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ARTICLE

Number of Risky Lifestyle Behaviors and Breast Cancer Risk

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Abstract

Background: Lifestyle factors are associated with overall breast cancer risk, but less is known about their associations, alone or jointly, with risk of specific breast cancer subtypes.
Methods: We conducted a case–control subjects study nested within a cohort of women who participated in the Norwegian Breast Cancer Screening Program during 2006–2014 to examine associations between risky lifestyle factors and breast cancer risk. In all, 4402 breast cancer cases subjects with information on risk factors and hormone receptor status were identified. Conditional logistic regression was used to estimate odds ratios (ORs), with 95% confidence intervals (CIs), in relation to five risky lifestyle factors: body mass index (BMI) of 25 kg/m^2 or greater, three or more glasses of alcoholic beverages per week, ever smoking, fewer than four hours of physical activity per week, and ever use of menopausal hormone therapy. Analyses were adjusted for education, age at menarche, number of pregnancies, and menopausal status. All statistical tests were two-sided.
Results: Compared with women with no risky lifestyle behaviors, those with five had 85% (OR = 1.85, 95% CI = 1.42 to 2.42, $P_{trend} < .0001$) increased risk of breast cancer overall. This association was limited to luminal A–like (OR = 2.20, 95% CI = 1.55 to 3.12, $P_{trend} < .0001$) and luminal B–like human epidermal growth factor receptor 2 (HER2)–positive (OR = 1.66, 95% CI = 0.61 to 4.54, $P_{trend} < .004$) subtypes. Number of risky lifestyle factors was not associated with increased risk of luminal B–like HER2-negative, HER2-positive, or triple-negative subtypes ($P_{trend} > .18$ for all).
Conclusions: Number of risky lifestyle factors was positively associated with increased risk for luminal A–like and luminal B–like HER2-positive breast cancer.

Previous studies have shown that alcohol (1–6), postmenopausal body mass index (BMI) (7), and menopausal hormone therapy (8–11) are risk factors for breast cancer, whereas physical activity is a protective factor for breast cancer (12). Smoking may not be a strong breast cancer risk factor (13–16), but it is strongly associated with other cancers, and thus must be considered a risky lifestyle behavior.

Often, risky lifestyle behaviors coexist, and it is therefore important to combine these behaviors, as opposed to simply looking at them individually, when studying breast cancer risk. Several studies have reported that the combined effect of risky lifestyle behaviors is associated with increased mortality overall (17–21), as well as cancer mortality (22). Very few studies have investigated the combined effect of lifestyle factors on breast cancer overall (23–25) or on the risk of specific breast cancer subtypes (23,26,27). However, although these studies have examined the association between breast cancer and BMI, food, alcohol, smoking, and physical activity (23,25–27), none have included menopausal hormone therapy use. Further, of the three studies that examined the effect on subtypes (23,26,27),

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none defined them using the full estrogen receptor (ER)/progesterone receptor (PR)/human epidermal growth factor 2 (HER2) status classification for a more refined stratification.

Breast cancer subtypes, defined as agreed upon at the 2013 St. Gallen Meeting (28), provide the basis for managing early invasive breast cancer. Different subtypes respond to different treatment regimens, suggesting that they may have a different biology and possibly also a different etiological profile. The published evidence (9,29–34) suggests that luminal A–like cancers have a hormonal etiology, but the association of hormonal-related factors with luminal B–like, HER2-positive, and triple-negative breast cancers is less clear. A large meta-analysis found stronger positive associations between alcohol and ER-positive tumors and weaker positive associations between alcohol and ER-negative tumors (35), and there is some evidence that smoking increases the risk of ER-positive and PR-positive breast tumors (36–39).

Our previous analyses from the Norwegian Breast Cancer Screening Program (40,41) found that BMI, smoking, alcohol, physical activity, and menopausal hormone therapy were individually associated with breast cancer overall, but the magnitude of these associations varied markedly according to ER/PR/HER2-defined subtypes, the latter taken as surrogates of the St. Gallen intrinsic subtypes (28). The aim of the present study was to extend these analyses by examining the combined effect of these lifestyle factors on risk of breast cancer overall and by ER/PR/HER2-defined subtypes. The study did not include dietary factors other than alcohol intake because no strong associations between such factors and breast cancer risk have been found in Norway (42,43).

Methods

Study Population

The methods have previously been described in detail (40). In brief, the Cancer Registry of Norway (CRN) is a population-based registry that is responsible for the administration of the Norwegian Breast Cancer Screening Program (NBCSP) (44). The registry is estimated to be 93.8% complete (45). All women in Norway age 50 to 69 years are invited to undergo a two-view mammography screening every two years. The average attendance rate in each round is about 75% (44). Women who attended the screening during 2006–2014 were asked to complete a questionnaire on a number of standard breast cancer risk factors before age 50 years and another questionnaire on current exposure variables at subsequent screenings.

Because of short follow-up, we conducted a matched case–control subjects study nested within a cohort of 344 348 women who attended the NBCSP during 2006–2014. Eligible women were those with no history of breast cancer, any other invasive cancer (except nonmelanoma skin cancer), or ductal carcinoma in situ of the breast before January 1, 2006. Participants who fulfilled these criteria and who had completed the questionnaires were included in the current study cohort from which cases and control subjects were identified. Information on cancer ascertainment among cohort members was obtained through linkage to the CRN records.

Case subjects were women diagnosed with a first occurrence of invasive breast cancer (ICD10: C50) during 2006–2014, with information on ER, PR, and HER2 receptor status (see below). Control subjects had to be cancer free, alive, and residing in the country at the time of diagnosis. Five control subjects were individually matched to each breast cancer case subjects by year of birth (+/-3 years) and year of last screening (+/-3 years).

The Regional Committee for Medical and Health Research Ethics in the South-East Health Region of Norway approved the study.

If a variable was missing on all the questionnaires a woman had completed, we excluded her from all analyses. Of the 6471 breast cancer case subjects, we excluded the following due to missing information on: BMI (n = 532), educational level (n = 135), age at menarche (n = 229), number of pregnancies (n = 164), menopausal status (n = 59), smoking habits (n = 62), alcohol intake (n = 154), and physical activity (n = 184). Finally, there were 4952 breast cancer case subjects for analysis. Of the 339 714 remaining women in the cohort, before we selected control subjects, we excluded women with missing information on: BMI (n = 67 813), educational level (n = 8362), age at menarche (n = 14 818), number of pregnancies (n = 8771), menopausal status (n = 6632), smoking (n = 6381), alcohol (n = 12 878), and physical activity (n = 16 205). This left us with 197 854 women in the cohort. Of these, we randomly selected five control subjects per case subjects, which left us with 24 760 control subjects for analysis.

Tumor Receptor Status Ascertainment

Information on ER, PR, and HER2 status, as assessed by immunohistochemistry (IHC), was extracted from pathology reports submitted to the CRN. Tumors were classified as being ER+ if they had 10% or greater reactivity from 2006 to January 2012, and if they had 1% or greater reactivity from February 2012 onwards. The change in threshold was a result of a change in treatment protocols of patients in the clinics in Norway. PR+ tumors were defined as those with a reactivity of 10% or greater throughout the study period. Case subjects with no (0) or weak (1+) immunostaining were classified as HER2-, whereas case subjects with strong immunostaining (3+) were defined as HER2+. In situ hybridization was used to confirm HER2 status if IHC yielded moderate staining (2+) results. If IHC was 2+ and fluorescence (FISH), chromogenic (CISH), or silver in situ hybridization (SISH) was missing, or if IHC was missing but FISH, CISH, or SISH were positive, the tumor was classified as HER2+. If IHC was 2+ and FISH, CISH, and SISH were negative, the tumor was regarded as HER2-.

We used a modified version of the classification of clinically defined subtypes proposed at the St. Gallen meeting in 2013 (28). Of the 4952 breast cancer case subjects, 550 case subjects had unknown hormone receptor status (ie, ER and/or PR) and HER2 status or could not be classified into subtypes. Of the 4402 breast cancer case subjects, 2761 (63%) were classified as luminal A–like (ER+PR+HER2-), 709 (16%) as luminal B–like HER2-negative (ER+PR-HER2-), 367 (9%) as luminal B–like HER2-positive (ER+PR-/PR+HER2+), 204 (5%) as HER2-positive (ER-PR-HER2+), and 361 (8%) as triple-negative (ER-PR-HER2-).

Risk Factors

Data on the exposures of interest were extracted from the questionnaires completed at the most recent screening before breast cancer diagnosis for the case subjects and the corresponding round for control subjects. Although this is less than ideal for exposures associated with initiation of cancer, the time point was chosen to capture recent exposures such as hormone therapy, for which we have previously found strong associations with breast cancer risk (40,46). The primary exposures of

interest were BMI, alcohol consumption, smoking habits, physical activity, and postmenopausal hormone therapy. Weight and height were self-reported. Women were asked about the amount of beer, wine, or liquor consumed in glasses per week. The amount of total alcohol intake was estimated assuming 14 grams of ethanol per glass of liquor, 20 grams per 0.5 liters of beer, and 12 grams per glass of wine. We converted the alcohol consumed per week into glasses per week, assuming every glass would have the same alcohol content as a glass of wine (12 grams). The tables therefore contain glasses per week estimated as total grams of alcohol per week divided by 12 grams of alcohol per glass.

Smoking status was categorized into never, past, and current smoking. Never smokers were defined as those women who had never smoked. Women who did not currently smoke but had smoked in the past were defined as past smokers, and current smokers were those women currently smoking. Physical activity was estimated as number of hours per week of high-intensity physical activity (running, aerobic, or cycling for at least 30 minutes each time) and low-intensity physical activity (walking, gardening, snow clearing). We added up hours of low- and high-intensity-level physical exercise into one combined variable. We analyzed high, low, and the combined activity variables separately, but we only present results for the combined low and high activity variable. Information on menopausal hormone therapy was examined as never, past, and current use, and the latter was separated into estrogen alone (ET) and combined estrogen and progestin therapy (EPT).

Creation of the Risky Lifestyle Behavior Variable

We used cut-points to define "risky" for each of the lifestyle factors based on our previously published results (40,47), that is, where the risk estimates (odds ratios [ORs]) showed a statistically significantly elevated risk. To sum up various risky lifestyle behaviors, we created binary variables for each behavior as follows: ever smoking, weekly consumption of more than three glasses of alcoholic beverage, less than four hours of physical activity per week, ever use of menopausal hormone (estrogen or estrogen and progesterone) therapy, and BMI ($\geq$25 kg/m^2); we made dummy variables of smoking (0 = never, 1 = ever), alcohol intake (0 = <3 glasses/wk, 1 = $\geq$3 glasses/wk), physical activity (0 = $\geq$4 h/wk, 1 = <4 h/wk), menopausal hormone therapy use (0 = never, 1 = ever), and BMI (0 = <25 kg/m^2, 1 = $\geq$25 kg/m^2). The risky lifestyle behavior variable was created as a sum of all the binary variables, with a resulting range from 0 to 5 risky lifestyle behaviors.

Selection of Confounders

Potential confounders were selected a priori: education (no formal education/primary school, high school, Bachelor's/Master's/higher university education), age at menarche (9–12, 13, 14, 15–18 years), number of pregnancies lasting at least six months (never, 1, 2, 3, $\geq$4), and menopausal status (premenopausal if a woman reported still having a regular menstrual period, perimenopausal if she reported irregular periods, and postmenopausal if she reported that menstruation had stopped or being on menopausal hormone therapy).

Statistical Analyses

Conditional logistic regression models were fitted to estimate odds ratios (with 95% confidence intervals [CIs]) as a measure of association between each individual risk factor, the number of risky lifestyle behaviors, and breast cancer (overall and by subtypes), adjusted for confounders.

Trend tests on the original continuous or categorical variables, as well as on the number of risky lifestyle behaviors, were performed by fitting ordinal values corresponding to exposure categories and testing whether the slope coefficient differed from zero. All analyses were performed using STATA (Stata Statistical Software: Release 14, StataCorp., College Station, TX). We considered a two-sided P value of less than .05 statistically significant.

Sensitivity Analyses

Because of the low numbers in the reference category (0 risky lifestyle behaviors), we did a sensitivity analysis where we defined the reference category as 0–1 risky lifestyle behaviors. Many of the other studies on breast cancer subtypes have combined the luminal A–like and luminal B–like HER2-negative subtype into one luminal A–like subtype. Therefore, we also performed a sensitivity analysis where we combined these two subtypes.

Given that some risk factors, such as overweight/obesity, have different associations with premenopausal vs postmenopausal breast cancer, we ran a sensitivity analysis excluding premenopausal women.

Interaction Analyses

To test whether the five lifestyle factors interacted with each other, we ran statistical analyses to test the interaction between the binary risky lifestyle factors and breast cancer overall. The $P_{interaction}$ (P_{int}) value was calculated by modeling interaction terms (cross-products) between the different binary lifestyle behaviors and breast cancer overall.

Results

BMI ($P_{trend} < .0001$), intake of alcohol ($P_{trend} = .003$), smoking status ($P_{trend} = .007$), and menopausal hormone therapy use ($P_{trend} < .0001$) were associated with an increased risk, and physical activity ($P_{trend} = .02$) was associated with a decreased risk for breast cancer overall (Table 1). Women with a BMI greater than 28 kg/m^2 had a 23% increased risk of breast cancer compared with women with low BMI ($\leq$22 kg/m^2), women who drank five or more glasses of alcohol beverages a week had a 20% increased breast cancer risk compared with never drinkers, current smokers had a 13% elevated breast cancer risk compared with never smokers, current users of estrogen and progesterone therapy had a more than twofold increased breast cancer risk compared with never users, and women who were physically active for four or more hours a week had an 11% decreased breast cancer risk compared with women who exercised zero hours to one hour per week (Table 1).

Each binary risk factor was associated with a 10%–38% increase in risk of luminal A–like breast cancer and a nonstatistical 18%–25% increase in risk of breast cancer of luminal B–like HER2-positive subtype, except for physical inactivity (Table 2). We found no associations between the binary risk factors and the other breast cancer subtypes.

When we combined the number of risky lifestyle behaviors, women with five risky lifestyle behaviors had an 85% increased risk (95% CI = 1.42 to 2.42) of breast cancer overall compared

Table 1. The association between alcohol, smoking, physical activity, hormone therapy use, body mass index and breast cancer overall

Breast cancer overall	Case subjects	Control subjects	OR* (95% CI)
BMI, kg/m^2†			
≤22	672	4162	1 (ref)
23–25	1318	7879	1.05 (0.95 to 1.16)
26–28	1175	6343	1.16 (1.04 to 1.29)
>28	1237	6376	1.23 (1.11 to 1.37)
P_{trend}			<.0001
Alcohol intake per week, glasses‡			
Never drinkers	725	4581	1 (ref)
1	935	5399	1.08 (0.97 to 1.20)
2	850	4853	1.08 (0.97 to 1.21)
3–4	1073	5887	1.11 (1.00 to 1.24)
5+	819	4040	1.20 (1.07 to 1.35)
P_{trend}			.003
Smoking§			
Never	1748	10 000	1 (ref)
Past	1579	8572	1.07 (0.99 to 1.15)
Current	1075	5726	1.13 (1.03 to 1.23)
P_{trend}			.007
Physical activity per week, h‖			
0–1	712	3758	1 (ref)
2–3	2055	11 000	0.97 (0.88 to 1.07)
4+	1635	9758	0.89 (0.81 to 0.98)
P_{trend}			.02
Menopausal hormone therapy use†			
Never	2062	13 000	1 (ref)
Past	1612	8315	1.19 (1.10 to 1.29)
Estrogen current	183	1120	1.08 (0.91 to 1.28)
Estrogen and progesterone current	224	661	2.23 (1.88 to 2.65)
P_{trend}			<.0001

*P_{trend} and OR mutually adjusted for BMI (≤22, 23–25, 26–28, >28 at screening), education (no education/primary school, high school, Bachelor's and Master's +), age at menarche (9–12, 13, 14, 15–18 years), number of pregnancies (never, 1, 2, 3, ≥4), and menopausal status (pre-, peri-, postmenopausal). BMI = body mass index; CI = confidence interval; OR = odds ratio.

†BMI and hormone therapy additionally adjusted for physical activity (never, 1 hour, 2–3 hours, 4–5 hours, 6+ hours), alcohol (never drinkers, 1 glass, 2 glasses, 3–4 glasses, 5+ glasses), and smoking (never, past, and current).

‡Alcohol additionally adjusted for physical activity (never, 1 hour, 2–3 hours, 4–5 hours, 6+ hours) and smoking (never, past, and current).

§Smoking additionally adjusted for alcohol (never drinkers, 1 glass, 2 glasses, 3–4 glasses, 5+ glasses) and physical activity (never, 1 hour, 2–3 hours, 4–5 hours, 6+ hours).

‖Physical activity additionally adjusted for alcohol (never drinkers, 1 glass, 2 glasses, 3–4 glasses, 5+ glasses) and smoking (never, past, and current).

with women with no risky lifestyle behaviors. However, this risk appeared to be limited to luminal breast cancers. The risk was strongest for luminal A–like breast cancer (OR = 2.20, 95% CI = 1.55 to 3.12), whereas women with five risky behaviors were at 66% increased risk (95% CI = 0.61 to 4.54) of luminal B–like HER2-positive breast cancer (Table 3).

In the sensitivity analysis where we defined the reference category as 0–1 risky lifestyle behaviors, the most important change was observed for HER2-positive breast cancer, where all the odds ratios were less than 1 (Supplementary Table 1, available online).

In the sensitivity analysis where we combined the luminal A–like and luminal B–like HER2-negative subtype into one luminal A–like subtype, the results remained largely the same as the results when we divided luminal A–like and luminal B–like HER2-negative breast cancers into two different subtypes (Supplementary Table 2, available online).

In the interaction analyses, the only statistically significant interaction was between BMI and smoking (P_{int} = .002) (Supplementary Table 3, available online).

The results for BMI excluding premenopausal women (OR = 1.28, 95% CI = 1.14 to 1.43) remained largely the same as for the analyses including premenopausal women (OR = 1.23, 95% CI = 1.11 to 1.37) when we compared the heaviest (BMI >28 kg/m^2) with the leanest women (BMI ≤22 kg/m^2) (Supplementary Appendix 2, available online), and therefore we report the results of the analyses including the premenopausal women.

Discussion

We found that the number of risky lifestyle behaviors was positively associated with an almost twofold increase in breast cancer risk overall. The risk was particularly strong for luminal A–like and luminal B–like HER2-positive breast cancers. In contrast, we found no statistical significant associations between the number of risky lifestyle behaviors and HER2-positive and triple-negative breast cancers. However, we observed increased risk estimates between five risky lifestyle factors and HER2-positive and triple-negative breast cancers, but these were not statistically significant. Our results suggest that by modifying risky lifestyle behavior, women could substantially reduce their breast cancer risk.

Our finding of an effect on breast cancer overall is consistent with the findings from several other studies (23–25,48). Several studies have examined the association between healthy lifestyle factors and breast cancer subtypes, including the EPIC study, a Spanish case–control subjects study, and the Vitamins and Lifestyle (VITAL) cohort study (23,26,27); these studies are less consistent with our findings on subtypes. The EPIC study included diet, physical activity, smoking, alcohol consumption, and anthropometry (23), the Spanish study looked at BMI, physical activity, diet, alcohol intake, and breastfeeding (26), and the VITAL study included BMI, physical activity, diet, and alcohol consumption (27). Our study differed from these previous studies in that it included use of menopausal hormone therapy, but it did not include dietary factors other than alcohol in its lifestyle index. In our study, we found that women with five risky lifestyle behaviors had more than a twofold increased risk of luminal A–like breast cancer and a 66% increased risk of luminal B–like HER2-positive breast cancer compared with women with no risky lifestyle behaviors. The EPIC study reported that the least healthy women had a 23% increased risk for both ER-positive and ER-negative subtypes compared with the more healthy women (23), the Spanish case–control subjects study reported that adherence to only three of the nine health recommendations from World Cancer Research Fund (WCRF)/ American Institute for Cancer Research (AICR) was associated with a more than twofold increased risk of luminal A–like and triple-negative breast cancer and a 64% increased risk of HER2-positive breast cancer compared with women who followed more than five of the recommendations (26), and the VITAL cohort study reported a 16% reduced risk of ER-negative breast cancer and a 10% reduced risk of ER-positive breast cancer for women

Table 2. Associations between alcohol, smoking, physical activity, menopausal hormone therapy use, body mass index and breast cancer subtypes, with odds ratios and 95% confidence intervals

	Luminal A–like		Luminal B–like HER2-negative		Luminal B–like HER2-positive		HER2-positive		Triple-negative	
	ER+PR+HER2-		ER+PR-HER2-		ER+PR+/PR-HER2+		ER-PR-HER2+		ER-PR-HER2-	
	No. ca/co	OR* (95% CI)	No. ca/co	OR (95% CI)	No. ca/co	OR (95% CI)	No. ca/co	OR (95% CI)	No. ca/co	OR (95% CI)
BMI, kg/m^2†										
<25	1217/6696	1 (ref)	368/1761	1 (ref)	149/864	1 (ref)	98/505	1 (ref)	158/865	1 (ref)
≥25	1544/7109	1.20 (1.11 to 1.31)	341/1784	0.92 (0.78 to 1.08)	218/971	1.25 (0.99 to 1.58)	106/515	1.06 (0.78 to 1.45)	203/940	1.21 (0.96 to 1.52)
Alcohol intake per week, glasses‡										
<3	1009/5441	1 (ref)	275/1378	1 (ref)	125/735	1 (ref)	78/413	1 (ref)	148/711	1 (ref)
≥3	1752/8364	1.13 (1.04 to 1.23)	434/2167	1.02 (0.86 to 1.21)	242/1100	1.25 (0.98 to 1.59)	126/607	1.07 (0.78 to 1.48)	213/1094	0.93 (0.74 to 1.17)
Smoking§										
Never	1555/8283	1 (ref)	417/2088	1 (ref)	204/1091	1 (ref)	130/584	1 (ref)	204/1111	1 (ref)
Ever	1206/5522	1.11 (1.02 to 1.21)	292/1457	0.97 (0.82 to 1.16)	163/744	1.18 (0.93 to 1.49)	74/436	0.74 (0.54 to 1.03)	157/694	1.25 (0.99 to 1.59)
Physical activity per week, h‖										
≥4	1081/5877	1 (ref)	273/1464	1 (ref)	154/792	1 (ref)	93/437	1 (ref)	147/735	1 (ref)
<4	1680/7928	1.14 (1.05 to 1.25)	436/2081	1.14 (0.96 to 1.36)	213/1043	0.97 (0.77 to 1.24)	111/583	0.91 (0.66 to 1.26)	214/1070	0.95 (0.74 to 1.21)
Menopausal hormone therapy use†										
Never	1257/7209	1 (ref)	337/1778	1 (ref)	177/969	1 (ref)	107/544	1 (ref)	184/913	1 (ref)
Ever	1307/5611	1.38 (1.26 to 1.51)	320/1516	1.09 (0.91 to 1.31)	169/717	1.24 (0.97 to 1.60)	76/391	0.93 (0.65 to 1.33)	147/772	0.92 (0.71 to 1.20)

*OR mutually adjusted for BMI (≤22, 23–25, 26–28, >28 at screening), education (no education/primary school, high school, Bachelor's and Master's +), age at menarche (9–12, 13, 14, 15–18 years), number of pregnancies (never, 1, 2, 3, ≥4), and menopausal status (pre-, peri-, postmenopausal). BMI = body mass index; ca/co = case/controls subjects; CI = confidence interval; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; OR = odds ratio; PR = progesterone receptor.

†BMI and hormone therapy additionally adjusted for physical activity (never, 1 hour, 2–3 hours, 4–5 hours, 6+ hours), alcohol (never drinkers, 1 glass, 2 glasses, 3–4 glasses, 5+ glasses), and smoking (never, past, and current).

‡Alcohol additionally adjusted for physical activity (never, 1 hour, 2–3 hours, 4–5 hours, 6+ hours) and smoking (never, past, and current).

§Smoking additionally adjusted for alcohol (never drinkers, 1 glass, 2 glasses, 3–4 glasses, 5+ glasses) and physical activity (never, 1 hour, 2–3 hours, 4–5 hours, 6+ hours).

‖Physical activity additionally adjusted for alcohol (never drinkers, 1 glass, 2 glasses, 3–4 glasses, 5+ glasses) and smoking (never, past, and current).

Table 3. The association between number of risky lifestyle behaviors and breast cancer overall and subtypes

			Luminal A–like		Luminal B–like HER2 negative		Luminal B–like HER2 positive		HER2-positive		Triple-negative	
			ER+PR+HER2-		ER+PR-HER2-		ER+PR+/PR-HER2+		ER-PR-HER2+		ER-PR-HER2-	
Breast cancer overall			No. ca/co	OR (95% CI)	No. ca/co	OR (95% CI)	No. ca/co	OR (95% CI)	No. ca/co	OR (95% CI)	No. ca/co	OR (95% CI)
	No. ca/co	OR* (95% CI)										
No. of risky lifestyle behaviors												
0	99/865	1 (ref)	56/496	1 (ref)	19/117	1 (ref)	6/58	1 (ref)	4/29	1 (ref)	14/67	1 (ref)
1	530/3401	1.34 (1.06 to 1.68)	307/1922	1.38 (1.02 to 1.88)	96/453	1.32 (0.77 to 2.26)	35/267	1.21 (0.48 to 3.04)	42/132	2.52 (0.81 to 7.78)	50/238	0.95 (0.49 to 1.84)
2	1076/6928	1.36 (1.09 to 1.70)	675/3842	1.57 (1.17 to 2.10)	184/994	1.17 (0.70 to 1.96)	90/518	1.58 (0.65 to 3.81)	47/290	1.23 (0.41 to 3.70)	80/517	0.72 (0.38 to 1.37)
3	1365/6990	1.67 (1.34 to 2.08)	847/3933	1.89 (1.41 to 2.53)	217/1030	1.32 (0.79 to 2.20)	135/506	2.29 (0.96 to 5.48)	56/307	1.35 (0.45 to 4.06)	110/483	1.05 (0.56 to 1.96)
4	824/3847	1.82 (1.45 to 2.28)	559/2144	2.29 (1.70 to 3.09)	116/570	1.24 (0.73 to 2.12)	65/260	2.11 (0.86 to 5.18)	28/154	1.26 (0.40 to 3.94)	56/317	0.79 (0.41 to 1.52)
5	187/877	1.85 (1.42 to 2.42)	120/483	2.20 (1.55 to 3.12)	25/130	1.18 (0.61 to 2.27)	15/77	1.66 (0.61 to 4.54)	6/23	1.82 (0.45 to 7.39)	21/63	1.53 (0.70 to 3.36)
OR per behavior		1.13 (1.10 to 1.17)		1.19 (1.14 to 1.24)		1.07 (0.93 to 1.10)		1.16 (1.03 to 1.30)		0.88 (0.75 to 1.04)		1.08 (0.96 to 1.22)
P_{trend}		<.0001		<.0001		.75		.004		.19		.42

*OR mutually adjusted for education (no education/primary school, high school, Bachelor's and Master's +), age at menarche (9–12, 13, 14, 15–18 years), number of pregnancies (never, 1, 2, 3, ≥4), and menopausal status (pre-, peri-, postmenopausal). BMI = body mass index; ca/co = case/control subjects; CI = confidence interval; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; OR = odds ratio; PR = progesterone receptor.

meeting the WCRF/AICR recommendations compared with those meeting no recommendations (27).

One explanation of the inconsistent finding between our study and the EPIC, Spanish, and VITAL studies on the association between combined lifestyle factors and ER-negative breast cancer could be that the latter studies included diet in their lifestyle index. The EPIC study looked at the ratio of polyunsaturated to saturated fat intake and intake of fatty fish, margarine, glycemic load, fruit, and vegetables (23). The Spanish study looked at the intake of high-density foods, plant foods, and animal foods (26), and the VITAL study included plant foods and red and processed meat in the index (27). Dietary factors have been found to be associated with ER-negative subtype and not so much with ER-positive breast cancer (49–52). However, a recent study from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial reported an association between an estrogen-related lifestyle score that included some aspects of diet, in addition to alcohol intake, BMI, and physical activity, and ER-positive breast cancer (48). The difference between this study and the EPIC, VITAL, and Spanish studies was that they identified a dietary pattern specifically associated with high unconjugated estradiol (E2) and a low ratio of 2- to 16-hydroxylated metabolites (2/16).

Another explanation of no findings in our study between lifestyle factors and HER2-positive and triple-negative breast cancers could be that we included menopausal hormone therapy in our health index, and previous studies have reported no association with this risk factor and HER2-positive and triple-negative breast cancer and a positive association between menopausal hormone therapy use and luminal-like breast cancers (30,33,40).

We did not observe an association between the risky lifestyle factors examined and luminal B–like HER2-negative breast cancer, whereas we found an association with luminal B–like HER2-positive cancer. This could possibly be due to low power. Alternatively, it is possible that these risk factors are associated with HER2+ tumors. HER2 is a transmembrane tyrosine kinase receptor protein involved in the signal transduction pathways that lead to cell growth and differentiation (53,54) and overexpression of HER2 may disrupt normal cell control subjects mechanisms, potentially leading to the formation of aggressive tumor cells (55). It is plausible that the number of risky lifestyle factors exerts an increased proliferative effect on breast cells if normal cell control subjects mechanisms have been disrupted or if overexpression of HER2 has increased the stem/progenitor cell population. Our results are consistent with a positive, though not statistically significant, association with the number of these risk factors and HER2-positive breast cancer.

The only statistically significant interaction we found in our study was between BMI and smoking. The association between smoking status (never vs ever) and breast cancer was modified by BMI. Consistent with our result, a prospective study from the Women's Health Initiative reported that the effect of smoking on the risk of breast cancer was statistically significantly modified by BMI among postmenopausal women (56). A statistically significant association between smoking and breast cancer risk was only found among nonobese women. One possible explanation of the lack of association between smoking and breast cancer risk among obese women could be through endogenous estrogen. Early reports have indicated that smoking lowers the level of estrogen (57), and thus one could hypothesize that the antiestrogenic effects of smoking may have counterbalanced the carcinogenic effects of tobacco smoking in the obese smokers compared with the obese nonsmokers (56). However, more

recent studies do not support a strong antiestrogenic effect of smoking (58,59). Another explanation could be that obese smokers may have a different genetic profile from that of the nonobese smokers; that is, smoking is associated with lower body weight (60,61). Women who became obese despite smoking may better metabolize tobacco-related toxins (including carcinogens) than leaner smoking women (62).

Strengths and Limitations

Strengths of this study include its population-based design, the large size, being one of the largest single studies on breast cancer subtypes conducted so far, and the availability of prospectively collected detailed information on many risk factors for breast cancer. Other strengths include complete follow-up and complete case subjects ascertainment as well as availability of data on ER, PR, and HER2 receptor status.

Another strength is that we did not combine luminal A–like subtype with luminal B–like HER2-negative as many other studies have done. Our results indicated that the number of risky lifestyle behaviors was associated with luminal A–like but not luminal B–like HER2-negative breast cancer, suggesting that these should be treated as two different subtypes.

A limitation of the current study was that we did not include information on food intake (ie, plant foods, red and processed meat). Further, women who attend screening might be more health conscious and have a healthier lifestyle than women who do not attend. This could have contributed to obliterating the protective effects of "healthy" habits. At the same time, women who attend screening are more likely to have their breast cancers detected. Thus, the picture becomes complicated with these potential biases, and it is not clear how this could explain the results of this paper. The associations of well-established risk factors with overall breast cancer risk were largely as expected. Furthermore, it is unlikely that any such bias would have differentially affected the subtype results. Although this study is one of the largest to date on breast cancer subtypes, there was limited power for the rare breast cancer subtypes. Another limitation of the study was that data on risk factors were self-reported.

In this large nested case–control subjects study, having just three of the risky lifestyle behaviors was positively associated with a markedly increased risk for breast cancer overall, which was limited to luminal A–like breast cancer and luminal B–like HER2-positive breast cancer. These findings suggest that the combination of risky lifestyle behaviors may play an important role in the etiology of some luminal-like breast cancer subtypes. However, for rarer subtypes, the study may have been underpowered.

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Participants were informed that submission of a completed questionnaire indicated that they gave their consent to participate in studies of breast cancer. The study was approved by the Regional Committee for Medical and Health Research Ethics in the South-East Health Region of Norway (2014/1167).

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