ASPECTS OF BREAST AND CERVICAL CANCER SCREENING

by
Inger Torhild Gram

University of Tromsø
Institute of Community Medicine

The Norwegian Cancer Society

University of Alabama at Birmingham,
School of Public Health
The opinions expressed in this publication are those of the authors and do not necessarily reflect the official policy of the institutions supporting this research.
ASPECTS OF BREAST AND CERVICAL CANCER SCREENING

by

Inger Torhild Gram

University of Tromsø, Institute of Community Medicine
The Norwegian Cancer Society,
University of Alabama at Birmingham, School of Public Health

Tromsø 1992
Dedicated to my children

INGVILD AND HÅVARD

SUCCESS

To laugh often and much;
to win the respect of intelligent people
and the affection of children; to earn the
appreciation of honest critics and
endure the betrayal of false friends;
to appreciate beauty, to find the best
in others; to leave the world a bit
better, whether by a healthy child,
a garden patch or a redeemed
social condition; to know even
one life has breathed easier because
you have lived. This is to have
succeeded.

- Ralph Waldo Emerson
ABSTRACT

The purpose of the thesis was to investigate aspects of breast cancer screening such as the feasibility, non-attendance and adverse effects of a general mammography screening program. A second objective was to examine whether risk factors for cervical neoplasia could be identified for potential utilization in a selective screening program for cervical cancer.

Five data sets were used; a cohort of women aged 40 or older (N = 4,290) invited to have a free screening mammogram in the Third Tromsø Study; a mailed questionnaire survey conducted after six months among 743 subjects (attenders, non-attenders and women never invited) and an interview survey conducted after 18 months among 126 women who had a false positive mammogram screening exam together with 152 women with a negative exam. Women aged 20 to 49, who participated in the Second Tromsø Study (N = 9,906), were followed for ten years for the development of cervical intraepithelial neoplasia and cervical cancer by linkage of their personal identification number in the Pathology Registry of the University Hospital in Tromsø. The fifth data set constituted all records pertaining to cervical specimens obtained from 1972 through June 1989 in Troms and Finnmark, the two northernmost counties in Norway (N = 352,718).

The results from this thesis show that organized breast cancer screening with mammography is technically feasible with a central unit responsible for the administration of the screening and the interpretation of the mammogram and with local responsibility for the diagnostic work-up. The most frequently reported reason for non-attendance was not having the opportunity. Non-attenders also reported a low level of breast cancer anxiety compared with the general population. The adverse effects suffered by women with a false positive mammogram in an organized screening is not of a magnitude that should discourage such screening. Current cigarette smoking, ever oral contraceptive use, cervico-vaginal infection with Trichomona Vaginalis and Human Papillomavirus identified by Pap-smear were found to be risk factors for cervical neoplasia. However, these risk factors did not fulfill the criteria of making selective screening for cervical cancer worthwhile compared with screening of the total population.

Key words: cancer anxiety; cervical cancer; cigarette smoking; follow-up studies; mammography screening; Norway; oral contraceptive use; papillomavirus; quality of life
Life is short
And the art long
The occasion instant
Experiment perilous
Decision difficult.

-Hippocrates

Nature is probabilistic
And information incomplete
Outcomes are valued
Resources limited
Decisions unavoidable.

-Weinstein et. al
# CONTENTS

1. Acknowledgements 6  
2. Original papers 8  
3. Aims of the thesis 9  
4. Abbreviations 9  
5. Introduction 10  
6. Background 12  
7. Materials 18  
8. Main results 20  
9. General discussion 22  
10. Conclusions 35  
11. References 36  

Appendix  
Papers I-VI  

Survey Instruments  
Mailed questionnaire  
Interview survey
1. ACKNOWLEDGEMENTS

These studies were carried out at the Institute of Community Medicine, University of Tromsø (1984-1989) and at the Department of Epidemiology, School of Public Health, University of Alabama at Birmingham (1989-1991). I am obliged to these Institutions for providing me with working facilities and to the Norwegian Cancer Society for financing my years abroad. The Tromsø Studies were done in cooperation with the National Health Screening Service, Oslo, Norway. I would like to thank all of you who have inspired, encouraged and helped me during my hard work with this thesis.

However, I want to extend my gratitude to a number of individuals. I want to express my thankfulness to Professor Egil Arnesen with the Institute of Community Medicine, for initiating the mammography screening, obtaining permission for the linkage between the Pathology Registry and the Tromsø Studies as well as for his specific advice regarding the mailed questionnaire survey. Furthermore, I want to emphasize the significance of his supportive visit while I was bed-ridden with a fractured back considering to terminate my career as a researcher.

I am indebted to Professor Philip Cole with the Department of Epidemiology, who introduced me to cancer epidemiology in 1986 and captured my interest for this field of science. I am especially thankful to Professor Knut Westlund with the National Health Screening Service, for supporting my ambition of being trained as a cancer epidemiologist and for encouraging me to approach Professor Cole with this intention. I am obliged to Professor Philip Cole for his ingenuity, constructive criticism and for sharing with me his rich knowledge and experience in cancer epidemiology during my stay in his Department. I sincerely appreciate his suggestion about applying for a position as a Visiting Associate Professor at the School of Public Health and as a adjunct scientist at the Comprehensive Cancer Center. I highly value the practice I got from working in these positions and I am convinced that it has tremendously improved my skills both as a teacher and scientist.

I also am thankful to Professor Eiliv Lund with the Institute of Community Medicine, who has been my long-distance adviser during the final months of this work. His enthusiastic
and excellent guidance in the field of epidemiology are highly appreciated. When my computer was hit by some special kind of lightening and my eighty megabyte harddisk had to be reformatted, Professor Lund had the ability to make me realize that life is never really as bad as it seems. His capability of being both highly productive in his work and a personable individual at the same time is an radiating example of how a scientist should be.

I also feel very fortunate having my friend from medical school Dr. Maja-Lisa Löchen as a female scientist next door during most of the years at the Institute of Community Medicine. I highly appreciate her wise and understanding comments when different problems were encountered and most of all for reminding me of seeing things in a broader perspective. I want to thank Secretary Sissel Andersen for working with several parts of the mammography project. I want to acknowledge my co-authors; Associate Professor Harland Austin, Doctoral Student Jeanetta Churchill, Professor Eivin Lund, Dr. Per-G Lund-Larsen, Dr. Alf F. Rosenlund, Dr. Suzanne Slender, Professor Helge Stalsberg, Dr. Jan Störmmer, for helpful input and fruitful discussions. A special thanks to Dr. Maurizio Macaluso for valuable co-operation and for patiently dealing with all the computing problems in connection with Paper VI.

Thanks to my friends and family who came and visited us while living in exile. Also thanks to my friend Ilene Brill for demonstrating for me that Birmingham have much more to offer than an impressive University. I want to express my gratitude to Arvid, my husband and best friend, for travelling with me from the "Far North" to the "Deep South" and for standing by my side "for better and for worse" during the course of this work. I also want to express my warm thanks to my two children Håvard and Ingvild for their support and patience.

Financial support has been given from The Norwegian Cancer Society, The Aakre Foundation for the fighting against cancer, The University of Tromsø and the University of Alabama at Birmingham.

Tromsø, February 4, 1992
Inger Torhild Gram
2. ORIGINAL PAPERS

This thesis is based on the following papers, referred to in the text by their Roman numerals:


3. AIMS OF THE THESIS

To investigate aspects of breast (Papers I-III) and cervical (Papers IV-VI) cancer screening.

Specifically to:

1 - examine the feasibility, non-attendance and adverse effects of mammography screening (Paper I-III).

2 - examine whether risk factors for cervical neoplasia can be identified for potential utilization in a selective screening program for cervical cancer (Papers IV - VI).

4. ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSE</td>
<td>Breast Self Examination</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CIN</td>
<td>Cervical Intraepithelial Neoplasia</td>
</tr>
<tr>
<td>CIN III</td>
<td>Cervical Intraepithelial Neoplasia Grade III</td>
</tr>
<tr>
<td>FP</td>
<td>False Positive</td>
</tr>
<tr>
<td>IR</td>
<td>Incidence Rate</td>
</tr>
<tr>
<td>NA</td>
<td>Non-attenders</td>
</tr>
<tr>
<td>OC</td>
<td>Oral Contraceptive</td>
</tr>
<tr>
<td>PS</td>
<td>Population Sample</td>
</tr>
<tr>
<td>SN</td>
<td>Screening Negative</td>
</tr>
<tr>
<td>HPV</td>
<td>Human Papillomavirus</td>
</tr>
<tr>
<td>TV</td>
<td>Trichomonas Vaginalis</td>
</tr>
</tbody>
</table>
5. INTRODUCTION

Worldwide, breast and cervical cancer are the most frequently diagnosed cancers in the female population. They comprise about one-third of all new cases of cancer among women (Parkin et al., 1988). Breast and cervical cancer rank number one and four, respectively, as causes of cancer death among women 35 to 54 years of age in the Western World (Muir et al., 1988).

Primary preventive measures involve entirely asymptomatic individuals, thus raising substantial ethical problems. Primary prevention of breast cancer through treatment with anti-estrogens (tamoxifen) (Cuzick et al., 1986) and for cervical cancer through vaccination have been suggested (zur Hausen, 1989). However, prevention by means of such measures is unlikely to be an option for women in the foreseeable future (Fentiman, 1989; zur Hausen, 1989).

In Norway, about 1900 women are diagnosed with breast cancer each year (The Cancer Registry of Norway, 1990) while close to 700 women will die from the disease (The Central Bureau of Statistics, 1990). The age-adjusted incidence of breast cancer increased by 50% from 1955 to 1984 (Tretli and Haldorsen, 1990). Although, the 5-year relative survival rate during the same decades increased significantly from 59% to 67% (Höst and Lund, 1986), this is believed to be due to an earlier stage distribution rather than improved treatment. Recently treatment with tamoxifen has shown a slight effect on short-term relative survival from breast cancer, while the long-term effect is still unknown (Early Breast Cancer Trialists' Collaborative Group, 1988).

Annually about 350 new cases of cervical cancer are diagnosed in Norway (The Cancer Registry of Norway, 1990), while approximately 130 women will die from the disease (The Central Bureau of Statistics, 1990). The incidence of cervical cancer rose from the 1950's to the mid 1970's after which a slow decline started. During the same period, the mortality rate has shown a downward trend for women aged 25 through 54 (Lund et al., 1984). Most of this reduction is also likely to be due to a more favorable stage distribution.
Control of breast and cervical cancer should ideally be achieved either by preventing the diseases from occurring or by curing individuals who develop the disease with effective treatment. Currently this is not so and other measures may be appropriate.

Secondary preventive measures identify and treat asymptomatic persons who have already developed preclinical disease, but in whom the disease itself has not become clinical evident. Secondary prevention, in the form of population screening, appears to be a reasonable approach as a means of breast and cervical cancer control. Nevertheless, screening is a difficult, complex, and not always a successful endeavor. Furthermore, a screening program entails intervention in a healthy population and therefore carries an ethical responsibility for the total impact on the population involved. As the costs and benefits of screening are stated in relative terms, the answer to the question of whether the benefits do outweigh the adverse effects will depend on how much weight the different factors are given and how strong the evidence needs to be on benefits and risks. This thesis examines some aspects of breast and cervical cancer screening which have not been sufficiently addressed.

The theoretical principles of cancer screening are reviewed in chapter 6. The five data sets utilized are described briefly in chapter 7. For more detailed information about methods, statistical analysis, and results of the different studies the reader is referred to the enclosed papers. The main results from the papers are summarized in chapter 8, while their contribution in the context of breast cancer and cervical cancer screening is discussed in chapter 9. In chapters 10 and 11 the conclusions and references are displayed, respectively. The six original papers and two of the survey instruments are enclosed in the appendix.
6. BACKGROUND

Screening for disease control can be defined as the examination of asymptomatic people in order to classify them as likely, or unlikely, to suffer from the disease that is the object of the screening. Subjects who appear likely to have the disease are evaluated further to arrive at a final diagnosis. The individuals who are then found to have the disease are treated. The organized application of early diagnosis and treatment activities in large groups is often described as mass screening or population screening (Morrison, 1985). Three scientific concepts for population screening for cancer will be considered.

1) Cancer suitable for screening

The cancer should cause considerable morbidity, disability or mortality and as such be a public health problem. A second prerequisite is that the cancer must have a treatment that when applied to the screen-detected stage of the disease, has a more favorable outcome than treatment applied after symptoms have led to diagnosis (Cole and Morrison, 1980).

The proportion of subjects who will benefit from this early detection is directly related to the natural history of the specific cancer. The preclinical phase of a disease begins when the pathological process is first present and ends when signs and symptoms appear. The detectable preclinical phase is the last part of the preclinical phase for which the pathological process can be detected by the screening test (Cole and Morrison, 1980). If few preclinical cancers progress to invasive cancer little is gained by screening. If a majority of them will later progress, early detection and effective treatment in the preclinical phase will decrease the incidence of invasive cancer. A third prerequisite is that the cancer must have a relatively long detectable preclinical phase to avoid continuous rescreening of the subjects.

Although treatment efficacy is a fundamental requirement for screening to be worthwhile, it is often difficult to determine with certainty whether early diagnosis truly improves the outcome. This is due to lead-time and length bias. Lead time is the interval beginning when a disease is detected by screening and ending when it would otherwise have been
diagnosed in the absence of screening. **Lead time bias** results from the apparent extended survival of persons diagnosed during screening because the amount of lead time is added to the usual length of the survival period (from symptom-based diagnosis to death). **Length bias** refers to the tendency of screening to detect a disproportionate number of cases of slowly progressive disease and miss aggressive cases that, due to the rapid progression, have a short duration of the detectable preclinical phase (Cole and Morrison, 1980; Morrison, 1985).

2) Suitable test
The screening test should be acceptable to the population targeted, as painless as possible, not cause morbidity, be easy to perform, and be inexpensive. The primary measure of a screening test is its validity. This refers to the extent to which a test measures what it purports to measure. The two basic measures of the validity of the screening test are sensitivity and specificity. The **sensitivity** is its ability to detect persons with preclinical disease; that is the number of positives detected divided by the number of persons screened who actually have the disease. The **specificity** of a test is its ability to identify persons free from disease, that is the number of negatives screened divided by the number of those screened who do not have the disease. The screening test may successfully label those with early disease as positive and those without as negative, do one, the other or neither. Hence, subjects participating in a screening program may be classified into four categories; true negatives, true positives, false negatives, and false positives. The gain versus adverse effects from the screening for an individual will vary according to which of the four groups the subject belongs (Cole and Morrison, 1980; Morrison, 1985). Another measure of the screening test is its **reliability**. This is the ability of the test to obtain the same result when repeated. The reliability may be low due to interobserver or intraobserver disagreement. A test that is highly sensitive must be highly reliable, while the opposite is not necessarily true (Morrison, 1985).

3) Suitable screening program
A screening program involves the use of a screening test to detect the preclinical phase of the disease of interest in a particular (target) population. Typically the indicators of effect of a screening program are classified according to process and outcome measures.
The first term is related to administrative and organizational aspects like the number of persons examined or the cost of the screening program. The outcome measures are related to the aim of the program i.e. for cancer usually a reduction in risk or mortality from the disease. The advantage of some process measures, is that they may be obtained readily. However, they may not give any indication on how successful the program is in achieving the goals of the screening (Cole and Morrison, 1980).

An example of a process measure is the predictive value of a positive test. It is the proportion of true positives among all who have screening positive results. The major determinants for the predictive value are, for rare diseases as cancer, the prevalence of the detectable preclinical disease in the examined population and the specificity of the screening test as the specificity operates on the vast majority of subjects who are disease free. As the predictive value is a proportion, it can have the same value for tests which differs greatly in how many preclinical cases they detect and in how much influence they can have on cancer control (Cole and Morrison, 1980).

The two measures of validity; sensitivity and specificity, may also be applied to the screening program. The program sensitivity is then the proportion of persons diagnosed as having the disease as a result of screening among all of the persons with the disease in the target population. Program specificity is the proportion of persons not diagnosed as having the disease in the disease-free part of the target population (Hakama, 1985).

There may be substantial differences in test sensitivity and program sensitivity on the one hand, and in test specificity and program specificity on the other. A valid screening test is a prerequisite for a successful program, but the program may fail even if the test is valid. The positive predictive value of a screening program may be enhanced by a high test specificity, by a high attendance rate in a general population, or by screening high-prevalence (i.e. high risk) persons (Hakama, 1985).

A screening program may be organized, opportunistic or selective. Hakama et al. has described the following as essential elements of an organized screening program: The target population should be identified as well as the individual subjects. Measures should be available to insure high coverage and attendance. The program should require adequate
facilities for field-, laboratory-, diagnostic confirmation, and treatment. Also necessary is
a referral system between the individual, the laboratory and the clinical facility for
diagnosis of abnormal screening tests, for management of any abnormalities found and for
providing information about normal screening tests. It is important to perform an
evaluation and monitoring of the total program in terms of incidence and mortality rates
among those attending, and among those not attending, at the level of the total target
population. Quality control of the epidemiological data as well as of each facility/part of
the program should be put into operation (Hakama et al., 1985). This quality control
should also entail measurements of possible adverse effects the program may produce in
the target population.

A screening may be called opportunistic (spontaneous) when the subjects go for a general
examination, during which the opportunity is taken to perform the screening test (Miller,
1985; Laara et al., 1987). An opportunistic screening tends to emphasize the sensitivity
more than the specificity. Thus, the case finding becomes the most important aspect of
the screening. This may easily result in an over-use of clinical services.

The main criticism against such screening is therefore that their objectives are related to
process measures (e.g. how many cases found, how many Pap-smears that are processed
during a period) rather than the outcome measures (e.g. reduction in mortality) (Anon.,
1985; Laara et al., 1987).

In a broad sense, all screening programs are selective to some extent as the target
population is always defined by age and often by gender. Selective screening usually
means applying the screening test to only a subpopulation that has a high risk for the
disease. The information on such factors should preferably be readily obtainable without
having to contact each person in the population (Morrison, 1985). The purpose of
selective screening is to reduce the cost of the program. If this goal is to be achieved the
risk factors classifying the subjects into risk groups should be easily recognized, strongly
related to the disease and not highly prevalent in the general population. The factors
utilized in defining the high-risk group need only be risk markers for the disease and not
necessarily causal factors. To be able to classify subjects as being at high or low risk and
thereby be able to perform selective screening, the target population must be defined. A
substantial proportion of the total number of cancers in the target population should then be detected in the high-risk group i.e., only a few cases should originate in the low-risk group not subjected to screening (Hakama, 1985).

The desired reduction in cost can be in terms of resources required or adverse effects of the program or both. A selective screening will change the program validity, i.e., the program sensitivity will decrease and the program specificity will increase, compared with screening the total population. The program sensitivity decreases since the ability to detect the true cases in the low-risk population disappears when only high-risk groups are screened. The program specificity increases since all the subjects in the low-risk group will be assumed test negative and the vast majority rightfully so. When the specificity increases, the number of false-positive cases and thereby the number of women exposed to possible adverse effects of the program decreases. Thus, there is a reduction in the cost in terms of money and adverse effects per true case found by a selective compared with a non-selective screening program (Hakama, 1985).

However, the success of a selective screening depends on what proportion of all cases of the disease in the target population the program is able to identify. This proportion depends heavily on the risk of disease in the high-risk group compared to the risk in the low-risk group (relative risk). In Table I (from Hakama, 1985 based on Hakama et al., 1979) the cost is given as the size of the high-risk group to be screened. The upper limit of the program sensitivity will then be the total number of cases in the high-risk group as a percentage of the total number of cases in the population. Table I shows that in order to detect more than 80% of the total cases in a high-risk group comprising 20% of the total population, the risk in the high-risk group would have to be almost 20 times that in the low-risk population (Hakama, 1985).

If a few strong risk factors are known selective screening can be based on a combination of several risk factors. A risk score can be constructed depending on what risk factors the subject has been exposed to. Subjects with a score over a certain level (several risk factors) may be defined as a high-risk group. If the risk factors are independent, the size of the population exposed decreases as the number of risk factors increases. Therefore,
when the high-risk group is defined by a combination of risk factors rather than by only one risk factor, program sensitivity decreases further as the high-risk group is decreasing in size. An alternative approach to reduce the cost of a screening program is to vary the screening interval according to the presence or absence of risk factors. This proposal is based on the notion that the risk factor not only increases the incidence, but also leads to a disease with a shorter detectable preclinical phase (Hakama, 1985).

Subjects who participate in screening programs select themselves. Compared to the general population, they are often healthier and more health conscious and their risk of developing disease is different from that of the non-attenders. This is often referred to as the healthy screenee bias (Morrison, 1985). This bias can be an important limitation to the success of any screening program.
7. MATERIALS

The original papers in this thesis are based on five different data sets which are described briefly below.

The Second and Third Tromsø Study

The Tromsø Studies are collaborative actions by the National Health Screening Service and the Faculty of Medicine of the University of Tromsø in close cooperation with the local health authorities. The main objectives are to examine changes in cardiovascular risk factors in the population and the determinants of these changes. The First Tromsø Study was conducted in 1974 and complete details of the methods are given elsewhere (Thelle et al., 1976). Between 1979 and 1980 all men (N = 11,423) aged 20 to 54 and all women (N = 9,906) aged 20 to 49 living in the municipality of Tromsø were invited to participate in the Second Tromsø Study (Thelle et al., 1983, Jacobsen and Thelle, 1988). The Third Tromsø Study was conducted in 1986-1987. Altogether 29,026 men and women were invited. An additional evaluation was performed in the Third Tromsø Study as women aged 40 or older (N = 4,290) were invited to have a free screening mammogram. Thirty-three women who met and had their mammogram taken without an invitation are also included in the material. This thesis utilizes data obtained from women in both the Second and Third Tromsø Study.

The Mailed Questionnaire Survey

A questionnaire was mailed to four groups of women six months after the mammography screening in the Third Tromsø Study was finished. The follow-up survey was conducted among 179 women with a false positive screening mammogram, a random sample of 250 women selected from those with a negative result, all the non-attenders (N = 670), and a random sample of 250 women (i.e. a population sample) who lived in another city, had not been invited, but were otherwise comparable. Altogether 743 women completed this questionnaire.
The Interview Survey

Women in the false positive and screening negative group who had indicated in the mailed questionnaire that they would allow a personal interview were contacted approximately one year after the first follow-up survey. Responses to the mammography screening were collected by interviewing 278 such women.

The Pathology Registry

The Department of Pathology of the University Hospital of Tromsø is a referral center for all cytologic and histologic specimens obtained in Troms and Finnmark, the two northernmost counties in Norway. To some extent the Department of Pathology is also used as a referral center for specimens obtained in Nordland. All records pertaining to cervical specimens obtained from 1972 through June 1989 (N=352,718) were extracted from the Pathology Registry.
8. MAIN RESULTS

Mammography screening: Feasibility, Non-attendance and Adverse effects

Paper I
Paper I describes a model for an organized screening program for breast cancer by mammography. It is concluded that a central administration of both the screening and the interpretation of the mammogram with subsequent local diagnostic work-up is technically feasible. A high attendance rate was achieved. It is recommended to have double readings of the screening results as this increases the predictive value of a positive mammogram.

Paper II
The results from the mailed questionnaire survey show that the most frequently reported reason for non-attendance was not having the opportunity. The non-attenders also reported to a lesser extent to have breast cancer anxiety than a random sample of women from the general population who were not invited, but otherwise comparable. More than 30% of women in the population sample reported anxiety about having breast cancer. At the time of the survey the prevalence of anxiety about having breast cancer was significantly lower among women who had had a negative mammogram compared with the population sample. The vast majority of the study subjects indicated a positive attitude toward mammography that had not been adversely affected by screening experience.

Paper III
This paper, based on the interview survey, shows that women with a false positive mammogram report the same quality of life as do women with a negative mammogram when interviewed 18 months after the mammography screening. A false positive mammogram was described by 5% of the women as the worst thing they ever had experienced. Almost a third of the women who underwent surgery were suffering long-term consequences in terms of pain and reduced sexual sensitivity in the biopsied breast. However, most women with a false positive result regarded this experience, in retrospect, as but one of many minor stressful experiences creating a temporary decrease in their quality of life.
Cervical cancer screening: Identification of risk-factors for a potential selective screening

Paper IV
This report investigates whether cigarette smoking can be identified as a risk factor for cervical intraepithelial neoplasia grade III (CIN III) or cervical cancer among a cohort of women from the Second Tromsø Study. The results indicate that current smokers (at the time of the health survey) experience a higher incidence of CIN III than do nonsmokers. The study also displays a dose response relation between various measures of smoking intensity and the CIN III incidence rates.

Paper V
This study focuses on oral contraceptive use as a potential risk factor for developing cervical neoplasia (CIN) in the cohort of women from the Second Tromsø Study. An increased risk of cervical neoplasia was found among both current and former (at the time of the survey) oral contraceptive users as compared with never users. The study also suggests a relationship between age at start of oral contraceptive use and CIN.

Paper VI
In this follow up study cervico-vaginal infections by Trichomonas vaginalis and Human Papillomavirus are investigated for their possible causal relationship with CIN III. The study is conducted among a cohort of women with Pap-smears referred from Troms and Finnmark Counties to the Pathology Registry of the University Hospital of Tromsø. An increased incidence rate of CIN III was found both among women with Trichomonas vaginalis infection and among women with Human Papillomavirus infection compared to women infected with neither of these.
9. GENERAL DISCUSSION

Breast cancer

Suitable disease, suitable test, suitable program
Breast cancer is the most important cancer in Norwegian women in terms of mortality and morbidity and must be considered a public health problem. The mammography procedure has the potential of detecting breast tumors in asymptomatic women (Tabar et al., 1985) and treatment of early detected cases offers advantages over later treatment in terms of morbidity and mortality (Miller et al., 1990; Sigurdsson et al., 1991). The preclinical phase of breast cancer is believed to be of such duration so that 2-yearly screening is recommended to be sufficient for women over the age of 50 (Tabar et al., 1987).

Nevertheless, the lack of effect of mammography screening on total mortality, the fact that not all programs achieve the same reduction on breast cancer mortality, and the cost and possible adverse effects have created some controversy about how large the net health benefit from mammography screening really is (Skrabanek, 1985; Wright, 1986; Eddy et al., 1988; Skrabanek, 1988; Devitt, 1989; Schmidt, 1990).

Reduction in mortality
Several studies have been undertaken to evaluate the effect of mammography screening on mortality (Shapiro et al., 1982; Collette et al., 1984; Verbeek et al., 1984; Tabar et al., 1985; Palli et al., 1986; Chamberlain et al., 1988; Anderson et al., 1988, Roberts et al., 1990). In three recent reports (Chamberlain et al., 1988; Anderson et al., 1988, Roberts et al., 1990) the mortality from breast cancer in the screened population was only slightly different from that among controls several years after the start of the study. The recent results of the Stockholm trial seem to be more favorable (Frisell et al., 1991), and the last results from the Swedish two-county trial are promising. After more then ten years of follow-up this program achieved some 40% reduction in breast cancer mortality for women over 50 years of age, screened every 33 months (Duffy et al., 1991). It seems reasonable to conclude from these studies that a reduction in mortality from breast cancer can be expected for women aged 50 and older.
Feasibility

Paper I was a feasibility study not designed to evaluate the reduction in mortality. It addressed how an organized population screening might be implemented in the Norwegian environment. Although not without problems, the model tried out was feasible (Paper I). A somewhat similar model, a central administration with 11 regional mammography centers has been chosen for the nationwide breast cancer screening program in Finland. A centralized Mass Screening Registry for identification, invitation and follow-up of the cohorts has been established within the Finnish Cancer Registry. After two years, an attendance rate of 88% was reported (Hakama et al., 1991). It seems reasonable to assume that nationwide screening could also be feasible in Norway if such a public health policy was implemented.

Non-attendance

As described earlier a high degree of compliance is important in order for a screening to be maximally effective. Several studies have indicated that non-compliers constitute a high-risk group for fatal breast cancer (Chamberlain et al., 1988; Anderson et al., 1988; Duffy et al., 1991). It is, however, difficult to investigate the reasons for non-attendance as they also tend to have a low response rate when surveyed (Paper II, Rutledge et al., 1988; Baines et al., 1990; Fallowfield et al., 1990). The results from these studies may therefore be distorted by selection bias. Nevertheless, inconvenience and travel distance seem to be important factors for non-attendance in our study as well as in others (Rutledge et al., 1988; Rimer et al., 1989; Baines et al., 1990). Thus, a convenient location of the mammography screening unit seems likely to enhance the compliance.

Another finding from this thesis is that the non-attenders do not have the same concern about breast cancer as do those attending or those not invited. Since perceived vulnerability to breast cancer has been shown to be related to attendance in other studies (Calnan, 1984; Nielsen, 1990; Lerman et al., 1990) the lack of such may be one pressing reason for non-compliance. One of the challenges is therefore to increase utilization, while avoiding an increase in the already significant prevalence of anxiety about breast cancer among women. Furthermore, education efforts aimed at informing women that
mammography can detect cancer in the absence of symptoms is believed to be more effective than increasing a woman's perception of her susceptibility (Vernon et al., 1990). The suggestion to collaborate with health promotion experts to improve screening attendance rates therefore seems reasonable (Rutquist et al., 1990). However, as there is still controversy about the net gain for the individual woman (Schmidt, 1990), she must be allowed to make her own decision whether to attend or not and should not be bothered by repeated screening invitations (Fallowfield et al., 1990; Hakama et al., 1991).

**Positive predictive value**

The significance of a low positive predictive value depends very much on the consequences of a positive test. If such a test is followed by an expensive or potentially dangerous diagnostic examination it is important to achieve a high predictive value (Morrison, 1985). There is an ongoing discussion on whether to use single or double readings, and single or multiple views. The advantage achieved if a single mediolateral-oblique view is used instead of two views (mediolateral-oblique and cephalocaudal) is a reduced cost and radiation exposure. However, the possible side effects of radiation with modern two-view, low-dose film mammography on an annual basis after age 40 is considered to be minimal, about 1-2 per 1000 breast cancers (Gohagan et al., 1986). In the Swedish two-county trial single view mammography seemed to be less sensitive for women under the age of 50 at entry (Tabar et al., 1989). The disadvantage with a single view, that more healthy women will be referred to diagnostic work-up examinations, have made some authors conclude that single view screening should not be performed (Bassett et al., 1987). Two view mammography, to a total cost of about $50 or less, were used both in a recent Canadian Pilot Study (Hislop et al., 1991) as well as in the Finnish national screening program (Hakama et al., 1991). These two programs achieved an overall proportion of false positives of about 10 and 5 percent, respectively. The Finnish program also used two readers (Hakama et al., 1991).

These results are in accordance with ours, as we found the predictive value of a positive screening mammogram to increase when the mammograms were read independently by two readers, as well as when multiple views were utilized. On the other hand, as the number of false positive subjects decreased, the number of false negative subjects
increased. The method with the highest predictive value (8.8 %) would have missed one out of ten cancers (Paper I). So far, it is not known whether the net benefit is greater by screening a large population by single-view or a smaller population by two-view/multiple readers (Rutquist et al., 1990).

As pointed out by the UICC workshop, it is important to build in procedures permitting rigorous evaluation of the quality of the screening program (Miller et al., 1990). Experience from screening studies show that the quality may vary with time (Hislop et al., 1991) and place (Baines et al., 1986; Hakama et al., 1991) depending on the equipment and skill of the personnel conducting the screening (Kopans, 1990; Miller et al., 1990).

The model described in Paper I could easily be followed by establishing a central administration responsible for both internal and external quality control. In the Netherlands, a national expert and training center is responsible for quality control regarding both mammography and pathology. They also have three centers cooperating to function as a national evaluation team to check on the effectiveness of the Dutch nationwide program (de Koning et al., 1991).

Adverse effects
In addition to the cost of screening there will be direct and indirect costs such as loss of working hours, travel, time and other non-medical costs incurred by the women involved. (Schmidt, 1990; Hurley and Livingston, 1991; de Koning et al., 1991). Flexible opening times would diminish some of these costs and perhaps also increase attendance rates (Fallowfield et al., 1990). An indirect cost which mammography screening also has been blamed for is increasing the anxiety about breast cancer among women (Schmidt, 1990). Against this it has been argued that the level of worry is high even without screening with mammography (Shapiro, 1990). As about one in every 13 women in Norway will contract breast cancer (Kvåle and Jacobsen, 1990) the likelihood that a woman 40 years of age or older knows somebody who has suffered from breast cancer is high. Nevertheless, it is intriguing that approximately one out of three women reports anxiety about breast cancer without being exposed to mammography screening (Paper II). This report also indicates a positive effect among women with negative mammograms, as they report to have less anxiety after the screening compared with the women never invited. Even a small
decrease in anxiety should be looked upon as important since the vast majority of the women will belong in the screening negative group. This may be considered a positive health benefit from the screening. It is, however, seldom listed on the positive side of the balance sheet when the net gain of screening is discussed (de Haes et al., 1991; de Koning et al., 1991).

Although we revealed (Paper II), as did others (Baines et al., 1990; Stomper et al., 1988; Fallowfield et al., 1990) that mammography is considered to be a painful procedure by some women, the willingness to attend another screening strongly suggests that the test is acceptable to the target population. Intention to attend was found to be the best discriminator for subsequent attendance at a mammography clinic (Calnan, 1984).

**True negatives, true positives**

As described earlier the women who are correctly classified as negatives are likely to benefit the most. To get assured from the fear of breast cancer by having a negative mammogram may be the underlying reason why women attend the screening (Paper II). As shown in Paper III this assurance did not seem to have much impact on their quality of life. However, a potential increase would likely be very small and also would have to be weighted against the temporary decrease they may suffer while awaiting the result from the screening mammogram (Paper III). An early diagnosis resulting in a less extensive treatment should cause the quality of life to improve, while knowing about the disease for a longer period of time is believed to have the opposite effect among the true positives (de Koning et al., 1991). It is difficult to estimate if there is any net benefit for women who are diagnosed with cancer and who die from the disease at the same point in time as they would have done without the screening. The women who have their lives prolonged are all assumed to have a net benefit of the screening.

**False negatives, false positives**

There will inevitably be false negatives and positives in a mammography screening due to the limitations of the technology, physical variation or misinterpretation of the screening test. False negative results reduce the efficacy of screening in achieving a reduced mortality. Another concern is that they may lead to patient delay in seeking care when
symptoms do appear. Having a false positive mammogram will lead to unnecessary additional diagnostic procedures which may progress from a clinical mammography to extensive surgery (Paper I,III). While reduction in breast cancer mortality is likely to remain the key measure of benefit from mammography screening, increasingly questions are being raised about the negative effects of screening especially those laid upon the women with a false positive mammogram (Wright, 1986; Eddy et al., 1988; Skrabanek, 1988; Devitt, 1989; Schmidt, 1990). The adverse effects sustained by false positive subjects are difficult to assess (Cole and Morrison, 1980). In addition to Paper III, a few studies have aspired to do so (Ellman et al., 1989; Baines et al., 1990). The method utilized in Paper III, self-reported quality of life, is currently assumed to be the state of the art when investigating this complex issue (Mastekaasa et al., 1988). Nevertheless, such measurements of quality of life are subjective and prone to information bias. A Norwegian study dealing with the quality of life and "yea-saying" found a positive association between this tendency and low education and income (Moum, 1988). Hence, the inclination to give a positive answer should be equally distributed between the two comparison groups and not distort the outcome. The results indicating no overall difference in quality of life between the two comparison groups are promising for the proportion of women who will inevitably be mislabeled as positive at a mammography screening (Paper III). These findings are in agreement with the few other investigations considering women with false positive mammograms (Ellman et al., 1989; Baines et al., 1990). Our results need to be verified and investigated further in countries where mammography screening is being implemented.

A small group of the women with a false positive mammogram report that the stress initiated by the false positive result was the worst they had ever encountered (Paper III). This emphasizes the need for the quality control also to assess possible psychological adverse effects of the program. It has been proposed to classify the mammograms according to the likelihood of malignancy and to word the recall letter correspondingly in order to minimize recall anxiety (Pamilo et al., 1991). As pointed out by Schmidt it is difficult to measure the relative importance of each event a woman may endure as the result of participating in a screening program. He therefore suggests to do the comparison in absolute terms (Schmidt, 1990). Two related studies from the Netherlands have
estimated the impact of a breast cancer screening program on quality-adjusted life years (de Haes et al., 1991) and the cost-effectiveness and policy alternatives of such a program (de Koning et al., 1991). The estimates are based on responses from clinicians or public health experts who were asked to evaluate the quality of life during the different phases a woman may pass through from the screening examination to advanced disease. This approach was chosen because the questionnaire utilized was considered to be too complicated to administer to either patients or the population at large. Both reports conclude that the negative changes in quality of life suffered by some women were not of a magnitude to justify impact in the decision whether or not to undertake a large-scale breast cancer screening program (de Haes et al., 1991; de Koning et al., 1991). The conclusions from these two studies, using complex and laborious methods in estimating the outcomes, are in accordance with those of Paper II and Paper III.

Cervical cancer

Suitable disease, suitable test, suitable program
Cervical cancer is a disease that is more frequent than breast cancer in developing countries, while the opposite is true in developed countries (Parkin et al., 1988). The majority of cervical cancers are squamous cell carcinomas which pass through a preclinical phase known as cervical intraepithelial neoplasia (CIN). During this phase the disease is symptomless, but detectable with the Pap-smear test. A Pap-smear test by itself carries basically no direct risk. The main risk is that of a false-positive test resulting in subsequent work-up examination and possible treatment with conization or hysterectomy. In addition to the anxiety and risks these procedures involve for the women, a Norwegian study found the perinatal death and prematurity to be increased among offspring of women who were treated for carcinoma in situ with conization, compared to those who were not (Lund and Bjerkedal, 1986).

A randomized trial to evaluate the effectiveness of cervical cancer screening was never done. However, the dramatic reduction in incidence of invasive disease following the implementation of cervical screening programs has made the scientific community accept that the incidence and mortality of cervical cancer can be reduced by organized Pap-
smear screening (Hakama et al., 1985).

Program Strategies - Organized versus opportunistic screening
In Finland, Iceland and Sweden organized screening programs for cervical cancer have been implemented since the mid-1960s (Laara et al., 1987). In Denmark, such screening became an integrated part of the health care after 1986 offered free of charge to all women. Before that, different counties had adopted different screening policies (Lynge, 1989). In Norway, a small pilot study was designed to evaluate the feasibility and effect of an organized nonselective screening on incidence and mortality from cervical cancer. This program was implemented in Østfold County as early as 1959. It continued until 1977 with a follow-up through 1982. The results showed that the observed incidence and mortality from cervical cancer within the study population were reduced compared to the expected (Magnus et al., 1987). During the same period, the spontaneous smear-taking activity had reached a considerable level in the rest of Norway. However, the widespread opportunistic screening did not have a similar effect on the incidence and mortality of cervical cancer as did the organized screening programs in Finland, Iceland and Sweden (Laara et al., 1987). These results have been used in support of the belief that organized screening programs for cervical cancer have a greater effect, while using less resources than unorganized or opportunistic screening programs (Hakama et al., 1985).

Selective screening
It has been suggested that preventive strategies for cervical cancer should be targeted to high-risk populations (Brinton and Fraumeni, 1986). The high-risk groups should then be small enough to result in a substantial reduction in monetary costs and negative effects. They should also have a high incidence of disease; in other words give a low cost and a high yield (Hakama, 1985). When the total population is screened the test sensitivity equals the program sensitivity. When a selective screening is performed based on the same test sensitivity, the program sensitivity decreases whereas the program specificity and the positive predictive value will increase.

Risk factors
As noted earlier, the risk factor for selecting high-risk groups need not be causally related
to the disease, but may be merely a marker of the disease when the objective is secondary prevention (Hakama, 1985). Cervical cancer is a disease that has been associated with several risk factors, sexual activity and age being the most important ones (Brinton and Fraumeni, 1986). Information on sexual behaviors are difficult to obtain in large scale settings and such risk factors are therefore not suitable as a basis for selective screening. On the other hand, all screening programs select on age. The Islandic program includes women aged 25-69 (Sigurdsson et al., 1991), the Swedish - women aged 30-49, and the Finnish - women aged 30-60 (Hakama, 1990).

The purpose of cervical cancer screening is to prevent invasive cancer by early diagnosis and treatment of the precursor lesions. It is therefore sufficient to start to screen a few years before the invasive disease occurs. The incidence of invasive cervical cancer is low under the age of 30 and increases rapidly with age thereafter (The Cancer Registry of Norway, 1990). In paper VI, the incidence rate of CIN III was twice as high among women aged 25-29 compared with those aged 20-24. For women 40 years or older the incidence rate of CIN III was about 60% of that of the youngest age group (data not shown). This finding, that the group that has the highest incidence of invasive cancer has the lowest incidence of the immediate precursor lesion to the invasive cancer and vice versa, provides further support for the belief that the detectable preclinical phase is of shorter duration among older compared with younger women (Miller et al., 1990).

There is yet not much scientific evidence for extending screening programs to women younger than 25 years of age. There is more controversy surrounding what age the screening should end. In a recent paper it is strongly advocated that elderly women, aged 65 or more, should be included in screening programs (Fletcher, 1990). Supportive of this view is a report showing a favorable cost-effectiveness ratio for screening elderly low income women (Mandelblatt and Fabs, 1988). The recommendation given by the UICC (International Union Against Cancer) workshop is to screen women aged 25-60 years. However, it is emphasized that women older than 65 who have not had at least two negative Pap-smears should be screened until they achieve this result (Miller et al., 1990). The four risk factors investigated in this thesis; cigarette smoking, oral contraceptive use
and cervico-vaginal infection with Trichomonas Vaginalis and Human Papillomavirus are known only for each individual in the population. Such risk indicators assume first an unselective screening or other contact with the women to acquire the basic information for further application of the selective screen. Nevertheless, information regarding cigarette smoking, oral contraceptive use and previous Pap-smear history would be more easily obtained than would information on sexual activity.

**Strength of association**

The relative risks found between current cigarette smoking and CIN III, and ever oral contraceptive use and CIN, were both less than two and the associations must be considered weak (Paper IV, V). Although the relative risk for CIN III among women with identified TV and HPV infection were somewhat stronger they must also be considered weak associations (Paper VI). Thus, the criterion about a strong association between the risk factor and the disease was fulfilled for neither of the risk factors examined in the three mentioned papers.

Table I demonstrates that with a relative risk of two, the high-risk group have to comprise 70 % of the target population to be able to diagnose 82 % of the cases. The high-risk group is then the same size as the proportion of attenders in a general screening program with a fair attendance rate. Accordingly, there will be virtually no reduction in costs which is the main objective of a selective versus a nonselective screening.

**Prevalence of risk factor in the target population**

In our studies, almost half of the women aged 20-49 were current smokers, while about one third were ever OC-users. As the population survey achieved a high attendance rate, we assume these figures to be representative for the general population at the time of the survey. Given the high prevalence of these two risk factors in the general population these factors do not meet the criteria of being restricted to a small proportion of the population. From Table 1 it can be read that screening only current cigarette smokers would give a program sensitivity of less than 67 %, while the corresponding figure for screening only ever OC-users would be even lower (Table 1, Paper IV, V).
Offering preventive health services only to subjects with a harmful behavior such as cigarette smoking, as long as their risk is only slightly elevated from those of subjects without such behavior, would not be an acceptable public health policy. On the other hand, the results from Paper IV may be used to provide young women with yet another incentive to stop or never begin smoking, whereas the results from Paper V should not mislead women to avoid using oral contraceptives if they otherwise would have. Compared to the benefits of OC-use the increased risk of CIN seems small. In a recent review it is also concluded that the health benefits of OC-use do outweigh the adverse effects for most healthy women (Peterson and Lee, 1990).

In paper VI, evidence of HPV infection was found in less than four percent of the women altogether (Paper VI). Thus, the criteria of a low proportion of the general population having the risk factor seems to be met. However, the ability of the Pap-smear test to correctly diagnose HPV infections is a concern. The proportion of women shown to have such infections is completely dependent on the technique used to analyze the presence of HPV. Methods as DNA hybridization or PCR amplification would have been able to also disclose latent HPV infections (Syrjanen, 1989). As described in Paper VI, the strength of association is diluted due to the pollution of women with latent HPV infection in the "non-infected" group (Paper VI). Although, the Pap-smear test is the only feasible means to conduct population screening of genital HPV, it may be concluded that it is not of much help in the context of selecting women for cervical cancer screening.

During follow-up the decreasing incidence of TV infection is striking (Paper VI). This result could be caused by a real reduction in new cases, or by different reporting practices. Neither way, may it be concluded that TV infection diagnosed by Pap-smear is of no value in selecting high-risk women for cervical cancer screening. The question of what brought about these changes is an intriguing one, but beyond the scope of this thesis.

Combining risk factors
Combining cigarette smoking and OC-use yielded a high-risk group comprising less than 20% of the target population (data not shown). This size would substantially reduce the cost of the screening. However, less than one fourth of the total cases of CIN III were
found among these women and the yield of the screening seems to be reduced to the same extent as the costs.

**Screening interval**

It has been suggested that it is reasonable to screen women with features indicating Papillomavirus more frequently than a general screening program would recommend. This suggestion is based on the strength of association, the crude measurement of the Pap-smear test to detect this infection and the possibility for misclassification between Papillomavirus and CIN I lesions (Syrjanen, 1985). As pointed out by Szklo, it is of limited use to screen high-risk groups more frequently than low-risk groups unless it is known that these subjects have a disease that have a more rapid progression beyond the point in time which screening detected cases have a similar prognosis as clinical detected cases (Szklo, 1990). In Paper VI, we did find that the average time between entry into follow-up and the diagnosis of CIN III was shorter for women in the TV and HPV subcohorts compared to those without such infections (Paper VI).

**Current status in Norway**

**Public Health Significance**

So far, breast and cervical cancer are the only two cancer sites for which screening has been demonstrated to be effective (Miller et al., 1990). During the course of the work on this thesis, two government reports concerning screening for breast and cervical cancer have been published in Norway. They both recommend nationally organized screening programs for breast cancer with mammography (NOU 1987:7), and for cervical cancer with Pap-smear (NOU 1987:8). Furthermore, screening with mammography has been debated at a national consensus conference, where the consensus statement was not to recommend a nationwide screening program with mammography (Backe ed., 1989). A decision about an organized screening program for cervical cancer has been made. This screening program will target all women aged 25 through 70. A pilot project is planned for implementation during 1992 (Gunbjörud and Stenling, 1991). So far, no similar decision has been made for breast cancer screening with mammography.
The three papers dealing with the mammography screening are studies that have contributed both relative and absolute figures to the debate for and against breast cancer screening with mammography (Paper I-III). The results from Paper IV-VI show that neither of the four risk factors examined; cigarette smoking, OC-use, cervico-vaginal infection by HPV, or TV identified by Pap-smears, alone nor combined are applicable as a basis for selective cervical cancer screening (Paper IV-VI).
10. CONCLUSIONS

Organized breast cancer screening with mammography is technically feasible with a central unit responsible for the administration of the screening and the interpretation of the mammogram and with local responsibility for the diagnostic work-up.

The most frequently reported reason for non-attendance was not having the opportunity. Non-attenders also reported a low level of breast cancer anxiety compared to the general population.

The adverse effects suffered by women with a false positive mammogram in an organized screening is not of a magnitude that should discourage such screening.

Current cigarette smoking, ever oral contraceptive use, cervico-vaginal infection with Trichomonas Vaginalis and Human Papillomavirus identified by Pap-smear were found to be risk factors for cervical neoplasia.

None of these risk factors fulfilled the criteria to make a selective screening for cervical cancer worthwhile compared with screening of the total population.
11. REFERENCES


### TABLE I

Proportion of Total Cases Diagnosed from the High-Risk Group by Size of the Group and Relative Risk (High Risk versus Low Risk)

<table>
<thead>
<tr>
<th>Size of high-risk group (percentage of total population)</th>
<th>2</th>
<th>5</th>
<th>Relative risk 10</th>
<th>20</th>
<th>50</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.02</td>
<td>0.05</td>
<td>0.09</td>
<td>0.17</td>
<td>0.34</td>
<td>0.50</td>
</tr>
<tr>
<td>5</td>
<td>0.10</td>
<td>0.21</td>
<td>0.26</td>
<td>0.51</td>
<td>0.72</td>
<td>0.84</td>
</tr>
<tr>
<td>10</td>
<td>0.18</td>
<td>0.36</td>
<td>0.53</td>
<td>0.69</td>
<td>0.88</td>
<td>0.92</td>
</tr>
<tr>
<td>20</td>
<td>0.33</td>
<td>0.56</td>
<td>0.71</td>
<td>0.83</td>
<td>0.93</td>
<td>0.96</td>
</tr>
<tr>
<td>50</td>
<td>0.67</td>
<td>0.83</td>
<td>0.91</td>
<td>0.95</td>
<td>0.98</td>
<td>0.99</td>
</tr>
<tr>
<td>70</td>
<td>0.82</td>
<td>0.92</td>
<td>0.96</td>
<td>0.98</td>
<td>0.99</td>
<td>1.00</td>
</tr>
<tr>
<td>90</td>
<td>0.95</td>
<td>0.98</td>
<td>0.99</td>
<td>0.99</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Source: Hakama, 1985
Appendix
Paper I
Mammografiscreening i Tromsø

Gjennomføring og resultat av den første mammografiscreening i Norge

Screeningen var en del av en helsetandsetisk studie. Kvinner 40 år fikk tilbudet (n = 4.290). I alt 84.4% ble mammografert. Av dem ble 5.3% undersøkt med klinisk mammografi, 1.7% hevnst til kirurgi og 1.1% fikk tatt biopsi. Hos ti kvinner ble det påvist breystkreft.

Alle mammogrammene ble tydet uavhengig to ganger og deretter tilbake-tydet. Et positivt mammogram hadde høyest prediktiv verdi når begge primærtiderne hadde anbefalt etterundersøkelser.

Om lag 98 og 79% av kvinnene som møtte til helseundersøkelse henholdsvis i sentrum og i distriktet, ble mammografert. Sistnevnte måtte bestille time og reise til sentrum for å bli mammografert.

Screeningen hadde sentral administrering av primærtid. Etterundersøkelsen ble organisert lokalt.

Fler kontrollerte studier har vist at mammografiscreening kan redusere dødeligheten av breystkreft for kvinner over 50 år (1–4). Et utvalg nedsatt av Helsedepartementet har tilskudd at de enkelte fylker skal ha ansvaret for mammografiscreening for kvinner i alderen 40–74 år (5).


Materiale og metode

I 1986–87 ble alle kvinner født i tid

<table>
<thead>
<tr>
<th>Tabell 1: Førstomte etter alder</th>
<th>Tromsø 1986–87</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alder</td>
<td>Inviterte Antall</td>
</tr>
<tr>
<td>40–44</td>
<td>1 703</td>
</tr>
<tr>
<td>45–49</td>
<td>1 168</td>
</tr>
<tr>
<td>50–54</td>
<td>952</td>
</tr>
<tr>
<td>55+</td>
<td>467</td>
</tr>
<tr>
<td>Total t</td>
<td>4 290</td>
</tr>
</tbody>
</table>

tilbud om mammografiundersøkelse. Friomstøtet var 84,4 % (3 629) (tab 1). I tillegg møttes 33 kvinner uten innkalling (flyttet til kommunen i løpet av undersøkelsen). De er i førstetteringen inkludert i materialet.

Mammografen var plassert i Tromsø sentrum, 85,5 % av kvinnene fra sentrum møtte til helseundersøkelse, og av disse ble 97,7 % mammografert. I distriktet møtte 94,1 % til helseundersøkelse, og 78,8 % av dem ble mammografert. Sistnevnte måtte bestille tane og reise til sentrum for å bli mammografert.


Prosedyre

Det ble tatt et mammogram pr. bytet i 30–45 skråprojeksjon. Efter at ved en tredjedel av kvinnene var undersøkt, ble det i tillegg tatt kroniskaudal projeksjon av dem mellom 40 og 49 år. Elektronert film ble sendt til Oslo samme dag. I helgene kunne det gå inntil fire dager før det ble fremkalt.

Tyding

Tre røntgenleger deltak i primærtidingen. Legen som hadde lengst erfaring i å tolke mammogrammer, tyded alle (tyder 1). De to andre skiftet på å tyde (tyder 2). Alle mammogrammene ble tydet uavhengig av teleg. Røntgenlegeren bare opplysnings om fekkelsa. Tyderne skulle være ja eller nei på om etterundersøkelse var nødvendig for å undgå krebssmitte.

Alle bildene ble tydet på nytt før det ble avgjort hvem som skulle etterundersøkelse. Da var primærtidens anbefalinger kjent. Røntgenlegeren i Tromsø
Etterundersøkelser
Kvinnene fikk hvert med beskjed om time for undersøkelse på røntgenavdelingen ved Regionssykehuset i Tromsø. Der ble det tatt kranioskende, mediolaterale og skråprosjektsjoner, samt kombider (kompressionbilder) i selekterte tilfelle. Røntgenlegen publiserte begge mammamøte rutinemessig. Hvis det ikke var tegn til malignitet etter klinisk mammografi, ble kvinnene informert av røntgenlegen og sendt hjem.

Der bildene ikke kunne utelukke maligne forandringer, ble kvinnens undersøkt på kirurgisk poliklinikk umiddelbart. Hvis tumor var palpabel, ble de heftige og i det ikke var stor misundelse om malignitet, ble det tatt biopsi poliklinisk.
Analyse
Norske mellom gruppene er beregnet med k likhets- og variansanalyser.

Resultater

Tabell 3 viser resultatet av den uavhengige tydingen, Tromsø 1988–87. Oversynstemmelser mellom de to tyderne, kappa = 0,58

<table>
<thead>
<tr>
<th>Tyder 2</th>
<th>Tyder 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nytte bilde</td>
<td>Etterundersøkelse</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Tyder 1</td>
<td>Nytte bilde</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Nytte bilde</td>
<td>6</td>
</tr>
<tr>
<td>Etterundersøkelse</td>
<td>5</td>
</tr>
<tr>
<td>Ja</td>
<td>35</td>
</tr>
<tr>
<td>Nei</td>
<td>46</td>
</tr>
<tr>
<td>Sum</td>
<td>101</td>
</tr>
</tbody>
</table>

Tabell 2: Etterundersøkelser i prosent etter aldersgruppe (år), Tromsø 1988–87

<table>
<thead>
<tr>
<th>Type undersøkelse</th>
<th>Alk</th>
<th>40–49</th>
<th>50–57</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klinisk mammografi</td>
<td>5,3</td>
<td>5,7</td>
<td>4,4</td>
</tr>
<tr>
<td>Undersøkelse kirurg</td>
<td>1,7</td>
<td>1,8</td>
<td>1,5</td>
</tr>
<tr>
<td>Tutt biopsi</td>
<td>1,1</td>
<td>1,2</td>
<td>1,0</td>
</tr>
<tr>
<td>Malign forandring</td>
<td>0,3</td>
<td>0,3</td>
<td>0,3</td>
</tr>
</tbody>
</table>

Avsakken kan være at såværende kvinner ikke var interessert. Redaksjonen i utklippene av de neste 20 % skilles mer sannsynlig at mammografinundersøkkelse ikke var så desentraliseret som helhetsevne. De mobil mammografinhet uke i distrikten ville sannsynligvis ha økt fremstøtet.

I ei sveise screeningundersøkelser som bare omfattet mammografi, holdt man et fremstøt på 89 (11 og 74 %) av de som skrev fremstøt.

Tid av flyktig poster og jennet av den gitt noen perioder avMH etter røntgenundersøkelse. De inviteres, derfor har 90 % av de inviteres mottoppes.

Etter et nasjonalt screeningprogram vil det være ønskelig at kvinner i forskjellige deler av landet får et mest mulig tilbud.

Uavhengig tyding
Uavhengig tyding er tidligere brukt ved tuberkuloscreening (6). Fra en epidemiologisk synspunkt er det viktig at mammografinene tydes uavhengig. Dette vil førelle om testens reproduserbarhet. Det blir altså hilt oversynstemmelser mellom tider som er uavhengig av hverandre. En oversynstemmelser mellom primarydenene med kappa på 0,58 er lav. Den viser det det er mulighet for store variasjoner i hvor mange og hvilke kvinner
Table 4 Testens prediktive verdi, antall falsk og ekte positive mammagrammer ved ulike kriterier for etterundersøkelse, Tromsø 1986–87

<table>
<thead>
<tr>
<th>Ettersøke grille</th>
<th>Prediktiv verdi</th>
<th>Falske positive mammagrammer</th>
<th>Ekte positive mammagrammer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ja</td>
<td>8,8</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Bare tyder 1</td>
<td>5,8</td>
<td>147</td>
<td>9</td>
</tr>
<tr>
<td>Tilfølgstyring</td>
<td>5,2</td>
<td>183</td>
<td>10</td>
</tr>
<tr>
<td>Bare tyder 2</td>
<td>4,5</td>
<td>213</td>
<td>10</td>
</tr>
<tr>
<td>Mest tyder</td>
<td>3,6</td>
<td>267</td>
<td>10</td>
</tr>
</tbody>
</table>

Som skal bli innkalt til ettersøkelse.

Ved et nasjonalt screeningprogram har man ha en kvalitetskontroll. Uavhengig tyding regionalt eller sentralt kan være en metode.

Prediktiv verdi

En mammografiscreening skal dele de fremme i to grupper: de med brystkreft og de uten. Det er foreløpig ukjent hvor mange brystkretsfille som ikke ble oppdaget på screeningen i Tromsø. Undersøkelsens sensitivitet og spesifikk kan derfor ikke beregnes. Den prediktive verdi er avhengig av disse størrelserne. Den er derfor indirekte avhengig av teknisk kvalitet på bildene, antall bilder og projeksjonene, samt hvor dypt de tyder er. Røntgenlegens erfaring og subjektive skjønn vil virke inn på vurderingen av mammagrammene. I tillegg er den prediktive verdi avhengig av prevalens av brystkref i den undersøkte gruppen.

Vi kunne velge mellom fem kriterier for hvilke kvinner som skulle ettersøkes (tab 4).

Ved høre å ettersøkes kvinner som tyder var noen om til disse kriteriene. Vi kaster prediktive verdi vara knapt 9 %. I en kardiatisk studie (10) var det en nømmelei prediktiv verdi på 8,6 % (3–16 %). I en studie til Taber og medarbeidere (3) var tilsvarende tall 14,3 %. Dette kan skyldes å kvinner i distriktene studie er eldre enn våre (større prevalenser) og at erfaringen med å tyde screeningbilder er større.

Den prediktive verdi ville synke til 3,6 % hvis vi ettersøkte kvinner som minst én tyder anbefalte. Sammenligg med tilfølgstyring, ville antall falsk positive olde være 85. Ingen flere brystkretsfille ville være oppdaget.


Endring av pressedyr


Etter at pressedyren ble forandret, var 81,4 % av de mammografierte i aldersgruppen 40–49 år. Høyste frekvense av de mammografierte var i den eldre aldersgruppen, hvor endringen sannsynligvis gitt massivt av effekten av det man ønsker.

Arsaken til at det ble flest ettersøkelseskrav ble det at 1 295 første undersøkte, kan være at overenstemmelsen i tydingen, og andel ettersøkte var størst i denne perioden. Ved stor overenstemmelse mellom de avhengige tyderne er det å vinne på tilfølgstyring.

Vår undersøkelse viser at det er viktig at tyderne for konklusjon på tydningen av deretter. Resultatene fra tyding av mammogrammer og ettersøkelse fra utgangspunktet for å løse denne problemet som skjer.

Konklusjon

Mammografiscreening lever seg gjenomført ved en trias: screening, primæravtale og med lokal ettersøkelse av de positive funn. Fremmetet ser at vi være imøtekommet av hvert billegren av mammografiscreening.

Tilfølgstyring av mammogrammer er lav reproduksjonsverdi. Det er derfor viktig at det er noe annet røntgenteknikk som avgir hvert som skal ettersøkes.

Et positiv mammogram hadde høyest prediktiv verdi når begge begge primærtyderne hadde anbefalt etterundersøkelse.

Det norske resultatet stemmer sann sett med røntgentechnikk.

Litteratur

Breast cancer screening with mammography in Tromsø

Jørgen Tjønnberg Grønn, MD
Per G. Lund Larsen, MD
Alf Finneboe Randhau, MD
Jan Stenersen, MD

The screening was carried out as a part of a health survey. Women aged 40 or more, (N = 4,261), were eligible. The acceptance rate was 88.4%. Altogether 5.2% was selected for detailed mammographic examination. 1.7% were referred to a surgeon and 1.1% underwent surgery. In ten (33%) of them breast cancer was proven histologically.

The mammograms were read independently by two radiologists. The predictive value was highest if only women on which both radiologists agreed were referred to detailed mammography.

Of the women attending the health survey, 98% in the urban and, 79% in the rural part of the municipality were screened for breast cancer.

The latter group had to make an appointment and travel to the city center to have their mammograms taken.

The interpretation of the breast cancer screening was centrally administered. The follow-up was organized locally.
Paper II
A mailed questionnaire survey was conducted among the following groups: 179 women who screened false positive at a free mammography screening; a random sample of 250 women who screened negative; 670 nonattenders of the screening; and a random population sample of 250 women who lived in another city and were not invited, but were otherwise comparable. The most frequently reported reason for nonattendance was not having the opportunity. Furthermore, only 18% of the nonattenders reported anxiety about breast cancer compared with 33% of the population sample (P < .05). Ninety-nine percent of the women who attended indicated a positive attitude toward mammography that had not been adversely affected by screening experiences. (Am J Public Health. 1992; 82:249-251)

Introduction

Mammographic screening has been the only effective means of reducing breast cancer mortality.1-5 However, several authors have questioned the magnitude of this mortality reduction and called attention to potential adverse effects of mammography screening.6-11 The few available studies of this topic indicate that most women cope well with the screening situation and its consequences.12-15 The purpose of this study was to investigate breast cancer anxiety and attitudes toward mammography among screening attenders, nonattenders, and women never invited to participate.

Methods

A free mammographic screening was offered to 422 women aged 40 or older as part of the Third Tromsø Study conducted in Tromsø, Norway, in 1986 and 1987.16 Altogether, 365 (86%) accepted the mammo- gram. A total of 193 (5%) of the screenings required further evaluation, which for 40 subjects included a biopsy. Details of the screening and case-finding procedures are given elsewhere.17 Of the 193 women requiring further examination, only those 197 who were not diagnosed with breast cancer were eligible for the present study, and they constituted the false positive (FP) group. The three other groups in this study were a random sample of 250 women who screened negative (SN), the 670 nonattenders, and a random population sample (PS) of 250 women living in the nearby city of Harstad. The latter women were not invited to the screening but were otherwise comparable to the Tromsø women and thus served as the reference group.

A questionnaire concerning perceptions about mammography, frequency of breast self-examination, and anxiety about having breast cancer was designed, pilot tested, and then mailed to all study subjects in 1987 after the mammography screening was completed. A reminder questionnaire was sent out to all nonrespondents. Among nonattenders, 120 women (18%) were excluded from the study (8 had died, 17 had breast cancer, 32 had moved, and 63 were unknown at address). The response rate among the remaining women was 64% among the SN group (n = 209), 89% among the FP group (n = 160), 38% among the nonattenders (n = 210), and 66% among the PS group (n = 164). Subjects were classified as residing in rural areas if their travel distance to the mammography unit was about 30 minutes or more.

Statistical analyses of the data were performed using the Pearson chi-square statistic for categorical data and Student’s t test for continuous data.18 The analyses were performed using SAS programs.19

Results

The median age of the study population was 46 years (range of 40 to 61 years), and the mean years of schooling was 10. Risk factors for breast cancer—such as a family history, age at menarche, age at

Inger Torhild Gram is with the Institute of Community Medicine, University of Tromsø, Norway. Suzanne Slonker is with the Department of Social and Behavioral Sciences, Boston University, School of Public Health.

Requests for reprints should be sent to I. T. Gran, Institute of Community Medicine, University of Tromsø, Postboks 6000, Tromsø, Norway.

This paper was submitted to the journal November 26, 1990, and accepted with revisions August 22, 1991.
TABLE 1.—Prevalence (%) of Breast Cancer Anxiety at Follow-up and Recalled Prevalence of Anxiety 1 Year before, by Group: Tromsø, Norway, 1987

<table>
<thead>
<tr>
<th>Screening Negative</th>
<th>False Positive</th>
<th>Nonattendees</th>
<th>Population Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 209)*</td>
<td>(n = 180)*</td>
<td>(n = 178)*</td>
<td>(n = 164)*</td>
</tr>
<tr>
<td>Follow-up</td>
<td>One year before</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22%</td>
<td>28</td>
<td>28</td>
<td>18%</td>
</tr>
<tr>
<td>33</td>
<td>31</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Percentages are based on smaller numbers due to missing responses.

Both groups were significantly different (P < .05) when compared with the PS group during the same period.

Table 1 shows that both the SN group and the nonattendees reported significantly lower breast cancer anxiety at follow-up than the PS group (P < .05). The nonattendees also recalled being less anxious about breast cancer 1 year before, compared with the PS group (P < .001). The changes within each group did not gain statistically significant P values.

 Altogether, 84% of the women reported having been given adequate information in the screening invitation, and 79% reported the same about the screening examination. Among women receiving the workup letter and examination, 61% and 72% respectively, were satisfied with the information.

Table 2 shows that more women in the FP group than in the SN group experienced the screening examination either as unpleasant or as both painful and unpleasant (P < .01). However, the majority in both groups found it neither painful nor unpleasant.

Table 3 shows that, among the FP group, women who recalled having anxiety about breast cancer 1 year before (prior to the screening), anxiety about the anticipated workup examination, or fear of breast cancer upon receiving the workup recommendation were more likely to have breast cancer anxiety at follow-up, after the reassurance, than those who did not (P < .001). Women who were content with the information in the workup letter had a higher prevalence of breast cancer anxiety than those who reported the opposite (P < .05). No association was found between the prevalence of anxiety about breast cancer and how the information was perceived at the invitation, the screening, or the workup examination.

Ninety-two percent of the nonattendees and 95% of the attendees and the women who never invited indicated willingness to participate in another free mammography screening in the future. Of the attenders, 99% said they would also recommend a similar screening to a friend.

first birth, and prior breast biopsy—did not vary by group. Data are not shown for these factors.

The nonattendees were more likely to live in rural areas than the attenders (P < .001); they were also more likely to be unemployed and never to practice breast self-examination than the PS group (P < .05). Thirty-two of the nonattendees had had a recent mammogram. This was considered a legitimate reason for nonattendance, and these women were removed from the analysis. The remaining women (n = 178) reported that not having the opportunity (39%); not wanting to participate in the Tromsø Study (15%); fear of X-rays (15%); concern about painful examination (4%); not receiving a personal invitation (4%); fear of discovering breast cancer (3%); and the potential of having a male examiner (3%) were the reasons for nonattendance. Some women gave more than one answer, 22% did not answer, while altogether 14% of the women claimed, without giving further explanations, that none of the listed factors were the rationale behind their nonattendance.

TABLE 2.—Proportion (%) of Women in the Screening Negative and False Positive Groups Describing the Screening Examination as Painful or Unpleasant: Tromsø, Norway, 1987

<table>
<thead>
<tr>
<th>Screening Negative</th>
<th>False Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 205)</td>
<td>(n = 157)</td>
</tr>
</tbody>
</table>

Unpleasant only 18 28
Painful only 4 4
Both 3 11
Neither 75 59

*Significantly different (P < .05) when compared with the PS group during the same period.

+Statistically significant, P < .01.

TABLE 3.—Prevalence of Breast Cancer Anxiety at Follow-up among Women in the False Positive Group (n = 100) According to Selected Responses: Tromsø, Norway, 1987

<table>
<thead>
<tr>
<th>Variables</th>
<th>Subjects (n)*</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recall anxiety 1 year before</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>95</td>
<td>19**</td>
</tr>
<tr>
<td>Yes</td>
<td>55</td>
<td>72</td>
</tr>
<tr>
<td>Recall anxiety at screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>107</td>
<td>20**</td>
</tr>
<tr>
<td>Yes</td>
<td>41</td>
<td>76</td>
</tr>
<tr>
<td>Anxiety about potential workup examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>79</td>
<td>20**</td>
</tr>
<tr>
<td>Yes</td>
<td>62</td>
<td>55</td>
</tr>
<tr>
<td>Information adequate in workup letter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>52</td>
<td>31*</td>
</tr>
<tr>
<td>Yes</td>
<td>51</td>
<td>48</td>
</tr>
<tr>
<td>Fear of having breast cancer at workup recommendation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>59</td>
<td>20**</td>
</tr>
<tr>
<td>Yes</td>
<td>76</td>
<td>54</td>
</tr>
</tbody>
</table>

*Totals do not add up to 100 due to missing responses.

+Significantly different (P < .05).

**Significantly different (P < .001).
Discussion

The present study shows that a high proportion of women in a general population, approximately one out of three, have anxiety about breast cancer. The results further suggest that having negative results on a screening mammogram decreases this prevalence and that women who elect not to attend a screening are less anxious about breast cancer than those who attend.

One strength of this study is that breast cancer anxiety among women who were invited to the mammographic screening can be compared with that of women who were not invited. Another is that reasons for nonattendance could be evaluated without taking the monetary cost of the mammogram into account.

One limitation of this study is the possibility of recall bias. Another is that the survey instrument was not of sufficient depth to explore the relationship of cancer anxiety to other related health-belief concerns. Nevertheless, our results, which suggest that anxiety about breast cancer may mediate attendance at breast cancer screening, are in accordance with other studies, which used survey instruments that focused on more attitude and belief dimensions—such as perceived susceptibility—than ours did.20-22

This study reveals a higher attendance rate than do most of the studies reviewed by Veron et al.22 The high acceptance may be due to the fact that the mammography screening was put in a broader context of a comprehensive health survey. Our results also reflect the fact that women living or working in the city center had easier access to the mammography screening facility than those who did not. This inference of convenient location as a significant factor in explaining nonattendance has been proposed in previous studies.14,16-18

We do consider the low response rate among nonattendees eligible for the study to be a limitation. The same problem was revealed in the study by Bailes et al.14 Although the 178 nonattendees may not be representative of all the women who declined, their answers should be of value in understanding reasons for nonattendance.

Our finding that 11% found the screening examination somewhat painful is in accordance with that of Bailes et al.14 but in contrast to that of Stromper et al., who found that only 1% reported the examination to be painful.15 That more women in the FP group than in the SN group perceived the screening examination to be both painful and unpleasant may be because women in the FP group have breasts that are more difficult to examine due to size or density, thus necessitating a stronger arm maneuver or painful compression of the breasts. These results indicate some drawbacks of screening that have also been revealed in other studies.13

The present study indicates that women who were anxious before the screening were more likely to remain so. Discouragingly, perceived adequacy information does not seem to prevent anxiety about breast cancer among those who had to go through a workup examination. Additional measures need to be found to minimize this negative effect of the screening.

Nearly all the women taking part in the present study reported that they would attend another mammography screening and also recommend a screening to their friends. These results reflect a positive attitude toward mammography and a willingness to participate that has not been adversely affected by screening experience.

Acknowledgments

A summary of this paper was presented at the annual meeting of the American Public Health Association in New York City, September 26-October 1, 1988.

References


American Journal of Public Health
Paper III
Quality of life following a false positive mammogram

I.T. Gram1, E. Lund1 & S.E. Slener2

1Institute of Community Medicine, Box 477, University of Tromsø, N-9037 Tromsø; and 2Department of Health Behavior, School of Public Health, University of Alabama at Birmingham, AL 35294, USA.

Summary. To assess how women regard having had a false positive mammogram screening exam, and the influence this had on their quality of life, 126 such women interviewed. Their responses were compared to those of 152 women randomly selected among screening with a negative exam. Eighteen months after the screening the reported prevalence of anxiety about breast cancer was 39% among women with a false positive and 13% among women with a negative mammogram (P = 0.01). Of 10 women biopsied, 8 (80%) had come in the breast and 10 (90%) had reduced recall sensitivity. A false positive mammogram was described by 17% (17%) of the women as the worst thing they would have experienced. However, most women with a false positive result regarded this experience, in retrospect, as one of many minor stressful experiences creating a temporary decrease in quality of life. They report the same quality of life today, women with negative screening results and 95% would attend another screening. Even so, false positive results are a matter of concern, and efforts should be made to minimize this cost whenever a screening programme is conducted.

The reduced breast cancer mortality found in several major studies (Shapiro et al., 1982; Collette et al., 1984; Verbeek et al., 1984; Tancer et al., 1985, 1989; Puhl et al., 1986) is the rationale for screening with mammography. In order to justify the continued use of a screening procedure, subjects correctly classified as positive at screening should receive a benefit. However, the magnitude of the reduction in breast cancer resulting from screening has been questioned, and issues regarding adverse effects of breast screening have been raised (Skrabanek, 1985; 1988; Wright, 1986a; Edery, 1988; Devins, 1989).

So far, breast screening has not been found to increase psychiatric morbidity as measured by the General Health Questionnaire, neither among women with negative (Dean et al., 1986) nor false positive screening results (Ellman et al., 1989). In the Canadian National Breast Screening Study (Baum et al., 1990) 93% of the women, receiving either annual mammography or physical examination for three or four years, reported this as a positive experience. Women’s attitudes and expectations lead upon their own experiences are important aspects of the screening issue that need to be addressed. Further study set out to investigate how women regard having had a false positive result at a mammography screening, and whether the experience has consequences for their attitude toward mammography and long-term quality of life.

Materials and methods

Screening:work-up examination

The mammography screening was a part of a health survey carried out in Tromsø, Norway 1986/87. Women aged 40 or older (n = 4,323), were offered a free mammogram, and 82% of those women had their mammogram taken. The women were told that only those with an abnormal mammogram would be notified by mail within three weeks. Altogether 193 (5%) of the screenings were selected for a work-up mammographic examination, and of these 61 were subsequently referred to a surgeon. Altogether 40 (1%) women underwent biopsy, mostly as hospital inpatients, and ten new cases of breast cancer were diagnosed. Details of the screening and case finding procedures are given elsewhere (Gram et al., 1989). Fourteen women were ineligable for the present study (two lost to migration before work-up, ten with a new and two with a previous diagnosis of breast cancer). The remaining 179 women with a false positive screening result formed the study group.

Questionnaire

A questionnaire concerning attitudes toward mammography, anxiety about having breast cancer and a request for a future interview were mailed to the study group six months after the screening mammogram. The questionnaire was also mailed to the following three groups: a random sample of 250 women selected from women with a negative screening result (reference sample), a random sample of 150 women not invited to screening living in the nearby city of Harstad (population sample) and women invited who did not attend (non-attenders, n = 670) (Figure 1). In the study group 97% completed the questionnaire. The corresponding completion rates for the eligible women in the reference group was 84%, among non-attenders 45%, and in the population sample 66%. Women completing the questionnaire although migrated (n = 31, non-attenders) are included in the analysis. The women in the combined comparison groups were within the same age range.

Interviews

Women in the study and reference group who had indicated that they would allow an interview were contacted about 1 year after returning their questionnaire. Women who did not show up were mailed a new time for appointment. Three still not responding were approached by telephone and their

TROMSØ HARSTAD

Invited YES NO

Attenders 3653 870

Non-attenders 870

Result screening Positive 153 2402

Negative 3640 460

Mailed questionnaire False Positive 179 250 165

Reference Sample 570 250

Population Sample 250

Figure 1 Flow chart of the mammography screening in Tromsø, Norway 1986/87 and questionnaire response status among the four comparison groups.
reason for lack of response sought. All women were interviewed in person by one of four female interviewers.

The interview comprised open-ended, dichotomous, scaled and paired comparison questions. Two cards showing different alternatives were handed the respondent when comparisons were used. Members of the study group were asked to recall the time interval between being informed of their abnormal mammogram result and the subsequent notification of their results from the work-up. For brevity this period is referred to in the text as the work-up period. Members of the reference group were asked to recall the 3 weeks subsequent to the screening when they did not know the result of screening mammogram. For brevity this period is referred to in the text as the screening period. As an indicator of well-being a ladder scale with ten rungs, derived from the Self Anchoring Scale of Hadley-Castelli (Contril, 1965) was used. The top rung was labelled ‘Best life I could expect to have’ and the bottom rung ‘Worst life I could expect to have’. The respondents were asked to rate themselves today. Afterwards, the study group rated themselves in the work-up period and the reference group in the screening period. The study group was questioned as to whether they would be willing to go through a similar work-up if it were free, or to pay any amount of money to get a reviewed and final result of the screening mammogram the next day without further assessments, assuming this was technically feasible. The reference group cited what they would pay to get the result of screening mammogram the following day. As an indicator of willingness to trade longevity for quality of life, some questions derived from the proportional trade-off method were used (Weinstein et al., 1980). Members of the study group were asked if they would trade-off, in the following order, 21, 1, 7, or 14 of their last days of life (assuming a life-span of 70 years and remaining health[s] to avoid going through the work-up period. Women in the reference group were asked the same question regarding the screening period.

Spontaneous comments on the different questions were recorded. The women were encouraged to talk freely at the end of the interview which took about 30 minutes to complete. The analyses were performed using the Pearson’s $P$ statistic and $t$-test procedures available in the SAS statistical package (SAS Version 6). Results were considered statistically significant with a $P$ value of 0.05 or less.

### Results

Analysis of questionnaire responses 6 months after the screening revealed a prevalence of anxiety about breast cancer in the study group of 40% and in the reference group of 22% ($P < 0.001$) (Table I). The corresponding prevalence was 21% in the non-attenders and 53% in the population group. The latter was significantly higher compared with the reference group ($P = 0.03$). Eighteen months after the screening the prevalence of anxiety about breast cancer was 26% in the study group and 33% in the reference group ($P = 0.001$).

Among the women completing the questionnaire 90% in the study group and 88% in the reference group indicated their willingness to be interviewed (Table II). When invited, 88% of the former and 83% of the latter group attended. Table III shows that the two groups were similar with respect to a number of selected characteristics at the time of the mammography screening. Neither of the groups interviewed had changed their frequency of visits to health professionals during the preceding year, compared to what they reported at the time of the screening. No significant differences were found between the study and reference groups with respect to their being easily worried, suffering from sleeplessness, taking sleeping pills or sedatives, or frequency of breast self-examination results not shown in tables).

Table IV shows that both groups had an average state of well-being of 7.7 on the Ladder scale at the time of the interview. The study group recalled a significant decrease in

### Table I

<table>
<thead>
<tr>
<th>Prevalence of anxiety about breast cancer reported by group according to questionnaire and interview</th>
<th>Group</th>
<th>Study</th>
<th>Reference</th>
<th>Study</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months after screening</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = (151)</td>
<td>49 (32)</td>
<td>43 (52)</td>
<td>12 (6)</td>
<td>11 (6)</td>
<td>22 (17)</td>
</tr>
<tr>
<td>Interview 18 months after screening</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n.s. Not significantly different from reference group. *Significantly different from reference group ($P = 0.001$). **Significantly different from reference group ($P < 0.001$).

### Table II

<table>
<thead>
<tr>
<th>Interview response status (%) of women completing the questionnaire by group</th>
<th>Study</th>
<th>Reference</th>
<th>Study</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Declined</td>
<td>16 (10)</td>
<td>26 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not attended</td>
<td>18 (11)</td>
<td>21 (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attended</td>
<td>126 (79)</td>
<td>152 (73)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table V: Women (%) in study and reference group considering listed minor events to be more stressful than described the work-up and screening period

<table>
<thead>
<tr>
<th>Event</th>
<th>Study Biopsy (n = 39)</th>
<th>Reference (n = 94)</th>
<th>Reference (n = 92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache one day</td>
<td>84%</td>
<td>81%</td>
<td>79%</td>
</tr>
<tr>
<td>Gas trothe one day</td>
<td>20%</td>
<td>21%</td>
<td>18%</td>
</tr>
<tr>
<td>Rain three weeks of vacation</td>
<td>31%</td>
<td>29%</td>
<td>27%</td>
</tr>
<tr>
<td>Sprain ankle</td>
<td>41%</td>
<td>37%</td>
<td>38%</td>
</tr>
</tbody>
</table>

*Interval between being informed of their abnormal mammogram result and subsequent notification of their result from the work-up.

Table VI: Highest amount of money ($) the women would pay to attend another mammography screening given as mean (sd) and median (range), by group

<table>
<thead>
<tr>
<th>Group</th>
<th>Study Biopsy</th>
<th>Reference (n = 94)</th>
<th>Reference (n = 147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of money in US dollars</td>
<td>$60 (12)</td>
<td>$40 (8)</td>
<td>$40 (12)</td>
</tr>
<tr>
<td>Amount of money</td>
<td>$10 (4)</td>
<td>$10 (4)</td>
<td>$10 (4)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>$0 (0-266)</td>
<td>$0 (0-249)</td>
<td>$0 (0-143)</td>
</tr>
</tbody>
</table>

*Significantly different from reference group (P < 0.005).

Table VII: Highest amount of money ($) the women would pay to get the results of the work-up and screening the next day, given as mean (sd) and median by group

<table>
<thead>
<tr>
<th>Group</th>
<th>Study Biopsy</th>
<th>Reference (n = 94)</th>
<th>Reference (n = 152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of money in US dollars</td>
<td>$66 (12)</td>
<td>$37 (6)</td>
<td>$37 (6)</td>
</tr>
<tr>
<td>Amount of money</td>
<td>$10 (2)</td>
<td>$10 (2)</td>
<td>$10 (2)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>$0 (0-286)</td>
<td>$0 (0-249)</td>
<td>$0 (0-143)</td>
</tr>
</tbody>
</table>

*Significantly different from reference group (P < 0.001).

Table VIII: Women (%) reporting how many days of their lives they would trade off in exchange for not experiencing the work-up or screening period, by group

<table>
<thead>
<tr>
<th>Group</th>
<th>Study Biopsy</th>
<th>Reference (n = 94)</th>
<th>Reference (n = 148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of days</td>
<td>$(n = 29)$</td>
<td>$(n = 48)$</td>
<td>$(n = 52)$</td>
</tr>
<tr>
<td>No more</td>
<td>27%</td>
<td>25%</td>
<td>26%</td>
</tr>
<tr>
<td>1, 7, 14</td>
<td>16%</td>
<td>16%</td>
<td>17%</td>
</tr>
<tr>
<td>21</td>
<td>66%</td>
<td>64%</td>
<td>66%</td>
</tr>
</tbody>
</table>

*Assuming a life-span of 70 years and remaining healthy.

their state of well-being during the work-up period (P = 0.0001). A slight decrease in well-being reported by the reference group was not statistically significant.

In the study group, 95 (80%) of 118 indicated the duration of the work-up period to be 4 weeks or less. The women's perceptions of the length of the work-up period was longer than documented in the hospital files (signed rank test, P = 0.05). Eighty (63%) of the women reported that they had been anxious during the work-up period. Among them, 14 (11%) claimed they had less capacity for work until learning the result of the work-up, while 19 (15%) reported they had this problem only on some days. In the reference group, 24 (16%) said they were anxious about the result of their mammography, and one of them reported having less capacity for work because of this anxiety.

Table V shows that about 49% of biopsied women regarded minor stressful events such as getting a mammogram or x-ray as probably causing them more inconvenience and stress than the work-up period did. Among women not having a diagnostic biopsy about 70% considered the mentioned events as probably more traumatic than the work-up period was. Most of the women, but not all, in the reference group considered the screening period as less stressful than the events they compared it to.

Women in the study group not biopsied were on the average, willing to pay $70 to attend another screening (Table VI). This was $10 more than the women biopsied were willing to pay (P = 0.5) and $24 more than women in the reference group were willing to pay (P = 0.02). While answering this question, many women made them own comparison saying they would pay a cost equal to that of a visit to a physician ($7), to a dentist ($50) or to a car repair ($150).

Table VII shows that biopsied women would be willing to pay the highest amount of money ($60) to get the result of the examination the next day without any further assessments. Only one of the women biopsied was willing to pay more than $150 to avoid the experience of going through the screening mammogram. The reference group 100 (66%) claimed that they would rather wait for 3 weeks than pay anything to get the result the next day.

However, as shown in Table VIII, 76% of biopsied women reported to be willing to trade off days of their lives in the future, assuming this could spare them another work-up period. Among the women in the study group not subjected to surgery 65% were willing to trade off days of life in exchange for the result of the screening mammogram the next day.

Of the 30 women who underwent biopsy, eight (27%) had pain from the scar, while ten (33%) had reduced sensitivity in the breast. Three (2%) women described that having a false alarm at the screening subsequently had an overall bad influence on their lives. Two of them this was due to problems from the scar caused by surgery. The third woman said she had become more anxious about breast cancer. In the study group 14% of the women claimed that the experience of going through the screening and the work-up had an overall positive impact on their lives. However, these women said more often than the rest of the study group that they had been anxious in the work-up period (P = 0.04). In the reference group 53% claimed that the mammography screening had an overall positive impact on their lives. The remaining women in both groups considered these experiences of minor significance and reported no overall impact. Only three (1%) of 278 women did not want to participate if they were
again offered a free screening with mammography, while another 11 (4%) said they would not attend if they had to pay.

Discussion

This study shows that most women with a false positive result at a mammography screening regard this experience, in retrospect, as but one of many minor stressful experiences in their lives. It also demonstrates that these women are in favour of attending another screening, and that they report the same quality of life today as women with negative screening results.

One long-term adverse effect found in this study is the physical morbidity, i.e. pain and reduced sexual sensitivity described by some of the women subjected to surgery. This negative impact on sexuality was also commented on by some of the women participating in the Canadian study (Baines et al., 1994).

Another effect found in our study is that women with a false positive screening result have a higher prevalence of anxiety about breast cancer compared with women with a negative mammogram result. The high prevalence of anxiety about breast cancer reported by the population not exposed to mammography screening indicates that this anxiety is widespread in the general population. The results from the questionnaire suggest that the screening is generating an increase in this prevalence among women in the false positive group and a decrease among women in the negative result group. This seems to have an impact on levels of anxiety about breast cancer, since both groups have a decreased prevalence at 18 months compared with 6 months after the screening. Of the women attending Edinburgh Breast Screening Clinic (Dean et al., 1986) 40% said they were worried about the possibility of having breast cancer before the screening. This proportion did not change 6 months after the screening. Among women attending the screening program in Canada (Baines et al., 1990) for 3 or 4 years, only 5% reported being anxious and another 5% that they were worried. Sixty-one per cent of the women offering explanations for their anxiety said it was because they had been referred to the screening clinic. In spite of this, the response to the question about anxiety induced by screening, were not found to differ significantly by review status.

In our study it is noteworthy that women willing to pay the highest amount of money to attend another screening are found among those who experienced a positive screening test, but who did not go through diagnostic surgery. It is also notable that a substantial proportion of the study group reported that this experience had a positive impact on their lives. Some of them stated explicitly that they were grateful for this experience, because they found life more precious afterwards. However, it seems unreasonable to put this on the positive side of the balance sheet of a screening, since first the fear, then the reed, are induced by the same screening. Nevertheless, the data suggest that women correctly classified as negative have gained a benefit from the screening, as the majority report that the screening had an overall positive impact on their lives.

With regard to the question of trading longevity, an inconsistency appears. That is, some biopsied women would rather go through another operation than trade a single day in the future, while others were willing to trade 3 weeks of their lives at exchange for having the screening result the next day. In our survey, answers to these questions do not seem to reflect what they were intended to measure, that is how much stress the women had been through. It rather reflects main differences in attitude toward longevity. The following two viewpoints emerged from spontaneous comments during the interview:

1. When an age of 50 was assumed, it mattered little to the women if they were alive 21 days more or less.

The other one was that if healthy, even 1 day that far away was too much to trade to avoid a reduction in quality of life today.

The fact that women recalled the duration of the work-up period to be longer than it probably was, can be interpreted as an indirect measure of the unpleasantness of the work-up period. This difference, however, may also be explained by missing information on later visits in the hospital files.

Since the purpose of this investigation was to focus on the consequences that a false positive result has on women attending a screening, subjects with a negative mammogram result were chosen as a reference group. This is not fully satisfactory since the two groups have to compare different experiences when answering some of the questions. The interview method was selected to allow observation of how the women responded to the questions. Based on hypotheses, some answers depend on the women's ability to abstract comparisons. A potential weakness of the method applied is the possible risk of bias due to the attitudes of the interviewers. An interesting observation is that all women subjected to surgery agreed to and were available for interview, as opposed women not subjected to surgery. This fact underlies a selection bias towards emphasizing the opinions of biopsied women more than their true proportions among women with false positive mammogram should imply.

The increased morbidity induced by mammography screening has led some authors advocate the abandonment (Wright, 1986) or disengagement (Devitt, 1989) of such screening before the age of 60. This paper is an attempt to evaluate the magnitude of this morbidity. Even if the women with a false alarm at the screening report the same quality of life today as do women with negative screening mammogram, our data suggest that some of them will suffer from undesirable long-term effects, and a small proportion will experience this as subsequently having an overall bad influence on their lives. Efforts should be made to mitigate this cost whenever a screening programme is conducted.

Dr. Gau is a research fellow of the Norwegian Cancer Society. We thank all women concerned for their permission in the completing the questionnaires and in attending the interview. We thank Dr. P. Cole for valuable comments during the preparation of the manuscript. Financial support was given by the Norwegian Cancer Society and the Åsaker Foundation.

References


Paper IV
Cigarette Smoking and the Incidence of Cervical Intraepithelial Neoplasia, Grade III, and Cancer of the Cervix Uteri

Inger T. Gram,† Harland Austin,‡ and Hege Stalsberg§

The relation between cigarette smoking and cervical intraepithelial neoplasia, grade III (CIN III), and cervical cancer was examined among a cohort of 6,812 women in Tromsø, Norway, between 1980 and 1989. During the 52,844 person-years of observation, 185 incident cases (177 women with CIN III and eight with cervical cancer) were recorded in the regional pathology registry. The age-adjusted incidence rates of CIN III and cervical cancer were 257/100,000 person-years among women who had never smoked, 183/100,000 person-years among ex-smokers, and 476/100,000 person-years among current smokers. A multivariate model containing terms for age, marital status, and frequency of intercourse yielded a relative rate for current smokers compared with nonsmokers of 1.5 (95% confidence interval 1.0–2.2). Statistical trend tests for the number of cigarettes smoked per day (never, 1–14, and ≥15 cigarettes), years of smoking (never, 1–9, and ≥10 years), and age started smoking (<16, 16–18, 19–21, and ≥22 years) all yielded significant results. These findings support the opinion that CIN III and cervical cancer are a smoking-related disease. Am J Epidemiol 1992;136:341–6.

cervix dysplasia; cervix neoplasms; follow-up studies; smoking

In a recent review, Winkelstein (1) concluded that scientific evidence supports the hypothesis that cigarette smoking is a cause of cervical cancer. He points out that neither

Materials and Methods

Between 1979 and 1980, all men (n = 1,423) aged 20–54 years and all women (n = 9,906) aged 20–49 years living in the municipality of Tromsø, Norway, were in-
vited to participate in the second Tromsø Study. Complete details of the study methods are given elsewhere (3). The participants filled out one questionnaire at the screening facility and another at home. The first questionnaire concerned disease history and aspects of living habits, such as cigarette smoking and oral contraceptive use. Former smokers were asked how long ago they had quit, and both current and former smokers were asked the number of years they had smoked and the average number of cigarettes they had smoked per day. The second questionnaire elicited information on dietary habits, alcohol and coffee consumption, previous diseases, and social and psychologic conditions. The participants were instructed to return this questionnaire by mail.

Women participating in the study (n = 8,143) were followed for the development of CIN III and cervical cancer (for brevity, referred to as CIN III in the text) by linkage of their national personal identification number with the information in the Pathology Registry of the University Hospital in Tromsø.

The following types of women were included in the analytical cohort: women with at least one non-case (i.e., absence of CIN III) specimen taken during 1977, 1978, or 1979 and at least one specimen taken after enrollment in 1980 (n = 5,496). For these subjects, a follow-up entry date of December 31, 1979, was assigned. Women also were included in the cohort if they had at least two specimens taken after 1979, with the first specimen indicating the absence of CIN III (n = 1,316). For these women, the date of their first specimen is their entry date. The analytical cohort comprised 6,812 subjects representing 84 percent of the women participating in the Tromsø Study.

The end of follow-up for women developing CIN III was the date of this diagnosis, while for the remaining women, it was the midpoint between the date of their last cervical smear and the study end date of June 1989. Diagnoses for which month and day are unknown, but for which the year is known, are assumed to have occurred on June 30. If a woman had two or three specimens obtained within the same year (with no recorded month or day for either), she was assigned an observation period of 6 or 4 months, respectively.

Crude incidence rates for a given exposure category were obtained by dividing the number of cases by the total number of person-years contributed by women in that category. Age-adjusted rates were calculated by the direct method by using the 5-year age categories of the person-year distribution of the entire analytical cohort (4).

Each of the following factors was evaluated as a potential confounder of the smoking-CIN III relation: age, ethnic origin, marital status, education, frequency of fruit and vegetable consumption, frequency of fish consumption, frequency of drunkenness, and oral contraceptive use. The relative rates for each of these factors also were estimated in both univariate and multivariate analyses. The Cox proportional hazards regression model was used for simultaneous evaluation of the effects of several potential confounders of the association between smoking and the incidence of CIN III (5). The follow-up experience of subjects was analyzed by blocking on the number of specimens (1-2, 3-4, 5-6, and ≥7 specimens) that they had accumulated during the follow-up period. This blocking was necessary because the likelihood that a CIN III diagnosis is made during the observation period increases with more frequent screening.

Statistical trend tests were obtained by creating an ordinal exposure variable with equally spaced scores and including it in a proportional hazards model. Results were considered as statistically significant if the p value was 0.05 or less, and 95 percent confidence intervals (CI) are reported throughout the paper. Multiplicative terms between smoking and possible confounders were entered in the proportional hazards models to evaluate interaction. The proportional hazards analyses were performed using the PHGLM procedure of the SAS statistical package (6).

RESULTS

During the 52,844 person-years of observation, 185 incident cases (177 women with
CIN III and eight with cervical cancer) were identified. Twenty-seven women had a cytologic CIN III diagnosis without histologic confirmation. These women are included in all analyses. We note that the exclusion of these 27 cases, as well as the eight cervical cancer cases, from the analysis did not change the results materially.

Seventy-eight percent of the subjects are of Norwegian ethnic origin, and 69 percent were married. Their median number of years of schooling was 10 and, at the beginning of the follow-up period, their median age was 32 years. The mean follow-up period was 8 years, and the average number of cervical specimens obtained during follow-up was five regardless of smoking status. Also, the length of time between various screenings was nearly identical for smokers and non-smokers.

A multivariate model that included terms for smoking status as well as age, marital status, education, ethnic origin, consumption of fish and of fruits and vegetables, current oral contraceptive use, and frequency of intoxication by alcohol was fit. The results indicated a significantly lower risk of CIN III among women aged 40–49 years (relative rate = 0.3; 95 percent CI 0.2–0.6) compared with those in the 20- to 29-year age group. Single women (relative rate = 1.6; 95 percent CI 1.1–2.4) as well as those divorced or widowed (relative rate = 2.2; 95 percent CI 1.4–4.1) displayed a statistically significant increased risk of CIN III as compared with married women. CIN III risk also was significantly increased among those who had been intoxicated by alcohol at least once (relative rate = 1.4; 95 percent CI 1.0–2.2) in the year preceding the health survey as compared with those who had not. Women frequently eating fish (relative rate = 1.6; 95 percent CI 0.9–3.3) and current oral contraceptive users (relative rate = 1.3; 95 percent CI 0.9–2.1) also had an increased risk of CIN III. The relation between oral contraceptive use and cervical intraepithelial neoplasia is explored in depth and reported elsewhere (6a). No meaningful associations were found between CIN III and years of schooling, ethnicity, and fruit and vegetable consumption.

Current smoking was more prevalent among younger women, the unmarried, and those reporting more frequent alcohol intoxication (data not shown). Thus, each of these factors was considered a potential confounder of the smoking-CIN III association, and adjustment was made for each in a multivariate proportional hazards model.

The age-adjusted incidence rate for CIN III was 267/100,000 person-years among women who never smoked (table 1). Among ex-smokers, the corresponding rate was 183/100,000 person-years, and among current smokers, it was 476/100,000 person-years. The relative rate of CIN III obtained from a proportional hazards regression model that included terms only for age and smoking history was 1.8 (95 percent CI 1.3–2.5) for current smokers and 0.7 (95 percent CI 0.4–1.2) for ex-smokers compared with non-smokers. However, among ex-smokers who had ceased smoking less than 3 months before the health survey (n = 127), the corresponding relative rate was 1.5 (95 percent CI 0.5–4.1).

A multivariate model based on 158 cases with complete information on the potential confounders (age in 5-year group), marital status (married, divorced/widowed, single), frequency of intoxication by alcohol (never, less than monthly, monthly, or more) yielded a slightly lower relative rate of 1.5 (table 1) for current smoking which nonetheless, remained statistically significant (p = 0.05).

Dose response was evaluated among current smokers using number of cigarettes smoked per day, years of smoking, and age at smoking (table 2). For light smokers (<15 cigarettes/day), the relative rate is slightly elevated, i.e., 1.4, whereas for heavy smokers the relative rate is nearly twice that of non-smokers. An ordinal trend test across the three categories of number of cigarettes smoked daily displayed in table 2 yields a p value of 0.02. There also was a statistically significant (p = 0.01) trend between years of smoking and CIN III. Furthermore, the relative rates pertaining to smoking were highest among women who started smoking at a younger age. A statistical trend test for age at smoking (with four categories
TABLE 1. Age-adjusted incidence rates (IR) and age-adjusted and multivariate relative estimates for cervical intraepithelial neoplasia, grade III, and cervical cancer according to smoking status, in a cohort of 6,812 women: Tromsø, Norway, 1980–1989

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Cases/ cohort</th>
<th>IR* (age adjusted)</th>
<th>Relative rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age adjusted</td>
</tr>
<tr>
<td>Never</td>
<td>43/2,284</td>
<td>267</td>
<td>1.0</td>
</tr>
<tr>
<td>Past</td>
<td>19/1,325</td>
<td>183</td>
<td>0.7 [0.4–1.2]</td>
</tr>
<tr>
<td>Current</td>
<td>123/3,223</td>
<td>476</td>
<td>1.8 [1.3–2.5]</td>
</tr>
</tbody>
</table>

* Per 100,000 person-years, age adjusted using the direct method for 5-year age categories of person-years with the distribution of the entire analytical cohort as standard.
† Based on age-adjusted regression coefficients from the proportional hazards model; total of 185 cases.
‡ Numbers in parentheses, 95% confidence interval.

TABLE 2. Relative rates of cervical intraepithelial neoplasia, grade III, and cervical cancer according to various measures of smoking intensity among current smokers, in a cohort of 6,812 women: Tromsø, Norway, 1980–1989

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Relative rates (multivariate)*</th>
<th>Trend test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average no. of cigarettes/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1.0</td>
<td>ρ = 0.02</td>
</tr>
<tr>
<td>1–14</td>
<td>1.4 (0.9–2.0)†</td>
<td></td>
</tr>
<tr>
<td>≥15</td>
<td>1.8 (1.1–3.0)</td>
<td></td>
</tr>
<tr>
<td>No. of years smoked</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1.0</td>
<td>ρ = 0.01</td>
</tr>
<tr>
<td>1–4</td>
<td>1.2 (0.7–1.9)</td>
<td></td>
</tr>
<tr>
<td>≥5</td>
<td>1.8 (1.2–2.8)</td>
<td></td>
</tr>
<tr>
<td>Age started smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1.0</td>
<td>ρ &lt; 0.01‡</td>
</tr>
<tr>
<td>≥22</td>
<td>0.9 (0.4–1.5)†</td>
<td></td>
</tr>
<tr>
<td>19–21</td>
<td>1.1 (0.6–2.0)</td>
<td></td>
</tr>
<tr>
<td>16–18</td>
<td>1.7 (1.1–2.7)</td>
<td></td>
</tr>
<tr>
<td>&lt;16</td>
<td>2.0 (1.1–3.5)</td>
<td></td>
</tr>
</tbody>
</table>

* Based upon 142 cases from model with age group, marital status, and frequency of intoxication by alcohol, blocking for number of specimens.
† Numbers in parentheses, 95% confidence interval.
‡ Trend test with four levels (four categories of age started smoking).

among current smokers) yielded a p value less than 0.01. The trend between age started smoking and CIN III risk was evident among both light (p = 0.08) and heavy (p = 0.07) smokers.

In table 3, the relative rates for current smokers compared with nonsmokers are displayed according to the levels of the potential confounding variables. Current smokers experience a higher risk of CIN III as compared with nonsmokers within each category of age, marital status, and alcohol intoxication.

None of the two-way interaction terms between smoking, age, marital status, and drinking evaluated in any proportional hazards model was statistically significant or meaningfully affected the relative rates presented above.

DISCUSSION

The results of this follow-up study indicate that current smokers (at the time of the health survey) experience a higher incidence of CIN III than do nonsmokers. A causal interpretation of these findings is supported by the presence of a dose-response relation between various measures of smoking intensity and the CIN III incidence rates in this study. Furthermore, smokers display a consistently higher risk of CIN III as compared with nonsmokers within each category of the possible confounders.

A major strength of this study is that it originates from a population-based survey with a high attendance rate. Thus, the women comprising the cohort should be representative of all women of this age in the region. Another strength is its prospective design. The smoking habits of subjects were classified at enrollment and, hence, were not subject to differential anamnestic bias typical of case-control studies.

We are aware of five other follow-up studies of cervical cancer or its precursors and cigarette smoking (7–11). All found a positive relation between smoking and either the precursor lesions (7, 8) or cervical cancer
TABLE 3. Relative rate estimates for cervical intraepithelial neoplasia, grade III, and cervical cancer associated with current smoking within levels of potential confounding variables, in a cohort of 8,812 women: Tromsø, Norway, 1980–1989

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases</th>
<th>Person-years</th>
<th>Relative rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–29</td>
<td>69</td>
<td>12,638</td>
<td>1.4 (0.8–2.6)†</td>
</tr>
<tr>
<td>30–39</td>
<td>71</td>
<td>18,636</td>
<td>1.6 (0.8–3.3)</td>
</tr>
<tr>
<td>40–49</td>
<td>18</td>
<td>13,940</td>
<td>1.9 (0.9–3.6)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>76</td>
<td>32,429</td>
<td>1.2 (0.7–2.1)</td>
</tr>
<tr>
<td>Divorced/widower</td>
<td>16</td>
<td>2,085</td>
<td>4.7 (0.5–37.0)</td>
</tr>
<tr>
<td>Single</td>
<td>66</td>
<td>10,687</td>
<td>1.6 (0.9–3.0)</td>
</tr>
<tr>
<td>Frequency of intox-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ication by</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>47</td>
<td>22,918</td>
<td>1.6 (0.9–3.0)</td>
</tr>
<tr>
<td>Less than monthly</td>
<td>83</td>
<td>19,837</td>
<td>1.2 (0.7–2.1)</td>
</tr>
<tr>
<td>Monthly or more</td>
<td>28</td>
<td>3,555</td>
<td>2.4 (0.6–10.3)</td>
</tr>
</tbody>
</table>

* Multivariate-adjusted estimates computed from stratiﬁed model with age group, marital status, and frequency of intoxication by alcohol, smoking for number of pack-years. Reference category was never-smokers.
† Numbers in parentheses, 95% conﬁdence interval.

Itself (9–11). A limitation the present study shares with these other studies is the lack of information on known risk factors for cervical cancer such as sexual behavior, which is thought to be related to cervical cancer through the transmission of an infectious organism (12–14). Our ﬁndings also are supportive of other previous studies that showed a positive relation between smoking and the precursor lesions of cervical cancer (12–23). In most of these studies (8, 12, 13, 19–21, 23), but not all (16, 22), a positive dose response was reported.

Information on sexual activity is difﬁcult to gather for the large number of subjects typically participating in follow-up studies. However, such information has been obtained in a number of case-control studies, and many have demonstrated an independent effect of cigarette smoking on the precursor lesions of cervical cancer after adjusting for sexual activity (12–22). In the present study, the unmarried and those frequently intoxicated experienced a higher incidence of CIN III than did married women or those using less alcohol. Although these positive associations may reﬂect a higher level of sexual activity among women in these groups, it is likely that subjects within these groups are more homogeneous with respect to sexual activity than are women overall. The fact that we did ﬁnd a positive smoking effect in each subgroup (table 3) suggests that our smoking ﬁndings are not confused by sexual activity. Nonetheless, we cannot rule out the possibility of some confusion from the smoking-CIN III relation by sexual behavior in the present study.

The increased risk found in the present study among current smokers who started smoking in their early teens compared with smokers starting later has also been reported in other studies (13, 19–21, 23), while another two found no such association (14, 15).

Our ﬁndings indicate that the increased risk of developing CIN III is restricted to women being current smokers when the cohort was established. In the cohort study reported by Greenberg et al. (8), former smokers experienced an increased risk of cervical dysplasia but not of invasive cancer, compared with nonsmokers. Several of the case-control studies (13–17, 19, 21, 22) found exsmokers at increased risk compared with never smokers, but the excess was statistically signiﬁcant only in two of the studies (15, 19). These results do not necessarily contradict our ﬁnding of no effect among former smokers since in these case-control studies, as opposed to our cohort study, it is possible that the precursor lesions, even though diagnosed when the woman was an exsmoker, actually were initiated when she smoked.

The accumulation of tobacco products in cervical epithelial cells and a local immunologic effect of smoking may explain how cigarette smoking contributes to the development of cervical neoplasia. Nicotine and its major metabolite, cotinine, accumulate in the cervical mucus in smokers with CIN III (24). The presence of cotinine in cervical mucus was accurate in distinguishing between smokers and nonsmokers, and the levels of these two substances in cervical
fluids were also found to mirror recent smoking intensity among current smokers (25). A recent study (26) found a significant positive association between nicotine levels in cervical lavages and self-reported exposure to passive smoking. Current cigarette smoking has also been associated with a significant decrease in the number of Langhans' cells in both normal cervical epithelium and CIN lesions (27).

In summary, although our study has some limitations with regard to an evaluation of the smoking-CIN III hypothesis, it is one of only a few follow-up studies of the topic, and it provides further support for the belief that CIN III and cervical cancer are a smoking-related disease. The credibility of the association recently has been enhanced by new biologic evidence demonstrating a direct effect of smoking on cervical cells.

REFERENCES

Paper V
Oral contraceptive use and the incidence of cervical intraepithelial neoplasia

Inger T. Gram, MD,* Maurizio Macaluso, MD, DrPH,§ and Helge Stalsberg, MD*
Tromsø, Norway, and Birmingham, Alabama

OBJECTIVE: Our objective was to examine the relationship between oral contraceptive use and the incidence of cervical intraepithelial neoplasia.

STUDY DESIGN: In a prospective follow-up study of 8622 women participating in the Second Tromsø Study conducted in 1979 and 1980 in Tromsø, Norway, women aged 20 to 49 years answered a questionnaire regarding their smoking history, dietary habits, alcohol consumption, and oral contraceptive use. They were then followed for 10 years with data from the Pathology Registry of the University Hospital.

RESULTS: The age-adjusted incidence rate of cervical intraepithelial neoplasia was 9.7 per 100,000 person years among noncurrent and 23.6 per 100,000 person years among current oral contraceptive users as of 1979. After adjusting for age, marital status, smoking, and frequency of alcohol intoxication the relative rate for current users was 1.5 (95% confidence interval 1.1 to 2.1), and the relative rate for past users was 1.4 (95% confidence interval 1.0 to 1.8), as compared with those who had never used oral contraceptives before 1979.

CONCLUSION: These findings support the hypothesis that the occurrence of cervical intraepithelial neoplasia is increased by oral contraceptive use. (Am J Obstet Gynecol 1992;167:666.)

Key words: Oral contraceptives, cervical dysplasia, follow-up studies, Norway, cervical neoplasms

In two extensive reviews it was concluded that a weak positive association seems to be emerging between oral contraceptive use and the risk of cervical neoplasia but this association may be due to bias and confounding. The relationship remains controversial. Recent epidemiologic studies continue to yield conflicting results. It has been proposed that the findings of positive studies reflect enhanced detection of cervical intraepithelial neoplasia among OC users rather than a causal association.
We observed that among women who participated in the Second Tromsø Study and who were current oral contraceptive users as of 1975, grade 3 cervical intraepithelial neoplasia incidence during the following 10 years was 1.4 times higher than among nonusers. Although this increased incidence among oral contraceptive users was not explained by confounding factors such as cigarette smoking or the number of cytologic examinations (Papanicolaou smears), it lacked statistical significance. In this report we expand the previous analysis by evaluating the relationship between oral contraceptive use and all cervical intraepithelial neoplasia grades and by adding information from the Third Tromsø Study.

**Material and methods**

Between 1979 and 1980 all women (n = 9006) aged 20 through 49 years and all men (n = 11423) aged 20 through 54 years living in the municipality of Tromsø were invited to participate in the Second Tromsø Study. Complete details of the study methods are given elsewhere. The participants filled out one questionnaire at the screening facility and another at home. The first questionnaire concerned disease history and aspects of living habits, including cigarette smoking and oral contraceptive use. The second questionnaire elicited information on dietary habits, alcohol and coffee consumption, previous diseases, and social and psychologic conditions. The participants were instructed to return this questionnaire by mail. The Third Tromsø Study was conducted in 1986 and 1987. At this survey the questionnaires were modified to add information on use and duration of oral contraceptives and intrauterine contraceptive devices, age at first marriage or cohabitation, and age at first pregnancy.

Women participating in the Second Tromsø Study (n = 8143) with no history of the disease were followed for the development of cervical intraepithelial neoplasia or cervical cancer. The follow-up was made possible by linkage of their national personal identification numbers with the computerized information in the Pathology Registry of the University Hospital in Tromsø. This registry provides complete records of all cytologic and histologic diagnoses made in the county where Tromsø is located. Altogether 7838 (96%) women from the Second Tromsø Study had a cervical specimen recorded in the registry during 1980 through 1989.
Criteria for inclusion in the analytic cohort were (1) no diagnosis of cervical intraepithelial neoplasia or cancer of the cervix before Jan. 1, 1980, and (2) at least one normal cervical specimen within 3 years before enrollment in the second Tromsø study or after enrollment. Excluded from follow-up were 398 women who had a diagnosis of cervical intraepithelial neoplasia or invasive cancer of the cervix before enrollment or as their first cervical specimen recorded in the registry. Follow-up began on Dec. 31, 1979, for 5413 women who had a normal specimen during the previous 3 years and on the date of the first normal specimen recorded for the remaining 1895 women. However, 683 women had no subsequent specims and contributed no information to the follow-up study. Thus the analysis is restricted to 6622 women (91% of all participants in second Tromsø study). Follow-up ended on the date of diagnosis of cervical intraepithelial neoplasia, autopsy or hysterectomy, or their last cervical specimen, whichever was earliest.

Incident cervical intraepithelial neoplasia cases were classified according to the first diagnosis. Thus, if during the study period a woman had a first diagnosis of grade 1 disease that later progressed to grade 3, she was counted only once as a grade 1 case.

Person years of follow-up were assigned to categories of potential determinants of risk for cervical intraepithelial neoplasia. Incidence rates were computed by dividing the number of cases by the number of person-years in that category. Age-adjusted rates were calculated by the direct method, using the age distribution of person-years in the entire analytic cohort as the standard.12 Data analysis included an evaluation of incidence rates by age, marital status, education, age at first pregnancy, age at first marriage or cohabitation, frequency of fruit and vegetable consumption, frequency of fish consumption, frequency of drunkenness, cigarette smoking, number of specimen, and time between specimens. Cases and person years were classified into current and noncurrent or contraceptive users as of 1979 on the basis of information obtained from the second Tromsø study. More detailed information on the history of oral contraceptive use was available for 4912 (74%) who also participated in the third Tromsø study. Data from the third study were used to ascertain whether women who were nonusers at the time of enrollment into the second study had ever used oral contraceptives before that date (past users). Thus cases and person years were reclassified into never users, past users, and current users. Women from the second Tromsø study who were noncurrent users at enrollment and who did not participate in the third study were classified as “other noncurrent users.” It is likely that this group is a mixture of never and past users.
The relative rate was used to compare category-specific incidence rates. Relative rates were also estimated with the Cox proportional hazards regression model to adjust simultaneously for the effects of several potential confounders.18 The follow-up experience of subjects was analyzed by blocking on the number of specimens (one or two, three or four, five or six, seven or more) that they had accumulated during the follow-up period. This blocking was done because the likelihood that a diagnosis of cervical intraepithelial neoplasia is made during the observation period increases with more frequent screening. However, the results did not change materially whether the analysis was performed without the blocking factor or by including the number of specimens as covariates.

Poisson regression models were also used to obtain relative rate estimates adjusted for time between screens (and the confounding variables included in the proportional hazards model) and to evaluate interaction among potential risk factors. The significance of a trend in the incidence of cervical intraepithelial neoplasia with increasing levels of a factor was evaluated by assigning equally spaced ordinal scores to categories of the factor and including the score as a continuous variable in a Poisson regression model.19 Multiplicative terms between OC use and possible confounders were included in the model to evaluate interaction.

Results were considered statistically significant if the p value was ≤0.05. The 95% confidence intervals are reported throughout the paper. The proportional hazards regression analyses were performed with the PHGLM procedure of the SAS statistical package.16 The Poisson regression analyses were performed with the EGRET statistical package.16

Results
During the 43,816 person years of observation, 401 incident cases (354 women with grade 1 or 2 cervical intraepithelial neoplasia as their first abnormal diagnosis, 44 with grade 3 cervical intraepithelial neoplasia, and three with cervical cancer) were identified. These women are included in all analyses. We note that inclusion of only the 354 women with grade 1 or 2 cervical intraepithelial neoplasia in the analysis did not change the results materially.
Seventy percent of the women were married, their median years of schooling were 11 (7 to 23), and at the beginning of the follow-up their median age was 31 (20 to 64) years. Only 9% of the women were current oral contraceptive users in 1979 and 1980.

For never, past, and current oral contraceptive users the mean follow-up time was 7 years and the average number of specimens obtained was five. The women who were nontcurrent users in 1979 with missing information on never users (women who did not participate in the third Tromsø study in 1986 and 1987) had an average number of four specimens obtained during the mean follow-up period of 5 years.

Prevalence of oral contraceptive use was higher among women of young age, among unmarried women, among cigarette smokers, and among women reporting frequent intoxication by alcohol (Table 1). The relative risk estimates of cervical intraepithelial neoplasia from the proportional hazards regression models show that these women also have a significantly increased risk for cervical intraepithelial neoplasia (Table 1). Thus each of these factors was considered a potential confounder of the oral contraceptive–cervical intraepithelial neoplasia association, and adjustment was made for each in a multivariate proportional hazards model. No meaningful associations were found between cervical intraepithelial neoplasia and years of schooling, fruit and vegetable consumption, or fish consumption.

The age-adjusted incidence rate of cervical intraepithelial neoplasia was 897 per 100,000 person years among nontcurrent and 1295 per 100,000 person years among current oral contraceptive users as of 1979 (p = 0.05). A multivariate proportional hazards regression model on 348 cases with complete information on potential confounders (age in 5-year groups, marital status [married, divorced/widowed, single], smoking status [never, past, current], frequency of intoxication by alcohol [never, less than monthly, monthly or more]) yielded increased relative rate estimates of cervical intraepithelial neoplasia among nontcurrent, past, and current oral contraceptive users as of 1979 as compared with never users. Women starting at an earlier age were at an increased risk as compared with those starting later. An ordinal trend test across the four categories for age started oral contraceptive use yielded a p value of 0.05 (Table III).

Women who married or cohabited for the first time at a young age had an increased risk for cervical intraepithelial neoplasia. This association was, however, explained by marital status. Neither did intrauterine contraceptive device use or age started intrauterine contraceptive device use explain the oral contraceptive–cervical intraepithelial neoplasia association reported.
None of the two-way interaction terms between oral contraceptive use and age, marital status, smoking, drunkenness, time between screens, and number of screens was statistically significant or meaningfully affected the relative rates presented above.

Comment

The results of this follow-up study suggest that both current and past oral contraceptive users experience a higher incidence of cervical intraepithelial neoplasia than do those who never used oral contraceptives. This finding is similar to those of four of five previous follow-up studies that evaluated the oral contraceptive–cervical intraepithelial neoplasia hypothesis. The present study also suggests a relationship between age at start of oral contraceptive use and cervical intraepithelial neoplasia incidence. This association may in fact reflect an increasing trend of cervical intraepithelial neoplasia incidence with duration of OC use. Three of the previously mentioned follow-up studies found a trend of increasing incidence with duration of OC use.

A major strength of this study is that it originates from a population-based survey with a high attendance rate. Thus the women constituting the cohort should be fairly representative of all women of similar age in the region. Strengths related to the prospective follow-up design are that women were known to be free of cervical intraepithelial neoplasia at enrollment and information on potential risk factors was collected before diagnosis. The oral contraceptive use among subjects was ascertained before outcome and hence is not subject to differential anamnestic bias, which may affect the results of case-control studies. Another strength of this study is the ability to control for confounding variables such as marital status, smoking status, and frequency of drunkenness. Because the number of Papnicolaou smears and the time between smears were also controlled for, it is unlikely that our results are explained by detection bias.
On the other hand, misclassification may result from higher rates of false-positive tests (from higher incidence of vaginal infections and cervical erosions) in oral contraceptive users. This misclassification would result in a spuriously high incidence of low-grade lesions (grade 1). We found that the incidence of grade 3 also was increased among oral contraceptive users. Also, the excess cervical intraepithelial neoplasia incidence should be experienced only by current users, whereas incidence is increased among past oral contraceptive users.

The most important limitation of this study is the lack of information on sexual behavior. As in the other follow-up studies, it was not feasible to collect such data. However, it is likely that the source of confounding was partially controlled for in the analysis by adjusting for marital status and frequency of drunkenness. Information on sexual behavior is easier to collect in case-control studies. Two recent case-control studies found a positive association between oral contraceptive use and cervical intraepithelial neoplasia after controlling for number of sexual partners.

In conclusion, the current study supports the hypothesis that the occurrence of cervical intraepithelial neoplasia is increased by OC use.

REFERENCES
3. Thomas DB. WHO collaborative study of neoplasia and steroid contraceptives: the influence of combined oral contraceptives on risk of neoplasms in developing and developed countries. Contraception 1991;43:695-710.


From the Institutes of Community Medicine and Medical Biology, University of Tromsø, and the Department of Epidemiology, School of Public Health, University of Alabama at Birmingham.

Received for publication August 9, 1991; revised December 2, 1991; accepted December 30, 1991.

Requests for reprints: Ingvar T. Gram, MD, Institute of Community Medicine, University of Tromsø, PB 600, N-9001 Tromsø, Norway. Supported by the Norwegian Cancer Society and the Akeba Foundation for the Fighting of Cancer. The Tromsø study was done in cooperation with the National Health Screening Service, Oslo, Norway.

6/1/1992
Table I. Distribution of study subjects according to selected characteristics and prevalence of current oral contraceptive use in a cohort of 6622 women, Tromsø, Norway, 1980 through 1989

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cohort (n = 6622)</th>
<th>Prevalence of current oral contraceptive use (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-24</td>
<td>1572</td>
<td>21</td>
</tr>
<tr>
<td>25-29</td>
<td>1461</td>
<td>11</td>
</tr>
<tr>
<td>30-34</td>
<td>1474</td>
<td>7</td>
</tr>
<tr>
<td>35-39</td>
<td>124</td>
<td>5</td>
</tr>
<tr>
<td>40-44</td>
<td>769</td>
<td>3</td>
</tr>
<tr>
<td>45-49</td>
<td>652</td>
<td>1</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>4578</td>
<td>6</td>
</tr>
<tr>
<td>Divorced/widowed</td>
<td>425</td>
<td>9</td>
</tr>
<tr>
<td>Single</td>
<td>1581</td>
<td>17</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1247</td>
<td>7</td>
</tr>
<tr>
<td>Past</td>
<td>769</td>
<td>8</td>
</tr>
<tr>
<td>Current</td>
<td>1044</td>
<td>11</td>
</tr>
<tr>
<td>Intoxication by alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>247</td>
<td>7</td>
</tr>
<tr>
<td>Less than monthly</td>
<td>1463</td>
<td>12</td>
</tr>
<tr>
<td>Monthly or more</td>
<td>437</td>
<td>14</td>
</tr>
</tbody>
</table>

*As of 1979.

Table II. Multivariate* relative rate estimates of cervical intraepithelial neoplasia with 95% confidence interval, according to selected characteristics, in a cohort of 6622 women, Tromsø, Norway, 1980 through 1989

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Relative rate</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marital status</td>
<td>1.0</td>
<td>1.0-3.1</td>
</tr>
<tr>
<td>Married</td>
<td>1.4</td>
<td>0.9-2.1</td>
</tr>
<tr>
<td>Divorced/widowed</td>
<td>1.6</td>
<td>1.2-2.1</td>
</tr>
<tr>
<td>Single</td>
<td>1.6</td>
<td>1.2-2.1</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>1.6</td>
<td>0.9-3.4</td>
</tr>
<tr>
<td>Current</td>
<td>1.6</td>
<td>1.2-2.1</td>
</tr>
<tr>
<td>Frequency of intoxication by alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Less than monthly</td>
<td>1.4</td>
<td>1.1-1.8</td>
</tr>
<tr>
<td>Monthly or more</td>
<td>1.9</td>
<td>1.3-2.7</td>
</tr>
</tbody>
</table>

*Based on 348 cases from Cox proportional hazards model with age group, marital status, smoking status, frequency of intoxication by alcohol, and oral contraceptive use blocking for number of specimens.
Table III. Multivariate relative rate estimates of cervical intraepithelial neoplasia according to various measures of oral contraceptive use in a cohort of 6622 women, Tromsø, Norway, 1980 through 1989.

<table>
<thead>
<tr>
<th>Oral contraceptive use</th>
<th>Relative risk*</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>1.0</td>
<td>1.0-1.3</td>
</tr>
<tr>
<td>No information†</td>
<td>1.3</td>
<td>1.0-1.8</td>
</tr>
<tr>
<td>Past</td>
<td>1.4</td>
<td>1.0-1.8</td>
</tr>
<tr>
<td>Current</td>
<td>1.3</td>
<td>1.1-2.1</td>
</tr>
<tr>
<td>Age started, ever users§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 24 yr</td>
<td>1.1</td>
<td>0.7-1.4</td>
</tr>
<tr>
<td>20-24 yr</td>
<td>1.3</td>
<td>1.1-2.0</td>
</tr>
<tr>
<td>&lt; 20 yr</td>
<td>1.3</td>
<td>0.9-1.9</td>
</tr>
</tbody>
</table>

*Based on 318 cases from Cox proportional hazards model with age group, marital status, smoking status, frequency of menstruation and alcohol and OC use blocking for number of specimens.
†These women were nonusers in 1970, missing information on ever users.
‡Based on 242 cases from Cox proportional hazards with complete covariate information. Trend test with four levels (never, three categories with age started oral contraceptive use, p = 0.03).
Paper VI
Trichomonas vaginalis (TV) and human papillomavirus (HPV) infection and the incidence of cervical intraepithelial neoplasia (CIN) grade III

Inger Torhild Gram, Maurizio Macaluso, Jeannette Churchill, and Helge Stalsberg

(Received 12 December 1991; accepted in revised form 2 March 1992)

The temporal relationship between cervical infection with trichomonas vaginalis (TV) or human papillomavirus (HPV) and the incidence rate of cervical intraepithelial neoplasia grade three (CIN III) was examined in a cohort of 43,016 Norwegian women. From 1982 to 1989, cervico-vaginal infection from TV and HPV was diagnosed cytologically in 988 and 678 women, respectively. During the 181,240 person-years of observation, 446 cases of CIN III/cervical cancer developed. The age-adjusted incidence rates (IR) of CIN III were 225 per 100,000 person-years among women with no cytologic evidence of infection, 459 among women with TV infection, and 729 among women with HPV infection. A multiple regression model yielded a relative risk of CIN III of 2.1 (95 percent confidence interval [CI] = 1.3-3.4) among women with TV infection and 3.5 (CI = 1.9-6.6) among women with HPV infection, compared with women with neither infection. As CIN can be misclassified as HPV infection, the entry Pap-smears of 10 women with HPV infection who later developed CIN III were re-examined. Excluding the four discordant cases with the corresponding person-years decreased the RR of CIN III to 2.1 (CI = 0.9-4.8). Our report demonstrates the limitations of studies that rely only on cytologic detection of HPV infection. Nevertheless, the results support the hypothesis that HPV is a causal factor for CIN III lesions, and also display an association between TV infection and cervical neoplasia.

Key words: Cervical cancer, follow-up studies, Norway, papillomavirus, trichomonas vaginalis.

Introduction

There is a substantial body of evidence for the concept that cervical cancer and its precursor lesions are caused by infectious agents transmitted through sexual intercourse. Among the sexually transmitted agents, recent research has focused on human papillomavirus (HPV). This hypothesis has been difficult to test in epidemiologic studies and it is far from proven.1 Trichomonas vaginalis (TV), Chlamydia trachomatis, and herpes simplex virus (HSV) also have been examined, but definitive conclusions about their contribution to the develop
opment of cervical neoplasia cannot be drawn yet.

Elucidation of the role of these infectious agents in cervical carcinogenesis has important implications for the management of infected subjects as well as for the organization of prevention programs. The purpose of this study was to evaluate the incidence of cervical intraepithelial neoplasia grade three (CIN III) following cytologic evidence of infections from TV and HPV.

Materials and methods

The Department of Pathology at the University Hospital of Tromso is the referral center for cervical specimens from women living in Tromso and Finnmark, the two northernmost counties in Norway. The Department keeps a computerized registry containing records of all cytologic and histologic diagnoses made in these two counties. The Department also sends out recommendations for follow-up examinations for abnormal cervical Pap smears. We obtained an abstract of all records pertaining to cervical specimens during the period 1972-89. Each abstract contains a subject, a number identifying year of birth, a referral number indicating where the specimen was obtained, the month and year of diagnosis, the type of specimen (autopsy, cytologic, histologic), and up to two codes for the diagnosis.

The analytical cohort consisted of women who met the following eligibility criteria: (i) were born from 1920 through 1969, (ii) were referred from Tromso or Finnmark, (iii) had no history of cervical cancer or CIN of any grade, (iv) had no history of cervical biopsy, and (v) had a negative entry Pap smear recorded in the Pathology Registry during the study period of 1989-89. Pap smears indicating infection by TV or HPV were considered as negative, unless additional evidence of dysplastic epithelium was reported.

Women comprising this cohort (n = 43,416) were followed for the development of CIN III/cervical squamous invasive cancer referred to as CIN III either by cyt- or histopathologic documentation.

Follow-up began on the date of the first Pap smear and ended on the date of diagnosis of CIN III, of any cervical biopsy, or on the date of the last cervical Pap smear, whichever was earliest. Women who developed Chlamydia infection, TV, HSV, or HPV infection during the follow-up period entered the corresponding subcohort on the date of diagnosis. Women who developed CIN I or CIN II prior to (or concurrently with) the TV (n = 1) or HPV (n = 15) diagnosis were withdrawn from follow-up on the date of diagnosis of the infection. Thus, they did not contrib-

ute any person-time to the subcohort of women with cervical infection.

The crude incidence rate (IR) for a given exposure category was obtained by dividing the number of cases by the total number of person-years contributed by women in that category. Age-adjusted IR rates were calculated by the direct method, using the five-year age categories of the person-year distribution of the entire analytical cohort. The CIN III IR was evaluated by categories of age, calendar period, and years since entry into follow-up, number of Pap smears, and time since last Pap smear. The RRs of CIN III were estimated according to the levels of potential confounding factors both in univariate and multivariate analysis. Poisson regression analysis was used for the simultaneous evaluation of the effect of these factors on the association between TV and HPV infection and the incidence of CIN III.

A diagnosis of infection would result, for most women, in a more intensive medical follow-up. We therefore considered the number of negative smears as a potential confounding factor. The number of negative smears was counted beginning with the entry Pap smear and ending with the last negative smear. The time since the last negative smear was computed accordingly and considered as an additional confounding factor.

Misclassification of CIN I as HPV infection would spuriously increase the association with CIN III. We therefore reevaluated the entry Pap smear in which an infection was diagnosed among the 27 women who later became CIN III cases in the two subcohorts, and among the 16 women who had a diagnosis of CIN I followed by a diagnosis of either infection before developing CIN III.

The Kappa coefficient was used as a measure of overall agreement. This measure does not require any assumption concerning the 'correct' diagnosis and includes a correction for the amount of agreement which would be expected by chance alone. Results were considered as statistically significant if the P value was 0.05 or less.

Results

Evidence of TV infection was found in 988 women (2.3 percent), HPV infection was found in 678 (1.6 percent) women, Chlamydia infection was found in 92 (0.2 percent) women, and HSV virus infection was found in only 46 (0.1 percent) women. The remaining 36 percent
of the 43,016 women contributed information to the subcohort of 'negative' women.

The mean ages at entry were 31, 33, and 25 years in the negative, TV, and HPV subcohorts, respectively (Table 1). The three subcohorts did not differ materially according to length of follow-up, number of negative Pap-smears and time since last negative Pap-smear.

The number of women with reported TV infection decreased consistently during follow-up from 172 in 1980 to 6 in 1988. There was a decline in all birth cohorts. The number of women diagnosed with HPV infection had a more variable course with time peaking in 1985 with a total of 151 women with reports of HPV.

During the 181,245 person-years of observation, 440 incident cases (31 with CIN III and nine with cervical cancer) were identified. Altogether, 332 (73 percent) women had a histologic confirmation of the diagnosis. Within the five-year age categories, the IR of CIN III peaked at 434 per 100,000 person-years among women aged 25-29.

The average time between entry into follow-up and diagnosis among CIN III cases was 4.2 (SE = 0.1) years in the negative subcohort. The corresponding figures

Table 1. The three subcohorts according to selected characteristics, Norway, 1980-89

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Subcohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>Age at entry into follow-up (years)</td>
<td>31</td>
</tr>
<tr>
<td>Length of follow-up (years)</td>
<td>4.5</td>
</tr>
<tr>
<td>Time since last negative Pap-smear (years)</td>
<td>1.1</td>
</tr>
<tr>
<td>No. of negative Pap-smears as of end of follow-up</td>
<td>2</td>
</tr>
</tbody>
</table>

for the women in the TV and HPV subcohorts were 3.8 (SE = 0.5) and 3.0 (SE = 0.6) years, respectively.

The age-adjusted IR of CIN III were 325 per 100,000 5 person-years among women without TV or HPV infections, 459 per 100,000 person-years among women with TV infection, and 729 per 100,000 person-years among women with HPV infection (Table 2).

The multivariate RR estimates of CIN III were 2.1 (CI = 1.3-3.4) for women with no TV infection. Excluding cases diagnosed during the first year of follow-up, yielded an RR of 2.2 (CI = 1.3-3.6) for women with TV infection and 3.7 (CI = 2.0-7.0) for women with HPV infection. Similar results were obtained in analyses not controlling for number of Pap-smears or time since last Pap-smear.

Among the 10 women who developed CIN III after a diagnosis of HPV without dysplasia at entry, four were reclassified as having dysplasia after reexamination. The multivariate RR was 1.9 (CI = 1.1-3.3) for women with TV and 4.3 (CI = 2.2-8.5) for women with HPV infection. Excluding cases diagnosed during the first year of follow-up, yielded an RR of 2.6 (CI = 1.3-5.3) for women with TV infection and 3.6 (CI = 1.9-6.6) for women with HPV infection. Similar results were obtained in analyses not controlling for number of Pap-smears or time since last Pap-smear.

The multivariate RR estimate from

Table 2. Age-adjusted incidence rates (IR) and age-adjusted and multivariate relative rate (RR) estimates for CIN III and cervical cancer according to cytologic evidence of infection in a cohort of 43,016 women, Norway, 1980-89

<table>
<thead>
<tr>
<th>Infection Status</th>
<th>IR</th>
<th>Age-adjusted</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases/person-years</td>
<td>Age-adjusted</td>
<td>RR (CI)</td>
<td>Age-adjusted</td>
</tr>
<tr>
<td>Non-IR</td>
<td>396/15,672</td>
<td>259</td>
<td>1.5</td>
</tr>
<tr>
<td>TV</td>
<td>177/3,862</td>
<td>459</td>
<td>2.1 (1.3-3.4)</td>
</tr>
<tr>
<td>HPV</td>
<td>120/1,622</td>
<td>729</td>
<td>2.9 (1.6-5.3)</td>
</tr>
<tr>
<td>HPV</td>
<td>86/1,514</td>
<td>400</td>
<td>1.8 (0.8-3.6)</td>
</tr>
</tbody>
</table>

1 Per 100,000 person-years; age-adjusted using the direct method for five-year age categories of person-years with the distribution of the entire analytical cohort as standard.

2 Based on age-adjusted regression coefficients from the Poisson regression model; total of 423 cases.

3 Based upon 423 cases from model with age group (five-year age groups); infection status (none, TV, HPV); years since entry into follow-up (<1, 1, 3, 4); calendar period of diagnosis (1980-84, 1985-89); number of negative Pap-smears (1, 2, 3, 4, 5, 6)+; and years since last negative Pap-smear (<1, 1, 2, 3, 4, 5, 6)+.

4 Based upon 419 cases from same model as 3 (excluding the four cases which were reclassified as having CIN I at entry and the corresponding person-years).

Cancer Causes and Control. Vol 3, 1992
the Poisson regression model from 3.7 to 2.1 (CI = 0.9-4.8). This estimate was no longer statistically significant.

Discussion

The results of this follow-up study suggest that women with Pap-scan will experience a higher risk of CIN III than do women without such reports. Overall, our data support the role of HPV as a causal factor for CIN III, but they also show that misclassification between the diagnosis of HPV infection and the diagnosis of dysplasia may explain a substantial proportion of the excess risk observed.

The major strength of the present investigation is the advantage of the follow-up design as the exposure to the risk factor(s) precedes the onset of disease. We therefore propose that the synergistic effects between diagnosis of infection and the diagnosis of CIN III among cases also suggests that it is very unlikely that an undetected neoplastic lesion precedes the infection. Our results are in accordance with those of two case-control studies showing that women with a history of previous TV infection had an increased risk of CIN and cervical cancer after adjustment for number of sexual partners. Our results are also in agreement with several recent epidemiologic follow-up studies examining the relationship between HPV and CIN. An additional advantage offered by our study is that the large number of women who were followed up in a similar way as the women with infection. A woman's previous infection status may make her more likely to seek medical attention, and thus occurrence of CIN III could be underestimated in these subcohorts. Thus, the ability to control for frequency of HPV infection is an additional strength of the present study.

Inherent in a record-based study is the lack of information on possible confounding factors. Some studies have shown a relationship between HPV infection and risk factors for cervical cancer, such as sexual activity\(^{22}\) and smoking,\(^{29}\) while other studies conducted in Latin America\(^{24}\) and Greenland/Denmark\(^{28}\) have not. We found a positive association between cigarette smoking and CIN III and between oral contraceptive use and CIN in a subgroup of this cohort for which such information was available through linkage with additional data sources. The associations revealed in these studies were weaker than those of the present study. Hence, the relationships discussed in this paper cannot be explained entirely by confounding due to cigarette smoking and oral contraceptive use. TV and HPV infections are both sexually transmitted diseases, and sexual activity can be a confounder of the TV/HPV-CIN III association only if there is another sexually transmitted agent that is the true cause. If this were the case, the lack of information on sexual activity is a concern. So far, other sexually transmitted diseases with a stronger relationship than HPV with cervical cancer or dysplasia have not yet been identified.\(^{19}\) However, we cannot dismiss the possibility that the associations found in this study may be due to chance or confounded by other sexually transmitted agents.

The most important limitation of the study is that the cytologic assessment of the infections is imprecise. In a study by Krieger et al.,\(^{19}\) the sensitivity of the Pap-smear test when read by a pathologist experienced in the cytology of sexually transmitted diseases, was as low as 16 percent. The Pap-smear is a traditional means of establishing the diagnosis of HPV and in practice the only method available for mass screening of large populations. However, due to the low sensitivity of the Pap-smear technique, the proportion of HPV detected by cytology may be as low as 15 percent.\(^{27}\) Thus, in our study, an unknown number of women were erroneously classified in the category of 'no infection,' a misclassification that would attenuate the real associations.

Assuming 100 percent specificity and that there is no differential misclassification between cases and person-years, one can estimate the real RR as follows:

\[
RR = \left( \frac{O_1 - O_2}{O_1 + (1-\lambda)} \right) / \left( \frac{P_1 - P_2}{P_1 + (1-\lambda)} \right)
\]

where RR is the relative rate, \(O\) is the number of cases observed among women with cytologically detected HPV infection, \(O_0\) is the number of cases among women with negative cytology, \(r\) is the sensitivity of cytologic detection of HPV infection, and \(P\) indicates the person-years of follow-up in the same categories. Under these circumstances, if the sensitivity were as low as 15 percent, the real crude RR would be 7.4, rather than the observed 2.9.

A more serious threat to validity is the potential for overestimating the strength of association between HPV and CIN/III because women who actually have low grade CIN are misclassified as having HPV infection. We found poor reliability of the identification of changes associated with HPV due to misclassification of low grade CIN. This finding is in agreement with the results of two other studies showing a high degree of interobserver differences.\(^{28,29}\) The result corroborates the suspicion that the incidence of CIN III among women with cytologic diagnosis of HPV infection may be increased spuriously due to underestimating of CIN lesions. In a study of 202 women, an understanding
of the cytologic diagnosis of CIN was found when col-
lopcytosis, the characteristic feature of HPV condi-
loma, was prominent. The difficulty of distinguishing 
HPV condyloma with or without superimposed CIN 
in biopsies was emphasized in a recent review paper. 
The cited follow-up studies 1, 2 made the initial classifi-
cation based on cytology alone and therefore may be 
affected by this problem. We attempted to correct the 
bias by excluding all cases (and the corresponding per-
son-years of follow-up) whose entry Pap smears were 
not confirmed as HPV without CIN at the second 
reading. This procedure may have resulted in an over-
adjustment—as we did not exclude the person-years 
for women classified as having HPV, but did not 
develop CIN III. We also excluded 15 women who de-
veloped CIN III after a diagnosis of HPV, but who 
were diagnosed with a CIN lesion prior to the HPV 
diagnosis. This also tended to dilute the association, 
as some of these women, in fact, could have HPV when 
diagnosed as CIN. Hence, we regard the residual two-
fold excess of CIN III among women with HPV infec-
tion as a conservative estimate.

Consideration of the biologic plausibility of an 
association is of critical importance in causal inference. 
Epithelial alterations have been produced in mice and 
mixed in women with TV infections suggesting a 
relationship with cervical cancer. However, the abnor-
malities were not severe enough to be described as neo-
plastic. 2 To our knowledge, no firm evidence for 
the biologic plausibility for the TV-cervical neoplasia has 
yet been demonstrated.

The role of HPV as an etiologic agent of cervical 
cancer is supported by laboratory findings showing that 
some papillomavirus are oncogenic in animals, that 
genital HPV infections induce dysplastic lesions simi-
lar to CIN, and that precocious and invasive cervical 
cancer contains HPV DNA. 

Our report clearly demonstrates the severe limita-
tions of studies that rely only on cytologic detection 
of HPV infection. The same limitations do not apply to 
the same extent on the diagnosis of TV. In conclusion, 
our study supports the current hypothesis of HPV as a 
causal factor for the precursor lesion to cervical cancer 
and also demonstrates an association between TV 
infected and cervical neoplasia.

References
1. Munoz N, Bosch FX, Epidemiology of cervical cancer. 
In: Munoz N, Bosch FX, Jensen OM, eds. Human Papil-
ломavirus and Cervical Cancer. Lyon, France, Inter-
national Agency for Research on Cancer, 1989; IARC 
2. Munoz N, Bosch FX, and Kaldas J M. Does human pap-
illomavirus cause cervical cancer? The state of the epi-
3. Macnab JCM, Kitchener HC. Sexually transmitted can-
4. Metzner CA. The epidemiology of human papilloma-
virus infection in relation to cervical cancer. Cancer Surv  
5. La Vecchia C, Franceschi S, Decarli A, et al. Sexual fac-
tors, venereal diseases, and the risk of intraepithelial and 
activity, contraception, genital infections, and cervical 
cancer: support for a sexually transmitted disease 
Papamokou smear. A population-based study of risk 
 factors in Greenlandic and Danish women. Acta Obst scenery 
Tidskr Nor Laegeforen 1977, 107: 1159-63. (In Norwegain.)
9. Rothman KJ. Modern Epidemiology. Boston, MA: Little, 
10. Breslow NE, Day NE. Statistical Methods in Cancer 
Research Vol II: The Design and Analysis of Cohort 
Studies. Lyon, France: International Agency for 
13. SAS Institute Inc. STUG Supplemental Library User’s 
follow-up of cervical HPV infections: life table analysis 
of histopathological, cytological and colposcopic data. 
15. Franceschi S, Doll R, Galloway L, La Vecchia C, Eto R, 
Spriggs AI. Genital warts and cervical neoplasia: An epi-
16. Mitchell T, Drake M, Medley G. Prospective evaluation 
of risk of cervical cancer after cytological evidence of 
17. Pugno R, Chianee W, Rome RM, Johnstone NR. The 
significance of human papillomavirus infection ("wart virus 
infection") found alone on cervical cytology screening. 
epithelial neoplasia among women with papillomavirus 
infected compared to women with trichomonas infec-
19. Syrjänen K, Vytvirtynen M, Castren O, et al. Sexual be-
havior of women with human papillomavirus (HPV) 
lesions of the uterine cervix. Br J Vener Dis 1984; 60: 
243-8.
genital human papillomavirus infection in young women. 
Condyloma and intraepithelial neoplasia of the uterine 
cervix: an case-control study. Am J Epidemiol 1988; 128: 
337-42.

Cervical infection and incidence of cervical neoplasms
Reaves WC, Brinton LA, Garcia M, et al.

Human papillomavirus infection and cervical cancer in Latin America.


Survey instruments
Kjære mottaker!

Det er nå kommet forslag om at helsemyndighetene skal gi alle norske kvinner mellom 40 og 74 år tilbud om en spesialundersøkelse for å oppsøke bras kjøret med en enkel røntgenundersøkelse av brystet (mammografi).

Vi ønsker å vite hvilke kvinner i Harstad og Tromsø ser på slike undersøkelser. I Tromsø har kvinner i alderen 40—56 år fått tilbud om mammografi. De som har tatt imot tilbudet, har derfor opplevd problemene en slik brasundersøkelse kan skape for den enkelte.

I Tromsø veër det ca. 400 kvinner som ikke benyttet seg av brasundersøkelsen. Det ville være nyttig å vite hvorfor de ikke gjorde det.

Kvinnene i Harstad har ennå ikke fått et slikt tilbud. Svarerne på denne spørreundersøkelsen skal hjelpe oss å gjøre slike brasundersøkelser så skjønsomme som mulig.

Skjemmer er innledt slik at de første spørsmålene beserves av alle. Deretter er det angitt hvilke spørsmål som skal besvares av kvinner fra Harstad. Kvinner fra Tromsø som ikke er mammografiert er.

Har De noen kommentarer til undersøkelsen kan De skrive dette helt til slut i merknadfeltet.

Navn og fødselsnummer er med for å sammenholde svarene med de opplysninger vi har fra Helseundersøkelsen i Tromsø. Dersom det skulle bli aktuelt å innhente tilsvarende opplysninger fra dem som ikke har ventt til Helseundersøkelsen, vil hver enkelt kvinne bli kontaktet for å gi sin tillatelse.

Gjennom denne undersøkelsen bidrar De til å klorlegge forhold som kan gjøre kampen mot kretter effektiv og skjønsom for den enkelte kvinne.

Vivst understreker at alle svar og resultat vil bli behandlet strengt fortrolig.

Utfyll skjermer sendes i vedleggelse avkvalvolut. Portoen er betalt.

På forhånd mange takk for hjelpen!

Med venlig hilsen

INSTITUTT FOR SAMFUNNSMEDISIN
Universitetet i Tromsø

---

<table>
<thead>
<tr>
<th>BESVARES AV ALLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dato før utfylling av skjemaet:</strong> ........................................ / ............................</td>
</tr>
</tbody>
</table>

**BRYSTKREFT**
- Er De engstelig for å ha bras kjøret? JA NEI
- Var De engstelig for å ha bras kjøret for et år siden? JA NEI

**SELVUNNERSØKELSE AV BRYSTENE**
3. Hvor ofte undersøker De brystet Deres selv?
   - Satt kryss i den ruten der "JA" passer best:  
     - Alde: ........................................ JA NEI  
     - 2-3 ganger pr. år: .................................................. JA NEI  
     - 1 gang pr. måned: .................................................. JA NEI  
     - 1 gang pr. uke: .................................................. JA NEI  
     - Hyppigere enn i dag: .................................................. JA NEI

4. Hvor ofte undersøkte De brystet Deres for et år siden?
   - Satt kryss i den ruten der "JA" passer best:  
     - Sjeldnere enn i dag: .................................................. JA NEI  
     - Like ofte som i dag: .................................................. JA NEI  
     - Hyppigere enn i dag: .................................................. JA NEI

**OPPSPORING AV BRYSTKREFT**
5. Hvis De om 2 år fikk tilbud om røntgenundersøkelse av brystet, ville De undersøke Deres bryst selv? JA NEI  
   - Hvis Ja, den eneste kollektive undersøkelse: ..................................................  
     - Deltatt selv: JA NEI  
     - Anbefalt Deres venninnever deltatt: JA NEI  

**SKOLEGANG/ARBEID**
6. Hvor mange år skolegang har De (medregnet folke- og ungdomsskolen)? .................................................. ANTTALL ÅR

7. Har De hatt lønnet arbeid hele siste år?  
   - Satt kryss i den ruten der "JA" passer best:  
     - Fulltidslønne: .................................................. JA NEI  
     - Deltidslønne: .................................................. JA NEI  
     - Ikke lønnet arbeid: .................................................. JA NEI

---

**LIVSSITUASJON**
6. Hvor ofte opplever De Deres livssituasjon i dag?
   - Satt kryss i den ruten der "JA" passer best:  
     - Meget dårlig: .................................................. JA NEI  
     - Dårlig: .................................................. JA NEI  
     - Bra: .................................................. JA NEI  
     - Utmerket: .................................................. JA NEI

**INTERVJU**
   - Kan vi ta kontakt med Dem igjen? JA NEI

**HELSERUNNERSØKELSE I TROMSØ**
10. Fikk De invitasjon til Helseundersøkelsen?
    - Hvis JA, fortsatt til spørsmål 22.  
    - Hvis NEI, fortsatt til spørsmål 12.  

---

**BESVARES AV DEM SOM IKKE EMMAMGRAFERT**
   **PÅ HEMEUNNERSØKELSE**
12. Har De røntgenundersøkelse brasen tidligere?
   - Hvis Ja, ble det tørt prøve av kolen?
13. Har De hatt (has) bras kjøret?
15. Har noen av Deres slektninger hatt bras kjøret?
   - Mor: JA NEI
   - Søster: JA NEI
   - Moder: JA NEI
   - Farmor: JA NEI
   - Tante: JA NEI

---

- **LIVSSITUASJON**
- **INTERVJU**
- **HELSERUNNERSØKELSE I TROMSØ**
- **BESVARES AV DEM SOM IKKE EMMAMGRAFERT**
- **PÅ HEMEUNNERSØKELSE**

---

- **LIVSSITUASJON**
- **INTERVJU**
- **HELSERUNNERSØKELSE I TROMSØ**
- **BESVARES AV DEM SOM IKKE EMMAMGRAFERT**
- **PÅ HEMEUNNERSØKELSE**
<table>
<thead>
<tr>
<th>Spørsmål</th>
<th>Ja/Nei</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 Hvor gammel var De første gang De fikk menstruasjon?</td>
<td>AR</td>
</tr>
<tr>
<td>17 Dersom menstruasjonen nå er sluttt, hvor gammel var De da den slutttet?</td>
<td>AR</td>
</tr>
<tr>
<td>18 Dersom De har ferd børn, hvor gammel var De første gang?</td>
<td>AR</td>
</tr>
<tr>
<td>19 Døren ykte:</td>
<td></td>
</tr>
<tr>
<td>Røsten av spørsmålene er til kvinner fra Troms. Til kvinnene fra Harstad tøkker vi for hjelpen.</td>
<td></td>
</tr>
<tr>
<td><strong>BESVARES AV DEM SOM IKKE BLE MAMMOGRAFERT</strong></td>
<td></td>
</tr>
<tr>
<td>20 Var De i tvil om De skulle ta Dem mammografer?</td>
<td>JA NEI</td>
</tr>
<tr>
<td>21 Hadde noen av følgende punkter betydning da De bestemte Dem for IKKE å bli mammografer? Sett et kryss for hvert punkt.</td>
<td></td>
</tr>
<tr>
<td>- Hadde ikke smerte</td>
<td>JA NEI</td>
</tr>
<tr>
<td>- Hadde beg tett av undersøkelsen var smertefull</td>
<td>JA NEI</td>
</tr>
<tr>
<td>- Hadde det vært en mannlig radiograf?</td>
<td>JA NEI</td>
</tr>
<tr>
<td>- Ville ikke utsette meg for røntgenstråler</td>
<td>JA NEI</td>
</tr>
<tr>
<td>- Var engselig for å få påviset brystkret</td>
<td>JA NEI</td>
</tr>
<tr>
<td>- Hadde nøyrik bitt mammografer</td>
<td>JA NEI</td>
</tr>
<tr>
<td>- Ønsket ikke å delta i Helseundersøkelsen</td>
<td>JA NEI</td>
</tr>
<tr>
<td>Eventuell andre ting av betydning kan De angi i merknadstettet.</td>
<td></td>
</tr>
<tr>
<td><strong>BESVARES AV ALLE SOM BLE MAMMOGRAFERT</strong></td>
<td></td>
</tr>
<tr>
<td>22 Var De engselig for å ha brystkret før De møtte til Helseundersøkelsen?</td>
<td>JA NEI</td>
</tr>
<tr>
<td>23 Var røntgenundersøkelsen ubehagelig?</td>
<td></td>
</tr>
<tr>
<td>24 Var røntgenundersøkelsen smertefull?</td>
<td></td>
</tr>
<tr>
<td><strong>INFORMASJON</strong></td>
<td></td>
</tr>
<tr>
<td>25 Var det tilstrekkelig informasjon om brystkretundersøkelsen?</td>
<td>JA NEI</td>
</tr>
<tr>
<td>- i invitasjonen til Helseundersøkelsen?</td>
<td></td>
</tr>
<tr>
<td>- ved frammøte til brystkretundersøkelse?</td>
<td></td>
</tr>
<tr>
<td>Angi i merknadstettet hva De eventuelt ønsket mer informasjon om.</td>
<td></td>
</tr>
<tr>
<td>29 Invitasjonen til Helseundersøkelsen står det: «Hvis resultatene fra brystkretundersøkelsen skulle gjøre det nødvendig med kontroll, blir det gitt beskjed fra Regionsykehuset innen 3 uker.»</td>
<td></td>
</tr>
<tr>
<td>29 Var De engselig for å få slik beskjed i disse tre ukene?</td>
<td>JA NEI</td>
</tr>
<tr>
<td>27 Formot De Dem noe uvanlig fordi De var engselig i disse tre ukene?</td>
<td></td>
</tr>
<tr>
<td>29 Angre De på at De møtte opp til brystkretundersøkelsen</td>
<td></td>
</tr>
<tr>
<td><strong>BESVARES AV DEM SOM BLE ETTERUNDERSØKT</strong></td>
<td></td>
</tr>
<tr>
<td>29 De ble innkalt til ny undersøkelse, regnet De med at det var stor sjansen for at De hadde brystkret?</td>
<td>JA NEI</td>
</tr>
<tr>
<td>30 De fleste plier å bli litt engselig når de blir innkalt til ny undersøkelse. Formot De Dem noe av dette i tiden fra brevet kom til De møtte på Regionsykehuset? Sett et kryss for hvert utsegn</td>
<td></td>
</tr>
<tr>
<td>- Snakk med familien om innkallingen</td>
<td>JA NEI</td>
</tr>
<tr>
<td>- Snakk med andre om innkallingen</td>
<td>JA NEI</td>
</tr>
<tr>
<td>- Kontakt andre som var etterundersøkt</td>
<td>JA NEI</td>
</tr>
<tr>
<td>- Kontaktet noen som hadde hatt brystkret</td>
<td>JA NEI</td>
</tr>
<tr>
<td>- Kontaktet legen</td>
<td>JA NEI</td>
</tr>
<tr>
<td>- Kontaktet en annet person</td>
<td>JA NEI</td>
</tr>
<tr>
<td>- Rekke mer enn vanlig</td>
<td>JA NEI</td>
</tr>
<tr>
<td>- Sov dårligere enn vanlig</td>
<td>JA NEI</td>
</tr>
<tr>
<td>- Brukte mer alkohol enn vanlig</td>
<td>JA NEI</td>
</tr>
<tr>
<td>- Oppførte meg stort sett som vanlig</td>
<td>JA NEI</td>
</tr>
<tr>
<td>- mer enn 1 uk</td>
<td>1</td>
</tr>
<tr>
<td>- mer enn 1 måned</td>
<td>2</td>
</tr>
<tr>
<td>- mer enn 6 måneder</td>
<td>3</td>
</tr>
<tr>
<td>- mer enn 1 år</td>
<td>4</td>
</tr>
<tr>
<td>- mer enn 3 år</td>
<td>5</td>
</tr>
<tr>
<td>- aldri har hatt en slik påkjenning før</td>
<td>6</td>
</tr>
<tr>
<td><strong>INFORMASJON</strong></td>
<td></td>
</tr>
<tr>
<td>32 Fikk De tilstrekkelig informasjon</td>
<td></td>
</tr>
<tr>
<td>- i innkallingen til etterundersøkelsen?</td>
<td>JA NEI</td>
</tr>
<tr>
<td>- på sykehuset?</td>
<td>JA NEI</td>
</tr>
<tr>
<td>Angi i merknadstettet hva De eventuelt ønsket mer informasjon om.</td>
<td></td>
</tr>
<tr>
<td><strong>MERKNADSTILT</strong></td>
<td></td>
</tr>
<tr>
<td>Takk for hjelpen! Husk å postlegge skjemaet i dag!</td>
<td></td>
</tr>
</tbody>
</table>
Navn .................................
Fødselsdato ...........................
Dato for utfylling av skjemaet ..........

INT: Først er det 3 ja/nej spørsmål:

1. Hvis du fikk tilbud om røntgenundersøkelse av brystene (mammografi) i dag, ville du deltatt? Ja/Nei

2. Er du engstelig for å ha brystkreft i dag? Ja/Nei

Eventuelt:

INT: Hva ville du svare hvis du må si ja eller nei (gjenta så spørsmålet)?

3. Undersøker du regelmessig brystene dine selv? Ja/Nei

INT: Så er det to spørsmål hvor svaralternativene står på dette kortet. VIS KORT A.

4. Hvor ofte undersøker du brystene dine selv?
   - Aldri
   - 2-3 ganger pr. år
   - 1 gang pr. måned
   - 1 gang pr. uke
   - Hver dag

   Ja/Nei

Event/INT: Oppgi den ruten der ja passer best:

5. Hvor ofte undersøkte du brystene dine før du ble mammografiert på Tromsøundersøkelsen? VIS KORT A.
   - Aldri
   - 2-3 ganger pr. år
   - 1 gang pr. måned
   - 1 gang pr. uke
   - Hver dag

   Ja/Nei

   - Hvis JA, har du søkt lege for kul i noen av brystene siste året?
   - Hvis JA, ble det tatt prøve av kullen?

   Ja/Nei
7. Har du tatt ny mammografi det siste året?
   (Hvis JA, ble undersøkelsen VIS KORT A2)
   - anbefalt av lege utenfor sykehus
   - anbefalt av lege på sykehus
   - foresatt etter eget ønske
   Ja/Nei

8. Hvor mange besøk har du hatt i løpet av det siste året på grunn av egen helse eller sykdom?
   Hos vanlig lege
   Hos specialist utenfor sykehus
   På legevakt
   Hos bedriftslege
   Hos fysioterapeut
   Hos kiropraktor
   Hos naturmedisiner
   På sykehusets poliklinikk
   Antall besøk

9. Hender det at du er plaget av søvnløshet?
   - Hvis JA, er du mer plaget av søvnløshet i dag enn for 2 år siden?
   Ja/Nei

10. Hender det at du bruker sovemedisin?
    - Hvis JA, bruker du mer sovemedisin i dag enn for 2 år siden?
    Ja/Nei

11. Hender det at du bruker nervemedisin?
    - Hvis JA, bruker du mer i dag enn for 2 år siden?
    Ja/Nei

12. Har du lett for å bekymre deg?
    Ja/Nei

13. Blir du ofte utlimodig når du må vente? Her er det fire svaralternativer. VIS KORT B.
    Svært ofte
    Ofte
    Sjelden
    Aldri

14. Blir du ofte irritert når du må vente? Her er de samme svaralternativer. VIS KORT B.
    Svært ofte
    Ofte
    Sjelden
    Aldri
15. Ble du innkalt til Regionsykehuset etter at du hadde vært til mammografiscreening?
   - Hvis NEI, fortsett på spørsmål 16.

16. Var du engstelig/urolig i de tre ukene du ventet på resultatet fra mammografisundersøkelsen?
   - Hvis JA, førte det at du var engstelig til at du hadde nedsatt arbeidsevne hjemme eller på jobb? VIS KORT C.
   
   Nedsatt i 2 uker  
   Nedsatt enkelte dager  
   Ikke nedsatt  

17. Nå skal jeg nevne eksempel på hendelser som kan oppleves som små eller store påkjenninger. Spørsmålet er om du keller vil oppleve noe av dette i stedet for å vente i tre uker på svar fra mammografisundersøkelsen? VID KORT D.
   
   Hodepine en dag  
   Ræksjuka (clare/oppløst) en dag  
   Regn i 3 uker av sommerferien  
   Uventet regnig i posten på kr. 1000  
   Forstøvning av aneklen  

   
   Svært ofte  
   Ofte  
   Av og til  
   Aldri  

19. Kan du nevne noe du har opplevd som du vil si var en stern paikjenning om det å måtte vente på svaret fra mammografisundersøkelsen?

   ..........................................................................................................
   ..........................................................................................................
   ..........................................................................................................

20. Kan du nevne noe du har opplevd som du vil si var like ubehekt eller belastende som det å måtte vente på svaret fra mammografisundersøkelsen?

   ..........................................................................................................
   ..........................................................................................................
   ..........................................................................................................

21. Hva er det høyeste beløpet du vil betale for en slik mammografisundersøkelse som du har vært med på? (Vi forutsetter at du ikke hadde noen tegn eller grunn til å tro at du hadde brystkreft.)

   Betale kroner .............................
INT: LEVER UT ARK MED STIGER

22. Her har vi en stige med 10 trinn. Hvis vi tenker oss at det høyeste
trinnet på denne stigen står for det best mulige livet du kunne
tenke deg, og det laveste trinnet for det verste mulige livet du kunne
tenke deg, hvilket trinn ville du si passer best for livet ditt i dag?
(Når du ser på hele livet ditt i dag.)

INT: FÅ KVINNEN TIL Å PEKE MED BLYANT, SKRIV OPP TRINN.

23. Hvilket trinn vil du si passet best når du tenker tilbake på de tre
ukene du ventet på svar fra mammografiundersøkelsen?

INT: FÅ KVINNEN TIL Å PEKE IGJEN. SKRIV OPP TRINN.

EVENTUELL KOMMENTAR..........................................................

24. Noen synes det er en stor belastning å ikke få vite resultatet med
en gang. Tenk deg at du hadde to valgmuligheter neste gang du
var til mammografiundersøkelse. VIS KORT F1 + F2. Det ene var å
vente på resultatet i 21 dager og leve til du var 79 (og være frisk).
Det andre var å få vite at resultatet var negativ med en gang, men
du måtte gi fra deg noen av dine siste levedager for å slippe å
vente. Hva vil du velge?

VIS KORT F1 + F2 21 dager
   * " F1 + F3    1 dag
   * " F1 + F4    7 dager
   * " F1 + F5    14 dager

KOMMENTAR.............................................................................

25. Hvis du i stedet hadde to andre valgmuligheter neste gang du var
til mammografiundersøkelse. VIS KORT G1 + G2.

Undersøkelsen var gratis hvis du ville vente på resultatet i 3 uker,
men hvis du ville betale, kunne du få resultatet neste dag. Hvor
mye vil du betale for å slippe å vente i tre uker?

Betale kroner .................

KOMMENTAR.............................................................................

26. Har livet ditt endret seg på grunn av undersøkelsen du har vært
igjennom? VIS KORT H.

Ja

Til det verre
Ingen innflytelse
Til det bedre

INT: NÅ VAR DET IKKE FLERE SPØRSMÅL. ER DET NOE DU VI S
OM UNDERSØKelsen, SOM VI IKKE HAR SPURT OM? JEG KAN
SKRIVE NED I STIKKORD HVA DU SIER.

Signatur INT..................
BESYRER AV ETTERUNDERSØKTE.

27. Hvor lang tid tok det fra du ble innkalt til etterundersøkelse og til du fikk vite at du ikke hadde brystkreft?
   - Antall Uker/Dager
   - Ja/Nei

28. Var du engstelig/urolig i denne perioden?
   - Hvis JA, førte det til at du hadde nedsatt arbeidsevne hjemme eller på jobb? VIS KORT C.
   - Nedsatt i hele perioden
   - Nedsatt enkelte dager
   - Ikke nedsatt
   - Ja

29. Nå skal jeg nevne eksempler på hendelser som kan oppleves som små eller store påkjenninger. Spørsmålet er om du heller ville oppleve noe av dette, enn å bli innkalt/etterundersøkt slik du ble. VIS KORT D.

INT: (Dvs. at bildene var i orden etter den første mammografiundersøkelsen.)

- Hodepine en dag
- Røksjuka (diare/oppkast) en dag
- Regn i 3 uker av sommerferien
- Uventet regning i posten på kr. 1000
- Forstuvning av aneklen

   - Ja/Nei


   - Svært ofte
   - Ofte
   - Av og til
   - Nesten aldri

31. Kan du nevne noe du har opplevd som du vil si var en større påkjennelse enn det å bli innkalt og etterundersøkt?

   ..............................................................................................................................................
   ..............................................................................................................................................

   - Ja/Nei

32. Kan du nevne noe du har opplevd som du vil si var like ubehagelig eller belastende som det å bli innkalt og etterundersøkt?

   ..............................................................................................................................................
   ..............................................................................................................................................

   - Ja/Nei


   Betale kr..................
INT: LEVER UT ARK MED STIGER

34. Her har vi en stige med 10 trinn. Hvis vi tenker oss at det høyeste trinnet på denne stigen står for det best mulige livet du kunne tenke deg, og det laveste trinnet for det verste mulige livet du kunne tenke deg, hvilket trinn ville du si passer best for livet ditt i dag? (Når du ser på hele livet ditt i dag.)

INT: FÅ KVINNERNEN TIL Å PEKE MED GLYNT; SKRIV OPP TRINN.

35. Hvilket trinn vil du si passet best når du tenker tilbake på den perioden fra du ble innkalt til etterundersøkelse, og til du fikk vite at du ikke hadde brystkreft?

INT: FÅ KVINNERNEN TIL Å PEKE IGJEN. SKRIV OPP TRINN.

EVENTUELL KOMMENTAR..........................................................


Den ene var å gjennomgå etterundersøkelse slik du måtte, før du fikk vite at du ikke hadde brystkreft + leve til du var 79 (og være frikt). Det andre var å få vite at resultatet var normalt med en gang, men du måtte gi fra deg noen av dine siste levedager for å slippe å vente. Hva vil du velge?

<table>
<thead>
<tr>
<th>VIS KORT F1 + F2</th>
<th>21 dager</th>
</tr>
</thead>
<tbody>
<tr>
<td>* F1 + F3</td>
<td>1 dag</td>
</tr>
<tr>
<td>* F1 + F4</td>
<td>7 dager</td>
</tr>
<tr>
<td>* F1 + F5</td>
<td>14 dager</td>
</tr>
</tbody>
</table>

KOMMENTAR .................................................................

37. Hvis du i stedet hadde to andre valgmuligheter neste gang du var til mammografundersøkelse, VIS KORT G1 + G2.

1. Hvis du måtte etterundersøkes før du fikk vite at det ikke var brystkreft, var undersøkelsen gratis.

2. Du kunne få vite at det ikke var brystkreft neste dag, men du måtte betale for dette. Hvor mye vil du betale for å slippe å bli etterundersøkt?

Betalte kroner ..............

KOMMENTAR .................................................................

38. Ble du undersøkt av kirurg da du var til etterundersøkelse?
   - Hvis NEI, gå til spørsmål 42.
   - Hvis JA

39. Ble det tatt prøve av brystet ditt?
   - Hvis NEI, gå til spørsmål 41.
   - Hvis JA
40. Måtte du innlegges på sykehus for å få tatt prøven?
   Ja/Nei

41. Var det smertefullt å ta prøve av brystet?
   Ja/Nei

KOMMENTAR

42. Har du noen plagre fra brystet det ble tatt prøve fra i dag?
   Ja/Nei

KOMMENTAR

43. Har du lik felsomhet i det brystet som det ble tatt prøve fra, som det i det andre, f.eks. i forbindelse med sexuallivet?
   Ja

KOMMENTAR

44. Har livet ditt endret seg på grunn av undersøkelsen du har vært igjenom? VIS KORT H.
   Til det verre
   Ingen innflytelse
   Til det bedre

INT: NÅ VAR DET IKKE FLERE SPØRSMÅL ER DET NCE DU VIL SI OM UNDERSAKSEN SOM VI IKKE HAR SPURT OM? JEG KAN SKRIVE NED I STIKKORD HVOR DU SIER.

Signatur INT.
God dag dette er ................., som ringer fra Universitetet i Tromsø.

Er de mulig å få snakke med:

Navn.......................... f. dato................

For snart 2 år siden så svarte du på et spørreskjema med spørsmål fra Universitetet i Tromsø. Spørsmålene ble lagt i forbindelse med den mammografiundersøkelsen (røntgenundersøkelse av brystene) som kvinner over 40 år fikk tilbud om i Tromsø i 1986/87.

På spørreskjemaet som du returnerte, svarte du JA på om vi kunne få intervju deg. Nå har vi et par spørsmål vi gjerne ville stille deg hvis det er greit?

Ja/nei

Ved en mammografiundersøkelse bruker en røntgenundersøkelse for å lete etter brystkreft.

En annen metode er å innta alle kvinner over en viss alder og la en sykepleier eller lege undersøke brystene for å lete etter kuler.

Har du noen gang blitt inntalt til/fått tilbud om å komme til en slik brystkreftundersøkelse? (Vi mener ikke røntgenundersøkelse av brystene.)

Ja/Nei

Hvis JA, når skjedde dette?

År ........

Husker du hvem som hadde ansvaret for at undersøkelsen ble gjort? (Husmorlag, Landsforeningen mot kreft.....)

Hvor foregikk undersøkelsen?
(På skolen, .......)}

Takk for at du tok deg tid til å snakke med oss!

Kommentar..................................................
The questionnaire was presented to the respondents in Norwegian and subsequently translated into English for the present publication.

To be completed by everybody

Date ........................

BREAST CANCER

1. Do you have anxiety about having breast cancer?  
   Yes/No

2. Did you have anxiety about having breast cancer one year ago?  
   Yes/No

BREAST SELF-EXAMINATION

3. How often do you practice BSE?  
   Mark the most appropriate box:
   Never  
   2-3 times a year  
   Once a month  
   Once a week  
   Every day
   Yes

4. How often did you examine your breasts a year ago?  
   Mark the most appropriate box:
   More infrequently than today  
   As often as today  
   More frequently than today  
   Yes

TRACING OF BREAST CANCER

5. If you were offered a mammogram two years from now, would you
   (mark "Yes" or "No" for each question)
   have a mammogram?  
   Yes/No
   recommend your friends to have a mammogram?  
   Yes/No
SCHOOLING/WORK

6. How many years of schooling do you have? (included elementary and junior high school)  
   Years

7. Have you had any job income during the last year?  
   Mark the most appropriate box.  
   Full-time occupation  
   Part-time job  
   No job income  
   Yes/No

ACTUAL CIRCUMSTANCES OF LIFE

8. How do you experience the present circumstances?  
   Mark the most appropriate box:  
   Very poor  
   Poor  
   Good  
   Excellent  
   Yes/No

INTERVIEW

9. Supposing we need to obtain more information through a personal interview, may we contact you again later?  
   Yes/No

THE GENERAL HEALTH SURVEY IN TROMSØ.

10. Were you invited to participate in this survey?  
    Yes/No

11. Did you have a mammogram at this health survey?  
    - If "Yes", continue to question 22.  
    - If "No", continue to question 12.  
    Yes/No
12. Have you ever had a mammogram?  Yes/No

13. Have you consulted a doctor for a lump in the breast?  
   - If yes; did you have a biopsy of the lump?  Yes/No

14. Have you ever had (or do you now have) breast cancer?  Yes/No

15. Have any of your relatives had breast cancer?
   - Mother  
   - Sister  
   - Grandmother - mother's mother  
   - Grandmother - father's mother  
   - Aunt

16. At what age did you have your first period?  Years

17. If you have reached the menopause; how old were you when that occurred?  Years

18. If you have given birth, how old were you when your first child was born?  Years

19. Your occupation: ..........................................

The remaining questions are for the respondents of Tromsø only. We thank the participants from Harstad for their cooperation.
TO BE COMPLETED BY THOSE WHO DID NOT HAVE A MAMMOGRAM

20. Did you have any doubt about having a mammogram? Yes/No

21. When you decided not to have a mammogram: were any of the listed factors important for you? (Mark either "Yes" or "No" for each point)

- Didn't have the time
- Had heard that the examination was painful Yes/No

- Had heard that the mammogram might be taken by a male
- Would not expose myself to X-ray
- Had anxiety about discovering breast cancer Yes/No

- Had recently had a mammogram
- Did not want to participate in the Health Survey

Other comments (please enter any further comments at the end of this questionnaire)

TO BE ANSWERED BY ALL WHO HAD A MAMMOGRAM

22. Did you have anxiety about having breast cancer before you attended the Health Survey? Yes/No

23. Was the mammography examination unpleasant? Yes/No

24. Was the mammography examination painful? Yes/No
25. Were you given adequate information about the Health Survey in the screening invitation?  
   - When you attended the breast cancer examination?  
   Yes/No

Other comments (please enter any further comments at the end of this questionnaire):

The invitation to the Health Survey states:  
"If the results from the breast cancer examination require further examination, you will receive a message from the hospital within three weeks."

26. Were you anxious that you might be getting a message like this during the subsequent three weeks?  
   Yes/No

27. During this period, did you do anything unusual because you were anxious?  
   Yes/No

28. Do you regret having attended the breast cancer examination?  
   Yes/No
TO BE ANSWERED BY THOSE WHO HAD A WORK-UP EXAMINATION

29. When you received the work-up recommendation, did you expect that the risk of your having breast cancer was considerable? [Yes/No]

30. Most people tend to be anxious when they are recommended to a work-up examination. From the time you received the letter from the hospital and until you actually had the work-up examination, did you do anything of the following? [Yes/No]
   - Talk with your family about the recommendation
   - Talk with others about the recommendation
   - Contact others who had already experienced a work-up examination
   - Contact somebody who has had breast cancer
   - Contact a physician
   - Contact other representatives from the health care profession
   - Smoke more than usual
   - Sleep less than usual
   - Drink more alcohol than usual
   - Behave almost as usual

31. In the course of a lifetime most people will experience situations of physiological and physical stress. To be recommended and having to go through a work-up will create stress for most people.

   How long has it been since you experienced stress at the same level as when you were recommended a work-up examination? (Mark one mark only) [Yes]
   - More than one week
   - More than one month
   - More than six months
   - More than one year
   - More than three years
   - Never experienced stress like this

INFORMATION

32. Were you given adequate information
   - in the recommendation letter to the work-up? [Yes/No]
   - at the hospital?

Please note below what, if anything, you would have liked to receive more information about.

COMMENTS

--------------------------------------------------------------------------------------------------

Thank you for your kind cooperation. Please remember to mail the questionnaire today!
Good morning/afternoon. My name is..., and I am calling from the University of Tromsø.

Could I please speak to:

Name:...................... Date of birth:.........

Approximately two years ago you were kind enough to fill out a questionnaire from the University of Tromsø. The questionnaire were compiled in connection with the Mammography screening (breast screening examination) offered to women over the age of 40 in Tromsø in 1986/87.

When you returned the questionnaire you had been kind enough to answer “Yes” to our request of being allowed to contact you again at a later stage for an interview. If it is convenient for you at this moment, we should very much like to ask you a couple of questions.

Yes/No

A mammographic examination involves the use of X-rays in order to locate breast cancer. Another method is to have a trained nurse or a physician examine the breasts in women past a certain age.

Have you ever been recommended/offered to have such an examination (we are not talking about the mammography)?

Yes/No

If the answer to the question is YES, when did you have the examination?

Year:.............

Do you remember who was in charge of the examination? (For instance The Women Council, The Norwegian Cancer Society...?)

...............................................................

Where did the examination take place? (For instance at the local school....)

...............................................................

Thank you for sparing the time to answer our questions!

Comments, if any.....................................................
The questionnaire was presented the respondents in Norwegian and subsequently translated into English for the present publication.

Name:........................
Date of birth:............
Date of filling in the questionnaire:............

Interviewer (INT): The answer to the first three questions should be restricted to "yes" or "no".

1. If you were offered a mammogram today, would you have accepted?  
Yes/No

2. Do you have anxiety about breast cancer today?  
Yes/No

Probes:

INT: What would your answer be if you had to confine yourself to answering simply "yes" or "no"? (The question is then repeated).

3. Do you practice breast self-examination regularly?  
Yes/No

INT: I will now ask you two questions. The alternative answers are written on this card. SHOW CARD A.

4. How often do you practice breast self-examination (BSE)?

   Never
   Two to three times a year
   Once a month
   Once a week
   Every day

Probes:

INT: Mark the box where "yes" fits best.

5. How often did you practice BSE before you had the mammogram at the Tromsø Survey? (SHOW CARD A)

   Never
   Two to three times a year
   Once a month
   Once a week
   Every day

   Yes
6. Have you consulted a physician during the last year for a breast examination? 
   - If Yes, did you consult the physician because of a lump in any of your breasts? 
   - If Yes, did you undergo a biopsy? 

7. Have you had a new mammogram during the last year? 
   - If Yes, was the mammogram (SHOW CARD A) recommended by a physician outside the hospital? 
   - If Yes, was the mammogram recommended by a physician at the hospital? 
   - If Yes, was the mammogram undertaken according to your own wishes?

8. How many consultations have you had during the last year for your personal health with: 
   - a general practitioner 
   - a specialist outside the hospital 
   - the emergency outpatient department 
   - the industrial medical officer 
   - a physiotherapist 
   - a chiropractor 
   - a naturopath 
   - the outpatient department 

9. Do you ever suffer from sleeplessness? 
   - If Yes, do you suffer more from sleeplessness now than you did two years ago?

10. Do you ever use sleeping pills? 
    - If Yes, are you taking more sleeping pills now than you did two years ago?

11. Do you ever take medication because you feel nervous? 
    - If Yes, are you using more medicines now than you did two years ago?

12. Do you worry easily?
13. Are you often impatient when you have to wait for something/sombody? There are four answer alternatives to this question. SHOW CARD E.

- Very often
- Often
- Seldom
- Never

Yes

14. Do you often get annoyed when you have to wait? You have the same four answer alternatives as in question 13. SHOW CARD E.

- Very often
- Often
- Seldom
- Never

Yes

15. Were you recommended a work-up examination at the hospital following the mammogram screening?  
   - If No, continue to question 16.

Yes/No

16. During the three weeks (the screening period) you were waiting for the results of the screening, were you anxious/troubled?
   - If Yes, did your anxiety lead to less capacity for work at home or at work? SHOW CARD C.
     - decreased for two weeks
     - decreased some days
     - did not decrease

Yes

17. I will now mention a few incidents which may be experienced as small or heavy strains. Would you rather experience some of these instead of having to wait for three weeks for the results of the mammogram screening? SHOW CARD D.

- Headache one day
- Gastric flu one day
- Rain during three weeks of vacation
- Unexpected bill of one thousand kroner ($150)
- Sprain the ankle

Yes/No

18. In the course of a lifetime most individuals will encounter various personal problems or problems among their closest family (such as for instance unemployment, financial problems, ailing parents, problems with the children, death in the family). How often have you experienced such problems? SHOW CARD E.

- Very often
- Often
- Now and then
- Never

Yes
19. Can you give us examples of incidents you have had that were more stressful than having to wait for the results from the screening mammogram?  
Yes/No

20. Can you give us examples of incidents that were as unpleasant or burdensome as having to wait for the results from the screening mammogram?  
Yes/no

21. Which is the highest amount of money you would be willing to pay for a screening mammogram like the one you have already had? (We assume that the examination didn’t show any sign of breast cancer or gave you any reason to suspect that you might suffer from breast cancer.)

Pay ........ (krone)

INT: HAND OUT SHEETS WITH LADDER SCALE OF TEN RUNGS.

22. This is a drawing of a ladder scale with ten rungs. We assume that the top rung on this ladder symbolizes the best life possible, and the bottom rung symbolizes the worst life possible. Which rung would you say describes your life today most adequately?  
Step no.

Probe: (Looking at your life as a whole).

INT: THE RESPONDENT SHOULD POINT OUT A RUNG WITH A PENCIL, MAKE A NOTE OF THE NUMBER OF THE RUNG.

23. Thinking back on the period of three weeks (the screening period) you had to wait for the results of the screening mammogram, which rung would you say describes this period most adequately?  
Step no.

INT: THE RESPONDENT SHOULD POINT OUT A RUNG WITH A PENCIL. WRITE DOWN THE RUNG POINTED OUT BY THE RESPONDENT.

COMMENTS IF ANY..............................................
24. Some women find it strenuous not being able to have the results immediately after the examination. Imagine that you are given two
options the next time you have a mammogram. SHOW CARD F1 + F2.
One of the options is waiting for the results for 21 days and then
live healthy till the age of 79. The other option is learning the
negative result immediately after the screening. In return for this
knowledge you had to trade off the last days of your life. What
would your choice be?

<table>
<thead>
<tr>
<th>SHOW CARD</th>
<th>F1 + F2</th>
<th>21 days</th>
<th>F1 + F3</th>
<th>1 day</th>
<th>F1 + F4</th>
<th>7 days</th>
<th>F1 + F5</th>
<th>14 days</th>
</tr>
</thead>
</table>

Comments...........................................................................................................................

25. If you instead had two other options next time you
should have a screening mammogram. SHOW CARD G1 + G2.

The examination would be free provided you were willing to wait
three weeks for the results. If you were willing to pay for the examination,
you could have the results the next day. How much
would you be willing to pay to avoid having to wait for three
weeks?

Pay....... (kroner)

Comments...........................................................................................................................

26. Has your life changed because of the mammography examination
you have had? SHOW CARD H.

- to the worse
- no impact
- to the better

Yes

INT: I HAVE NO FURTHER QUESTIONS. DO YOU HAVE ANY COMMENTS CONCERNING THE
QUESTIONNAIRE. PARTS WHICH WE HAVEN'T TOUCHEP? I SHALL BE PLEASED TO MAKE
A NOTE OF YOUR COMMENTS.

Signature INT...............................
TO BE ANSWERED BY WOMEN HAVING TO GO THROUGH A WORK-UP EXAMINATION

27. How long was the period from the time when you received the recommendation letter for the work-up until you were assured that you did not have breast cancer? \[\text{Weeks/Days}\]

28. Did you have anxiety during this period? \[\text{Yes/No}\]
   - If Yes, did the anxiety lead to less capacity for work at home or at work? SHOW CARD C
     - decreased during the whole period
     - decreased some days
     - did not decrease

29. I will now mention a few incidents which may be experienced as small or heavy strains. Would you rather experience any of these incidents, than having to go through a work-up the way you did? SHOW CARD D
   
   Probe: (Presupposing that original screening mammogram was negative).
   - Headache one day
   - Gastric flu one day
   - Rain during three weeks of vacation
   - Unexpected bill of one thousand kroner ($150)
   - Sprain the ankle

30. In the course of a lifetime most individuals will encounter various personal problems or problems among their closest family (such as for instance unemployment, financial problems, ailing parents, problems with the children, death in the family). How often have you experienced such problems? SHOW CARD E
   
   - Very often
   - Often
   - Now and then
   - Never

31. Can you give us examples of personal experiences that you felt were more stressful than being recommended/having to go through a work-up examination? \[\text{Yes/No}\]
32. Can you give us examples of personal experiences that were as unpleasant or burdensome as having to go through the work-up examination? 

.................................................................................................................................
.................................................................................................................................
.................................................................................................................................

33. Which is the highest amount of money you would be willing to pay for a screening mammogram like the one you had? We assume that the examination didn’t show any sign of breast cancer or gave you any reason to suspect that you might be suffering from breast cancer.

Pay............ (kroner)

**INT: HAND OUT SHEETS WITH LADDER SCALE OF TEN RUNGS.**

34. This is a drawing of a ladder scale with ten rungs. We assume that the top rung on this ladder symbolizes the best life possible and the bottom rung symbolizes the worst life possible. Which rung would you say describes your life today most adequately?

Probe: (Looking at your life as a whole).

**INT: THE RESPONDENT SHOULD POINT OUT A RUNG WITH A PENCIL—MAKE A NOTE OF THE RUNG.**

35. Thinking back on the period from the time when you received the recommendation letter until you were assured that you did not have breast cancer, what rung would you say describes this period most adequately?

**INT: WRITE DOWN THE NUMBER OF THE RUNG POINTED OUT BY THE RESPONDENT.**

**COMMENTS IF ANY........................................................................................................**
36. Some women find it strenuous having to go through a work-up examination and then be assured they do not in fact have breast cancer. Imagine that you are given two options the next time you have a mammogram screening. SHOW CARD F1 + F2

One of the options is to go through a work-up examination like you did, whereupon you were told that you didn’t have breast cancer + that you would live healthy till the age of 79. The other option is learning the negative result immediately after the screening. In return for this knowledge you had to trade off the last days of your life. What would your choice be?

<table>
<thead>
<tr>
<th>SHOW CARD F1 + F2</th>
<th>21 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot; F1 + F3</td>
<td>1 day</td>
</tr>
<tr>
<td>&quot; F1 + F4</td>
<td>7 days</td>
</tr>
<tr>
<td>&quot; F1 + F5</td>
<td>14 days</td>
</tr>
</tbody>
</table>

Comments...........................................................................................................................................

37. If you instead had two other options the next time you were taking the screening mammogram: SHOW CARD G1 + G2

1. You have to go through an ordinary work-up procedure before you are assured that you do not have breast cancer. The work-up examination is then free of charge.

2. Your other option is being informed the day subsequent to the screening that you do not have breast cancer. However, you have to pay for this information. How much would you be willing to pay to avoid the work-up examination?

Pay........... (krone)

Comments...........................................................................................................................................

38. Were you examined by a surgeon at the work-up examination? Yes/No

- If No, continue to question 42
- If Yes

39. Did you undergo a biopsy of the breast? Yes/No

- If No, continue to question 41
- If Yes

40. Did you have to be hospitalized for the biopsy? Yes/No
41. Was the biopsy painful? 
   Comments: 
   
42. Do you feel any pain in the biopsied breast? 
   Comments: 
   
43. Do you have the same degree of sensibility in the breast that were biopsied as in the other breast, in relation with sexual activity? 
   Comments: 
   
44. Has your life changed because of the examination? 
   SHOW CARD H: 
   - to the worse 
   - no impact 
   - to the better 

INT: THESE WERE ALL THE QUESTIONS. DO YOU HAVE ANY COMMENTS CONCERNING THE QUESTIONNAIRE. PARTS WHICH WE HAVEN'T TOUCHED? I WILL BE PLEASED TO MAKE A NOTE OF YOUR COMMENTS.

Signature INT: 


<table>
<thead>
<tr>
<th>BEST LIFE POSSIBLE</th>
<th>BEST LIFE POSSIBLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>WORST LIFE POSSIBLE/DEATH</td>
<td>WORST LIFE POSSIBLE/DEATH</td>
</tr>
</tbody>
</table>


Av Anne Johanne Søgaard, 1989.


