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Research Article

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Alcohol, Physical Activity, Smoking, and Breast Cancer Subtypes in a Large, Nested Case–Control Study from the Norwegian Breast Cancer Screening Program

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Abstract

Background: To what extent alcohol, smoking, and physical activity are associated with the various subtypes of breast cancer is not clear. We took advantage of a large population-based screening cohort to determine whether these risk factors also increase the risk of the poor prognosis subtypes.

Methods: We conducted a matched case–control study nested within the Norwegian Breast Cancer Screening Program during 2006–2014. A total of 4,402 breast cancer cases with risk factor and receptor data were identified. Five controls were matched to each case on year of birth and year of screening. Conditional logistic regression was used to estimate ORs of breast cancer subtypes adjusted for potential confounders.

Results: There were 2,761 luminal A–like, 709 luminal B–like HER2-negative, 367 luminal B–like HER2-positive, 204 HER2-positive, and 361 triple-negative cancers. Current alcohol consumption was associated with breast cancer risk overall [OR 1.26; 95% confidence interval (CI), 1.09–1.45] comparing 6+ glasses a week to never drinkers. However, this risk increase was found only for luminal A–like breast cancer. Smoking 20+ cigarettes a day was associated with an OR of 1.41 (95% CI, 1.06–1.89) overall, with significant trends for luminal A–like and luminal B–like HER2-negative cancer. Current physical activity (4+ hours/week compared with none) was associated with 15% decreased risk of luminal A–like cancer, but not clearly with other subtypes.

Conclusions: In this large study, alcohol, smoking, and physical activity were predominantly associated with luminal A–like breast cancer.

Impact: Alcohol, smoking, and physical activity were associated with luminal A–like breast cancer subtype. *Cancer Epidemiol Biomarkers Prev; 26(12); 1736–44. ©2017 AACR.*

Introduction

Breast cancer is the most common cancer and the leading cause of cancer-related death among women worldwide (1). It has been suggested that modifiable risk factors account for more than one-third of postmenopausal breast cancers in the United States (2).

We have previously reported that hormonal variables, such as parity and hormonal therapy, were associated only with luminal A–like breast cancer (3). Therefore, modifying these hormonal variables would not be expected to lead to reductions in risk of triple-negative or HER2-positive breast cancers. An important question is therefore whether there are other modifiable risk factors that are associated with triple-negative or HER2-positive cancers.

Alcohol consumption, physical activity, and smoking are modifiable risk factors that have been associated with breast cancer overall to some or larger degree (4–6). Several studies have investigated the association between alcohol (7–18), smoking (14, 19–25), physical activity (26–36), and subtypes of breast cancer. A large meta-analysis suggested stronger positive associations between alcohol and estrogen receptor (ER)-positive tumors and weaker positive associations between alcohol and ER-negative tumors (18). There is some evidence that smoking increases risk of hormone receptor–positive [ER-positive and progesterone receptor (PR)-positive tumors] or luminal subtypes (14, 20, 23, 25). However, studies may have been too small to identify associations with triple-negative ($ER^-PR^-HER2^-$) or HER2-positive cancers. Greater risk reduction has been reported for ER^-PR^- than for ER^+PR^+ breast cancer and physical activity and physical activity later compared with early in life (30). However, findings are not entirely consistent (32–34, 37), and it remains unclear whether physical activity protects against all breast cancer subtypes as defined by the expression of ER, PR, and HER2.

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A challenge in previous studies has been that the subtypes have not been consistently defined. Often all ER^-, $HER2^-$ tumors have been defined as "luminal A" tumors regardless of whether PR was positive or negative and luminal A–like subtype have included cases considered luminal B–like HER2 negative. However, clinical criteria have suggested that the ER^+, PR^-, $HER2^-$ tumors may represent a particular type of luminal B–like tumors (38). We wanted to use the definition suggested at the St. Gallen meeting in 2013 (38), and divide breast cancer subtypes into five different subtypes, luminal A–like ($ER^+PR^-HER2^-$), luminal B–like HER2-negative ($ER^+PR^-HER2^-$), luminal B–like HER2-positive (ER^+PR^+/PR^-HER2^+), HER2-positive ($ER^-PR^-HER2^+$), and triple-negative ($ER^-PR^-HER2^-$) cancer. Although this was a clinical subdivision, defined to better identify a subgroup of women that could benefit from chemotherapy, we hypothesized that perhaps this would also help better identify a group of luminal A–like cancers with similar etiology.

This is the first study to investigate the association between alcohol intake, smoking, and physical activity and subtypes of breast cancer in a large Norwegian study. We therefore took advantage of the nationwide Norwegian Breast Cancer Screening Program, and conducted a nested case–control study within this cohort.

Materials and Methods

Study population

The methods are described in detail previously (3). In brief, the Cancer Registry of Norway (CRN) is a population-based registry that has collected data on cancer in Norway since 1952. The registry is 98.8% complete (39). CRN is also responsible for the administration of the Norwegian Breast Cancer Screening Program (40). As a part of this screening program, invitations are sent to all women ages 50–69 years old to undergo a two-view mammography screening (standard cranio-caudal and mediolateral views) every two years. The average attendance rate in each round is about 75%. Women who attended the mammographic screening during 2006–2014 were asked to complete a questionnaire on a number of standard breast cancer risk factors before age 50 and another questionnaire on current exposure variables at subsequent screenings.

Because of the short follow-up (38% of the cases was detected in the first screening round), and because we were concerned, we needed to define equivalent time windows of exposure in controls as cases, we chose a case–control design. We conducted a case–control study nested within the study cohort. Information on cancer cases was obtained through linkage to the CRN records using a unique 11-digit personal identification number. Eligible women had no history of invasive cancer (except nonmelanoma skin cancer) or ductal carcinoma *in situ* of the breast prior to January 1, 2006. Participants who fulfilled these criteria and had completed the questionnaires were eligible for inclusion in the current study cohort ($N = 344{,}348$).

Cases were defined as 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), regardless of screening history. Each breast cancer case was individually matched to five controls on year of birth (±3 years) and year of last screening before breast cancer diagnosis (±3 years). Controls had to be cancer free, alive, and resident in the country at the time of the case's diagnosis.

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

Tumor receptor status ascertainment

Information on ER, PR, and HER2 status was assessed by IHC and extracted from pathology reports submitted to the CRN. Tumors were classified as being ER^+ if $\geq$ 10% reactivity from 2006 to January 2012, and if $\geq$1% reactivity from February 2012 onwards. The latter threshold was introduced as a result of change in treatment protocols of patients in the clinics in Norway. We used these official thresholds. PR^+ tumors were defined as those with a reactivity of $\geq$ 10% throughout the study period. HER2 expression status was determined at each laboratory with IHC. Cases with no (0) or weak (1+) immunostaining were classified as $HER2^-$, whereas cases with strong immunostaining (3+) were defined as $HER2^+$. *In situ* hybridization was used to confirm the HER2 status if IHC yielded moderate staining (2+) results. If IHC was 2+ and FISH, chromogenic (CISH), or silver *in situ* (SISH) were 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 $HER2^-$.

Classification of breast cancer subtypes

Breast cancer cases were categorized according to subtype using a modified version of the classification of clinically defined subtypes proposed at the St. Gallen meeting in 2013 (38). Of the 4,952 breast cancer cases with no missing information on confounders, 550 cases had unknown hormone receptor (i.e., ER and/or PR) and HER2 status or could not be classified into subtypes. Of the remaining 4,402 breast cancer cases, 2,761 were classified as luminal A-like ($ER^+PR^+HER2^-$), 709 as luminal B-like HER2 negative ($ER^+PR^-HER2^-$), 367 as luminal B-like HER2 positive (ER^+PR^-/PR^+HER2^+), 204 as HER2 positive ($ER^-PR^-HER2^+$), and 361 as triple negative ($ER^-PR^-HER2^-$). As we did not have Ki-67 results, we conducted a sensitivity analysis whereby grade was added to the luminal subtype definitions in an attempt to better separate out these subtypes (38). In this analysis, luminal A–like subtype was defined as $ER^+PR^+HER2^-$, low or medium grade, luminal B–like HER2-negative as $ER^+PR^-HER2^-$, high grade, and luminal B–like HER2-positive as ER^+PR^+/PR^-HER2^+, any grade. This sensitivity analysis showed that the results remained largely the same and thus only the results without information on grade are presented here. Furthermore, we ran a sensitivity analysis including luminal B–like HER2-negative in the luminal A–like subtype, and another sensitivity analysis to determine whether the cases with no subtype information differed from those with luminal A–like subtype.

The observed subtype distribution in our study—luminal A–like (63%), luminal B–like HER2 negative (16%), luminal B–like HER2 positive (9%), HER2 positive (5%), and triple negative (8%)—was similar to that found in white U.S. women (41).

Risk factors

Data on the exposures of interest were extracted from the questionnaires completed at the last screening prior to breast cancer diagnosis for the cases, and the corresponding round for controls. If a woman's questionnaire, or data on relevant

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variables, were missing, information from the questionnaire completed in the previous screening round was used. Approximately 16.5% of the questionnaires were replaced by a questionnaire from the previous round. The primary exposures of interest were alcohol consumption, physical activity, and smoking habits. Participants were asked to recall these exposures at different time periods (before 50 years and currently). 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 L of beer, and 12 grams per glass of wine. To make the number easier to relate to, 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 g). The tables therefore contain glasses per week estimated as total grams of alcohol per week divided by 12 g of alcohol per glass.

Smoking status was categorized into never, past, and current smoking. Pack-years of smoking was calculated as the average number of cigarettes smoked per day/20 (i.e., 20 cigarettes in one pack) and multiplied by the number of years the subject smoked. 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 only present results for the combined low- and high-activity variable.

Weight and height were self-reported and are not as reliable as measured weight and height. Body mass index (BMI) was defined as weight (kg)/height (m^2). Menopausal status was defined as premenopausal if a woman reported to still have a regular menstrual period, perimenopausal if she reported irregular periods, and postmenopausal if she reported menstruation had stopped or being on menopausal hormone therapy.

Selection of confounders

We considered the following variables as potential confounders: body mass index (BMI; $\leq$22, 23–25, 26–28, >28 kg/m^2), education (no formal education/primary school, high school, bachelor/master), age at menarche (9–12, 13, 14, 15–18 years), number of pregnancies lasting at least 6 months (never, 1, 2, 3, $\geq$4), menopausal status (pre-, peri-, postmenopausal), and, where appropriate, alcohol intake (never drinkers, 1, 2, 3–4, and 5+ glasses per week), high intensity physical activity (no high intensity, 1, 2–3, 4+ hours per week), and smoking habits (never, past, and current).

Missing values and selection of matched controls

If a variable was missing on all the questionnaires a woman had completed, we excluded her from all analyses. Of the 6,471 breast cancer cases, we excluded the following due to missing information: BMI ($n = 532$), education ($n = 135$), age at menarche ($n = 229$), number of pregnancies ($n = 164$), menopausal status ($n = 59$), smoking ($n = 62$), alcohol ($n = 154$), and physical activity ($n = 184$). This left us with 4,952 breast cancer cases for analysis. Of the 339,714 remaining women in the cohort, before we selected controls, we excluded women with missing information on: BMI ($n = 67,813$), education ($n = 8,362$), age at menarche ($n = 14,818$), number of pregnancies ($n = 8,771$), menopausal status ($n = 6,632$), smoking ($n = 6,381$), alcohol ($n = 12,878$), and physical activity ($n = 16,205$). This left us with 197,854 women in the cohort. Of these, we matched five controls per case on year of birth and year of screening, which left us with 24,760 controls for analysis.

Statistical analyses

Conditional logistic regression models were fitted, to estimate ORs (with 95% confidence intervals; CI) as a measure of association between the exposures of interest and breast cancer (overall and by subtypes), adjusted for confounders.

We matched on date of birth and date of screening with $\pm$3 years. Because of concern there could still be residual confounding by age, we conducted a sensitivity analysis where we controlled more tightly for age at screening using a continuous variable, but the results remained largely the same, and we therefore decided that the matching variable with the matched analyses were sufficient.

Trend tests were performed by fitting ordinal values corresponding to exposure categories and testing whether the slope coefficient differed from zero. Case–case analyses were conducted to test for heterogeneity between breast cancer subtypes taking the luminal-A–like subtype as the reference. We used likelihood ratio tests comparing the likelihood ratio of the case–case model with confounders only to that of the same model also including the exposure variable.

We also assessed potential effect modification by BMI (<25, $\geq$25 kg/m^2), parity (nulliparous, parous), smoking status (never, past, and current smokers), and estrogen and progesterone therapy (never hormone therapy users, current estrogen, and progesterone therapy users).

All analyses were performed using STATA (Stata Statistical Software: Release 14, StataCorp.). We considered a two-sided P value less than 0.05 as being statistically significant.

Results

Both current and past alcohol consumption were positively associated with overall breast cancer risk ($P_{trend} < 0.03$ for all), with women who reported drinking 6+ glasses/week currently and at ages 40–49 and 30–39 years having, respectively, a 1.26 (95% CI, 1.09–1.45; Table 1), 1.34 (1.12–1.60), and 1.31 (1.06–1.62; Supplementary Table S1) increased risk relative to never drinkers (Table 1). Type of alcohol (beer, liquor, wine) was not independently associated with breast cancer overall (Table 1). Smoking status was positively associated with breast cancer overall ($P_{trend} = 0.006$), with current smokers having a 13% increased risk (OR = 1.13; 95% CI, 1.03–1.23) relative to never smokers (Table 1). The risk of developing a breast cancer increased progressively with increasing number of cigarettes smoked at the time of questionnaire completion ($P_{trend} = 0.01$; Table 1) and at ages 40–49 years and 30–39 years ($P_{trend} < 0.0001$) with women who smoked 20+ cigarettes per day having a 31%–41% increased risk relative to never-smokers (Supplementary Table S1). Positive trends in the odds of breast cancer with smoking intensity were also present when analyses were restricted to never drinkers (OR = 1.28; 95% CI, 0.87–1.90; current vs. never smokers). Current physical activity (low and high intensity combined) was negatively associated with overall breast cancer ($P_{trend} = 0.01$), with women who reported 6+ hours of physical activity per week having a 16% lower risk of developing breast cancer (OR = 0.84;

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Table 1. Adjusted ORs and 95% CI for alcohol, smoking, physical activity, height, and BMI associated with breast cancer overall

	Breast cancer overall		
	Cases	**Controls**	**OR[a] (95% CI)**
Alcohol intake per week, current[a]			
Never drinkers	725	4,581	1 (Ref)
1 glass	935	5,399	1.07 (0.96–1.19)
2 glasses	850	4,853	1.07 (0.96–1.20)
3–4 glasses	1,073	5,887	1.11 (1.00–1.24)
5–6 glasses	448	2,305	1.16 (1.02–1.33)
6+ glasses	371	1,735	1.26 (1.09–1.45)
P_{trend}[b]			**0.001**
Beer intake per week[c]			
Never drinkers	725	4,581	1 (Ref)
1 glass	921	5,123	1.11 (0.84–1.47)
2 glasses	387	2,168	1.08 (0.78–1.50)
3–4 glasses	178	833	1.09 (0.77–1.53)
5+ glasses	47	230	1.17 (0.80–1.73)
P_{trend}			0.14
Liquor intake per week[c]			
Never drinkers	725	4,581	1 (Ref)
1 glass	934	5,278	1.15 (0.87–1.51)
2 glasses	234	1,447	1.33 (0.95–1.87)
3–4 glasses	96	505	1.48 (0.95–2.29)
5+ glasses	34	126	0.84 (0.38–1.86)
P_{trend}			0.41
Wine intake per week[c]			
Never drinkers	725	4,581	1 (Ref)
1 glass	1,342	7,581	1.00 (0.76–1.32)
2 glasses	794	4,519	0.97 (0.66–1.44)
3–4 glasses	820	4,483	0.76 (0.44–1.30)
5+ glasses	480	2,351	0.95 (0.39–2.35)
P_{trend}			0.63
Smoking[d]			
Never	1,748	10,000	1 (Ref)
Past	1,579	8,572	1.06 (0.98–1.15)
Current	1,075	5,726	1.13 (1.03–1.23)
P_{trend}			**0.006**
Number of cigarettes per day, current[d]			
Never smokers	1,748	10,000	1 (Ref)
1–4	262	1,407	1.11 (0.95–1.29)
5–9	373	2,200	1.09 (0.95–1.24)
10–19	390	1,934	1.22 (1.06–1.39)
20+	73	285	1.41 (1.06–1.89)
P_{trend}			**0.001**
Pack-years of smoking[d]			
<2.5	1,461	9,061	1 (Ref)
2.5–4.9	151	757	1.24 (1.01–1.52)
5.0–9.9	252	1,359	1.14 (0.97–1.35)
10.0–14.9	258	1,294	1.23 (1.04–1.44)
15–19.9	162	943	0.99 (0.82–1.21)
≥20	325	1,540	1.26 (1.08–1.46)
P_{trend}			**0.004**
Low- and high-intensity physical activity per week, current[e]			
Never	166	817	1 (Ref)
1 hour	540	2,896	0.91 (0.75–1.10)
2–3 hours	2,055	11,000	0.90 (0.75–1.07)
4–5 hours	974	5,896	0.81 (0.67–0.97)
6+ hours	661	3,862	0.84 (0.70–1.02)
P_{trend}			**0.01**
Height/cm[f]			
<159 cm	393	2,677	1 (Ref)
160–164 cm	1,166	6,969	1.11 (0.98–1.25)
165–169 cm	1,412	8,139	1.13 (1.00–1.28)
170–174 cm	1,025	5,238	1.23 (1.08–1.41)
175–179	340	1,480	1.40 (1.19–1.66)
>180 cm	66	257	1.55 (1.15–2.09)
P_{trend}			**<0.0001**
BMI (kg/m^2)			
<20	164	1,100	1 (Ref)
20–21	199	1,237	1.06 (0.85–1.33)
22–23	692	4,174	1.10 (0.92–1.32)
24–25	935	5,530	1.13 (0.95–1.35)
26–27	837	4,527	1.24 (1.03–1.48)
28–29	591	3,197	1.22 (1.01–1.48)
>29	984	4,995	1.32 (1.10–1.58)
P_{trend}			**<0.0001**

(Continued on the following column)

Table 1. Adjusted ORs and 95% CI for alcohol, smoking, physical activity, height, and BMI associated with breast cancer overall (Cont'd)

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

[a]P_{trend} and OR mutual adjusted BMI (≤22, 23–25, 26–28, >28 at screening), education (no education/primary school, high school, bachelor, and master), age at menarche (9–12, 13, 14, 15–18), number of pregnancies (never, 1, 2, 3, ≥4), and menopausal status (pre-, peri-, postmenopausal).

[c]Type of alcohol mutual adjusted for each other.

[d]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).

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

[f]Height additionally adjusted for weight.

95% CI, 0.70–1.02) than those who reported never exercising (Table 1). Height and BMI were both positively associated with overall breast cancer risk ($P_{trend} < 0.0001$ for both; Table 1).

Analyses by breast cancer subtypes showed that current (Table 2) and past alcohol intake (Supplementary Table S2) were both positively associated with luminal A–like breast cancer risk ($P_{trend} < 0.05$ for all), with women who reported drinking 3+ glasses/week having an approximately 15% increased risk relative to those who reported drinking only 0–1 glasses/week. Alcohol intake (current; Table 2) and (at 30–39 years; Supplementary Table S2) was not associated with risk of luminal B–like HER2-negative disease ($P_{heterogeneity} = 0.02$). In contrast, current alcohol intake ($P_{trend} = 0.01$) and, to a lesser extent, intake at ages 30–39 ($P_{trend} = 0.04$) were inversely associated with risk of HER2-positive subtype albeit with no clear evidence of heterogeneity of effects with the luminal A–like subtype (Table 2). Alcohol intake was not associated with risk of triple-negative disease.

Relative to never smoking, current smoking was positively associated with luminal A–like breast cancer (OR = 1.18; 95% CI, 1.05–1.32). Women who reported smoking 10+ cigarettes/day, currently (Table 2) or in their 30s or 40s (Supplementary Table S2), were at a 19%–27% increased risk of luminal A–like subtype compared with never smokers. Risk of luminal B–like HER2-negative subtype was also positively associated with intensity of smoking (Table 2). Smoking was not associated with risk of any other breast cancer subtype.

Only current physical activity (low- and high-intensity combined) was inversely associated with risk of luminal A–like breast cancer ($P_{trend} = 0.01$), with women who reported currently exercising 4+ hours/week having a 15% lower risk (OR = 0.85; 95% CI, 0.75–0.97) than those who reported 0–1 hour/week (Table 2). Current physical activity was not associated with a

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Table 2. Adjusted ORs and 95% CI for alcohol, smoking, and physical activity associated with breast cancer subtypes

	Luminal A–like $ER^+PR^+HER2^-$		Luminal B–like HER2 negative $ER^+PR^-HER2^-$		Luminal B–like HER2 positive ER^+PR^+/PR^-HER2^+		HER2 positive $ER^-PR^-HER2^+$		Triple negative $ER^-PR^-HER2^-$	
	ca/co	OR[a] (95% CI)	ca/co	OR (95% CI)	ca/co	OR (95% CI)	ca/co	OR (95% CI)	ca/co	OR (95% CI)
Alcohol intake per week, current[b]										
0–1 glass	1025/5543	1 (Ref)	262/1411	1 (Ref)	138/750	1 (Ref)	93/388	1 (Ref)	142/736	1 (Ref)
2 glasses	530/2740	1.03 (0.92–1.16)	155/677	1.24 (0.99–1.56)	66/341	1.06 (0.76–1.48)	37/196	0.81 (0.52–1.25)	62/375	0.87 (0.62–1.21)
3+ glasses	1206/5522	1.14 (1.04–1.26)	292/1457	1.05 (0.87–1.28)	163/744	1.23 (0.94–1.62)	74/436	0.68 (0.47–0.97)	157/694	1.20 (0.93–1.57)
P_{trend}[a]		**0.01**		0.46		0.14		**0.03**		0.24
$P_{heterogeneity}$[c]				**0.02**		0.22		0.14		0.23
Smoking[d]										
Never	1,081/5,877	1 (Ref)	273/1,464	1 (Ref)	154/792	1 (Ref)	93/437	1 (Ref)	147/735	1 (Ref)
Past	1,014/4,794	1.12 (1.01–1.23)	248/1,254	1.06 (0.87–1.29)	119/635	0.88 (0.67–1.15)	67/331	1.01 (0.70–1.47)	131/615	1.01 (0.77–1.33)
Current	666/3,134	1.18 (1.05–1.32)	188/827	1.22 (0.98–1.52)	94/408	1.15 (0.85–1.56)	44/252	0.86 (0.56–1.30)	83/455	0.88 (0.64–1.20)
P_{trend}		**0.003**		0.08		0.50		0.51		0.46
$P_{heterogeneity}$				0.05		0.13		0.31		0.95
Number of cigarettes per day, current[d]										
Never	1,081/5,877	1 (Ref)	273/1,464	1.00 (Ref)	154/792	1 (Ref)	93/437	1 (Ref)	147/735	1 (Ref)
1–4	170/774	1.18 (0.97–1.43)	41/217	1.03 (0.70–1.52)	26/95	1.36 (0.81–2.27)	10/57	0.93 (0.39–2.19)	15/116	0.63 (0.34–1.15)
5–9	225/1,204	1.09 (0.91–1.29)	68/331	1.27 (0.91–1.77)	31/161	1.00 (0.62–1.62)	16/98	0.96 (0.49–1.88)	33/159	0.93 (0.58–1.49)
10+	281/1,220	1.27 (1.07–1.50)	83/314	1.38 (1.00–1.89)	37/165	1.00 (0.63–1.58)	20/96	0.94 (0.50–1.77)	42/185	1.14 (0.74–1.76)
P_{trend}		**0.01**		**0.03**		0.95		0.83		0.69
$P_{heterogeneity}$				0.34		0.48		0.22		0.91
Pack-years of smoking[d]										
<2.5	905/5,087	1 (Ref)	226/1,271	1.00 (Ref)	124	1 (Ref)	80/366	1 (Ref)	126/653	1 (Ref)
2.5–4.9	91/426	1.17 (0.90–1.52)	27/104	1.75 (1.04–2.94)	11	1.28 (0.60–2.75)	10/34	1.80 (0.73–4.42)	12/49	1.20 (0.56–2.56)
5.0–9.9	169/759	1.26 (1.03–1.55)	31/189	0.90 (0.56–1.44)	12	0.63 (0.32–1.27)	10/53	1.05 (0.47–2.35)	30/92	1.51 (0.88–2.60)
10.0–14.9	156/711	1.22 (0.99–1.51)	42/180	1.28 (0.84–1.96)	29	1.60 (0.93–2.77)	13/50	1.18 (0.54–2.59)	18/96	0.94 (0.51–1.73)
15–19.9	108/527	1.04 (0.82–1.33)	27/137	1.19 (0.71–2.01)	12	0.76 (0.36–1.58)	7/36	1.15 (0.43–3.06)	8/75	0.44 (0.19–1.02)
≥20	202/857	1.27 (1.04–1.54)	57/205	1.62 (1.09–2.40)	22	0.93 (0.52–1.69)	15/58	1.09 (0.53–2.26)	29/137	1.19 (0.71–2.02)
P_{trend}		**0.01**		**0.03**		0.96		0.76		0.93
$P_{heterogeneity}$				0.79		0.73		0.24		0.44
Low- and high-intensity physical activity per week, current[e]										
0–1 hours	450/2,040	1 (Ref)	110/524	1 (Ref)	59/314	1 (Ref)	37/143	1 (Ref)	50/274	1 (Ref)
2–3 hours	1,298/6,297	0.94 (0.84–1.06)	322/1,635	0.93 (0.73–1.18)	183/783	1.35 (0.97–1.89)	89/463	0.68 (0.43–1.05)	163/818	1.08 (0.77–1.53)
4+ hours	1,009/5,441	0.85 (0.75–0.97)	275/1,378	0.92 (0.72–1.18)	125/735	1.02 (0.72–1.45)	78/413	0.67 (0.42–1.06)	148/711	1.14 (0.80–1.64)
P_{trend}		**0.01**		0.54		0.98		0.10		0.46
$P_{heterogeneity}$				0.08		0.55		0.58		0.60

Abbreviations: ca, case; co, controls.

[a]P_{trend} and OR mutual adjusted BMI (≤22, 23–25, 26–28, >28 at screening), education (no education/primary school, high school, bachelor, and master), age at menarche (9–12, 13, 14, 15–18), number of pregnancies (never, 1, 2, 3, ≥4), and menopausal status (pre-, peri-, postmenopausal).

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

[c]$P_{heterogeneity}$ across subtypes was determined in a case–case model. See Materials and Methods for details.

[d]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).

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

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decreased risk of luminal B–like HER2-negative breast cancer ($P_{heterogeneity} = 0.08$) or any of the other breast cancer subtypes.

We conducted a sensitivity analysis to determine whether the cases with no subtype information differed from those with subtype luminal A-like. We found no case–case differences for alcohol, smoking, and physical activity between luminal A–like cases and cases with no subtype information (not significant $P_{heterogeneity}$; Supplementary Table S3).

The results of a sensitivity analysis including luminal B–like HER2-negative in the luminal A-like subtype remained largely the same as the results when these subtypes were divided (Supplementary Table S4).

Discussion

In this large nested case–control study, we found that alcohol was associated with an increased risk of luminal A–like breast cancer, smoking was associated with an increased risk of luminal A–like and luminal B–like HER2-negative breast cancer, and physical activity associated with a decreased risk of luminal A–like breast cancer. These modifiable risk factors were not associated with the other subtypes.

In our study, we defined luminal A–like slightly differentially than a number of other studies. Often other studies have included our luminal B–like HER2-negative subtype into the luminal A–like subtype. However, our results suggested that alcohol and physical activity were differently associated with luminal A–like and luminal B–like HER2-negative subtypes, suggesting that these subtypes have different etiology and should not be included into one luminal A–like subtype.

Alcohol

Several studies have investigated the association between alcohol and subtypes of breast cancer (7, 9, 13–16, 42). One study had information on ER only (15), two studies on ER and PR (9, 13), and four studies on ER, PR, and HER2 (7, 14, 16, 42). The pooled analysis from the Nurses' Health Study (NHS) reported that alcohol consumption was associated with an increased risk of both ER^+ and ER^- breast cancer (15). Although this was a well powered study (more than 20,000 ER^+ cases), no results were reported for more detailed subtypes. Other studies with both ER and PR information and moderate sizes (2,500–2,800 cases) have found that alcohol was positively associated with hormone receptor–positive breast cancer, and not with and ER^-PR^- tumors (9, 13, 14).

These inconsistencies are also found in studies with HER2 information. The NHS (2,760 cases) found that alcohol was associated with an increased risk for luminal A and HER2-positive breast cancers (16). On the other hand, a Spanish case–control study with 1,766 cases reported a positive association between alcohol and all breast cancer subtypes, except HER2-positive subtype (7). Furthermore, the large European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (11,576 cases) reported a positive association between alcohol consumption and ER^+PR^+, ER^-PR^-, $HER2^-$ and $ER^-PR^-HER2^-$ breast cancers (42), but again, no association between alcohol and HER2-positive breast cancer. Overall, there is consistency in the results that alcohol is associated with luminal A–like breast cancer. This is also consistent with our finding. We found no significant positive association with HER2-positive or triple-negative breast cancer, similarly to some, but not all of the previous studies. The differences in sample size do not seem to explain the alcohol discrepancies.

When we considered type of alcohol separately and adjusted for the other types of alcohol, intake of beer, liquor, and wine were not associated with any of the subtypes. These results are not consistent with the findings in the Women's Health Initiative study, which reported that wine and liquor were positively associated with ER^+ breast cancer (14), possibly because they did not adjust for other types of alcohol.

Biological mechanisms of alcohol on breast cancer. It has been suggested that the biological mechanisms of alcohol on breast cancer can be both hormonal and nonhormonal. The nonhormonal explanation is that alcohol is metabolized to acetaldehyde that can induce DNA damage (43). Acetaldehyde may also be broken down to reactive oxygen species (ROS), which could cause breast malignancies via DNA mutation, base deletion, and single and double strand breaks (43). The hormonal explanation is that alcohol intake is associated with increased levels of estrogen among both pre- and postmenopausal women (44–48), and alcohol has also shown to influence the estrogen receptor (30, 34, 49) and may affect the breast tissue's sensitivity to estrogen and enhance growth in ER-positive tumors (32). Our findings alone would be compatible with the hormonal explanation, but not with the finding in the EPIC study where alcohol was associated also with ER^-PR^- tumors.

Smoking

Several studies with information on ER, PR, and HER2, have looked at the association between smoking and subtypes of breast cancer (14, 19, 20, 22, 24). One of these studies was a small study (224 cases; ref. 19), another included 900 cases (20) and three studies contained from 1,800 to 2,500 cases (14, 22, 24). Despite the differences in sample size, all these studies reported that smoking was associated with an increased risk of ER^+ and luminal-like breast cancers, and no association with triple-negative and basal-like breast cancers. This is consistent with our finding of a positive association between smoking and luminal A–like and luminal B–like breast cancer and no association with triple-negative tumors. The fact that we separated the luminal B–like HER2-negative from luminal A–like subtype, could be one explanation of our finding of a positive association between smoking with both luminal A–like and luminal B–like HER2-negative breast cancer.

Biological mechanisms of smoking on breast cancer. The presence of chemicals generated by smoking has been detected in mammary gland tissue of both healthy women and breast cancer patients (50–52). *In vitro* studies suggest that nicotine (31), benzo(a) pyrene (53), 1-methylanthracene (54), and penanthrene (55) may provoke alterations in epigenetic and transcriptional mechanisms which regulates the expression of genes that are involved in transformation of healthy epithelial cells, proliferation, and metastasis of tumor epithelial cells into the mammary gland (26). There are carcinogens in tobacco smoke such as polycyclic aromatic hydrocarbons (PAH), aromatic amines, and nitrosoamines (20), and these carcinogens can have both estrogenic (56) and antiestrogenic effects (57, 58). The estrogenic effect of these carcinogens can explain the current study finding of a positive association between smoking and luminal A–like and luminal B–like HER2 negative breast cancer.

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Physical activity

The association between physical activity and breast cancer subtypes have been investigated in several studies (26–32, 35–37). Some of these studies had information on ER only, ER and PR (27, 30–32, 37), and others had information on ER, PR, and HER2 (26, 28, 29, 35, 36). Of all these studies, two of them had fewer than 700 cases (29, 35) and six studies included from 1,921 to 5,882 cases (26–28, 31, 32, 36). The majority of these studies found that physical activity was associated with a decreased risk of ER^+, ER^+PR^+ and luminal A–like subtype, and found no association with ER^-, ER^-PR^- and triple-negative breast cancers. Consistent with these findings, our study found that physical activity was associated with a decreased risk of luminal A–like breast cancer, and no association with the other subtypes. However, a review of 47 studies reported a greater risk reduction of physical activity on ER^-PR^- tumors than on ER^+PR^+ tumors (30), but the review did not say whether the results for ER^-PR^- tumors were statistically significant. In addition, this latter review only included studies with information on ER and PR. The California Teachers Study found that long-term and baseline strenuous physical activities were associated with a reduction only in triple-negative breast cancer, but the association did not reach statistical significance (28).

Biological mechanisms of physical activity on breast cancer. Physical activity improves insulin sensitivity (59) and decreases estradiol bioavailability by increasing sex hormone–binding globulin (SHBG) levels (60). Furthermore, nonhormonal mechanisms involved in physical activity are decreased inflammation (59), interference with the glycolytic switch (61), decreased DNA damage, or immunomodulation (59). We did not find a statistically significant interaction between estrogen and progesterone therapy and physical activity, but we observed a protective effect of physical activity only in never users, suggesting that biological mechanisms of physical activity on breast cancer works through hormones. The hormonal explanation is also consistent with our finding, and that of others, that physical activity appears to protect predominantly against luminal A–like cancer.

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.

Another strength is that we did not combine luminal A–like subtype with the luminal B–like HER2 negative as many other studies have done. Our results suggested that alcohol and physical activity were associated differently with these two subtypes, suggesting that these should be treated as two different subtypes.

Although this study is one of the largest to date on breast cancer subtypes, there was still limited power for the rare breast cancer subtypes. Another weakness was the lack of molecular expression data. This may have obscured differences between the subtypes.

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 obliterate protective effects of physical activity and the increased risk of alcohol and smoking. At the same time, women who attend screening are more likely to have their breast cancers detected. The associations of alcohol, smoking, and physical activity with overall breast cancer risk were largely as expected. Furthermore, it is unlikely that any such bias would have differentially affected the subtype results.

Conclusion

In this large nested case–control study, alcohol and smoking were associated with an increased risk and physical activity with a decreased risk of breast cancer overall and with luminal A–like breast cancer. In contrast, none of these risk factors were associated with HER2-positive or triple-negative breast cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: M. Ellingjord-Dale, S. Hofvind, I. dos-Santos-Silva, G. Ursin

Development of methodology: L. Vos, I. dos-Santos-Silva, G. Ursin

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Ellingjord-Dale

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Ellingjord-Dale, L. Vos, H.G. Russnes, S. Tretli, S. Hofvind, I. dos-Santos-Silva, G. Ursin

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References

1. M. Ervik FL, Ferlay J, Mery L, Soerjomataram I, Bray F. Lyon, France: International Agency for Research on Cancer; 2016.
2. Tamimi RM, Spiegelman D, Smith-Warner SA, Wang M, Pazaris M, Willett WC, et al. Population attributable risk of modifiable and nonmodifiable breast cancer risk factors in postmenopausal breast cancer. Am J Epidemiol 2016;184:884–93.
3. Ellingjord-Dale M, Vos L, Tretli S, Hofvind S, Dos-Santos-Silva I, Ursin G. Parity, hormones and breast cancer subtypes - results from a large nested case-control study in a national screening program. Breast Cancer Res 2017;19:10.
4. Rice MS, Eliassen AH, Hankinson SE, Lenart EB, Willett WC, Tamimi RM. Breast cancer research in the Nurses' Health Studies: exposures across the life course. Am J Public Health 2016;106:1592–8.
5. Macacu A, Autier P, Boniol M, Boyle P. Active and passive smoking and risk of breast cancer: a meta-analysis. Breast Cancer Res Treat 2015;154:213–24.
6. Kerr J, Anderson C, Lippman SM. Physical activity, sedentary behaviour, diet, and cancer: an update and emerging new evidence. Lancet Oncol 2017;18:e457–e71.
7. Gago-Dominguez M, Castelao JE, Gude F, Fernandez MP, Aguado-Barrera ME, Ponte SM, et al. Alcohol and breast cancer tumor subtypes in a Spanish Cohort. SpringerPlus 2016;5:39.
8. Strumylaite L, Sharp SJ, Kregzdyte R, Poskiene L, Bogusevicius A, Pranys D. The association of low-to-moderate alcohol consumption with breast cancer subtypes defined by hormone receptor status. PLoS One 2015; 10:e0144680.

9. Fagherazzi G, Vilier A, Boutron-Ruault MC, Mesrine S, Clavel-Chapelon F. Alcohol consumption and breast cancer risk subtypes in the E3N-EPIC cohort. Eur J Cancer Prev 2015;24:209–14.
10. Millikan RC, Newman B, Tse CK, Moorman PG, Conway K, Dressler LG, et al. Epidemiology of basal-like breast cancer. Breast Cancer Res Treat 2008;109:123–39.
11. Tamimi RM, Colditz GA, Hazra A, Baer HJ, Hankinson SE, Rosner B, et al. Traditional breast cancer risk factors in relation to molecular subtypes of breast cancer. Breast Cancer Res Treat 2012;131:159–67.
12. Rauh C, Gass P, Heusinger K, Haeberle L, Jud SM, Hein A, et al. Association of molecular subtypes with breast cancer risk factors: a case-only analysis. Eur J Cancer Prev 2015;24:484–90.
13. Falk RT, Maas P, Schairer C, Chatterjee N, Mabie JE, Cunningham C, et al. Alcohol and risk of breast cancer in postmenopausal women: an analysis of etiological heterogeneity by multiple tumor characteristics. Am J Epidemiol 2014;180:705–17.
14. Kabat GC, Kim M, Phipps AI, Li CI, Messina CR, Wactawski-Wende J, et al. Smoking and alcohol consumption in relation to risk of triple-negative breast cancer in a cohort of postmenopausal women. Cancer Causes Control 2011;22:775–83.
15. Jung S, Wang M, Anderson K, Baglietto L, Bergkvist L, Bernstein L, et al. Alcohol consumption and breast cancer risk by estrogen receptor status: in a pooled analysis of 20 studies. Int J Epidemiol 2016;45:916–28.
16. Hirko KA, Chen WY, Willett WC, Rosner BA, Hankinson SE, Beck AH, et al. Alcohol consumption and risk of breast cancer by molecular subtype: Prospective analysis of the Nurses' Health Study after 26 years of follow-up. Int J Cancer 2016;138:1094–101.
17. Tjonneland A, Christensen J, Thomsen BL, Olsen A, Stripp C, Overvad K, et al. Lifetime alcohol consumption and postmenopausal breast cancer rate in Denmark: a prospective cohort study. J Nutr 2004;134:173–8.
18. Suzuki R, Orsini N, Mignone L, Saji S, Wolk A. Alcohol intake and risk of breast cancer defined by estrogen and progesterone receptor status–a meta-analysis of epidemiological studies. Int J Cancer 2008;122:1832–41.
19. Atkinson RL, El-Zein R, Valero V, Lucci A, Bevers TB, Fouad T, et al. Epidemiological risk factors associated with inflammatory breast cancer subtypes. Cancer Causes Control 2016;27:359–66.
20. Kawai M, Malone KE, Tang MT, Li CI. Active smoking and the risk of estrogen receptor-positive and triple-negative breast cancer among women ages 20 to 44 years. Cancer 2014;120:1026–34.
21. Nishino Y, Minami Y, Kawai M, Fukamachi K, Sato I, Ohuchi N, et al. Cigarette smoking and breast cancer risk in relation to joint estrogen and progesterone receptor status: a case-control study in Japan. SpringerPlus 2014;3:65.
22. Butler EN, Tse CK, Bell ME, Conway K, Olshan AF, Troester MA. Active smoking and risk of Luminal and Basal-like breast cancer subtypes in the Carolina Breast Cancer Study. Cancer Causes Control 2016;27:775–86.
23. Morabia A, Bernstein M, Ruiz J, Heritier S, Diebold Berger S, Borisch B. Relation of smoking to breast cancer by estrogen receptor status. Int J Cancer 1998;75:339–42.
24. Turkoz FP, Solak M, Petekkaya I, Keskin O, Kertmen N, Sarici F, et al. Association between common risk factors and molecular subtypes in breast cancer patients. Breast 2013;22:344–50.
25. Dossus L, Boutron-Ruault MC, Kaaks R, Gram IT, Vilier A, Fervers B, et al. Active and passive cigarette smoking and breast cancer risk: results from the EPIC cohort. Int J Cancer 2014;134:1871–88.
26. Ma H, Xu X, Ursin G, Simon MS, Marchbanks PA, Malone KE, et al. Reduced risk of breast cancer associated with recreational physical activity varies by HER2 status. Cancer Med 2015;4:1122–35.
27. Gong Z, Hong CC, Bandera EV, Adams-Campbell LL, Troester MA, Park SY, et al. Vigorous physical activity and risk of breast cancer in the African American breast cancer epidemiology and risk consortium. Breast Cancer Res Treat 2016;159:347–56.
28. Ma H, Xu X, Clague J, Lu Y, Togawa K, Wang SS, et al. Recreational physical activity and risk of triple negative breast cancer in the California Teachers Study. Breast Cancer Res 2016;18:62.
29. Lope V, Martin M, Castello A, Casla S, Ruiz A, Baena-Canada JM, et al. Physical activity and breast cancer risk by pathological subtype. Gynecol Oncol 2017;144:577–85.
30. Friedenreich CM, Cust AE. Physical activity and breast cancer risk: impact of timing, type and dose of activity and population subgroup effects. Br J Sports Med 2008;42:636–47.
31. Bernstein L, Patel AV, Ursin G, Sullivan-Halley J, Press MF, Deapen D, et al. Lifetime recreational exercise activity and breast cancer risk among black women and white women. J Natl Cancer Inst 2005;97:1671–9.
32. Schmidt ME, Steindorf K, Mutschelknauss E, Slanger T, Kropp S, Obi N, et al. Physical activity and postmenopausal breast cancer: effect modification by breast cancer subtypes and effective periods in life. Cancer Epidemiol Biomarkers Prev 2008;17:3402–10.
33. Dallal CM, Sullivan-Halley J, Ross RK, Wang Y, Deapen D, Horn-Ross PL, et al. Long-term recreational physical activity and risk of invasive and in situ breast cancer: the California teachers study. Arch Intern Med 2007;167:408–15.
34. Bardia A, Hartmann LC, Vachon CM, Vierkant RA, Wang AH, Olson JE, et al. Recreational physical activity and risk of postmenopausal breast cancer based on hormone receptor status. Arch Intern Med 2006;166:2478–83.
35. Trivers KF, Lund MJ, Porter PL, Liff JM, Flagg EW, Coates RJ, et al. The epidemiology of triple-negative breast cancer, including race. Cancer Causes Control 2009;20:1071–82.
36. Phipps AI, Chlebowski RT, Prentice R, McTiernan A, Stefanick ML, Wactawski-Wende J, et al. Body size, physical activity, and risk of triple-negative and estrogen receptor-positive breast cancer. Cancer Epidemiol Biomarkers Prev 2011;20:454–63.
37. Fournier A, Dos Santos G, Guillas G, Bertsch J, Duclos M, Boutron-Ruault MC, et al. Recent recreational physical activity and breast cancer risk in postmenopausal women in the E3N cohort. Cancer Epidemiol Biomarkers Prev 2014;23:1893–902.
38. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thurlimann B, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol 2013;24:2206–23.
39. Larsen IK, Smastuen M, Johannesen TB, Langmark F, Parkin DM, Bray F, et al. Data quality at the Cancer Registry of Norway: An overview of comparability, completeness, validity and timeliness. Eur J Cancer 2009;45:1218–31.
40. Hofvind S, Geller B, Vacek PM, Thoresen S, Skaane P. Using the European guidelines to evaluate the Norwegian Breast Cancer Screening Program. Eur J Epidemiol 2007;22:447–55.
41. DeSantis CE, Fedewa SA, Sauer AG, Kramer JL, Smith RA, Jemal A. Breast cancer statistics, 2015: convergence of incidence rates between black and white women. CA Cancer J Clin 2016;66:31–42.
42. Romieu I, Scoccianti C, Chajes V, de Batlle J, Biessy C, Dossus L, et al. Alcohol intake and breast cancer in the European prospective investigation into cancer and nutrition. Int J Cancer 2015;137:1921–30.
43. Beral V, Hamajima N, Hirose K, Rohan T, Calle EE, Heath CW, et al. Alcohol, tobacco and breast cancer - collaborative reanalysis of individual data from 53 epidemiological studies, including 58515 women with breast cancer and 95067 women without the disease. Br J Cancer 2002;87:1234–45.
44. Bloom HJ, Richardson WW. Histological grading and prognosis in breast cancer; a study of 1409 cases of which 359 have been followed for 15 years. Br J Cancer 1957;11:359–77.
45. International Agency for Research on Cancer. GLOBOCAN 2012: Estimated cancer incidence, mortality anf prevalence wordlwide in 2012; 2012. Available from: http://globocan.iarc.fr/Default.aspx
46. Russnes HG, Navin N, Hicks J, Borresen-Dale AL. Insight into the heterogeneity of breast cancer through next-generation sequencing. J Clin Invest 2011;121:3810–8.
47. Longnecker MP. Alcoholic beverage consumption in relation to risk of breast cancer: meta-analysis and review. Cancer Causes Control 1994;5:73–82.
48. Key J, Hodgson S, Omar RZ, Jensen TK, Thompson SG, Boobis AR, et al. Meta-analysis of studies of alcohol and breast cancer with consideration of the methodological issues. Cancer Causes Control 2006;17:759–70.
49. Beral V, Banks E, Reeves G. Evidence from randomised trials on the long-term effects of hormone replacement therapy. Lancet 2002;360:942–4.
50. Enger SM, Ross RK, Paganini-Hill A, Carpenter CL, Bernstein L. Body size, physical activity, and breast cancer hormone receptor status: results from

Published OnlineFirst September 6, 2017; DOI: 10.1158/1055-9965.EPI-17-0611

two case-control studies. Cancer Epidemiol Biomarkers Prev 2000;9: 681–7.
51. Lee IM, Rexrode KM, Cook NR, Hennekens CH, Burin JE. Physical activity and breast cancer risk: the Women's Health Study (United States). Cancer Causes Control 2001;12:137–45.
52. Britton JA, Gammon MD, Schoenberg JB, Stanford JL, Coates RJ, Swanson CA, et al. Risk of breast cancer classified by joint estrogen receptor and progesterone receptor status among women 20–44 years of age. Am J Epidemiol 2002;156:507–16.
53. Adams SA, Matthews CE, Hebert JR, Moore CG, Cunningham JE, Shu XO, et al. Association of physical activity with hormone receptor status: the Shanghai Breast Cancer Study. Cancer Epidemiol Biomarkers Prev 2006;15:1170–8.
54. Slattery ML, Edwards S, Murtaugh MA, Sweeney C, Herrick J, Byers T, et al. Physical activity and breast cancer risk among women in the southwestern United States. Ann Epidemiol 2007;17:342–53.
55. Leitzmann MF, Moore SC, Peters TM, Lacey JV Jr, Schatzkin A, Schairer C, et al. Prospective study of physical activity and risk of postmenopausal breast cancer. Breast Cancer Res 2008;10:R92.
56. Meek MD, Finch GL. Diluted mainstream cigarette smoke condensates activate estrogen receptor and aryl hydrocarbon receptor-mediated gene transcription. Environ Res 1999;80:9–17.
57. Tanko LB, Christiansen C. An update on the antiestrogenic effect of smoking: a literature review with implications for researchers and practitioners. Menopause 2004;11:104–9.
58. Baron JA. Smoking and estrogen-related disease. Am J Epidemiol 1984; 119:9–22.
59. Peplonska B, Lissowska J, Hartman TJ, Szeszenia-Dabrowska N, Blair A, Zatonski W, et al. Adulthood lifetime physical activity and breast cancer. Epidemiology 2008;19:226–36.
60. Peters TM, Moore SC, Gierach GL, Wareham NJ, Ekelund U, Hollenbeck AR, et al. Intensity and timing of physical activity in relation to postmenopausal breast cancer risk: the prospective NIH-AARP diet and health study. BMC Cancer 2009;9:349.
61. Dey S, Boffetta P, Mathews A, Brennan P, Soliman A, Mathew A. Risk factors according to estrogen receptor status of breast cancer patients in Trivandrum, South India. Int J Cancer 2009;125:1663–70.

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