IJC
International Journal of Cancer

The impact of alcohol consumption and physical activity on breast cancer: The role of breast cancer risk

Linda Rainey [1], Mikael Eriksson [2], Thang Trinh [2], Kamila Czene [2], Mireille J.M. Broeders [1,3], Daniëlle van der Waal [1] and Per Hall [2,4]

[1]Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands
[2]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[3]Dutch Expert Centre for Screening, Nijmegen, The Netherlands
[4]Department of Oncology, Södersjukhuset, Stockholm, Sweden

High alcohol consumption and physical inactivity are known breast cancer risk factors. However, whether the association between these lifestyle factors and breast cancer is modified by a woman's additional breast cancer risk factors has never been studied. Therefore, a population-based prospective cohort study of 57,654 Swedish women aged 40–74 years, including 957 breast cancer cases, was performed. Alcohol consumption and physical activity were measured with validated web-based self-report questionnaires. The Tyrer–Cuzick risk prediction model was used to determine a woman's 10-year risk of developing breast cancer. Logistic regression models were used to explore whether the effect of alcohol consumption and physical activity on breast cancer was modified by additional breast cancer risk factors. Findings showed that increased alcohol consumption was associated with a higher breast cancer risk (OR = 1.26, 95% CI 1.01, 1.59). However, the association between lifestyle factors (alcohol consumption and physical activity) and breast cancer was generally the same for women at below average, average and above average risk of developing breast cancer. Therefore, additional breast cancer risk factors do not appear to modify the association between lifestyle (alcohol consumption and physical activity) and breast cancer. Considering the general health benefits, preventative lifestyle recommendations can be formulated about alcohol consumption and physical activity for women at all levels of breast cancer risk.

Cancer Epidemiology

Introduction

Breast cancer is the most commonly diagnosed cancer among women worldwide.[1] Lifestyle factors, such as physical inactivity and alcohol consumption, have consistently been shown to increase breast cancer risk.[2–5] The population attributable risks of physical inactivity and high alcohol intake in the US are 3.3 and 5.9%, respectively for postmenopausal invasive breast cancer, and 2.9 and 7.0% for postmenopausal ER+ breast cancer.[6] Therefore, there is benefit in targeting lifestyle prevention strategies to reduce breast cancer incidence. However, it is currently unclear which women would benefit most from a lifestyle intervention to prevent breast cancer, since the aetiological pathways through which physical activity and alcohol consumption influence risk are not well understood.[5,7]

Previous studies showed that breast cancer risk, assessed with the Tyrer–Cuzick (TC) risk prediction model, influences the association between lifestyle factors and mammographic breast density,[8,9] which is a potential intermediate marker of breast cancer risk.[10] The association between alcohol intake and mammographic density was stronger for women at above average risk, than women with a low or average risk of developing breast cancer.[8] The association between physical activity and mammographic density also varied according to risk, with the association being weaker for women at above average risk than for women at below average

Additional Supporting Information may be found in the online version of this article.

Key words: alcohol consumption, physical activity, breast cancer, Tyrer–Cuzick model, breast cancer risk

Abbreviations: BMI: body mass index; CC: craniocaudal; ER: oestrogen receptor status; INCA: Information Network for Cancer Care; KARMA: KARolinska MAmmography project for risk reduction of breast cancer; MET: metabolic equivalent of task; MHT: menopausal hormone therapy; MLO: mediolateral oblique; TC: Tyrer–Cuzick

DOI: 10.1002/ijc.32846
History: Received 10 Jan 2019; Accepted 10 Dec 2019; Online 21 Dec 2019

Correspondence to: Linda Rainey, E-mail: linda.rainey@radboudumc.nl

What's new?
Alcohol consumption and physical inactivity are known breast cancer risk factors but it is currently unclear whether all women would benefit equally from drinking less alcohol and being more physically active. The authors found no difference in association between these lifestyle factors and breast cancer in women with below average, average or above average risk of developing breast cancer. They conclude that general preventative lifestyle recommendations about alcohol intake and physical activity apply to all women regardless of their breast cancer risk.

risk.[9] Since breast density is a strong predictor of breast cancer,[11] breast cancer risk may also modify the association between lifestyle and breast cancer.

Breast cancer risk reflects several factors which affect endogenous hormone levels, for example, parity and menopausal status. Several suggested pathways through which lifestyle influences breast cancer development are hormone-dependent.[5,7] Alcohol consumption has a stronger positive association with oestrogen receptor-positive (ER+) breast cancers than ER− breast cancers.[5] It has additionally been suggested that physical activity may lead to a greater risk reduction in postmenopausal women, women who are normal weight, have no family history of breast cancer, and are parous.[7] Since these are all known breast cancer risk factors, several of which affect oestrogen levels, the association between lifestyle and breast cancer could be modified by additional breast cancer risk factors.

Breast cancer risk is likely to play an increasingly larger part in the early detection and prevention of breast cancer. Increased knowledge of breast cancer risk factors may permit a shift from age-based screening to risk-stratified screening. Classifying women based on breast cancer risk categories will enable, for example, targeted screening intervals and modalities.[12] Moreover, by utilising the existing screening infrastructure, a large number of women can be informed of ways to reduce their breast cancer risk with preventative measures.[13]

Understanding which women would benefit most from a lifestyle intervention to decrease their breast cancer risk could enable more (cost) effective prevention. Women who would benefit most could be offered an organised lifestyle programme, whereas general information might suffice for women who are expected to benefit less. Additionally, tailored lifestyle recommendations may ultimately facilitate uptake and decrease overall breast cancer incidence. Therefore, the aim of the present study is to evaluate the effect of alcohol consumption and physical activity on breast cancer for women with different levels of breast cancer risk assessed with the TC risk prediction model.

Materials and Methods

Study population

Women who attended mammographic screening at four hospitals in Sweden between January 2011 and March 2013 were asked to participate in the 'KARolinska MAmmography project for risk reduction of breast cancer' (KARMA).[14] This is a large prospective cohort study which collects information on breast cancer risk factors to ultimately develop a risk prediction model of breast cancer. Each participant completed a comprehensive web-based survey, donated blood, and allowed for their full-field digital mammograms to be stored.

Women were included if they were aged 40–74 years (n = 68,733). Exclusion criteria were a previous cancer diagnosis other than nonmelanoma skin cancer (n = 10,690) and being a 'lifestyle outlier', that is, having a reported alcohol intake of >40 bottles of beer per week (n = 7) or >40 g of alcohol per day (n = 398). The final selection included 57,654 women of whom 957 were breast cancer cases.

The ethics review board at Karolinska Institutet approved the study. All participants provided written informed consent prior to the start of the study.

Breast cancer diagnosis

Breast cancer diagnosis was obtained through linkage with the Swedish Information Network for Cancer Care (INCA), a web-based breast cancer registry founded in 2007 and managed by the six regional Swedish cancer centres. INCA holds information on breast cancer diagnosis and treatment. Data were linked up to January 1, 2017, resulting in a maximum follow-up time of 6 years. We acquired information on the type of breast cancer (invasive or ductal carcinoma *in situ*), hormone receptor status (ER+ or ER−) and date of diagnosis. Participants' breast cancers diagnosed after the start of the KARMA study were included in the analyses, that is, all breast cancer cases had a negative mammogram at baseline.

Lifestyle measures

Alcohol consumption was measured at baseline with a web-based self-report questionnaire based on the validated MiniMeal-Q.[15] Women reported the frequency and amount of alcoholic beverages consumed at least once per month in the months prior to study entry. The volume consumed per day was calculated using the reported frequency and amount of each beverage. Daily alcohol consumption in grams per day (g/day) was obtained by multiplying daily volume with the corresponding ethanol concentration of the beverage. Ethanol concentration figures were based on a report from the Swedish National Food Agency.[16] Total alcohol consumption was calculated for each participant by summing the alcohol consumption of all beverages. Women who reported drinking less than once a month or not at all were defined as nondrinkers.

Physical activity was measured at baseline with a web-based version of the validated self-report questionnaire Active-Q.[17] Women reported type, frequency and duration of physical activities performed in the year prior to study entry across four domains: daily occupation, transportation to and from occupation, leisure time activity and sports and sleep duration. For each activity, the average daily duration was calculated in hours (hr/day) using the duration and frequency. Next, each activity was multiplied with the corresponding 'metabolic equivalent of task' (MET) value to obtain MET-hr/day for a 24-hr period.[18] A more detailed description of the coding process is described by Trinh *et al.*[8] We assessed total physical activity; daily duration of moderately intense activity, including occupational activity (MET = 3.0–6.0); vigorously intense activity (MET > 6.0); and recreational activity defined as the daily duration of activity performed at a moderate to vigorous intensity during leisure time and sports.

Breast cancer risk assessment

The TC model (Version 7) was used to calculate a woman's individual risk of developing breast cancer in the next 10 years.[19] The model contains the following self-reported risk factors: family history of breast cancer, age at menarche, parity, age at first childbirth, age at menopause, atypical hyperplasia, lobular carcinoma *in situ*, height and BMI.

TC scores were stratified into three risk categories conform established cut-off points.[20] Since the established high-risk cut-off point of 8% resulted in only 2.7% of the study sample having a high-risk score, we set the cut-off to 5%, that is, below average risk (10-year risk <3%), average risk (10-year risk <5%, ≥3%) and above average risk (10-year risk ≥5%).

Mammographic breast density

All screening examinations were performed at baseline with full-field digital mammography systems. Mammographic density was determined with the area-based STRATUS method, using processed mammograms from the mediolateral oblique (MLO) and craniocaudal (CC) views of both breasts.[21] Percentage mammographic density was calculated by dividing the dense area by the total breast area.

Statistical analyses

We used multiple imputation to impute missing data on education level (7.0%), BMI (7.0%), European ancestry (7.2%), menopausal hormone therapy (MHT) use (8.6%), contraception use (8.9%), age at first menarche (9.5%), parity (7.9%), family history of breast cancer (9.5%), smoking status (8.3%), alcohol intake (8.7%) and physical activity (10.0%). Missing data were due to women omitting to supply an answer to these questions in the survey. All variables with missing data were added to the multiple imputation model in addition to age, menopausal status and breast cancer diagnosis which were used as indicators. A total of 10 imputed datasets were created using univariate regression without rounding. In addition, a complete-case analysis was performed using the complete data of 47,527 women, of whom 809 are breast cancer cases (Supporting Information S1). The risk estimates obtained with the complete-case analysis were similar in size and direction to those reported using the imputed dataset.

We performed logistic regression modelling. With only 31 recorded deaths during our follow-up time (0.05%), Cox regression modelling would not have led to significant changes in our effect estimates. Odds ratios and 95%-confidence intervals from logistic regression were used to study the association between lifestyle (alcohol consumption and physical activity) and breast cancer diagnosis (invasive and *in situ*). Both models were adjusted for age, BMI (<25.0, 25.0–29.9, ≥30.0 kg/m^2), ethnicity (European ancestry yes/no), oral contraceptive use (ever, never), use of MHT (ever, never), family history of breast cancer in mother or sister(s) (yes, no), age at menarche (<13, 13, 14, ≥15 years), parity and age at first birth (nulliparous; one or two births, age at first birth <26 years; one or two births, age at first birth ≥26 years; ≥3 births, age at first birth <26 years; ≥3 births, age at first birth ≥26 years), education level (secondary school, gymnasium, university or higher, other), smoking status (never, past, current) and menopausal status (post or premenopausal). Women were classified as premenopausal if they reported having had a menstruation in the 12 months before study participation. Women who reported an absence of menstruation or having undergone an oophorectomy in the previous 12 months were considered postmenopausal. Women with missing data on menopausal status or who reported absence of menstruation due to gynaecological surgery other than oophorectomy were classified according to their age at study enrolment: ≤55 years was considered premenopausal and > 55 years postmenopausal.

Variation between the two logistic regression models is described below. The model exploring the impact of *alcohol consumption* on breast cancer diagnosis was additionally adjusted for physical activity (<40.0, 40.0–44.9 and ≥45.0 MET-hr/day). Alcohol consumption was studied both continuously and categorically. The following categories were defined: 0 (nondrinkers), 0.1–9.9, and 10.0–40.0 g/day.[22] Additional analyses were performed exploring the association between alcohol consumption and breast cancer hormone receptor status. Women with an ER+ cancer were compared to women who did not develop breast cancer; and women with an ER− cancer were compared to women who did not develop cancer.

The model evaluating the impact of *physical activity* on breast cancer diagnosis was additionally adjusted for alcohol consumption (none, 0.1–9.9, and 10.0–40.0 g/day). Physical activity was studied as a continuous and categorical exposure variable, distinguishing between total activity, moderate activity, vigorous activity and moderate to vigorous recreational activity. Total activity was categorised as <40.0, 40.0–44.9 and ≥45 MET-hr/day; moderate activity as <2.0, 2.0–4.9 and ≥5.0 hr/day; vigorous activity as <0.2, and ≥0.2 hr/day; and moderate to vigorous recreational activity as <1.5, 1.5–2.5, and ≥2.5 hr/day. The cut-off point for the lowest category of vigorous activity was chosen because it corresponds to the minimally recommended amount of physical activity for cancer prevention.[23]

We chose to assign higher cut-off values for total, moderate–vigorous, and recreational activity, because most women met the cancer prevention guidelines.

Mammographic density was added continuously to all models after initial corrections for confounding variables to study its effect as a potential intermediate, that is, the association between lifestyle and breast cancer not through mammographic density. All analyses were performed with SPSS 23.0.

Data availability

The data that support the findings of our study are available from the corresponding author upon reasonable request.

Results

Participant characteristics

Table 1 provides an overview of participant characteristics. Mean age at mammography screening was 54.0 years (SD 9.7) and mean BMI was 25.2 kg/m^2 (SD 4.2). Approximately 12.9% of women reported a family history of breast cancer and 85.3% reported previous or current contraceptive use. Around 56% of women were postmenopausal, of which 5.1% was taking MHT. Most women consumed up to one glass of alcohol per day (61.9%) and were minimally (36.2%) to moderately (35.6%) physically active.

In line with expectations of known breast cancer risk factors, women with ≥5.0% TC 10-year risk of developing breast cancer were, on average, older, more likely to be nulliparous

Table 1. Characteristics of the total study population and by Tyrer–Cuzick 10-year breast cancer risk

		TC 10-year breast cancer risk		
Characteristics	**All women**	**‹3.0%**	**3.0–4.9%**	**≥5.0%**
Participants (*n*)	57,654[1]	27,901	18,054	7,233
Breast cancer cases (*n*)	957	352	321	226
Age (years), mean (SD)	54.0 (9.7)	51.3 (9.9)	57.1 (8.6)	58.2 (7.8)
BMI, mean (SD)	25.2 (4.2)	24.9 (4.3)	25.5 (4.2)	25.7 (4.2)
Age at menarche (years), mean (SD)	13.1 (1.5)	13.2 (1.5)	13.0 (1.4)	12.9 (1.4)
Nulliparous (%)	12.6	9.6	15.7	16.4
Parous women only				
Age at first birth (years), mean (SD)	27.2 (5.3)	26.3 (5.2)	28.2 (5.1)	28.5 (5.3)
Number of childbirths, mean (SD)	2.2 (0.8)	2.3 (0.8)	2.1 (0.8)	2.1 (0.8)
Family history of breast cancer (% yes)	12.9	0.6	10.0	64.7
Education level (%)				
Secondary school	12.5	12.4	12.7	12.1
Gymnasium	30.9	34.2	28.0	25.8
University or higher	53.0	50.2	55.4	58.3
Other	3.6	3.2	3.9	3.8
Oral contraceptive use, ever (%)	85.3	86.6	83.9	83.7
Premenopausal (%)	44.1	57.9	29.2	24.4
Postmenopausal women only				
Age at menopause (years), mean (SD)	50.0 (5.1)	47.7 (5.7)	51.1 (4.3)	51.7 (4.3)
MHT use (% ever)	42.1	39.8	43.3	43.3
Smoking status (%)				
Never	48.6	50.5	47.0	45.2
Past	39.8	37.1	42.5	43.8
Current	11.6	12.5	10.5	10.9
Alcohol consumption (g/day, %)				
None	19.2	20.8	17.3	17.3
0.1–9.9	61.9	62.1	61.9	61.0
≥10.0	19.0	17.1	20.8	21.7
Total physical activity (MET-hr/day, %)				
‹40.0	36.2	34.6	37.7	38.4
40.0–44.9	35.6	34.5	36.9	36.8
≥45.0	28.2	30.9	25.4	24.8

[1]For 4,466 participants, of which 58 are cases, a TC risk score could not be computed.

or older at first birth, postmenopausal, on MHT, to have a family history of breast cancer, to consume more than one glass of alcohol per day and to be less physically active than women with <3.0% TC 10-year risk.

The mean total level of physical activity was 42.0 (SD 6.0) MET-hr/day, with a reported average of 3.4, 0.2, and 2.3 hr/day spent on moderate, vigorous, and recreational activity, respectively. The mean total amount of alcohol consumption was 7.3 (SD 8.2) g/day (data not shown).

Alcohol consumption and breast cancer

Table 2 shows the relationship between alcohol consumption and breast cancer. Increased alcohol consumption was associated with higher risk of breast cancer. Women who consumed

Table 2. Effect of alcohol consumption and physical activity on breast cancer for all women

Lifestyle factor				Breast cancer		Breast cancer	
Alcohol (g/day)	n total	%	*n* all cases	Crude OR [95% CI]		Adj.[3] OR [95% CI]	
0	11,101	19.3	159	Reference		Reference	
0.1–9.9	34,930	60.6	579	1.16	[0.97, 1.40]	1.17	[0.96, 1.41]
10.0–40.0	11,623	20.2	220	1.33	[1.06, 1.67]	1.26	[1.01, 1.59]
Per 10 g/day	57,654	100	957	1.13	[1.04, 1.23]	1.09	[1.00, 1.18]
Alcohol (g/day)	*n* total	%	*n* ER+ cases[1]	Crude OR [95% CI]		Adj.[3] OR [95% CI]	
0	11,082	19.3	117	Reference		Reference	
0.1–9.9	34,870	60.6	442	1.21	[0.97, 1.51]	1.25	[1.00, 1.56]
10.0–40.0	11,601	20.1	165	1.36	[1.04, 1.78]	1.34	[1.03, 1.74]
Per 10 g/day	57,553	100	724	1.16	[1.05, 1.27]	1.13	[1.03, 1.23]
Alcohol (g/day)	*n* total	%	*n* ER– cases[2]	Crude OR [95% CI]		Adj.[3] OR [95% CI]	
0	10,984	19.3	19	Reference		Reference	
0.1–9.9	34,488	60.6	60	1.04	[0.61, 1.76]	0.94	[0.54, 1.65]
10.0–40.0	11,458	20.1	22	1.13	[0.60, 2.15]	0.93	[0.46, 1.85]
Per 10 g/day	56,930	100	101	1.00	[0.77, 1.29]	0.94	[0.71, 1.25]
Physical activity	*n* total	%	*n* all cases	Crude OR [95% CI]		Adj.[3] OR [95% CI]	
Total activity (MET-hr/day)							
<40.0	20,762	36.0	329	Reference		Reference	
40.0–44.9	20,280	35.2	364	1.13	[0.97, 1.32]	1.17	[0.99, 1.37]
≥45.0	16,612	28.8	265	1.01	[0.85, 1.19]	1.21	[1.01, 1.45]
Per 5 MET-hr/day increase	57,654	100	957	0.98	[0.93, 1.03]	1.03	[0.98, 1.09]
Moderate activity (hr/day)							
<2.0	21,848	37.9	357	Reference		Reference	
2.0–4.9	18,562	32.2	333	1.10	[0.94, 1.29]	1.08	[0.92, 1.27]
≥5.0	17,244	29.9	267	0.95	[0.80, 1.12]	1.13	[0.95, 1.34]
Per 1 hr/day increase	57,654	100	957	0.99	[0.97, 1.01]	1.02	[0.99, 1.04]
Vigorous activity (hr/day)							
<0.2	38,090	66.1	628	Reference		Reference	
≥0.2	19,564	33.9	329	1.02	[0.89, 1.18]	1.07	[0.93, 1.24]
Per 1 hr/day increase	57,654	100	957	1.05	[0.86, 1.27]	1.08	[0.89, 1.31]
Recreational activity (hr/day)							
<1.5	21,224	36.8	334	Reference		Reference	
1.5–2.5	16,337	28.3	273	1.06	[0.89, 1.26]	1.07	[0.90, 1.27]
≥2.5	20,093	34.9	350	1.11	[0.94, 1.30]	1.11	[0.94, 1.31]
Per 1 hr/day increase	57,654	100	957	1.01	[0.97, 1.04]	1.01	[0.97, 1.05]

[1]Breast cancer patients with ER– status were excluded from the analysis (*n* = 101).
[2]Breast cancer patients with ER+ status were excluded from the analysis (*n* = 724).
[3]Adjusted for age, BMI (<25.0, 25.0–29.9, ≥30.0 kg/m^2), ethnicity (European ancestry yes/no), oral contraceptive use (ever, never), use of menopausal hormone therapy (never, ever), family history of breast cancer in mother or sister(s) (yes, no), age at menarche (<13, 13, 14, ≥15 years), parity and age at first birth (nulliparous; one or two births, age at first birth <26 years; one or two births, age at first birth ≥26 years; ≥3 births, age at first birth <26 years; ≥3 births, age at first birth ≥26 years), education level (secondary school, high school, university or higher, other) and menopausal status (post or premenopausal).

Cancer Epidemiology

Table 3. Effect of alcohol consumption and physical activity on breast cancer for women at varying levels of risk based on 10-year Tyrer–Cuzick predictions

Lifestyle factor	10-year TC risk <3.0%					10-year TC risk 3.0–4.9%					10-year TC risk >5.0%				
	Breast cancer					Breast cancer					Breast cancer				
Alcohol (g/day)	*n* total	%	*n* all cases	Adj.[1] OR	[95% CI]	*n* total	%	*n* all cases	Adj.[1] OR	[95% CI]	*n* total	%	*n* all cases	Adj.[1] OR	[95% CI]
0	5,809	20.8	64	Reference		3,130	17.3	45	Reference		1,249	17.3	39	Reference	
0.1–9.9	17,287	62.0	218	1.09	[0.82, 1.46]	11,144	61.7	199	1.34	[0.95, 1.90]	4,404	60.9	135	1.02	[0.70, 1.48]
10.0–40.0	4,806	17.2	70	1.13	[0.79, 1.62]	3,781	20.9	77	1.51	[1.02, 2.24]	1,580	21.8	52	1.16	[0.75, 1.81]
10 g/day	27,901	100	352	1.11	[0.97 1.27]	18,054	100	321	1.06	[0.93, 1.22]	7,233	100	226	1.07	[0.91 1.26]
Alcohol (g/day)	*n* total	%	ER+ cases[2] (*n*)	Adj.[1] OR	[95% CI]	*n* total	%	ER+ cases[2] (*n*)	Adj.[1] OR	[95% CI]	*n* total	%	ER+ cases[2] (*n*)	Adj.[1] OR	[95% CI]
0	5,801	20.8	45	Reference		3,126	17.3	34	Reference		1,244	17.3	29	Reference	
0.1–9.9	17,266	62.0	165	1.21	[0.86, 1.71]	11,128	61.7	154	1.41	[0.95, 2.11]	4,385	60.9	102	1.05	[0.68, 1.61]
10.0–40.0	4,794	17.2	51	1.25	[0.82, 1.92]	3,777	21.0	61	1.63	[1.03, 2.56]	1,577	21.8	37	1.12	[0.67, 1.87]
10 g/day	27,860	100	261	1.16	[0.99, 1.35]	18,030	100	249	1.12	[0.97 1.30]	7,206	100	168	1.08	[0.90 1.30]
Physical activity	*n* total	%	*n* all cases	Adj.[1] OR	[95% CI]	*n* total	%	*n* all cases	Adj.[1] OR	[95% CI]	*n* total	%	*n* all cases	Adj.[1] OR	[95% CI]
Total activity (MET-hr/day)															
<40.0	9,647	34.6	106	Reference		6,816	37.8	121	Reference		2,778	38.4	82	Reference	
40.0–44.9	9,594	34.4	143	1.40	[1.07, 1.82]	6,644	36.8	116	0.98	[0.75, 1.28]	2,653	36.7	86	1.09	[0.79, 1.51]
≥45.0	8,660	31.0	104	1.27	[0.95, 1.70]	4,594	25.4	83	1.18	[0.88, 1.58]	1,802	24.9	59	1.20	[0.84, 1.72]
5 MET-hr/day increase	27,901	100	352	1.00	[0.92, 1.09]	18,054	100	321	1.04	[0.95 1.14]	7,233	100	226	1.05	[0.94, 1.18]
Moderate activity (hr/day)															
<2.0	10,200	36.6	124	Reference		7,359	40.8	124	Reference		3,015	41.7	91	Reference	
2.0–4.9	8,630	30.9	120	1.05	[0.81, 1.37]	5,865	32.5	116	1.12	[0.86, 1.46]	2,346	32.4	75	1.10	[0.79, 1.52]
≥5.0	9,071	32.5	108	1.11	[0.84, 1.46]	4,829	26.7	81	1.09	[0.81, 1.46]	1,872	25.9	60	1.17	[0.82, 1.66]
1 hr/day increase	27,901	100	352	1.00	[0.96, 1.04]	18,054	100	321	1.02	[0.98, 1.07]	7,233	100	226	1.03	[0.98, 1.08]
Vigorous activity (hr/day)															
<0.2	18,437	66.1	225	Reference		12,217	67.7	216	Reference		4,981	68.9	156	Reference	
≥0.2	9,465	33.9	127	1.14	[0.91 1.44]	5,837	32.3	105	1.08	[0.85 1.38]	2,252	31.1	70	0.99	[0.73, 1.34]
1 hr/day increase	27,901	100	352	1.08	[0.81, 1.45]	18,054	100	321	1.26	[0.93, 1.69]	7,233	100	226	0.84	[0.52, 1.37]
Recreational activity (hr/day)															
<1.5	9,939	35.6	117	Reference		7,009	38.8	110	Reference		2,824	39.0	88	Reference	
1.5–2.5	7,947	28.5	94	0.96	[0.72, 1.28]	5,224	28.9	96	1.16	[0.87 1.55]	2,149	29.7	72	1.13	[0.81, 1.56]
≥2.5	10,016	35.9	141	1.11	[0.85, 1.44]	5,821	32.3	115	1.26	[0.95, 1.66]	2,260	31.3	66	0.94	[0.67, 1.33]
1 hr/day increase	27,901	100	352	1.02	[0.97, 1.08]	18,054	100	321	1.03	[0.97, 1.10]	7,233	100	226	0.95	[0.87, 1.04]

[1]Adjusted for age, BMI (<25.0, 25.0–29.9, ≥30.0 kg/m^2), ethnicity (European ancestry yes/no), oral contraceptive use (ever, never), use of menopausal hormone therapy (never, ever), family history of breast cancer in mother or sister(s) (yes, no), age at menarche (<13, 13, 14, ≥15 years), parity and age at first birth (nulliparous; one or two births, age at first birth <26 years; one or two births, age at first birth ≥26 years; ≥3 births, age at first birth <26 years; ≥3 births, age at first birth ≥26 years), education level (secondary school, high school, university or higher, other) and menopausal status (post or premenopausal).
[2]Breast cancer patients with ER– status were excluded from the analysis (n = 101).

≥1 glass of alcohol per day (i.e. 10–40 g) had a 33% higher risk of breast cancer than nondrinkers (95% CI 1.01–1.67) in the unadjusted analysis and 26% in the adjusted analysis (95% CI 1.01–1.59). A dose–response relationship between alcohol consumption and breast cancer was also found with each 10 g/day increment resulting in a 9% higher risk of breast cancer in the adjusted analysis (95% CI 1.00–1.18). Adjusting the analyses for mammographic density did not change the effect estimates (data not shown).

We further analysed the association between alcohol consumption and breast cancer ER status for all women (Table 2). The consumption of 1 glass of alcohol per day was associated with a 25% higher risk of ER+ breast cancer than no consumption after adjusting for confounders (95% CI 1.00–1.56). More than 1 glass of alcohol per day was associated with a 34% higher risk of ER+ breast cancer after correction (95% CI 1.03–1.74). A dose–response relationship between alcohol consumption and ER+ breast cancer was also found, with a 13% increase in risk per 10 g/day increment (95% CI 1.01–1.23) after correcting for confounders. No association was found between alcohol consumption and ER− breast cancers.

Table 3 shows the effect of alcohol consumption on breast cancer stratified by 10-year TC breast cancer risk. The association between alcohol consumption and breast cancer was mostly the same for women at below average, average and above average risk of developing breast cancer. However, women with an average breast cancer risk who consumed ≥1 glass of alcohol per day had a significant 51% higher risk of developing breast cancer in general, and a 63% higher risk of developing ER+ breast cancer than average risk nondrinkers (95% CI 1.02–2.24 and 1.03–2.56, respectively). Additionally, we observed a stronger positive association between alcohol consumption and breast cancer for postmenopausal women compared to premenopausal women (Supporting Information S2).

Physical activity and breast cancer

Women who had a total physical activity of ≥45.0 MET-hr/day appear to have a 21% increased risk of breast cancer compared to women who spent <40.0 MET-hr/day being physically active (95% CI 1.01–1.45). A dose–response relationship between physical activity and breast cancer was not found. Neither was an association between moderate, vigorous or recreational activity and breast cancer found (Table 2). The association between all levels of physical activity and breast cancer was generally unobserved for all women, regardless of breast cancer risk or menopausal status (Table 3, Supporting Information S2), although a few effect estimates stand out. We observed an association for below average-risk women between total physical activity and breast cancer (OR = 1.40, 95% CI 1.07–1.82). No association was found between physical activity and breast cancer for postmenopausal women. For premenopausal women, we observed an association between recreational activity and breast cancer (OR = 1.37, 95% CI 1.02–1.86). Adjusting the analyses for mammographic density did not change the effect estimates (data not shown).

Discussion

The present study found that higher alcohol consumption is associated with a higher risk of breast cancer. Yet we found no protective effect of physical activity on breast cancer. Moreover, the association between alcohol consumption and physical activity, and breast cancer was generally the same for women at below average, average and above average risk of developing breast cancer. The additional TC breast cancer risk factors therefore do not appear to modify the association between lifestyle and breast cancer.

Alcohol consumption is the lifestyle factor most consistently associated with increased breast cancer risk.[5] Women with high levels of alcohol consumption have a 40–50% higher risk of developing breast cancer than abstainers, regardless of the type of alcoholic beverage consumed.[4,5,22,24] A dose–response relationship between alcohol consumption and breast cancer has been reported, with every 10 g of alcohol consumed per day increases breast cancer risk by 9–12%.[4,24] We found an increased risk of 9%, which is in line with previous findings. In concurrence with a recent meta-analysis, we found that the association between alcohol consumption and breast cancer was stronger for ER+ than ER− breast cancers.[5] However, some caution is required due to the relatively low number of ER- cases (n = 101) in our study sample, which may have affected the estimate for ER− cancers.

Alcohol consumption can elevate oestrogen levels through several biological mechanisms, which in turn may increase breast cancer risk, particularly for hormone-dependent cancers.[25] A proposed mechanism for postmenopausal women specifically suggests that alcohol may promote the activity of the aromatase enzyme, which is responsible for converting androgen to oestrogen.[25] This is an important source of oestrogen for postmenopausal women in particular.[25] Our results confirmed that alcohol consumption is more strongly associated with breast cancer in postmenopausal than premenopausal women, however, the underlying mechanism remains unclear.[5] It is proposed that alcohol consumption has a more pronounced effect on breast tissue after menopause.[5]

Contrary to expectations, we did not find a protective effect of physical activity on breast cancer. Studies have shown that physical activity decreases breast cancer risk, although estimated risk reductions vary substantially from 20% to 80%.[2] A recent meta-analysis established a 12% decrease in breast cancer risk when comparing the most to the least physically active women.[26] Engagement in a recreational activity, activity sustained over a woman's lifetime or after menopause, and of moderate to vigorous intensity appear to offer the greatest risk reduction.[7] A dose–response relationship has been established with a breast cancer risk reduction of 3% for every 10 MET-hr/week increase in recreational physical activity.[3] Multiple interrelated biological pathways may account for

Cancer Epidemiology

the effect of physical activity in reducing breast cancer risk, which may involve adiposity, sex hormones, insulin resistance, adipokines and chronic inflammation.[7]

The protective effect of physical activity on breast cancer appears more pronounced for postmenopausal women, whereas a recent meta-analysis showed no significant breast cancer risk reduction in premenopausal women.[2,7,27] Although our results reflect this trend, we did not observe any significant associations between physical activity and breast cancer for postmenopausal Swedish women. There have been other studies that have found no association between physical activity and breast cancer, or that have found that higher levels of physical activity actually increase breast cancer risk.[2] A previous systematic review concluded that, in general, lower-quality studies showed greater risk reductions than higher-quality studies.[2] Conspicuously, two other cohort studies performed in a population of Swedish women also showed no significant effect of physical activity on breast cancer risk.[28,29] This could be due to the general physical activity habits of Swedish women. Most women in the present study already met the physical activity guidelines for cancer prevention,[23] limiting variation in physical activity scores. This lack of contrast could explain why we were unable to find an association between physical activity and breast cancer. Moreover, it may also indicate that Swedish women will gain little by becoming more physically active, permitting them to maintain current exercise habits.

Additional breast cancer risk factors generally did not modify the association between both alcohol consumption and physical activity, and breast cancer. This was not in line with our *a priori* hypothesis based on a previous study which showed that breast cancer risk moderates the association between alcohol consumption and physical activity, and mammographic density.[8,9] Since mammographic density has been established as one of the strongest breast cancer risk factors, the applicability of these results to breast cancer diagnosis appeared likely. We were able to reproduce the risk estimates of the previous studies evaluating whether breast cancer risk modifies the association between lifestyle and mammographic density in Swedish women (data not shown).[8,9] This supports the hypothesis that lifestyle affects mammographic density differently to breast cancer. Mammographic density reflects long-term hormonal breast cancer risk but can be modified short-term by lifestyle factors, such as physical activity and alcohol consumption. Breast cancer appears to require more long-term lifestyle efforts which may not have been adequately represented by our measurement of a woman's lifestyle behaviours in the past year. Moreover, we stratified women based on their 10-year TC breast cancer risk score, considering this score as an illustration of a woman's lifetime exposure to (endogenous) sex hormones. However, TC risk score is a complex construct consisting of many different factors that all contribute to a woman's breast cancer risk, through different aetiological pathways.

Although our findings suggest that additional breast cancer risk factors do not modify the association between lifestyle and breast cancer, this may not account for variation in other factors relating to alcohol consumption and physical activity, such as BMI and its opposing effect on breast cancer risk at premenopausal and postmenopausal ages.[27,30,31] It is imaginable that breast cancer risk does play a role when exploring further subgroups of women based on, for example, menopausal status, BMI and short *versus* long-term risk. We felt this was beyond the scope of the current study, being mindful of multiple testing and subsequent chance findings. However, further research into subgroups of women for whom breast cancer risk can be an important indicator of lifestyle change is recommended.

The Swedish women in this prospective cohort provided us with detailed information on alcohol consumption, physical activity, confounders and breast cancer risk factors. This enabled us to explore whether additional breast cancer risk factors modify the association between lifestyle and breast cancer. However, a number of limitations need to be considered. Our findings have to be interpreted with some caution due to our relatively short follow-up time and subsequent limited number of deaths and cases for subgroup analyses. We chose to perform logistic regression modelling. Given the limited number of deaths ($n = 31$) during our follow-up time, there would have been very small changes in effect estimates, if any, from censoring using Cox regression modelling. Moreover, KARMA participants were recruited at breast cancer screening centres, leading to a selection of women attending screening and participating in scientific research. There is no available data comparing the characteristics of screening and/or KARMA participants *versus* nonparticipants; however, it is likely that the two groups are not entirely comparable. Additionally, the study relied on self-reported lifestyle data, which is prone to misclassification.[32] Women are likely to have under-reported their alcohol consumption and over-reported their physical activity. Additionally, women's lifestyles were only measured at baseline, which may not have been representative of a woman's general lifestyle. Moreover, cross-sectional measurements of physical activity, in particular, have previously produced weaker results than longitudinal measurements when assessing the effect of physical activity on breast cancer.[33] Physical activity levels at earlier stages in life have also been shown to be important, supporting the assessment of lifetime physical activity.[34] It is conceivable that lifetime alcohol consumption is also a more accurate breast cancer risk factor than a cross-sectional measurement of alcohol intake. Moreover, although the Active-Q is a validated physical activity measure,[17] it has not yet been used in many studies, limiting a more comprehensive evaluation of its validity. Future research should aim for more consistency and standardisation in the measurement of lifestyle factors, aiming for the evaluation of lifetime exposure.

Conclusion

Our results suggest that the association between past-year lifestyle behaviours (alcohol consumption and physical activity) and breast cancer is not affected by additional breast cancer risk factors. This implies that general preventative lifestyle recommendations can be formulated about alcohol consumption for women at all levels of breast cancer risk. Although we did not find a protective effect of physical activity on breast cancer in our study, it is well known that physical activity is generally beneficial for a person's health. Therefore, guidelines about reduced alcohol consumption and increased physical activity remain pertinent to general health and breast cancer prevention for all women.

Acknowledgements

We thank all the participants of the KARMA study and the study team for their devoted work during data collection.

Conflict of interest

All authors declare to have no conflict of interest.

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359–86.
2. Monninkhof EM, Elias SG, Vlems FA, et al. Physical activity and breast cancer: a systematic review. *Epidemiology* 2007;18:137–57.
3. Wu Y, Zhang D, Kang S. Physical activity and risk of breast cancer: a meta-analysis of prospective studies. *Breast Cancer Res Treat* 2013;137:869–82.
4. Smith-Warner SA, Spiegelman D, Yuan SS, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. *JAMA* 1998;279: 535–40.
5. Jung S, Wang M, Anderson K, et al. Alcohol consumption and breast cancer risk by estrogen receptor status: in a pooled analysis of 20 studies. *Int J Epidemiol* 2015;45:916–28.
6. Tamimi RM, Spiegelman D, Smith-Warner SA, et al. Population attributable risk of modifiable and nonmodifiable breast cancer risk factors in postmenopausal breast cancer. *Am J Epidemiol* 2016;184:884–93.
7. Friedenreich CM. Physical activity and breast cancer: review of the epidemiologic evidence and biologic mechanisms. *Recent Results Cancer Res* 2011;188:125–39.
8. Trinh T, Christensen SE, Brand JS, et al. Background risk of breast cancer influences the association between alcohol consumption and mammographic density. *Br J Cancer* 2015;113: 159–65.
9. Trinh T, Eriksson M, Darabi H, et al. Background risk of breast cancer and the association between physical activity and mammographic density. *Breast Cancer Res* 2015;17:50.
10. Boyd NF, Rommens JM, Vogt K, et al. Mammographic breast density as an intermediate phenotype for breast cancer. *Lancet Oncol* 2005;6: 798–808.
11. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2006;15:1159–69.
12. Vilaprinyo E, Forne C, Carles M, et al. Cost-effectiveness and harm-benefit analyses of risk-based screening strategies for breast cancer. *PLoS One* 2014;9:e86858.
13. Senore C, Giordano L, Bellisario C, et al. Population based cancer screening programmes as a teachable moment for primary prevention interventions. A review of the literature. *Front Oncol* 2012;2:45.
14. Gabrielson M, Eriksson M, Hammarström M, et al. Cohort profile: the Karolinska mammography project for risk prediction of breast cancer (KARMA). *Int J Epidemiol* 2017;46:740–741g.
15. Christensen SE, Moller E, Bonn SE, et al. Two new meal-and web-based interactive food frequency questionnaires: validation of energy and macronutrient intake. *J Med Internet Res* 2013;15: e109.
16. Swedish National Food Agency: Nutrient Database (2014). Available from: http://www.livsmedelsverket.se/en/foodandcontent/naringsamnen/livsmedelsdatabasen/.
17. Bonn SE, Lagerros YT, Christensen SE, et al. Active-Q: validation of the web-based physical activity questionnaire using doubly labeled water. *J Med Internet Res* 2012;14:e29.
18. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 compendium of physical activities: a second update of codes and MET values. *Med Sci Sports Exerc* 2011;43:1575–81.
19. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. *Stat Med* 2004;23:1111–30.
20. Evans DG, Graham J, O'Connell S, et al. Familial breast cancer: summary of updated NICE guidance. *BMJ* 2013;346:f3829.
21. Eriksson M, Li J, Leifland K, et al. A comprehensive tool for measuring mammographic density changes over time. *Breast Cancer Res Treat* 2018; 169:371–9.
22. Chen WY, Rosner B, Hankinson SE, et al. Moderate alcohol consumption during adult life, drinking patterns and breast cancer risk. *JAMA* 2011; 306:1884–90.
23. Kushi LH, Doyle C, McCullough M, et al. American Cancer Society guidelines on nutrition and physical activity for cancer prevention. *CA Cancer J Clin* 2012;62:30–67.
24. Allen NE, Beral V, Casabonne D, et al. Moderate alcohol intake and cancer incidence in women. *J Natl Cancer Inst* 2009;101:296–305.
25. Singletary KW, Gapstur SM. Alcohol and breast cancer: review of epidemiologic and experimental evidence and potential mechanisms. *JAMA* 2001; 286:2143–51.
26. Pizot C, Boniol M, Mullie P, et al. Physical activity, hormone replacement therapy and breast cancer risk: a meta-analysis of prospective studies. *Eur J Cancer* 2016;52:138–54.
27. Neil-Sztramko SE, Boyle T, Milosevic E, et al. Does obesity modify the relationship between physical activity and breast cancer risk? *Breast Cancer Res Treat* 2017;166:367–81.
28. Moradi T, Adami HO, Ekbom A, et al. Physical activity and risk for breast cancer a prospective cohort study among Swedish twins. *Int J Cancer* 2002;100:76–81.
29. Margolis KL, Mucci L, Braaten T, et al. Physical activity in different periods of life and the risk of breast cancer: the Norwegian–Swedish Women's lifestyle and health cohort study. *Cancer Epidemiol Biomarkers Prev* 2005;14:27–32.
30. Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008;371:569–78.
31. Premenopausal Breast Cancer Collaborative Group, Schoemaker MJ, Nichols HB, et al. Association of body mass index and age with subsequent breast cancer risk in premenopausal women. *JAMA Oncol* 2018;4:e181771.
32. Bernstein L, Henderson BE, Hanisch R, et al. Physical exercise and reduced risk of breast cancer in young women. *J Natl Cancer Inst* 1994;86: 1403–8.
33. Rockhill B, Willett WC, Hunter DJ, et al. A prospective study of recreational physical activity and breast cancer risk. *Arch Intern Med* 1999;159: 2290–6.
34. McTiernan A, Kooperberg C, White E, et al. Recreational physical activity and the risk of breast cancer in postmenopausal women: the Women's Health Initiative cohort study. *JAMA* 2003;290: 1331–6.