The incidence and treatment of breast cancer in Norway over three decades.

The relationship between mammography, hormone therapy use and overdiagnosis.

Pål Suhrke
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**Acknowledgements**

In my work as a pathologist, I am used to studying breast cancer under a microscope. By working on this thesis, I have had the pleasure of expanding my horizons by studying several other interesting aspects of breast cancer. First of all, I would like to thank my supervisor Per-Henrik Zahl at the Norwegian Institute of Public Health for all the support and encouragement through nearly 8 years. I have appreciated all our interesting morning discussions over a cup of coffee. Per-Henrik has taught me mathematics, epidemiology and statistics, both strengths and weaknesses, and also co-authored all the papers.

I would also like to thank my co-supervisor Jan Mæhlen who introduced me to breast cancer epidemiology when I worked as a resident at Ullevål University Hospital in Oslo. I have always admired his wide interests and knowledge in different fields of medicine and also his ability to ask questions. Jan introduced me to writing scientific English and co-authored my first and second publication.

I have enjoyed the collaboration with experienced and knowledgeable co-authors: Ellen Schlichting, Peter Gøtzsche, Karsten Jørgensen, Erik Nord and Mette Kallager. Thank you for sharing your expertise and for all I have learnt from you. Also warm thanks to my brother-in-law, Øyvind, for improving my English language.

During all the years I have worked with this thesis, I have also worked at the Department of Pathology at Vestfold Hospital Trust in Tønsberg. Warm thanks go to all my good colleagues there. Thank you for your patience. Henning Jørgensen, Tor-Audun Klingen and my former leader Ying Chen have been especially important for me.

Finally I would like to thank my family, Hilde and our three children Tobias, Ole and Tiril. Without you, I would never have finished this thesis. I would also like to thank my parents, my father, Tor, who has encouraged me through all these years and my always supporting mother, Ingunn, who sadly died of breast cancer far too young in 2009.
**Terms and abbreviations**

AORH: Four Norwegian counties (Akershus, Oslo, Rogaland and Hordaland)

APC: Annual Percentage Change

ATC-group: Anatomical Therapeutic Chemical system for classification of drugs

BRCA mutations: Mutations in tumor suppression genes causing hereditary breast cancer

DCIS: Ductal Carcinoma in Situ, a non-invasive breast tumor

DDD: Defined Daily Dose

Her-2: Human Epidermal growth factor Receptor. Overexpression of this oncogene stimulates cancer growth in 30% of breast tumors.

HR: Hazard Ratio

HT: Peri- and postmenopausal Hormone Therapy (hormone replacement therapy)

IDC: Invasive Ductal Carcinoma, the most common breast cancer subtype

ICD-O-2 codes: International Classification of Disease for Oncology

ILC: Invasive Lobular Carcinoma, the second most common breast cancer subtype

KI67: Protein associated with cellular proliferation, an important parameter for breast cancer treatment

MRI: Magnetic Resonance Imaging

NBCSP: Norwegian Breast Cancer Screening Program

PAF: Population Attributable Fraction

QALY: Quality Adjusted Life Year

SNOMED codes: Systemized Nomenclature of Medicine, a coding system used in pathology

WHI trial: Women’s Health Initiative trial
List of papers

The thesis is based on the following four papers:


General introduction

Breast cancer mortality

Under the microscope, breast cancer is defined as a disease where atypical or malignant cells originating in the breast, grow into normal tissues. Breast cancer is the most frequent female cancer worldwide. The estimated number of new cases was 1.7 million in 2012.[1] In Norway there are around 3000 new cases each year. In addition, around 300 cases of ductal carcinoma in situ (DCIS), a potential breast cancer precursor lesion, are detected. Breast cancer is the leading cause of death from cancer among women with 0.5 million deaths per year.[1] In Norway there are around 600 breast cancer deaths each year. Since 1990 the breast cancer mortality has fallen in several European countries, including Norway and Sweden.[2, 3] Most breast cancer deaths take place the first 5 years after diagnosis. However, the cancer development and progression might be very slow, and even several decades after diagnosis, the breast cancer mortality is increased.[4-6]

Figure 1: Breast cancer mortality for women 30 years and older in Norway and Sweden from 1954-2012 (from Nordcan[7]) Rates have been smoothed using 3 years average.
Breast cancer incidence in Norway

Incidence data have been recorded by the Norwegian Cancer Registry since 1953 (Figure 2). Over a 40-year period, the breast cancer incidence increased by more than 50% for both younger women (<45 years), middle-aged women (45-69 years) and older women (>69 years). The annual percentage change for middle-aged women was 1.4% (calculated as the annual percentage change (APC) from 105 per 100,000 in 1953-57 to 166 per 100,000 in 1990-4). During the 1990s, the breast cancer incidence increased steeply for middle-aged women, the breast cancer incidence nearly doubled and the disease became more common for middle-aged than older women.[8] Over the same period, the incidence has increased from 37 per 100,000 in 1953-57 to 55 per 100,000 in 1990-94 for women aged 30-44 years (the APC is 1.2% increase per year). After year 2000, the breast cancer incidence has dropped marginally for women aged 45-69 years. For women aged 70 years or above and women aged 30-44 years, breast cancer incidence rates have been almost constant after 1995.

Figure 2: Incidences of breast cancer by age groups in Norway from 1954-2013 (from Nordcan[7]).
Age effects are the consequences of growing older. Figure 3 shows how the breast cancer incidence in both Sweden and Norway increased continuously by age before screening started, and each curve represents one time period. When screening was introduced the shape of the age specific incidence curve changed, and today breast cancer is most frequent in the age group 50-69 years, the age group which is invited to screening.

A cohort effect affects people who were born at about the same time, such as during a given year or a particular decade, who share various characteristics as a group. Complete age-specific breast cancer incidence rates for specific birth cohorts are not available yet, because in Norway we only have incidence data from 1953 and thus birth cohorts cannot be followed-up for 90 years so far. In opposite to cohort effects, period effects are the consequences of influences that vary through time. Period effects typically cause sudden changes affecting all age groups simultaneously. The sudden increase in breast cancer incidence in Sweden and Norway in the age groups 45-69 years is an age-specific period effect (interaction between age and period).[9, 10] Figure 3 shows that for the youngest women, the age-specific incidence rates are unchanged over the time period 1981-2001, indicating no cohort effects on the breast cancer incidence, while for the age group 45-69 years the incidence increased from 140 per 100,000 to 260 per 100,000 women.

Under the microscope, DCIS is defined as proliferation of atypical cells that are confined to normal breast ducts or lobules. In contrast to invasive breast cancer, there is no growth of the atypical cells into the supporting tissue. DCIS has been considered to be a precursor lesion for

Figure 3: Age specific incidence of breast cancer in Norway and Sweden before, during and after establishment of national screening programs (from Hemminki[8]).
breast cancer, where the development of invasive cancer often is preceded by a stage of DCIS.[11] However, others have suggested that both invasive breast cancer and DCIS can develop from common progenitor cells and that the development of invasive breast cancer is independent of DCIS.[12] DCIS has been recorded by the Norwegian Cancer Registry since 1993. The DCIS incidence has increased 4-5 times in the invited age group since registration started, but hardly not in other age groups.[13] There are several interesting aspects concerning DCIS which can be mentioned:

- Since DCIS has been considered to be a precursor lesion, removal of these lesions should theoretically reduce the numbers of invasive breast cancer.
- Even though DCIS is not breast cancer according to the pathologic definitions, the entity is often perceived as breast cancer and hence a change in names by exchanging the word “carcinoma” has been proposed.[14]
- It is common to find DCIS together with invasive breast cancer in surgical specimens.
- The surgical treatment is similar for breast cancer and DCIS.

Figure 4: Incidences of ductal carcinoma in situ by age groups in Norway 1993-2007 (from Sørum et al [13]).
Based on radiological and pathological data as well as clinical examination, breast cancer and DCIS patients are categorized (staged) at the time of diagnosis into 5 clinical stages:

- **Stage 0 (DCIS)**
- **Stage I** (invasive breast cancers with diameter ≤ 2.0 cm and no lymph node involvement or distant metastasis)
- **Stage II** (either invasive breast cancers with diameter ≤ 5.0 cm and 1-3 positive lymph nodes but no distant metastasis or invasive tumors with diameter >2.0 cm with no positive lymph nodes or distant metastasis)
- **Stage III** (either tumors > 5 cm and 1-3 positive lymph nodes, or any tumor with direct extension to chest wall/skin, or any tumor with > 3 positive lymph nodes and no distant metastasis)
- **Stage IV** (any tumor with distant metastasis)

Severity and prognosis of the disease worsen by increasing stage. Breast cancer has become a disease that is more often diagnosed at early stages (stage I and II) among women invited to screening. As illustrated by figure 5, the incidence of more advanced stages shows only minor changes.[15]

![Figure 5: Trends in stage-specific incidence, before, during and after establishment of national mammography screening in Norway (from Lousdal et.al [15]).](image)

**Breast cancer incidence in Sweden**

There are some important differences in the breast cancer incidence trends in Norway and Sweden during the past 30 years. Swedish data show that the breast cancer incidence
increased by 20-30% for both younger women (30-44 years), middle aged women (45-69 years) and older women (>70 years) over a period of 25 years from 1961 to the middle of the 1980ties. The APC for middle aged women was 1.0% in this period, a little bit lower than the Norwegian number of 1.4%. From the middle of the 1980s, over a period of 15 years, the breast cancer incidence increased by 65% for middle aged women. Importantly, this steep incidence increase took place 10 years before a similar incidence increase occurred in Norway. After year 2000, the breast cancer incidence has declined marginally for the middle-aged group. For younger women the breast cancer incidence has increased by 20% over the period of 25 years after 1986. For older women the incidence declined in the 1990s, but started increasing after year 2000.

Figure 6: Incidences of breast cancer by age groups in Sweden from 1961-2013) (from Nordcan[7]).

Breast cancer risk factors

For a long time hormonal and reproductive factors have been established as risk factors for breast cancer.[16] Early menarche and late menopause both increase the breast cancer risk. Breast cancer risk also increases with increasing time of estrogen exposure and doses over lifetime. Fertility affects the breast cancer risk since the estrogen levels are decreased during pregnancy. Women not having childbirths have increased breast cancer risk compared to women who have had childbirths and the risk also decreases with increasing number of
children and by having childbirths at low age. A family history of breast cancer in a first
degree relative increases the breast cancer risk as well.
Other established risk factors are heritage of certain genetic alterations or mutations,
especially in the BRCA1 and BRCA2 genes, which increases breast cancer risk markedly.[17-
19] However, these mutations are very rare and can only explain a small percentage of the
breast cancer cases.
A high intake of alcohol has been reported to increase breast cancer risk,[20] and physical
activity may reduce the breast cancer risk.[21] Over the past decades the use of peri- and
postmenopausal hormone therapy or hormone replacement therapy (HT) has been established
as important risk factor.[22, 23] Finally, the introduction of mammography has introduced
dense breasts at as a risk factor.[24]

**Tumor growth and early detection**

Breast cancer treatment usually starts shortly after a tumor has been detected and almost all
small primary tumors are treated immediately by surgical excision. Therefore, tumor growth
rate is difficult to study and to estimate. Breast cancer is clinically a very heterogenic disease;
some tumors grow fast and some tumors grow slow. Some tumors disseminate or metastasize
early and some tumors metastasize decades after the initial diagnosis.[25] Cancer has over
centuries been regarded as a disease where all tumors are constantly growing and where the
natural course is fatal. This traditional view of breast cancer as a disease with orderly
progression through different stages is illustrated by Esserman and colleagues.[26] In this
model early detection is intuitively appealing since detection of a disease at an early stage
implies better prognosis than detection at late stages.
Figure 7: Linear model of cancer progression (from Esserman et.al [26]).

An alternative model (Figure 8) for tumor growth has been proposed by Welch and Black.[27] This model incorporates in addition to the traditional one dimensional view of tumor growth, the possibilities of tumor dormancy, where the tumor ceases dividing and stays in a quiescent state, as well as tumor regression, where the cancer regresses and finally disappears. The differences in tumor progression are explained by differences in biology. Using this model for the understanding of tumor progression, screening can in theory only affect mortality for some tumors - those who keep on growing. Early detection of non-progressive tumors will not affect mortality.

Figure 8: Heterogeneity of cancer progression (from Welch et. al [27]).

Early diagnosis of fast growing tumors is relatively inefficient because the preclinical time period (sojourn time) where they can be detected is shorter than for slow-growing tumors. The probability of being detected is proportional to the length of the sojourn time; thus slow
growing tumors are more likely to be detected at regular screening. And moreover, fast growing tumors are more likely to be detected as interval cancers (between two mammograms). Mammography detected tumors have a better prognosis than clinically detected tumors, and this phenomenon is called length-time bias.[28] Detection of slow growing tumors by screening has a potential to reduce breast cancer mortality, but if many of the tumors supposed to be slow-growing in fact are dormant or regressive, the potential of screening is reduced.

Fryback and colleagues have developed a simulation model, the Wisconsin Breast Cancer Simulation Model, which tried to replicate the breast cancer incidence and mortality in the US. To fit the model to observed statistics, a class of breast tumors of limited malignant potential (LMP-tumors) had to be postulated, constituting 30-50% of the initiated tumors.[29]

**Diagnosis and overdiagnosis**

Diagnosis can be defined as a process to establish the cause and nature of a person’s illness. Overdiagnosis is defined as the detection or diagnosis of a disease that otherwise would not have caused symptoms during the patients remaining life.[27] Overdiagnosis is usually caused by changes in the diagnostic process. Without changes in the diagnostic process, the disease would not have been detected. Overdiagnosis, of both invasive breast cancer and DCIS caused by mammography screening, has been discussed since the introduction of the Cochrane review in 2001.[30, 31]

Overdiagnosis of breast cancer was originally supposed to be caused either by detection of preclinical tumors just before a non-breast cancer death or by the detection of DCIS which were known to sometimes regress. [32] The ideal way of studying the level of overdiagnosis is in a randomized controlled trial with long follow up and no screening in the follow-up period. The Malmö trial was the first randomized trial to publish data on extra incidence when screening with mammography.[33] Since screening increases the rate of breast cancer in the screening period due to early detection, a compensatory drop in incidence is assumed to occur after screening has stopped, causing less than 2% extra breast cancer cases during the lifetime, as illustrated by Boer et. al as an comment to the Malmö trial.[34] The level of overdiagnosis in the randomized mammography trials has later been quantified in the Cochrane review of mammography screening at about 30%. [35]
Later observational data has been used to estimate the level of overdiagnosis and the results differ considerably.[36-39] Differences can be explained by how overdiagnosis is defined and by the method used in the calculations. Overdiagnosis is usually presented as a ratio where the numerator is the estimated number of overdiagnosed cases. There are several options for the denominator causing very different results. A simple example is if the number of breast cancers in a population over a certain period increases from 200 to 300 without a compensatory incidence drop later on, then there are 100 extra cases of breast cancer. Overdiagnosis can be calculated as either $100/200 = 50\%$ or $100/300 = 33\%$.

In addition to the choice of the denominator, the level of overdiagnosis will also be influenced by the method used in the calculation. Etzioni and colleagues have described two fundamentally different approaches, the excess incidence approach and the lead-time approach.[36] The excess incidence approach uses observed incidences, and the calculations will be influenced by modeling of a potential underlying incidence trend, the length of the follow-up period after screening was stopped (to adjust for earlier diagnosis) and whether prevalence screening is included or not. The lead-time approach relies in addition on the assumption of breast cancer as a progressive disease only. Based on observed incidence rates, statistical modeling of lead time (to adjust for earlier diagnosis) and modeling of underlying incidence trends, the level of overdiagnosis is calculated. The level of overdiagnosis using the
lead-time approach is strongly influenced by the assumption of the lead time. Generally, estimates of overdiagnosis using the excess incidence approach, is much higher than using the lead-time approach.[36, 37, 40] This is mainly because assumptions of long lead times implies that most of the incidence increase which can be observed during screening, is assumed to be caused by earlier diagnosis.[41]

**Mammography screening in Norway and Sweden**

There are two fundamental prerequisites for a screening method to work.[42] The first is that the screening method must detect the disease earlier than without screening. The second is that earlier treatment improves prognosis. This would theoretically increase the number of early stage cancer and reduce the number of late stage cancer, and thereby reduce breast cancer mortality.

The prognosis for breast cancer patients is highly dependent on the stage when the cancer is detected. Breast cancer with distant metastasis is not curable. Smaller tumors have better prognosis than larger tumors. Patients with local lymph node metastasis will be offered treatment with the aim of cure but the prognosis is worse than for patients without metastasis. Consequently, the concept of early detection of breast cancer by detection of smaller tumors before they grow and disseminate is very appealing.

The simplest approach to breast cancer screening would be through self-examination programs. However, there is no evidence for any beneficial effects of self-examination.[43] Mammography uses x-ray to detect breast cancer before the disease can be detected clinically. Several randomized trials have in the past 50 years been conducted to study the effect of both clinical examination and mammography in breast cancer screening programs to reduce breast cancer mortality. The first trial was conducted in New York in the 1960s.[44] In the 1970s and 1980s several large trials were conducted in Sweden, Canada and the UK.[45-47] Most of the randomized trials have shown reduced breast cancer mortality for women attending screening programs compared with non-screened women, and even though the results of the trials have been highly debated, mammography screening is now widely used.[35, 48]

The Norwegian Breast Cancer Screening Program (NBCSP) was initiated late in 1995. The program has been organized by the Cancer Registry of Norway as a population based screening program. During 1996 four counties (Akershus, Oslo, Rogaland and Hordaland) started screening, covering around 40% of the Norwegian population. In the period 1999-
2004 the remaining 15 counties were stepwise included in the program.[49] The age group 50-69 years is invited to biennial screening and the results are recorded at the Norwegian Cancer Registry.

Several of the randomized mammography trials which have been conducted were done in Sweden, and the Swedish health authorities published guidelines on mammography screening in 1986 where the county councils were advised to start mammography screening. Like in Norway, initiation of screening was done in a stepwise manner. Several counties started screening in the late 1980s, and the last county started screening in 1997.[50]

**Hormone therapy**

Postmenopausal hormone therapy (HT) or hormone replacement therapy is the administration of drugs containing estrogen often along with progesterone to peri- or postmenopausal women. For many years it has been well known that administration of estrogen increases the risk of uterine cancer.[51] When progesterone was added to estrogen, the risk of uterine cancer was reduced.[52] Consequently, for women having an intact uterus, the HT must include progesterone in addition to estrogen. The medication can be used either symptomatically, to reduce peri- or postmenopausal symptoms, or preventively, to reduce the risk of osteoporosis.[53] In the 1990s there were numerous observational studies suggesting that HT also reduced the risk of cardiovascular disease and therefore prolonged lives.[54-56] As a result, use of HT increased substantially. To explore the effect of HT in a randomized study, the randomized WHI trial was established. Preliminary results were published in 2002 suggesting that the use of HT increased the risk for cardiovascular disease and also increased the risk of breast cancer with 24% after almost 6 years use.[23] Subsequently sales rates of HT drugs dropped markedly in both Sweden and Norway, as well as in the rest of the world.[57, 58] Another important observation concerning use of HT is that breast density increases, and thus the sensitivity of mammography screening is reduced for HT users.[59] As a consequence, many breast cancer diagnoses are delayed.

In Norway the introduction of mammography screening and the increased use of HT occurred simultaneously in the1990s. As a result there has been a discussion of how much of the incidence increase is explained by mammography screening versus increased HT use.[10, 60, 61] In Sweden, the situation was different. Here mammography screening was already
introduced in most of the counties before HT use started to increase and finally peaked around year 2000.

**Treatment and overtreatment**

The treatment of breast cancer has changed a lot over the past 100 years. Halsted introduced radical mastectomy in 1907 as treatment for breast cancer.[62] This treatment was based upon the hypothesis of breast cancer as a disease that grows and metastasizes locally. Therefore extensive and mutilating surgery was proposed, including the removal of the whole breast, the chest muscle (pectoralis major), axillary and even mediastinal and cervical lymph nodes. In the 1960s and 1970s the view of breast cancer as a loco-regional disease was challenged. Lumpectomy or breast conserving surgery where only the tumor and a small part of the surrounding normal breast tissue is removed, was shown to be as effective to reduce breast cancer mortality as mastectomy.[63, 64] In addition, use of adjuvant systemic chemotherapy showed reduced breast cancer mortality.[65] Fisher proposed breast cancer as a systemic disease with hematogenous spread of cancer cells (by blood vessels) which often occurs before diagnosis. Today, treatment of breast cancer in Norway has been standardized. Surgical treatment is mainly based on tumor size, the number of tumors and the localization of the tumor in the breast.[66] The adjuvant therapy is based upon tumor size, lymph node involvement and the predictive markers Ki-67 proliferation index, Her-2 and hormone receptor status. The aim of mammography screening is to detect breast cancer earlier and thereafter treat the patient with surgery and adjuvant therapy to ultimately reduce breast cancer mortality. Since mammography screening is based upon the hypothesis of early detection, a potential additional benefit of screening would be less aggressive treatment in the sense of more tumors being eligible for breast conserving therapy due to detection of smaller tumors.

**Pathology**

The diagnosis and treatment of breast cancer is based on decisions in multidisciplinary teams where nurses, radiologists, oncologists, surgeons and pathologists are included. The diagnosis of breast cancer is based on interpretation of histological or cytological specimens under the microscope. Core needle biopsy or fine needle aspiration cytology is mainly used
preoperatively. Here small samples of the tumor are taken from the patient to establish the diagnosis and to plan the treatment. The surgical specimen is also examined by the pathologist to subtype the tumor, give prognostic information and to decide adjuvant treatment after evaluation of the predictive markers; Ki-67 proliferation index, Her-2 and hormone receptor status (estrogen and progesterone).

The subtyping of breast cancer is based on the classification system proposed by the WHO. [67] The most common breast cancer subtype, invasive ductal carcinoma (invasive carcinoma NOS), represents the majority of breast cancer cases which according to WHO includes 50-80% of all breast cancer cases. The second most common form of breast cancer, invasive lobular carcinoma, represents 5-15% of all breast cancer cases. In addition, there are several other different histological subtypes of breast cancer, all of them representing less than 5% of the breast cancer cases each. The distinctions between the histological subtypes are primarily based on morphology. Immunohistochemistry can be used to differentiate between the different histological types.[68] Here antibodies are added to tumor slides, and the different expression of antigens in tumors can be studied. The definition of lobular carcinoma has not changed over the past years.[67, 69] The traditional histological classification of breast tumors does not add neither prognostic nor predictive value to breast cancer patients. However, the recognition of the subtypes has some important implications. Invasive lobular carcinomas can be difficult to detect by mammography and hence the diagnosis can be delayed. Since tumor growth is diffuse, MRI might be needed to evaluate the size of the tumors.[70] In addition, several authors have suggested that the risk of invasive lobular carcinoma is more strongly associated with the use of hormone therapy than the risk of invasive ductal carcinoma.[71, 72]

In the last 15 years a molecular classification system of breast cancer has been developed based on molecular techniques and studies of gene expression.[73] Today this system is not used routinely in the pathology reports in Norway. However, this system is closely related to the predictive markers and adjuvant treatment of breast cancer. The Ki-67 proliferation index, Her-2 and hormone receptor status are parts of a standard report, and these markers can be used to define the four major molecular subtypes.
**Quality Adjusted Life Year (QALY)**

The Quality Adjusted Life Year (QALY) is a common metric for simultaneously studying both the benefits and the harms generated by a healthcare intervention.[74] If costs of the interventions are calculated, QALY analysis can be used in cost-utility analysis.[75] In QALY analysis the quality of life is made comparable to the length of life through the assignment of a value (utility) between 0 and 1 to all health states. Perfect health corresponds to 1 and a health state as bad as dead corresponds to 0. A gain in life expectancy due to a healthcare intervention will be more valuable in QALY analysis if the patient is in good health compared to bad health after the intervention. Whether mammography screening does more harm than good has been extensively debated,[35, 76, 77] and the QALY approach has been used to evaluate mammography screening in the UK.[78, 79]
Aims of the thesis

Main aims

- To evaluate the simultaneous impact of mammography screening and use of peri- and post menopausal hormone therapy (HT) on the breast cancer incidence in Norway during the past 30 years.
- To study how the introduction of mammography screening has affected breast cancer treatment.

Specific aims

Paper I: To examine how the introduction of mammography screening in Norway affected the surgical treatment for breast cancer, and in particular how the rates of mastectomy were affected by the introduction of screening when comparing screened and non-screened women between 1993 and 2008.

Paper II: To investigate how the use of hormone therapy (HT) and the introduction of mammography screening have affected the breast cancer incidence and distribution of subtypes of breast cancer in Sweden and Norway from 1980 to 2007.

Paper III: To explore how prescriptions of HT has affected the risk for breast cancer using individual data. We also studied how different types of prescriptions affected the risk and if different subtypes of breast cancer were affected differently.

Paper IV: To study how QALYs are affected by the introduction of mammography screening. Since it is unclear to which extent loss in quality of life due to harms of screening counterbalance the benefits, we developed a Markov model to simulate the Norwegian breast cancer screening program and to calculate how the introduction of mammography screening in Norway has affected QALY for women invited to screening compared to a non-screened control group.
Materials and methods

Data sources

Paper I:
From the Norwegian Cancer Registry we obtained aggregated data on surgical treatment of women aged 40-79 years (aggregated in 5-years age groups) with breast cancer and DCIS between 1993 and 2008. The data were stratified by stage at the time of diagnosis. In the Norwegian Cancer Registry the national person identification number is used when treatment is classified according to pathology reports and clinical notifications. We obtained data on the first case of breast cancer for each woman, and the treatment was classified to either mastectomy or breast conserving therapy.

Population data was downloaded from Statistics Norway.[80]

We also obtained a second data set from the Norwegian Patient Registry on surgical treatment of all Norwegian women with breast cancer or DCIS in the period 1995-2006. These data were aggregated as above. The national personal identification number was not used at the Norwegian Patient Registry at that time. Consequently one individual could add several surgical procedures to the data set. Due to this limitation we used the data set from the Cancer Registry in the publication.

Paper II:
We obtained Swedish sales figures of HT from the National Board of Health and Welfare and Norwegian sale figures from the Norwegian Institute of Public Health. These data are based on sales from wholesalers and included the period from 1990 to 2007. Since we also wanted to explore how HT use differed by age, we requested data on prescription of HT in 5-year age groups. These data were available from year 2000 in Sweden and from 2004 in Norway. Norwegian data were downloaded from the Norwegian Prescription Database.[81]

From the cancer registries we requested breast cancer incidence data for women aged 40-79 years (aggregated in 5-years age groups) from 1980 to 2007. From 1993 these data also include information on histological subtypes of breast cancer.

Population data was downloaded from Statistics Norway.[80]

Paper III:
As a part of the evaluation of the Norwegian mammography screening program, we received anonymized individual data from nationwide registries; the Norwegian Cancer Registry, Statistics Norway, the Norwegian Prescription Database and the Medical Birth Registry of Norway. All data files included a unique number for each individual woman that enabled us to merge the files. From the Cancer Registry we obtained information on public mammography screening activity and information on all cases of breast cancer and DCIS, including histological tumor type and detection mode. Statistics Norway gave information on death date, causes of death and date of emigration, and the Medical Birth Registry had information on number of births. From the Prescription Database we got information on all prescriptions of hormone therapy (starting in 2004), including date of prescription, the name and type of the drug, the ATC-group and the defined daily dose (DDD) prescribed.

Paper IV:

In our model we used published results from the Norwegian screening program on attendance rates, rates of false positive tests and frequency of the different treatment courses. The number of women at risk for breast cancer and breast cancer death was estimated from population data from Statistics Norway.[80]

Since there have been extensive discussions on the level of overdiagnosis and mortality reduction associated with mammography screening, we used four different levels of both overdiagnosis and breast cancer mortality reduction in the model. The different estimates were chosen from both Norwegian and international studies, including both randomized trials and observational studies.

Based on published data on quality of life in breast cancer patients and an interview with an experienced breast cancer surgeon and a breast cancer nurse, we estimated health profiles using the 5-level version of the quality-of-life instrument EQ-5D, applied to the different health states occurring in women undergoing mammography screening or treatment for breast cancer. The EQ-5D instrument covers five health dimensions: Ability to walk, ability to wash and dress (self-care), ability to do usual activities, pain/discomfort, and anxiety/depression.

**Study design and statistics**

Paper I:
We calculated age-specific incidence rates, rates of breast operations (breast conserving therapy plus mastectomy) and rates of mastectomy for three age groups (40-49, 50-69 and 70-79 years). The calculations were also done stratified by stage. The Excel software was used in these calculations.

Then the study period was divided into three intervals; the pre-screening period (1993-95), the screening introduction period (1996-2004) and the screening period (2005-08). We used a Poisson regression model, adjusting for age only, to estimate changes in mastectomy and breast operation rates in the age groups 40-49, 50-69 and 70-79 years from the pre-screening to the screening introduction period and from the pre-screening to the screening period. Poisson regression was also used to compare the relative changes between age groups.

Changes in rates of surgery over time were presented as hazard ratios (HR). Since mammography screening was gradually implemented in Norway, we also used a Poisson regression model to compare how rates of surgery changed in 4 countries where screening started in 1995-96 (AORH) to 15 countries where screening started in 1999-2004 (non-AORH). We used the software Egret for these calculations.

Paper II:

We report total sales of HT and sales of HT containing estrogens and progesterone for Sweden and Norway, respectively. To report the use in different age groups, we used two different approaches. The Norwegian data from the Prescription database report the number of users (people who have had at least one prescription) per 100 women in 5-year age groups. The Swedish data included information on sales in 5-year age groups, and hence we estimated the number of users in different age groups by calculating the use in DDD per day per 100 women. The Excel software was used for these calculations, including the calculation of breast cancer incidence from 1980-2007.

From the Norwegian Cancer Registry we received information on histological subtypes based on 4 different ICD-O-2 codes (invasive ductal carcinoma, invasive lobular carcinoma, tubular carcinoma and adenocarcinoma NOS). From the Swedish Cancer Registry we received information on all subtypes of breast cancer based on the SNOMED classification system. We used a Poisson regression model to estimate the incidence trends in the period with increasing use of HT (1993-2001) compared to a period with decreasing use (2002-2007). We report

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annual percentage change (APC) for the two periods, adjusting for 5-year age groups only. The software Egret was used for these calculations.

Paper III:

To estimate the risk of breast cancer associated with use of hormone therapy, we used individual data and a Cox regression model. We estimated HRs with 95% confidence intervals and adjusted for available risk factors such as age, number of childbirths and whether or not the woman attended the Norwegian breast screening program between 2004 and 2009. The study population consisted of all Norwegian women aged 50-65 years in 2006. Based on HT prescriptions in 2004 and 2005, the population was divided into four different groups; women with no prescriptions, prescriptions of 1-180 DDD, 181-365 DDD or more than 365 DDD. All calculations were done with HT use stratified into four different groups; estrogen and progesterone combinations, tibolone, vaginal estrogens and systemic estrogens without progesterone. The event was defined as the time from January 1st, 2006 to either an invasive breast cancer diagnosis or to a DCIS diagnosis. The follow-up period ended December 31st 2009. We did separate analysis for DCIS and invasive breast cancer and also stratified on histological tumor types (invasive lobular carcinoma or non-lobular invasive carcinoma). The calculations were done using the software SPSS statistics.

The population attributable fraction (PAF) describes the proportion of avoidable breast cancer cases if the HT use was fully eliminated. The PAF was calculated as \( P(HR-1)/(1+P(HR-1)) \), where \( P \) is the proportion of the population using HT and \( HR \) is the hazard rate for invasive breast cancer.

Paper IV:

We calculated QALYs using four different levels of overdiagnosis (20, 30, 50 and 75%) and four different levels of breast cancer mortality reduction (10, 15, 20 and 30%).

The quality-of-life instrument EQ-5D was used to estimate health profiles. We also conducted analyses using an alternative set of health state values (for EQ-5D) that assign more weight to gained life years relative to losses in quality of life to calculate so-called ‘equity weighted QALYs’. We present conventional QALYs and equity weighted QALYs, both undiscounted and discounted (using a 4% discounting factor).
Finally, since there is uncertainty to which extent the reduction in breast cancer mortality is accompanied by a reduction in overall mortality, we did our calculations assuming that only a part of the breast cancer mortality reduction (20, 50 and 80%) translates into a reduction in overall mortality. We used the software Excel for programming the Markov model.

**Main Results**

**Paper I:**

In the study period from 1993-2007 there were 32 200 cases of invasive breast cancer and 3208 cases of DCIS in women aged 40-79 years. Information on surgical treatment was available for 94% of the invasive cases and 98% of the DCIS cases.

For the age group invited to mammography screening, 50-69 years, both incidence- and surgery rates for invasive breast cancer and DCIS increased steeply during the period. The total number of breast operations increased by 70% in women aged 50-69 years from the pre-screening to the screening period compared to an increase of 8% in the age group 40-49 years and a decrease of 8% in women aged 70-79 years. In the same period, the mastectomy rates fell by 30% in the age group 50-69 years, and by 35% and 41% in women aged 40-49 and 70-79 years respectively, however the decline in mastectomy rates for the three age groups did not differ significantly. The changes in both mastectomy and surgery rates affect stage 0, 1 and 2. For stage 3 and 4 the rates were relatively unchanged.

During the screening introduction phase the mastectomy rates increased by 9% in the age group 50-69 years, but fell by 17% and 13% in women aged 40-49 and 70-79 years respectively. Compared to the younger women we calculated a 31% increase in the relative risk to undergo mastectomy in women aged 50-69 years in the screening introduction period.

**Paper II:**

In the study period 1980-2007, 127 596 and 48 028 cases of invasive breast cancer were diagnosed in women aged 40-79 years in Sweden and Norway respectively. The sales of HT peaked in 1999-2001. By 2007 the sales of CHT had fallen by 74% in Sweden and 71% in Norway and the-sales figures for 2007 were at the same level as in 1990-1991. More than 80% of the CHT use was in the age group 50-69 years.
In 2002 to 2007, a period with decreasing use of HT and relatively constant mammography use, the annual decrease in breast cancer incidence rates for women aged 50-69 was 1.5% in Sweden and 0.8% in the part of Norway not confounded by prevalence screening. Most of the decline was in the rates of the second most common subtype of breast cancer, ILC, which dropped by 4.7% and 7.0% per year, respectively. The rates of IDC were stable in this period.

In period 1993 to 2001, with increasing use of HT as well as introduction of mammography screening, especially in Norway, the annual increase in breast cancer incidence was 3.0% in Sweden and 6.3% in Norway for women aged 50-69 years.

Paper III:

4,597 cases of invasive cancer and 681 cases of ductal carcinoma in situ (DCIS) diagnosed in 2006-2009 were included in the analysis. At the beginning of the study period, the population included 449,717 women aged 50-65 years.

Long-term prescription of HT (for more than one year) containing estrogen and progesterone is associated with an increased breast cancer risk, the HR is 2.06 (1.90-2.06). Short term prescription, less than half a year, does not increase the risk. Prescription between half a year and one year is associated with a slightly increased risk, the HR is 1.24. Prescription of estrogens alone is not associated with an increased breast cancer risk.

The association between long-term prescription of HT and breast cancer risk was stronger for invasive lobular carcinoma than non-lobular carcinoma (HR is 3.10 versus 1.94). Even for DCIS a significant increased risk was observed (HR is 1.61).

Based on the calculated HR of 2.06 for long-term users of estrogen and progesterone combinations, we estimated the population attributable fraction to 8.2%, corresponding to around 90 breast cancer cases in 2006.

Paper IV:

In the life table model we follow the 100 000 women in the screening cohort for 36 years. 120 to 360 women are prevented from dying of breast cancer (10-30% mortality reduction) and 756 to 2,805 women are overdiagnosed (20-75% overdiagnosis). Depending on the proportion of breast cancer mortality reduction that is translated into overall mortality reduction, 24 to 288 women are prevented from dying.
The calculated gains or losses in QALYs depend considerably on the assumptions made regarding the level of overdiagnosis and mortality reduction used. Under the assumption that 20% of the breast cancer mortality reduction is translated into a reduction in overall mortality, a loss in QALYs (both conventional and equity weighted), were generally found, except for a small gain in the case of low levels of overdiagnosis and high levels of breast cancer mortality reduction. Assuming that 50% of the breast cancer mortality reduction is translated into a reduction in overall mortality, we found a marginal gain in the equity weighted QALYs. Assuming that 80% of the breast cancer mortality reduction is translated into a reduction in overall mortality, a gain in both equity-weighted and conventional QALYs were found, including scenarios with higher levels of overdiagnosis and lower levels of breast cancer mortality reduction.

**Discussion**

**Paper I:**

A potential benefit of mammography screening could be less extensive surgery and reduced mastectomy rates due to tumor detection at earlier stages. However, the Cochrane review of the randomized mammography trials reported 20% more mastectomies in women exposed to screening than in the control group. We considered two fundamentally different options on how to report our results. The first was reporting relative numbers with women treated with mastectomy or women treated with breast conserving treatment in the numerator, and all women surgically treated in the denominator. The second option was reporting absolute numbers, rates of mastectomy, rates of breast conserving therapy and rates of all surgery. Since overdiagnosis would highly influence the proportions of women treated and since information on proportions does not give information on numbers of women treated, we decided to use the second option and reported absolute rates. We observe that the mastectomy rates declined similarly in screened and non-screened women when screening was introduced, and we suggest that this was caused by changes in surgical practice. In the screening introduction period, the mastectomy rates increased in the screened age group, while there was a decline in the non-screened age groups. Consequently, we conclude that mammography service screening was associated with an increase in mastectomy rates, especially during the introduction of screening.
Hofvind et al. have reported that in Norway the proportion of women with invasive breast cancer treated with mastectomy declined from 85% (prescreening period) to 45% (screening period). [82] More tumors eligible for breast conserving therapy and decreasing proportions of women undergoing mastectomy, has also been reported from other countries. [83-85] However, several of these studies do not include a control group and it is difficult to separate the effect of earlier diagnosis due to mammography screening from changes in surgical practice. Walsh et al. reported similar time trends in mastectomy rates during 1994-99 in Northern Ireland (with screening) and the Republic of Ireland (without screening). [86] A study from the UK showed that both numbers of mastectomies and breast conserving treatments increased in the first 12 years after screening was fully implemented in the UK. [87] A recent published national study from Germany reported markedly increased breast surgery rates associated with the introduction of mammography screening between 2005 and 2009, while there were only minor changes in mastectomy rates. [88]

Paper II:

First, we studied the introduction of mammography screening in Norway in the 1990s that occurred simultaneously with the increasing use of HT, by using an ecological design. We compared Norwegian observations with observations from Sweden where mammography screening was mainly introduced in the 1980s. In Sweden the frequency of mammography use was almost constant in the period when HT use increased. Second, we studied the decline in breast cancer incidence rates in both Sweden and Norway after year 2002 when HT use dropped 70 percent. We observed a small incidence decline after 2002, which are in line with several other publications using ecological design that have explained decreases in breast cancer incidence by reduced HT consumption. [57, 61, 89-94] In Sweden the decline of 1.5% per year was statistically significant. In Norway however, the decline of 0.8% per year was not statistically significant in the part of Norway not confounded by prevalence screening.

Our observation, of a stronger decrease in the incidence of invasive lobular carcinoma compared to other subtypes, is also in line with other publications using similar study design. One large publication from the US found that the incidence of invasive lobular carcinoma decreased by 4.6% per year compared to 3.3% per year for invasive ductal carcinoma from 1999 to 2004. [95] Studies from Europe show similar results. [96, 97] In a review of 24 observational studies evaluating the breast cancer risk by histological subtypes for current
users of combined hormone therapy, a 1.5 increased relative risk for invasive ductal carcinoma and a 2.0 increased relative risk for invasive lobular carcinoma were reported compared with non users.[98] The WHI trial however had limited statistical power to assess the relationship between different subtypes, but reported that 9.4% of the tumors were of lobular type in the intervention group and 6.8% of the tumors were lobular in the placebo group. [99] Invasive lobular carcinomas are more often estrogen receptor positive than invasive ductal carcinomas, which might partly explain the difference in risk. However, Li et al. have studied the association between use of HT and estrogen receptor positive cases and reported that estrogen receptor positive invasive lobular carcinomas have a much stronger association with HT use than estrogen receptor positive invasive ductal carcinomas, suggesting that the difference in risk is not explained by differences in frequency of estrogen receptor positive tumors only. [72]

Paper III:

As several other observational cohort studies have shown,[22, 100, 101] we found a significant increased breast cancer risk for women who had had long term prescriptions (more than 1 year) of estrogen-progesterone combinations. Our study design, using registry based data, has an important advantage because reporting of hormone prescription is not prone to recall bias. In most of the published cohort studies, reporting of hormone prescription is done retrospectively, based on interviews or questionnaires. Another advantage by our design is that changes in medication in the follow-up period can be studied. Limitations of our study compared to other cohort studies include that we do not know if women who have had HT prescribed, actually do take the medicine. In addition, prescription data begins in 2004, and we do not have information on whether or not the women have had prescriptions earlier. This means that many of those who have had prescriptions for 1-2 years in 2004-2005, in reality might have had prescriptions for several years before 2004 as well. Another limitation of this study is that most women go to mammography, and we do not have information on private mammography screening, both for those attending public mammography screening and those never attending public screening. Therefore it is not possible to create a reliable control group consisting of women not going to mammography.

The WHI randomized trial reported a 24% increased breast cancer risk for users of combined hormone therapy over an average of 5.6 years.[102] Importantly, the risk was dependent on
the amount of time since treatment started. The breast cancer risk decreased by 41% the first 2 years of the follow up period (for those who had never used HT before randomization) and after 4.5 years the breast cancer risk was equal in the intervention and in the control group.[103] This is probably because HT causes increased breast density and consequently small tumors become difficult to detect by mammography, and for many tumors the diagnosis is delayed.[59] It is difficult to study such time-dependent effects in our data set. Since the estimated effect of HT on breast cancer risk is much lower in the WHI trial, it is likely that our study design overestimates the effect of HT on the breast cancer risk.[104, 105]

As several others have done previously, we found different risk estimates for different subtypes of breast cancer. Invasive lobular carcinoma had a higher HR than invasive ductal carcinoma. Also the risk of ductal carcinoma in situ was associated with long-term use of combined hormone therapy. Our estimated HR for DCIS are similar to those reported in the observational WHI trial.[106]

Paper IV:

Because of uncertainty concerning several of the parameters used in the model, in particular utility loss, as well as the level of overdiagnosis and the level of mortality reduction, the calculated gains or losses of QALY’s differ considerably across different scenarios. In contrast to two publications from the UK by Raftery et al. and Pharoah et al.[78, 79] we have incorporated the possibility that a reduction in breast cancer mortality only partially translates into a reduction in all-cause mortality. A reduction in breast specific mortality can, as a result of fatal complications to invasive procedures or treatment, be counterbalanced by deaths of other causes. Mammography has never been shown to reduce all-cause mortality.[35, 107]

We have done our calculations for several levels of both overdiagnosis and mortality reduction. These levels have been chosen based on published results from both randomized trials as well as more recent observational studies.[35, 38, 60, 76, 108-110] The levels are mostly the same as the levels chosen by Raftery et al.[78] However, in contrast to the publications from the UK,[78, 79] we have assigned different utility losses to different treatment options; quality of life is affected differently for a patient treated with breast conserving therapy compared to a patient treated with both mastectomy and chemotherapy. The level of utility loss associated with different treatment options and false positive screening, is associated with uncertainty. We have based our estimates of utility loss on
published literature as well as an interview with experienced clinicians.[111-114] Raftery’s results suggest that the introduction of mammography screening might have caused net harm, especially the first years after screening started while Pharoah et al. in particular have focused on cost effectiveness analysis. Our results indicate that mammography might do more harm than good since most scenarios give negative QALY’s after 36 years of follow-up if we assume that less than 50% of the breast cancer mortality reduction results in a reduction in all-cause mortality.

Conclusions

We found that the introduction of mammography service screening was associated with a significant increase in total breast operation rates for women invited to screening. Contrary to what might have been expected, also mastectomy rates increased in the screening introduction period. In the recent years, due to surgical policy changes, mastectomy rates have declined for all age groups, but most for the non-screened age groups.

Our results indicate that long term prescriptions of estrogen and progesterone combinations increase the breast cancer risk. However, we observed no association between prescriptions of estrogen only and breast cancer risk. We found that the second-most common subtype of breast cancer, invasive lobular carcinoma, is more strongly associated with hormone therapy use than other subtypes. Our results support the hypothesis that the reduction in breast cancer incidence after 2002 is associated with reduced hormone therapy use, even though the reduction is relatively small compared to the incidence increase observed when mammography screening was introduced.

By using a Markov model, we found that calculated QALY’s associated with mammography screening vary considerably across models. Assuming that less than 50% of the breast cancer mortality reduction results in a reduction in all-cause mortality, most scenarios give negative QALY’s after 36 years of follow-up, indicating that mammography screening might do more harm than good.
References


66. Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av pasienter med brystkreft


Papers I – IV
Effect of mammography screening on surgical treatment for breast cancer in Norway: comparative analysis of cancer registry data

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Abstract

Objective To determine the effect of mammography screening on surgical treatment for breast cancer.

Design Comparative analysis of data from Norwegian cancer registry.

Setting Mammography screening, Norway (screening of women aged 50-69 was introduced sequentially from 1996 to 2004).

Participants 35 408 women aged 40-79 with invasive breast cancer or ductal carcinoma in situ treated surgically from 1993 to 2008.

Main outcome measures Rates of breast surgery (mastectomy plus breast conserving treatment) and rates of mastectomy for three age groups of women: 40-49, 50-69, and 70-79. Changes in rates from pre-screening period (1993-5) to introduction of screening phase (1996-2004) and then to screening period (2005-8) are presented as hazard ratios in invited and non-invited women.

Results The annual rate for breast surgery from the pre-screening period (1993-5) to screening period (2005-8) in Norway increased by 70% (hazard ratio 1.70, 95% confidence interval 1.62 to 1.78), from 180 to 305 per 100 000 women in the invited age group (50-69 years). In the younger, non-invited age group (40-49 years), however, the increase was only 8% (1.08, 1.00 to 1.16), from 133 to 144 per 100 000 women per year, whereas in the older, non-invited age group (70-79 years) the rate decreased by 8% (0.92, 0.86 to 1.00), from 227 to 214 per 100 000 women per year. The rates for mastectomy decreased similarly from the pre-screening period to screening period in invited and non-invited women. From the pre-screening period to the introduction phase of screening (1996-2004), however, the annual mastectomy rate in women aged 50-69 invited to screening increased by 9% (1.09, 1.03 to 1.14), from 156 to 167 per 100 000 women, and in the younger non-invited women declined by 17% (0.83, 0.78 to 0.90), from 109 to 91 per 100 000 women. In consequence, the mastectomy rate was 31% (1.31, 1.20 to 1.43) higher in the invited than in the non-invited younger age group.

Conclusions Mammography screening in Norway was associated with a noticeable increase in rates for breast cancer surgery in women aged 50-69 (the age group invited to screening) and also an increase in mastectomy rates. Although over-diagnosis is likely to have caused the initial increase in mastectomy rates and the overall increase in surgery rates in the age group screened, the more recent decline in mastectomy rates has affected all age groups and is likely to have resulted from changes in surgical policy.

Introduction

The objective of mammography screening is to improve the timing of breast cancer diagnosis, thereby reducing the number of associated deaths. A potential additional benefit often stated in invitations to screening and on websites supported by governmental screening institutions is that screening reduces the need for mastectomies and increases the potential for breast conserving treatment. In contrast, a Cochrane review of randomised trials on mammography reported a 31% increase in breast surgery (mastectomy plus breast conserving treatment) and 20% more mastectomies in women exposed to screening than in the control group.

In the Norwegian breast cancer screening programme, women aged 50-69 are invited to biennial screening. The programme started in 1996 in the four counties of Akershus, Oslo, Rogaland, and Hordaland and included 40% of the Norwegian population. From 1999 to 2004 the remaining 15 counties were successively included.

We used Norwegian population based data for the period 1993 to 2008 to assess how the stepwise introduction of mammography screening has affected surgical treatment for breast cancer—that is, the number of women undergoing mastectomy or breast surgery (mastectomy or breast conserving treatment) for invasive breast cancer or ductal carcinoma in situ.
We also determined how surgical treatment by disease stage at diagnosis has changed during the period.

Methods
From the Norwegian cancer registry we obtained aggregate data on incidence and surgical treatment of women aged 40-79 with ductal carcinoma in situ or invasive breast cancer. The data were stratified by stage and included the period 1993-2008. The cancer registry collects information on stage of disease at the time of diagnosis; stage 0 (ductal carcinoma in situ), stage I (invasive breast cancers of diameter ≤2.0 cm and no lymph node involvement or distant metastasis), stage II (invasive breast cancers of diameter ≤5.0 cm and 1-3 positive lymph nodes but no distant metastasis, or invasive breast cancers of diameter >2.0 cm with no positive lymph nodes or distant metastasis), and stage III and IV (tumours of diameter >5 cm and 1-3 positive lymph nodes, any tumour with direct extension to chest wall or skin, any tumour with >3 positive lymph nodes, or any tumour with distant metastasis).

Based on clinical notifications and pathology reports the cancer registry classifies each patient (identified by a unique personal identification number) to have undergone either breast conserving treatment or mastectomy or neither. If breast conserving treatment is followed by mastectomy within four months, the case is coded as a mastectomy. We requested data on the treatment of primary cases—that is, the first episode of breast cancer for each woman. Cases of invasive cancer are counted whether or not the women have had ductal carcinoma in situ previously. Cases of ductal carcinoma in situ are counted only when the lesions have no invasive component, the women have not had invasive breast cancer previously, and the ductal carcinoma in situ is not followed by invasive breast cancer within four months.

Statistical analysis
We calculated age specific incidence rates, rates of breast surgery (breast conserving treatment plus mastectomy), and rates of mastectomy for invasive breast cancer and ductal carcinoma in situ grouped together for three age groups of women: 40-49, 50-69, and 70-79 years. Depending on the start of mammography screening, we stratified women aged 50-69 into two geographical subgroups (those from the counties of Akershus, Oslo, Rogaland, and Hordaland and those from the remaining 15 Norwegian counties) and calculated age specific mastectomy rates. To determine how the introduction of screening affected breast cancer surgery by stage, we calculated age specific mastectomy and breast surgery rates for stages 0, I, II, and III/IV for women aged 50-69 years.

Based on the national availability of mammography screening, we divided the study period into pre-screening (1993-5), introduction of screening phase (1996-2004), and screening (2005-8). To compare changes in use of breast cancer surgery between periods with and without screening, we estimated changes in mastectomy and breast surgery rates in the three age groups from pre-screening to the introduction of screening phase and from pre-screening to screening. We used a Poisson regression model adjusting for age only. Changes in rates of surgery over time are presented as hazard ratios.

To determine changes in use of breast cancer surgery between screened and non-screened age groups, we used a Poisson model to compare the changes in mastectomy and breast surgery rates in women aged 50-69 versus women aged 40-49, adjusting for changes in age distribution and for an underlying linear trend.

Finally, we divided the data into two geographical subgroups, taking advantage of regional variations in the start of screening in Akershus, Oslo, Rogaland, and Hordaland counties and the remaining 15 counties. We compared mastectomy rates between women aged 50-69 and 40-49 in two periods; pre-screening (1993-5 in Akershus, Oslo, Rogaland, and Hordaland and 1993-8 in the other counties) and introduction of screening (1996-7 in Akershus, Oslo, Rogaland, and Hordaland and 1999-2004 in the other counties). In this analysis we used a Poisson model, adjusting for changes in age distribution and an underlying linear trend.

Results
In 2008 the Norwegian population included one million women aged 40-79. In the study period from 1993-2007 the cancer registry recorded 32 200 cases of invasive breast cancer and 3208 cases of ductal carcinoma in situ in this age group. Data on surgical treatment were available for 94% of the invasive cancer cases and 98% of the ductal carcinoma in situ cases (table 1). Figure 1 presents the age specific incidence rates and rates of breast surgery and mastectomy for ductal carcinoma in situ and invasive breast cancer for the age groups 40-49, 50-69, and 70-79 combined. From 1996 to 2002 mastectomy rates decreased gradually in the 40-49 and 70-79 age groups but temporarily increased in the 50-69 age group. The increase was evident only in Akershus, Oslo, Rogaland, and Hordaland where prevalence screening was carried out in 1996-7 (fig 2). In the remaining counties where screening started later, mastectomy rates were stable from 1996-2002 (fig 2). From 2002-3 mastectomy rates declined in all counties.

Figure 3 shows the national rates for surgery stratified by stage of disease for women aged 50-69. Rates of breast surgery for stages 0, I, and II all increased during the study period. Mastectomy rates for stage I noticeably increased temporarily in the first three years when screening was introduced, and decreased after 2002. The mastectomy rates for stage 0 and stage II increased from 1996 but decreased from about 2003. Rates of mastectomies and breast surgery for stage III and IV tumours did not change noticeably.

Table 2 shows the annual rates of mastectomy and breast surgery for all stages of invasive cancer and for ductal carcinoma in situ in the three periods. The estimated hazard ratios comparing the pre-screening period with the screening introduction phase and the pre-screening period with screening period are also presented. During the screening introduction phase, mastectomy rates increased by 9% in the 50-69 age group but decreased by 17% in the 40-49 age group and by 13% in the 70-79 age group. Using Poisson regression to compare the 1.09 relative change (invited women aged 50-69) with the expected 0.83 relative change (assuming a similar reduction between age groups 50-69 and 40-49) the relative risk of mastectomy in the 50-69 age group increases by 31% (hazard ratio 1.31, 95% confidence interval 1.20 to 1.43).

From the pre-screening period to screening period the mastectomy rates decreased by 30% in the 50-69 age group, 35% in the 40-49 age group, and 41% in the 70-79 age group (table 2). Using a Poisson model the decrease in mastectomy rates did not differ significantly between the 50-69 and 40-49 age groups (1.08, 0.97 to 1.21). The total number of breast operations from the pre-screening to screening period increased by 70% in the 50-69 age group compared with 8% in the 40-49 age group and decreased by 8% in the 70-79 age group.

In contrast with Akershus, Oslo, Rogaland, and Hordaland, the mastectomy rate in the remaining counties did not increase in

Statistical analysis
We calculated age specific incidence rates, rates of breast surgery (breast conserving treatment plus mastectomy), and rates of mastectomy for invasive breast cancer and ductal carcinoma in situ grouped together for three age groups of women: 40-49, 50-69, and 70-79 years. Depending on the start of mammography screening, we stratified women aged 50-69 into two geographical subgroups (those from the counties of Akershus, Oslo, Rogaland, and Hordaland and those from the remaining 15 Norwegian counties) and calculated age specific mastectomy rates. To determine how the introduction of screening affected breast cancer surgery by stage, we calculated age specific mastectomy and breast surgery rates for stages 0, I, II, and III/IV for women aged 50-69 years.

Based on the national availability of mammography screening, we divided the study period into pre-screening (1993-5), introduction of screening phase (1996-2004), and screening (2005-8). To compare changes in use of breast cancer surgery between periods with and without screening, we estimated changes in mastectomy and breast surgery rates in the three age groups from pre-screening to the introduction of screening phase and from pre-screening to screening. We used a Poisson regression model adjusting for age only. Changes in rates of surgery over time are presented as hazard ratios.

To determine changes in use of breast cancer surgery between screened and non-screened age groups, we used a Poisson model to compare the changes in mastectomy and breast surgery rates in women aged 50-69 versus women aged 40-49, adjusting for changes in age distribution and for an underlying linear trend.
the screening introduction phase (fig 2). Women aged 50-69 were stratified in Akershus, Oslo, Rogaland, and Hordaland and the remaining counties and the hazard ratio for mastectomy compared between the pre-screening period and the screening introduction phase. During the screening introduction phase in Akershus, Oslo, Rogaland, and Hordaland (1996-7) mastectomy rates increased by 48% (1.48, 1.23 to 1.78) in the 50-69 age group relative to the rates in the 40-49 age group. In the remaining counties, screening was introduced later and more gradually. During the introduction of screening in these counties (1999-2004) mastectomy rates increased by 21% (1.21, 1.09 to 1.34) in the 50-69 age group relative to the rates in the 40-49 age group.

Discussion

A potential benefit of mammography screening—a reduction in mastectomy rates and an increase in the use of less invasive surgery—was not corroborated by our results, which show that mastectomy rates in Norway have declined similarly in invited and non-invited age groups from the pre-screening period (1993-5) to the more recent screening period (2005-8). During the introduction of screening, mastectomy rates in invited women aged 50-69 increased by 9%. In contrast, during the same period the rates in non-invited women decreased by 17% in the 40-49 age group and by 13% in the 70-79 age group. This corresponds to a 31% increase in the relative risk of mastectomy in women invited to screening compared with the non-invited younger age group. Mastectomy rates noticeably increased in Akershus, Oslo, Rogaland, and Hordaland counties when screening started in 1996. Since the detection rate is higher during prevalence screening than in the subsequent screening rounds, more mastectomies would be expected in the prevalence screening round. In the remaining 15 Norwegian counties where screening was introduced later and more gradually in 1999-2004, the absolute number of mastectomies did not increase during the screening introduction phase; although in relative terms, the increase was 21% compared with the younger non-invited age group. The more modest change in mastectomy rates in the 15 counties in the screening introduction phase (smaller prevalence peak than in Akershus, Oslo, Rogaland, and Hordaland) can be explained by the more gradual introduction of the screening programme and the non-organised private screening activity before the screening programme started. In addition, during the observation period changes in surgical practice in Norway have reduced mastectomy rates in all age groups. As part of the mammography screening programme, specialist breast clinics with a focus on multidisciplinary teamwork between radiologists, pathologists, and surgeons were established. As a consequence, the numbers of Norwegian hospitals carrying out breast cancer surgery have declined, from around 60 to 20. It is likely that this has influenced the treatment of non-screened age groups as a spin-off effect.

The mastectomy rates for stages 0, I, and II increased in women aged 50-69 in the first years of the screening introduction phase. Rates decreased for all stages except III and IV from 2002-3, reflecting that changes in surgical practice affect both lymph node positive and negative invasive cancers with a diameter less than 5 cm, as well as ductal carcinoma in situ. Rates of breast surgery have increased especially for stages 0 and I, but also for stage II.

The risk of surgery for invasive breast cancer or ductal carcinoma in situ increased by 70% in the 50-69 age group in the screening period compared with pre-screening period. In contrast, the risk increased by 8% in non-invited women in the 40-49 age group. The introduction of the Norwegian mammography screening programme was associated with a more than 50% increase in the incidence of invasive breast cancer in women aged 50-69. In addition many cases of ductal carcinoma in situ are detected by screening, and ductal carcinoma in situ now constitutes 13% of breast cancer diagnoses in Norway in the screened age group. A recent systematic review of five screening programmes estimated that screening is associated with a 52% over-diagnosis of breast cancer, including cases of ductal carcinoma in situ, which would not have been identified clinically in the women’s remaining lifetimes.

Strengths and limitations of the study

We used population based data from the Norwegian cancer registry, which contains virtually all cancers diagnosed in Norway, with only 0.5% of the cases lacking information on stage. The information on type of surgical treatment is also nearly complete, with only 5% of cases lacking a surgery code, either because of missing data or because the patient did not have surgery.

The rates of attendance in the Norwegian mammography screening programme are high and stable: 75-77% in 2002-6. In Norway the rates for ductal carcinoma in situ increased from 9 to 40 per 100 000 women aged 50-69 from 1993 to 2008. In contrast the rates for ductal carcinoma in situ for women aged 40-49 and 70-79 have been essentially constant, indicating little screening activity outside the invited age group.

This study also has limitations. In addition to the stage and size of tumours, surgical treatment is influenced by several other factors, including patient, surgeon, and hospital factors. Since we used aggregated data, our options to adjust for factors other than the introduction of screening were limited. Geographical differences may have influenced the type of surgery chosen because of variation in surgical tradition and skills and because of the long travelling distances to radiation therapy units from some parts of Norway. By using the age group 40-49 as a control group, we limited potential bias from geographical differences because screen and non-screen detected cancers from an area are treated at the same breast clinics, and women aged 40-49 are generally expected to be offered the same treatment as women aged 50-69. Some cancers that currently are detected by screening in women aged 50-69 would in the absence of screening have been diagnosed after 69 years. This is expected to result in reduced incidence and surgery rates for women aged 70-79. But the decline in incidence and breast surgery rates in women aged 70-79 was small and can only compensate for a fraction of the increase in incidence and breast surgery rates in women invited to screening.

In a recent review, preoperative magnetic resonance imaging was associated with more radical surgery. Increased access to modern breast reconstruction after mastectomy may have a similar effect. In Norway, however, the use of preoperative magnetic resonance imaging and breast reconstruction after mastectomy were limited during the study period. In the United States an increase in the proportion of breast cancer cases treated by mastectomy has been reported in recent years, mainly explained by changes in patients’ attitudes and choices. Until 2008 this trend was not seen in data from Norway.

Comparison with other studies

Published data on how the introduction of mammography screening affects the type of surgery are limited. Similar trends in mastectomy rates were found in a study that compared surgery...
during 1994-9 in Northern Ireland (with screening) with that in the Republic of Ireland (without screening). 15 Studies from Italy have shown declining mastectomy rates in the screening period, 16 17 but control groups have been missing. A study from the United Kingdom reported increased mastectomy rates for ductal carcinoma in situ within the screening programme but did not report data for invasive breast cancer. 18 Recent data from Denmark show a large increase in mastectomies when screening first started that was not compensated for later on. 19

Conclusions

Mammography screening is associated with a noticeable increase in breast surgery rates. In contrast with what has been claimed in invitations to screening and on websites supported by numerous governmental screening institutions and cancer charities, screening does not lead to a reduction in mastectomy rates. When screening was introduced in Norway, mastectomy rates increased. In recent years, as a result of changes to surgical policy, mastectomy rates have declined for all age groups, but mostly for the non-screened age groups.

Contributors: PS acquired and analysed the data and wrote the initial draft of the manuscript. JM designed the study. ES provided expert clinical advice. PHZ designed the study and led the statistical analysis. All authors interpreted the data, contributed and commented on drafts of the article, and approved the final version. JM and PHZ are guarantors.

Funding: PS is supported by the South-Eastern Norway Regional Health Authority.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: No additional data available.


Accepted: 7 July 2011

Cite this as: BMJ 2011;343:d4692

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What is already known on this topic

Mammography screening increases overall rates of breast surgery
Women invited to mammography screening are informed that participation reduces their risk of having a mastectomy

What this study adds

Mammography screening is associated with an increase in mastectomy rates, especially when screening is in its introduction phase
Women should be informed that higher overall breast surgery rates in those invited to mammography screening partly result from higher mastectomy rates

Tables

Table 1 | Number of cases and surgical treatment of invasive breast cancer and ductal carcinoma in situ in Norwegian women aged 40-79, 1993 to 2008

<table>
<thead>
<tr>
<th></th>
<th></th>
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<td>899</td>
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<td>1</td>
<td>964 939</td>
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<td>104</td>
<td>150</td>
<td>208</td>
<td>14</td>
<td>1 017 298</td>
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</tbody>
</table>
Table 2 | Rates of breast surgery and mastectomies and changes in rates of both invasive breast cancer and ductal carcinoma in situ for women aged 40-49, 50-69, and 70-79 in Norway in relation to screening periods

<table>
<thead>
<tr>
<th>Outcome by age group</th>
<th>Rate per 100 000 women per year</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast surgery:</strong></td>
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<td></td>
</tr>
<tr>
<td>40-49</td>
<td>132.5</td>
<td>140.7</td>
</tr>
<tr>
<td>50-69*</td>
<td>179.7</td>
<td>298.1</td>
</tr>
<tr>
<td>70-79</td>
<td>226.9</td>
<td>225.4</td>
</tr>
<tr>
<td><strong>Mastectomy:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>109.5</td>
<td>90.9</td>
</tr>
<tr>
<td>50-69*</td>
<td>155.7</td>
<td>166.9</td>
</tr>
<tr>
<td>70-79</td>
<td>205.6</td>
<td>180.9</td>
</tr>
</tbody>
</table>

*Invited age group in screening programme.
Figures

Fig 1  Age specific mastectomy, breast surgery (mastectomy plus breast conserving treatment), and incidence rates in Norwegian women with invasive breast cancer or ductal carcinoma in situ according to age group (women aged 50-69 are invited to screening).

Fig 2  Mastectomy rates in Norwegian women aged 50-69 (age group invited to screening) with invasive breast cancer or ductal carcinoma in situ in Akershus, Oslo, Rogaland, and Hordaland counties (screening started in 1996) and remaining 15 counties (screening started 1999-2004).
Fig 3 Age specific rates of breast surgery (mastectomy plus breast conserving treatment) and mastectomy in Norwegian women aged 50-69 (age group invited to screening) stratified by stage.
Breast cancer incidence and menopausal hormone therapy in Norway from 2004 to 2009: a register-based cohort study

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Keywords
Breast cancer, hormone therapy, mammography and invasive lobular carcinoma

Abstract
In Norway, the breast cancer incidence increased by 50% in the 1990s, during a period with initiation of mammography screening as well as a fourfold increase in use of menopausal hormone therapy (HT). After 2002, the HT use has dropped substantially; however, the breast cancer incidence has declined only marginally. How much mammography screening contributed to the breast cancer incidence increase in the 1990s compared with HT use and specifically different types of HT use, has thus been discussed. Whether HT affects the incidence of subtypes of breast cancer differently has also been questioned. We have linked individual data from several national registries from 2004 to 2009 on 449,717 women aged 50–65 years. 4597 cases of invasive cancer and 681 cases of ductal carcinoma in situ (DCIS) were included in the analysis. We used Cox regression to estimate hazard ratio (HR) as a measure of the relative risk of breast cancer associated with use of HT. The HRs associated with prescriptions of HT for more than 1 year were 2.06 (1.90–2.24) for estrogen and progesterone combinations, 1.03 (0.85–1.25) for systemic estrogens, and 1.23 (1.01–1.51) for tibolone. Invasive lobular carcinoma was more strongly associated with use of estrogen and progesterone combinations, HR = 3.10 (2.51–3.81), than nonlobular carcinoma, HR = 1.94 (1.78–2.12). The corresponding value for DCIS was 1.61 (1.28–2.02). We estimated the population attributable fraction to 8.2%, corresponding to 90 breast cancer cases in 2006 indicating that HT use still caused a major number of breast cancer cases.

Introduction
The breast cancer incidence increased rapidly during the 1990’s [1], and several observational studies linked the increase to widespread use of menopausal hormone therapy (HT) [2–7]. After the publication of the randomized controlled Women’s Health Initiative trial in 2002 [8] and the large observational Million Women Study in 2003 [9], the use of HT has dropped substantially in Norway [10–12]. Norwegian observational studies have reported 58% [2] and 110% [3] increased risk of having breast cancer diagnosed for HT users. In Norway, the breast cancer incidence increased by 50% in the 1990s [13], during a period with a fourfold increase in HT use; however, the breast cancer incidence declined only marginally after 2002 [10–12]. The Norwegian breast cancer screening program (NBCSP) started in 1996 and covered whole of Norway from 2004 [14]. How much mammography screening contributed to the breast cancer incidence increase in the 1990s compared with HT use has thus been questioned [10, 12, 15].

Several studies have shown that HT use affects breast cancer risk differently for different histological subtypes, and in particular increases the risk of the second most common subtype of breast cancer, invasive lobular...
carcinoma [16–19]. Whether HT affects the incidence of ductal carcinoma in situ (DCIS), a possible precursor lesion of invasive breast cancer, has been questioned [20].

Here, we have linked individual data from several high-quality Norwegian registries and studied how breast cancer incidence is associated with both different types of HT use and duration of use. The study period begins in 2004, since individual data on prescription of HT are not available before 2004 and the NBCSP covered all Norwegian counties from 2004. We also present data stratified on histological subtypes.

**Material and Methods**

**Data**

As part of the evaluation of the NBCSP, funded by the Research Council of Norway, we received anonymized individual data from the nationwide Norwegian Cancer Registry, Statistics Norway, the Norwegian Prescription Database, and the Medical Birth Registry of Norway. We included all Norwegian women aged 50–65 years in 2006 in our analysis. Data from the Cancer Registry cover the period until December 31, 2009. All data files included a unique number for each individual woman which enabled us to merge the files. From the Cancer Registry, we used two different files. One consisted of information on mammography screening activity, including scheduled dates and whether or not each woman underwent screening. The second file from the Cancer Registry included information on all cases of breast cancer and DCIS, including detection date, histological tumor type, and detection mode (whether a cancer is detected through screening, detected between two screening rounds [interval cancer], detected in invited women who did not attend screening or detected in women who are not yet invited to screening). Data from Statistics Norway included information on death date, causes of death, and date of emigration. From the Medical Birth Registry, we received information on number of births. Data from the Prescription Database included information on all women who had prescriptions of estrogen preparation or combined estrogen progesterone preparations from 2004, including date of prescription, the name of the drug, the ATC-group, and the defined daily dose (DDD) prescribed (http://www.whocc.no/atc_ddd_methodology/purpose_of_the_atc_ddd_system/). DDD is an estimate on the average maintenance dose of a drug used per day (365 DDD correspond to 1 year use).

**Statistical analysis**

We used Cox regression to estimate hazard ratio (HR) as a measure of the relative risk of breast cancer associated with use of HT. Based on ATC codes and sales names, we stratified the HT into four different groups: estrogen and progesterone combinations (G03F), tibolone (G03CX), vaginal estrogens (estriol [G03CA04] and low dose vaginal estradiol [G03CA03]) and finally systemic estrogens without progesterone (G03C, except tibolone and low dose vaginal estrogens). Based on the number of prescribed DDD in 2004 and 2005, the women who were 50–65 years old in 2006 (born 1941–1956) were stratified into four different groups: women with no prescriptions, prescriptions of 1–180 DDD, 181–365 DDD, or more than 365 DDD. The event was defined as the time from January 1, 2006 to either an invasive breast cancer diagnosis or to a DCIS diagnosis. The follow-up period ended on 31.12.2009. We estimated HRs with 95% confidence intervals and adjusted for available risk factors such as age, number of childbirths, and whether or not the woman attended the Norwegian Breast Screening Program between 2004 and 2009. We excluded 84 cases of invasive breast cancer and four cases of DCIS from the analysis because they were detected before the woman got an invitation to screening. We did separate analysis for DCIS and invasive breast cancer and also stratified on histological tumor type, invasive lobular carcinoma, or nonlobular invasive carcinoma.

The population attributable fraction (PAF) is a measurement which describes the proportion of avoidable breast cancer cases if the HT use was eliminated. The PAF was calculated as \( P(\text{HR} - 1)/(1 + P(\text{HR} - 1)) \), where \( P \) is the proportion of the population using HT, and \( \text{HR} \) is the hazard rate for invasive breast cancer.

**Results**

The study population includes a total number of 449,717 women aged 50–65 years at the beginning of the study period in 2006. In the analysis, we included 4597 cases of invasive cancer and 681 cases of DCIS diagnosed in 2006–2009. By the end of the study period, 187 of these women had died of breast cancer. Eighty-three percent of the population attended one or more of the three screening rounds in 2004–2009. HT use is described in Table 1. In 2004–2005, 26.5% of the population had one or more prescriptions of HT. For estrogen and progesterone combinations, 14% of the population had one or more prescriptions, while 8.4% had prescriptions of more than 365 DDD.

Table 2 shows HRs of invasive breast cancer and DCIS associated with recorded risk factors; age, the number of childbirths, and whether or not the woman attends the mammography screening program.

The HRs of invasive breast cancer associated with different types of HT prescriptions and different duration of
Table 1. The number and percentages in parentheses of women aged 50–65 years in 2006 with prescriptions of different types of HT in DDD in 2004 and 2005.

<table>
<thead>
<tr>
<th>Prescription in DDD</th>
<th>Estrogen and progesterone combinations</th>
<th>Systemic estrogens</th>
<th>Tibolone</th>
<th>Low dose vaginal estrogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>386,657 (86.0)</td>
<td>430,782 (96.8)</td>
<td>443,996 (96.5)</td>
<td>416,364 (92.6)</td>
</tr>
<tr>
<td>1–180</td>
<td>13,653 (3.0)</td>
<td>4981 (1.1)</td>
<td>29,565 (6.6)</td>
<td></td>
</tr>
<tr>
<td>181–365</td>
<td>11,602 (2.6)</td>
<td>4228 (1.0)</td>
<td>3185 (0.7)</td>
<td>2935 (0.6)</td>
</tr>
<tr>
<td>&gt;365</td>
<td>37,805 (8.4)</td>
<td>9924 (2.2)</td>
<td>7555 (1.7)</td>
<td>853 (0.2)</td>
</tr>
</tbody>
</table>

Table 2. Hazard ratio of invasive breast cancer and DCIS associated with available risk factors; age, the number of childbirths, whether or not the woman attends the mammography screening program.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Invasive breast cancer</th>
<th>Ductal carcinoma in situ</th>
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</thead>
<tbody>
<tr>
<td>Invasive breast cancer</td>
<td>HR with 95% CI</td>
<td>Number</td>
</tr>
<tr>
<td>Age in 2006</td>
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<tr>
<td>50–53</td>
<td>1.50 (1.22–1.82)</td>
<td>1039</td>
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<tr>
<td>54–57</td>
<td>1.14 (1.04–1.24)</td>
<td>1101</td>
</tr>
<tr>
<td>58–61</td>
<td>1.34 (1.23–1.45)</td>
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<tr>
<td>62–65</td>
<td>1.53 (1.40–1.67)</td>
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<tr>
<td>Childbirth</td>
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<td>0</td>
<td>1.23 (1.01–1.51)</td>
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<tr>
<td>1–2</td>
<td>1.32 (1.06–1.66)</td>
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<tr>
<td>&gt;3</td>
<td>1.50 (1.28–1.72)</td>
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<tr>
<td>Attending the screening program in 2004–2009</td>
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<tr>
<td>No</td>
<td>0.93 (0.75–1.16)</td>
<td>623</td>
</tr>
<tr>
<td>Yes</td>
<td>1.15 (1.05–1.24)</td>
<td>3890</td>
</tr>
</tbody>
</table>

HT use in 2004–2005 are presented in Table 3. For estrogen and progesterone combinations, the adjusted HR associated with prescriptions of more than 365 DDD, corresponding to more than 1 year of use, is 2.06 (1.90–2.24). More short-term users, between half a year and 1 year of use, have a slightly increased risk, HR is 1.24 (1.04–1.47). For women with less than half a year of use of estrogen and progesterone combinations, the breast cancer risk is not increased. For users of systemic estrogens, the breast cancer risk is not increased, independent of the duration of use. Tibolone users have a slightly increased risk for breast cancer, HR is 1.23 (1.01–1.51) for users more than 1 year.

Table 4 shows the risk of DCIS, invasive lobular carcinoma, and invasive nonlobular carcinoma associated with different duration of use of estrogen and progesterone combinations. For women with prescriptions of more than 365 DDD, corresponding to use for more than 1 year, the HR for lobular carcinoma is 3.10 (2.51–3.81) and 1.94 (1.78–2.12) for nonlobular carcinoma. The corresponding value for DCIS is 1.61 (1.28–2.02). For short-term users, less than 1 year, only the nonlobular carcinomas have a slightly increases risk.

Based on the calculated HR of 2.06 in table 3 for long-term users of estrogen and progesterone combination and the proportion of long-term users of 8.4%, we estimated the PAF to 8.2%, corresponding to around 90 breast cancer cases in 2006.

**Discussion**

In this study, we observe a 106% increased risk of breast cancer associated with long-term prescription (>1 year) of estrogen and progesterone combinations. The breast cancer risk is not increased by short term prescription (<½ year). For tibolone, we found a 23% increase in the breast cancer risk for long-term prescription. Our estimates correspond with the estimates in the Million Women Study [9] for tibolone and for estrogen and progesterone combinations, but not for estrogen only HT, since we did not find any association between the prescription of estrogen-only HT and breast cancer risk. The Million Women Study [9] observed a 30% increased risk, while another study from Norway found an 80% increased risk for estrogen only HT users [3]. A second Norwegian study did not stratify on the type of HT use, and the risk of estrogen–progesterone combinations could not be separated from estrogen only [2]. The PAF was estimated to 8.2% in the age group 50–65 years in 2006, which suggests that even after the decline in HT use after year 2002, 90 cases of breast cancer were still caused by HT use in 2006. Jørgensen and Gøtzsche have estimated 52% overdiagnosis of breast cancer in populations offered organized mammography screening [1]. In 2006, there were 1142 cases of invasive breast cancer in women aged 50–65 years in Norway, corresponding to almost 400 overdiagnosed women, suggesting that there were four times more overdiagnosed women than breast cancer cases caused by HT use in 2006. These results combined with only a marginally decline in breast cancer in Norway after 2002, support the theory that breast cancer increase in Norway in the 1990-ties was mainly caused by mammography screening and overdiagnosis.

As already published by several authors [10, 16–19], we observe that the risk of the second most common type of breast cancer, invasive lobular carcinoma is more strongly associated with HT use than the risk of other nonlobular...
invasive subtypes; HR = 3.10 (2.51–3.81) versus 1.94 (1.78–2.12). For DCIS, published data have varied. Data from the WHI trial showed a 23%, nonsignificant increased DCIS risk for users of estrogen and progesterone combinations compared with placebo, while observational data from the same study showed a 65% increased risk for users compared with nonusers [20]. Our data give support to these data and suggests that the risk of DCIS is associated with long term use of estrogen and progesterone combinations; HR = 1.61 (1.28–2.02).

We also tried to calculate how breast cancer death was affected by HT use, but since there were only 187 breast cancer deaths in the follow-up period, the data were not able to answer this question.

A strength of this study is the prospective study design: First, we have used individual data from national registries. Second, data on HT use are not affected by the possibility of recall bias as when using questionnaires. Third, we have also included data on whether or not the women attend the Norwegian Breast Screening Program. Due to overdiagnosis, screening increases the risk of both invasive breast cancer and DCIS [1]. If HT users attended the screening program differently from non HT users, adjustment for mammography activity would be important. We observe a HR of 1.15 for invasive breast cancer and 3.32 for DCIS for attendees versus nonattendees in 2004.

Table 3. The HR of invasive breast cancer associated with different type of HT prescription and different duration of use in 2004–2005.

<table>
<thead>
<tr>
<th>Prescription in DDD</th>
<th>Estrogen and progesterone combinations</th>
<th>Systemic estrogens</th>
<th>Tibolone</th>
<th>Vaginal estrogens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>HR</td>
<td>Number</td>
<td>HR</td>
</tr>
<tr>
<td>0</td>
<td>3584</td>
<td>1</td>
<td>4398</td>
<td>1</td>
</tr>
<tr>
<td>1–180</td>
<td>134</td>
<td>1.07 (0.90–1.27)</td>
<td>41</td>
<td>0.86 (0.63–1.17)</td>
</tr>
<tr>
<td>181–365</td>
<td>135</td>
<td>1.24 (1.04–1.47)</td>
<td>52</td>
<td>1.12 (0.85–1.48)</td>
</tr>
<tr>
<td>&gt;365</td>
<td>744</td>
<td>2.06 (1.90–2.24)</td>
<td>106</td>
<td>1.03 (0.85–1.25)</td>
</tr>
</tbody>
</table>

All values are adjusted for age, number of child births, whether or not the women attended the screening program in 2004–2009 and whether or not a nonuser in 2004–2005 started with HT use in 2006–2009.

Table 4. The HR for invasive lobular carcinoma, invasive nonlobular carcinoma and DCIS associated with different duration of use of estrogen and progesterone combinations in 2004–2005.

<table>
<thead>
<tr>
<th>Prescription in DDD</th>
<th>Invasive lobular carcinoma</th>
<th>Invasive nonlobular carcinoma</th>
<th>Ductal carcinoma in situ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>HR</td>
<td>Number</td>
</tr>
<tr>
<td>0</td>
<td>391</td>
<td>1</td>
<td>3193</td>
</tr>
<tr>
<td>1–180</td>
<td>16</td>
<td>1.17 (0.71–1.93)</td>
<td>118</td>
</tr>
<tr>
<td>180–365</td>
<td>12</td>
<td>1.01 (0.57–1.80)</td>
<td>123</td>
</tr>
<tr>
<td>&gt;365</td>
<td>120</td>
<td>3.10 (2.51–3.81)</td>
<td>624</td>
</tr>
</tbody>
</table>

All values are adjusted for age, number of child births, whether or not the women attended the screening program in 2004–2009 and whether or not a nonuser in 2004–2005 started with HT use in 2006–2009.

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intervention was stopped [21]. Since breast cancer cases in our analysis are counted from 2006, the nonusers have had no prescription of HT at least 2 years preceding a breast cancer diagnosis. Consequently, our calculations should not be strongly influenced by lacking possibility to separate past from never users.

Third, the information on HT use is based on prescriptions. We do not have information on compliance, but we would assume that women who have more than one prescription with many DDD prescribed, do use the drug more regularly than those having only one prescription with a lower DDD prescribed.

In conclusion, we observe a 106% increased risk of breast cancer associated with long-term prescription (>1 year) of estrogen and progesterone combinations, but we did not find any association between prescription of estrogen-only HT and breast cancer risk. The second most common subtype of breast cancer, invasive lobular carcinoma was more strongly associated with HT use than other subtypes. The risk of the possible precursor lesion, DCIS, was also increased for HT users. The PAF was estimated to 8.2%, corresponding to 90 breast cancer cases in 2006, indicating that even after substantial drop in HT use, still a major number of breast cancer cases were caused by HT-use.

Acknowledgments

Pal Suhrke has been supported by the South-Eastern Norway Regional Health Authority. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The study was also supported by the Research Council of Norway as part of the evaluation of the NBCSP.

Disclaimer

The study has used data from the Cancer Registry of Norway. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred.

Conflict of Interest

None declared.

References


