2016-11-29

Cause-specific mortality in women with breast cancer in situ

He, Wei; Lindström, Linda Sofie; Hall, Per; Czene, Kamila

Int J Cancer. 2017 Jun 1;140(11):2414-2421.
http://doi.org/10.1002/ijc.30413
http://hdl.handle.net/10616/45412

Cause-specific mortality in women with breast cancer in situ

Wei He,[1*] Linda Sofie Lindström,[2] Per Hall,[1] Kamila Czene[1]

[1] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

[2] Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden

Corresponding Author

*Wei He, PhD

Department of Medical Epidemiology and Biostatistics

Karolinska Institutet

Nobels väg 12 A, Stockholm 171 77 Sweden

Tel: +46-7-021 594 22

Fax: +46 8 31 49 75

Email: wei.he@ki.se

Keywords: Breast cancer in situ; cause-specific mortality; over-diagnosis and over-treatment. **Abbreviation**: BCIS, breast cancer in situ; SMR, standardized mortality ratio; HR, hazard ratio; 95% CI, 95% confidence intervals.

Article category: cancer epidemiology.

Novelty and Impact: The long-term mortality remains unknown in women diagnosed with breast cancer in situ (BCIS). Here we presented the 30-year cumulative incidence of cause-specific mortality and their predictors in BCIS patients. We conclude that most women diagnosed with BCIS die from causes other than breast cancer, which highlights the need for actions not only to reduce non-breast cancer mortality but also to identify patient where extensive curative BCIS treatment is not adding to survival.

Abstract

The long-term mortality remains unknown in women diagnosed with breast cancer in situ (BCIS). Here we assessed the cause-specific mortality in BCIS patients. This population-based cohort study included 12 243 women diagnosed with BCIS in Sweden between 1980 and 2011. Patients were followed until death, emigration, or 31 December 2013, whichever came first. The 30-year cumulative incidence of breast cancer-specific mortality was 6.3%, which is considerably lower than 49.7% observed for other-cause mortality. Women diagnosed with BCIS were more likely to die from breast cancer (standardize mortality ratio [SMR], 3.85; 95%CI, 3.47-4.27) but less likely to die from cardiovascular disease (SMR, 0.88; 95% CI, 0.82-0.95) than women in the general population. Specifically, the SMRs for breast cancer-specific mortality decreased over time from 5.17 (95%CI, 3.95-6.81) among BCIS diagnosed during 1980-1989 to 3.03 (95%CI, 2.35-3.91) among those diagnosed during 2000-2011. Furthermore, higher risk of death from other causes was seen among those with older age at BCIS diagnosis, lower levels of education, nulliparity, higher Charlson Comorbidity Index, and being hospitalized before BCIS diagnosis; whereas lower risk of death from breast cancer was seen among BCIS diagnosed in the later time period and those with younger age at first birth. We conclude that most women diagnosed with BCIS die from causes other than breast cancer, which highlights the need for actions not only to reduce non-breast cancer mortality but also to identify patient where extensive curative BCIS treatment is not adding to survival.

Introduction

Mammography screening may reduce the risk of invasive breast cancer[1-3] at the price of overdiagnosing breast cancer in situ (BCIS) [4-9]. A recent study has found that for every three screen-detected ductal carcinoma in situ, there was one fewer invasive interval cancer in the next 3 years[2]. However, on the other hand, 1-50% of the screen-detected breast cancer have been estimated to be overdiagnosed[1, 10-12]. Therefore, actions should be taken not only to maximize the use of mammography screening, but also to minimize the numbers of overdiagnosis to prevent unnecessary treatment and suffering[1, 4, 13].

Overdiagnosis can be defined as detection of BCIS in a person who will die from causes other than breast cancer. Based on this definition, whether over-diagnosis of BCIS will happen depends on both the risk of BCIS progression and the risk of dying from other causes. However, previous studies usually focused only on BCIS prognostic factors without considering the factors that might increase the risk of death from other causes [14, 15], thus provided limited information regarding the potential risk of over-diagnosis.

In this study, we aimed to investigate the cause-specific mortality in women diagnosed with BCIS, with specific objectives including: 1) to calculate the 30-year cumulative incidence of cause-specific mortality in BCIS patients; 2) to identify factors that predict higher risk of death from other causes but lower risk of death from breast cancer in BCIS patients; 3) to calculate standardized mortality ratios of BCIS by age at diagnosis, calendar years of diagnosis, and years since diagnosis; and 4) to investigate the calendar change in the treatment of BCIS. For comparison, we also examined the cause-specific mortality and treatment in women diagnosed with invasive breast cancer.

Materials and methods

Data sources

This study was based on six Swedish nationwide registers, namely the Swedish Cancer Register, the Inpatient Register, the Multi-generation Register, the Total Population Register, the Education Register, and the Emigration/Immigration Register. The Swedish Cancer Register has used a code for histological type (WHO/HS/CANC/24.1) since 1958 and it is compulsory by law in Sweden for every healthcare provider to report all newly detected cancer.[16] The unique Swedish Multi-generation Register includes information on parent-offspring relations for Swedish citizens born since 1932 [17]. All the six registers cover the whole population of Sweden and have proved to be of high quality [17-19]. Record-linkage between different registers were made using the Personal Identification Number, a unique identifier assigned to all residents in Sweden [20].

In addition, to investigate the calendar change in the treatment of BCIS and invasive breast cancer, we also retrieved regional data from Stockholm-Gotland Breast Cancer Register.

Study population

A total of 20 666 women diagnosed with BCIS were reported to the Swedish Cancer Register between 1980 and 2011. Among them, we excluded 6 133 BCIS with synchronous invasive breast cancer (defined as invasive breast cancer diagnosed within three months)[21], 2 002 BCIS diagnosed before age 40 or after age 75 years (ages not covered by Swedish mammography screening), and 288 BCIS diagnosed without histological confirmation, leaving a total of 12 243 BCIS for the final analysis.

Baseline predictors

Baseline predictors were selected based on their clinical relevance to cause-specific mortality, and their availability in our database, including: age at diagnosis and multifocal BCIS (International Classification of Diseases [ICD], 7th edition codes 170.7, 170.8) derived from the Swedish Cancer Register; years of education derived from the Swedish Education Register; parity and age at first birth derived from the Multi-generation Register; and days of pre-diagnosis hospitalization (due to any causes) and Charlson Comorbidity Index[22] derived from the Swedish Inpatient Register (restricted to 5 years prior to BCIS diagnosis). Family history of breast cancer was defined as the presence of breast cancer in a first-degree relative (mother, sister, and daughter) by linking data from Swedish Cancer Register and Swedish Multi-generation Register.

Statistical analysis

Patients were followed from the date of the cancer diagnosis until emigration, death, or 31 December 2013, whichever came first. The 30-year cumulative incidence of cause-specific mortality was graphically shown in a competing risks framework. Competing risk regression was also used to determine the predictors of cause-specific mortality in BCIS patients, after accounting for each other as the competing events [23]. The standardized mortality ratio (SMR) was calculated by dividing the observed number of deaths by the expected number of deaths. The expected number of deaths was calculated by applying age- and calendar period-stratified person-years of observation to corresponding mortality rates in the general population.

All statistical tests were two-sided with a significance level of $P<0.05$. We used SAS software (v 9.4; SAS Institute Inc., Cary, NC, USA) and Stata software (v 13.0; Stata Corporation, College Station, TX, USA) for all statistical analysis. This study was approved by the Regional Ethical Reviewer Board in Stockholm, Sweden.

Results

Proportion of women dying from breast cancer

Among the 12 243 BCIS diagnosed between 1980 and 2011, 361 died from breast cancer and 2 065 died from causes other than breast cancer over a mean of 12.5 years of follow up. The proportion of women dying from breast cancer decreased from 37% to 8% as age at BCIS diagnosis increased from 40-49 years to 70-74 years, from 24% to 18% as calendar year of BCIS diagnosis increased from 1980-1989 to 2000-2011, and from 20% to 6% as years of follow-up increased from 0-9 years to 20-29 years (**Figure 1**).

Cumulative incidence of cause-specific mortality

The 10-, 20- and 30-year cumulative incidence of death from breast cancer was 2.0%, 4.6%, and 6.3%, respectively, in women diagnosed with BCIS (**Figure 2**). The life-time risk of breast cancer mortality decreased with increasing age at diagnosis, from 9.0% among BCIS diagnosed at 40-50 years to 3.3% among those diagnosed at 70-74 years (**Figure S1**). The 30-year cumulative incidence of death from causes other than breast cancer was 49.7% in BCIS patients, which could translate to 14.7% of death from other cancers, 18.0% of death from cardiovascular disease, and 17.0% of death from causes other than breast cancer or above-mentioned diseases (**Figure 2**).

For comparison, the 30-year cumulative incidence of death from breast cancer was 27.0%, and the 30-year cumulative incidence of death from causes other than breast cancer was 47.7%, among women diagnosed with invasive breast cancer (**Figure 2**).

Predictors of cause-specific mortality

Higher risk of death from causes other than breast cancer was seen among patients who were older, less educated, nulliparity, with higher Charlson Comorbidity Index, and being hospitalized before BCIS diagnosis (**Table 1**). Lower risk of death from breast cancer was seen among patients who were younger at first childbirth and among BCIS patients diagnosed in the later time period (**Table 2**).

Standardized mortality ratio

Women diagnosed with BCIS were more likely to die from breast cancer than women in the general population, with a SMR of 3.85 (95% CI, 3.47-4.27). Specifically, the SMRs decreased over age from 6.26 (95%CI, 5.14-7.62) among BCIS diagnosed at 40-49 years to 2.96 (95%CI, 2.52-3.49) among those diagnosed at 60-74 years, and decreased over time from 5.19 (95%CI, 3.95-6.81) among BCIS diagnosed during 1980-1989 to 3.03 (95%CI, 2.35-3.91) among those diagnosed during 2000-2011. By comparison, the SMRs for invasive breast cancer also decreased over age at BCIS diagnosis, years of BCIS diagnosis, and years since BCIS diagnosis (**Figure 3**).

Women diagnosed with BCIS were less likely to die from cardiovascular disease than women in the general population (SMR, 0.88; 95% CI, 0.82-0.95), especially within the first 10 years of follow-up (SMR, 0.83; 95%CI, 0.73-0.94). By comparison, women diagnosed with invasive breast cancer experienced higher risk of mortality from cardiovascular disease (SMR, 1.03; 95% CI, 1.01-1.05), mortality from other cancer (SMR, 1.12; 95% CI, 1.09-1.15), and mortality from causes other than breast cancer or above-mentioned diseases (SMR, 1.15; 95% CI, 1.12-1.17), than women in the general population (**Figure 3**).

Trends in the treatment of BCIS

The proportion of patients undergoing mastectomy decreased 1.3% annually for BCIS patients and 2.0% annually for invasive breast cancer patients, respectively, between 1980

and 2008. In contrary, the proportion of patients undergoing lumpectomy with radiotherapy increased 1.4% annually for BCIS patients and increased 2.1% annually for invasive breast cancer, respectively, between 1980 and 2008(**Figure 4**).

Discussion

In this population-based cohort study, a 30-year cumulative incidence of 6.3% was observed for breast cancer mortality in BCIS patients, which is considerably lower than the 49.7% observed for other-cause mortality. Higher risk of death from other causes was seen among patients who were older, less educated, nulliparity, with higher Charlson Comorbidity Index, and being hospitalized before BCIS diagnosis; whereas lower risk of death from breast cancer was seen among patients who were younger at first childbirth and BCIS diagnosed in the later time period. As compared with the general population, women diagnosed with BCIS were more likely to die from breast cancer, but less likely to die from cardiovascular disease. For comparison, women diagnosed with invasive breast cancer were more likely to die from breast cancer, cardiovascular disease, other cancers, and causes other than breast cancer or above-mentioned diseases than women in the general population.

Non-breast cancer death is the leading causes of death in women diagnosed with BCIS. Out of every 9 deaths observed in BCIS patients during the 30 years of follow-up, 8 deaths are attributed to causes other than breast cancer. This high proportion of death from other causes contradicts with the low awareness to reduce death from other causes in BCIS patients in the current practice. To address this issue, physician should not only counsel patients on BCIS treatment but also on modifying lifestyles to reduce the patients' risk of death from causes other than breast cancer. Since women are more likely to be persuaded to change their lifestyles after a tumor diagnosis [24], and most of the non-breast cancer death observed in our study, such as cardiovascular diseases, were lifestyle-related, integrating lifestyle interventions into BCIS management can thus greatly improve the over-all survival in BCIS patients.

After the introduction of the biennially mammography screening to women aged 40-74 years[25], the incidence of BCIS has increased 4-7 fold, representing now about 20% of all screen-detected breast cancer in Sweden[26]. Among them, a proportion of BCIS may never become life-threatening because only 20-30% of BCIS managed with biopsy alone will eventually progress into invasive cancer [27]. Despite this heterogeneity, 82.4% of patients with BCIS ≤20 mm underwent breast conserving surgery, and 72.7% of patients with BCIS≥15mm underwent radiation therapy in Sweden in 2012 [28]. These facts together suggest that a proportion of BCIS patients may have been treated unnecessary for a clinically insignificant disease, thus suffering from unnecessary surgical morbidity and radiation side effects.

To prevent overtreatment, the risk of death from other causes should be considered since treatment is unnecessary if the BCIS patients were destined to die from causes other than breast cancer. However, previous studies usually focused only on breast cancer incidence/mortality without considering factors that might increase the risk of death from other causes [14, 15]. Our study filled this knowledge gap and found that higher risk of death from other causes was found among patients who were older, less educated, nulliparity, with higher Charlson Comorbidity Index, and being hospitalized before BCIS diagnosis. These predictors identified in our study, together with predictors of lower risk of death from breast cancer [14], can help to identify patients who are more likely to die from causes other than breast cancer, thus may have implications for treatment decision-making to prevent BCIS overtreatment.

Age at diagnosis is the most important predictor for causes of death (due to breast cancer or due to other causes) in women diagnosed with BCIS. The proportion of women dying from breast cancer decreased from 37% among BCIS diagnosed at 40-49 years to only 8% among those diagnosed at 70-74 years. Older patients have relatively shorter life expectancy, thus

may not live long enough to develop breast cancer. This hypothesis is supported by the fact that in our study, older patients had much higher risk of death from other causes but lower lifetime risk of death from breast cancer and lower SMRs for breast cancer-specific mortality as compared with younger patients. Therefore, overdiagnosis may be more common in older BCIS patients, especially if they had severe comorbidities and low-risk BCIS.

Calendar year of BCIS diagnosis is another predictor for causes of death in BCIS patients. The proportion of women dying from breast cancer decreased from 24% among women diagnosed in 1980-1989 to 18% among those diagnosed in 2000-2011. Consistently, the SMRs for breast cancer-specific mortality decreased over time, from 5.17 (95%CI, 3.95-6.81) among BCIS diagnosed during 1980-1989 to 3.03 (95%CI, 2.35-3.91) among those diagnosed during 2000-2011. These decreases may be explained by several hypotheses. First, the increased use of mammography screening after a BCIS diagnosis has made the detection of subsequent invasive cancer easier, thus may help to reduce the risk of death from breast cancer. Second, therapy for both BCIS and invasive breast cancer has improved over the years [29], leading to fewer women with a previous BCIS being diagnosed with invasive breast cancer and fewer deaths after developing invasive breast cancer. Third, it is possible that the increased sensitivity of screening technology has led to the detection of more favourable BCIS[30], which would reduce the risk of death from breast cancer.

Consistent with previous findings,[31] women diagnosed with BCIS are less likely to die from cardiovascular disease than women in the general population. This result is not surprising given that higher level of estrogen – which is an established risk factor for BCIS – has been suggested to provide protection against cardiovascular disease.[32] Furthermore, the reduced death from cardiovascular disease may also be due, at least in part, to a “healthy adherer” effect. That is, BCIS patients are more likely to be adherers of mammography screening, and adherers have been reported to be highly educated and more likely to perform

healthy behaviors such as regular physical activity and non-smoking, as compared with non-adherers.[33, 34] In contrary, women diagnosed with invasive breast cancer were more likely to die from cardiovascular disease than women in the general population. This heterogeneity may partially be due to the fact that radiotherapy– which has been reported to increase the risk of cardiovascular disease[35]– is more frequently used in invasive breast cancer than in BCIS. However, our results on cardiovascular disease mortality by laterality (left tumors versus right tumors) did not adequately support the radiotherapy hypothesis, with a hazard ratio of 1.04 (95% CI, 1.00-1.09) for invasive breast cancer and 1.07 (95% CI, 0.93-1.25) for BCIS.

The patterns of SMRs for breast cancer-specific mortality differ considerably between BCIS and invasive breast cancer. The SMRs remained constant among BCIS patients, but decreased with increasing years of follow-up among invasive breast cancer patients. Furthermore, during the 20-29 years of follow-up, the SMRs for BCIS and invasive breast cancer was 3.05 (95% CI, 2.06-4.51) and 8.42 (95% CI, 7.78-9.10), respectively. Since most invasive breast cancer patients who can survive ≥20 years are likely to be early-stage invasive breast cancer, this difference raises concerns on the current use of similar treatment strategies for BCIS and early-stage invasive breast cancer.[36-39]

The present study has several limitations. First, in the current practice, almost all BCIS were treated with mastectomy or breast conserving surgery with or without radiotherapy, [28, 36-39]. These therapies could affect not only the risk of death from breast cancer, but also death from other causes[35, 40]. Therefore, it is impossible to determine the causes of death in women diagnosed with BCIS if they were left untreated. Second, since the Swedish Cancer Register doesn't collect data on treatment, we were unable to investigate the impact of BCIS treatment on mortality. This limitation is minimized by the fact that different BCIS treatments have only small impact on breast cancer-specific mortality [27]. Finally, since the Swedish Cancer

Register adopted the use of SNOMED histology only since 1993,[16] we were unable to distinguish ductal carcinoma in situ (DCIS) from lobular carcinoma in situ (LCIS) for BCIS diagnosed between 1980 and 1993. This limitation is reduced by the fact that for BCIS diagnosed since1993, LCIS accounted for only 6% of BCIS in our study and further restricting our analysis to DCIS patients provided similar results as the main analysis (SMR=3.68 [95% CI, 3.14-4.32] for breast cancer mortality; SMR=1.02[95% CI, 0.90-1.15] for other-cancer mortality; SMR=0.75[0.65-0.87] for cardiovascular disease mortality; and SMR=0.96[95% CI, 0.86-1.08] for other-cause mortality).

In conclusion, over the 30 years of follow-up, the absolute risk of dying from breast cancer is low compared with BCIS patients' risk of dying from other causes, thus highlighting the need for actions not only to reduce non-breast cancer mortality but also to identify patient where extensive curative BCIS treatment is not adding to survival. Predictors identified in our study can help to identify BCIS patients who are more likely to die from causes other than breast cancer, thus may have implications for treatment decision-making to prevent BCIS overtreatment.

Acknowledgement

Competing interests

The authors declare that they have no competing interests.

References

1. Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M. The benefits and harms of breast cancer screening: an independent review. *British journal of cancer* 2013;**108**: 2205-40.

2. Duffy SW, Dibden A, Michalopoulos D, Offman J, Parmar D, Jenkins J, Collins B, Robson T, Scorfield S, Green K, Hall C, Liao XH, et al. Screen detection of ductal carcinoma in situ and subsequent incidence of invasive interval breast cancers: a retrospective population-based study. *The lancet oncology* 2016;**17**: 109-14.

3. McCann J, Treasure P, Duffy S. Modelling the impact of detecting and treating ductal carcinoma in situ in a breast screening programme. *Journal of medical screening* 2004;**11**: 117-25.

4. Independent UKPoBCS. The benefits and harms of breast cancer screening: an independent review. *Lancet* 2012;**380**: 1778-86.

5. Esserman LJ, Thompson IM, Jr., Reid B. Overdiagnosis and overtreatment in cancer: an opportunity for improvement. *Jama* 2013;**310**: 797-8.

6. Esserman L, Shieh Y, Thompson I. Rethinking screening for breast cancer and prostate cancer. *Jama* 2009;**302**: 1685-92.

7. Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. *The New England journal of medicine* 2012;**367**: 1998-2005.

8. Lauby-Secretan B, Scoccianti C, Loomis D, Benbrahim-Tallaa L, Bouvard V, Bianchini F, Straif K, International Agency for Research on Cancer Handbook Working G. Breast-cancer screening--viewpoint of the IARC Working Group. *The New England journal of medicine* 2015;**372**: 2353-8.

9. Mayor S. Experts question IARC report saying benefits of mammography in older women outweigh risks. *Bmj* 2015;**350**: h3156.

10. Jorgensen KJ, Gotzsche PC. Overdiagnosis in publicly organised mammography screening programmes: systematic review of incidence trends. *Bmj* 2009;**339**: b2587.

11. Duffy SW, Agbaje O, Tabar L, Vitak B, Bjurstam N, Bjorneld L, Myles JP, Warwick J. Overdiagnosis and overtreatment of breast cancer: estimates of overdiagnosis from two trials of mammographic screening for breast cancer. *Breast cancer research : BCR* 2005;**7**: 258-65.

12. Miller AB, Wall C, Baines CJ, Sun P, To T, Narod SA. Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial. *Bmj* 2014;**348**: g366.

13. Woloshin S, Schwartz LM. The benefits and harms of mammography screening: understanding the trade-offs. *Jama* 2010;**303**: 164-5.

14. Silverstein MJ, Poller DN, Waisman JR, Colburn WJ, Barth A, Gierson ED, Lewinsky B, Gamagami P, Slamon DJ. Prognostic classification of breast ductal carcinoma-in-situ. *Lancet* 1995;**345**: 1154-7.

15. Ozanne EM, Shieh Y, Barnes J, Bouzan C, Hwang ES, Esserman LJ. Characterizing the impact of 25 years of DCIS treatment. *Breast cancer research and treatment* 2011;**129**: 165-73.

16. Hemminki K, Ji J, Brandt A, Mousavi SM, Sundquist J. The Swedish Family-Cancer Database 2009: prospects for histology-specific and immigrant studies. *International journal of cancer Journal international du cancer* 2010;**126**: 2259-67.

17. Ekbom A. The Swedish Multi-generation Register. *Methods in molecular biology* 2011;**675**: 215-20.

18. Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. *Acta oncologica* 2009;**48**: 27-33.

19. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, Heurgren M, Olausson PO. External review and validation of the Swedish national inpatient register. *BMC public health* 2011;**11**: 450.

20. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *European journal of epidemiology* 2009;**24**: 659-67.

21. Hartman M, Czene K, Reilly M, Bergh J, Lagiou P, Trichopoulos D, Adami HO, Hall P. Genetic implications of bilateral breast cancer: a population based cohort study. *The lancet oncology* 2005;**6**: 377-82.

22. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *Journal of clinical epidemiology* 2004;**57**: 1288-94.

23. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. *American journal of epidemiology* 2009;**170**: 244-56.

24. Blanchard CM, Denniston MM, Baker F, Ainsworth SR, Courneya KS, Hann DM, Gesme DH, Reding D, Flynn T, Kennedy JS. Do adults change their lifestyle behaviors after a cancer diagnosis? *American journal of health behavior* 2003;**27**: 246-56.

25. Autier P, Koechlin A, Smans M, Vatten L, Boniol M. Mammography screening and breast cancer mortality in Sweden. *Journal of the National Cancer Institute* 2012;**104**: 1080-93.

26. Styrgruppen för Nationella Bröstcancerregistret, Bröstcancer: Nationell rapport diagnosår 2009, 2011.

27. Worni M, Akushevich I, Greenup R, Sarma D, Ryser MD, Myers ER, Hwang ES. Trends in treatment patterns and outcomes for ductal carcinoma in situ. *Journal of the National Cancer Institute* 2015;**107**: djv263.

28. Styrgruppen för Nationella Bröstcancerregistret., Årsrapport: rapport från Nationella bröstcancerregistret 2012.

29. Chen L, Linden HM, Anderson BO, Li CI. Trends in 5-year survival rates among breast cancer patients by hormone receptor status and stage. *Breast cancer research and treatment* 2014;**147**: 609-16.

30. Narod S. Breast cancer: The importance of overdiagnosis in breast-cancer screening. *Nature reviews Clinical oncology* 2015;**13**: 5-6.

31. Ernster VL, Barclay J, Kerlikowske K, Wilkie H, Ballard-Barbash R. Mortality among women with ductal carcinoma in situ of the breast in the population-based surveillance, epidemiology and end results program. *Archives of internal medicine* 2000;**160**: 953-8.

32. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *The New England journal of medicine* 1999;**340**: 1801-11.

33. Calle EE, Flanders WD, Thun MJ, Martin LM. Demographic predictors of mammography and Pap smear screening in US women. *American journal of public health* 1993;**83**: 53-60.

34. Maxwell CJ, Bancej CM, Snider J. Predictors of mammography use among Canadian women aged 50-69: findings from the 1996/97 National Population Health Survey. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 2001;**164**: 329-34.

35. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, Correa C, Cutter D, Gagliardi G, Gigante B, Jensen MB, Nisbet A, et al. Risk of ischemic

heart disease in women after radiotherapy for breast cancer. *The New England journal of medicine* 2013;**368**: 987-98.

36. Yen MF, Tabar L, Vitak B, Smith RA, Chen HH, Duffy SW. Quantifying the potential problem of overdiagnosis of ductal carcinoma in situ in breast cancer screening. *European journal of cancer* 2003;**39**: 1746-54.

37. Morrow M, Strom EA, Bassett LW, Dershaw DD, Fowble B, Harris J, O'Malley F, Schnitt SJ, Singletary SE, Winchester DP, American College of S, College of American P, et al. Standard for the management of ductal carcinoma in situ of the breast (DCIS). *CA: a cancer journal for clinicians* 2002;**52**: 256-76.

38. Katz SJ, Lantz PM, Zemencuk JK. Correlates of surgical treatment type for women with noninvasive and invasive breast cancer. *Journal of women's health & gender-based medicine* 2001;**10**: 659-70.

39. Ernster VL, Barclay J, Kerlikowske K, Grady D, Henderson C. Incidence of and treatment for ductal carcinoma in situ of the breast. *Jama* 1996;**275**: 913-8.

40. Cooke AL, Metge C, Lix L, Prior HJ, Leslie WD. Tamoxifen use and osteoporotic fracture risk: a population-based analysis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2008;**26**: 5227-32.

Figure legend

Figure 1. Causes of death in women diagnosed with BCIS in Sweden, 1980-2013. (A) by age at BCIS diagnosis; (B) by calendar year of BCIS diagnosis; and (C) by years of follow-up. Abbreviation: BCIS, breast cancer in situ. Analyses were restricted to those who died within 10 years of follow-up in part (B).

Figure 2. Cumulative incidence of cause-specific mortality in women diagnosed with BCIS in Sweden, 1980-2013. Abbreviation: BCIS, breast cancer in situ. Causes of death was ascertained by using International Classification of Diseases (ICD): death from breast cancer (ICD-9 codes 174, ICD-10 codes C50); death from other cancers (ICD-9 codes 140-173, 175-239, ICD-10 codes C00-C49, C51-D48); and death from cardiovascular diseases (ICD-9 codes 390-459, ICD-10 codes I00-I99).

Figure 3. Standardized Mortality Ratios (SMRs) among women diagnosed with BCIS and women diagnosed with invasive breast cancer in Sweden, 1980-2013, compared with women in the general population. The square and horizontal line shows the estimated SMR and 95% CI. Subgroup analyses of years of diagnosis were restricted to 10 years of follow-up.

Figure 4. Trend in treatment over time in women diagnosed with BCIS and invasive breast cancer in Stockholm-Gotland Region, Sweden, 1980-2008.

Figure S1. Lifetime risk of death from breast cancer in women diagnosed with BCIS in Sweden, 1980-2013, by age at BCIS diagnosis. Death from breast cancer cumulated after accounting for death from other causes as the competing event.

Figure 1

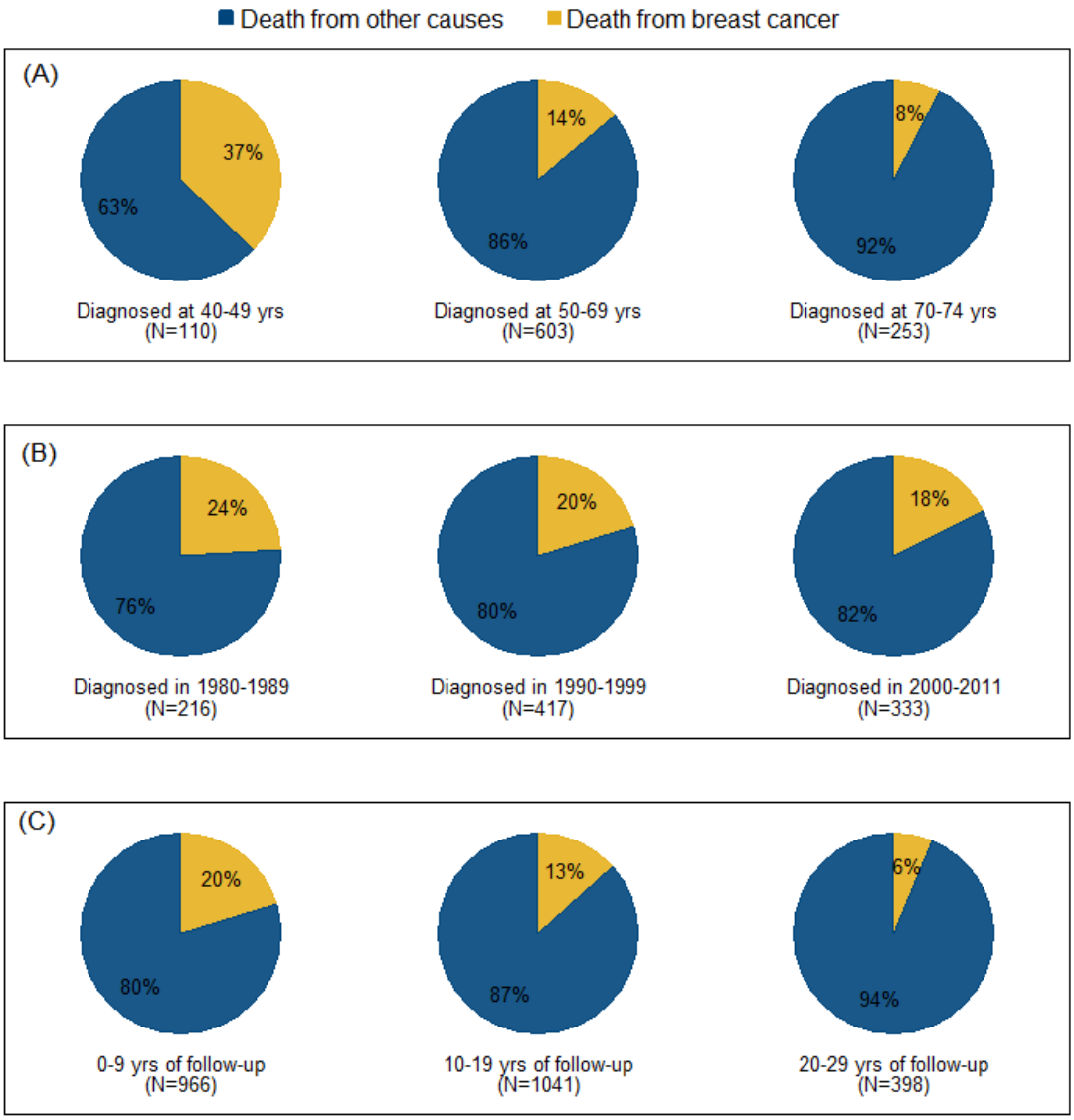

Death from other causes
Death from breast cancer
(A)
37%
63%
Diagnosed at 40-49 yrs
(N=110)
14%
86%
Diagnosed at 50-69 yrs
(N=603)
8%
92%
Diagnosed at 70-74 yrs
(N=253)
(B)
24%
76%
Diagnosed in 1980-1989
(N=216)
20%
80%
Diagnosed in 1990-1999
(N=417)
18%
82%
Diagnosed in 2000-2011
(N=333)
(C)
20%
80%
0-9 yrs of follow-up
(N=966)
13%
87%
10-19 yrs of follow-up
(N=1041)
6%
94%
20-29 yrs of follow-up
(N=398)

Figure 2

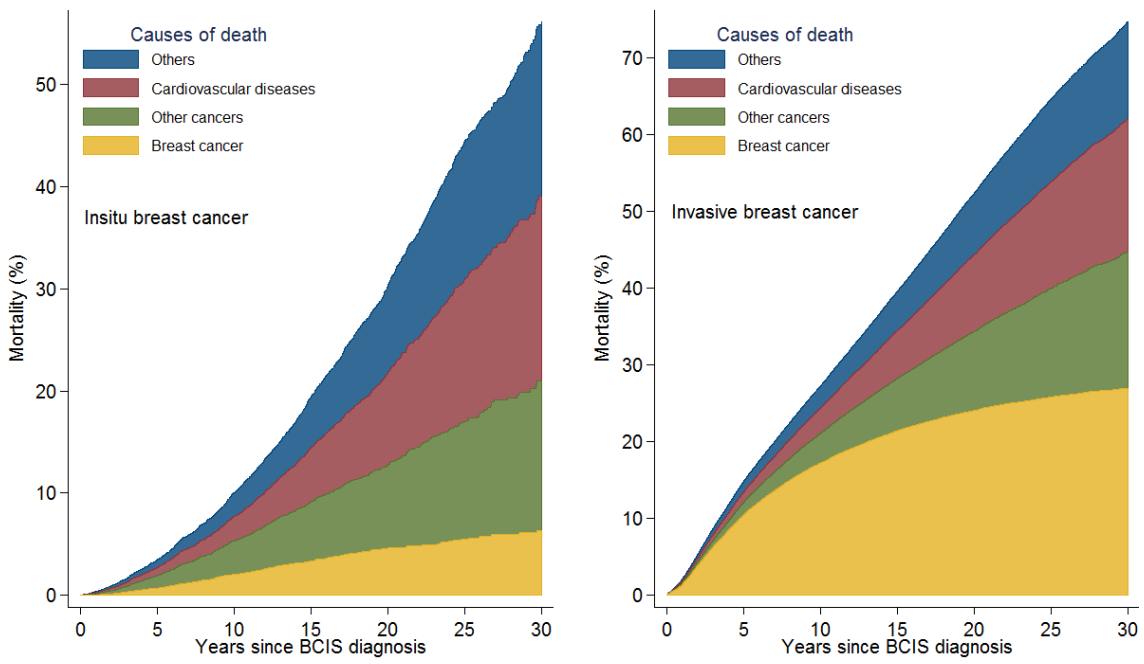

Causes of death
Others
Cardiovascular diseases
Other cancers
Breast cancer
Insitu breast cancer
Mortality (%)
0
10
20
30
40
50
0
5
10
15
20
25
30
Years since BCIS diagnosis
Causes of death
Others
Cardiovascular diseases
Other cancers
Breast cancer
Invasive breast cancer
Mortality (%)
0
10
20
30
40
50
60
70
0
5
10
15
20
25
30
Years since BCIS diagnosis

Figure 3

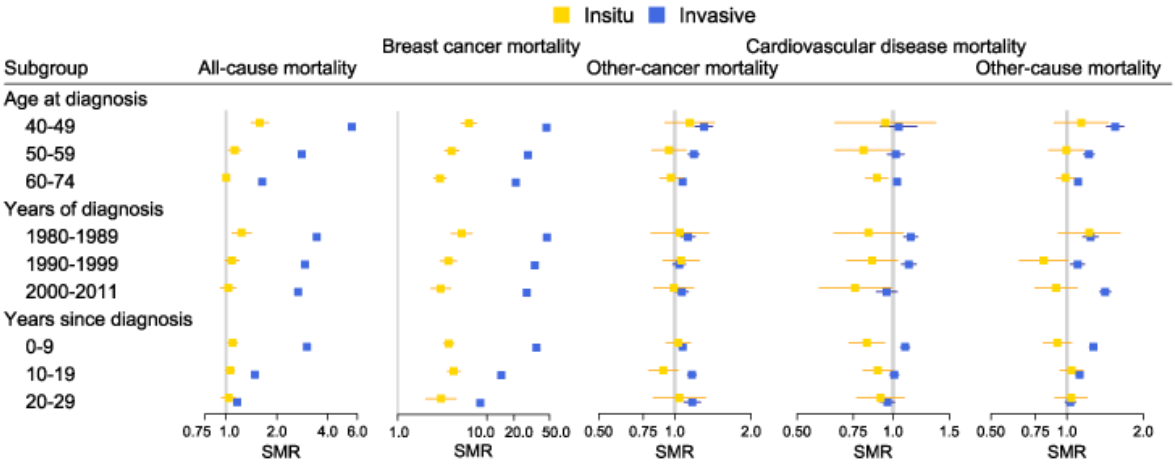

Insitu
Invasive
Subgroup
All-cause mortality
Breast cancer mortality
Other-cancer mortality
Cardiovascular disease mortality
Other-cause mortality
Age at diagnosis
40-49
50-59
60-74
Years of diagnosis
1980-1989
1990-1999
2000-2011
Years since diagnosis
0-9
10-19
20-29
0.75 1.0 2.0 4.0 6.0
1.0 10.0 20.0 50.0
0.50 0.75 1.0 2.0
0.50 0.75 1.0 1.5
0.50 0.75 1.0 2.0
SMR

Figure 4

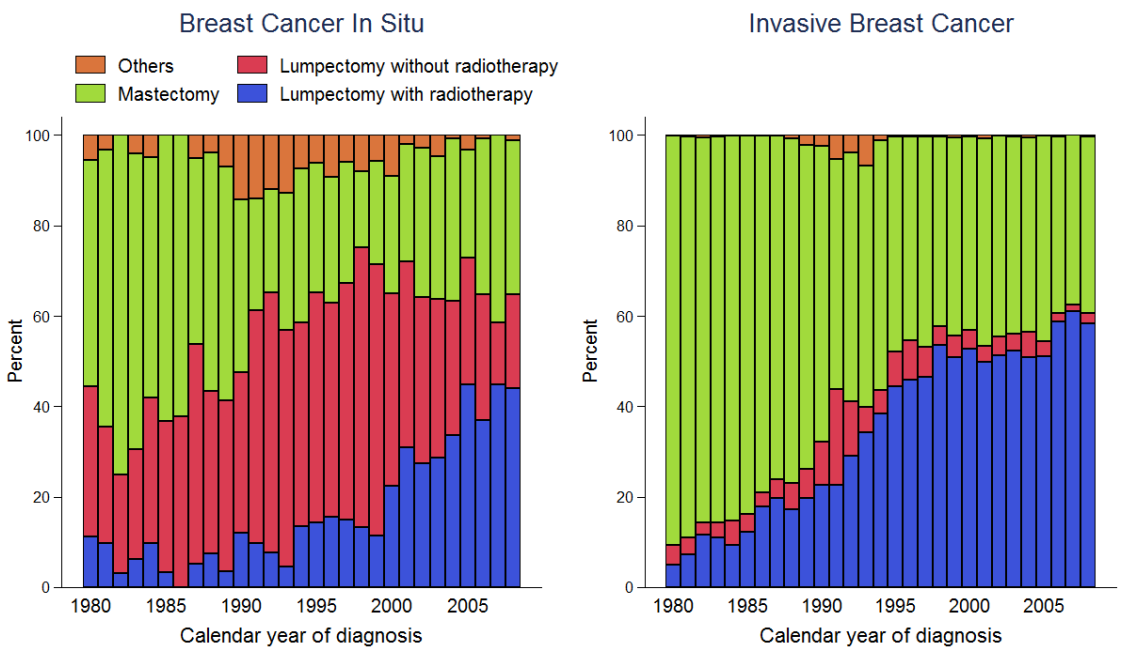
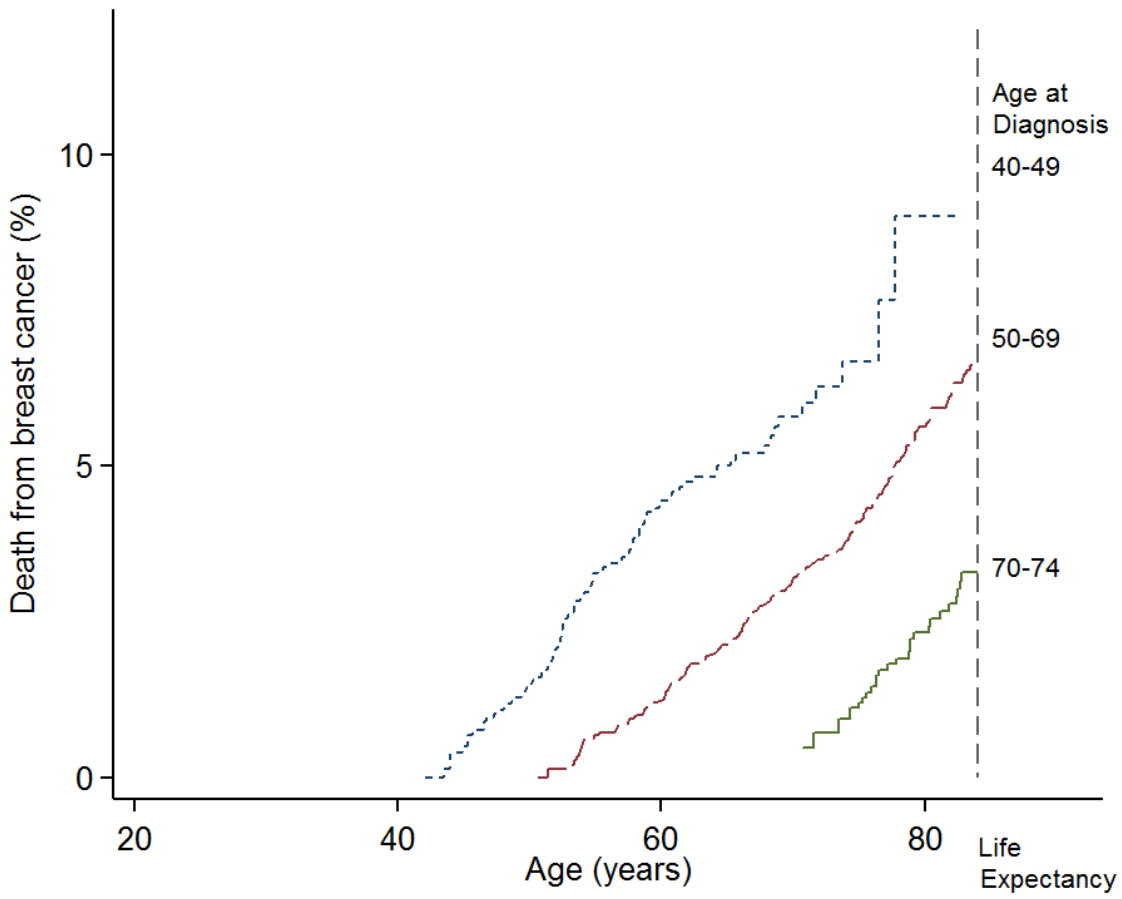

Breast Cancer In Situ
Invasive Breast Cancer
Others
Mastectomy
Lumpectomy without radiotherapy
Lumpectomy with radiotherapy
Percent
0
20
40
60
80
100
1980
1985
1990
1995
2000
2005
Calendar year of diagnosis

Figure s1


Death from breast cancer (%)
10
5
0
20
40
60
80
Age (years)
Age at
Diagnosis
40-49
50-69
70-74
Life
Expectancy