Changing socioeconomic patterns of breast cancer incidence, mortality and survival in Norway

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PhD Thesis

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My PhD journey began when I was nine months pregnant with my first child. Just days before I gave birth, I submitted my research proposal. Throughout the Phd period, I produced three research papers and three children. Little did I know when I started, how challenging it would be for me to combine motherhood with research. Most of my analyses were conducted with baby brain. Add two broken arms and one broken ankle to the mix and time became time * π.

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Cassia Trewin-Nybråten

Oslo, January 2022

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ABBREVIATIONS

Abbreviation	Definition
ASR	Age-Standardised Incidence Rate
CDR	Cause of Death Registry
CI	Confidence Interval
CPR	Central Population Registry
CRN	Cancer Registry of Norway
EMRR	Excess Mortality Rate Ratio
ER	Estrogen Receptor
GDPR	European General Data Protection Regulation
HER2	Human Epidermal growth factor Receptor 2
HUNT	Trøndelag Health Study (Helseundersøkelsen i Trøndelag)
ICD	International Classification of Disease
MRI	Magnetic Resonance Imaging
NED	National Education Database
NOK	Norwegian Krone
NOWAC	Norwegian Women and Cancer cohort study
PR	Progesterone Receptor
Q	Quintile
RD	Rate Difference
RII	Relative Index of Inequality
RR	Rate Ratio
RS	Relative Survival
RTP	Register for Personal Tax Payers
SEER	Surveillance, Epidemiology, and End Results Program
SES	Socioeconomic Status
SII	Slope Index of Inequality
TNM	T=Tumour size, N=lymph Node metastasis, M=distant Metastasis
WHO	World Health Organisation
WSP	World Standard Population

DEFINITIONS

Term	Definition
Young women	Women aged below 50 years.
Screening-aged women	Women in the target mammography screening age in Norway, 50 to 69 years.
Older women	Women aged 70 years and over.
Breast cancer incidence	Number of new breast cancer cases diagnosed within a specific population and period.
Breast cancer mortality	Number of new breast cancer deaths within a specific population and period.
Observed survival	Proportion of breast cancer patients who survive to a given time after diagnosis.
Expected survival	Proportion of the cancer-free population expected to survive to a given age and calendar year.
Relative survival	Ratio of the observed and expected survival of a population group.
Mammography screening	Organised mammograms (x-rays of the breast) on a healthy symptom-free population, with the aim to reduce breast cancer mortality by detecting breast cancers at an early stage of disease when prognosis is better.
Lead-time bias	A superfluous increase in survival time due to bringing the date of diagnosis forwards without altering the date of death. For example, with early pre-symptomatic detection through mammography screening.
Length-time bias	A superfluous increase in survival time due to increased detection through mammography screening of slow growing tumours with a longer pre-symptomatic phase that also have less capacity to be fatal.
Observed mortality	Observed mortality rate, for example among breast cancer patients
Expected Mortality	Mortality rate in a population group with a given demographic (age, sex) and calendar year.

Excess mortality rate	Difference between the observed mortality of breast cancer patients and expected mortality rate for women of the same age and year in the population.
Excess mortality rate ratio	Ratio of excess mortality rates between two groups.
Cumulative net survival	The probability of surviving in a hypothetical world where breast cancer is the only possible cause of death.
Rate difference	Absolute rate difference between two groups.
Rate ratio	Relative rate difference between two groups.
Slope index of inequality	Measure of absolute inequality between the highest and lowest ranked individuals in the population, accounting for the relative size of groups. Similar to a rate difference.
Relative index of inequality	Measure of relative inequality between the highest and lowest ranked individuals in the population, accounting for the relative size of groups. Similar to a rate ratio.
Age-standardised rates	Hypothetical rates that are weighted to another age distribution than the one in the observed data.
World standard population	An artificial population proposed by Segi (1) and modified by Doll (2) for the purpose of estimating comparable disease rates across countries with respect to age.

THESIS SUMMARY

Breast cancer is the most diagnosed cancer and leading cause of cancer death in females. Worldwide, there were around 1.7 million new cases and 530,000 breast cancer deaths in 2016. In Norway, 3,424 women were diagnosed and 591 died from breast cancer in 2020. Over the past decades, incidence has risen but survival has improved, so breast cancer mortality has fallen. A high socioeconomic status (SES) has traditionally been associated with higher incidence and mortality, but better survival from breast cancer. Since the new millennium, socioeconomic patterns for breast cancer incidence and mortality seem to be changing. To better understand these changing patterns, this thesis aimed to describe socioeconomic differences over time in incidence, stage-specific incidence, stage-specific survival, and mortality from breast cancer using individually-linked Norwegian registry data.

In the first study, we used education level as a measure of SES. We studied educational differences in breast cancer incidence and mortality among over 2 million women aged 35 years and older during 1971 to 2009. Breast cancer incidence increased over time in all education groups, but most rapidly for lower educated women. Breast cancer mortality declined from the mid-1990s in all education groups, but most rapidly for higher educated women. For younger women, aged 35-49 years, the education gradient for breast cancer mortality reversed, and breast cancer mortality rates became lowest for higher educated young women during 2000-2009. For screening-aged women, 50-69 years, breast cancer mortality no longer varied by education level, whereas for older women, 70 years and over, breast cancer mortality was still higher for higher educated women during 2000-2009.

In the second study, we compared stage-specific breast cancer incidence by education and income for 1.1 million women aged 30-48 years during 2000 to 2015. We aimed to understand

whether the reversal of the socioeconomic gradient for breast cancer mortality in young women after year 2000 was related to stage at diagnosis. Our hypothesis was that young women with a high SES were diagnosed at an earlier stage of disease, and therefore had a better prognosis. We found some indication of earlier detection of breast cancer for high SES women, but high SES women had the highest absolute rates of breast cancer with regional spread, which was the largest group with respect to number of cases and deaths. We therefore found only partial support for our hypothesis that earlier detection explains the lower mortality from breast cancer after year 2000 for young women with high SES.

In the third study, we assessed socioeconomic differences in stage-specific survival in 7,501 young women diagnosed with breast cancer at ages 30-48 years during 2000-2015. Very few deaths occurred among women with localized tumours, and survival from localized breast cancer was high in all education and income groups. On the other hand, survival from non-localized breast cancer with regional or distant spread improved markedly over time for young patients with high education or income level, but not at all for patients with low education and low income. Improved survival from advanced breast cancer most likely explains the lower breast cancer mortality for high versus low SES young women in Norway.

Since the new millennium, low SES women have been losing their breast cancer advantage to high SES women. Breast cancer incidence is increasing more rapidly and breast cancer mortality declining more gradually for women with low compared to high SES in Norway. Young women with a low SES are still less often diagnosed with breast cancer but now die more often from breast cancer than young women with high SES. Even in a country with universal health care, socioeconomic factors such as education and income level, seem to play a role for breast cancer outcomes.

NORWEGIAN SUMMARY

Brystkreft er den hyppigste kreftformen og den viktigste årsaken til kreftdød hos kvinner i Norge. På verdensbasis var det anslagsvis 1,7 millioner nye tilfeller og 530,000 dødsfall av brystkreft i 2016. I 2020 fikk 3,424 kvinner en ny brystkreftdiagnose, og det ble registrert 591 dødsfall av brystkreft i Norge. I løpet av de siste tiårene har forekomsten vært økende, men overlevelsen er blitt bedre, og dødeligheten av brystkreft har falt. Høy sosioøkonomisk status (SES) har tradisjonelt sett vært forbundet med høyere forekomst og dødelighet av brystkreft, men kvinner med høy SES har hatt høyere overlevelse. Dette mønstret ser imidlertid ut til å ha endret seg de siste tiårene. Målet med dette prosjektet var å beskrive sosioøkonomiske forskjeller over tid i forekomst, stadiumsspesifikk forekomst, stadiumsspesifikk overlevelse og dødelighet av brystkreft blant kvinner i Norge.

I den første delen av dette prosjektet studerte vi utdanningsforskjeller i brystkreftforekomst og brystkreftdødelighet blant mer enn 2 millioner kvinner i alderen 35 år og eldre i perioden 1971-2009. Brystkreftforekomsten økte over tid i alle utdanningsgrupper, men mest for lavt utdannede kvinner. Brystkreftdødeligheten falt fra midten av 1990-tallet i alle utdanningsgrupper, men mest for høyt utdannede kvinner. For kvinner i alderen 35-49 år, snudde utdanningsgradienten, og etter år 2000 ble dødeligheten av brystkreft lavest for høyt utdannede kvinner i denne aldersgruppen. For kvinner i screeningalder, 50-69 år, har det etter år 2000 ikke vært forskjeller i dødelighet på tvers av utdanningsgruppene. For eldre kvinner, 70 år og over, forble dødeligheten av brystkreft signifikant høyere for høyt versus lavt utdannede kvinner.

I den andre delen av dette prosjektet, sammenlignet vi stadiumsspesifikk brystkreftforekomst etter utdanning og inntekt blant 1,1 millioner kvinner i alderen 30-48 år i perioden 2000-2015.

Målet var å se om endringen i den sosioøkonomiske gradienten for dødelighet av brystkreft blant unge kvinner kunne ha sammenheng med stadium ved diagnose. Hypotesen var at unge kvinner med høy SES fikk diagnosen i et tidligere stadium, og derfor hadde en bedre prognose. Kvinner med høy SES hadde noe høyere forekomst av svulster med lavt stadium, men hadde absolutt høyest forekomst av brystkreft med regional spredning, og denne gruppen utgjorde den største både med hensyn til nye tilfeller og dødsfall. Vi fant derfor kun en delvis støtte til hypotesen om at tidlig diagnostikk kunne forklare lavest dødelighet av brystkreft, etter år 2000, blant unge kvinner med høy SES.

I den tredje delen av dette prosjektet, så vi på utdanning- og inntektsforskjeller i stadiumsspesifikk overlevelse hos 7,501 kvinner diagnostisert med brystkreft i alderen 30-48 år i perioden 2000-2015. Overlevelsen etter lokalisert brystkreft var svært høyt i alle SES gruppene. Overlevelsen fra brystkreft med regional- eller fjernspredning ble markant forbedret over tid for unge kvinner med høy utdanning og/eller inntekt, men ikke for kvinner med både lav utdanning og lav inntekt. Forbedret overlevelse fra avansert brystkreft forklarer mest sannsynlig nedgangen i brystkreftdødeligheten over tid for unge kvinner med høy SES i Norge.

Etter år 2000 har kvinner med lav SES hatt dårligere utvikling i brystkreftforekomst, -overlevelse, og -dødelighet enn kvinner med høy SES. Forekomsten av brystkreft øker raskere og brystkreftdødeligheten avtar mer gradvis for kvinner med lav sammenlignet med høy SES i Norge. Unge kvinner med lav SES har fortsatt mindre sannsynlighet for å bli diagnostisert med brystkreft, men har høyere risiko for å dø av brystkreft enn unge kvinner med høy SES. Selv i et land med universell tilgang på helsetjenester, ser sosioøkonomiske faktorer, som utdanning og inntekt, ut til å ha betydning både for forekomst og dødelighet av brystkreft.

1 INTRODUCTION

1.1 Breast cancer

Breast cancer is the most diagnosed cancer and the leading cause of cancer death in females worldwide (3, 4). In 2016, there was an estimated 1.7 million new cases and 530,000 breast cancer deaths in 195 countries (4). The lifetime risk of developing breast cancer is around 1 in 20 globally, and 1 in 10 in socioeconomically developed countries such as Norway (4). Compared to other cancer types, the probability of surviving breast cancer is high (5). Consequently, the disease burden is also high (6) because women with breast cancer may live for many years with reduced life-quality after treatment.

Globally, breast cancer incidence has increased over the past decades (7). At the same time, survival from breast cancer has also increased (5). Breast cancer mortality rates were steady or increasing for many decades but started declining in the 1990s in many countries, including Norway (figure 1) (8, 9).

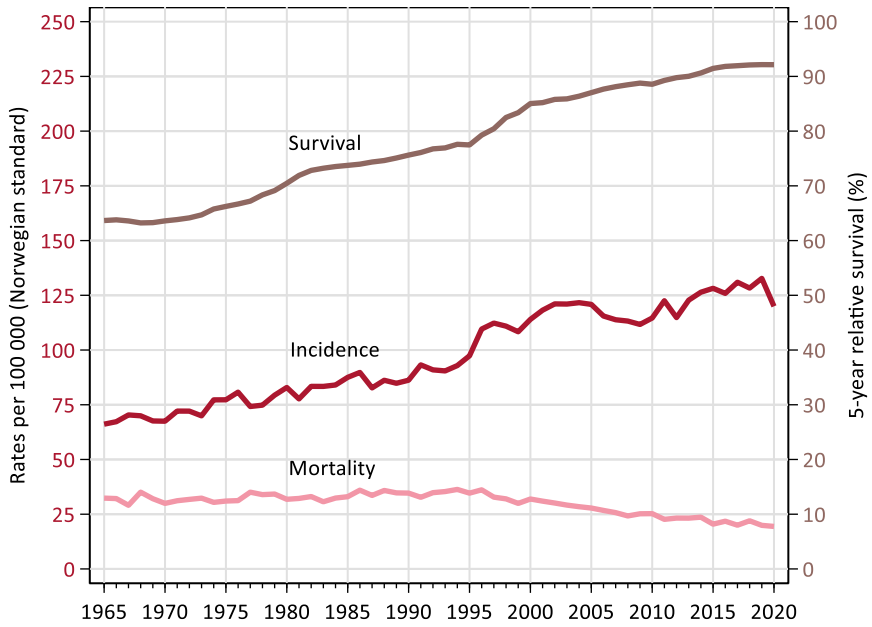

Figure 1: *Breast cancer incidence, mortality, and five-year relative survival in Norway for women of all ages, 1965-2020.*[1]

[1] Figure adapted with permission from the Cancer Registry of Norway. Cancer in Norway 2020 – Cancer incidence, mortality, survival, and prevalence in Norway. Oslo: Cancer Registry of Norway, 2021.

1.1.1 Incidence, survival, and mortality

Incidence, survival and mortality are key epidemiological measures of disease burden (10). Incidence measures disease risk, whereas survival and mortality measure outcome. Breast cancer incidence and mortality rates count the number of new cases and deaths of breast cancer in the population. Survival measures the probability that breast cancer patients are still alive at certain time points after diagnosis, often one or five years. Survival can be estimated by the case-fatality rate of patients, or more commonly with relative survival methods that compare the observed all-cause mortality of patients to the expected all-cause mortality of a comparable group in the population.

Breast cancer incidence is influenced by underlying risk, detection, and completeness of reporting of breast cancer cases. Underlying risk increases with older age, reproductive factors such as early menarche, late menopause, high age at first birth and low parity (11-13), use of postmenopausal hormone therapy (14-16), alcohol consumption (17, 18), overweight (post-menopause) (19, 20), physical inactivity (21, 22), and presence of genetic variants such as the high-risk BRCA1/2 gene mutations (23). Detection of breast cancer increases with increased symptom awareness, presence of organised mammography screening programmes and increased use of diagnostic magnetic resonance imaging (MRI), for example for young women with increased genetic or familial risk (23, 24).

Breast cancer mortality rates are determined by incidence rates and survival, as well as completeness of registration of breast cancer deaths. Factors influencing the probability of surviving breast cancer include stage of detection, tumour characteristics, treatment, age and comorbidity (25-27).

1.1.2 Mammography screening

Mammography screening aims to reduce breast cancer mortality by detecting breast cancer at an earlier pre-symptomatic stage of disease when treatment is more effective. Screening participants are more likely to be diagnosed with early-stage breast cancer and less likely to be diagnosed with late-stage breast cancer than invited non-participants (28). Reviews of the overall benefits and harms of screening point towards sufficient evidence for a net benefit of screening for women aged 50-69 years and limited evidence for women aged 40-49 and 70-74 years (29-32). Most developed countries offer biennial screening to women aged 50-69 years. Some countries, such as Sweden and the United States, start younger from 40-45 years and continue up to 74 years (29).

In Norway, biennial screening was introduced in four pilot counties (Akershus, Oslo, Rogaland, Hordaland) during 1996-1999, including Norway's largest cities and covering around 40 % of women aged 50-69 years in Norway. The screening programme, known as BreastScreen Norway, was further implemented county-wise from 2000, and became nationwide in 2005 (33). Throughout the first 20 years of the program, 84 % of invited women attended at least once. Average attendance per round was 75 % of invited women (34). Concurrent with the screening program rollout, multidisciplinary breast centres were established, and breast surgery was centralised from around 50 to 20 hospitals (33). Improved management of breast cancer has probably also contributed to reduced breast cancer mortality since introduction of the mammography screening programme (35).

Disentangling the independent effects of screening and treatment on mortality from breast cancer can be challenging. Estimates of the reduction in breast cancer mortality due to screening vary, but studies with long follow-up that utilise all available data suggest around 20-30 %

mortality reduction for women invited to screening (34, 36, 37) and around 40 % reduction for screening participants (38). Two studies that found only around 10 % mortality reduction due to screening were limited by short follow-up (39, 40). Reduced breast cancer mortality over time is likely due to earlier detection through screening as well as treatment advancements, and not one factor alone (34, 35, 41).

1.1.2.1 Overdiagnosis due to screening

Some breast cancers grow very slowly. Over-diagnosed cases are those that would not have been detected during a woman's lifetime unless she had undergone screening and had the cancer detected. Currently, it is not possible to identify which breast cancers will continue to grow slowly, and which will progress to advanced disease and become fatal. Therefore, all women diagnosed with breast cancer are offered treatment. Appropriate methods to estimate overdiagnosis are highly debated (31) and estimates vary widely from 0 to 50 % (32, 33). A review by the Euroscreen Working group concluded that overdiagnosis is likely to be in the range of 1-10 % (31).

1.1.2.2 Lead-time bias and length-time bias

While a positive effect of screening is to delay or avoid death by detecting breast cancer at a less serious stage of disease, early detection of breast cancer through screening also brings forward the date of diagnosis, irrespective of whether the date of death is delayed. This superfluous increase in survival time is known as lead-time bias (42). It can be thought of as the time interval between when a breast cancer can be detected by screening and when a breast cancer can be detected symptomatically. Another type of bias due to screening is length-time bias. Slow growing tumours are more likely to be detected with screening than without

screening. When slow growing tumours make up a higher proportion of all detected tumours, average survival time will be longer. This is known as length-time bias (42).

Lead-time bias and length-time bias not only increase time from diagnosis to death, but also increase the proportion of women still alive at certain times after diagnosis. The commonly used one- and five-year survival estimates will therefore be higher in populations with organised screening than in populations without screening (43). This is why breast cancer mortality, rather than survival, is used to evaluate breast cancer screening programmes.

1.1.3 Detection outside of screening

For women not invited to organised screening, detection of breast cancer is dependent on women recognising symptoms and seeking help. They must attend their general practitioners for clinical examination and referral to diagnostic testing. Young women with increased genetic or familial risk of breast cancer may be offered regular MRI scans from 25 years of age if they have a known breast cancer gene mutation, or biannual mammograms from 40 years of age if they have a family history of breast cancer (24).

Younger or older women outside the target screening age may also screen themselves opportunistically in the absence of symptoms. Unfortunately, we do not have any data on how many women screen themselves privately in Norway. Norwegian authorities discourage private mammography use through legislation to reduce unnecessary radiation of women through private mammography. A clinical referral is therefore required for mammography outside of the national screening programme.[2]

[2] Radiation protection regulation § 39, 2010. https://lovdata.no/dokument/SFO/forskrift/2010-10-29-1380

Figure 2 shows the reason for initial diagnostic testing from clinical reports sent by the hospitals to the Cancer Registry of Norway for women diagnosed with breast cancer during 2016-2020. For younger (< 50 years) and older (≥ 70 years) women, symptoms were the primary reason for first evaluation, whereas mammography screening was the first contact for over half of screening-aged women (50-69 years) diagnosed with breast cancer during 2016-2020. Private screening was the first contact point for just 2 % of young women, 2 % of screening-aged women, and 4 % of older women, but 8 % of older women diagnosed with TNM stage I tumours.

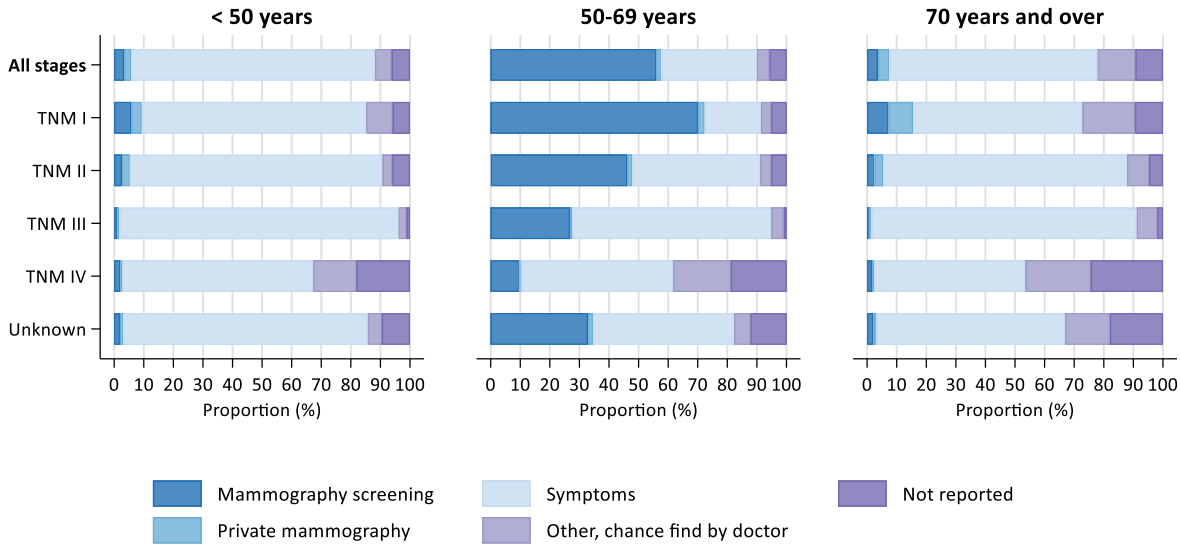

Figure 2: *Reason for initial testing of women diagnosed with invasive breast cancer, by age and stage at diagnosis in Norway, 2016-2020 (N = 17,542).*[3]

1.1.4 Stage at diagnosis

Breast cancer stage at diagnosis is strongly related to extent of disease burden and mortality. Tumours detected at an early disease stage have very good prognosis, whereas those detected later in the disease process require more aggressive treatment and have poorer outcome. Stage

[3] Figure data from the Norwegian Breast Cancer Registry, Cancer Registry of Norway. Data accessed 18.1.2022

at diagnosis can be classified according to tumour size (T), the extent of lymph node spread (N) and metastasis to distant organs (M), the so-called TNM classification system (44). Many cancer registries do not have access to such detailed information on TNM stage, and instead use three broader groups, localized, regional and distant stage, defined by the Surveillance, Epidemiology and End Results Program (SEER) [4]. This thesis had access to the SEER summary stage based on pathological and clinical reports. In brief, localized stage (TNM stage I) is tumours with no disease spread outside the breast; regional stage (TNM stage II-III) is large tumours or tumours with infiltration to the skin or chest wall or with metastasis to regional lymph nodes; and distant stage (TNM stage IV) is tumours with metastasis to other organs (45). Table 1 shows the distribution of breast cancer cases by TNM stage and age in Norway during 2016-2020.

Table 1: *Invasive breast cancer cases, by TNM stage and age at diagnosis in Norway, 2016-2020 (N = 17,542).*[5]

TNM stage	< 50 years		50-69 years		70 years and over	
	Screening age					
	Cases	%	Cases	%	Cases	%
All stages	3,508	100	8,954	100	5,080	100
I	1,159	33.0	4,983	55.7	1,598	31.5
II	1,216	34.7	2,441	27.3	1,716	33.8
III	525	15.0	683	7.6	598	11.8
IV	144	4.1	303	3.4	308	6.1
Unknown	464	13.2	544	6.1	860	16.9

Over the past decades, incidence of localized and regional stage breast cancer has increased, while incidence of distant stage breast cancer has remained steady in Norway (45). The greatest

[4] Surveillance, Epidemiology, and End Results Program, Summary Stage Manual 2000. https://seer.cancer.gov/tools/ssm/

[5] Data from the Norwegian Breast Cancer Registry, Cancer Registry of Norway. Data accessed 18.1.2022.

increase in incidence has been for localized stage among women aged 50-69 years during in the period when the national screening programme was implemented (1996-2004). Survival has improved over time at all breast cancer stages (45, 46).

Figure 3 shows stage-specific incidence and survival trends for women of all ages in Norway. Part of the decline in stage II incidence and increase in stage III incidence in 2011-2015 was a change in coding practice that led to a stage migration from stage II to III (45). Further, part of the increase in incidence of unknown stage in 2016-2020 was due to stricter rules for clinical notification of M status, leading to a stage migration from stage I to unknown stage.

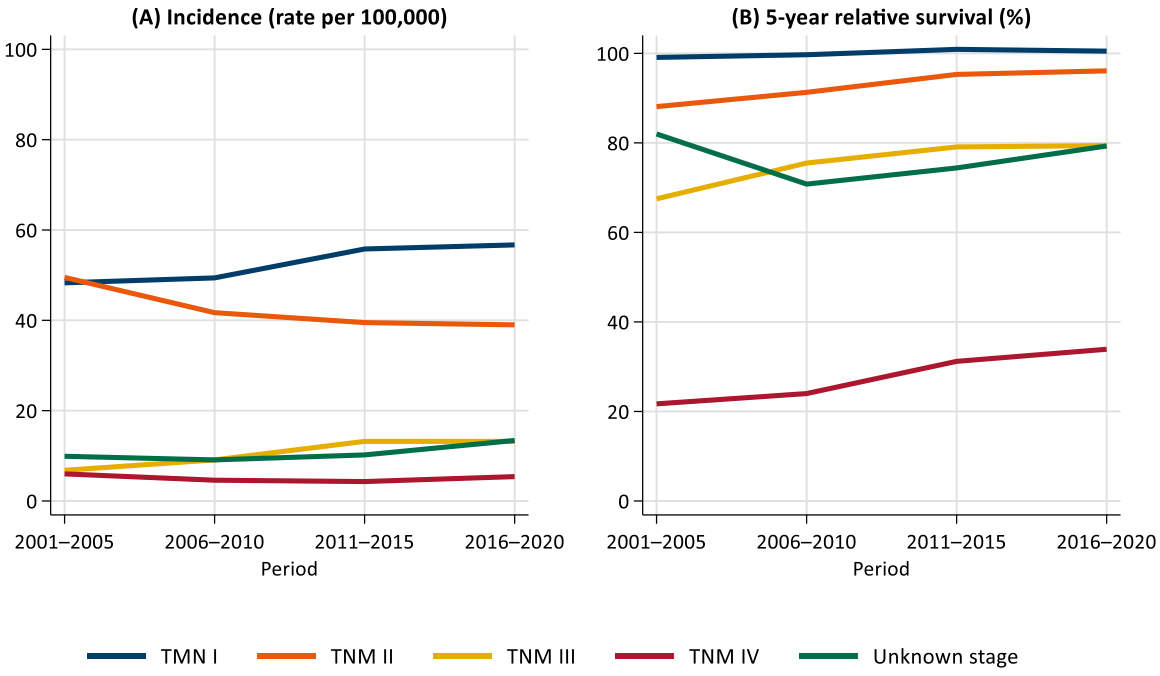

Figure 3: (A) *Age-standardised stage-specific breast cancer incidence (Norwegian standard)*[6]*, and* ***(B)*** *stage-specific relative survival of breast cancer patients*[7] *in five-year periods for women of all ages in Norway, 2001-2020.*

[6] Figure data from the Cancer Registry of Norway. Incidence statistics bank. https://sb.kreftregisteret.no/insidens/?lang=en. Data accessed 6.1.2022.
[7] Figure data from the Cancer Registry of Norway. Cancer in Norway 2020 – Cancer incidence, mortality, survival and prevalence in Norway. Oslo: Cancer Registry of Norway, 2021.

1.1.5 Subtypes of breast cancer

Breast cancer is a heterogeneous disease that can be divided into different tumour subtypes, based on the positive or negative status of the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) (47). The ER, PR and HER2 status, along with tumour grade, cell proliferation (Ki-67), and stage at diagnosis determine treatment (48, 49) and prognosis (25, 50).

In brief, low grade/low ki67 tumours that are ER and/or PR positive and HER2 negative are the most common and have the best prognosis (25). Triple negative breast cancers (ER-PR-HER2-) are less common, but more frequently appear at a young age than other subtypes and have the worst prognosis (26). The prognosis of patients with HER2 positive tumours (ER-PR-HER2+) is somewhere in between, although survival has improved since introduction of Herceptin, a therapy targeting HER2 receptors (51, 52). Tumour subtype has been categorized in several ways in the past. Table 2 shows the clinical subtypes based on immunohistochemistry analyses that were used in this thesis.

Table 2: *Clinical subtype of breast tumour. Proportion of cases and relative risk of breast cancer-specific mortality with 95 % confidence intervals for women aged 20-89 years at diagnosis during 2005-2015 in Norway (N = 27,120)[8]. For further details, see reference (26).*

Subtype	Definition	Proportion of cases (%)	Hazard ratio for breast cancer mortality[a]
Luminal A-like	ER[b] and/or PR[c] positive, HER2[d] negative, low grade	60.5	1.00 (ref)

[8] Data from Johansson ALV, Trewin CB, Hjerkind KV, Ellingjord-Dale M, Johannesen TB, Ursin G: Breast cancer-specific survival by clinical subtype after seven years follow-up of young and elderly women in a nationwide cohort. *Int J Cancer* 2018.

Luminal B-like/HER2-	ER and/or PR positive, HER2 negative, medium/high grade	14.5	1.68 (1.42-1.97)
Luminal B-like/HER2+	ER and/or PR positive, HER2 positive, any grade	10.2	0.99 (0.82-1.21)
HER2+	ER and PR negative, HER2 positive, any grade	4.9	1.32 (1.06-1.65)
Triple negative	ER and PR negative, HER2 negative, any grade	9.7	3.12 (2.64-3.68)

[a] Adjusted for year, age, grade, stage and surgery; [b]ER: Estrogen receptor; [c] PR: Progesterone receptor. [d] HER2: Human epidermal growth factor receptor 2.

1.1.6 Treatment of breast cancer

Treatment of breast cancer is complex and may include surgery, radiotherapy, chemotherapy, hormone therapy, targeted drugs, or immunotherapy. Appropriate treatment depends largely on tumour stage, grade, and subtype, but also age at diagnosis, comorbidity, and patient preference. In Norway, national guidelines for diagnosis, treatment and follow-up of breast cancer patients have been regularly published and revised since 1981 (24). Patients are automatically referred to their nearest breast treatment centre but may choose to be treated at another centre.

In essence, surgery is the first line of treatment for patients without metastasis to distant organs. Depending on the extent of the disease and patient choices, breast-conserving therapy or mastectomy may be performed. If there is metastasis to regional lymph nodes, an axillary clearance may also be performed. For larger tumours, neoadjuvant therapy comprising of chemotherapy or hormone therapy may be given for up to eight months before surgery to shrink the tumour to a more operable size. Large tumours that have grown into the skin or chest wall or metastasized to distant organs are not usually operable, and these patients are usually treated systemically only.

Radiotherapy is routinely given following breast-conserving surgery. During the study period for this thesis, chemotherapy was normally recommended for patients with high grade tumours or high Ki-67 expression, HER2 positive tumours or triple negative tumours. Patients with hormone receptor positive tumours (ER+ and/or PR+) were generally treated with anti-hormone therapy such as Tamoxifen, while patients with HER2 positive tumours were treated with Herceptin. New immunotherapy medications such as Pertuzumab were not approved until 2014 which was the very end of the study period for this thesis.

1.2 Socioeconomic status

In Norway, education is free, and welfare is generous. Regardless of family socioeconomic background, all women should have an opportunity to complete a higher education and earn their own income. Ideally, more than one measure of socioeconomic status (SES) should be used in health research (53). This thesis had access to education level and personal income as SES measures. Another commonly used individual SES measure is occupation. The Nordic countries are in a unique position to link individual SES to individual health data for the entire population, such has been done in this thesis.

Many countries do not have access to individual SES, and instead use group or area-based SES measured at the county, postcode, or electoral ward level. Area-based SES measures often describe the proportion of residents with a university education, median income of residents, proportion who are employed, or other factors such as crime, housing conditions or house ownership. Area-based SES measures may combine several factors into a single index, such as

the English index of deprivation[9] that is commonly used in studies of socioeconomic inequalities in cancer in England (54, 55).

Individual and area-based SES measures are likely correlated, but not interchangeable (56). This should be kept in mind when comparing findings of studies that use different SES measures. Education level is a marker of early-life socioeconomic circumstances (57) and may also reflect knowledge, whereas personal income reflects material wealth. Another key difference between these two socioeconomic measures is that education level will be reasonably stable in adult life, whereas income may fluctuate up or down throughout adult life and may be influenced by health status (58). For women in particular, income may fall after having children. Income is also known to fall after a cancer diagnosis (59). Thus, studies of socioeconomic inequalities and cancer should use income earned before cancer diagnosis.

1.3 Socioeconomic inequalities in breast cancer

1.3.1 Incidence inequalities

For decades, breast cancer incidence in developed countries has been highest for affluent women, such as those with a high education level, high income, skilled occupation or living in affluent areas (60, 61). Most of the incidence inequalities can be explained by the socioeconomic distribution of common risk factors for breast cancer. High SES women often have older age at first birth and fewer children than low SES women, which explains around one quarter to a half of the increased breast cancer incidence risk for high SES women (62-65). Other factors that contribute to the increased breast cancer risk for high SES women include greater alcohol consumption, earlier menarche, later menopause, greater height, lower

[9] English indices of deprivation. https://www.gov.uk/government/collections/english-indices-of-deprivation

occupational physical activity, greater use of postmenopausal hormone therapy and greater screening attendance (62, 64, 65).

Two trend studies from Denmark (66) and Finland (67) reported narrowing differences in breast cancer incidence by occupational social class from the 1970s to the 1990s. Two Norwegian studies by education level suggested the opposite (62, 68), with smaller incidence inequalities in the first study spanning 1964-1992 (68) than in the second study spanning 1991-2001 (62). It is not clear whether there has been a true increase over time in breast cancer incidence inequalities in Norway or whether these contrasting findings could be due to study population or methodological differences between the studies. More recent trend studies of socioeconomic inequalities in breast cancer incidence are lacking.

1.3.1.1 Stage-specific incidence inequalities

Socioeconomic inequalities in stage-specific incidence of breast cancer are not well studied. We found just one study of United States women diagnosed in 1991 (69). Most studies have instead compared the stage distribution of breast cancer cases. These studies suggest that breast cancer is detected at an earlier stage among high compared to low SES women (55, 70-78). However, studies of stage distribution do not account for the higher absolute incidence of breast cancer for women with high compared to low SES. It is therefore not clear whether high SES women only have increased incidence of early-stage (localized) breast cancer, or if they also have increased incidence of late-stage breast cancer with regional or distant spread, compared to low SES women. To better understand how the burden of breast cancer varies in the population, absolute stage-specific incidence rates should be compared.

1.3.2 Survival inequalities

Although socioeconomically affluent women are more likely to be diagnosed with breast cancer, they are also more likely to survive their breast cancer (60), also in Norway (68, 79). The better survival of high compared to low SES breast cancer patients could be due to earlier detection but also due to factors such as better treatment, healthier lifestyle or less comorbidity (80). The better survival of high SES women with breast cancer could partly be spurious also due to lead-time and length-time bias if high SES women are more likely to have their breast cancer detected by screening than low SES women (43).

1.3.2.1 Stage-specific survival inequalities

Socioeconomic inequalities in stage-specific survival are not well studied. By studying stage-specific survival, one can disentangle the effects of stage at diagnosis from other factors influencing survival. The few existing studies of stage-specific survival from the United States (1991-1992) (69), Netherlands (1995-2005) (81), and Sweden (1977-1997) (77) and (1992-2012) (82) have all reported better survival within each stage of breast cancer for patients with high compared to low SES. These studies all concluded that earlier detection and better stage-specific survival likely both played a role in the better overall survival of breast cancer patients with high compared to low SES. Trends in socioeconomic inequalities in stage-specific survival over time have not previously been studied.

1.3.3 Mortality inequalities

Breast cancer mortality is generally highest for high SES women (60, 61, 83-85), although the socioeconomic gradient for breast cancer mortality is less consistent across countries than the socioeconomic gradient for breast cancer incidence and survival (60, 61). This is because mortality inequalities are a balance between incidence and survival inequalities. Most countries

have reported significantly higher breast cancer mortality for women with high compared to low SES, but some counties have found no socioeconomic differences in breast cancer mortality, and a few have reported lower breast cancer mortality for women with high compared to low SES (60, 61, 86).

To fully understand socioeconomic inequalities in breast cancer mortality, inequalities in breast cancer incidence, survival and mortality should therefore be studied together. This will help to better understand where in the disease process the socioeconomic inequalities are occurring and what type of interventions may be appropriate to reduce any inequalities.

1.3.4 Young women

Young women below screening age have received less attention in studies of socioeconomic inequalities in breast cancer incidence, survival, and mortality. Most studies report socioeconomic patterns for all ages combined, which makes it difficult to disentangle the potential effects of mammography screening from other factors influencing socioeconomic inequalities in breast cancer incidence, survival, and mortality.

Outcomes for young women with breast cancer tend to be poorer compared to screen aged women, even after accounting for differences in stage at diagnosis and tumour subtype (26, 47). Each breast cancer death in young women represents many potential life-years lost. Young women who survive their breast cancer may also live many years with reduced life-quality due to late effects of treatment (87). Young women therefore deserve more attention in studies of socioeconomic inequalities in breast cancer.

2 AIMS AND OBJECTIVES

2.1 Thesis aims

The overall aim of this thesis was to use individually-linked national registry data to investigate socioeconomic inequalities in breast cancer incidence, mortality, and survival in the female population of Norway.

2.2 Research objectives

- Paper 1: Compare trends in breast cancer incidence and mortality, by education level, over four decades in Norway, 1971-2009.

- Paper 2: Determine how stage-specific incidence of breast cancer varies by education and income level in young women in Norway, 2000-2015.

- Paper 3: Determine how stage-specific survival of young breast cancer patients varies by education and income level in Norway, 2000-2015.

3 MATERIALS AND METHODS

3.1 Summary of papers

Table 3: *Summary of materials and methods used in the three papers included in this thesis.*

	Paper I Incidence and Mortality	**Paper II Stage-specific incidence**	**Paper III Stage-specific survival**
Title	Changing patterns of breast cancer incidence and mortality by education level over four decades in Norway, 1971-2009.	Socioeconomic inequalities in stage-specific breast cancer incidence: a nationwide registry study of 1.1 million young women in Norway, 2000-2015.	Stage-specific survival has improved for young breast cancer patients since 2000: but not equally.
Study design	Population-based cohort study	Population-based cohort study	Population-based cohort study
Study population	Women 35 years and over during 1971-2009.	Women 30-48 years during 2000-2015.	Women diagnosed at 30-48 years during 2000-2015.
Number of women	2,059,719 (incidence) 2,084,143 (mortality)	1,106,863	7,501
Breast cancer cases, deaths	69,380 cases 25,630 deaths	7,531 cases	7,501 cases
Data sources[a]	CPR, CRN, NED, CDR	CPR, CRN, NED, RTP	CPR, CRN, NED, RTP
Socioeconomic measure	Education level	Education level, Personal income	Education level, Personal income
Breast cancer Outcome	Incidence, mortality	Stage-specific incidence	Stage-specific excess mortality, relative survival
Covariates	Age, period	Age, period, immigration history, stage	Age, period, immigration history, stage, subtype
Statistical methods	Poisson models with bootstrapping	Poisson models.	Flexible parametric models, non-parametric net survival
Outcome measures	Relative Index of Inequality, Slope Index of Inequality	Rate Ratio, Rate Difference	Excess Mortality Rate Ratio, Relative Survival

[a] *CPR: Central Population Registry; CRN: Cancer Registry of Norway, NED: Norwegian Education Database; CDR: Cause of Death Registry; RTP: Register for Personal Tax Payers.*

3.2 Data Materials

3.2.1 Study design and population

This thesis includes three population-based cohort studies. Paper I evaluated educational differences in breast cancer incidence and mortality. The study cohort was all female Norwegian residents aged 35 years and over during 1971-2009. The mortality analysis included 2,084,143 women and 25,630 breast cancer deaths. The incidence analysis included 2,059,719 women with no prior cancer diagnosis, and 69,380 were diagnosed with breast cancer during follow-up (figure 4).

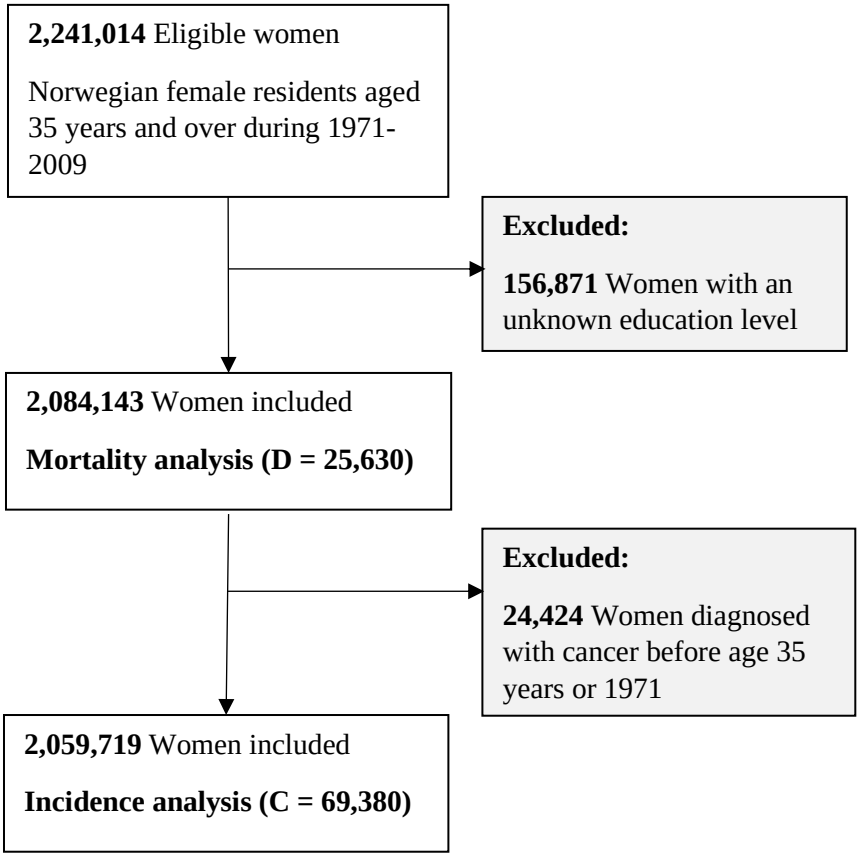

Figure 4: *Eligible and included women in paper I. D: Breast cancer deaths, C: Breast cancer cases.*

Paper II assessed educational and income differences in stage-specific incidence. The study cohort was all female Norwegian residents aged 30 to 48 years during 2000-2015. The analysis included 1,106,863 women and 7,531 breast cancer cases (figure 5).

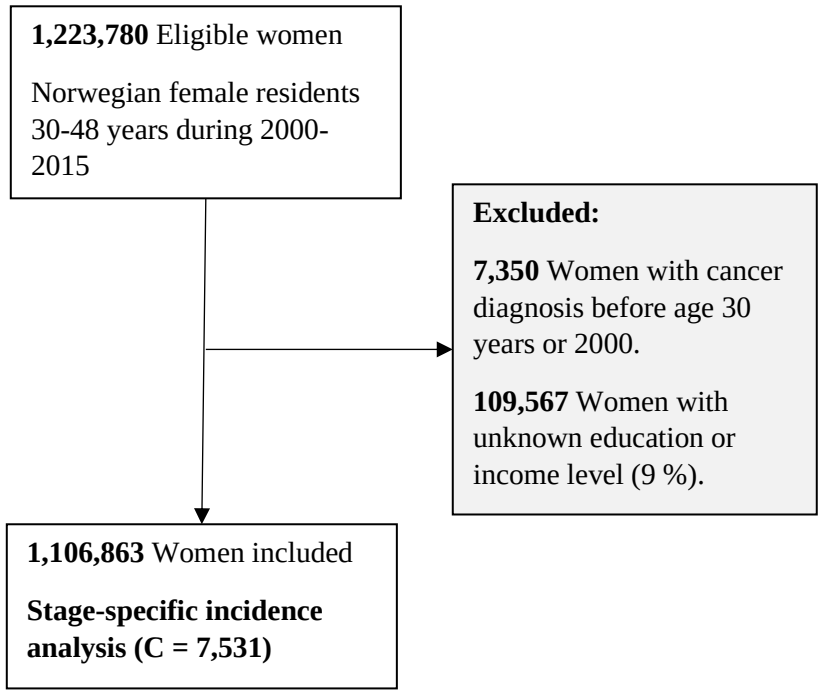

Figure 5: *Eligible and included women in paper II. C: Breast cancer cases.*

Paper III studied educational and income differences in stage-specific survival. The study cohort included 7,501 women diagnosed with breast cancer at 30-48 years in 2000-2015 (figure 6). Paper III had 30 fewer cases than paper II because the Cancer Registry data was updated, and we excluded more women with a cancer history before their breast cancer diagnosis in paper III.

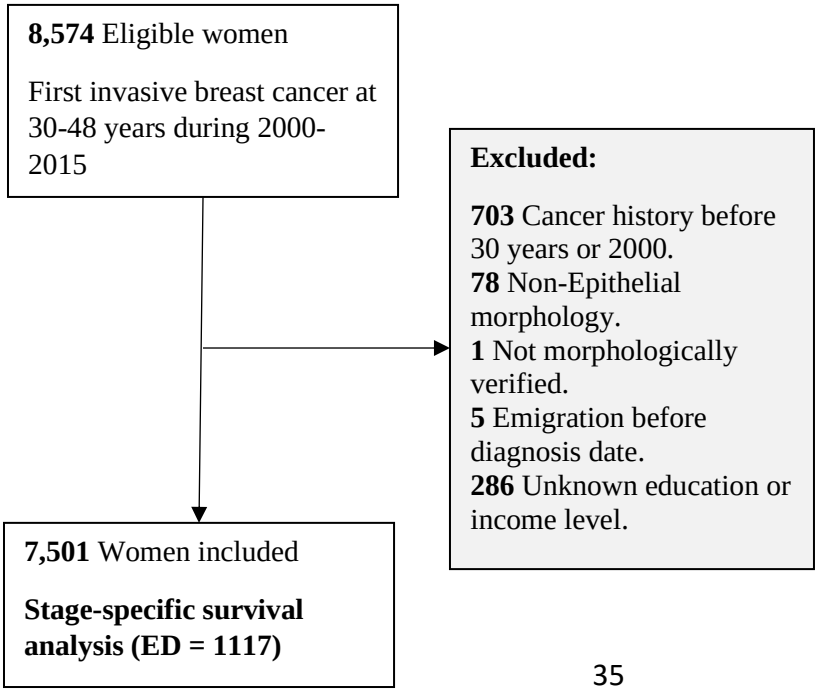

Figure 6: *Eligible and included women in paper III. ED: Excess deaths during follow-up.*

The study populations excluded women with a prior cancer diagnosis (mortality analysis excepted) and women with an unknown SES (education and/or income level) throughout follow-up. The minimum age for inclusion was 35 years for paper I and 30 years for papers II-III to ensure most women had completed their education or started earning income before entry to the studies. The maximum age for inclusion in papers II and III was 48 years to ensure the study population did not include women invited to the national mammography screening programme, BreastScreen Norway.

3.2.2 Data linkages

This thesis used two different data linkages with largely overlapping information. Both datasets were nationwide, with population and health registry data linked together by unique personal identification numbers. The first dataset was used in paper I and included data from the Central Population Registry, Cause of Death Registry, National Education Database and Cancer Registry of Norway during 1971-2009. The second dataset was used in papers II-III and included data from the Central Population Registry, National Education Database, Register for Personal Tax Payers and Cancer Registry of Norway during 1995-2015. Table 4 shows a summary of data sources and variables in each dataset.

Table 4: *Data sources and variables in the two datasets used in this thesis.*

Data source	Variables	Dataset I (paper I)	Dataset II (paper II, III)
Central Population Registry	Month and year of birth Month and year of death Sex Immigration history Migration dates to/from Norway	Residents during 1971-2009	Residents during 1995-2015

Cause of Death Registry	Underlying cause of death	1971-2009	
National Education Database	Highest attained education level	1971-2009	1999-2015
Register for Personal Tax Payers	Five-year average annual personal income		1995-2015
Cancer Registry of Norway	Month and year of cancer diagnosis Tumour number Topography Morphology Vital status Date of vital status	1971-2009	2000-2015
Cancer Registry of Norway	Estrogen receptor (ER) status Progesterone receptor (PR) status Human Epidermal growth factor Receptor 2 (HER2) status		2005-2015

3.2.3 Central Population Registry

The Central Population Registry (CPR) is administered by The Norwegian Tax Administration and includes personal identification numbers for all Norwegian inhabitants. This unique 11-digit number has been assigned to inhabitants in Norway since 1 October 1964 and was used to link information from the different data sources. Both datasets included the following information from the Population Registry: month and year of birth, sex, immigration history (table 5), dates of migration in and out of Norway (dataset 1 only), and month and year of death.

Table 5: *Definition of immigration history used in all three papers.*

Immigration history	Definition
Norwegian	Norwegian-born of Norwegian-born parents Norwegian-born of two foreign-born parents (2nd generation immigrant) Foreign-born of at least one Norwegian-born parent.
Immigrant	Foreign-born of two foreign-born parents (1st generation immigrant).

3.2.4 Cause of Death Registry

The Cause of Death Registry (CDR) was previously administrated by Statistics Norway but is now administered by the Norwegian Institute of Public Health. The registry holds digitalised information on cause of death since 1951 and the national coverage is estimated to be 98 % (88). Quality and completeness are high for deaths occurring in Norway but cause of death may be unknown for Norwegian residents who die abroad. The first dataset included information on underlying cause of death from the Cause of Death Registry.

3.2.4.1 Definition of breast cancer death

In paper I, breast cancer mortality rates included all women with breast cancer as the underlying cause of death. Table 6 shows the definition of breast cancer death according to the International Classification of Diseases (ICD) (89).

Table 6: *Definition of breast cancer death used in paper I.*

Year of death	Definition
1971-1985	ICD[a] version 8 code 174
1986-1995	ICD version 9 code 174-175
1996-2009	ICD version 10 code C50

[a] *ICD: International Classification of Diseases.*

3.2.5 National Education Database

The National Education Database, administered by Statistics Norway, includes all educations completed by residents aged 16 years and over since 1970 (90). Reporting is mandatory for all Norwegian educational institutions. Education completed abroad by Norwegian-born residents and supported by the State Education Loan Fund are also reported to the database. The Education database is virtually complete for individuals who completed their education in Norway, but education level is missing for 21 % of foreign-born residents who completed their education before arriving in Norway and have not responded to surveys of education level among immigrants conducted in 1991, 1999 and 2011 (91). Both datasets contained information on highest attained education level throughout the study periods.

3.2.5.1 Definition of education level

Education level was used as a measure of SES in all three papers. In papers I and II (incidence and mortality), women were categorised according to current education level, and contributed person-years to more than one level if they attained a higher level during follow-up. In paper III (survival), women were categorised according to education level before diagnosis.

A change in coding practice by Statistics Norway made it no longer possible to differentiate between basic and final year upper secondary school completed after 2006 (90). This made it necessary to adjust our definition of middle and high education level between paper I (dataset I) and papers II and III (dataset II). In short, final year upper secondary school (13 years education) was categorised as a high level in paper I, but middle level in papers II and III. Table 7 shows the definitions of education level used in this thesis.

Table 7: *Definition of education level.*

Education level	Dataset I Paper I	Dataset II Papers II and III
Low	Compulsory school or less, ≤ 10 years	Compulsory school or less, ≤ 10 years
Middle	Basic upper secondary school, 11-12 years	Upper secondary or vocational education, 11-13 years
High	Final year upper secondary, vocational, or tertiary education, ≥ 13 years	Tertiary education, ≥ 14 years

3.2.6 Register for Personal Tax Payers

The Personal Tax Payers Register is administered by the Norwegian Tax Administration. The register covers all taxable persons in Norway and is near complete (99.8 %) for residents. Personal income was used as a measure of SES in papers II and III. The second dataset, used in papers II and III, included five-year average annual personal income for the periods 1995-1999, 2000-2004, and 2005-2009.

3.2.6.1 Definition of income level

In paper II (stage-specific incidence), income was categorised into five-year age- and period-specific quintiles Q1 (low), Q2, Q3, Q4 and Q5 (high) of average personal income earned during the five-year period before follow-up. Thus, income earned during 1995-1999 was used for follow-up in 2000-2004; income earned during 2000-2004 was used for follow-up in 2005-2009; and income earned during 2005-2009 was used for follow-up in 2010-2015. Women contributed person-years to more than one quintile if their income quintile changed between the five-year periods. The median income in the age- and period-specific quintiles can be found in paper II, Supplemental Table S1. Table 8 shows the median income in quintiles used for follow-up in 2010-2015.

Table 8: *Median income by quintile for all women residing in Norway at ages 30-48 years during 2010-2015[a] (N = 1,106,863) (Paper II).*

All women in Norway 2010-2015	**Income quintiles[a], median (NOK)**				
	Q1 (low)	**Q2**	**Q3**	**Q4**	**Q5 (high)**
30-34 years	93,100	176,900	236,300	294,300	377,500
35-39 years	141,100	236,700	295,400	349,900	442,000
40-44 years	164,700	258,200	317,500	376,100	486,300
45-48 years	170,400	263,000	323,600	387,700	510,300

[a] *Income earned during 2005-2009 was used for follow-up during 2010-2015.*

In paper III (stage-specific survival), breast cancer patients were divided into five-year period-specific income quintiles Q1 (low), Q2-Q4 (middle) and Q5 (high) based on average personal income during the five-year period before breast cancer diagnosis. Thus, women diagnosed in 2000-2004 were categorised by income earned during 1995-1999; women diagnosed in 2005-2009 were categorised by income earned during 2000-2004; and women diagnosed in 2010-2015 were categorised by income earned during 2005-2009. Table 9 shows the median income for income quintiles used in paper III.

Table 9: *Median income by quintile for breast cancer patients in Norway aged 30-48 years at diagnosis during 2000-2015 (N = 7,501) (Paper III).*

Breast cancer patients 30-48 years	**Income quintiles[a], median (NOK)**				
	Q1 (low)	**Q2**	**Q3**	**Q4**	**Q5 (high)**
2000-2004	90,700	158,000	203,400	237,600	308,600
2005-2009	138,000	216,000	262,100	310,200	405,900
2010-2015	168,600	268,800	329,800	386,300	507,700

[a] *Quintiles are based on average personal income during the five-year period before breast cancer diagnosis. For example, income earned during 2005-2009 was used to create quintiles for women diagnosed with breast cancer in 2010-2015.*

A key difference between papers II and III was that the quintiles in paper II were based on the income of all women in the population, whereas the quintiles in paper III were based on the income of breast cancer patients only.

Past income was not known for foreign-born women who did not reside in Norway during the previous five-year period. Thus, past income was unknown for 34 % of eligible immigrants in paper II and 18 % of eligible immigrants in paper III. However, these foreign-born women comprised just 7 % of all eligible women in paper II and 2 % of all eligible women in paper III.

3.2.6.2 Definition of combined SES

In papers II and III, a combined SES variable was formed using education level from the education database and income quintile from the register for tax payers. We were interested in differentiating the lowest education and income levels from higher levels, so used the four socioeconomic groups shown in table 10.

Table 10: *Definition of combined education and income status used in papers II and III.*

Education-Income group	Education level	Income quintile (Q)
Low-Low	Compulsory or less (≤ 10 years)	Q1
Low-High	Compulsory or less (≤ 10 years)	Q2-Q5
High-Low	Secondary or tertiary (≥ 11 years)	Q1
High-High	Secondary or tertiary (≥ 11 years)	Q2-Q5

3.2.7 Cancer Registry of Norway

The Cancer Registry of Norway is nationwide and has had mandatory reporting of new cancer cases since 1953. The registry has 98.8 % completeness and 99.3 % histologically verified breast cancer cases (92). Both datasets contained month and year of cancer diagnosis, tumour

number, topography (ICD-7 in the first dataset, ICD-10 in the second dataset), morphology (ICD-O-3), vital status (resident, emigrated, dead) and date of last vital status change. The second dataset additionally included information on tumour stage, ER, PR and HER2 status.

3.2.7.1 Definition of breast cancer

Breast cancer was defined as a first invasive breast cancer with ICD-7 code 170 (paper I) or ICD-10 code C50 (papers II and III), see table 11. In paper I, incidence rates excluded women diagnosed with a non-epithelial breast cancer. These women were instead censored at diagnosis. In papers II and III, women with invasive breast cancer that was not morphologically verified or was non-epithelial (1 % of breast cancer cases) were censored at diagnosis in paper II (stage-specific incidence) and excluded from paper III (stage-specific survival).

Table 11: *Definition of breast cancer used in this thesis.*

	Dataset I **Paper I**	**Dataset II** **Papers II and III**
Definition	ICD[a] version 7 code 170	ICD version 10 code C50
Exclusions	Non-invasive tumours Non-Epithelial morphology Not morphologically verified	Non-invasive tumours Non-Epithelial morphology Not morphologically verified

[a] *ICD: International Classification of Diseases.*

3.2.7.2 Definition of stage at diagnosis

Stage was based on pathological tumour size, nodal status, and metastasis (TNM), supplemented with clinical notifications of stage if pathological TNM was missing. In clinical notifications, stage was based on the Surveillance Epidemiology and End Results Program (SEER) summary stage. Tumours localized to the breast were considered TNM stage I. Tumours with metastasis to regional lymph nodes were TNM stage II, tumours with metastasis

to skin and/or chest wall were TNM stage III, and tumours with metastasis to distant lymph nodes or other organs were TNM stage IV. If pathological TNM and clinical notifications were missing or incomplete, stage was classified as unknown. Stage was additionally set to unknown for patients who received neoadjuvant treatment, gradually introduced from 2003 (45).

In 2008, the Cancer Registry changed the coding practice for lymph node spread, resulting in a substantial migration from TNM stages II to III (45). We therefore decided to combine TNM stages II and III into a single group. Stage was therefore categorized as localised (TNM I), regional (TNM II-III), distant (TNM IV) or unknown in papers II and III (Table 12).

Table 12: *Breast cancer stages according to the Surveillance, Epidemiology and End Results Program (SEER) summary stage*[10] *and TNM classification system (44).*

SEER stage	SEER definition	TNM classification	TNM stage
Localized	No spread outside breast	T1N0M0	I
Regional	Metastasis to regional lymph nodes	T1-2N1M0 T2-3N0M0	II
Regional	Local infiltration to skin and/or chest wall	T1-2N2M0 T3N1-2M0 T4N0-2M0 Any T, N3M0	III
Distant	Metastasis to distant lymph nodes or organs	Any T, Any N, M1	IV
Unknown	Missing or unknown metastasis stage	TX, NX or MX	Unknown

[10] Surveillance, Epidemiology, and End Results Program, Summary Stage Manual 2000. https://seer.cancer.gov/tools/ssm/

3.2.7.3 Definition of tumour subtype

Clinical subtype was categorised according to ER, PR, HER2 status and grade in paper III (table 13) (47). ER, PR and HER2 status were obtained from pathology reports of immunohistochemistry assessments, which have relatively high concordance (75-90 %) with molecular subtypes from microarrays (93). Up until January 2012, the Norwegian Cancer Registry classified tumours as ER negative if there was < 10 % reactivity. From February 2012 onwards, < 1 % reactivity was considered ER negative. This change in classification was in accordance with changes to treatment protocols for patients in Norway[11]. For PR, < 10 % reactivity was considered negative. HER2 expression was tested by immunohistochemistry, supplemented with in situ hybridization if immunohistochemistry results were borderline.

Table 13: *Definition of tumour subtype according to estrogen receptor (ER), progesterone receptor (PR) and Human epidermal growth factor receptor 2 (HER2) status and grade. Used in paper III.*

Subtype	Definition
Luminal A-like	ER and/or PR positive, HER2 negative, low grade
Luminal B-like/HER2-	ER and/or PR positive, HER2 negative, medium/high grade
Luminal B-like/HER2+	ER and/or PR positive, HER2 positive, any grade
HER2+	ER and PR negative, HER2 positive, any grade
Triple negative	ER and PR negative, HER2 negative, any grade
Unknown	Missing ER, PR, HER2 or grade

[11] National guidelines for diagnosis, treatment and follow-up of women with breast cancer. https://nbcg.no/retningslinjer/ (in Norwegian only).

3.3 Statistical Methods

In all three studies, we quantified the socioeconomic gradient in absolute and relative terms. Reporting absolute and relative measures of inequality together is particularly important when comparing groups with differing absolute disease rates (94). Relative effects can be large even when absolute rates are low and the impact on women as a whole is small. Similarly, relative rates can be small, but if the underlying absolute rate is large a small relative effect may still impact a lot of women. Hence, absolute and relative effects should always be evaluated in the context of each other. Examples of where this thesis compared groups with differing absolute rates includes comparison of rates over time, by age and by stage at diagnosis. Figure 7 illustrates how absolute and relative measures of effect vary at different absolute rates.

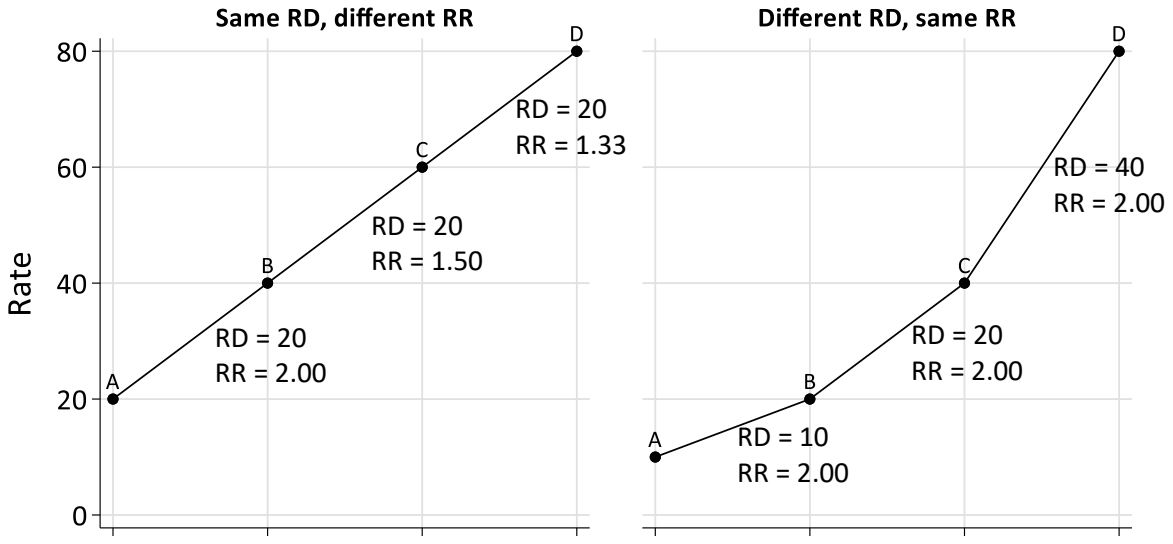

Figure 7: *Absolute and relative measures of effect at different absolute disease rates. Examples of rate differences (RD) and rate ratios (RR) for B vs A, C vs B, and D vs C.*

In papers I-II, breast cancer incidence and mortality rates per 100,000 person-years were directly age-standardised using the World Standard Population (1, 2). Smoothed age-

standardised incidence and mortality curves were presented in paper I, using locally weighted scatterplot smoothing (LOWESS) (95).

Age-standardisation creates hypothetical rates that are weighted to another age distribution than the one in the observed data. The standardised rates are therefore not the truly observed rates but are comparable across groups with respect to age. The rates are therefore comparable across socioeconomic groups within our population and to rates reported in other studies where the World Standard Population has been used for age-standardisation.

3.3.1 Outcome measures

In paper I, we used the Slope Index of Inequality (SII) and Relative Index of Inequality (RII) to estimate absolute and relative educational inequalities in breast cancer incidence and mortality, respectively. In paper II, we used the more traditional rate difference (RD) and rate ratio (RR) measures to estimate educational and income inequalities in stage-specific incidence. In paper III, we compared five-year relative survival and estimated excess mortality rate ratios (EMRR) by education and income level of breast cancer patients.

3.3.2 Relative and Slope Index of Inequality

The RII and SII provide single estimates of inequality across all socioeconomic groups, considering the relative size of each group (96, 97). These measures enable valid comparisons of socioeconomic inequalities between populations with different SES distributions, for example between countries, between birth cohorts, or over time. To calculate RII and SII, each socioeconomic group is assigned a rank score in the range zero to one. The rank score represents the mid-point of the cumulative population at each socioeconomic level, ordered from lowest to highest.

As an example, figure 8 shows rank scores plotted against incidence rates for women aged 50-69 years during 1990-1999. The education distribution was compulsory 43.4 %, secondary 37.0 %, and tertiary 19.6 %. The respective rank scores were therefore compulsory: 0.434/2 = 0.217; secondary: 0.434 + (0.37/2) = 0.619; and tertiary: 0.434 + 0.37 + (0.196/2) = 0.902. A linear curve was then fitted to obtain the estimate incidence rates for the theoretical lowest (rank score zero) and highest (rank score one) educated women. In this example, 151 and 274 cases per 100,000 person-years, respectively.

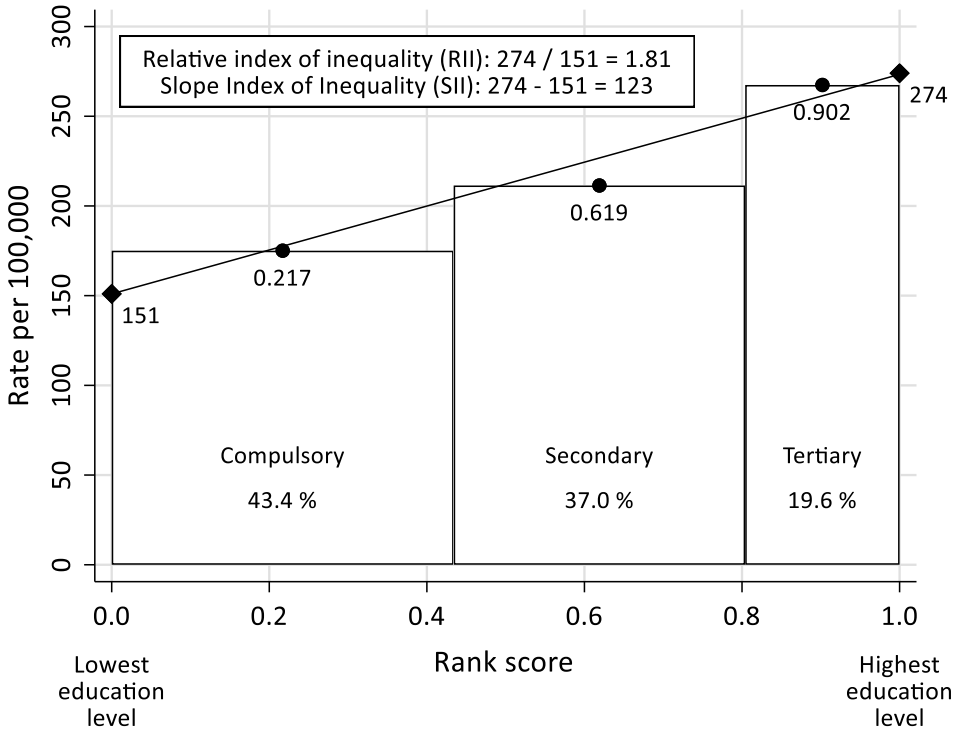

Figure 8: *Illustration of how the rank score, relative index of inequality (RII) and slope index of inequality (SII) are calculated, using breast cancer incidence among women aged 50-69 years during 1990-1999 as an example.*

The RII is the ratio of estimated rates at rank score one versus rank score zero and can be estimated directly with 95 % confidence intervals from a regression model where the rank score is included as a continuous variable. The SII is the difference between the estimated rates at rank score one and rank score zero. The rank score assumes linearity, which we visually assessed by plotting incidence and mortality rates against rank scores for each age and period strata included in the incidence and mortality models.

In paper I, we estimated SII as age-standardised rate differences (World standard population). To age-standardise the SII, we first estimated age-specific rates in five year bands in the regression models for rank score zero and rank score one. We then age-standardised these rates and took the difference (97). We estimated age-standardised SIIs because breast cancer rates, in particular mortality, are strongly related to age. Mortality rates increase with age, as do rate differences, given the same relative risk. SII estimates obtained directly from age-adjusted models will be influenced by the age structure of the population and unsuitable for comparing populations with different age structures, such as when comparing ageing populations over time. With an age-standardised SII, age-specific rate differences are given the same weighting and will not be influenced by the age structure of the population.

3.3.3 Bootstrapping

The 95 % confidence intervals for the age-standardised SII estimates were estimated with a non-parametric bootstrap procedure (98-100). Bootstrapping works by taking a large number of repeated random samples from the study population and then estimating an age-standardised SII for each random sample. The variability of these SII estimates is then used to calculate the 95 % confidence interval. A key assumption of bootstrapping is that the study population sample is representative of the target population (99). A large sample size and high number of

bootstrap repetitions play key roles in obtaining unbiased estimates. Estimating bias-corrected confidence intervals will also correct for any bias between the predicted value from the model and the average of the simulated predicted values from bootstrapping (99, 100). In paper I, we estimated bias-corrected confidence intervals from 5000 bootstrap repetitions on a large sample of all eligible females in the Norwegian population.

3.3.4 Regression models

In all studies, we explored the main exposure variables (education, income, SES) and covariates with descriptive statistics and plotted breast cancer outcome rates over time and by age, stratified by covariates. We assessed the effect of SES and covariates on breast cancer incidence and mortality with Poisson regression models (101) and on breast cancer survival with flexible parametric models (102, 103). Incidence and mortality analyses were adjusted for current age and year during follow-up. Survival analyses were adjusted for age and year at diagnosis. We did not further adjust the models for factors that mediated the association between SES and breast cancer outcome because we were primarily interested in estimating the total effect of socioeconomic inequalities in breast cancer outcomes.

3.3.4.1 Poisson Regression

A Poisson model (101) assumes that the rate at which an event occurs is constant within each covariate pattern in the model. Breast cancer incidence and mortality rates vary by age and over time. To adjust for age and period, which change during follow-up, we split follow-up time for each woman into age and period bands and included these bands in the Poisson models as covariates. This created an underlying baseline rate which was a step-function over time and age. We used five-year age bands in papers I and II, ten-year period bands in paper I (1971-1979, 1980-1989, 1990-1999, 2000-2009), and five-year period bands in paper II (2000-2004,

2005-2009, 2010-2015). Further details of the Poisson models can be found in the methods sections of papers I and II.

In paper I, we estimated the RII and SII for breast cancer incidence and mortality for the age groups 35-49, 50-69 and 70 years and over for decades 1971-1979, 1980-1989, 1990-1999 and 2000-2009. We tested whether the RII and SII varied significantly between consecutive decades and tested for linear trend over four decades. In paper II, we estimated stage-specific RR and RD for breast cancer incidence for women aged 30-48 years during 2000-2015. Rate ratios were obtained directly from Poisson models. Rate differences were post-estimated using pairwise comparisons of predicted incidence rates between socioeconomic groups.

A key strength of the Poisson model is that it is fully parametric, which means that we had parameters for both the absolute and relative rates, and both RD and RR were easily obtained from the model. The RR came directly from the model and the RD via post-estimation.

3.3.4.2 Flexible Parametric Models

Flexible parametric models (102, 103) compare cumulative hazard rates with survival models or cumulative excess hazard rates with relative survival models, as used in paper III. Excess mortality rate ratios obtained from relative survival models are ratios of the cumulative excess hazard rate. Excess hazard, or excess mortality, is a way to estimate cancer mortality without using cause-of-death information, simply by counting the excess deaths observed in cancer patients compared to deaths in a comparable population. In paper III, we estimated the stage-specific excess mortality for breast cancer patients by comparing the all-cause mortality of patients to the expected all-cause mortality of females in the Norwegian population of the same age and calendar year.

In flexible parametric models, the baseline hazard is estimated using restricted cubic splines, providing smooth estimates of excess mortality and relative survival. Our models allowed the hazards for different stages at diagnosis to be non-proportional over time to the baseline hazard. Models were adjusted for age at diagnosis as a linear effect and year of diagnosis as a non-linear effect. From these models, we post-estimated stage-specific five-year relative survival over time and stage-specific relative survival up to 12 years from diagnosis for patients diagnosed in 2000 and 2015. Relative survival post-estimations were made for a reference group of women aged 40 years at diagnosis. Further details of the models can be found in the methods section of paper III.

3.3.4.3 Non-parametric net survival

Some of our model-based post-estimates of relative survival were outside the scope of the data. For comparison, we estimated relative survival non-parametrically for patients diagnosed during 2005-2015 and followed-up until end 2017. We used the Pohar Perme estimator (104), which is an internally age-standardised estimate of relative survival that gives greater weight to individuals with higher risk of other cause mortality, a so-called inverse probability of censoring weights. To allow for potential variation in age distribution between socioeconomic groups, we initially performed external age-standardisation on the Pohar Perme estimates using the World Standard Population. However, age-standardised estimates were almost identical to crude estimates in our young population, so we used the simpler crude Pohar Perme estimates of relative survival instead.

3.3.5 Life tables

The life tables of expected mortality used in paper III were stratified by sex, age, and calendar year. In preliminary analyses, life tables were additionally stratified by socioeconomic group to avoid bias (105). The socioeconomic-stratified life tables were created from individually linked nationwide data of mortality, education, and income, and were smoothed using a multivariable flexible Poisson model (106). Figure 9 shows smoothing for one of the education-stratified life tables that we created. However, we found that the additional stratification by socioeconomic group made little difference to estimates of excess mortality and relative survival, so we used the simpler age- and year-specific life tables instead.

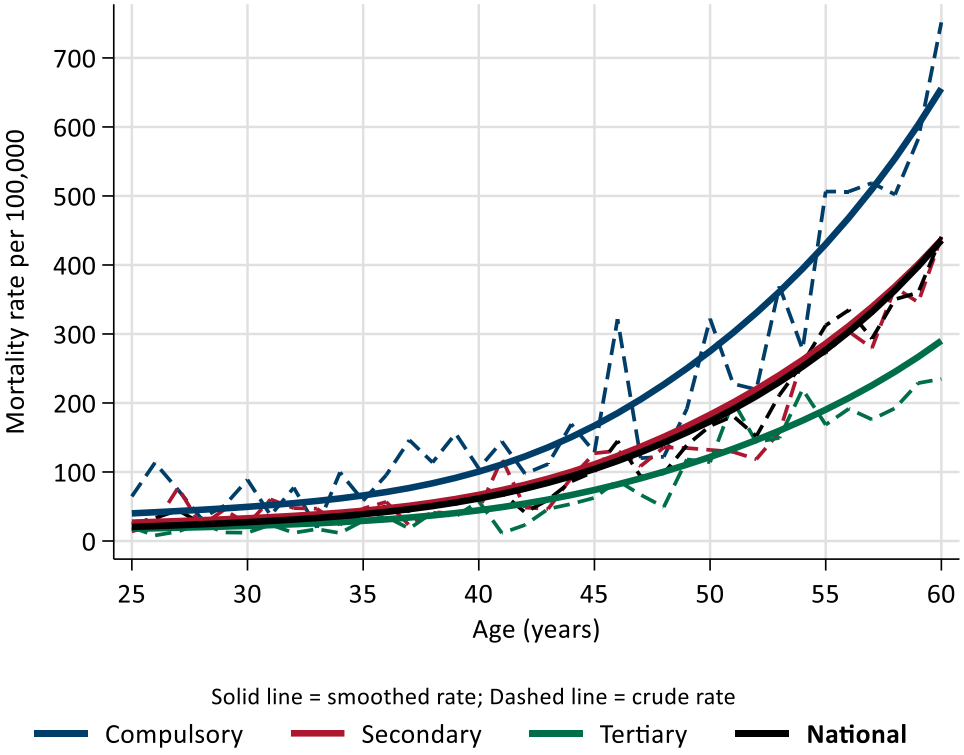

Figure 9: *Norwegian national and education-stratified life tables for 2015, smoothed with a multivariable flexible Poisson model (106).*

3.4 Ethical considerations and approvals

All three papers in this thesis were approved by the Regional Committee for Medical and Health Research Ethics in South-Eastern Norway, reference 2012/1138 (paper I) and 2013/2376 (papers II and III).

All papers were registry studies using mandatory reportable data and no informed consent was required. Anonymity was ensured by not presenting data in too small groups. The datasets were pseudominized and managed in accordance with the European General Data Protection Regulation (GDPR).

4 RESULTS

4.1.1 Paper I: Incidence and mortality

This study included over 2 million women aged 35 years and over, with 69,380 breast cancer cases and 25,630 breast cancer deaths in the period 1971-2009. Overall, for women aged 35 years and over, relative educational differences in breast cancer incidence and breast cancer mortality became smaller between 1971 and 2009. During 2000-2009, the highest educated women still had significantly higher breast cancer incidence than the lowest educated women, but breast cancer mortality no longer varied significantly by education level.

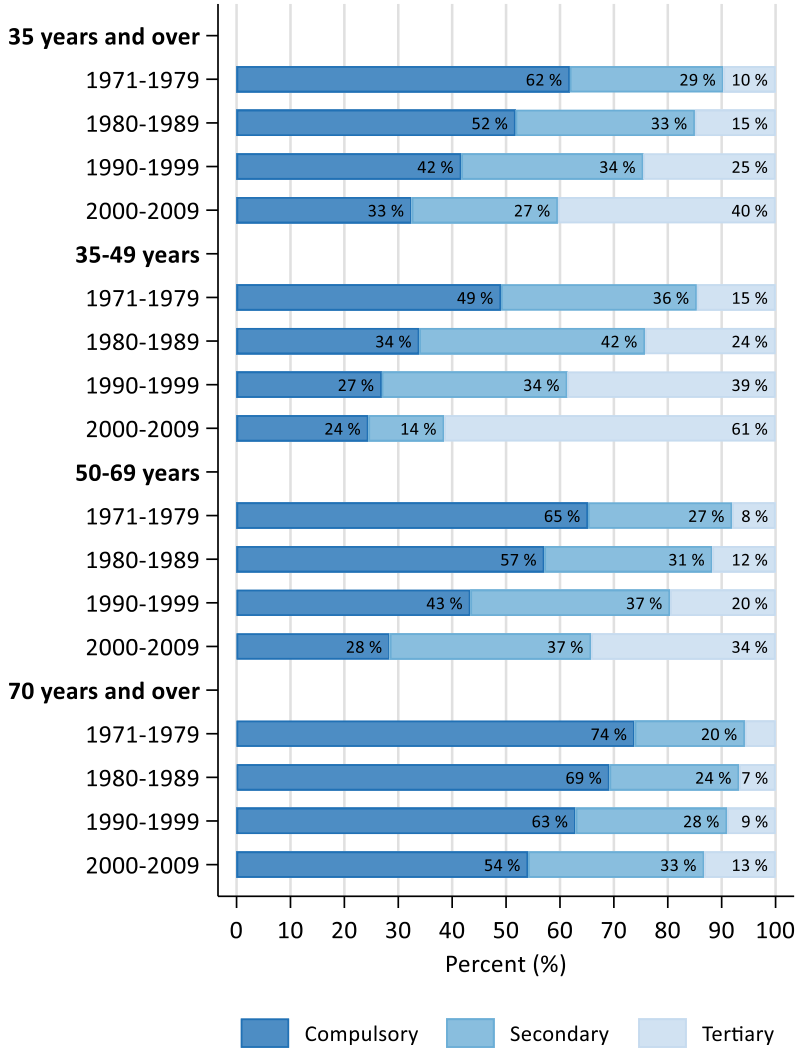

Figure 10 shows that the distribution of education level among women in Norway varied substantially over time and across age groups in paper I. For women aged 35 years and over, the proportion with a tertiary education increased four-fold from the 1970s to the 2000s.

Figure 10: *Education distribution by age group and period in the Norwegian female population (N = 2,059,719 women) (Paper I).*

4.1.1.1 Breast cancer incidence

Breast cancer incidence remained significantly higher for higher compared to lower educated women in all age groups and periods. For young women aged 35-49 years, breast cancer incidence rose most rapidly over time for the lowest educated women, and incidence inequalities narrowed from the 1970s to the 2000s (figure 11). For screening-aged women, 50-69 years, breast cancer incidence rose most rapidly for the highest educated women in the 1990s, and incidence inequalities widened. Then in the 2000s, incidence rates rose most rapidly for the lowest educated women, and incidence inequalities narrowed. For older women aged 70 years and over, the incidence inequalities narrowed in the 1990s, but widened again in the 2000s when incidence rose for the highest educated women but fell for the lowest educated women.

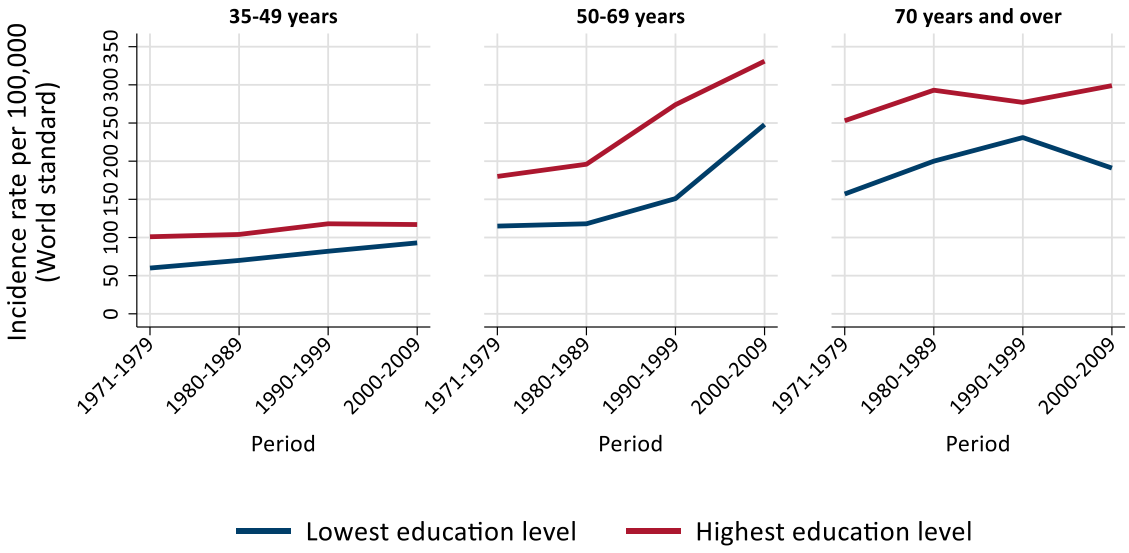

Figure 11: *Breast cancer incidence: estimated age-standardised incidence rates per 100,000 person-years (World Standard Population), by age and decade, for the lowest and highest educated women during 1971-2009 (N = 2,059,719 women, n = 69,380 deaths) (Paper I).*

4.1.1.2 Breast cancer mortality

Educational differences in breast cancer mortality were smaller than educational differences in breast cancer incidence. For young women aged 35-49 years, breast cancer mortality declined most rapidly for the highest educated women from the 1990s and led to the education gradient for breast cancer mortality reversing in the 2000s. For the first time, breast cancer mortality before age 50 became lowest for the highest educated women during 2000-2009 (figure 12). Also, for women aged 50-69 years, breast cancer mortality declined most rapidly for the highest educated women, and breast cancer mortality no longer varied by education level in the 2000s. For women aged 70 years and over, breast cancer mortality inequalities were reduced over time but remained significant in the 2000s.

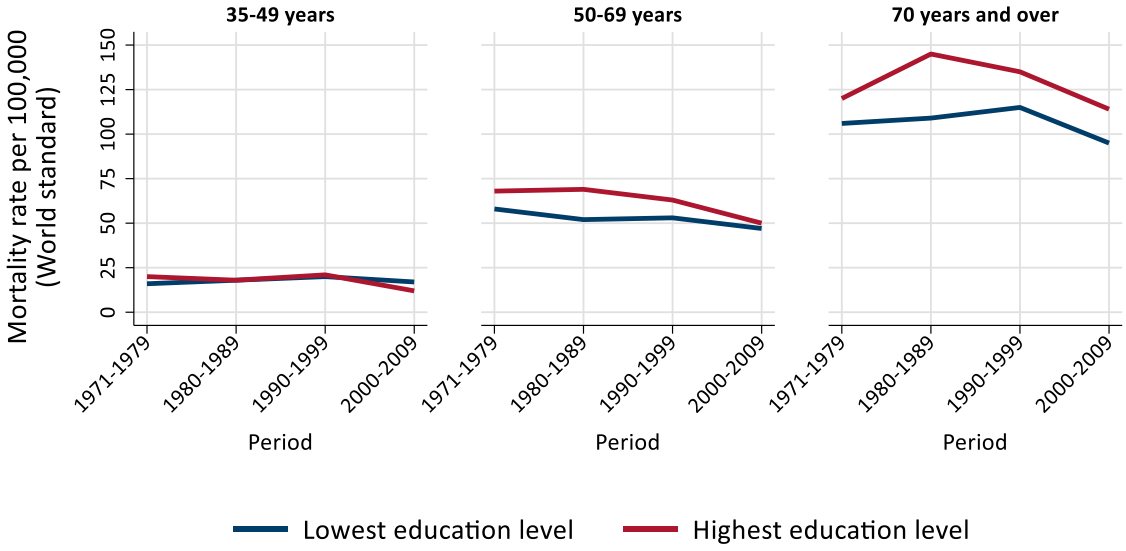

Figure 12: *Breast cancer mortality: Estimated age-standardised mortality rates per 100,000 person-years (World Standard Population), by age and decade, for the lowest and highest educated women during 1971-2009 (N = 2,084,143 women, n = 25,630 deaths) (Paper I).*

4.1.1.3 Young women

Table 14 shows the breast cancer incidence and mortality results for young women below screening age, who were also studied in papers 2 and 3.

Table 14: *Summary of breast cancer incidence and breast cancer mortality results for young women aged 35-49 years during 1971-2009 (Paper I).*

Period	Rate per 100,000		SII[a] per 100,000	RII[a]
	Lowest education level	Highest education level	Highest vs lowest education	Highest vs lowest education
Breast cancer incidence (N = 1,456,488 women; n = 13,868 cases)				
1971-1979	60	101	41 (28-54)	1.68 (1.43-1.97)
1980-1989	70	104	34 (21-45)	1.48 (1.29-1.69)
1990-1999	82	118	35 (24-47)	1.43 (1.27-1.61)
2000-2009	93	117	24 (13-36)	1.26 (1.31-1.42)
Breast cancer mortality (N = 1,465,357 women; n = 2,648 deaths)				
1971-1979	16	20	3 (-3 – 10)	1.21 (0.87-1.71)
1980-1989	18	18	-0 (-5 – 5)	1.00 (0.74-1.34)
1990-1999	20	21	1 (-4 – 6)	1.04 (0.82-1.33)
2000-2009	17	12	-5 (-9 – 0)	0.72 (0.54-0.97)

[a] *RII: Relative Index of Inequality; SII: Slope Index of Inequality.*

4.1.2 Paper II: Stage-specific incidence in young women

This study included over 1.1 million young women aged 30 to 48 years during 2000-2015. There were 7,531 breast cancer cases diagnosed over 9.5 million person-years follow-up, and the overall age-standardised rate was 78.3 cases per 100,000 person-years. The stage-specific age-standardised rates were 24.2 for localised, 46.6 for regional, 2.4 for distant, and 5.2 cases per 100,000 person-years for unknown stage. Figure 13 shows the stage-specific age standardised incidence rates by combined education-income level.

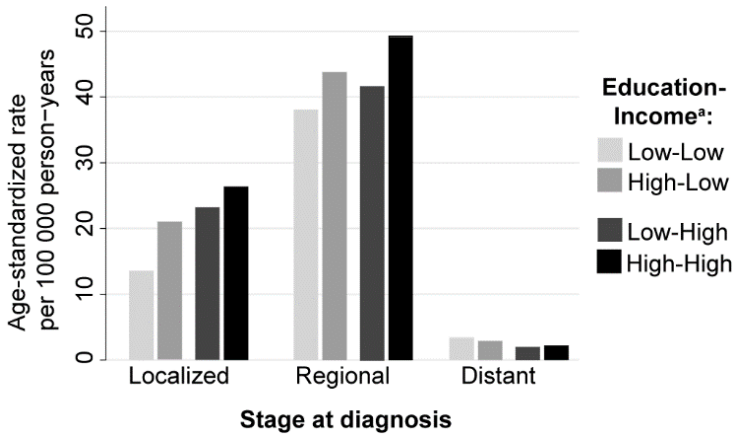

Figure 13: *Localized, regional and distant stage age-standardised incidence (World standard population), by combined education and income status among women aged 30-48 years during 2000-2015 (N = 1,106,863 women, 7036 breast cancer cases) (Paper II).* [a] *Education: low = compulsory; high = secondary-tertiary. Income: low = quintile 1, high = quintiles 2-5.*

Localized and regional stage rates increased significantly with increasing education and income level. Distant stage rates did not vary significantly by education level but were significantly lower for women in the four highest compared to the lowest income quintile. Rates of breast cancer with unknown stage increased with higher education level but did not vary significantly by income.

Stage-specific incidence differences between the highest and lowest education and income groups were much larger at localised and regional stage, around 8-11 cases per 100,000 person-years, than at distant stage, around 0-1 case per 100,000 person-years. Table 15 shows the stage-specific incidence results by education level.

Table 15: *Summary of stage-specific incidence results by education level for young women aged 30-48 years during 2000-2015 (N = 1,106,863 women; n = 7,531 cases) (Paper II).*

Education level	Total	Stage at diagnosis			
		Localized	Regional	Distant	Unknown
Person-years					
Compulsory	2,039,147	2,039,147	2,039,147	2,039,147	2,039,147
Secondary	3,650,558	3,650,558	3,650,558	3,650,558	3,650,558
Tertiary	3,879,663	3,879,663	3,879,663	3,879,663	3,879,663
Breast cancer cases					
Compulsory	1,480	436	892	58	94
Secondary	2,894	878	1,733	89	194
Tertiary	3,157	1008	1,856	86	207
Age-standardised incidence per 100,000 person-years					
Compulsory	67.1	19.8	40.4	2.6	4.3
Secondary	76.5	23.1	45.9	2.4	5.1
Tertiary	87.1	28.2	50.8	2.3	5.7
Incidence rate ratio (95 % CI)[a]					
Tertiary vs Compulsory	1.28 (1.21-1.37)	1.40 (1.25-1.56)	1.25 (1.15-1.35)	0.90 (0.64-1.26)	1.32 (1.03-1.69)
Incidence rate difference per 100,000 (95 % CI)[a]					
Tertiary vs Compulsory	4,7 (3.6-5.8)	7.9 (5.3-10.5)	9.9 (6.4-13.3)	-0.2 (-1.0-0.5)	1.4 (0.2-2.6)

[a] *CI: Confidence Interval. Stage-specific rate ratios and rate differences are adjusted for age, period, and immigration history (all as interactions with stage). Overall rate ratios and rate differences are adjusted for stage, age, period, and immigration history. Rate ratios were obtained directly from Poisson models; rate differences were post-estimated using pairwise comparisons of predicted incidence rates between education groups.*

4.1.3 Paper III: Stage-specific survival in young women

This study included 7,501 young women diagnosed with breast cancer at age 30 to 48 years during 2000-2015. Among women with localized breast cancer, there were few deaths and excess mortality did not vary by education or income level. However, for women with regional and distant stage breast cancer, excess mortality was significantly higher for compulsory versus tertiary educated patients and for women in the lowest and middle income groups compared to the highest income group during 2000-2015. Excess mortality for women with unknown stage at diagnosis did not vary by education or income level. Table 16 shows stage-specific excess mortality results by education level.

Table 16: *Summary of excess mortality results by education level for young breast cancer patients aged 30-48 years at diagnosis during 2000-2015 (N = 7,501 women) (Paper III).*

Education level	Total	Stage at diagnosis			
		Localized	Regional	Distant	Unknown
Breast cancer cases					
Compulsory	1,475	430	892	58	95
Secondary	2,896	885	1,726	91	194
Tertiary	3,130	1,002	1,839	84	205
Excess deaths					
Compulsory	323	33	216	55	16
Secondary	436	56	291	63	26
Tertiary	425	46	292	58	28
Excess mortality rate per 1,000 person-years					
Compulsory	27.2	7.6	29.2	417.1	19.0
Secondary	18.8	6.2	20.1	185.0	16.9
Tertiary	18.3	4.8	20.4	173.5	19.0
Excess mortality rate ratio (95 % CI)[a]					
Compulsory vs Tertiary	1.69 (1.40-2.05)	1.67 (0.95-2.93)	1.57 (1.27-1.95)	2.44 (1.66-3.59)	1.06 (0.53-2.12)

[a] *CI: Confidence Interval.*

From excess mortality models, we also predicted five-year relative survival during 2000-2015 for patients aged 40 years at diagnosis with a known stage at diagnosis. Predicted five-year relative survival was very high in all education and income groups, ranging from 96 to 99 % throughout 2000-2015. However, for regional and distant stage, five-year relative survival improved markedly over time for patients with a high education and/or high income level, but not at all for patients with both low education and low income level. Figure 14 shows the regional and distant stage five-year survival trends for women aged 40 years at diagnosis in the highest and lowest SES groups.

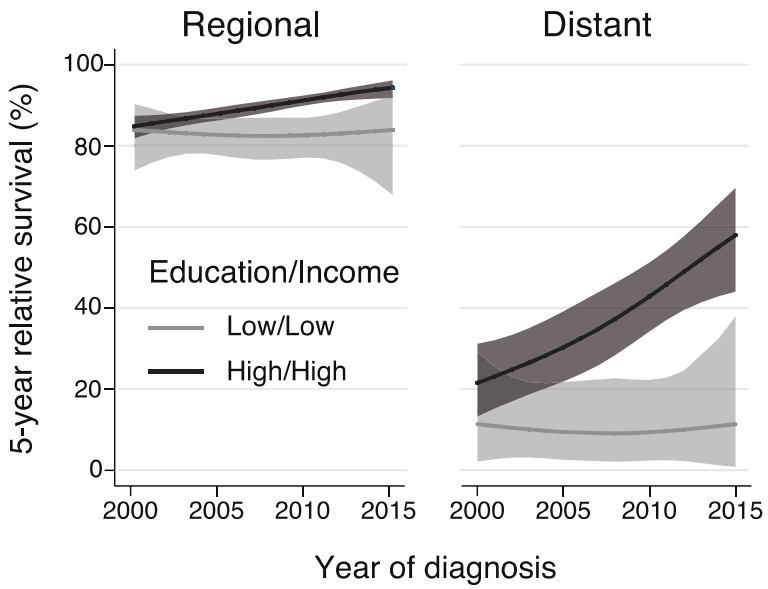

Figure 14: *Model-based predictions of regional and distant stage five-year relative survival with 95 % confidence intervals for breast cancer patients aged 40 years at diagnosis. Models based on women with the lowest and highest education/income level*[12] *(N = 3425 women) (Paper III).*

[12] *Education/Income group: Low/Low = Compulsory/Income quintile 1. High/High = Secondary-Tertiary/Income quintile 2-5.*

We also modelled relative survival up to 12 years from diagnosis for women aged 40 years at diagnosis in 2015. Figure 15 shows the predicted regional and distant stage relative survival by combined education and income group. These predictions suggest that at distant stage, lower educated patients do clearly worse than higher educated patients, regardless of income.

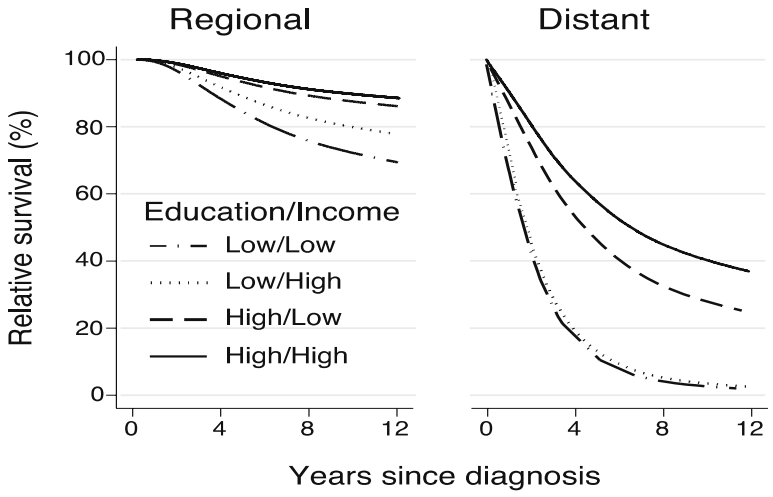

Figure 15: *Model-based predictions of regional and distant stage relative survival for breast cancer patients aged 40 years at diagnosis in 2015, by combined education/income*[13] *(Paper III).*

For comparison, we estimated relative survival from diagnosis using non-parametric methods for women diagnosed at 30-48 years during 2005-2015, and the results were similar (figure 16).

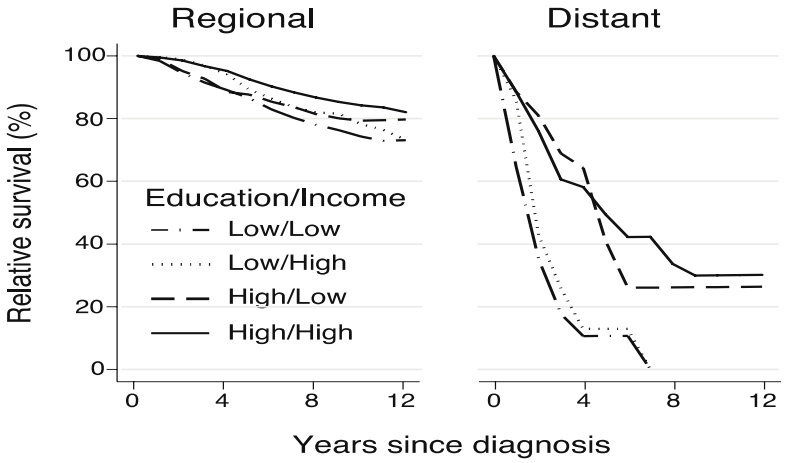

Figure 16: *Non-parametric estimates of relative survival for patients aged 30-48 years at diagnosis during 2005-2015, by combined education/income level*[13] *(Paper III).*

[13] *Education: low = compulsory; high = secondary-tertiary. Income: low = quintile 1, high = quintiles 2-5.*

Table 17 shows that the stage-specific relative survival estimates were similar using model-based predictions and non-parametric Pohar Perme estimates of relative survival.

Table 17: *Parametric[a] and non-parametric[b] estimates of stage-specific five-year relative survival with 95 % confidence intervals, by education level. Based on breast cancer patients aged 30-48 years with a known stage at diagnosis during 2000-2015 (N = 7007 women) (Paper III).*

Education level	Total	Stage at diagnosis		
		Localized	Regional	Distant
Predicted 5-year relative survival, 2015[a]				
Compulsory	86 (77-91)	97 (95-99)	86 (77-92)	12 (2-30)
Secondary	94 (90-96)	99 (98-100)	95 (92-97)	61 (42-75)
Tertiary	94 (91-96)	99 (98-99)	93 (89-95)	51 (35-66)
Difference in predicted relative survival in 2015				
Tertiary – Compulsory	9 (1 – 16)	1 (-1 – 3)	7 (-1 – 14)	39 (18–61)
Non-parametric 5-year relative survival, 2005-2015				
Compulsory	89 (87-91)	98 (95-99)	88 (85-87)	12 (3-27)
Secondary	93 (91-94)	98 (96-99)	91 (84-90)	51 (36-64)
Tertiary	93 (91-94)	98 (97-99)	92 (83-89)	46 (32-59)
Difference in non-parametric relative survival				
Tertiary – Compulsory	4	0	4	34

[a] *Estimated relative survival of breast cancer patients five years after diagnosis, compared to the expected survival for the Norwegian female population. Predicted for patients aged 40 years at diagnosis in 2015.*

[b]*Since the 2015 model-based predictions are outside the scope of the data, non-parametric (Pohar Perme) relative survival estimates for 2005-2015 are provided for comparison.*

5 DISCUSSION

5.1 Main findings

In the entire female Norwegian population, breast cancer incidence has increased over time from 1971 to 2015, whereas breast cancer mortality was steady until the mid-1990s and then started declining. Stage-specific survival improved between 2000 and 2015. The proportion of women aged 35 years and over with a higher education increased four-fold between 1971 and 2009. The national screening programme, BreastScreen Norway, was implemented county-wise for women aged 50 to 69 years during 1996-2004 and became nationwide from 2005.

Women with a high education level had higher incidence and mortality of breast cancer than women with a low education level throughout 1971 to 2009, although the incidence and mortality inequalities diminished over time for women below 70 years (paper I). Breast cancer incidence rates increased more gradually, and mortality rates declined more rapidly over time for women with a high compared to low education level. For young women below 50 years, the education gradient for breast cancer mortality reversed, and mortality rates became lowest for women with a high education level during 2000-2009 (paper I).

When breast cancer was assessed by stage, young women 30-48 years with high education or income level had a higher incidence of localized and regional stage breast cancer, but lower incidence of distant stage breast cancer, compared to young women with low education or income level during 2000-2015 (paper II). Five-year relative survival from localized breast cancer was very high in all education and income groups. However, five-year relative survival from regional or distant stage breast cancer was significantly better for young women with high compared to low education or income level, and the survival inequalities widened between 2000 and 2015. This was because five-year relative survival for regional and distant stage breast

cancer improved markedly over time for patients with high education or high income level, but not at all for patients with both low education and low income (paper III).

5.2 Young women below screening-age

5.2.1 Incidence inequalities

High SES women have the highest incidence, but low SES women are catching up

For decades, high SES has been associated with increased risk of breast cancer (60-64, 68, 107, 108). Our findings for young women confirmed this. We found significantly higher breast cancer incidence for high compared to low SES women aged 35-49 years throughout 1971 to 2009 (paper I). However, the incidence difference between high and low SES young women became smaller over time. Incidence rates increased in all SES groups, but most rapidly for low SES women (paper I). These findings were consistent with trend studies from Denmark (66) and Finland (67).

The underlying risk of breast cancer has probably increased the most over time for low SES women. Low SES women have had a greater increase in age at first birth and greater decrease in number of children over the past decades than high SES women (109). Age at first birth and parity are important risk factors for breast cancer and explain up to half of the socioeconomic inequalities in breast cancer incidence (62-65). We cannot rule out the possibility that increased screening use has also contributed to increased breast cancer incidence rates for young women in Norway. However, our young women were not invited to organised screening and it is unlikely that low SES women used private screening to a greater extent than high SES women (110-113).

5.2.2 Mortality inequalities

The socioeconomic gradient for mortality has turned

Previously, high SES women had the highest breast cancer mortality rates (60, 61, 63, 68, 83-86). However, we found that the socioeconomic gradient for breast cancer mortality has turned in the 2000s, and high SES women now have the lowest breast cancer mortality before age 50 years (paper I). A study of 18 European populations has also reported a similar turn of the SES gradient for breast cancer mortality for young women in the 2000s (114).

Low SES women lag behind in terms of reduced mortality

Low SES women lag behind with a more modest reduction in mortality over time compared to high SES young women (paper I). Breast cancer mortality started declining in the 1990s in most developed countries, including Norway (115). Studies in the United States (116), Finland (117), France (118) and New Zealand (119) all reported that the initial decline in breast cancer mortality in the 1990s occurred only among high SES women. The more modest mortality decline over time for our low SES women likely explains why high SES women have surpassed low SES women and now have the lowest breast cancer mortality rates before age 50.

Why has breast cancer mortality not fallen for low SES women?

Has the increase in breast cancer incidence hindered a fall in breast cancer mortality for low SES women? Or may have low SES women benefited less from diagnostic and treatment advances that have reduced mortality after breast cancer (41, 120-122)? The increase in breast cancer incidence will play some role but cannot be the whole story because high SES women are still diagnosed more often with breast cancer than low SES women.

Alternatively, do high SES young women die less often from breast cancer because they detect their tumours earlier when prognosis is better, or because they have better prognosis within each stage of diagnosis?

5.2.3 Stage-specific incidence inequalities

High SES women have the highest rates of localized and regional stage tumours

To address the question of whether earlier detection contributes to lower breast cancer mortality for high compared to low SES young women, we compared the stage-specific incidence of breast cancer between SES groups. High SES women had the highest incidence of localized and regional stage breast cancer, but the lowest incidence of distant stage breast cancer (paper II).

Others found less, but we found more regional stage tumours for high SES women

Our findings were consistent with studies of the stage distribution of breast cancer cases at localized and distant stage, but not at regional stage (55, 71-73, 77, 78). Our high SES women had higher regional stage incidence rates than low SES women. Other studies of stage distribution have reported a lower proportion of regional stage tumours for high compared to low SES women. Findings by stage distribution were generally consistent across different countries, age groups, periods, and type of SES measure. Other populations may therefore have a more extreme shift towards earlier detection for high compared to low SES women than we found for young women in Norway.

Screening may explain contrasting findings at regional stage

Other studies may have found a greater shift towards early detection, with a smaller proportion of regional stage tumours for high compared to low SES women, if high SES women more

often attended screening than low SES women in the other populations studied. When opportunistic and organised screening are considered together, high SES women are more likely to attend screening than low SES women (112, 113). Screening use is associated with an increase in overall incidence as well as a shift towards earlier detection (28, 123). For example, among 50 to 69 year-olds invited to organised screening in Norway, participants had 346 localized and 200 regional cases per 100,000 person-years, whereas non-participants had 173 localized and 172 regional cases per 100,000 person-years during 1996-2007 (28).

Our young women were not invited to organised screening. Private screening has been discouraged in Norway, and figure 2 suggests that few tumours were detected through private screening during 2016-2020. Our localized incidence rates were low, around half the rates of regional stage in all SES groups, suggesting that opportunistic screening was not widespread in our study population either during 2000-2015. We cannot exclude some possibility of a screening effect but believe that low rates of screen-detected cancers may explain why high SES women did not have a greater shift towards earlier detection or lower rates of regional stage breast cancer than low SES women in our young population.

Higher incidence of regional stage breast cancer for high SES women was a disadvantage. Breast cancer with regional spread has higher mortality than localized disease (45) and requires more aggressive treatment that can negatively impact the women's quality of life (87). Increased rates of regional stage disease for high compared to low SES women also indicates that high SES women had a true increased risk of breast cancer and not just increased detection of small, localized tumours due to excessive screening.

Modest inequalities at distant stage

Consistent with other studies (55, 70-73, 77, 78), we found that high SES women had less distant stage breast cancer than low SES women. However, our socioeconomic differences at distant stage were very modest and only significant when income was used as an SES measure. The very lowest income earners stood out with the highest distant stage rates, but absolute rates of distant stage breast cancer were very low in all SES groups, ranging from just two to three cases per 100,000 person-years. Universal health care access and good breast awareness may have helped to minimise late detection and minimise socioeconomic differences in distant stage breast cancer in our young population.

Other studies have generally reported more extreme socioeconomic differences at distant stage than we found. This may be a screening effect, with a more extreme shift away from late detection for high compared to low SES women in populations with more screen-detected cancers than was likely in our young population. Among women aged 50 to 69 years invited to organised screening in Norway, distant stage incidence was 9 cases per 100,000 person-years for participants and 31 cases per 100,000 person-years for non-participants of the screening programme during 1996-2007 (28).

In South-East England where the health care system is comparable to Norway, socioeconomic differences in distant stage breast cancer were modest for young women but more substantial for screening-aged women (55). This United Kingdom study and two United States studies of screened populations, one in California (72) and another using 11 SEER registries (70), all found that the likelihood of being diagnosed at distant stage was around half for high compared to low SES women. These findings were consistent using various individual and area-based SES measures. The United States studies hypothesized that socioeconomic differences in late-

stage breast cancer diagnoses were due to unequal health care access and differences in screening use between SES groups.

5.2.3.1 Impact of stage-specific incidence inequalities

What impact may the inequalities in stage-specific incidence have on inequalities in breast cancer mortality? First, we need to understand the link between stage and breast cancer mortality, which depends on how many women are diagnosed, and how many die, at each stage of diagnosis.

Around one third of our young women with breast cancer were diagnosed with localized tumours (paper III). However, few women die from breast cancer diagnosed at localized stage. The mortality of women with localized breast cancer is no worse than that of the same aged general population (46). Localized stage therefore contributed only 10 % of deaths within 12 years after diagnosis in young women with breast cancer (paper III).

Almost two thirds of our young women with breast cancer were diagnosed with regional spread (paper III). Most women diagnosed at regional stage will survive their breast cancer. Five years after diagnosis, the probability of being alive compared to the same aged general population is 96 % for early-regional stage (TNM stage II) and 79 % for late-regional stage (TNM stage III) in Norway (46). However, the sheer number of women diagnosed at regional stage, twice as many as localized stage and twenty times as many as distant stage, means that regional stage accounted for 70 % of deaths within 12 years of diagnosis among young women with breast cancer (paper III).

Just 3 % of our young women with breast cancer were diagnosed at distant stage (paper III). However, most women diagnosed at distant stage die from their breast cancer. Five years after diagnosis, just one third of women diagnosed at distant stage are still alive, compared to what we expect for the same aged general population in Norway (46). However, due to the small proportion of women diagnosed at distant stage, just 15 % of all deaths within 12 years after diagnosis were among women diagnosed at distant stage (paper III).

Seven in ten breast cancer deaths from regional stage

Combined, localized and distant stage represented 25 % of deaths within 12 years of diagnosis for young women with breast cancer. An additional 5 % of the deaths occurred among women with unknown stage at diagnosis. The remaining 70 % of deaths came from women with regional spread at diagnosis. Incidence rates of regional stage breast cancer therefore have the most bearing on mortality rates of breast cancer.

Earlier diagnosis is not the key to lower breast cancer mortality for high SES women

Inequalities in regional stage breast cancer incidence have the most bearing on inequalities in breast cancer mortality. Inequalities at localized and distant stage will have some bearing.

We found that high SES women had the highest rates of both localised and regional stage breast cancer, and only marginally less distant stage breast cancer than low SES women. Thus, earlier detection cannot be the main explanation for why breast cancer mortality is lowest for high SES young women in Norway.

5.2.4 Stage-specific survival inequalities

High SES women have better regional and distant stage survival

We next addressed whether better prognosis within each stage of diagnosis may explain the lower breast cancer mortality for high SES women. We compared the stage-specific survival of breast cancer between SES groups for women aged 30-48 years during 2000-2015 (paper III). We found that five-year relative survival for women diagnosed with localized breast cancer was very high in all SES groups, but high SES women had significantly better regional and distant stage survival than low SES women, and survival differences widened over time.

Our findings were in line with previous studies, with better stage-specific survival for high compared to low SES women (69, 77, 81). However, our finding of no significant difference at localized stage contrasts with other studies (69, 77, 81). Our high SES women did have somewhat better localized survival than low SES women, but the difference was non-significant, probably because there were so few deaths among women diagnosed at localized stage in our population.

Low SES women lag behind in terms of improved regional and distant stage survival

Our study extends on earlier research by additionally assessing trends over time in stage-specific survival inequalities. We found that regional and distant stage survival improved markedly between 2000 and 2015 for high SES women, but there was little gain for low SES young women. For women with the lowest education and income level, there was no gain at all over time in regional or distant stage survival (paper III).

To our knowledge, no earlier studies have assessed trends over time in stage-specific survival by SES. Several studies have assessed SES trends for overall breast cancer survival for women

of all ages (79, 124-128). Studies conducted in Denmark (124), England (125), Japan (126), New Zealand (127) and Australia (128) have all reported improved survival over time for all SES groups, but persistent survival inequalities throughout the 1990s and 2000s. The exception was a Norwegian study that found a greater survival gain over time for higher compared to lower educated women of all ages between 1970 and 2007 (79). This was consistent with our findings of greater regional and distant stage survival gains for high compared to low SES young women between 2000 and 2015 (paper III).

Thus, it seems that equal access to health care has not been sufficient to ensure that women from all socioeconomic backgrounds have benefited from diagnostic and treatment advances that have improved survival after breast cancer for young women in Norway.

Why have low SES women not experienced the same survival gain as high SES women?

Why has survival from breast cancer stagnated for low SES women? Have they not had equal access to new treatment? Has an unhealthy lifestyle hindered them from surviving? Did their place of residence influence treatment? Or has communication with physicians, access to information, or level of social support played a role? We do not have any definitive answers but will discuss the possibilities.

First, we must address the possibility that treatment was differential, even in a country with universal health care and national treatment guidelines. Several Norwegian studies have found differential treatment of cancer patients by socioeconomic background (129-131). These studies have found that high SES cancer patients received more hospital-based medical services (130) and more palliative radiotherapy (129) than low SES cancer patients. High SES lung cancer patients received more surgery and more radical and palliative radiotherapy than low SES lung

cancer patients (131). Studies from other countries with universal health care have also reported that low SES breast cancer patients were less likely to receive surgery or radiotherapy than high SES patients, for example in the United Kingdom (71, 132) and Sweden (133, 134). It therefore seems viable that some of our observed survival inequalities for regional and distant stage breast cancer could be due to differential treatment by socioeconomic background.

While breast cancer treatment may have differed by socioeconomic background, the treatment differences may not have been systematic due to SES. For example, an unhealthy lifestyle or comorbidities may have more often prevented low SES women from receiving the recommended treatment than high SES women. A Danish study reported that low SES women more often had comorbidity or an unhealthy lifestyle at the time of breast cancer diagnosis than high SES women (135). Comorbidity only seems to play a minor role in breast cancer survival inequalities (135, 136), but lifestyle factors, such as smoking and obesity, seem to contribute more so to survival inequalities (135).

Another possibility is that treatment differences arose due to place of residence. Low SES women more often live rurally and further away from the larger university hospitals where treatment is most cutting edge and clinical studies of new treatments are most often conducted. A recent Norwegian study found significant regional variation in breast cancer survival, even after accounting for tumour and patient factors, and whether patients had received surgery or radiotherapy (137). These authors hypothesized that unexplained regional variation in survival were due to differences in the quality of cancer care provided between regions. Patients have free choice of hospital, but low SES women living rurally may be less able or willing to travel long distances to the larger university hospitals than high SES women who live rurally.

Communication and involvement in the decision-making process are also factors that could have contributed to any treatment differences between high and low SES women. A United Kingdom survey reported that breast cancer patients living in affluent areas were more likely to seek information from hospital specialists, nurses or family and friends, than patients living in deprived areas (138). A recent Swedish survey also found that patients who reported that they were well informed and involved in the decision-making process were more likely to receive immediate breast reconstruction (134). The same study reported that high SES patients more often received immediate breast reconstruction than low SES patients.

Finally, psychosocial factors may have contributed to survival differences between SES groups. High SES breast cancer patients tend to have better social support (138), which is associated with seeking timely and appropriate diagnosis and treatment (139) and with better survival (80, 140). High SES breast cancer patients are also less likely to suffer from psychological distress (138), which has been linked to poorer breast cancer survival (141).

5.2.4.1 Impact of stage-specific survival inequalities

Improved regional and distant stage survival key to reduced mortality for high SES women

For young women in Norway, improved regional and distant stage survival seems to have contributed more than earlier detection to the greater fall in breast cancer mortality for high compared to low SES young women. Likewise, a recent Swedish study found that young women had more life years to gain by removing inequalities in stage-specific relative survival than by removing differences in stage distribution between higher and lower educated women (82). Further, stage has been found to explain only one third of socioeconomic inequalities in breast cancer survival among women of all ages in the United Kingdom (132) and New Zealand (142, 143).

Most to gain by improving regional stage survival of low SES women

Low SES women have had a greater increase in risk of breast cancer and at the same time have not experienced the same improvement in survival after diagnosis as high SES women. These two factors combined explain why low SES women have only had a modest reduction in breast cancer mortality and now die more often from breast cancer than high SES young women.

Women with regional stage breast cancer is the largest group of patients with respect to number of new cases and number of deaths. Thus, efforts to improve the survival of low SES patients diagnosed at regional stage could be the most effective means for reducing mortality from breast cancer among young women in Norway.

5.3 Screening-aged and older women

5.3.1 Incidence inequalities

Breast cancer incidence remained significantly higher for high SES women of screening age (50-69 years) and older (70 years and over) throughout the period before, during, and after screening implementation (paper I). Screening was introduced county-wise for women aged 50-69 years, starting with large city counties during 1996-1999 and then remaining counties during 2000 to 2004. The programme was nationwide from 2005 (33).

5.3.1.1 Screening-aged women

Incidence inequalities widened in the 1990s then narrowed in the 2000s

In the 1990s, breast cancer incidence rose more steeply for high SES women, and incidence differences between high and low SES women widened, consistent with findings from earlier Norwegian studies (62, 68). In the 2000s, incidence rates flattened out for high SES women but

rose more steeply for low SES women, and incidence differences narrowed (paper I). Most probably, screening implementation and patterns of postmenopausal hormone therapy use explain incidence trends for high and low SES women of screening age in the 1990s and 2000s.

An increase in breast cancer incidence is expected after the first wave of organised screening (144). High SES women were overrepresented in the large city counties that first started screening during 1996-1999, whereas low SES women were overrepresented in more rural counties where screening implementation came later during 2000-2004. This incremented implementation of screening may partly explain why incidence first rose for high SES women in the 1990s, then later for low SES women in the 2000s.

Further, use of combined postmenopausal hormone therapy increases risk of breast cancer (14-16). In Norway, postmenopausal hormone therapy sales increased drastically in the late 1990s, peaked around 1997-2002, then fell drastically from 2003 (145), after publication of the Women's Health Initiative randomized clinical trial linking hormone therapy to breast cancer (146). A Norwegian survey found that high SES women were the most frequent users of postmenopausal hormone therapy when sales were at their peak in 1997 and 2002 but had reduced their hormone therapy use to the same level as low SES women by 2005, after sales had declined (147). A reduction in use of hormone therapy among high SES women after 2002 probably contributed to the flattening of their incidence curve in the 2000s.

It is difficult to separate the effects of screening from hormone therapy because the Norwegian Prescription Database did not collect individual data on prescriptions before 2005. However, two ecological studies estimated that screening and hormone therapy use contributed approximately equally to rises in breast cancer incidence during the 1990s and early 2000s (144, 148).

To sum up, saturation of screening uptake and reduced use of hormone therapy probably contributed to the flattening of incidence rates for high SES screening-aged women in the 2000s, whereas delayed screening uptake on average for low SES women may explain their later rise in breast cancer incidence in the 2000s.

5.3.1.2 Older women

Incidence inequalities narrowed in the 1990s then widened in the 2000s

For older women aged 70 years and over, incidence trends by SES were different to screening-aged women. Incidence inequalities first narrowed in the 1990s and then widened significantly again in the 2000s, when incidence rates rose for high SES women but fell for low SES women over 70 years (paper I).

It is possible that elevated incidence rates for high SES older women in the 2000s was partly due to their more frequent use of combined postmenopausal hormone therapy in the late 1990s and early 2000s. Excess risk of breast cancer seems to persist for more than 10 years after ceasing use (14, 149).

Patterns of screening use may have also contributed to the differing incidence trends by SES in the 2000s. We expect a fall in breast cancer incidence in the first years after women leave a screening program (144). We observed such a decline for low SES women in the 2000s, but not for high SES women. Perhaps high SES women continued with private screening after exiting the national screening programme at age 70 years?

We do not have any individual data on private screening use, but other studies suggest that high SES women more often attend private screening than low SES women (112). Further, statistics from the Norwegian Breast Cancer Registry show that women over 70 years are more likely to have their breast cancer detected through private screening than screening-aged or younger women (figure 2). For women diagnosed with localized breast cancer, the proportion who were diagnosed via private screening was 8 % for women aged 70 years and over, compared to just 2 % for screening-aged women and 4 % for younger women.

Further, we have unpublished results shown in table 18 that the presence of organised screening seems to be associated with reduced incidence inequalities while women are in the screening program, but increased incidence inequalities after women leave the program at age 70 years (table 18). Among older women who were potentially invited to organised screening before they turned 70 years, higher educated women had twice the incidence of breast cancer as lower educated women after age 70 years. On the other hand, breast cancer incidence did not vary significantly by education level for women aged 70-82 years who did not reside in a county where screening was implemented before they turned 70 years.

Table 18. *Breast cancer incidence rate ratios (RR) with 95 % confidence intervals (CI) for tertiary versus compulsory educated women before, during and after screening implementation in Norway, 1988-2009 (2,796,702 person-years; 26,080 breast cancer cases). Findings published in an abstract*[14].

Period		Screening status before age 70[a]	52-69 years RR[b] (95 % CI)	70-82 years RR[b] (95 % CI)
Pre-screening	**1988-1995**	Not invited	1.38 (1.26-1.52)	1.22 (1.07-1.40)
Screening implementation	**1998-2005**	Not invited	1.42 (1.25-1.62)	1.20 (0.92-1.57)
		Potentially invited	1.26 (1.15-1.38)	1.98 (1.68-2.38)
Post-screening	**2006-2009**	Potentially invited	1.21 (1.12-1.31)	Not available

[a] *Screening status: Not invited = women who did not reside in a county where screening was offered while they were aged 50-69 years; Potentially invited = women who resided in a county where screening was offered for at least two years while they were aged 50-69 years. Since invitations were biennial, women who resided in a county where screening was offered for 0 to 23 months while they were aged 50-69 years were excluded from the analysis.*

[b] *Rate Ratios were adjusted for age, calendar year, birth cohort and county of residence.*

We cannot link with any certainty these unpublished results to continued private screening use by high SES women after exiting organised screening. However, it seems that the presence of organised screening is in some way associated with greater incidence inequalities after exiting the screening programme.

To sum up, previous use of postmenopausal hormone therapy may have increased breast cancer risk in the 2000s to a greater extent for high compared to low SES older women. High SES women may have also continued with private screening to a greater extent than low SES women

[14] Trewin CB, Ursin G, Weedon-Fekjær H, Strand BH. How does mammography screening influence educational inequalities in breast cancer incidence in Norway? Abstract at the Association of the Nordic Cancer Registries (ANCR) Symposium, 2015, Helsingør, Denmark.

after exiting the organised screening programme at age 70 years, contributing to their elevated incidence rates after age 70 years in the 2000s.

5.3.1.3 Possible effects of screening implementation on stage inequalities

A recent Norwegian study reported similar attendance rates at screening for higher and lower educated women who were invited to 10 screening rounds during 1996-2019 (150). Screening attendance was actually somewhat lower for higher compared to lower educated women, although the differences were small. A review of organized screening in 17 European countries (113) supports the Norwegian study findings of somewhat lower organised screening attendance among higher compared to lower educated women. The authors of both the Norwegian (150) and European (113) study hypothesized that higher educated women may prefer to use private screening at their convenience rather than attending a scheduled invitation. Supporting this notion, a 2006 survey of organised and opportunistic screening among 5,327 screening-aged women in 27 European countries (excluding Norway) found that higher educated women had marginally lower organised screening attendance, but significantly higher opportunistic screening attendance, compared to lower educated women (112).

For our women aged 50 to 69 years, organised screening implementation probably led to a fairly similar increase in incidence of localized breast cancer and a shift towards earlier detection for all SES groups (28, 151). However, if our hypothesis is true that high SES women aged 70 years and over more often continued with private screening after exiting the screening programme, there may have been a somewhat greater increase in localized incidence rates and shift towards earlier detection for high compared to low SES women aged 70 years and over.

5.3.2 Mortality inequalities

5.3.2.1 Screening-aged women

Greatest reduction in mortality for high SES women

Throughout the 1970s to 1990s, breast cancer mortality remained significantly higher for high compared to low SES women of screening age (paper I), in line with finding for 11 European populations in the 1990s (85, 86). However, we found that high SES women had a greater decline in breast cancer mortality than low SES women of screening age from the mid-1990s, consistent with findings from other countries (65, 116, 117, 119) and with our findings for young women below screening age. In the 2000s, breast cancer mortality no longer varied significantly by SES for screening-aged women (paper I). Our mortality trends for screening-aged women from the 1990s to the 2000s are also consistent with a study of breast cancer mortality inequalities in 18 European populations (114).

Why has mortality not fallen so much for low SES screening-aged women?

Implementation of organised screening is linked to reduced breast cancer mortality (34, 36-38). So why have low SES women not had the same mortality reduction as high SES women during and after screening implementation?

Low SES women entered the screening programme later in time on average, so may have a delayed reduction in breast cancer mortality compared to high SES women, just as we saw a delayed increase in incidence for low SES women during the screening implementation period. Further, stage-specific survival could have improved more over time for high compared to low SES screening-aged women, just as we observed for young women. This could be if our hypotheses for young women also applied to screening-aged women, such as differential

treatment by SES or lesser comorbidity and healthier lifestyle among high compared to low SES women.

To sum up, both earlier detection through screening and improved stage-specific survival could have played a role in the greater breast cancer mortality reduction for high compared to low SES screening-aged women since the mid-1990s. Over time as we see the full effects of organised screening for both high and low SES women, any differences in early detection between high and low SES women may be reduced. Thus, any remaining mortality inequalities may be most likely due to differences in stage-specific survival, for example due to differential treatment or patient factors.

5.3.2.2 Older women

Persistently higher mortality for high SES older women

Breast cancer mortality remained significantly higher for high compared to low SES older women throughout 1971 to 2009 (paper I). We did not see a greater fall in mortality for high compared to low SES older women from the mid-1990s, as we observed for screening-aged and younger women. Instead, breast cancer mortality fell similarly over time for high and low SES older women.

Perhaps SES has not played such a role for breast cancer mortality in older women, as we found for screening-aged and younger women? Perhaps treatment or other factors influencing stage-specific survival have been more equable among older women?

Alternatively, the positive effects of screening and negative effects of hormone therapy use on breast cancer mortality may have cancelled each other out for high SES women. Given that

screening started earlier in urban high SES cities, there were potentially more high than low SES women who had their breast cancer detected through screening before they turned 70 and therefore had reduced mortality due to earlier detection. At the same time, more high SES older women will have been previous users of postmenopausal hormone therapy, which is associated with elevated breast cancer mortality for more than a decade after ceasing use (14, 152). Thus, elevated mortality due to previous hormone therapy use may have offset any greater mortality reductions due to earlier screening implementation for high SES women.

5.3.3 Summary of incidence and mortality inequalities

For screening-aged women, high SES women are still diagnosed more often with breast cancer, but no longer die more often from breast cancer than low SES women. We believe that improved stage-specific survival likely plays a greater role than earlier detection in the greater reduction in breast cancer mortality over time for high compared to low SES screening-aged women, in line with our observations for younger women.

Among older women, high SES women are still more likely to be diagnosed and to die from breast cancer than low SES women. Either SES plays less of a role for mortality after breast cancer for older women, or different factors in favour or disfavour of high SES women cancel each other out.

5.4 Methodological considerations

5.4.1 Data quality

This thesis used Norwegian registry data of high quality and high completeness with mandatory reporting. The Norwegian Standard Classification of Education has good comparability with the International Standard Classification of Education (90). The Cancer and Cause of Death

Registries also follow the international classification of disease (89, 92). The Cause of Death Registry has high completeness and quality (88). An evaluation of data quality at the Cancer Registry of Norway found 98.8 % completeness of cancer cases and 99.3 % histologically verified breast cancer cases during the registration period 2001-2005 (92). From an international perspective, few breast cancers in Norway were based on death certificate only (5), which is an important indicator of validity (153).

5.4.2 Bias and confounding

5.4.2.1 Information and selection bias

Our target study population was the entire female Norwegian population for the breast cancer incidence and mortality analyses (papers I and II) and all women diagnosed with breast cancer for the survival analysis (paper III). In our data, cancer and cause of death data were individually linked for every female inhabitant of Norway. Follow up for cancer, migration or death was virtually complete. All data was registry-based and not self-reported, so there was likely minimal information bias.

One limitation was that personal income was only available as five-year averages. Women were classified by income prior to diagnosis in our survival analyses. Five-year average income may have varied from actual income at diagnosis for women with fluctuating income over time. However, five-year average income would have been a reasonable indicator of accumulated wealth at the time of diagnosis. Given that the results for income and education were similar, we believe that any bias from misclassification of income was likely minimal.

In terms of selection bias, we included the entire female population, and therefore the possibilities for selection bias should be small. However, we excluded 7-9 % of eligible women

from our studies due to unknown SES level. Nearly all of these women were immigrants, and immigrants from low income countries have lower risk of breast cancer (154, 155). We therefore performed two sensitivity analyses for breast cancer incidence and mortality (paper I). First excluding all immigrants, and second adjusting for immigration status and ethnic background. These analyses did not alter our findings, so we believe our findings were minimally influenced by selection bias due to excluding women with unknown SES.

5.4.2.2 Unknown stage at diagnosis

Another potential source of bias for papers II and III was missing stage information. Less than 7 % of women had unknown breast cancer stage at diagnosis, but a higher proportion of high SES than low SES women had unknown stage. Stage is unknown when hospitals have not sent in clinical or pathological reports, and for women who have received neoadjuvant treatment to shrink the tumour size before surgery. In the first instance, there is no reason to believe hospital reporting varied by patient's socioeconomic background. More probably, high SES women more often received neoadjuvant treatment than low SES women. This could simply be because high SES women were more often treated at university hospitals where neoadjuvant treatment is most frequently used (156).

Missing stage due to lack of reporting is probably randomly distributed across stages (missing at random), whereas missing stage due to neoadjuvant treatment will be primarily regional stage tumours (not missing at random). Regional stage incidence may have therefore been underestimated most for high SES women, who already had the highest rates of regional stage disease. Incidence of unknown stage was low, just one tenth the rate of regional stage. Therefore, missing stage was unlikely to have impacted our findings for stage-specific incidence inequalities (paper II). In paper III, we found the survival of women with unknown

stage at diagnosis did not vary by SES. Missing stage was therefore unlikely to have impacted our findings for stage-specific survival (paper III).

5.4.2.3 Stage migration

Over time, changes to stage classifications can lead to tumours becoming categorised as either a more advanced stage (upstaging) or less advanced stage (downstaging) than previously (45). With upstaging, the "worst" tumours in a lower stage will become the "best" tumours in a higher stage, and survival will improve for patients in both stages. The opposite is true with downstaging. Upstaging may be more likely than downstaging.

One source of upstaging is more modern and increased use of diagnostic equipment, such as MRI and positron emission tomography (PET), and improved methods for sentinel node detection. With more diagnostic testing and better sentinel node detection, more metastases will be found. Thus, breast cancers may be assigned to a higher stage than otherwise. Norway has national guidelines for diagnostic testing, so socioeconomic background should not influence diagnostic testing or sentinel node detection.

However, as discussed earlier, high SES women may more often live in large cities near university hospitals, where diagnosis and treatment are most cutting edge. Thus, due to their place of residence, high SES women may have had more diagnostic testing and sentinel node detection than low SES women and hence been more influenced by upstaging. It is reasonable that upstaging explains some of our observed improvements in regional and distant stage survival over time for high SES women. Nevertheless, the lack of any improvement at all over time in regional or distant stage survival for low SES women is of greater concern.

One potential weakness of this thesis is that we did not have more detailed information on TNM stage and could not divide regional stage into TNM stages II and III. Nevertheless, coding changes performed by the Cancer Registry in 2008 resulted in substantial stage migration between TNM stages II and III (45), which would have made it complicated to compare stage-specific survival trends over time for stages II and III.

5.4.2.4 Lead-time and length time bias

Asymptomatic breast cancer detected through screening is particularly susceptible to lead-time and length-time bias. This can lead to a superfluous increase in estimated survival from diagnosis. We therefore restricted our survival analyses to young women who were not invited to organised screening. Some of these women may have attended private screening. Evidence from other countries suggest that high SES women more often screen themselves opportunistically (112). However, our low localized disease rates and modest stage variations by SES in paper II suggest that opportunistic screening was not widespread among high SES women in our study population (paper II). Data from the Norwegian Breast Cancer Registry also show that private screening was the first contact point for just 2 % of women diagnosed with breast cancer before age 50 years during 2016-2020 (figure 2).

To further minimise issues with lead-time and length-time bias, we compared stage-specific survival rather than overall survival in paper III. Lead-time and length-time bias may have the greatest impact on estimates of survival for localized tumours. We found that survival from localized disease was very high in all SES groups, again suggesting that there were no great differences between SES groups in rates of asymptomatic screen-detected tumours in our young population (paper III). Our greatest observed survival differences were at regional and distant stage, where lead-time and length-time bias are less likely to be an issue.

5.4.2.5 Residual confounding and effect modification

We adjusted for age and calendar period in all three papers. Immigration status was assessed as a potential confounder in all analyses, but only included in the final model for stage-specific incidence (paper II). In survival analyses, tumour grade and subtype were assessed as potential confounders but not included in final models (paper III). We lacked information on residential area, which was a potential confounder or effect modifier in all analyses. Place of residence (rural/urban) could be associated with both socioeconomic level and breast cancer outcomes (68), possibly through factors such as screening, diagnostic testing, and treatment.

Age at first birth and parity have been shown to explain around half of the socioeconomic inequalities in breast cancer incidence (62-65) and all the inequalities in breast cancer mortality among parous women in Norway during the 1990s (85). No studies have assessed to what extent reproductive factors explain changing patterns of breast cancer incidence and mortality inequalities over time. It would have been an advantage to have data on reproductive factors as well as postmenopausal hormone therapy and screening to better understand how these factors have influenced incidence and mortality trends over the 1990s and 2000s.

Interpretation of our observed trends in survival inequalities would have been strengthened if we had data on potential mediating factors, such as treatment, lifestyle factors or comorbidity. However, such data was either not readily available for our study period or did not have sufficient completeness or quality at the time that the datasets for this thesis were created. We have instead discussed above the possible role of these factors based on findings from other studies.

5.4.3 Measures of inequality

A strength of this thesis was that we used different SES measures. Our interpretations are strengthened by the fact that we had similar findings for both education and income as socioeconomic measures (53). One potential weakness was that the Norwegian education classification was changed in 2006 (90), and our definition of high education level became stricter in papers II and III, but on the other hand more internationally comparable. We used a less strict definition of high education in paper I, but also more extreme estimates of inequality, RII and SII, that compared the theoretically highest and lowest ranked individual in the population, rather than the highest and lowest group. Use of the RII and SII was particularly important for paper I where the distribution of education level varied greatly over time and age. The RII and SII are particularly well suited for comparing populations where the relative sizes of socioeconomic groups differ (97).

5.4.4 Statistical methods

In paper II, we compared stage-specific incidence rather than the more commonly used stage distribution of breast cancer cases. Stage-specific incidence measures absolute risk in the population and has the advantage of having the same denominator as breast cancer mortality. Comparing the stage distribution of cases does not account for the higher absolute risk of breast cancer among high compared to low SES women in the population. High SES women could potentially have a smaller proportion of breast cancer cases at a given stage, but still higher absolute incidence rate at that stage. Stage-specific incidence is easier to interpret than stage distribution of cases in the context of whether earlier detection plays a role in breast cancer mortality inequalities in the population. This was a key strength of our methods chosen for paper II.

In paper III, a small number of patients were diagnosed at distant stage, which was a potential weakness for our stage-specific survival models. Consequently, our distant stage survival estimates had wide confidence intervals. However, our findings at distant stage were strengthened by similar survival trends at regional stage, where patient numbers were much higher. We also found similar regional and distant stage survival trends with non-parametric and parametric estimates of relative survival, which further strengthens the plausibility of our findings for inequalities in stage-specific survival.

We considered several alternative methods for paper III. First, the number of avoidable deaths if we eliminated socioeconomic differences in stage at diagnosis (54, 55); second, the potential gain in life years if we eliminated differences in stage and survival (54, 82); and third, the restricted mean survival time (157, 158). We instead chose to estimate stage-specific relative survival because it would be easier to interpret the findings for paper II (stage-specific incidence) and paper III (stage-specific survival) in the context of each other. Cause of death reporting should be very complete for young women, so relative and cause-specific survival should have been very similar.

With the flexible parametric model used in paper III, we could also model changing trends over time in survival inequalities, even with our small population size at distant stage. Modelling survival trends enabled us to interpret the findings of paper III in the context of breast cancer mortality trends in paper I. By choosing comparable methods for papers I, II and III, we were able to draw the conclusion that improved stage-specific survival most likely played a greater role than earlier detection in the more rapid decline in breast cancer mortality over time for high compared to low SES women in Norway.

6 CONCLUSIONS

6.1 Conclusions

Breast cancer has been a disease of affluence, with higher incidence and mortality, despite better survival, for women with high compared to low SES. This thesis revealed a changing pattern of inequality in incidence, survival and mortality from breast cancer favouring high SES women. Incidence rates remained highest for high SES women, but inequalities have reduced over time. Survival has improved, and mortality from breast cancer declined, to a greater extent for high compared to low SES women. For screening-aged women, high SES women previously had the highest breast cancer mortality, but now have the same breast cancer mortality as low SES screening-aged women. For young women below screening-age, breast cancer mortality inequalities have reversed, and high SES young women now have the lowest breast cancer mortality rates.

Earlier detection does not seem to explain the better outcomes for young women with high SES. Instead, high SES women have had greater gains in survival from breast cancer with regional or distant spread. In a country with universal health care, the main challenge does not seem to lie in equality of stage of detection of breast cancer, but rather in equality of prognosis after diagnosis. It is not clear whether inequalities in prognosis after diagnosis are related to patient factors or to quality of healthcare delivered. Given that women with regional stage breast cancer is the largest group with respect to number of new cases and deaths, improving the survival of low SES patients diagnosed at regional stage could be the most effective means for reducing mortality from breast cancer in the population.

6.2 Future perspectives

An important next step would be to determine whether socioeconomic inequalities in survival from regional and distant stage breast cancer are also widening for screening-aged or older women. Mammography screening provides an added challenge for comparing the survival of women diagnosed at 50-69 years. It would therefore be important to account for screening history and detection mode when comparing the survival of screening-aged women.

Another important next step would be to determine why low SES women lag behind in terms of improved regional and distant stage survival, and what we can do about it. Potential factors that would be interesting to assess include lifestyle choices before and after diagnosis, comorbidities, residential area or hospital, neoadjuvant treatment, surgery, radiotherapy, and systemic treatment. It would also be interesting to find out if patient reported experience measures (PREMs) such as involvement in treatment decisions or patient reported outcome measures (PROMs) such as quality of life or side effects after breast cancer treatment, vary by socioeconomic background.

With existing data and the appropriate permissions and data linkages, it would be possible to investigate the role of socioeconomic differences in comorbidity, neoadjuvant treatment, type of surgery, extent of reoperations, operation volume where surgery is performed and radiotherapy. Access to good information on systemic treatment has been limited but will be soon available in Norway for patients diagnosed from 2019. Patient reported experience and outcome measures have been collected since 2020. Information on the lifestyle of patients is less readily available but may be obtained for a selection of the Norwegian population through health surveys, such as the Trøndelag Health (HUNT) Study, the Trømso Study, the Norwegian Women and Cancer (NOWAC) cohort study, and mammography screening questionnaires.

Future studies should also include more detailed information tumour size and extent of nodal spread at diagnosis than was available in this thesis, to give the possibility to assess stage-specific incidence and stage-specific survival within more refined staging groups according to TNM stage.

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Paper I

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I

Paper II

Trewin CB, Hjerkind KV, Johansson ALV, Strand BH, Kiserud CE, Ursin G: Socioeconomic inequalities in stage-specific breast cancer incidence: a nationwide registry study of 1.1 million young women in Norway, 2000–2015. *Acta Oncologica* 2020, 59(11): 1284-1290. Doi: 10.1080/0284186X.2020.1753888.

II

Paper III

Trewin CB, Johansson ALV, Hjerkind KV, Strand BH, Kiserud CE, Ursin G: Stage-specific survival has improved for young breast cancer patients since 2000: but not equally. *Breast Cancer Res Treat.* 2020, 182(2):477-489. Doi: 10.1007/s10549-020-05698-z.

III

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EPIDEMIOLOGY

Stage-specific survival has improved for young breast cancer patients since 2000: but not equally

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Abstract

Purpose The stage-specific survival of young breast cancer patients has improved, likely due to diagnostic and treatment advances. We addressed whether survival improvements have reached all socioeconomic groups in a country with universal health care and national treatment guidelines.

Methods Using Norwegian registry data, we assessed stage-specific breast cancer survival by education and income level of 7501 patients (2317 localized, 4457 regional, 233 distant and 494 unknown stage) aged 30–48 years at diagnosis during 2000–2015. Using flexible parametric models and national life tables, we compared excess mortality up to 12 years from diagnosis and 5-year relative survival trends, by education and income as measures of socioeconomic status (SES).

Results Throughout 2000–2015, regional and distant stage 5-year relative survival improved steadily for patients with high education and high income (high SES), but not for patients with low education and low income (low SES). Regional stage 5-year relative survival improved from 85 to 94% for high SES patients (9% change; 95% confidence interval: 6, 13%), but remained at 84% for low SES patients (0% change; − 12, 12%). Distant stage 5-year relative survival improved from 22 to 58% for high SES patients (36% change; 24, 49%), but remained at 11% for low SES patients (0% change; − 19, 19%).

Conclusions Regional and distant stage breast cancer survival has improved markedly for high SES patients, but there has been little survival gain for low SES patients. Socioeconomic status matters for the stage-specific survival of young breast cancer patients, even with universal health care.

Keywords Breast neoplasms · Stage at diagnosis · Socioeconomic factors · Relative survival · Excess mortality

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Abbreviations

SES	Socioeconomic status
HER2	Human epidermal growth factor receptor 2
ER	Estrogen receptor
PR	Progesterone receptor
Q	Quintile
TNM	Tumor size, nodal status and metastasis
CI	Confidence interval

Introduction

Stage-specific and overall survival of breast cancer patients has improved over time [1, 2], probably due to advances in diagnostics and treatment. More precise diagnosis of tumor type and stage has enabled treatment to become more tailored to the patient [3–6]. New treatments have also improved the survival of patients with certain tumor subtypes, for example Herceptin has improved the survival of HER2 positive patients [7, 8]. Although breast cancer survival has been improving, there is concern that patients with low socioeconomic status (SES) have not gained as much from recent advancements [9–14].

Like several other countries, Norway has a universal tax funded health care system with the aim to minimize socioeconomic differences in access to diagnostic and treatment care. A nationwide screening program, gradually introduced during 1996–2004, has also ensured universal access to early detection of breast cancer for women aged 50–69 years in Norway. However, younger women may have different diagnostic and care seeking behavior than screen-aged women. Young women fare worse than screen-aged women in terms of breast cancer survival, even after adjustment for tumor characteristics [15–17].

Thus, we were interested to know whether access to universal health care has been sufficient to ensure that breast cancer survival has improved for young women from all socioeconomic backgrounds. Studies of socioeconomic inequalities in survival of young patients are lacking. Only a few studies have assessed socioeconomic inequalities in stage-specific survival [18–21], and none have assessed trends over time.

We took advantage of high-quality Norwegian registry data with individually linked education and income information, to compare trends over time in the stage-specific survival of young women diagnosed before entry to the Breast Cancer Screening Program. We aimed to determine whether survival improvements have reached all socioeconomic groups in a country with universal health care and national treatment guidelines.

Materials and methods

Study design and materials

Using a cohort study design, we assessed the relative survival of all women in Norway diagnosed with invasive breast cancer between Jan 2000 and Dec 2015 at age 30 to 48 years. This age range ensured most patients had completed their education and started earning income, but not yet been invited to mammography screening, before diagnosis. The target screening age in Norway is 50–69 years, although some counties start at 49 years. Breast cancer patients were identified via the nationwide Cancer Registry of Norway, which has had mandatory reporting of new cancer cases since 1953 and is 99% complete [22]. Demographic and socioeconomic characteristics of patients were individually linked from the Central Population Registry, National Education database and Register for Personal Tax Payers.

Study population and follow-up

We identified 8574 potentially eligible women diagnosed with a primary invasive breast cancer (International Classification of Diseases-10 code C50). Of these, 703 (8.2%) patients were ineligible due to a prior invasive cancer diagnosis, 78 (0.9%) had non-epithelial tumors, one had a tumor that was not morphologically verified and five were registered as emigrating before their diagnosis date. Among 7787 remaining eligible women, we excluded 286 (3.7%) women (248 immigrants and 38 Norwegian) due to an unknown education or income level, leaving a final study population of 7501 breast cancer patients. Follow-up for survival started on the 15th of the month of breast cancer diagnosis and ended upon first emigration from Norway, death, after 12 years follow-up, or 31 December 2017, whichever came first.

Education level

We categorized patients by their most recently recorded education level before diagnosis: compulsory (lower secondary school, ≤ 10 years), secondary (upper secondary school or vocational education, 11–13 years) or tertiary (university or vocational education, ≥ 14 years). Our data included education level per 1 October 1999, 2000, 2005, 2010 and 2015. Norwegian educational institutions have mandatory reporting to the National Education Database. In our cohort, education level was 99.7% complete for Norwegian-born patients but was missing for 17.3% of eligible immigrants (2.0% of all eligible patients), most likely because these

immigrants had not completed any education in Norway [23].

Income quintile

We divided patients into quintiles of average personal income during the five-year period before breast cancer diagnosis. We categorized patients by income before diagnosis since income is likely to fall after diagnosis [24]. We categorized income quintile (Q) as low (Q1), middle (Q2-Q4) or high (Q5). Our data included average annual income during 1995–1999, 2000–2004 and 2005–2009. We therefore divided patients diagnosed in 2000–2004 into quintiles of average income during 1995–1999, patients diagnosed in 2005–2009 into quintiles of average income during 2000–2004, and patients diagnosed in 2010–2015 into quintiles of average income during 2005–2009. Past income was 99.8% complete for Norwegian-born patients but was missing for 17.8% of eligible immigrants (2.1% of all eligible patients), probably because these immigrants did not reside in Norway during the period before diagnosis when income was recorded.

Socioeconomic status

We were interested in the effect of having both low education and low income, so formed a combined SES categorization of education and income level, where we separated the lowest education and income levels from higher levels. We divided patients into four SES groups: low/low (compulsory education/Q1 income), low/high (compulsory education/Q2–Q5 income), high/low (secondary or tertiary education/Q1 income) and high/high (secondary or tertiary education/Q2–Q5 income).

Covariates

We categorized immigration history as immigrant if patients were foreign-born with foreign-born parents, or Norwegian if otherwise. For patients diagnosed in 2005–2015, we had information on tumor grade (low = 1, medium = 2, high = 3–4) and status (positive or negative) of the estrogen receptor (ER), progesterone receptor (PR) and HER2. Criteria for determining ER, PR and HER2 status by the Cancer Registry of Norway are described elsewhere [15]. We combined information on ER, PR, HER2 and grade to classify clinical subtype as: luminal A-like (ER and/or PR positive, HER2 negative, low grade), luminal B-like/HER2− (ER and/or PR positive, HER2 negative, medium/high grade), luminal B-like/HER2+ (ER and/or PR positive, HER2 positive, any grade), HER2+ (ER and PR negative, HER2 positive, any grade) or triple-negative (ER and PR negative, HER2 negative, any grade) [25]. Subtype was set to unknown if any of ER, PR, HER2 or grade were missing.

Stage at diagnosis

We categorized tumor stage by pathological tumor size, nodal status and metastasis (TNM), supplemented with information from clinical reports of stage according to the Surveillance Epidemiology and End Results Program [1]. We categorized stage as localized (TNM stage I; tumors localized to the breast); regional (TNM stages II-III; metastasis to regional lymph nodes or to skin and/or chest wall); distant (TNM stage IV; metastasis to distant lymph nodes or other organs) or unknown (pathological and clinical reports were missing or incomplete). We combined TNM stages II and III because the coding practice for lymph node spread was updated at the Cancer Registry of Norway in 2008, leading to a migration between TNM stages II and III.

Statistical analysis

We used Pearson's Chi-squared tests to determine associations between socioeconomic variables and covariates (tumor stage, age group, diagnostic period, immigration history and clinical subtype). Associations between socioeconomic variables and breast cancer death were determined by relative survival methods, which estimate excess mortality rates due to breast cancer by comparing the observed all-cause mortality rates of patients to the expected all-cause mortality rates for females in the Norwegian population of the same age and calendar year. In preliminary analyses, we used life tables stratified by age, calendar year and socioeconomic variables to avoid bias [26]. The SES-stratified life tables were created from individually linked nationwide data of mortality, education and income, and smoothed using a multivariable flexible Poisson model [27]. We found, however, that relative survival estimates were similar when using national life tables, so therefore used the simpler un-stratified national life tables in all analyses.

We first estimated stage-specific socioeconomic inequalities in excess mortality pooled over the study period (2000–2015). We used flexible parametric models [28, 29] to estimate stage-specific excess mortality rate ratios, with 95% confidence intervals (CI), by education, income and SES group, while adjusting for age and year at diagnosis. Immigration history and clinical subtype were assessed, but not included in final models because neither were important confounders or mediators of the main effects of education, income or SES group. In all models, the baseline hazard spline utilized four degrees of freedom and varied by stage at diagnosis with two degrees of freedom [28, 29]. Year at diagnosis was modeled non-linearly using restricted cubic splines with two degrees of freedom [30]. Modeling

Table 1 Breast cancer patient and tumor characteristics ($n = 7501$)

	Total		Education level						Income quintile						
			Compulsory		Secondary		Tertiary		Chi^2 P	Q1 (low)		Q2–Q4		Q5 (high)		Chi^2 P
Covariate	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	χ^2 *p*	*n*	(%)	*n*	(%)	*n*	(%)	χ^2 *p*
Total	7501	(100)	1475	(100)	2896	(100)	3130	(100)		1499	(100)	4500	(100)	1502	(100)	
Stage																
Localized	2317	(33.1)	430	(31.2)	885	(32.8)	1002	(34.3)	0.079	398	(28.8)	1417	(33.7)	502	(35.2)	< 0.001
Regional	4457	(63.6)	892	(64.6)	1726	(63.9)	1839	(62.9)		913	(66.1)	2656	(63.3)	888	(62.3)	
Distant	233	(3.3)	58	(4.2)	91	(3.4)	84	(2.9)		71	(5.1)	126	(3.0)	36	(2.5)	
Unknown[a]	494		95		194		205			117		301		76		
Diagnosis period																
2000–2004	2177	(29.0)	502	(34.0)	930	(32.1)	745	(23.8)	< 0.001	435	(29.0)	1306	(29.0)	436	(29.0)	1.000
2005–2009	2276	(30.3)	514	(34.8)	871	(30.1)	891	(28.5)		455	(30.4)	1365	(30.3)	456	(30.4)	
2010–2015	3048	(40.6)	459	(31.1)	1095	(37.8)	1494	(47.7)		609	(40.6)	1829	(40.6)	610	(40.6)	
Age at diagnosis																
30–34 years	469	(6.3)	70	(4.7)	165	(5.7)	234	(7.5)	< 0.001	147	(9.8)	291	(6.5)	31	(2.1)	< 0.001
35–59 years	1276	(17.0)	213	(14.4)	455	(15.7)	608	(19.4)		269	(17.9)	834	(18.5)	173	(11.5)	
40–44 years	2575	(34.3)	507	(34.4)	989	(34.2)	1079	(34.5)		499	(33.3)	1491	(33.1)	585	(38.9)	
45–48 years	3181	(42.4)	685	(46.4)	1287	(44.4)	1209	(38.6)		584	(39.0)	1884	(41.9)	713	(47.5)	
Immigration history																
Norwegian	6849	(91.3)	1311	(88.9)	2705	(93.4)	2833	(90.5)	< 0.001	1218	(81.3)	4206	(93.5)	1425	(94.9)	< 0.001
Immigrant	652	(8.7)	164	(11.1)	191	(6.6)	297	(9.5)		281	(18.7)	294	(6.5)	77	(5.1)	
Tumor subtype, 2005–2015																
Luminal A-like	2239	(49.2)	409	(50.0)	815	(48.0)	1015	(49.9)	0.336	423	(47.1)	1327	(48.8)	489	(52.6)	0.376
Luminal B-like/ HER2−	775	(17.0)	132	(16.1)	294	(17.3)	349	(17.2)		154	(17.1)	468	(17.2)	153	(16.5)	
Luminal B-like/ HER2+	677	(14.9)	108	(13.2)	256	(15.1)	313	(15.4)		139	(15.5)	407	(15.0)	131	(14.1)	
HER2+	262	(5.8)	48	(5.9)	96	(5.7)	118	(5.8)		55	(6.1)	153	(5.6)	54	(5.8)	
Triple negative	596	(13.1)	121	(14.8)	237	(14.0)	238	(11.7)		128	(14.2)	366	(13.5)	102	(11.0)	
Unknown[b]	764		154		265		345			162		467		135		

[a]Missing stage: Compulsory: 6.4%, secondary: 6.7%, tertiary: 6.5%; Q1 income: 7.8%, Q2–Q4: 6.7%, Q5: 5.1%

[b]Missing subtype: Compulsory: 15.9%, secondary: 13.6%, tertiary: 14.7%; Q1 income: 15.4%, Q2–Q4: 14.8%, Q5: 12.8%

Table 2 Stage-specific excess mortality of breast cancer patients up to 12 years from diagnosis, by education level and income quintile. Patients with a known stage at diagnosis ($n = 7007$)

		No. of patients	No. of deaths	Excess mortality rate per 1000 person-years	Excess mortality rate ratio[a] (95% CI)	p value[b]
Stage	Education level					
Localized	Compulsory	430	33	7.6	1.67 (0.95–2.93)	0.151
	Secondary	885	56	6.2	1.05 (0.62–1.79)	
	Tertiary	1002	46	4.8	1	
Regional	Compulsory	892	216	29.2	1.57 (1.27–1.95)	< 0.001
	Secondary	1726	291	20.1	0.91 (0.74–1.12)	
	Tertiary	1839	292	20.4	1	
Distant	Compulsory	58	55	417.1	2.44 (1.66–3.59)	< 0.001
	Secondary	91	63	185.0	1.07 (0.75–1.55)	
	Tertiary	84	58	173.5	1	
Stage	Income quintile					
Localized	Q1 (low)	398	26	6.5	1.27 (0.63–2.53)	0.609
	Q2–Q4	1417	81	5.7	0.95 (0.53–1.70)	
	Q5 (high)	502	31	6.1	1	
Regional	Q1 (low)	913	182	25.4	1.68 (1.23–2.28)	0.005
	Q2–Q4	2656	488	22.7	1.41 (1.07–1.87)	
	Q5 (high)	888	130	17.3	1	
Distant	1 (low)	71	59	269.4	2.23 (1.31–3.78)	0.012
	Q2–Q4	126	96	224.7	1.78 (1.07–2.94)	
	Q5 (high)	36	21	131.0	1	

[a]Age and year adjusted rate ratios of the excess mortality of breast cancer patients, compared to the expected mortality for the Norwegian female population of the same age and calendar year. Estimated from flexible parametric models

[b]Wald test for overall significance of education/income at each stage

Table 3 Model-based predictions of stage-specific five-year relative survival of breast cancer patients, by education level and income quintile. Patients with a known stage at diagnosis ($n=7007$)

		Estimated five-year relative survival[a]		Change in relative survival
		2000	2015	2000 to 2015
		% (95% CI)	% (95% CI)	% (95% CI)
Stage	Education level			
Localized	Compulsory	96 (93, 98)	97 (95, 99)	1 (0, 3)
	Secondary	97 (95, 98)	99 (98, 100)	2 (1, 3)
	Tertiary	97 (96, 98)	99 (98, 99)	1 (0, 2)
	Tertiary–Compulsory	1 (−1, 4)	1 (−1, 3)	
Regional	Compulsory	80 (74, 85)	86 (77, 92)	6 (−1, 13)
	Secondary	85 (82, 88)	95 (92, 97)	10 (7, 13)
	Tertiary	86 (82, 89)	93 (89, 95)	7 (3, 11)
	Tertiary–Compulsory	6 (0, 12)	7 (−1, 14)	
Distant	Compulsory	4 (1, 11)	12 (2, 30)	8 (−5, 21)
	Secondary	19 (10, 29)	61 (42, 75)	42 (26, 58)
	Tertiary	26 (14, 38)	51 (35, 66)	26 (11, 41)
	Tertiary–Compulsory	21 (8, 34)	39 (18, 61)	
Stage	Income quintile			
Localized	Q1 (low)	97 (95, 99)	98 (96, 99)	1 (0, 2)
	Q2–Q4	97 (95, 98)	99 (98, 99)	2 (1, 3)
	Q5 (high)	96 (93, 98)	99 (98, 100)	3 (1, 5)
	Q5 (high)–Q1 (low)	−1 (−4, 1)	1 (−1, 2)	
Regional	Q1 (low)	87 (82, 90)	91 (86, 95)	4 (0, 9)
	Q2–Q4	83 (80, 86)	93 (90, 95)	10 (7, 13)
	Q5 (high)	85 (79, 89)	97 (92, 99)	12 (7, 17)
	Q5 (high)–Q1 (low)	−2 (−8, 4)	5 (0, 11)	
Distant	Q1 (low)	21 (10, 34)	36 (18, 54)	15 (−3, 34)
	Q2–Q4	14 (8, 22)	48 (33, 61)	33 (21, 46)
	Q5 (high)	25 (10, 44)	75 (47, 90)	50 (29, 71)
	Q5 (high)–Q1 (low)	5 (−17, 26)	39 (11, 67)	

[a]Estimated relative survival of breast cancer patients five years after diagnosis, compared to expected survival for the Norwegian female population. Predicted for patients aged 40 years at diagnosis in 2000 and 2015. Note that 2015 predictions are outside the scope of the data. See Supplementary Table 1 for non-parametric relative survival estimates

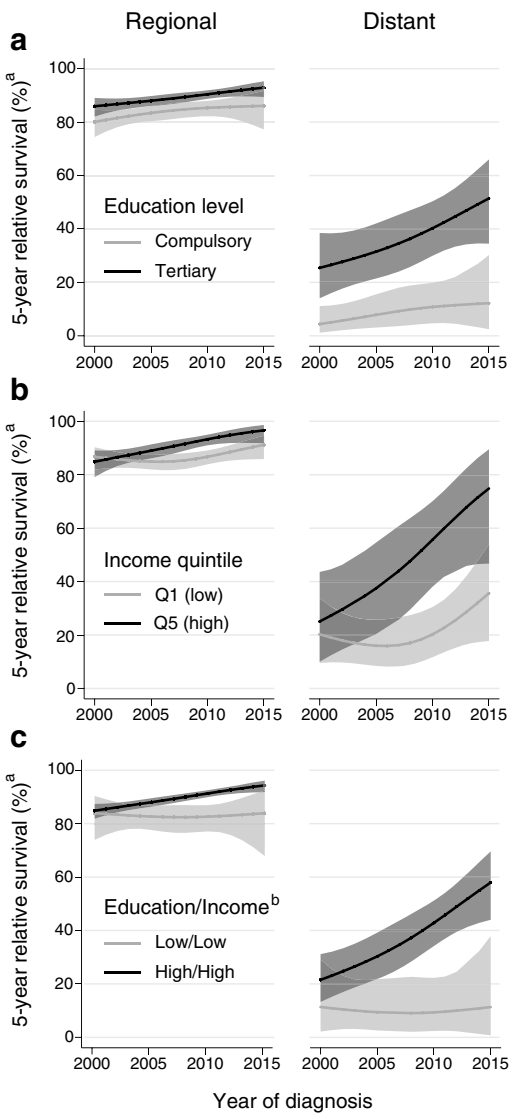

Fig. 1 Trends in regional and distant stage 5-year relative survival, for **a** compulsory and tertiary educated patients ($n=2873$); **b** patients in income quintiles Q1 and Q5 ($n=1908$); and **c)** patients with compulsory education/Q1 income and secondary-tertiary education/Q2-Q5 income ($n=3425$). [a]Model-based predictions of relative survival, with 95% CI, for patients aged 40 years at diagnosis, compared to expected survival for the Norwegian female population. Note that predictions after 2012 are outside the scope of the data. [b]Education/Income group: Low/Low = Compulsory/Income quintile Q1; High/High = Secondary-Tertiary/Income quintiles Q2–Q5

with splines allowed us to capture any changes in the rate of survival gain at a certain time points, for example after implementation of a new treatment. Three-way interactions between year, stage and socioeconomic variable allowed rates of survival gain to vary by both stage and socioeconomic group.

From these flexible parametric models, we made model-based predictions of 5-year relative survival with 95% confidence intervals (CI) for patients aged 40 years at diagnosis. We first predicted stage-specific 5-year relative survival over time for each socioeconomic group, then predicted difference in 5-year relative survival between the highest and lowest socioeconomic groups in 2000 and 2015. For patients diagnosed in 2015, we also made model-based predictions of relative survival up to 12 years from diagnosis. These 2015 predictions are outside the scope of the data and hence based on model parameters, so for comparison we calculated non-parametric Pohar Perme estimates of net survival [31] for patients diagnosed during 2005–2015 (Online Resource 1 and 2). The results were similar between model-based and non-parametric estimates.

We performed our analysis using STATA version 15.1 (StataCorp LLC, College Station, TX, USA, RRID:SCR_012763) [32]. We considered a two-sided p value less than 0.05 as statistically significant. Ethical approval was obtained from the Regional Committee for Medical and Health Research Ethics in Norway (Ref. 2013/2376). The dataset is managed in accordance with the European General Data Protection Regulation (GDPR).

Results

This study included 7501 patients, among whom we observed 1117 excess deaths due to breast cancer over 58418 person-years follow-up from diagnosis. There were 2317 (30.9%) patients with localized stage, 4457 (59.4%) with regional stage, 233 (3.1%) with distant stage, and 494 (6.6%) with unknown stage at diagnosis. Average follow-up per patient diagnosed with localized, regional, distant and unknown stage breast cancer was 8.3, 7.7, 3.4 and 7.8 years, respectively. High education was associated with more recent diagnosis ($p<0.001$) and younger age at diagnosis ($p<0.001$), while high income was associated with older age at diagnosis ($p<0.001$) (Table 1). Neither education ($p=0.336$) nor income ($p=0.376$) were associated with tumor subtype.

Stage-specific excess mortality

In all socioeconomic groups, excess mortality rates were clearly highest at distant stage, but regional stage accounted for the greatest number of excess deaths, because of the high number of patients diagnosed at regional stage (Table 2). After adjustment for diagnosis age and year, excess mortality due to regional and distant stage breast cancer was significantly higher for compulsory versus tertiary educated patients, and for patients in the lowest and middle quintiles compared to the highest income quintile. There was a tendency for greater educational and income inequalities in excess mortality with more advanced stage at diagnosis.

Table 4 Model-based predictions of stage-specific five-year relative survival of breast cancer patients, by education/income group. Patients with a known stage at diagnosis ($n = 7007$)

Stage		Estimated five-year relative survival[b]		Change in relative survival
		2000	2015	2000 to 2015
	Education/Income[a]	% (95% CI)	% (95% CI)	% (95% CI)
Localized	Low/Low	98 (94, 100)	98 (93, 100)	0 (−1, 1)
	Low/High	95 (91, 97)	97 (94, 99)	3 (0, 5)
	High/Low	97 (94, 98)	98 (96, 99)	1 (0, 3)
	High/High	97 (96, 98)	99 (98, 99)	2 (1, 3)
	High/High–Low/Low	−1 (−3, 1)	1 (−2, 3)	
Regional	Low/Low	84 (74, 90)	84 (68, 92)	0 (−12, 12)
	Low/High	79 (71, 84)	89 (77, 95)	10 (1, 19)
	High/Low	88 (82, 92)	93 (87, 96)	5 (−1, 10)
	High/High	85 (82, 87)	94 (92, 96)	9 (6, 13)
	High/High–Low/Low	1 (−7, 9)	10 (−1, 22)	
Distant	Low/Low	11 (2, 29)	11 (1, 38)	0 (−19, 19)
	Low/High	2 (0, 8)	13 (1, 40)	12 (−9, 32)
	High/Low	26 (10, 45)	47 (22, 68)	20 (−3, 44)
	High/High	22 (13, 31)	58 (44, 70)	36 (24, 49)
	High/High–Low/Low	10 (−6, 27)	47 (23, 70)	

[a]Education/Income group: Low/Low: Compulsory/Income quintile Q1; Low/High: Compulsory/ Income quintiles Q2–Q5; High/Low: Secondary–Tertiary/Q1; High/High: Secondary–Tertiary/Q2–Q5

[b]Estimated relative survival of breast cancer patients five years after diagnosis, compared to expected survival for the Norwegian female population. Predicted for patients aged 40 years at diagnosis in 2000 and 2015. Note that 2015 predictions are outside the scope of the data. See Supplementary Table 1 for non-parametric relative survival estimates

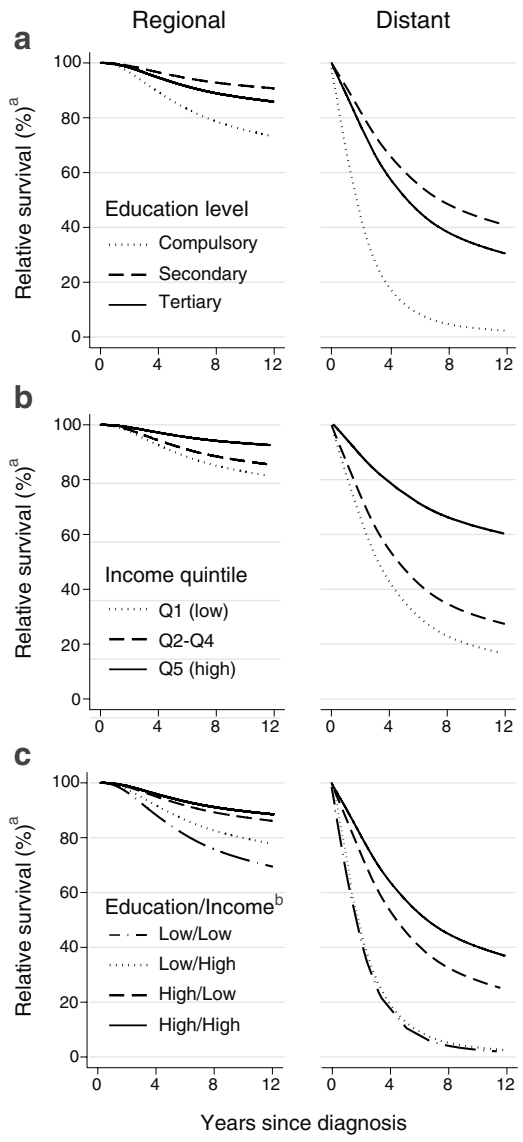

Fig. 2 Model-based predictions of regional and distant stage relative survival for breast cancer patients aged 40 years at diagnosis in 2015, by **a** education level; **b** income quintile; and **c** education/income group ($n=7007$). [a]Relative survival of patients compared to the expected survival for the Norwegian female population. Note that predictions beyond two years after diagnosis are outside the scope of the data, see Online Resource 1 for non-parametric relative survival curves. [b]Education/Income group: Low/Low: Compulsory/Income quintile Q1; Low/High: Compulsory/ Income quintiles Q2–Q5; High/Low: Secondary–Tertiary/Q1; High/High: Secondary–Tertiary/Q2–Q5

Trends in stage-specific 5-year relative survival

Over time, regional and distant stage 5-year relative survival improved the least for patients with compulsory education and for patients in the lowest income quintile (Table 3, Fig. 1a and b). Patients with both low (compulsory) education and low (Q1) income had no improvement at all over time in 5-year relative survival from localized, regional or distant stage disease (Table 4, Fig. 1c). Educational and income differences in 5-year relative survival widened particularly over time for distant stage disease. Between 2000 and 2015, the difference in distant stage relative survival widened from 21 to 39% for tertiary versus compulsory educated patients, from 5 to 39% for patients in the highest versus lowest income quintiles, and from 10 to 47% for patients with high education and high income versus low education and low income.

By 2015, model-based predictions of regional and distant stage relative survival were clearly better for tertiary and secondary compared to compulsory educated patients (Fig. 2a) and for patients in the highest income quintile versus the middle and lowest income quintiles (Fig. 2b). When education and income were examined in combination, we found both socioeconomic factors influenced regional stage relative survival, but education seemed a stronger predictor than income of distant stage relative survival (Fig. 2c). In 2015, the 5-year relative survival predictions for patients with low/low, low/high, high/low and high/high education/income level were, respectively: 98%, 97%, 98% and 99% for localized disease; 84%, 89%, 93% and 94% for regional stage disease; and 11%, 13%, 47% and 58% for distant stage disease (Table 4).

Discussion

In Norway, a country with universal health care and national treatment guidelines, regional and distant stage survival improved more rapidly over time for young breast cancer patients with high SES compared to those with low SES. This widening survival gap over time between high and low SES patients was most pronounced for patients with distant spread at diagnosis. Survival from localized breast cancer was high for all socioeconomic groups throughout the study period, 2000–2015.

The reasons why low SES women lag behind high SES women in terms of survival gain are likely multifactorial. Potential reasons may include lifestyle, comorbidity, participation in clinical trials, differential access to new treatments, the opportunity or ability of patients to make informed treatment choices, motivation to adhere to treatment, or quality of care and follow-up provided by physicians. We and others [33, 34] have found no association between SES and tumor type, indicating that biological differences are unlikely to explain the association between SES and stage-specific survival.

Delayed access to new treatments may have delayed survival improvements for low SES patients [35]. There is evidence that differential treatment contributes to socioeconomic inequalities in survival, also in countries with universal health care [36, 37]. Despite universal health care and national treatment guidelines in Norway, high SES cancer patients have been reported to receive more hospital-based medical services [38] and more palliative radiotherapy [39], and high SES lung cancer patients have received more surgery and radiotherapy than low SES patients [40]. Similar surgical and radiotherapy differences have also been reported for breast cancer patients in the United Kingdom, where health care is also universal [41]. In Sweden, high SES patients were more likely to receive breast conserving surgery over mastectomy [42]. A recent study in the United Kingdom suggests that differential treatment contributes more to breast cancer survival inequalities than previously thought [36].

Scandinavian studies have found that comorbidity only plays a minor role in socioeconomic inequalities in breast cancer survival [43, 44]. On the other hand, lifestyle-related factors, such as overweight, smoking and alcohol, may partly explain poorer survival of low SES patients [44]. Unhealthy behavior has also been hypothesized to reduce the ability of low SES patients to respond to treatment [37]. If true, then a less healthy lifestyle may have potentially hindered low SES patients from benefitting from new treatments to the same extent as high SES patients.

For distant stage patients, education mattered more than income for survival. In a country with universal health care, survival inequalities may therefore not be about high SES patients affording better treatment, but about making better treatment choices. Particularly in the modern world, where treatment is becoming more personalized and complex, and the pros and cons must be continually weighed up by the patient and clinician. More educated patients may be more able to acquire knowledge about their diagnosis and take an active role in their treatment choices. A review of factors influencing socioeconomic inequalities in cancer survival [37] found that more affluent cancer patients communicated better with health care professionals than socioeconomically deprived patients. Affluent patients were also more likely to receive information from hospital specialists, had better psychological health and increased social support, which led to appropriate treatment being sought. Physicians may therefore need to pay more attention to socioeconomically deprived patients to ensure they receive equal access and standard of care [45].

Our findings of better regional and distant stage survival for high compared to low SES patients were in line with earlier studies of stage-specific survival from the USA [20], Netherlands [18] and Sweden [21]. However, we found no significant survival differences for localized disease, in contrast to earlier studies, possibly because we focused on young patients, whereas earlier studies included patients of all ages [18, 21] or only those over 55 years [20]. Nevertheless, our observation of better survival for high SES patients at regional and distant stage, where most deaths occurred, suggests that equal access to health care was not sufficient to offset any effect of SES on patient survival after diagnosis.

One important question is where there would be most to gain, by reducing SES differences in regional or distant stage survival? We found greater survival inequalities for distant stage patients than for regional stage patients, in line with earlier studies [18, 21]. However, twenty times more patients were diagnosed at regional stage compared to distant stage. The greatest number of deaths therefore occurred among patients with regional stage disease. Efforts to improve the regional stage survival of low SES patients would therefore be most effective for reducing breast cancer mortality in the population.

Our study had some limitations. We lacked information on lifestyle and treatment, so were not able to determine whether these factors explained our findings. Also, patient income was only available as five-year averages, so may not have reflected actual income at the time of diagnosis. However, income over five years may be reasonably correlated with accumulated disposable wealth at the time of diagnosis. Another potential study limitation was that some subgroups were small, particularly the number of distant stage patients. We nevertheless believe that our models for distant stage gave a good estimation of the true survival trends because we observed quite similar trends for regional stage, where patient numbers were much higher than for distant stage.

A major strength of our study was the population-wide registry data of high quality and completeness [22]. We had individually linked information on socioeconomic background and virtually complete follow-up of breast cancer patients for migration and death. Our life tables were constructed from individually linked demographic, migration and mortality data for the entire female Norwegian population. From an international perspective, Norwegian Cancer Registry data have high quality, with a very high proportion of morphologically verified cancers and a very small proportion identified through death certificate only [46], demonstrating high validity of our Cancer Registry data [47]. Further, a low proportion of our patient population had unknown stage at diagnosis, and the survival of these patients did not vary by SES. Thus, selection bias due to missing stage information was unlikely to explain our findings.

Conclusions

Despite Norway having universal health care and national treatment guidelines, we found that young breast cancer patients with low SES lag behind, with less improved regional and distant stage survival over time. Why socioeconomic status still matters for survival, even with equal health care access, is likely multifactorial and deserves more attention. Given the number of patients with regional stage disease, improving the survival of low SES patients with regional stage breast cancer would be most effective for reducing breast cancer mortality in the population.

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Data availability The data that support the findings of this study are available from the Cancer Registry of Norway but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors onsite at the Cancer Registry of Norway upon reasonable request and with permission of the Regional Committee for Medical and Health Research Ethics in Norway.

Compliance with Ethical Standards

Conflict of interest Cassia Bree Trewin declares that she has no conflict of interest. Anna Louise Viktoria Johansson declares that she has no conflict of interest. Kirsti Vik Hjerkind declares that she has no conflict of interest. Bjørn Heine Strand declares that he has no conflict of interest. Cecilie Essholt Kiserud declares that she has no conflict of interest. Giske Ursin declares that she has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Regional Committee for Medical and Health Research Ethics in Norway (Ref. 2013/2376) and with the 1964 Helsinki declaration and its later amendments.

Informed consent This study uses data from national population and health registries. The Regional Committee for Medical and Health Research Ethics in Norway (Ref. 2013/2376) determined that informed consent was not required.

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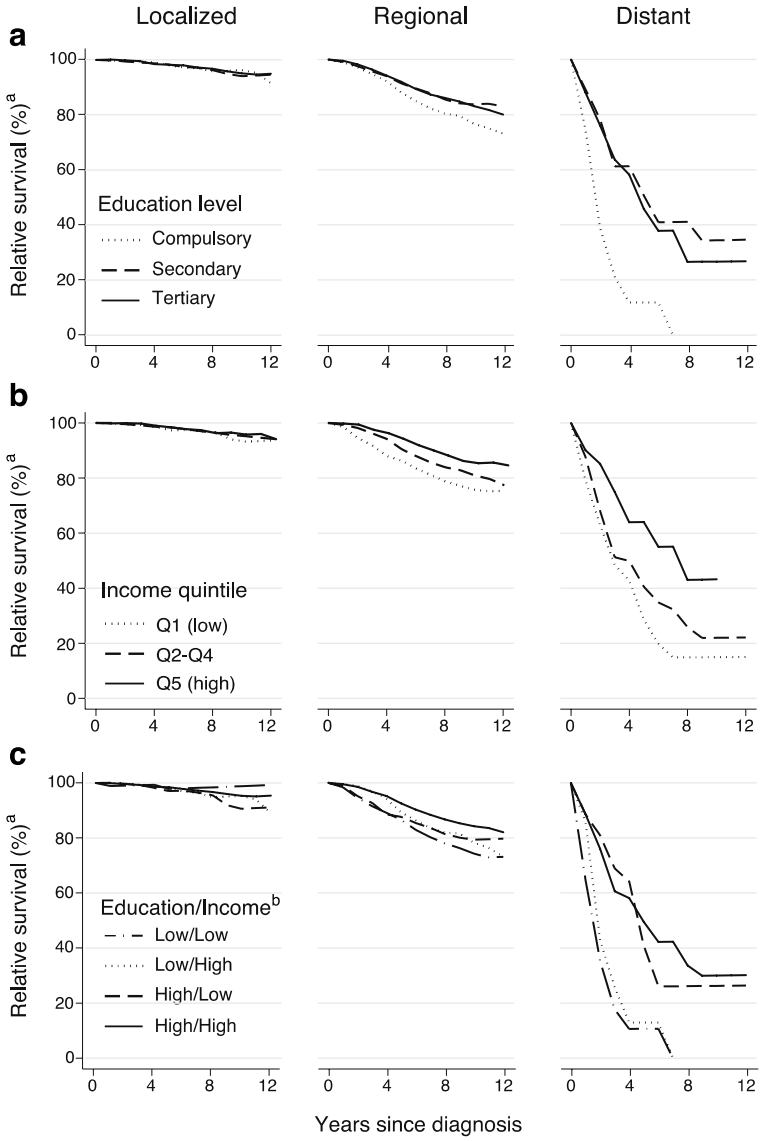
Online Resource 1

Non-parametric Pohar Perme estimates of stage-specific relative survival up to 12 years from diagnosis, by **a)** education level, **b)** income quintile and **c)** combined education/income group. Patients diagnosed at 30-48 years during 2005-2015 (n = 4,985).



[a]Pohar Perme estimates of relative survival of breast cancer patients, compared to the expected survival of the Norwegian female population of the same age and calendar year as the patients.

[b]Education/Income group: Low/Low: Compulsory/Income quintile Q1; Low/High: Compulsory/ Income quintiles Q2-Q5; High/Low: Secondary-Tertiary/Q1; High/High: Secondary-Tertiary/Q2-Q5.

Journal: Breast Cancer Research and Treatment

Title: Stage-specific survival has improved for young breast cancer patients since 2000: but not equally

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Online Resource 2

Non-parametric Pohar Perme estimates of stage-specific 5-year relative survival, by education level, income quintile and combined education/income group. Breast cancer patients aged 30-48 years at diagnosis during 2000-2004 or 2005-2015, with a known stage at diagnosis (N = 7007).

		Estimated five-year relative survival[a]				Change in relative survival 2000-2004 to 2005-2015
		Diagnosed during 2000-2004		Diagnosed during 2005-2015		
		%	(95% CI)	%	(95% CI)	%
Stage	Education level					
Localized	Compulsory	97	(91, 99)	98	(95, 99)	1
	Secondary	97	(94, 99)	98	(96, 99)	1
	Tertiary	99	(94, 100)	98	(97, 99)	-1
	Tertiary – Compulsory	2		0		
Regional	Compulsory	83	(78, 87)	88	(85, 87)	5
	Secondary	87	(84, 90)	91	(84, 90)	4
	Tertiary	86	(83, 89)	92	(83, 89)	6
	Tertiary – Compulsory	3		4		
Distant	Compulsory	15	(5, 30)	12	(3, 27)	-3
	Secondary	17	(7, 30)	51	(36, 64)	34
	Tertiary	17	(6, 34)	46	(32, 59)	29
	Tertiary – Compulsory	2		34		
Stage	Income quintile					
Localized	Q1 (low)	99	(90, 100)	97	(94, 99)	-2
	Q2-Q4	98	(95, 99)	98	(97, 99)	0
	Q5 (high)	96	(91, 99)	98	(95, 99)	2
	Q5 (high) – Q1 (low)	-3		1		
Regional	Q1 (low)	87	(82, 91)	87	(84, 90)	0
	Q2-Q4	85	(82, 87)	91	(89, 92)	4
	Q5 (high)	88	(83, 91)	95	(92, 96)	7
	Q5 (high) – Q1 (low)	1		8		
Distant	Q1 (low)	18	(7, 34)	29	(15, 44)	11
	Q2-Q4	11	(4, 22)	41	(29, 51)	30
	Q5 (high)	29	(9, 52)	64	(39, 81)	35
	Q5 (high) – Q1 (low)	11		35		
Stage	Education/Income[b]					
Localized	Low/Low	101	(101, 101)	98	(88, 101)	-3
	Low/High	96	(89, 98)	98	(94, 98)	2
	High/Low	98	(88, 100)	97	(92, 100)	-1
	High/High	98	(95, 99)	98	(97, 99)	0
	High/High – Low/Low	-3		0		

Regional	Low/Low	86	(77, 92)	86	(81, 91)	0
	Low/High	82	(76, 86)	89	(85, 92)	7
	High/Low	87	(81, 92)	88	(84, 91)	1
	High/High	87	(84, 89)	92	(91, 94)	5
	High/High – Low/Low	1		6		
Distant	Low/Low	34	(11, 59)	11	(2, 30)	-23
	Low/High	0		13	(1, 39)	13
	High/Low	6	(1, 23)	41	(20, 61)	35
	High/High	21	(11, 33)	50	(38, 60)	29
	High/High – Low/Low	-13		39		

[a]Pohar Perme estimates of relative survival of breast cancer patients five years after diagnosis, compared to the expected survival of the Norwegian female population of the same age and calendar year as the patients.

[b]Education/Income group: Low/Low: Compulsory/Income quintile Q1; Low/High: Compulsory/ Income quintiles Q2-Q5; High/Low: Secondary-Tertiary/Q1; High/High: Secondary-Tertiary/Q2-Q5.

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Appendix

Errata

Candidate: Cassia Bree Trewin-Nybråten

Title: Changing socioeconomic patterns of breast cancer incidence, mortality and survival in Norway.

Page	Where on page	Original text	Corrected text
8	Paper II reference	... a nationwide study …	… a nationwide registry study …
Paper II title page	Title page before published article	Trewin CB, Strand BH, Weedon-Fekjaer H, Ursin G: Changing patterns of breast cancer incidence and mortality by education level over four decades in Norway, 1971-2009. *Eur J Public Health* 2017, 27(1):160-166. Doi: 10.1093/eurpub/ckw148.	Trewin CB, Hjerkind KV, Johansson ALV, Strand BH, Kiserud CE, Ursin G: Socioeconomic inequalities in stage-specific breast cancer incidence: a nationwide registry study of 1.1 million young women in Norway, 2000-2015. *Acta Oncologica* 2020, 59(11): 1284-1290. Doi: 10.1080/0284186X.2020.1753888.