Received: 12 June 2020 | Revised: 11 April 2021 | Accepted: 28 April 2021

DOI: 10.1002/ijc.33680

CANCER EPIDEMIOLOGY

IJC International Journal of Cancer

Can breast cancer be stopped? Modifiable risk factors of breast cancer among women with a prior benign or premalignant lesion

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Funding information
Norwegian Cancer Society, Grant/Award Number: 5746604

Abstract

Physical inactivity, high postmenopausal body mass index, alcohol consumption and use of menopausal hormone therapy are established risk factors for breast cancer. Less is known about whether these factors influence the risk of progression of benign and premalignant breast lesions to invasive breast cancer. This registry-based cohort study was based on women with a precancerous lesion who were followed for breast cancer. The cohort consisted of 11 270 women with a benign lesion, 972 women with hyperplasia with atypia and 2379 women with carcinoma in situ diagnosed and treated after participation in BreastScreen Norway, 2006-2016. Information on breast cancer risk factors was collected by a questionnaire administered with the invitation letter. Cox regression analysis was used to estimate the association between breast cancer and physical activity, body mass index, alcohol consumption, tobacco smoking and menopausal hormone therapy, adjusted for age. During follow-up, 274 women with a benign lesion, 34 women with hyperplasia with atypia and 118 women with carcinoma in situ were diagnosed with invasive breast cancer. We observed an increased risk of breast cancer associated with use of menopausal hormone therapy for women with a benign or premalignant lesion. Alcohol consumption and tobacco smoking showed suggestive increased risk of breast cancer among women with a benign lesion. We were only to a limited degree able to identify associations between modifiable risk factors of breast cancer and the disease among women with a precancerous lesion, and a larger study is needed to confirm or refute associations.

KEYWORDS

alcohol, body mass index, early detection of breast cancer, menopausal hormone therapy, physical activity

Abbreviations: BMI, body mass index; CRN, Cancer Registry of Norway; DCIS, ductal carcinoma in situ; EPT, combined estrogen and progestin therapy; HT, menopausal hormone therapy; LCIS, lobular carcinoma in situ.

1 | INTRODUCTION

Breast cancer is the most frequent diagnosed cancer among women worldwide. It is a heterogeneous disease on the molecular level, and substantial effort has been made to characterize the disease and describe its progression.[1] Epidemiological risk factors for breast cancer have been established and several models for mechanisms involved in progression of the disease have been proposed.[2] The main factors influencing the risk of breast cancer are gender and age. Several risk factors for breast cancer are related to hormone exposure (mainly estrogen and progesterone).[2] Nonmodifiable risk factors for breast cancer include early menarche, late menopause, family history of breast cancer, race, height, mammographic density and certain gene alterations. Modifiable risk factors include age at first live birth, parity, breast feeding, exogenous hormones, postmenopausal body mass index (BMI), physical activity, educational level and alcohol consumption.[2] Concerning lifestyle after age 50 years, several studies have confirmed that high BMI,[3,4] limited physical activity,[5-7] alcohol consumption[5,7-9] and menopausal hormone therapy (HT) use[6,10,11] are associated with an increased risk of breast cancer. Moreover, studies have shown that tobacco smoking is associated with increased risk of breast cancer,[5,12] however its association with breast cancer is less clear.

The associations between known risk factors and breast cancer among women participating in the population-based mammographic screening program BreastScreen Norway have been reported in several articles.[13-19] Participants with a false-positive screening examination and those diagnosed with a premalignant lesion had an increased long-term risk of invasive breast cancer compared to women screened negative (2-fold relative risk after additional imaging or a biopsy with benign results, 3-fold after detection of hyperplasia with atypia, 4-fold after a carcinoma in situ diagnosis).[20]

Genetic and environmental risk factors for carcinoma in situ are similar to those for invasive breast cancer.[21-27] This suggests that premalignant lesions and invasive breast cancer share the same etiology,[21,23] and that most risk factors for invasive breast cancer are important for tumor initiation.[24,27] However, there is remaining uncertainty regarding the association between tumor progression and HT,[28,29] alcohol consumption[30-32] and BMI and physical activity.[31-33]

The aim of our study was to estimate the association between the modifiable factors physical activity, BMI, alcohol consumption, tobacco smoking, HT use and the risk of breast cancer among women with a benign lesion, hyperplasia with atypia or carcinoma in situ detected after participation in BreastScreen Norway.

What's New?

Whether established lifestyle risk factors for breast cancer, such as physical inactivity, use of hormone therapy (HT), and alcohol consumption, fuel cancer development in women with benign or premalignant breast lesions remains uncertain. In this investigation, increased risk of breast cancer development was observed among women with benign breast lesions who used menopausal HT. HT was not significantly linked to premalignant lesions. Likewise, only suggestive associations were detected for alcohol intake, smoking, and physical inactivity in women with benign or premalignant lesions. The findings warrant further study to better understand the impact of lifestyle factors on prior breast lesions.

2 | METHODS

BreastScreen Norway is a population-based screening program administered by the Cancer Registry of Norway (CRN).[13] The screening program started as a pilot project in four counties in 1995/96 and became nationwide by 2005. Today, 650 000 women aged 50-69 years are offered biennial two-view digital mammographic screening. The participation rate is approximately 75%, and 84% of the invited women have attended at least once during the first 20 years.[13] The recall rate was 3%-4%, whereas about 40% included a needle biopsy. About half of all women selected for a needle biopsy were diagnosed with ductal carcinoma in situ (DCIS) or breast cancer.

Results of the screening examination and the radiological procedures are reported electronically from the breast centers to the CRN.[13] Pathology reports describing results of needle biopsies (cytological or histological) are sent to the CRN electronically or on paper forms. We received information about benign outcomes, hyperplasia with atypia and lobular carcinoma in situ (LCIS) as a result of screening, while information about DCIS and breast cancer was available regardless of detection mode. The Cancer Registry Regulation ensures reporting of all cancer cases to the CRN.[34] This allows us to follow the screened women for breast cancer regardless of her screening adherence and eventual moving from one county to another. If several forms were used for reporting histologic type of the same lesion within a period of 6 months (diagnosis period), we used the report describing the most aberrant type of lesion.[20] BreastScreen Norway used SNOMED codes to classify benign and premalignant lesions while malignant cases were reported according to ICD-10. Throughout our study, the term breast cancer refers to invasive breast cancer (ICD10: C50).[35]

2.1 | Study population

We obtained data from the CRN with information concerning 767 572 women. Inclusion criteria were no prior diagnosis of DCIS or breast cancer before her first attendance in BreastScreen Norway and at least 6 months of follow-up after her first screen. We excluded 4180 women with breast cancer or another type of cancer located in the breast detected at first screen, and 749 women with inconclusive histology results after first screen. We classified the follow-up time of each woman to four groups according to her prior screening results: negative screen (not analyzed), benign, atypia and carcinoma in situ

(Table 1). For simplicity, we let the phrase "women with atypia" include all women with a prior diagnosis of atypia diagnosed after participation in BreastScreen Norway, and correspondingly for carcinoma in situ or a benign lesion.

We identified a total of 11 270 women with a benign lesion, 972 women with atypia and 2379 women with carcinoma in situ diagnosed during the study period (2006-2016). The cohort was followed from date of inclusion in each group to the diagnosis of breast cancer or end of follow-up, regardless of detection mode.

2.2 | Study variables

Information about risk factors for breast cancer was collected through a questionnaire administered together with invitations to BreastScreen Norway. More than 600 000 women responded on 1.7 million questionnaires in the period August 2006 to December 2015.[13] Overall, there was 69% response on the repeated questionnaire, and 88% of the attending women have handed in at least one questionnaire. The questionnaire included questions on menstrual and reproductive factors, current weight, attained height, physical activity, alcohol consumption, smoking and use of HT.

Strenuous physical activity was summarized into 0-1, 2-3 or 4+ hours per week. BMI was calculated as the ratio of body weight (kg) by height squared (m). Alcohol consumption was reported as number of glasses consumed per month of wine, beer and liquor, respectively. Weekly consumption of alcohol in wine glass equivalents was calculated assuming 12 g of ethanol per glass of wine, 20 g per 0.5 L of beer and 14 g per glass of liquor.[14] Smoking status was reported as being a current smoker, former smoker or never having smoked. Current and former use and duration of HT use were reported for the following HT-formulations: Kliogest, Activelle, Trisekvens, Novofem, Eviana, Indivina, Livial, Ovestrin, Oestriol, Progynova, Estronorm and for HT skin patches and vaginal estrogen products. A woman was included as a current HT user if she reported use of HT within the last 3 months before her inclusion screen. Current users were further categorized as combined estrogen and progestin therapy (EPT) or other types (estrogen not in combination with progestin). Age at inclusion was calculated from date of inclusion screen (month, year) and date of birth (month, year), and available for all women in the study.

Year of inclusion to study group and information on sociodemographic factors and health-related variables before age 50 were included in the multiple imputation model; age at menarche, use of oral contraceptives (ever, never at age 50), number of live born children, smoking status (ever, never at age 50), physical activity, alcohol consumption, birth weight, birth place (Norway, Europe outside Norway, outside Europe) and education (≤elementary school, high school, college or university degree).

2.3 | Statistical analysis

We used individual level data to classify each woman's follow-up time to the study groups benign, atypia and carcinoma in situ (Figure 1). Women were censored at end of follow-up (December 2016), age 80 years or at diagnosis of other types of cancer located in the breast (details on morphologies can be found as a supplement to a previous article[20]). Women's inclusion screen was defined as the screen resulting in inclusion to the group (the last screen prior to inclusion). We have not censored a woman's contribution of follow-up time to the benign group at a subsequent inclusion in the atypia group, as this would be censoring at an event on the causal pathway toward the outcome. However, we did censor a woman's contribution of follow-up time to a prior group at inclusion in the carcinoma in situ group, due to the treatment of the carcinoma in situ lesion. Hence, after a diagnosis of carcinoma in situ, a woman contributed follow-up time to the carcinoma in situ group only.

Information about physical activity, BMI, alcohol consumption, smoking and HT use was collected from the questionnaire returned at inclusion screen. At inclusion screen, 57% of the women in the carcinoma in situ group and 64%-65% in the benign and atypia group had filled out and returned the most current questionnaire. Information from repeated questionnaires was used to impute missing values at the inclusion screen.

We generated 50 multiple imputations[36] iteratively conducted by chain equations (MICE)[37] as implemented in the *mi impute* procedure in Stata. Information concerning lifestyle before age 50 (listed above) was included to improve the quality of the imputed values. Information from repeated questionnaires was summarized as average self-reported value (physical activity, BMI and alcohol consumption) or max self-reported value (ever use of EPT, other HT, previous HT and ever smoked). The multiple imputation model included age at inclusion, the outcome indicator and the Nelson-Aalen estimate of the cumulative hazard as regular (complete) variables to avoid bias.[38]

TABLE 1 The woman-years per screened woman were classified to one or more groups depending on her screening history[24]

	Classification of women years
Screened negative	Women-years were classified to the screened negative group (not analyzed) from first time screened negative until first positive screen resulting in a needle biopsy, diagnosis of carcinoma in situ (LCIS or DCIS) or breast cancer. Hence, the definition of screened negative includes both negative screens and false-positive screens resolved at recall by additional imaging only.
Benign	The women were followed in the benign group from first screen resulting in a needle biopsy with benign result, and until diagnosis of carcinoma in situ (censored due to treatment) or breast cancer (outcome), or end of follow-up.
Atypia	The women were followed in the atypia group from first screen resulting in a needle biopsy with hyperplasia with atypia, and until diagnosis of carcinoma in situ (censored due to treatment) or breast cancer (outcome), or end of follow-up.
Carcinoma in situ	The women were followed in the carcinoma in situ group from first screen resulting in a diagnosis of carcinoma in situ (LCIS or DCIS), and until diagnosis of breast cancer (outcome), or end of follow-up.

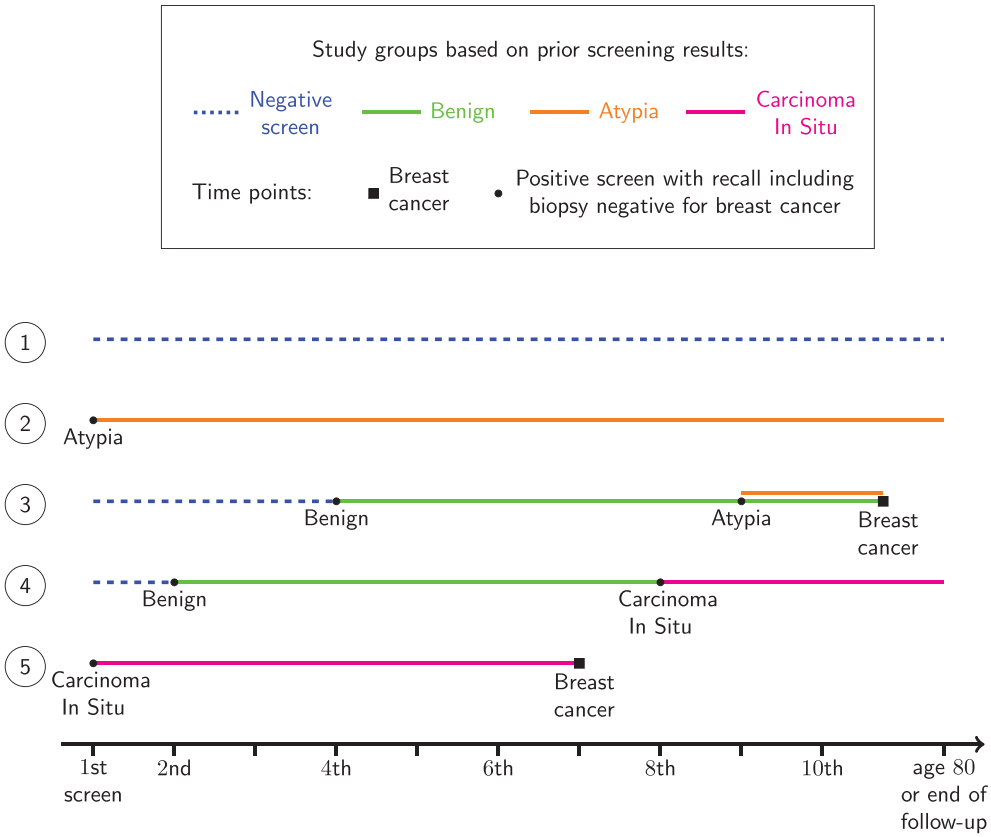

FIGURE 1 Classification of follow-up time into four groups based on prior screening results for five examples of screened women. See Table 1 for further information. Graphics program used to create the artwork: LaTeX Tikz, compiled with Texmaker [Color figure can be viewed at wileyonlinelibrary.com]

	Benign	Atypia	Carcinoma in situ
Study population			
No. of women	11 270	972	2379
No. of breast cancers	274	34	118
Absolute risk of breast cancer			
IR per 1000 wy	4.7 (95% CI 4.2-5.3)	6.7 (95% CI 4.8-9.4)	10.4 (95% CI 8.7-12.5)
Complete case analysis			
No. of women	5191	434	908
No. of outcomes	125	14	41

TABLE 2 Number of women and breast cancer cases and crude incidence rate in the study period, and number of women and breast cancer cases available for complete case analysis

Abbreviations: CI, confidence interval; IR, incidence rate; wy, woman-years.

Cox regression analysis was applied to estimate the association of each of the five modifiable risk factors physical activity, BMI, alcohol consumption, tobacco smoking and HT, both in univariate analyses adjusted for age and in multivariate analyses adjusted for age and the remaining four risk factors. Associations were measured as hazard ratios (HR) and presented with 95% confidence intervals (CI). Model parameters were estimated separately for each imputed dataset, and their point estimates and standard errors were combined using Rubin's rules. Descriptive statistics were presented as frequencies, proportions and median with interquartile range (IQR).

Several sensitivity analyses were performed. (a) We excluded women who were self-reported premenopausal (benign: 15%, atypia: 13% and carcinoma in situ: 7%). (b) The in situ group were restricted to women with DCIS, that is, excluding LCIS. (c) The main analyses were repeated with different random seeds for the multiple imputation procedure, to confirm the results. (d) The analyses were repeated on the subset of women with complete information.

Data preparations and analyses were performed using Stata (version 16, StataCorp, College Station, Texas). We considered a two-sided *P*-value less than .05 as being statistically significant.

3 | RESULTS

Among 11 270 women with a benign biopsy, 274 were diagnosed with breast cancer after a median follow-up of 5.2 years (Table 2).

Among 972 women with atypia, 34 were diagnosed with breast cancer after a median follow-up of 5.3 years. And among 2379 women with a carcinoma in situ, 118 were diagnosed with breast cancer after a median follow-up of 4.6 years.

The median age at inclusion was increasing from the benign group (54 years) to the atypia group (57 years) to the carcinoma in situ group (60 years) (Table 3). Most of the women were born in Norway (92%-94%) and had finished high school and/or a college or university degree (74%-78%, Table S1). The study groups were similar with respect to body size (height, weight and BMI) and levels of physical activity. One in five women were abstainers of alcohol, and current drinkers had a weekly alcohol consumption of 1.8 wine glass equivalents per week. There were fewer current smokers among women with carcinoma in situ compared to women with benign or atypia (22% vs 32%). The fraction of never HT users was highest in the benign group (67%). Former use and current use of other HT types (estrogen not in combination with progestin) were increasing from the benign group to the atypia group to the carcinoma in situ group. This might be related to the increasing median inclusion age across the study groups in the same direction.

We observed a tendency of higher levels of physical activity being associated with lower risk of breast cancer (Table 4), however all estimates were inconclusive with wide confidence intervals (benign: HR 0.92, 95% CI 0.49-1.75; atypia: HR 0. 76, 95% CI 0.10-5.45; in situ: HR 0.80, 95% CI 0.26-2.44 for 4+ hour compared to 0-1 hour of weekly strenuous physical activity). BMI was not associated with the risk of breast cancer in any study group. There was a suggestive increased risk of breast cancer among former and current smokers compared to nonsmokers (benign: HR 1.18, 95% CI 0.85-1.66 among former smokers and HR 1.38, 95% CI 0.99-1.92

TABLE 3 Median age at diagnosis and self-reported characteristics of women within each study group

	Benign		Atypia		Carcinoma in situ	
	n	% or median (IQR)	n	% or median (IQR)	n	% or median (IQR)
Median age (y)	11 270	54 (51-61)	972	57 (52-63)	2379	60 (55-65)
Strenuous physical activity						
0–1 hour/week	4514	68.3%	379	68.3%	828	68.2%
2–3 hours/week	1638	24.8%	131	23.6%	304	25.0%
4+ hours/week	453	6.9%	45	8.1%	83	6.8%
Missing value[a]	4665		417		1164	
Body size						
Height (cm)	7173	167 (163-170)	608	166 (163-170)	1308	167 (163-170)
Weight (kg)	6593	70 (63-80)	570	70 (62-78)	1220	68 (62-78)
BMI (kg/m^2)	6553	25 (23-28)	565	25 (23-28)	1208	25 (23–28)
Missing value[a]	4717		407		1171	
Alcohol consumption[b]						
Not consuming	1368	20.2%	127	22.2%	240	19.4%
Current drinker	5406	79.8%	445	77.8%	1000	80.6%
Consumption among drinkers	5406	1.8 (0.9-3.5)	445	1.8 (0.9-3.8)	1000	2.0 (0.9-3.7)
Missing value[a]	4496		400		1139	
Smoking status						
Never	2559	36.6%	219	37.4%	539	42.3%
Former	2216	31.7%	179	30.5%	450	35.3%
Current	2218	31.7%	188	32.1%	285	22.4%
Missing value[a]	4277		386		1105	
Menopausal hormone therapy						
Never	4401	66.8%	324	58.5%	697	56.9%
Former	1018	15.4%	102	18.4%	257	21.0%
Current EPT	533	8.1%	53	9.6%	98	8.0%
Current other[c]	638	9.7%	75	13.5%	172	14.1%
Missing value[a]	4680		418		1155	

Abbreviations: BMI, body mass index; EPT, estrogen plus progestin combination therapy; IQR, interquartile range.

[a]Missing the questionnaire value from the inclusion screen.

[b]Total weekly amount of ethanol converted to wine glass-equivalents.

[c]Current user of other types of hormone therapy, that is, estrogen not in combination with progestin.

TABLE 4 Age-adjusted hazard ratio (with 95% confidence interval) from multiple imputation analysis with 50 imputed datasets

	Benign		Atypia		Carcinoma in situ	
	Univariate	Multivariate	Univariate	Multivariate	Univariate[a]	Multivariate[a]
Strenuous physical activity						
0–1 hour/week	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
2–3 hours/week	1.17 (0.85-1.64)	1.20 (0.86-1.67)	0.77 (0.26-2.24)	0.73 (0.24-2.20)	0.94 (0.53-1.66)	0.93 (0.52-1.66)
4+ hours/week	0.90 (0.48-1.69)	0.92 (0.49-1.75)	0.77 (0.11-5.36)	0.76 (0.10-5.45)	0.86 (0.29-2.56)	0.80 (0.26-2.44)
Body mass index						
Linear per kg/m^2	1.00 (0.97-1.03)	1.01 (0.98-1.04)	0.98 (0.89-1.08)	0.98 (0.89-1.09)	0.98 (0.92-1.03)	0.98 (0.93-1.04)
Alcohol consumption[b]						
Linear per glass of wine	1.05 (0.99-1.11)	1.04 (0.97-1.10)	1.01 (0.86-1.19)	1.00 (0.84-1.19)	1.06 (0.95-1.18)	1.05 (0.94-1.18)
Smoking status						
Never	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Former	1.28 (0.92-1.77)	1.18 (0.85–1.66)	1.24 (0.46-3.38)	1.21 (0.44-3.29)	0.91 (0.55-1.52)	0.86 (0.51-1.46)
Current	**1.40 (1.02-1.93)**	1.38 (0.99-1.92)	1.27 (0.46-3.47)	1.21 (0.44-3.38)	1.14 (0.66-1.98)	1.05 (0.59-1.87)
Menopausal hormone therapy						
Never used	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Former user	**1.49 (1.01-2.19)**	**1.47 (1.00-2.16)**	1.06 (0.32-3.51)	1.04 (0.31-3.48)	1.15 (0.65-2.04)	1.13 (0.63-2.01)
Current EPT	**1.99 (1.29-3.06)**	**1.96 (1.27-3.02)**	1.60 (0.40-6.35)	1.55 (0.37-6.45)	1.84 (0.88-3.88)	1.75 (0.80-3.85)
Current other[c]	1.30 (0.78-2.14)	1.29 (0.78-2.14)	1.39 (0.40-4.80)	1.39 (0.39-4.99)	1.17 (0.55-2.48)	1.16 (0.55-2.47)

Note: Statistical significant results are emphasized by bold type.
Abbreviation: EPT, estrogen plus progestin combination therapy.
[a]Analyses of the in situ group are adjusted for treatment, grade and tumor size in addition to age at inclusion.
[b]Total weekly amount of ethanol converted to wine glass-equivalents.
[c]Current user of other types of hormone therapy, that is, estrogen not in combination with progestin.

among current smokers), while a less clear trend was observed per weekly glass of wine. We observed a higher risk of breast cancer associated with HT use among women with a benign or premalignant lesion, however only statistically significant for the benign group concerning current users of EPT (HR 2.0, 95% CI 1.3-3.0) and former users of HT (HR 1.5, 95% CI 1.0-2.2).

Restricting the regression analyses to women who did not self-report to be premenopausal yielded similar results (not shown). Restricting the in situ regression analyses to women with a prior DCIS yielded similar results (Tables S2 to S4). Regression analyses using data from the subset of women with complete information for all variables did not change the conclusions (Table 5).

4 | DISCUSSION

We observed an increased risk of breast cancer associated with HT use among women with a benign lesion, and a suggestive increased risk among women with a premalignant lesion. Among women with a benign or premalignant lesion, there was a suggestive increased risk among smokers, and less clear trend per weekly glass of wine. BMI was not associated with the risk of breast cancer in any study group.

The proportion of benign biopsies in Norway was in between, and not unexpectedly far from, those reported in Spain[39] and in Vermont, The United States.[40] Among women included in our study, lesions with atypia or LCIS were surgically excised, and women with DCIS were treated with mastectomy or breast conserving treatment with or without radiotherapy. Norwegian women diagnosed and treated for DCIS undergo annual mammography in addition to a clinical exam annually, for 10 years after the treatment regime is finished.

Strengths of our study include the prospectively collected information of risk factors for breast cancer, and the population-based design. Limitations include lack of data about mammographic density, chemoprevention use and breast cancer subtypes and that breast cancer risk was analyzed with respect to the values of the selected risk factors at inclusion. Women might have undergone lifestyle changes after inclusion, related or not related to the positive screening result, and, if any, these changes were not accounted for by our design. Another limitation of our study is the limited statistical power due to a relatively low number of women with atypia and women with carcinoma in situ. The length of the study period was 11 years, median follow-up was around 5 years and our data contains little information about risk of breast cancer 7+ years after a benign or premalignant breast lesion.

Our study had a high proportion of missing values for the study variables, up to nearly half of the values missing per variable. However, 87% of the women (carcinoma in situ group: 80%, atypia and benign groups: 87%) had handed in at least one questionnaire in the study period, and we applied a multiple imputation procedure to preserve existing relations in the data and their uncertainty.

TABLE 5 Age-adjusted hazard ratio (with 95% CI) from complete case analysis

	Benign (n = 5191)		Atypia (n = 434)		Carcinoma in situ (n = 908)	
	Univariate	Multivariate	Univariate	Multivariate	Univariate[a]	Multivariate[a]
Strenuous physical activity						
0–1 hour/week	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
2–3 hours/week	1.12 (0.74-1.69)	1.16 (0.76-1.76)	0.53 (0.12-2.41)	0.62 (0.13-2.94)	1.03 (0.50-2.13)	1.04 (0.49-2.21)
4+ hours/week	1.23 (0.62-2.45)	1.30 (0.65-2.61)	0.88 (0.11-6.88)	0.94 (0.11-7.80)	1.00 (0.23-4.32)	1.11 (0.25-4.88)
Body mass index						
Linear per kg/m^2	1.00 (0.96-1.04)	1.02 (0.98-1.06)	1.02 (0.89-1.16)	1.03 (0.90-1.18)	0.99 (0.92-1.06)	0.99 (0.92-1.07)
Alcohol consumption[b]						
Linear per glass of wine	1.04 (0.96-1.12)	1.02 (0.94-1.10)	1.05 (0.86-1.28)	1.03 (0.83-1.26)	1.01 (0.87-1.17)	0.99 (0.85-1.15)
Smoking status						
Never	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Former	1.50 (0.95-2.36)	1.40 (0.88-2.21)	1.72 (0.38-7.69)	1.62 (0.36-7.35)	0.72 (0.33-1.57)	0.74 (0.33-1.67)
Current	**1.80 (1.15-2.82)**	**1.79 (1.13-2.84)**	3.05 (0.79-11.80)	2.68 (0.66-10.91)	2.01 (0.86-4.71)	2.07 (0.84-5.11)
Menopausal hormone therapy						
Never used	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Former user	1.42 (0.87-2.31)	1.35 (0.83-2.19)	1.71 (0.39-7.49)	1.48 (0.33-6.54)	0.67 (0.29-1.54)	0.71 (0.30-1.67)
Current EPT	**2.16 (1.29-3.62)**	**2.11 (1.25-3.55)**	1.85 (0.37-9.33)	1.68 (0.32-8.73)	1.22 (0.42-3.54)	1.34 (0.45-4.00)
Current other[c]	1.18 (0.64-2.18)	1.18 (0.64-2.18)	1.89 (0.45-7.90)	1.95 (0.45-8.48)	0.66 (0.22-2.01)	0.67 (0.22-2.08)

Note: Statistical significant results are emphasized by bold type.

Abbreviation: EPT, estrogen plus progestin combination therapy.

[a]Analyses of the in situ group are adjusted for treatment, grade and tumor size in addition to age at inclusion.

[b]Total weekly amount of ethanol converted to wine glass-equivalents.

[c]Current user of other types of hormone therapy, that is, estrogen not in combination with progestin.

Self-reported information on physical activity, height, weight, alcohol consumption, smoking and HT use was available from the questionnaire routinely administered with invitations to BreastScreen Norway in the period 2006-2015. Self-reported information has obvious limitations.[41-44] Self-reported height and weight are found to be reported consistently among women participating in BreastScreen Norway.[41] It is well known that weight is usually underreported while height is overreported; hence both contributing bias in the same direction to underreported values for BMI.[42] Self-reported smoking is usually underestimated.[43] Still, smoking habits and alcohol consumption are observed to be highly accurately self-reported.[44] Self-reported HT use in BreastScreen Norway correspond well to dispensed prescription data.[18] Nonsystematic measurement errors in the covariates are associated with effect estimates biased toward a null result.

Use of HT was associated with risk of breast cancer in our study. Among women with a benign biopsy, those who were current users of EPT had a 2-fold risk of subsequent breast cancer compared to never-users of HT. Similar tendencies for the effect of EPT being associated with an increased risk of progression to breast cancer was present among women with atypia and carcinoma in situ, however not statistically significant. The effect of other types of HT (estrogen not in combination with progestin) and prior HT use was smaller and did not reach statistical significance, however still indicated an increased risk. That HT, in addition to age, appeared as the most influential risk factor for breast cancer among women with a benign or premalignant lesion, is in line with a previous study[45] on stratified screening based on prior screening results, age and self-reported physical activity, BMI, smoking, HT, family history of breast cancer and reproductive history. However, our results are contrasting a previous study reporting decreased risk of progression to invasive breast cancer among HT users at diagnosis of carcinoma in situ[28] (proposedly through removal of the main etiological driver as the women quit their use of HT). A previous study reported no additional risk of breast cancer associated with HT use among women with proliferate benign breast disease compared to women with nonproliferative benign conditions.[29]

Alcohol showed a suggestive association with risk of breast cancer in our study. The statistically nonsignificant effect of alcohol might be due to limited power to detect the existing effect size, and possibly nondifferential misclassification of individual alcohol consumption. Larger studies or studies with a lower fraction of missing data on alcohol consumption are needed to evaluate this hypothesis. The measured effect of alcohol consumption might also depend on consumption patterns (binge drinking vs more frequent lower intensity drinking). Our effect estimate of alcohol on the risk of breast cancer for the carcinoma in situ group was in line with a previous study among women with DCIS.[32] Women with proliferate benign breast disease experienced no additional risk of breast cancer with increased alcohol consumption[30] compared to women with nonproliferative benign conditions. However, in a more recent study, alcohol

consumption increased risk more among women with versus without atypia in a high-risk cohort.[31]

Overweight after menopause is associated with increased risk of breast cancer, while overweight before menopause decreases risk.[18] In our study, exclusion of self-reported premenopausal women did not change our results. Women with dense breasts and atypia or a carcinoma in situ lesion may be of higher risk of subsequent breast cancer.[46,47] The statistically nonsignificant effect of BMI in our study might be due to failure to adjust for mammographic density, as high mammographic density is a risk factor for breast cancer and negatively correlated with BMI. The estimated effect of BMI on the risk of breast cancer for the carcinoma in situ group was similar to previously published estimates.[31,32,46]

Physical activity was not associated with risk of breast cancer in our study. This might be due to the self-reported values in broad categories and variable interpersonal interpretation of what is considered a strenuous workout activity. Nondifferential misclassification of physical activity levels would tend to attenuate the observed association, that is, contribute to an underestimation of the effect. Our effect estimates of physical activity on the risk of breast cancer for the carcinoma in situ group were in line with a previous study among women with DCIS.[32] A larger study with more precise data on physical activity is required to evaluate the effect of physical activity on breast cancer. Randomized trials of lifestyle interventions in women with premalignant lesions have additional potential in evaluating the causality of associations between lifestyle and risk of breast cancer.

Considering the excellent prognosis, the diagnosis of a premalignant lesion may represent a unique opportunity to intervene and educate women on positive lifestyle behaviors.[48] Women diagnosed with DCIS are more likely to die from cardiovascular disease (CVD) or other causes than from breast cancer, and mortality has been shown to be associated with physical activity (all-cause and CVD-specific), smoking (all-cause and cancer-specific) and alcohol consumption (all-cause).[49] Physical activity, weight management and reducing alcohol intake are safe lifestyle choices with several benefits and should be recommended to women with a benign or premalignant lesion.[50] Ultimately, all women should be empowered to make the best choices for her own life according to her family life, culture, resources, belief systems and personal preferences.

In conclusion, we observed an increased risk of breast cancer associated with HT use among women with a benign lesion, as our single statistically significant result. We were only to a limited degree able to identify associations between modifiable risk factors of breast cancer and the disease among women with a diagnosed benign, atypia or carcinoma in situ lesion detected as a result of participation in BreastScreen Norway, and a larger study is needed to confirm or refute associations.

ACKNOWLEDGMENTS

We are thankful to all participants in BreastScreen Norway who over a period of 10 years voluntarily handed in a total of 1.7 million questionnaires regarding risk factors for breast cancer. The authors would like to thank members of our multidisciplinary project group "Premalignant lesions in the breast" for inspiring discussions. The work was funded by The Norwegian Cancer Society (grant no. 5746604).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from The Cancer Registry of Norway (CRN) at https://www.kreftregisteret.no/en/The-Registries/data-delivery-unit/ following ethical approval of use.

ETHICS STATEMENT

Ninety-eight percent of women screened in BreastScreen Norway have approved of their data to be used for research and quality control through not opting for their reservation right.[12] The Regional Ethical Committee approved the study (2012/576b), which was based on indirectly identifiable data about women who attended at least one screening examination in BreastScreen Norway during the study period, from 2006 through 2016.

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How to cite this article: Lilleborge M, Falk RS, Sørlie T, Ursin G, Hofvind S. Can breast cancer be stopped? Modifiable risk factors of breast cancer among women with a prior benign or premalignant lesion. *Int. J. Cancer*. 2021;149(6):1247–1256. https://doi.org/10.1002/ijc.33680