryss):

- i påsken
- i Norge eller utenfor syden

Hvilken solfaktor bruker du i disse periodene? (påsken, i Norge eller solferie i syden, aldi)

- I dag: [ ]
- For 10 år siden: [ ]

Hvor ofte har du solt deg i solarium?

- Alder: Aldri, Sjelden, 1 gang pr. måned, 2 ganger pr. måned, 3-4 ganger pr. måned, oftere enn 1 gang pr. måned.

- Før 10 år
- 10-19 år
- 20-29 år
- 30-44 år
- 45+ år
- Siste 12 måned.

Hvor mange ganger pr. år er du blitt forbrent av solen slik at du har fått svie og blemmer med avflassing etterpå? (Ett kryss for hver aldersgruppe)

- Alder: Aldri, 1 gang pr. år, 2-3 ganger pr. år, 4-5 ganger pr. år, 6 eller flere ganger.

Hvor mange uker soler du deg pr. år i syden?

- Alder: Aldri, 1 uke, 2-3 uker, 4-5 uker, 7 uker eller mer.

Hvor mange uker pr. år soler du deg i Norge eller utenfor syden?

- Alder: Aldri, 1 uke, 2-3 uker, 4-5 uker, 7 uker eller mer.

Hvor mange uregelmessige føflekker større enn 5 mm har du sammenlagt på begge beina (fra tærne til lysken)? Tre eksempler på føflekker større enn 5 mm med uregelmessig form er vist i nedenfor.

- aldri/ sjelden
- 1-3 pr. måned.
- 1 pr. uke.
- 2-4 pr. uke.
- 5-6 pr. uke.
- 1 pr. dag.
- 2+ pr. dag.

Spar krem... [ ]
Håndkrem... [ ]
Body lotion... [ ]
Parfyme... [ ]

Til slutt vil vi spørre deg om ditt samtykke til å kontakte deg på nytt pr. post. Vi vil hente adressen fra det sentrale personregister.

Ja [ ]
Nei [ ]

Er du villig til å avgi en blodprøve?

Ja [ ]
Nei [ ]

Takk for at du ville delta i undersøkelsen.
KVINNER OG KREFT

Orientering om undersøkelsen


Vi retter nå en ny forespørsel til deg om du nok en gang vil besvare det vedlagte spørreskjema. Begrunnelsen for å kontakte deg på ny er at mange av de spørsmålene du besvarte sist gjaldt levevaner som vi vet endrer seg med alderen. De fleste spørsmålene vil dreie seg om årene siden siste utfylling. Vi vil i tillegg spørre om du i løpet av de siste 6-7 år har fått enkelte andre sykdommer enn kreft.

Undersøkelsen er tilradd av Regional komite for medisinsk forskningsetikk i Nord-Norge. Adressen din henter vi fra det sentrale personregister ved hjelp av Statistisk Sentralbyrå. Som forrige gang inneholder spørreskjemaet kun løpenummer uten annen identifikasjon, for derved å gi dine opplysninger et bedre personvern.


Vi vil be deg om å besvare det vedlagte spørreskjemaet så riktig som mulig. Dersom ingen av de oppgitte svaralternativ dekker din situasjon, sett kryss for det alternativet som ligger nærmest. Gi eventuelt merknader eller tilleggsopplysninger i skjemaet. Vi spør også alle som deltar om tillatelse til formet kontakt om noen år i form av et liknende spørreskjema.

For spørsmål om p-pille bruk og bruk av hormoner i overgangsalderen finner du bilder i denne brosjyren som skal være et hjelpemiddel (brosjyren skal ikke returneres). Spørreskjemaet sendes tilbake i vedlagte konvolutt som vi betaler svarporto for.

Med hilsen

Eiliv Lund
professor dr.med.
Bruk av østrogener i og etter overgangsalderen

Denne brosjyren er et hjelpemiddel for å huske riktig navn på de hormontabletter/plaster/salver/stikkpiller du har brukt. Under bildene er det oppgitt hvilke år disse var i salg. For noen hormontabletter/plaster finnes det esker med samme utseende, men med ulik styrke av hormonene. Vi ber deg tenke nøye gjennom navnet på de hormon-tabletter/plaster/salver/stikkpiller du har brukt. Eldre avregistrerte preparater er ikke gjengitt med bilder, det gjelder:

Nr. 201 Diethylstilbestrol 1mg stikkpiller til skjøden (1976-92)
Nr. 202 Diethylstilbestrol 0,1 mg tabletter (1980-85)
Nr. 203 Diethylstilbestrol 0,5 mg stikkpiller (1976-81)
Nr. 204 Primodos tabletter (1961-74)
Nr. 205 Østriol 1 mg tabletter (1975-95)
Nr. 206 Østriol 0,25 mg tabletter (1961-83)

Nr. 101. Solgt fra 1978

Nr. 102. Solgt fra 1978

Nr. 104. Solgt fra 1953

Nr. 107. Solgt fra 1967

Nr. 106. Solgt fra 1970

Nr. 108. Solgt fra 1976

Nr. 109. Solgt fra 1954

Nr. 110. Solgt fra 1994

Nr. 111. Solgt fra 1971

Nr. 112. Solgt fra 1989

Nr. 113. Solgt fra 1983

Nr. 114. Solgt fra 1984

Nr. 115. Solgt fra 1995

Nr. 116. Solgt fra 1995

Nr. 117. Solgt fra 1994

Nr. 118. Solgt fra 1989

Nr. 119. Solgt fra 1989

Nr. 120. Solgt fra 1989
P-pille merker i salg 1991-98

Takk for innsatsen!
KVINNER OG KREFT

Hvis du samtykker i å være med, sett kryss for JA i ruten ved siden av. Dersom du ikke ønsker å delta kan du unngå purring ved å sette kryss for NEI og returnere skjemaet i vedlagte svarekonvolute.

Hvis du vil være med, så ber vi deg fylle ut spørreskjemaet så nøyde som mulig, se orienteringen på brosjyren for nærmere opplysninger.

Med vennlig hilsen

Eiliv Lund
Professor dr. med

Forhold i oppveksten

I hvilken kommune har du bodd lengre enn ett år?
Kommune: 

<table>
<thead>
<tr>
<th>Alder</th>
<th>Fra</th>
<th>År til</th>
<th>År</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fødested:</td>
<td>0</td>
<td>årtill</td>
<td>år</td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kroppstype i 1. klasse. (Sett ett kryss)
☐ veldig tynn  ☐ tynn  ☐ normal  ☐ tykk  ☐ veldig tykk

Hvor mange års skolegang/yrkesutdannelse har du i alt, ta med folkeskole og ungdomsskole? .............. år

Graviditeter, fødsler og ammning


<table>
<thead>
<tr>
<th>Barn</th>
<th>Fødselsår</th>
<th>Antall måneder med amning</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hormonbruk i overgangsalderen

Har du noen gang brukt hormontabletter/plaster?

☐ Ja  ☐ Nei

Hvis Ja; hvor lenge har du brukt hormontabletter/plaster i alt?

..... år

Hvor gammel var du første gang du brukte hormontabletter/plaster?

..... år

Hvorfor begynte du å bruke hormontabletter/plaster?

☐ Lindre plager i overgangsalderen
☐ (hetetokter, oppopplysthet, underlivsmønstre)
☐ Forebygge benskjørr
☐ Forebygge hjerte/kar sykdom
☐ Annet

Bruker du tabletter/plaster nå?

☐ Ja  ☐ Nei

HORMONPREPARAT TIL LOKAL BRUK I SKJEDEN

Har du noen gang brukt hormonkrem/stikkpille?

☐ Ja  ☐ Nei

Hvis Ja; hvor lenge har du brukt krem/stikkpille i alt?

..... år

Hvor gammel var du første gang du brukte hormonkrem/stikkpille?

..... år

Bruker du krem/stikkpille nå?

☐ Ja  ☐ Nei

<table>
<thead>
<tr>
<th>Periode</th>
<th>Alder ved start</th>
<th>Brukt samme hormon-tablett/plaster/krem/stikkpille sammenhengende år</th>
<th>Hormontablett/plaster/krem/stikkpille (se brosjyre) Nr.</th>
<th>Navn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Første</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andre</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tredje</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fjerde</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femte</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Har hormon preparatene gitt deg bivirkninger? □ Ja □ Nei

Hvis ja; kryss av for hvilke bivirkninger:
- Uregelmessige blodninger
- Brystspenning
- Kvalme/magesmerter
- Hodepinne
- Hudreaksjoner
- Vektøkning
- Annet

Forrige de overnevnte bivirkninger til at du forandret hormon behandlingen din? □ Ja □ Nei

Hvis ja;
- Skiftet fra et hormon preparat til et annet
- Sluttet på egen hånd?
- Sluttet i samråd med lege
- Annet

Har vekten din økt etter at du begynte å bruke hormoner □ Ja □ Nei

Hvis ja; Hvor mange kg? ..........kg

Hvis du har brukte hormon preparater i 1 år eller mindre;
- Hvorfor har du brukt midlene så kort tid?
  - Har nettopp startet behandlingen
  - Er kvitt plagene
  - Manglende effekt av legemidlene
  - Redd for skadevirkninger
  - Fikk plagesomme bivirkninger
  - Annet

Hvor har du skaffet deg informasjon/ kunnskap om hormonbehandlingen?
- Lite viktig □ □ □
- Viktig □ □ □
- Meget viktig □ □ □
- Allmen praktiserende lege □ □ □
- Gynekolog □ □ □
- Apotek □ □ □
- Radio/TV □ □ □
- Ukeblader/avisar □ □ □

**P-pillere**

Har du noen gang brukt p-pillere, minipiller inkludert? □ Ja □ Nei

Hvis Ja;
Hvor lenge har du brukt p-pillere i alt? ..........år
Hvor gammel var du første gang du brukte p-pillere? ..........år

Hvis du har født barn, brukte du p-pillere før første fødsel? □ Ja □ Nei

Bruker du p-pillere nå? □ Ja □ Nei


<table>
<thead>
<tr>
<th>Periode</th>
<th>Alder ved start</th>
<th>Brukt samme p-pille sammenhengende år</th>
<th>P-pillene (se brosjyren) Nr.</th>
<th>Navn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Første</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andre</td>
<td></td>
<td></td>
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<tr>
<td>Tredje</td>
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<tr>
<td>Fjerde</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Femte</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abort og infertility**

Har du hatt noe svangerskap som varte mindre enn seks måneder dvs. spontan abort eller selvforsøkt abort? □ Ja □ Nei

Hvis Ja, hvor gammel var du ved første abort? ..........år

Hvor mange aborter har du hatt i alt? ..........nummer

Har du noen gang provdi i mer enn 1 år å bli gravid? □ Ja □ Nei

Hvis Ja, hvor gammel var du? ..........år
Hvor lenge provde du? ..........år
**Sykdom**

Har du eller har du hatt noen av følgende sykdommer?

- Høyt blodtrykk  
- Hjertesvikt/hjertekrampe  
- Årebetennelse  
- Blodpropp i legg eller lår  
- Hjerteinfarkt  
- Sle  
- Migrene  
- Epilepsi  
- Sukkerson (diabetes)  
- Osteoporose  
- Depresjon (besøkt lege)  

Oppfatter du din egen fysiske helse som? (Sett ett kryss)

- meget god  
- god  
- dårlig  
- meget dårlig  

Oppfatter du din egen psykiske helse som? (Sett ett kryss)

- meget god  
- god  
- dårlig  
- meget dårlig  

---

**Brystkreft i nærmeste familie**

Har noen nær slektnings hatt brystkreft;

- datter  
- mor  
- mormor  
- farmor  
- søster  

Hvis ja, Alder ved start

---

**Høyde og vekt**

Hvor høy er du?  

Hvor mye veier du i dag?  

Hvor mye veide du da du var 18 år?  

Har du lagt på deg etter at du ble 50 år?  

I tilfelle ja; hvor mange kg?  

---

**Røykevaner**

Hvis ja, ber vi deg om å fylle ut for hver aldersgruppe i livet hvor mange sigaretter du i gjennomsnitt røkte pr. dag i den perioden.

<table>
<thead>
<tr>
<th>Antall sigaretter hver dag</th>
<th>0</th>
<th>1-4</th>
<th>5-9</th>
<th>10-14</th>
<th>15-19</th>
<th>20-24</th>
<th>25+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alder</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>15-19</td>
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<tr>
<td>20-29</td>
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<tr>
<td>30-39</td>
<td></td>
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<tr>
<td>40-49</td>
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<tr>
<td>50-59</td>
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<td></td>
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<tr>
<td>60-69</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Undersøkelser for kreft**

Hvor ofte undersøker du brystene dine selv? (Sett ett kryss)

- Aldri  

Uregelmessig  

Regelmessig (omtrent hver måned)  

Går du til regelmessig undersøkelse av brystene dine med mammografi? (Sett ett kryss)

- Nei  

Ja, med 2 års mellomrom eller mindre  

Ja, med mer enn 2 års mellomrom  

Har du tatt Kreftproble fra livmorhalsen regelmessig?

- Aldri  

Sjeldnere enn hvert 3. år  

Hvert 3. år eller oftere

---

Røker du daglig nå?  

Bor du sammen med noen som røker?  

Hvis ja, hvor mange sigaretter røker de til sammen pr. dag?

---

**Sosiale forhold**

Er du: (Sett ett kryss)

- gift  
- samboer  
- skilt/seperert  
- ugift  
- enke

Hvor mange personer er det i ditt hushold?

Antall: ..........
Hvor høy er bruttoinntekten i husholdet pr. år?

- under 150 000 kr
- 151 000–300 000 kr
- 301 000–450 000 kr
- 451 000–600 000 kr
- over 600 000 kr

Yrke: 

Arbeider du utendørs i yrkesammenheng?

Ja  Nei

Hvis ja: hvor mange timer pr. uke? .........Sommer .........vinter

**Fysisk aktivitet**


<table>
<thead>
<tr>
<th>Alder</th>
<th>Svært lite</th>
<th>Svært mye</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 år</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
<tr>
<td>30 år</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
<tr>
<td>I dag</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
</tbody>
</table>

Hvilken fysisk aktivitet har du i fritiden?

(Sett kryss i den ruten hvor «Ja» passer best.)

Leser, ser på fjernsyn eller annen 
stilllesittende beskjeftigelse?........... 

Spaserer, sykler eller beveger deg 
pa annen måte minst 4 timer i uken?

(Heri medregnes også gang eller sykling) 
(til arbeidssstedet, søndagsturer m.m.)

Driver mosjonsidrett, tyngre hagearbeid el.?
(Merk at virksomheten skal være minst 4 timer i uka.)

Trener hardt eller driver konkurranseidrett, regelmessig og flere ganger i uka.

Hvis du har drevet konkurranseidrett, 
how mange år i alt?

Hvor mye går du pr. uke?

(spasere, skiturer, turer i skog og mark, går til arbeid)

**Kosthold**

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, og hvor mye du pleier å spise/drikke hver gang.

**Hvor mange glass melk drikker du vanligvis av hver type?** (Sett ett kryss pr. linje)

<table>
<thead>
<tr>
<th>Aldri / sjelden</th>
<th>1-4 pr. uke</th>
<th>5-6 pr. uke</th>
<th>1 pr. dag</th>
<th>2-3 pr. dag</th>
<th>4-pr. dag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helmelk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lettmelk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skummet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hvor mange kopper kaffe drikker du vanligvis av hver sort? (Sett ett kryss for hver linje)

<table>
<thead>
<tr>
<th>Aldri / sjelden</th>
<th>1-6 pr. uke</th>
<th>1 pr. 2-3 pr.</th>
<th>4-5 pr. 6-7 pr.</th>
<th>8-8 pr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kokokaffe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traktekaffe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulverkaffe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hvor ofte spiser du yoghurt (1 beger)? (Sett ett kryss)

<table>
<thead>
<tr>
<th>Aldri / sjelden</th>
<th>1 pr. uke</th>
<th>2-3 pr. uke</th>
<th>4 pr. uke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldri / sjelden</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hvor ofte har du i gjennomsnitt siste året spist kornblanding, havregryn eller müsli? (Sett ett kryss)

<table>
<thead>
<tr>
<th>Aldri / sjelden</th>
<th>1-3 pr. uke</th>
<th>4-6 pr. uke</th>
<th>1 pr. dag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldri / sjelden</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hvor mange skiver brød/rundstykker og knækbrød/skonrokker spiser du vanligvis? (1/2 rundstykke = 1 brødslice) (Sett ett kryss for hver linje)

<table>
<thead>
<tr>
<th>Aldri / sjelden</th>
<th>1-4 pr. uke</th>
<th>5-7 pr. uke</th>
<th>2-3 pr. dag</th>
<th>4-5 pr. dag</th>
<th>6-8 pr. dag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldri / sjelden</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Grovt brød
Fintrøst
Knekkebrød o.l.

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 vaffler, frokostblanding, grøt), ber vi om at du tar med dette når du beviser spørsmålene.

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

<table>
<thead>
<tr>
<th>Syltetøy og annet sett pålegg</th>
<th>0 pr. uke</th>
<th>1-3 pr. uke</th>
<th>4-6 pr. uke</th>
<th>1 pr. dag</th>
<th>2-3 pr. dag</th>
<th>4-6 pr. dag</th>
<th>7-9 pr. dag</th>
<th>10+ pr. dag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brun ost, heltet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brun ost, halvtet/marger</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hvit ost, heltet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hvit ost, halvtet/marger</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Kjøttspis og leverpostei</td>
<td></td>
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</tr>
</tbody>
</table>

Videre kommer spørsmål om fiskepålegg.

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

| Makrell i tomat, røkt mekrell | 0 pr. uke | 1 pr. uke | 2-3 pr. uke | 4-6 pr. uke | 7-9 pr. uke | 10+ pr. uke |

Hva slags fett bruker du vanligvis på brødet?

(Sett gerne flere kryss)

- bruker ikke fett på brødet
- smør
- hard margarin (f.eks. Per, Melange)
- myk margarin (f.eks. Soft)
smørblendet margarin (f. eks. Bremykt)
Breullet
lettmargin (f. eks. Soft light, Letta)

Dersom du bruker fett på brødet, hvor tykt lag pleier du smøre på? (En kuvertpakke med margarin veier 12 gram).
(Sett ett kryss)
□ skrapet (3 g) □ tynt lag (5 g) □ godt dekket (8 g)
□ tykt lag (12 g)

Hvor ofte spiser du frukt? (Sett ett kryss pr. linje)

<table>
<thead>
<tr>
<th>Aldri/sjelden</th>
<th>1-3 pr. måned</th>
<th>1 pr. uk</th>
<th>2-4 pr. uk</th>
<th>5-6 pr. uk</th>
<th>1 pr. dag</th>
<th>2+ pr. dag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epler/pærer</td>
<td></td>
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<tr>
<td>Appleriser a. l.</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Bananer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annen frukt</td>
<td>(f.eks. druer, fersken)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Hvor ofte spiser du ulike typer grønnsaker?
(Sett ett kryss pr. linje)

<table>
<thead>
<tr>
<th>Aldri/sjelden</th>
<th>1-3 pr. månd</th>
<th>1 pr. uk</th>
<th>2 pr. uk</th>
<th>3 pr. uk</th>
<th>4-5 pr. uk</th>
<th>6-7 pr. uk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gulrotter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kål</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broccolibromkål</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blandet salat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grønnakblanding (frosken)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andre grønnsaker</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

For de grønnsakene du spiser, kryss av for hvor mye du spiser hver gang. (Sett ett kryss for hver sort)

- gulrotter □ 1/2 stk. □ 1 stk. □ 1 1/2 stk. □ 2+ stk.
- kål □ 1/2 dl □ 1 dl □ 1 1/2 dl □ 2+ dl
- kålrot □ 1/2 dl □ 1 dl □ 1 1/2 dl □ 2+ dl
- broccolibromkål □ 1-2 bukker □ 3-4 bukker □ 5+ bukker
- blandet salat □ 1 dl □ 2 dl □ 3 dl □ 4+ dl
- grønnakblanding □ 1/2 dl □ 1 dl □ 2 dl □ 3+ dl

Hvor mange poteter spiser du vanligvis (kokte, steekte, mos)? (Sett ett kryss)
□ spiser ikke/poteter sjelden poteter
□ 1-4 pr. uk □ 5-6 pr. uk □ 1 pr. dag □ 2 pr. dag □ 3 pr. dag □ 4+ pr dag

Hvor ofte bruker du ris og spaghetti/makaroni?
(Sett ett kryss pr. linje)

<table>
<thead>
<tr>
<th>Aldri/sjelden</th>
<th>1-3 pr. månd</th>
<th>1 pr. uk</th>
<th>2 pr. uk</th>
<th>3+ pr. uk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ris</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spaghetti, makaroni</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Hva slags fett blir vanligvis brukt til matlaging i din husholdning? (Sett gjeme flere kryss)
□ smør
□ hard margarin (f. eks. Per, Melange)
□ myk margarin (f. eks. Soft)
□ smørblendet margarin (f. eks. Bremykt)
□ soyaolje □ olivenolje □ maisolje

Fisk
Vi vil gjerne vite hvor ofte du pleier å spise fisk, og ber deg fylle ut spørsmålene om fisketforbruk så godt du kan.
Tilgangen på fisk kan variere gjennom året. Vær vennlig å markere i hvilke årstider du spiser de ulike fiskeslagene.

<table>
<thead>
<tr>
<th>Aldri/sjelden</th>
<th>Like mye hele året</th>
<th>Vinter</th>
<th>Vår</th>
<th>Sommer</th>
<th>Hest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torsk, sei, hyse, lry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steinbit, flyndre, uer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laks, orret</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Makrell</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sild</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Aldri/sjelden</th>
<th>1 pr. månd</th>
<th>2-3 pr. månd</th>
<th>1 pr. uk</th>
<th>2 pr. uk</th>
<th>3+ pr. uk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kokt torsk, sei, hyse, lry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stekt torsk, sei, hyse, lry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steinbit, flyndre, uer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laks, orret</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Makrell</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sild</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dersom du spiser fisk, hvor mye spiser du vanligvis pr. gang? (1 skive/stykke = 150 gram)
(Sett ett kryss for hver linje)
□ kokt fisk (skive) □ 1 □ 1,5 □ 2 □ 3+
□ stekt fisk (stykke) □ 1 □ 1,5 □ 2 □ 3+

Hvor mange ganger pr. år spiser du fiskeinnet?
(Sett ett kryss pr. linje)
0 □ □ □ □ □
1-3 □ □ □ □ □
4-6 □ □ □ □ □
7-9 □ □ □ □ □
10+ □ □ □ □ □

Rogn □ □ □ □ □
Fiskelever □ □ □ □ □

Dersom du spiser fiskelever, hvor mange spiseskjær pleier du å spise hver gang? (Sett ett kryss)
□ 1 □ 2 □ 3-4 □ 5-6 □ 7+
### Hvor ofte bruker du følgende typer fiskemåt?
(Sett ett kryss pr. linje)

<table>
<thead>
<tr>
<th>Aldri</th>
<th>1 pr.</th>
<th>2 pr.</th>
<th>3 pr.</th>
<th>4 pr.</th>
<th>2 pr. uke</th>
<th>1 pr. uke</th>
<th>3 pr. uke</th>
<th>4 pr. uke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiskekaker/pudding/boller</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plukkfisk, fiskegrateng</td>
<td>1-2</td>
<td>3-4</td>
<td>5+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frityrfisk, fiskepinner</td>
<td>1-2</td>
<td>3-4</td>
<td>6-6</td>
<td>7+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andre fiskeretter</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

### Hvor stor mengde pleier du vanligvis å spise av de ulike rettene?
(Sett ett kryss for hver linje)

- fiskekaker/pudding/boller (stlk.)
  - Aldri: 1
  - 1 pr. mindre: 2
  - 2 pr. mindre: 3
  - 3 pr. mindre: 4
  - 4 pr. mindre: 4

- plukkfisk, fiskegrateng (dl)
  - Aldri: 1-2
  - 1 pr. mindre: 3-4
  - 2 pr. mindre: 5

- frityrfisk, fiskepinner (stlk.)
  - Aldri: 1-2
  - 1 pr. mindre: 3-4
  - 2 pr. mindre: 6-6
  - 3 pr. mindre: 7+

### Hvor ofte spiser du skalldyr (f. eks. reker, krabbe)?
(Sett ett kryss)

<table>
<thead>
<tr>
<th>Aldri</th>
<th>1 pr.</th>
<th>2 pr.</th>
<th>3 pr.</th>
<th>4 pr.</th>
<th>2 pr. uke</th>
<th>1 pr. uke</th>
<th>3 pr. uke</th>
<th>4 pr. uke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smetter eller fast fett (få kartlagt hvilket tilbehør som blir servert til fisk.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sæterromme (35%)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Lettromme (20%)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Saus med fett (hvit brun)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Saus uten fett (hvit brun)</td>
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</tbody>
</table>

### Andere matvarer

### Hvor ofte spiser du følgende kjøtt- og fjærkeretter?
(Sett ett kryss for hver rett)

<table>
<thead>
<tr>
<th>Aldri</th>
<th>1 pr.</th>
<th>2 pr.</th>
<th>3 pr.</th>
<th>4 pr.</th>
<th>2 pr. uke</th>
<th>1 pr. uke</th>
<th>3 pr. uke</th>
<th>4 pr. uke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steik (okse, svin, får)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Kotletter</td>
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<td></td>
</tr>
<tr>
<td>Biff</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Kjøttkaker, karbonader</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Polser</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Gryterett, lapskau</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pizza m/kjøtt</td>
<td></td>
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<td></td>
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<tr>
<td>Kylling</td>
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<td></td>
</tr>
<tr>
<td>Andre kjøttreetter</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

- steik (skiver)
  - Aldri: 1
  - 1/2 pr. mindre: 2
  - 1 pr. mindre: 3
  - 1,5 pr. mindre: 4

- kjøttkaker, karbonader (stlk.)
  - Aldri: 1
  - 1/2 pr. mindre: 2
  - 1 pr. mindre: 3
  - 1,5 pr. mindre: 4

- polser (stlk. til 150g)
  - Aldri: 1
  - 1/2 pr. mindre: 2
  - 1 pr. mindre: 3
  - 1,5 pr. mindre: 4

- gryterrett, lapskau (dl)
  - Aldri: 1-2
  - 1/2 pr. mindre: 3
  - 1 pr. mindre: 4
  - 1,5 pr. mindre: 5

- pizza m/kjøtt (stykke til 100g)
  - Aldri: 1
  - 1/2 pr. mindre: 2
  - 1 pr. mindre: 3
  - 1,5 pr. mindre: 4

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

<table>
<thead>
<tr>
<th>Aldri</th>
<th>1 pr.</th>
<th>2 pr.</th>
<th>3 pr.</th>
<th>4 pr.</th>
<th>2 pr. uke</th>
<th>1 pr. uke</th>
<th>3 pr. uke</th>
<th>4 pr. uke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rent kjøtt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oppmalt kjøtt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fett fisk (makrell, laks o.l.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mager fisk (torsk o.l.)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Fiskemåt</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Aldri</th>
<th>1 pr.</th>
<th>2 pr.</th>
<th>3 pr.</th>
<th>4 pr.</th>
<th>2 pr. uke</th>
<th>1 pr. uke</th>
<th>3 pr. uke</th>
<th>4 pr. uke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riktig sommeren</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riktig resten av året</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Aldri</th>
<th>1 pr.</th>
<th>2 pr.</th>
<th>3 pr.</th>
<th>4 pr.</th>
<th>2 pr. uke</th>
<th>1 pr. uke</th>
<th>3 pr. uke</th>
<th>4 pr. uke</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Hvor ofte spiser du bakervarer som boller, kaker, wienerbrød, vafler, småkaker?
(Sett ett kryss)

<table>
<thead>
<tr>
<th>Aldri</th>
<th>1 pr.</th>
<th>2 pr.</th>
<th>3 pr.</th>
<th>4 pr.</th>
<th>2 pr. uke</th>
<th>1 pr. uke</th>
<th>3 pr. uke</th>
<th>4 pr. uke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakervarer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Hvor ofte spiser du sjokolade?
(Sett ett kryss)

<table>
<thead>
<tr>
<th>Aldri</th>
<th>1 pr.</th>
<th>2 pr.</th>
<th>3 pr.</th>
<th>4 pr.</th>
<th>2 pr. uke</th>
<th>1 pr. uke</th>
<th>3 pr. uke</th>
<th>4 pr. uke</th>
</tr>
</thead>
</table>
| Dersom du spiser sjokolade, hvor mye pleier du vanligvis å spise hver gang?
Tenk deg størrelsen på en Kvik-Lunej sjokolade, og oppgi hvor mye du spiser i forhold til den.

<table>
<thead>
<tr>
<th>Aldri</th>
<th>1/4</th>
<th>1/2</th>
<th>3/4</th>
<th>1</th>
<th>1,5</th>
<th>2+</th>
</tr>
</thead>
</table>
Tilberedningsmåte

Har du mikrobølgeovn? □ Ja □ Nei

Hvis Ja; hvor mange ganger pr. uke bruker du mikrobølgeovnen til middagslagning? □ ganger pr. uke □ annet?

Hvilken farve foretrekker du på stekeskorpen? □ Lys brun □ Middels □ Mørk brun

Hvor ofte spiser du stekt eller grillt mat?

<table>
<thead>
<tr>
<th>Aldri/ sjelden</th>
<th>1-3 pr. mnd</th>
<th>1 pr. uke</th>
<th>2-3 pr. uke</th>
<th>4-6 pr. uke</th>
<th>7 pr. uke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mørkt kjøtt</td>
<td>(blott at)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lyset kjøtt</td>
<td>(lytthoyt)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oppmalt kjøtt</td>
<td>(øietkaker ol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacon</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bruker du stekefettet eller sjøyen etter steking?
□ nei, aldri □ av og til □ ja, alltid

Kosthold som barn

Hvor mye melk drakk du som barn hver dag?
□ drakk ikke □ 1-3 glass □ 4-6 glass □ 7+ glass

Hvor ofte spiste du grønnsaker til middag som barn?
□ aldri □ 1 gang i uken eller mer sjelden □ 2-3 ganger i uken □ 4 eller flere ganger pr. uke

Hvor ofte spiste du fisk til middag som barn?
□ aldri/ sjelden □ 1 pr. mnd. □ 2-3 pr. mnd. □ 1 pr. uke
□ 2 pr. uke □ 3 pr. uke □ 4 pr. uke

I hvilken grad mener du kostholdet ditt har betydning for helsa?
□ ingen/svært liten □ noen □ stor □ svært stor

Tran og fiskeoljekapsler

Bruker du tran (flytende)? □ Ja □ Nei

Hvis ja; hvor ofte tar du tran?
Sett ett kryss for hver linje.

- om vinteren □ □ □ □ □ □ □
- resten av året □ □ □ □ □ □ □

Hvor mye tran pleier du å ta hver gang?
□ 1 ts □ 1/2ss □ 1+ss

Bruker du tranpiller/kapsler? □ Ja □ Nei

Hvis ja; hvor ofte tar du tranpiller/kapsler?
Sett ett kryss for hver linje.

- om vinteren □ □ □ □ □ □ □
- resten av året □ □ □ □ □ □ □

Hvilken type tranpiller/kapsler bruker du vanligvis, og hvor mange pleier du å ta hver gang?
□ ja □ antall pr. gang

Møllers trankapsler □ □ □ □ □ □ □
Møllers omega-3 kapsler □ □ □ □ □ □ □
Møllers dobbel □ □ □ □ □ □ □
annet, navn □ □ □ □ □ □ □

Bruker du fiskeoljekapsler? □ Ja □ Nei

Hvis ja; hvor ofte tar du fiskeoljekapsler?
□ aldri/ sjelden □ 1-3 pr. mnd □ 1 pr. uke □ 2-6 pr. uke □ daglig
□ □ □ □ □ □ □

Hvilken type fiskeoljekapsler bruker du vanligvis, og hvor mange pleier du å ta hver gang?
□ ja □ antall pr. gang

Triomar □ □ □ □ □ □ □
Almarin □ □ □ □ □ □ □
Nycomed Omega-3 □ □ □ □ □ □ □
annet, navn □ □ □ □ □ □ □

Kosttilskudd

Bruker du annet kosttilskudd (eks. vitaminer, mineraler)? □ Ja □ Nei

Hvis ja; hvor ofte tar du slike kosttilskudd?
□ aldri/ sjelden □ 1-3 pr. mnd □ 1 pr. uke □ 2-6 pr. uke □ daglig
□ □ □ □ □ □ □

Navn □ □ □ □ □ □ □

Alkohol

Er du total avholdskvinne? □ Ja □ Nei

Hvis Nei, hvor ofte og hvor mye drakk du i gjennomsnitt siste året? (Sett ett kryss for hver linje)
□ aldri/ sjelden □ 1-3 pr. mnd □ 1 pr. uke □ 2-4 pr. uke □ 5-6 pr. uke □ 1 pr. dag
□ □ □ □ □ □ □

Øl (½ L) □ □ □ □ □ □ □
Vin (glass) □ □ □ □ □ □ □
Brennevin (drinker) □ □ □ □ □ □ □
Solvaner

Dersom du i begynnelsen av sommeren soler deg kraftig, blir huden din; (sett ett kryss)
- brun uten først å være rød
- rød med svie
- rød med svie og blemmer

Etter gjenatt og lenge soling, blir huden din; (sett ett kryss)
- dypt brun
- brun
- lys brun
- aldri brun

Hvor mange uregelmessige følsomker større enn 5 mm har du sammenlagt på begge beina (fra tærne til lysken)? Tre eksempler på følsomker større enn 5 mm med uregelmessig form er vist i nedenfor.

[Images of skin lesions]

Hvor mange små, regelmessige følsomker har du sammenlagt på begge beina (fra tærne til lysken)?
- 0
- 1-10
- 11-50
- 51+

Hvilken øyefarge har du? (sett ett kryss)
- brun
- grå, grønn eller blanding
- blå

Hva er din opprinnelige hårfarge? (sett ett kryss)
- mørkbrunt, svart
- brun
- blond, gul
- rød

For å kunne studere effekten av solning på risiko for hudkreft ber vi deg gi opplysninger om hudfarge
Slett ett kryss på den fargen som best passer din hudfarge (uten soling)

[Hair color options]

Hvor ofte dusjer eller bader du?

<table>
<thead>
<tr>
<th>Ofte dusjer eller bader du?</th>
<th>Mer enn 1 g dag</th>
<th>1 g dag</th>
<th>4-6 g pr. uke</th>
<th>2-3 g pr. uke</th>
<th>1 g pr. uke</th>
<th>2-3 g pr. mond</th>
<th>Med såpe/shampoo</th>
<th>Uten såpe/shampoo</th>
</tr>
</thead>
</table>

Hvor mange ganger pr. år er du blitt forbrent av solen slik at du har fått svie og blemmer med avflassing etterpå? (ett kryss for hver aldersgruppe)

<table>
<thead>
<tr>
<th>Alder</th>
<th>Aldri</th>
<th>Høyst antall ganger</th>
<th>6 eller flere ganger</th>
</tr>
</thead>
<tbody>
<tr>
<td>Før 10 år</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-19 år</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-44 år</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45+ år</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hvor mange uker soler du deg pr. år i syden?

<table>
<thead>
<tr>
<th>Alder</th>
<th>Aldri</th>
<th>1 uke</th>
<th>2-3 uker</th>
<th>4-5 uker</th>
<th>7 uker eller mer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Før 10 år</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-19 år</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-45 år</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45+ år</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Hvor mange uker pr. år soler du deg i Norge eller utenfor syden?

<table>
<thead>
<tr>
<th>Alder</th>
<th>Aldri</th>
<th>1 uke</th>
<th>2-3 uker</th>
<th>4-5 uker</th>
<th>7 uker eller mer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Før 10 år</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-19 år</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>20-45 år</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45+ år</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Når bruker du krem med solfaktor (sett evt. flere kryss):
- påsken
- i Norge eller utenfor syden
- solfrie i syden

Hvilke solfaktorer bruker du i disse periodene?

<table>
<thead>
<tr>
<th>Pålser</th>
<th>i Norge eller</th>
<th>Solfrie i syden</th>
</tr>
</thead>
</table>

- I dag
- For 10 år siden

Hvilke solkremmermer bruker du? Angi faktor hvis du husker.

<table>
<thead>
<tr>
<th>Piz Buin</th>
<th>Ambre Solairé</th>
<th>Delial</th>
<th>Nivea</th>
<th>Natusan</th>
<th>HTH</th>
<th>Cosmica</th>
<th>Andre</th>
</tr>
</thead>
</table>

Hvor ofte har du solt deg i solarium?

<table>
<thead>
<tr>
<th>Alder</th>
<th>Aldri</th>
<th>Sjelden</th>
<th>1 gang pr. mond</th>
<th>2 ganger pr. mond</th>
<th>3-4 ganger pr. mond</th>
<th>Ofre ganger pr. ute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Før 10 år</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-19 år</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-44 år</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45+ år</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Till slut vil vi spørre deg om ditt samtykke til å kontakte deg på nytt pr. post. Vi vil hente adressen fra det sentrale personregister.
- Ja
- Nei

Takk for at du ville delta iundersøkelsen
We would like to ask for your permission to contact you again via mail. Your address will be provided from the national person register.
Yes / No

Are you willing to give a blood sample?
Yes / No

Original questions in Norwegian, as they appear on the questionnaire:

Til slutt vil vi spørre deg om ditt samtykke til å kontakte deg på nytt pr. post.
Vi vil hente adressen fra det sentrale personregister.

Ja [ ] Nei [ ]

Er du villig til å avgi en blodprøve?

Ja [ ] Nei [ ]
Norwegian women and cancer study

The Department of community medicine at the University of Tromsø is conducting a survey on lifestyle and cancer in women. The survey will provide a valuable basis for studying associations between diet, child births, oral contraceptives, tanning habits, and cancer. The results will be published in the daily press and international scientific journals. The principal investigator of the survey is professor Eiliv Lund.

You are hereby asked to participate in the survey. All participants were randomly drawn by Statistics Norway, who will also send out the questionnaires.

The information given in the survey will be coupled with information from the Cancer registry, the Mammography registry and the Cause of death registry. By answering and returning the questionnaire, you give your consent to this coupling. Information from the survey will be handled confidentially and in accordance with the conditions of the approvals from the Norwegian data inspectorate and the Norwegian directorate of health. On the questionnaire, your name and national identity number is replaced with a serial number so that your identity is not revealed to those receiving and handling the questionnaires. The survey was approved by the Regional Ethical Committee for Medical Research in North Norway.

At a later time, collection of blood samples from survey participants may be initiated. The blood sample will be taken at a general physician’s office, and will be of no cost to participants. Some participants may also be invited for a dietary recall interview by phone. Only the participants who have agreed beforehand will be contacted again, and they will then receive further information and will have to sign a consent form.

Participation in the survey is voluntary. You have the opportunity to withdraw from participation at any time, and your information will be deleted upon your request.

Yours sincerely,

Eiliv Lund
Professor dr. med.

Bente A. Augdal
Project staff
English translation of the questionnaire from series 39
Confidential Autumn 2004

If you agree to take part, tick YES in the box to the right.
If you do not wish to take part, avoid reminders by ticking NO and return the questionnaire in the envelope provided.

We ask you to fill out the questionnaire as accurately as possible.

The questionnaire is to be read optically. Please use blue or black pen. Use of comma is not allowed, round up from 0.5 to 1. Use block letters.

Best wishes,
Eiliv Lund
Professor dr. med.

Menopause
Do you still have regular periods?
... Yes
... Have irregular periods
... Unknown (Absent because of illness, etc.)
... Unknown (Current use of medication containing estrogen)
... No

If No;
  Have they stopped of their own accord? ..... 
  Have both your fallopian tubes been removed?...
  Have you had your womb removed (hysterectomy)?...
Other? …

Age when periods stopped? .....years

Pregnancies, births and breastfeeding
Have you ever been pregnant? Yes/No
  If Yes; how many children have you born totally? .....children
  How old were you at last birth? .....years

Use of contraceptive pill
Have you ever used the pill or minipill Yes/No
  If Yes; In how many years have you used the pill totally? .....years
  Are you currently on the pill? Yes/No

Use of hormone preparations with estrogen in menopause
Have you ever used estrogen pills/plasters? Yes/No
  If Yes; how long have you used estrogen pills/plasters in all? .....years
  How old were you when you first used estrogen pills/plasters? .....years
  Are you currently using pills/plasters? Yes/No

If you replied “Yes”, we ask you to elaborate further on this by answering the questions below. For each period of continuous use of the same estrogen preparation, we hope you can tell us how old you were when you started, how long you used the same hormone preparation, and what it was called. If you stopped using it for a while, or switched to other preparations, you should count this as a new period. If you cannot remember the name of the hormone preparation, write ‘Unsure’. To help you remember the names of estrogen preparations, please use the brochure provided, which contains pictures of estrogen preparations that have been sold in Norway. Please also give the number of the estrogen pill/plaster given in the brochure.
Age at start

<table>
<thead>
<tr>
<th>Used same estrogen pill/plaster continuously from 1998</th>
<th>Name of estrogen pill/plaster (see brouchure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>Month</td>
</tr>
<tr>
<td>1.</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td></td>
</tr>
</tbody>
</table>

**Estrogen preparations for vaginal use**

- Have you ever used estrogen creams/suppositories? Yes/No
  - If Yes; Are you currently using creams/suppositories? Yes/No

**Intrauterine device**

- Have you ever used an intrauterine device (Levonova)? Yes/No
  - If Yes; for how long have you used an IUD all together? ..... years
  - How old were you the first time you got an IUD inserted? ..... years
  - Are you currently using an IUD? Yes/No

**Self-perceived health**

- Do you rate your own current state of health as (tick one box only):
  - Very good ...
  - Good ...
  - Poor ...
  - Very poor

**Illness**

- Do you have or have you had any of the following illnesses? (tick one or more boxes)
  - Cancer
  - High blood pressure
  - Heart failure/heart cramps
  - Heart attack
  - Stroke
  - Diabetes
  - Depression (seen a doctor)
  - Hypothyreosis

**For the following conditions, tick which year they emerged, or give the year for the period before 1991.**

<table>
<thead>
<tr>
<th>Muscle pains (myalgia)</th>
<th>before '98</th>
<th>98</th>
<th>99</th>
<th>00</th>
<th>01</th>
<th>02</th>
<th>03</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibromyalgia/fibrositis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronical fatigue syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Backpains of unknown cause</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whiplash</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fractures**

- Forearm (wrist)
- Spine (compression)
- Other fractures, describe..........

**Other medication**

- Do you currently use any of these preparations daily? Yes/No
  - Fontex, Fluoxetine
  - Cipramil, Citalopram, Desital
  - Seroxat, Paroxetine
  - Zoloft
  - Fevarin
  - Cipralex

  - If Yes; for how long time have you used this preparation continuously? Months..... Years.....

- Have you ever used any of these preparations? Yes/No
  - If Yes; For how long time did you use these preparations continuously? Months..... Years.....
Height and weight
How tall are you? ....cm
How much do you weigh at the moment? ....kg
What was your weight at age 18? ....kg
Body type 1st degree (tick one box only):
....Very thin …. Thin ….Normal ….Heavy ….Very heavy

Smoking habits
During life, have you smoked more than 100 cigarettes totally? Yes/No
If yes, please fill in how many cigarettes you smoked on average per day the last five years.
Number of cigarettes smoked per day
<table>
<thead>
<tr>
<th>0</th>
<th>1-4</th>
<th>5-9</th>
<th>10-14</th>
<th>15-19</th>
<th>20-24</th>
<th>25+</th>
</tr>
</thead>
</table>
How old were you when you smoked your first cigarette? ..... years
Do you smoke on a daily basis at the moment? Yes/No
If No, how old were you when you quit? ..... years
Did any of your parents smoke when you were child? Yes/No
If Yes, how many cigarettes did they smoke in total per day? .... cigarettes

Breast cancer in the family
Have any of your close relatives had breast cancer:
Daughter
Mother
Sister

Mammography screening
Have you ever been to mammography screening of your breasts? Yes/No
If Yes; How old were you first time? ..... years
How many times have you been screened?
- After invitation from the Mammography Programme ..... times
- After referral from doctor ..... times
- Without referral from doctor ..... times

Physical activity
Please indicate the level of your physical activity on a scale from very low to very high by age 14, 30 and today.
The scale goes from 1-10. By physical activity we mean both work in and outside the home, as well as
training/exercise and other physical activity, such as walking, etc.

<table>
<thead>
<tr>
<th>Age</th>
<th>Very low</th>
<th>Very high</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 years</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
<tr>
<td>30 years</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
<tr>
<td>Today</td>
<td>1 2 3 4 5 6 7 8 9 10</td>
<td></td>
</tr>
</tbody>
</table>

How many hours per day do you walk or stroll outdoors at mean?

<table>
<thead>
<tr>
<th>Seldom/ Never</th>
<th>Less than ½ hour</th>
<th>½-1 hour</th>
<th>1-2 hours</th>
<th>more than 2 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spring</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autumn</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

How many stairs (whole floors) do you walk per day on average? .......... For each of the following activities you partake in, we ask you to estimate how many minutes per day you use on these activities on average.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watch TV</td>
<td>Winter Spring Summer Fall</td>
</tr>
<tr>
<td>Reading</td>
<td></td>
</tr>
<tr>
<td>Handicraft</td>
<td></td>
</tr>
</tbody>
</table>
Gardening
Shower/bath/
personal care
Exercise/jogging
Bicycling

How many hours per day on the workplace do you on average use to

<table>
<thead>
<tr>
<th>Activity</th>
<th>Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sit</td>
<td></td>
</tr>
<tr>
<td>Stand</td>
<td></td>
</tr>
<tr>
<td>Walk</td>
<td></td>
</tr>
<tr>
<td>Lift</td>
<td></td>
</tr>
<tr>
<td>Heavy lifting/caretaking</td>
<td></td>
</tr>
</tbody>
</table>

Diet
Do any of the following affect your diet? (More than one tick allowed)
Vegetarian… Do not eat Norwegian diet on daily basis… Have allergy/intolerance… Chronic illness…
Anorexia…
Bulimia… Try to lose weight… Low GI food…

We are interested in finding out about your usual eating habits. For each question, tick how often in the last twelve months you have eaten the food in question, and how much you usually eat/drink each time.

Drink
How many glasses of each kind of milk do you usually drink? (Tick one box on each line).

<table>
<thead>
<tr>
<th>Milk Type</th>
<th>Never/</th>
<th>1-4/</th>
<th>5-6/</th>
<th>1/</th>
<th>2-3/</th>
<th>4+/</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full cream milk (sweet, sour)</td>
<td>seldom</td>
<td>wk</td>
<td>wk</td>
<td>day</td>
<td>day</td>
<td>day</td>
</tr>
<tr>
<td>Semi-skinned milk (sweet, sour)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extra skimmed milk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skimmed milk (sweet, sour)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

How many cups of each kind of coffee/tea do you usually drink? (Tick one box on each line)

<table>
<thead>
<tr>
<th>Drink</th>
<th>Never/</th>
<th>1-6/</th>
<th>1/</th>
<th>2-3/</th>
<th>4-5/</th>
<th>6-7/</th>
<th>8+/</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boiled coffee (kokekaffe)</td>
<td>seldom</td>
<td>wk</td>
<td>day</td>
<td>day</td>
<td>day</td>
<td>day</td>
<td></td>
</tr>
<tr>
<td>Filter coffee</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Instant coffee</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black tea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green tea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Do you use the following in coffee or tea:

|  | Coffee | Tea |
|  | Yes/No | Yes/No |
| Sugar (non-artificial sweetener) | Yes/No | Yes/No |
| Milk or cream | Yes/Yes |

How many glasses of water do you usually drink?

<table>
<thead>
<tr>
<th>Water Type</th>
<th>Never/</th>
<th>1-6/</th>
<th>1/</th>
<th>2-3/</th>
<th>4-5/</th>
<th>6-7/</th>
<th>8+/</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tap water and bottled water</td>
<td>seldom</td>
<td>wk</td>
<td>day</td>
<td>day</td>
<td>day</td>
<td>day</td>
<td></td>
</tr>
</tbody>
</table>

How many glasses of juice, limonade and soft drinks do you usually drink? (Tick one box on each line)

<table>
<thead>
<tr>
<th>Drink Type</th>
<th>Never/</th>
<th>1-4/</th>
<th>5-6/</th>
<th>1/</th>
<th>2-3/</th>
<th>4+/</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orange juice</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lemonade/soft drinks with sugar</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lemonade/soft drinks with sugar</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sugarfree lemonade/soft drinks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Yoghurt/cereals
How often do you eat yoghurt (equivalent to 1 carton)? (Tick one box only)

......never/seldom ....1/wk .....2-3/wk ....4+/wk
How often do you eat cereals, oat flakes or muesli? (Tick one box only)

.....never/seldom .....1-3/wk .....4-6/wk .....1/day

Bread

How many slices of bread/rolls and crisps bread do you normally eat? (1/2 roll = 1 slice of bread) (Tick one box on each line)

<table>
<thead>
<tr>
<th>Never/1-4</th>
<th>5-7/wk</th>
<th>2-3/day</th>
<th>4-5/day</th>
<th>6+/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>seldom</td>
<td>wk</td>
<td>day</td>
<td>day</td>
<td>day</td>
</tr>
</tbody>
</table>

Wholemeal bread
Kneippbrød (semi white)
White bread
Crispbread, etc.

Below are some questions on use of various kinds of sandwich filling/spread. We want to know how many slices of bread with these fillings/spreads you usually eat. If you also use these products on other things than bread (e.g., on waffles, in breakfast cereals, porridge), please take this into account when answering the questions.

How many slices of bread do you eat with? (Tick one box on each line)

<table>
<thead>
<tr>
<th>Never/1-3</th>
<th>4-6/wk</th>
<th>1/day</th>
<th>2-3/day</th>
<th>4+/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>seldom</td>
<td>wk</td>
<td>day</td>
<td>day</td>
<td>day</td>
</tr>
</tbody>
</table>

Jam
Brown cheese, full cream
Brown cheese, low-fat
White cheese, full cream
White cheese, low-fat
Meat fillings/spreads, liver paté
Shrimp salad, Italian salad, etc.

How many slices of bread per week on average in the last twelve months have you eaten with? (Tick one box on each line)

<table>
<thead>
<tr>
<th>Never/1/2</th>
<th>2-3/week</th>
<th>4-6/week</th>
<th>7-9/week</th>
<th>10+/week</th>
</tr>
</thead>
<tbody>
<tr>
<td>seldom</td>
<td>wk</td>
<td>day</td>
<td>week</td>
<td>week</td>
</tr>
</tbody>
</table>

Mackerel in tomato sauce, smoked mackerel
Caviar
Herring/Anchovies
Salmon (cured and smoked)
Other fish fillings/spreads

What kind of fat do you usually spread on your bread? (Tick more than one box if necessary)

..... I do not use fat on bread
..... butter
..... hard margarine (e.g., Per, Melange)
..... soft margarine (e.g., Soft)
..... margarine/butter mix (e.g., Bremyk)
..... Brelett
..... low-fat margarine (e.g., Soft light, Letta)
..... Middle fat margarine (Olivero, Omega)

If you use fat on your bread, how thick a layer do you usually spread on it? (Tick one box only)

..... very thin scraping (3g)
..... thin layer (5g)
..... well-covered (8g)
..... thick layer (12g)

Fruits and vegetables

How often do you eat fruit? (Tick one box per line only)

<table>
<thead>
<tr>
<th>Never/1-3</th>
<th>4-6/wk</th>
<th>1/month</th>
<th>2-4/wk</th>
<th>5-6/wk</th>
<th>1/day</th>
<th>2+/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>seldom</td>
<td>wk</td>
<td>wk</td>
<td>wk</td>
<td>day</td>
<td>day</td>
<td>day</td>
</tr>
</tbody>
</table>

Apples/pears
Oranges, etc.
Bananas
Other fruit
How often do you eat various kinds of vegetables? (Tick one box per line)

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>1-3</th>
<th>1/2</th>
<th>1/3</th>
<th>4-5/6</th>
<th>6-7/8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrots</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cabbage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turnip</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broccoli/cauliflower</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed salad</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tomatoes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed vegetables (frozen)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other vegetables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For the vegetables you eat, tick how much you eat each time. (Tick one box for each kind)

- carrots ....1/2 ....1 .....1 1/2 .......2+
- cabbage ....1/2dl .....1dl .....11/2dl .....2+dl
- turnip .....1/2dl .....1dl .....11/2dl .....2+dl
- broccoli/cauliflower .....1-2 rosette(s) .....3-4 rosettes .....5+ rosettes
- mixed salad .....1dl .....2dl .....3dl .....4+dl
- tomatoes .....1/4 .....1/2 .....1 .....2+
- mixed vegetables .....1/2dl .....1dl .....2dl .....3+dl

How many potatoes do you usually eat (boiled, fried, mashed)? (Tick one box)

..... I do not/I seldom eat potatoes
..... 1-4/wk .....5-6/wk ..... 1/day ..... 2/day ..... 3/day .....4+/day

Rice, spaghetti, porridge, soup

How often do you eat rice and spaghetti/macaroni? (Tick one box on each line)

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>1/</th>
<th>2/</th>
<th>3+/</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rice</td>
<td></td>
<td>1/</td>
<td>1/</td>
<td>2/</td>
</tr>
<tr>
<td>Spaghetti</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>macaroni</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>noodles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

How often do you eat porridge? (Tick one box only)

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>1/</th>
<th>2-3/</th>
<th>1/</th>
<th>2-6/</th>
<th>1+/</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rice porridge</td>
<td></td>
<td>1/</td>
<td>2/</td>
<td>1/</td>
<td>2/</td>
<td>1/</td>
</tr>
<tr>
<td>Other porridge (oatmeal, etc.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

How often do you eat soup? (Tick one box on each line)

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>1/</th>
<th>2/</th>
<th>3+/</th>
</tr>
</thead>
<tbody>
<tr>
<td>As main course</td>
<td></td>
<td>1/</td>
<td>2/</td>
<td>3+</td>
</tr>
<tr>
<td>As appetizer/lunch/evening meal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fish

We would like to know how often you eat fish. Please fill in answers to the questions on fish consumption as fully as possible. The availability of fish may vary throughout the year. Please indicate in which seasons you eat the different kinds of fish.

<table>
<thead>
<tr>
<th></th>
<th>Never/</th>
<th>Same amount</th>
<th>Winter</th>
<th>Spring</th>
<th>Summer</th>
<th>Fall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>seldom</td>
<td>all year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cod, saithe, halibut, pollack</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wolfish, flounder, redfish</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmon, trout</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mackerel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herring</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other fish types</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In the periods of the year when you eat fish, how often do you usually eat the following? (Tick one box per line)

<table>
<thead>
<tr>
<th></th>
<th>Never/</th>
<th>1/</th>
<th>2-3/</th>
<th>1/</th>
<th>2+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>seldom</td>
<td>1/month</td>
<td>1/month</td>
<td>1/wk</td>
<td>1/wk</td>
</tr>
</tbody>
</table>
Boiled cod, saithe, halibut, pollack
Fried cod, saithe, halibut, pollack
Wolfish, flounder, redfish
Salmon, trout
Mackerel
Herring
Other fish types

If you eat fish, how much do you usually eat each time? (1 slice/piece = 150g) (Tick one box on each line)
- boiled fish (slice).....1 .....1.5 .....2 .....3+
- fried fish (piece).....1 .....1.5 .....2 .....3+

How many times per year do you eat fish feed? (Tick one box only per line)

0 1-3 4-6 7-9 10+

Roe
Fish liver

If you eat fish liver, how many tablespoonfuls do you usually take each time? (Tick one box only)

.....1 .....2 .....3-4 .....5-6 .....7+

How often do you eat the following kinds of fish dish? (Tick one box only per line)

Fishcakes/pudding/balls
Fish stew, fish pie
Fried fish (in batter), fish fingers

How much do you usually eat of the various dishes? (Tick one box only on each line)
Fishcakes/pudding/balls (pcs.) (2 fish balls = 1 fishcake).....1 .....2 .....3 .....4+
Fish stew, fish pie (dl).....1-2 .....3-4 .....5+
Fried fish (in batter), fish fingers (pcs.) .....1-2 .....3-4 .....5-6 .....7+

In addition to information regarding fish consumption, it is important to gather information on the accompaniments served with fish. How often do you use the following together with fish? (Tick one box per line only)

Melted or solid butter
Melted or solid margarine
Clotted cream (35%)
Reduced-fat cream (20%)
Sauce containing fat (white/brown)
Non-fat sauce (white/brown)

For the various kinds of accompaniments you eat with fish, please tick how much you would normally eat.
Melted or solid butter (tbs) .....1/2 .....1 .....2-3 .....4+
Melted or solid margarine (tbs) .....1/2 .....1 .....2-3 .....4+
Clotted cream (tbs) .....1/2 .....1 .....2-3 .....4+
Reduced-fat cream (tbs) .....1/2 .....1 .....2-3 .....4+
Sauce containing fat (dl) .....1/4 .....1/2 .....3/4 .....1 .....2+
Non-fat sauce (dl) .....1/4 .....1/2 .....3/4 .....1 .....2+

How often do you eat shellfish (e.g., shrimp, crab)? (Tick one box only)
..... never/seldom ..... 1/mth ..... 2-3/mth ..... 1+/wk

Meat
How often do you eat reindeer meat?
... Never/seldom ... 1/month ... 2-3/month ... 1/wk ... 2-3/wk ... 4+/wk

How often do you usually eat the following meat and poultry dishes? (Tick only one box for each dish)

Never/1/2-3/1/2+/seldom/month/month/wk/wk
Steak (cow, pork, mutton)
Chops
Beef
Meat balls, patties
Sausages
Stews, hash
Pizza with meat
Chicken
Bacon, pork
Other meat dishes

If you eat the following dishes, how much do you usually eat? (Tick one box per line)
Steak (slices) .....1 .....2 .....3 .....4 .....5+
- Chops (pcs.) .....1/2 .....1 .....1.5 .....2+
- meat balls, - cakes (pcs.) .....1 .....2 .....3 .....4+
- sausages (pcs.a 150g) .....1/2 .....1 .....1.5 .....2+
- stew, hash (dl) .....1-2 .....3 .....4 .....5+
- pizza with meat (pcs a 100g) .....1 .....2 .....3 .....4+

Which sauces do you use to meat dishes and pasta dishes?

Gravy
Broth
Tomato sauce
Creamy sauce

How much do you usually eat of these sauces?
Gravy (dl) …1/4 …1/2 …3/4 …1 …2+
Broth …1/4 …1/2 …3/4 …1 …2+
Tomato sauce …1/4 …1/2 …3/4 …1 …2+
Creamy sauce …1/4 …1/2 …3/4 …1 …2+

Other types of food
How many eggs do you usually eat in the course of a week (fried, boiled, scrambled, omelette)? (Tick one box)
.....0 .....1 .....2 .....3-4 .....5-6 .....7+

How often do you eat ice cream (for dessert, ice lollies, etc.)? (Tick one box)
(One box to indicate how often you eat ice cream in summer, and once for the rest of the year)
- in summer
- rest of the year

How much ice cream do you normally eat each time? (Tick one box)
.....1dl .....2dl .....3dl .....4+dl

How often do you eat sweet buns, cakes, Danish pastry, waffles, etc. (Tick one box)
(Yeast baking (buns, etc.)
Pastry(Danish, cream-filled)
Cakes
Pancakes
Waffles
Biscuits, cookies
Lefser/lomper (Norwegian specialities)
How often do you eat dessert?  (Tick one box)

<table>
<thead>
<tr>
<th>Never/ seldom</th>
<th>1-3/ month</th>
<th>1/ wk</th>
<th>2-3/ wk</th>
<th>4-6/ wk</th>
<th>1+/ day</th>
</tr>
</thead>
</table>

Pudding (chocolate, caramel)
Ricercme, mousse
Compote, fruit porridge, canned fruits
Strawberries (fresh, frozen)
Other berries (fresh, frozen)

How often do you eat chocolate?  (Tick one box)

<table>
<thead>
<tr>
<th>Never/ seldom</th>
<th>1-3/ month</th>
<th>1/ wk</th>
<th>2-3/ wk</th>
<th>4-6/ wk</th>
<th>1+/ day</th>
</tr>
</thead>
</table>

Dark chocolate
Light chocolate

If you eat chocolate, how much do you usually eat each time?
Use the size of a Kvikk-Lunsj (Kit-Kat) as a guide, and indicate how much you eat in relation to that (Tick one box)

| .....1/4 | .....1/2 | .....3/4 | .....1 | .....1.5 | .....2+ |

How often do you eat salty snacks?  (Tick one box)

<table>
<thead>
<tr>
<th>Never/ seldom</th>
<th>1-3/ month</th>
<th>1/ wk</th>
<th>2-3/ wk</th>
<th>4-6/ wk</th>
<th>1+/ day</th>
</tr>
</thead>
</table>

Potato chips
Peanuts
Other nuts
Other snacks

Cod liver oil and fish oil capsules
Do you use cod liver oil (liquid)? Yes/No
If yes, how often do you use it?  (Tick one box for each line)

<table>
<thead>
<tr>
<th>Never/ seldom</th>
<th>1-3/ month</th>
<th>1/ wk</th>
<th>2-6/ wk</th>
<th>Daily</th>
</tr>
</thead>
</table>
- in the winter
- the rest of the year

How much cod liver oil do you usually take at one time?

| .....1ts | .....1/2ts | .....1+ts |

Do you use cod liver oil pills/capsules? Yes/No
If yes, how often do you take cod liver oil pills/capsules?  (Tick one box for each line)

<table>
<thead>
<tr>
<th>Never/ seldom</th>
<th>1-3/ month</th>
<th>1/ wk</th>
<th>2-6/ wk</th>
<th>Daily</th>
</tr>
</thead>
</table>
- in the winter
- the rest of the year

Which type of cod liver oil pills/capsules do you usually use, and how many do you use to take each time?
Name:....................Amount:.....

Dietary supplements
Do you use other dietary supplements? Yes/No
If yes, how often do you take such supplements?

<table>
<thead>
<tr>
<th>Never/ seldom</th>
<th>1-3/ month</th>
<th>1/ wk</th>
<th>2-6/ wk</th>
<th>Daily</th>
</tr>
</thead>
</table>
Brand name:................................
Brand name:................................
Brand name:................................

Warm meals
How many times during a month do you eat warm meals?

... Breakfast ...Dinner
... Lunch ... Evening meal
Alcohol

Are you a teetotaller? Yes/No

If No, how often and how much have you drunk on average in the last twelve months?
(Tick one box on each line)

<table>
<thead>
<tr>
<th>Never/ seldom</th>
<th>1/ month</th>
<th>2-3/ month</th>
<th>1/ wk</th>
<th>2-4/ wk</th>
<th>5-6/ wk</th>
<th>1/ day</th>
<th>2+/ day</th>
</tr>
</thead>
</table>

Beer (1/2l)
Wine (glass)
Spirits (shorts/cocktails)
Liqueurs

Social conditions

Are you (tick one box only):
.....married ....cohabitant ....single…other …divorced …widow

How many persons are there in your household? Number: .....

What is your household's gross annual income?
.....less than 150 000 kr .....151 000-300 000 kr
.....301 000-450 000 kr .....451 000-600 000 kr
.....more than 750 000 kr

What is your work situation?
… work full time … work part-time …retired … work at home …education …disabled … rehabilitation …unemployed

Do you work outdoors in your job? Yes/No
If Yes; how many hours per week? …Summer …Winter

Sun habits

Do you get freckles when you sunbathe? Yes/No

To study the effect of sunbathing on risk of melanoma, we ask you to give information about skin colour.
Tick on the colour that best matches your skin colour (without sunbathing).
(coloured scale 1-10)

How many times per year have you been sunburnt to the extent that you skin has become irritated and blistered, and peeled afterwards? (One tick for each age-group)

<table>
<thead>
<tr>
<th>Age</th>
<th>Never</th>
<th>Max 1/ year</th>
<th>2-3/ year</th>
<th>4-5/ year</th>
<th>6 or more/ year</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

How many weeks on average per year have you taken sunbathes in southern Europe?

<table>
<thead>
<tr>
<th>Age</th>
<th>Never</th>
<th>1 wk</th>
<th>2-3 wk</th>
<th>4-5 wk</th>
<th>7+wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The last 12 months

How often have you been sunbathing in solarium?

<table>
<thead>
<tr>
<th>Age</th>
<th>Never</th>
<th>Seldom</th>
<th>1/month</th>
<th>2-3/month</th>
<th>3-4/month</th>
<th>1+/wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The last 12 months

How often do you shower or take a bath?

<table>
<thead>
<tr>
<th>1+/ day</th>
<th>1/ day</th>
<th>4-6/ wk</th>
<th>2-3/ wk</th>
<th>1/ wk</th>
<th>2-3/ month</th>
<th>Seldom/ never</th>
</tr>
</thead>
</table>

With soap/shampoo
Without soap/shampoo
When do you use cream with sun screen? (more than one tick possible)
....At Easter ....in Norway or outside southern Europe? ....sunbathing in southern Europe

Which sun factors do/did you use in these periods?

<table>
<thead>
<tr>
<th>Easter</th>
<th>Norway/outside south Europe</th>
<th>South Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1-4</td>
<td>5-9</td>
</tr>
<tr>
<td>10-14</td>
<td>15+</td>
<td></td>
</tr>
</tbody>
</table>

How many irregularly shaped moles larger than 5mm do you have in total on both legs (between the toes and the groin)? Three examples of moles larger than 5mm are shown below.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2-3</th>
<th>4-6</th>
<th>7-12</th>
<th>13-24</th>
<th>25+</th>
</tr>
</thead>
</table>

How often do you use the following skin care products? (Tick one box)

<table>
<thead>
<tr>
<th>Face cream</th>
<th>Hand cream</th>
<th>Body lotion</th>
<th>Perfume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>1/ month</td>
<td>2-3/ month</td>
<td>1/ wk</td>
</tr>
<tr>
<td>seldom</td>
<td>2-4/ wk</td>
<td>5-6/ wk</td>
<td>1/ day</td>
</tr>
<tr>
<td></td>
<td>1/ day</td>
<td>2+/ day</td>
<td></td>
</tr>
</tbody>
</table>

Finally we would ask about your permission to contact you again per post. We will get your address from the central person registry. Yes/No

Are you willing to give a blood sample? Yes/No