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Pre-diagnostic alcohol consumption and postmenopausal breast cancer survival: a prospective patient cohort study

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Abstract Study results on the association of alcohol consumption with breast cancer survival are inconsistent, partly due to the use of different survival outcomes. We assessed the association of pre-diagnostic alcohol consumption with survival and recurrence in a prospective cohort study in Germany including 2,522 postmenopausal breast cancer patients aged 50–74 years. Patients were diagnosed between 2001 and 2005 and vital status, causes of death, and recurrences were verified through the end of 2009. Cox proportional hazards models were stratified by age at diagnosis and study center and adjusted for relevant prognostic factors. Alcohol consumption was non-linearly associated with increased breast cancer-specific mortality [e.g., ≥12 vs. <0.5 g/day: hazard ratio (HR) = 1.74, 95 % confidence interval (CI): 1.13, 2.67]. Results were independent of estrogen receptor status. A non-significantly decreased risk of mortality due to other causes was found (≥12 vs. <0.5 g/day: HR = 0.67, 95 % CI: 0.35, 1.29). Alcohol consumption was not associated with overall mortality (≥12 vs. <0.5 g/day: HR = 1.28, 95 % CI: 0.90, 1.81) and breast cancer recurrence (≥12 vs. <0.5 g/day: HR = 1.08, 95 % CI: 0.73, 1.58). In conclusion, our findings show that consumption of alcohol before diagnosis is non-linearly associated with increased breast cancer-specific mortality but may be associated with decreased risk of mortality due to other causes.

Keywords Breast cancer · Alcohol · Mortality · Recurrence

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Introduction

Alcohol consumption has been consistently associated with breast cancer risk [1]. However, studies on its association with breast cancer survival have produced inconsistent results [2]. Next to methodological limitations (e.g., small study numbers, restricted consumption range, measurement error, no or limited adjustment for important prognostic factors), these inconsistent findings may be explained by use of different survival outcomes [2].

Alcohol may have both cardioprotective [3] and hormonal effects [4], and moderate alcohol consumption has been associated with a decreased risk of dying from cardiovascular disease whereas heavier drinking was associated with an increased risk of dying from breast cancer [5]. Many studies in breast cancer patients only investigated alcohol consumption in relation to overall mortality [6–11].

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Since overall mortality is a composite of breast cancer-specific mortality and mortality due to other causes, results of these studies are difficult to interpret. For breast cancer-specific mortality, nine studies observed an increased risk with higher beer [12] or total alcohol consumption [13–21], four of which were statistically significant [12, 13, 17, 18]. Two studies observed a decreased risk with higher total alcohol consumption, statistically significant in one [22] but not in the other [23], and three studies found no association with breast cancer death [24–26]. Risk of recurrence has also been found significantly increased with higher beer consumption [12] and total alcohol consumption [17, 21], but in three other studies no significant association with total alcohol consumption was shown [9, 23, 27]. To date, only two recent studies specifically investigated alcohol consumption in relation to risk of other causes of death (including cardiovascular disease) in breast cancer patients, one finding a non-significantly [17] and the other a significantly [20] decreased risk. However, evidence for the role of alcohol consumption in breast cancer-specific mortality and mortality due to other causes is still limited, and no clear advice can be given to breast cancer patients yet.

Thus, we aimed to investigate the association of pre-diagnostic alcohol consumption with overall mortality, breast cancer-specific mortality, mortality due to other causes, and breast cancer recurrence in a large cohort of German postmenopausal breast cancer survivors with a large range of alcohol intake. In addition, we examined whether this association may be modified by tumor stage, tumor grade, estrogen receptor (ER) status of the tumor, body mass index (BMI), use of hormone replacement therapy (HRT), and smoking status.

Materials and methods

Study population

Patients were recruited from 2002 to 2005 within a large population-based case–control study on breast cancer in two regions in Germany (MARIE study, Mamma Carcinoma Risk factor Investigation) [28], and a follow-up of all patients was performed up to the end of 2009. Patients had histologically confirmed primary invasive (stage I–IV) or in situ breast cancer and were diagnosed between 1 January 2001 and 30 September 2005 in Hamburg, and between 1 August 2002 and 31 July 2005 in the Rhein-Neckar–Karlsruhe region. Patients were identified through the Cancer Registry of Hamburg and participating clinics. A total of 3,464 patients were aged between 50 and 74 years and postmenopausal (defined as last menstrual bleeding at least 12 months before the date of diagnosis, a bilateral oophorectomy, cessation of menses due to radiation or chemotherapy, >55 years with unclear menopausal status due to hysterectomy or hormone use). After exclusion of patients that had no data on alcohol consumption from a food frequency questionnaire (FFQ) ($n = 520$), patients with previous cancer (other than basal or squamous skin cancers or in situ cancers) or missing information on previous cancer ($n = 207$), patients with in situ breast cancer ($n = 165$), and patients with energy intake in the bottom or top 1.0 percentile (<796 or >3,821 kcal/day, respectively, $n = 50$), 2,522 postmenopausal invasive breast cancer patients were available for analysis.

This study was approved by the ethics committee of the University of Heidelberg, the ethical review board of Hamburg Medical Council, and the Medical Board of the State of Rheinland-Pfalz, and conducted in accordance with the Declaration of Helsinki. All study participants provided written informed consent at recruitment and during follow-up.

Data collection

At recruitment, patients completed a self-administered 176-items FFQ referring to the year before breast cancer diagnosis. This FFQ was comparable to the one used for the German part of the European Prospective into Cancer and Nutrition study which has been validated for food group, energy and nutrient intake by 12 24 h diet recalls ($r = 0.88$ for alcohol) [29, 30]. For each food item, the questionnaire asked for the typical portion size and the consumption frequency (times per day, week, month, or year). Patients reported the number of glasses of beer (including cider), wine (including sparkling wine), fortified wines, spirits, aniseed drinks, and liqueurs. Alcohol intake was calculated based on the average glass volume and ethanol content for each type of alcoholic beverage, using information collected in highly standardized 24 h recalls from a random subset of the EPIC Heidelberg cohort [31, 32]. The following ethanol contents were used: beer (38.5 g/L), cider (50 g/L), wine (87.8 g/L), sparkling wine (89.0 g/L), fortified wines (205.8 g/L), spirits (314.8 g/L), aniseed drinks (292.3 g/L), and liqueurs (175.3 g/L).

Clinical and pathological characteristics were abstracted from hospital and pathology records. All patients were interviewed at recruitment (2002–2005) by trained personnel to obtain information on sociodemographic factors, anthropometric measures, lifetime HRT exposure, and other potential breast cancer risk factors.

Outcome assessment

Vital status of participants was determined through population registries up to the end of 2009 (100 % completeness

of follow-up). Primary causes of death were extracted from death certificates. Medical records were checked or treating physicians were contacted to identify recurrences or second cancers, and to verify such information collected during a follow-up telephone interview conducted from May to September 2009. Self-reported events from the interview were taken when medical records were not available.

The outcomes considered were overall mortality, breast cancer-specific mortality, mortality from causes other than breast cancer, and recurrence. Recurrence included ipsilateral/contralateral/local/regional invasive recurrence and distant recurrence, and analyses for this endpoint were restricted to participants with stage I–IIIa disease as well as information on recurrences occurring after recruitment into the study ($n = 2{,}184$; 98 % completeness of follow-up). Participants were censored at date of last contact or 31 December 2009, whichever came first.

Statistical analyses

Delayed-entry Cox proportional hazards models, based on time since study enrollment until event or censoring, were used to examine the association of pre-diagnostic alcohol consumption with survival and recurrence [33]. Hazard ratios (HR) and 95 % confidence intervals (CI) were calculated using alcohol consumption as categorical variable divided into four categories based on an estimated 12 g of alcohol per drink (<0.5, 0.5 to <6.0, ≥6.0 to <12.0, ≥12.0 g/day). The lowest category was defined as the reference category. All analyses were stratified by age at diagnosis (in 1 year categories) and study center. Analyses were adjusted for the traditional prognostic variables, i.e., tumor size (≤2, 2–5, >5 cm, growth in chest wall/skin, neoadjuvant chemotherapy), nodal status (0, 1–3, 4–9, ≥10, neoadjuvant chemotherapy), primary metastasis (yes, no), tumor grade (low + moderate, high, neoadjuvant chemotherapy), and joint estrogen/progesterone receptor (ERPR) status (ER^+PR^+, ER^+PR^-/ER^-PR^+, ER^-PR^-, neoadjuvant chemotherapy). In addition, analyses were adjusted for variables that were statistically significant (<0.05) when tested in the model, i.e., radiotherapy, mode of detection (physician-detected by routine investigation/mammography/ultrasound, self-detected by palpation/secretion/pain), and HRT use at diagnosis. Other potentially confounding variables were not statistically significant and did not change the risk estimates by ≥10 % when tested in the model and were therefore not included in the final model, i.e., human epidermal growth factor receptor 2 (HER2) status, type of surgery, chemotherapy, hormonal therapy (tamoxifen and/or aromatase inhibitors), adult BMI, leisure time physical activity since age 50, dietary folate intake, self-reported prevalent diabetes, cardiovascular disease, smoking status, educational level, and occupational level. We used the method of fractional polynomials to further examine dose–response relation and non-linearity of the log HR for alcohol consumption [34]. The continuous alcohol consumption was entered into the multivariate Cox proportional hazards model via a set of defined transformations [x^{-2}, x^{-1}, $x^{-0.5}$, $x^{0.5}$, x^2, x^3, and $\log(x)$], allowing a maximum of two terms (including the untransformed variable) in the model. The function that best fitted the data was selected on the basis of the −2 log likelihood of the respective model. The concordance (C) index and R_E measure as proposed by Stare et al. were used to assess the predictive discriminatory capability of the multivariate model and the variation explained by the model [35, 36], respectively, and 95 % CIs were calculated from 1,000 bootstrap samples.

For mortality endpoints, we performed sensitivity analyses by restriction to stage I–IIIa disease. For breast cancer-specific mortality, we also performed a sensitivity analysis by exclusion of women who recurred or died within 1 year of diagnosis.

We performed stratified analyses to examine whether the associations between alcohol consumption and breast cancer-specific mortality varied by tumor stage (I–IIIa vs. IIIB–IV), tumor grade (low + moderate vs. high), ER status (ER^+ vs. ER^-), adult BMI (< vs. ≥ median kg/m^2), HRT use at time of diagnosis (yes vs. no), smoking status (never vs. ever), educational level (low vs. medium/high), and time between diagnosis and FFQ completion (< vs. ≥ median). We then included interaction terms of the categorical alcohol consumption variable and the variables of interest in the fully adjusted model and evaluated statistical significance with the likelihood ratio test.

All tests were two-sided and considered to be statistically significant if P value <0.05. All statistical analyses were performed using SAS software 9.2 (SAS Institute, Cary, NC) and R, version 2.13.2 [37].

Results

Baseline characteristics according to categories of alcohol consumption are shown in Table 1. Compared to women with <0.5 g/day of alcohol consumption, those with ≥12 g/day of alcohol consumption were generally younger, had a lower BMI, and a higher folate intake. They were less likely to have diabetes or cardiovascular disease, and more likely to have a physician-detected tumor, to use HRT at time of diagnosis, to be past or current smoker, and to have a higher occupational and educational level. No differences in tumor and therapy characteristics were observed.

Among the women drinking ≥0.5 g/day of alcohol (76.8 % of total population), 97.0 % drank wine, 66.5 % drank beer, and 57.6 % drank spirits/liquor. The median amount of alcohol consumed was 5.87 g/day [range, 0.51–289; mean (SD) 11.8 (17.6)].

Table 1 Baseline characteristics of 2,522 postmenopausal breast cancer patients in the MARIE study according to alcohol consumption status, Germany, 2001–2005

	Alcohol consumption (g/day)			
	<0.5	≥0.5–<6.0	≥6.0–<12.0	≥12.0
No. of patients	584	982	406	550
Mean age at diagnosis (years)	63.3 (5.6)[a]	62.7 (5.5)	62.7 (5.6)	61.9 (5.2)
Mean adult BMI (kg/m^2)	23.8 (3.6)	23.4 (3.1)	22.7 (2.6)	22.7 (2.9)
Mean folate intake (μg/day)	209.4 (67.2)	210.9 (61.6)	212.9 (56.0)	213.8 (67.0)
Stage, *n* (%)[b]				
I	242 (41.4)	450 (45.8)	177 (43.6)	260 (47.3)
II	232 (39.7)	386 (39.3)	165 (40.6)	200 (36.4)
III	69 (11.8)	88 (9.0)	39 (9.6)	56 (10.2)
IV	18 (3.1)	23 (2.3)	8 (2.0)	16 (2.9)
Neoadjuvant CT	23 (3.9)	35 (3.6)	17 (4.2)	18 (3.3)
Tumor size, *n* (%)[b]				
≤2 cm	299 (51.2)	553 (56.3)	230 (56.7)	320 (58.2)
>2–≤5 cm	218 (37.3)	347 (35.3)	134 (33.0)	177 (32.2)
>5 cm	25 (4.3)	27 (2.7)	12 (3.0)	19 (3.5)
Growth into chest wall/skin	18 (3.1)	19 (1.9)	12 (3.0)	15 (2.7)
Neoadjuvant CT	23 (3.9)	35 (3.6)	17 (4.2)	17 (3.1)
Missing	1 (0.2)	1 (0.1)	1 (0.2)	2 (0.4)
Nodal status, *n* (%)				
0	368 (63.0)	646 (65.8)	265 (65.3)	373 (67.8)
1–3	133 (22.8)	226 (23.0)	89 (21.9)	110 (20.0)
4–9	43 (7.4)	43 (4.4)	16 (3.9)	29 (5.3)
≥10	15 (2.6)	31 (3.2)	19 (4.7)	19 (3.5)
Neoadjuvant CT	23 (3.9)	35 (3.6)	17 (4.2)	17 (3.1)
Missing	2 (0.3)	1 (0.1)	0 (0.0)	2 (0.4)
Metastases, *n* (%)				
No	566 (96.9)	955 (97.3)	393 (96.8)	531 (96.5)
Yes	18 (3.1)	26 (2.6)	13 (3.2)	18 (3.3)
Missing	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)
Tumor grade, *n* (%)				
Low + moderate	385 (65.9)	681 (69.3)	281 (69.2)	408 (74.2)
High	173 (29.6)	261 (26.6)	107 (26.4)	123 (22.4)
Neoadjuvant CT	23 (3.9)	35 (3.6)	17 (4.2)	17 (3.1)
Missing	3 (0.5)	5 (0.5)	1 (0.2)	2 (0.4)
ERPR, *n* (%)				
ER^+PR^+	359 (61.5)	610 (62.1)	249 (61.3)	364 (66.2)
ER^+PR^-/ER^-PR^+	94 (16.1)	174 (17.7)	84 (20.7)	96 (17.5)
ER^-PR^-	107 (18.3)	163 (16.6)	56 (13.8)	73 (13.3)
Neoadjuvant CT	23 (3.9)	35 (3.6)	17 (4.2)	17 (3.1)
Missing	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
HER2, *n* (%)				
$HER2^+$	109 (18.7)	160 (16.3)	68 (16.8)	99 (18.0)
$HER2^-$	390 (66.8)	701 (71.4)	283 (69.7)	384 (69.8)
Neoadjuvant CT	23 (3.9)	35 (3.6)	17 (4.2)	17 (3.1)
Missing	62 (10.6)	86 (8.8)	38 (9.4)	50 (9.1)
Type of surgery, *n* (%)				
Ablatio	197 (33.7)	273 (27.7)	121 (29.8)	156 (28.4)
BCT	381 (65.2)	703 (71.4)	283 (69.7)	391 (71.1)
Missing	6 (1.0)	6 (0.6)	2 (0.5)	3 (0.5)

Table 1 continued

	Alcohol consumption (g/day)			
	<0.5	≥0.5–<6.0	≥6.0–<12.0	≥12.0
Chemotherapy, *n* (%)				
No	295 (50.5)	464 (47.3)	208 (51.2)	290 (52.7)
Yes	281 (48.1)	506 (51.5)	195 (48.0)	256 (46.5)
Missing	8 (1.4)	12 (1.2)	4 (0.7)	4 (0.7)
Radiotherapy, *n* (%)				
No	134 (22.9)	170 (17.3)	74 (18.2)	114 (20.7)
Yes	445 (76.2)	801 (81.6)	327 (80.5)	434 (78.9)
Missing	5 (0.9)	11 (1.1)	5 (1.2)	2 (0.4)
Hormonal therapy, *n* (%)				
No	111 (19.0)	157 (16.0)	52 (12.8)	83 (15.1)
Yes	443 (75.9)	784 (79.8)	340 (83.7)	446 (81.1)
Missing	30 (5.1)	41 (4.2)	14 (3.4)	21 (3.8)
Diabetes, *n* (%)				
No	495 (84.8)	909 (92.6)	380 (93.6)	529 (96.2)
Yes	87 (14.9)	72 (7.3)	25 (6.2)	21 (3.8)
Missing	2 (0.3)	1 (0.1)	1 (0.2)	0 (0.0)
Cardiovascular disease, *n* (%)				
No	228 (39.0)	500 (50.9)	216 (53.2)	306 (55.6)
Yes	356 (61.0)	482 (49.1)	190 (46.8)	244 (44.4)
Mode of detection, *n* (%)				
Self-detected	367 (62.8)	528 (53.8)	213 (52.5)	270 (49.1)
Physician-detected	216 (37.0)	450 (45.8)	190 (46.8)	280 (50.9)
Missing	1 (0.2)	4 (0.4)	3 (0.7)	0 (0.0)
HRT use at diagnosis, *n* (%)				
Never, past	354 (60.6)	515 (52.4)	192 (47.3)	260 (47.3)
Current	227 (38.9)	458 (46.6)	214 (52.7)	285 (51.8)
Missing	3 (0.5)	9 (0.9)	0 (0.0)	5 (0.9)
Smoking status, *n* (%)				
Never	351 (60.1)	579 (59.0)	223 (54.9)	220 (40.0)
Past	121 (20.7)	261 (26.6)	123 (30.3)	189 (34.4)
Current	112 (19.2)	142 (14.5)	60 (14.8)	141 (25.6)
Leisure time PA since age 50, *n* (%)				
<28 METh/week	184 (31.5)	256 (26.1)	85 (20.9)	146 (26.5)
≥28 METh/week	394 (67.5)	720 (73.3)	317 (78.1)	397 (72.2)
Missing	6 (1.0)	6 (0.6)	4 (1.0)	7 (1.3)
Occupation, *n* (%)				
Low	291 (49.8)	395 (37.5)	125 (30.8)	125 (22.7)
Medium	199 (34.1)	408 (38.5)	178 (43.8)	233 (42.4)
High	91 (15.6)	251 (23.6)	103 (25.4)	191 (34.7)
Missing	3 (0.5)	4 (0.4)	0 (0.0)	1 (0.2)
Education, *n* (%)				
Low	394 (67.5)	608 (61.9)	208 (51.2)	241 (43.8)
Medium	134 (23.0)	261 (26.6)	118 (29.1)	185 (33.6)
High	55 (9.4)	113 (11.5)	80 (19.7)	124 (22.6)
Missing	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

BCT breast conserving therapy, *BMI* body mass index, *CT* chemotherapy, *ERPR* estrogen receptor/progesterone receptor, *HER2* human epidermal growth factor receptor 2, *HRT* hormone replacement therapy, *MET* metabolic equivalent value, *PA* physical activity

[a] Number in parentheses, standard deviation

[b] Percentages do not always add up to 100 due to rounding

Table 2 Hazard ratios of overall mortality, breast cancer-specific mortality, and other mortality according to total alcohol consumption in the MARIE study, Germany, 2001–2009

Total alcohol (g/day)	Overall mortality				Breast cancer-specific mortality			Other mortality		
	No. of subjects	No. of deaths	HR	95 % CI	No. of deaths	HR	95 % CI	No. of deaths	HR	95 % CI
Model 1[a]										
<0.5	584	83	1.00		52	1.00		31	1.00	
≥0.5–<6.0	982	119	0.85	0.64, 1.12	94	1.09	0.77, 1.53	25	0.45	0.26, 0.77
≥6.0–<12.0	406	41	0.79	0.54, 1.15	32	0.99	0.63, 1.54	9	0.46	0.22, 0.98
≥12.0	550	73	1.03	0.75, 1.42	57	1.30	0.89, 1.91	16	0.59	0.32, 1.09
Model 2[b]										
<0.5	578	81	1.00		51	1.00		30	1.00	
≥0.5–<6.0	975	117	0.98	0.73, 1.32	93	1.44	0.99, 2.09	24	0.46	0.26, 0.81
≥6.0–<12.0	405	40	0.68	0.45, 1.03	31	0.85	0.51, 1.41	9	0.46	0.21, 0.98
≥12.0	545	70	1.19	0.85, 1.68	54	1.60	1.05, 2.45	16	0.64	0.34, 1.21
Model 3[c]										
<0.5	569	79	1.00		50	1.00		29	1.00	
≥0.5–<6.0	952	112	1.05	0.77, 1.42	88	1.51	1.04, 2.21	24	0.51	0.29, 0.90
≥6.0–<12.0	397	39	0.74	0.49, 1.13	31	0.92	0.56, 1.53	8	0.47	0.21, 1.06
≥12.0	538	69	1.28	0.90, 1.81	54	1.74	1.13, 2.67	15	0.67	0.35, 1.29

CI confidence interval, *ERPR* estrogen receptor/progesterone receptor, *HR* hazard ratio, *HRT* hormone replacement therapy

[a] The model was stratified by age at diagnosis and study center

[b] The model was stratified by age at diagnosis and study center, and adjusted for tumor size, nodal status, metastases, tumor grade, ERPR status; due to missing covariates, 19 observations were not included in model 2

[c] The model was stratified by age at diagnosis and study center, and adjusted for tumor size, nodal status, metastases, tumor grade, ERPR status, radiotherapy, HRT use at diagnosis, mode of detection; due to missing covariate values, 66 observations were not included in model 3

Women were enrolled in the study a median time of 97 days after diagnosis. Median follow-up time from recruitment until death/censoring was 5.5 years (range 44–7.4 years). Overall, 316 deaths occurred, 235 (74.4 %) due to breast cancer. Further causes of death were other cancers ($n = 39$, 12.3 %), cardiovascular disease ($n = 20$, 6.3 %), and other causes ($n = 22$, 7.0 %). Of the 2,184 patients with stage I–IIIa disease and available data on recurrence status, 247 had a breast cancer recurrence.

We assessed the association of alcohol consumption with overall mortality, breast cancer-specific mortality, mortality due to other causes, and breast cancer recurrence. Consumption of ≥12 g/day compared with <0.5 g/day of alcohol was not significantly associated with overall mortality (HR = 1.28, 95 % CI: 0.90, 1.81). However, women drinking ≥0.5 to <6 g/day and ≥12 g/day of alcohol had a significantly higher risk of breast cancer-specific mortality compared with women drinking <0.5 g/day of alcohol (HR = 1.51, 95 % CI: 1.04, 2.21 and HR = 1.74, 95 % CI: 1.13, 2.67, respectively) whereas no significant association was found for women drinking ≥6 to <12 g/day of alcohol (HR = 0.92, 95 % CI: 0.56, 1.53) (Table 2). The discriminatory capability of the multivariate model was found to be high (C index = 0.801, 95 % CI: 0.760, 0.846), and $R_E = 0.602$ (95 % CI: 0.520, 0.692) documents sufficient explained variation. Modelling with fractional polynomials resulted in a non-linear second-degree association between the log HR and alcohol levels. However, the discriminatory capability and the explained variation of the fractional polynomials model were equivalent to those of the categorical model (C index = 0.800, 95 % CI: 0.759, 0.847 and $R_E = 0.600$, 95 % CI: 0.518, 0.694). Interestingly, consumption of ≥12 g/day compared with <0.5 g/day of alcohol was associated with a non-significant decreased risk of mortality due to other causes (HR = 0.67, 95 % CI: 0.35, 1.29). We did not find an association of alcohol consumption with risk of breast cancer recurrence (HR = 1.08; 95 % CI: 0.73, 1.58) (Table 3).

Results for breast cancer-specific mortality were in the same direction but no longer significant after exclusion of ex-drinkers from the lowest category of alcohol consumption (data not shown). Results were also similar after exclusion of 63 women who recurred or died within 1 year of diagnosis (≥12 vs. <0.5 g/day: HR = 1.87, 95 % CI: 1.15, 3.04). When restricted to stage I–IIIa patients, results were no longer significant (≥12 vs. <0.5 g/day: HR = 1.31, 95 % CI: 0.76, 2.26) (Table 4). Hazard ratios tended to be higher for stage IIIb–IV patients (HR = 3.21, 95 % CI: 0.90, 11.4) and patients treated with neoadjuvant

Table 3 Hazard ratios of recurrence among stage I–IIIa breast cancer patients according to total alcohol consumption in the MARIE study, Germany, 2001–2009

Total alcohol (g/day)	No. of subjects	No. of recurrences	HR	95 % CI
Model 1[a]				
<0.5	501	62	1.00	
≥0.5–<6.0	854	102	0.96	0.69, 1.32
≥6.0–<12.0	350	30	0.74	0.47, 1.14
≥12.0	479	53	0.89	0.61, 1.29
Model 2[b]				
<0.5	497	62	1.00	
≥0.5–<6.0	849	102	1.00	0.72, 1.39
≥6.0–<12.0	349	29	0.75	0.48, 1.18
≥12.0	478	53	1.00	0.68, 1.46
Model 3[c]				
<0.5	489	61	1.00	
≥0.5–<6.0	830	97	1.03	0.74, 1.44
≥6.0–<12.0	342	29	0.86	0.54, 1.36
≥12.0	474	52	1.08	0.73, 1.58

CI confidence interval, *ERPR* estrogen receptor/progesterone receptor, *HR* hazard ratio, *HRT* hormone replacement therapy

[a] The model was stratified by age at diagnosis and study center

[b] The model was stratified by age at diagnosis and study center, and adjusted for tumor size, nodal status, tumor grade, ERPR status; due to missing covariates, 11 observations were not included in model 2

[c] The model was stratified by age at diagnosis and study center, and adjusted for tumor size, nodal status, tumor grade, ERPR status, radiotherapy, HRT use at diagnosis, mode of detection; due to missing covariate values, 49 observations were not included in model 3

chemotherapy (HR = 2.86, 95 % CI: 0.42, 19.3), but no significant effect modification by tumor stage was observed (*P* interaction = 0.39). We also observed no effect modification by tumor grade, ER status, BMI, HRT use, and smoking status (Table 5). Further, results were similar by median time between diagnosis and FFQ completion and by education (data not shown). Consumption of ≥12 g/day compared with <0.5 g/day of alcohol from wine or beer was not individually significantly associated with breast cancer-specific mortality (HR = 1.39, 95 % CI: 0.88, 2.19 and HR = 1.57, 95 % CI: 0.77, 3.16, respectively). Also no association with spirits/liquor consumption was found (≥0.5 g/day compared with <0.5 g/day of alcohol from spirits/liquor: HR = 1.13, 95 % CI: 0.73, 1.75).

Discussion

In our study of German postmenopausal breast cancer patients, we found a non-linear association between pre-diagnostic alcohol consumption and breast cancer-specific mortality. Consumption of ≥0.5 to <6 g/day and ≥12 g/day compared with <0.5 g/day of alcohol were both significantly associated with increased risk of breast cancer-specific mortality whereas no association was found for ≥6 to < 12 g/day of alcohol. In contrast, a non-significantly decreased risk of mortality due to other causes was found. No significant associations were observed for overall mortality and breast cancer recurrence.

Studies on alcohol consumption and survival in breast cancer patients have used various outcomes. These different outcome measures may have contributed to the inconsistent findings reported thus far. Alcohol consumption is likely to be differentially associated with breast cancer-specific mortality and mortality due to other causes [5], and deaths due to breast cancer and other causes may differ according to follow-up time and study population. For breast cancer-specific mortality, nine studies observed an increased risk with higher beer [12] or total alcohol consumption [13–21], four of which were statistically significant [12, 13, 17, 18]. This is in line with our results. Three studies found no association with total alcohol consumption [24–26] and two further studies reported even a significant [22], respectively, non-significant [23] inverse association with total alcohol consumption. However, study results are difficult to compare due to methodological limitations (e.g., small study numbers, restricted consumption range, measurement error, no or limited adjustment for important prognostic factors), differences in study design (e.g., pre- vs. postmenopausal women, pre- vs. post-diagnostic consumption), and differences in categorization of alcohol consumption (Table 6).

Next to our study, only two previous studies investigated whether alcohol consumption is differentially associated with breast cancer-specific mortality and mortality due to other causes [17, 20]. Both studies included pre- and postmenopausal women, but stated that results were similar when restricted to postmenopausal women. Kwan et al. [17] conducted a study in 1,897 stage I–IIIa breast cancer patients and found that consumption of >6 vs. <0.5 g/day alcohol about 2 years after diagnosis was associated with an increased risk of breast cancer death (HR = 1.51, 95 % CI: 1.00, 2.29) and a non-significant decreased risk of other deaths (HR = 0.77, 95 % CI: 0.47, 1.27). Harris et al. [20] showed in a study of 3,146 stage I–IV breast cancer patients that ≥10 g/day vs. no alcohol consumption about 12 years before diagnosis was associated with a non-significant increased risk of breast cancer deaths (HR = 1.36, 95 % CI: 0.82, 2.26). For mortality due to other causes, they observed a significant risk reduction for the intermediate alcohol consumption categories (<3.4 g/day: HR = 0.77, 95 % CI: 0.47, 1.27; 3.4–9.9 g/day: HR = 0.67, 95 % CI: 0.50, 0.90) [20]. Risk was not significantly decreased for the highest category of ≥10 g/day

Table 4 Hazard ratios of overall mortality, breast cancer-specific mortality, and other mortality among stage I–IIIa breast cancer patients according to total alcohol consumption in the MARIE study, Germany, 2001–2009

Total alcohol (g/day)	Overall mortality				Breast cancer-specific mortality			Other mortality		
	No. of subjects	No. of deaths	HR	95 % CI	No. of deaths	HR	95 % CI	No. of deaths	HR	95 % CI
Model 1[a]										
<0.5	519	57	1.00		32	1.00		25	1.00	
≥0.5– <6.0	883	87	0.86	0.61, 1.21	64	1.16	0.75, 1.78	23	0.49	0.27, 0.87
≥6.0–<12.0	360	21	0.56	0.33, 0.92	14	0.65	0.34, 1.23	7	0.44	0.19, 1.02
≥12.0	494	41	0.80	0.53, 1.21	28	0.99	0.59, 1.67	13	0.57	0.29, 1.12
Model 2[b]										
<0.5	515	57	1.00		32	1.00		25	1.00	
≥0.5–<6.0	878	86	0.87	0.62, 1.23	64	1.26	0.81, 1.95	22	0.47	0.26, 0.85
≥6.0–<12.0	359	20	0.53	0.32, 0.90	13	0.64	0.33, 1.24	7	0.43	0.18, 1.01
≥12.0	493	41	0.88	0.58, 1.34	28	1.15	0.68, 1.97	13	0.59	0.29, 1.17
Model 3[c]										
<0.5	507	55	1.00		31	1.00		24	1.00	
≥0.5–<6.0	858	81	0.91	0.64, 1.30	59	1.29	0.82, 2.04	22	0.51	0.28, 0.94
≥6.0–<12.0	351	19	0.58	0.34, 0.99	13	0.73	0.37, 1.44	6	0.42	0.17, 1.06
≥12.0	488	40	0.96	0.63, 1.48	28	1.31	0.76, 2.26	12	0.59	0.29, 1.21

CI confidence interval, *ERPR* estrogen receptor/progesterone receptor, *HR* hazard ratio, *HRT* hormone replacement therapy

[a] The model was stratified by age at diagnosis and study center

[b] The model was stratified by age at diagnosis and study center, and adjusted for tumor size, nodal status, tumor grade, ERPR status; due to missing covariates, 11 observations were not included in model 2

[c] The model was stratified by age at diagnosis and study center, and adjusted for tumor size, nodal status, tumor grade, ERPR status, radiotherapy, HRT use at diagnosis, mode of detection; due to missing covariate values, 52 observations were not included in model 3

(HR = 0.81, 95 % CI: 0.46, 1.43), which comprised only 5 % of total person-years. In our study, with a relatively higher alcohol intake, we found a significant association with breast cancer-specific mortality. In contrast to the results of Kwan et al. [17], this association became non-significant when restricted to stage I–IIIa patients. This may be due to the fact that pre-diagnostic and post-diagnostic alcohol consumption may be differentially associated with breast cancer-specific mortality. All three studies consistently observed a reduction in risk of other deaths by 20–30 % associated with alcohol consumption.

The potentially differential effects of alcohol consumption on non-breast cancer and breast cancer-specific mortality are biologically plausible. On the one hand, alcohol has cardioprotective effects [3] and may thereby decrease the risk of non-breast cancer mortality that comprises mortality due to cardiovascular disease. Since the number of cardiovascular deaths in our study was only limited, we could not investigate this as a separate outcome. On the other hand, alcohol consumption has been associated with increased endogenous sex hormone levels [4], which may contribute to the increased risk of breast cancer-specific mortality. The proposed association between alcohol consumption and breast cancer-specific mortality is also likely to be modified by other factors affecting hormone levels, e.g., ER status and BMI. In contrast to the study by Kwan et al. [17] where the positive association between alcohol consumption and breast cancer-specific mortality seemed to be limited to overweight/obese women, in our study this association seemed to be stronger among women with a BMI below the median of 22.8 kg/m^2. However, in both studies no significant heterogeneity was observed. In line with the results by Kwan et al. we found no effect modification by ER status. Also, no effect modification by HRT use and smoking was observed.

The association between alcohol consumption and breast cancer-specific mortality tended to be stronger for stage IIIb–IV compared to stage I–IIIa patients. Although effect modification by tumor stage was not significant, this analysis was based on small numbers and effect modification cannot be excluded. Since alcohol consumption did not differ by tumor stage or other tumor characteristics, it is unlikely that it has affected the severity of disease at onset. It is possible that alcohol consumption interferes with treatment effectiveness particularly among stage IIIb–IV patients, but this is speculative and further investigation is needed.

Table 5 Stratified hazard ratios of breast cancer-specific mortality according to total alcohol consumption in the MARIE study, Germany, 2001–2009

			Total alcohol consumption (g/day)								
			<0.5		≥0.5–<6.0		≥6.0–<12.0		≥12.0		
Parameter	No. of subjects	No. of deaths	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	*P* interaction
Stage											
I–IIIa	2,204	131	1.00		1.29	0.82, 2.04	0.73	0.37, 1.44	1.31	0.76, 2.26	0.39
IIIb–IV	163	71	1.00		1.55	0.53, 4.49	1.46	0.43, 4.97	3.21	0.90, 11.4	
Grade											
Low + moderate	1,721	97	1.00		1.63	0.86, 3.09	1.51	0.66, 3.45	2.23	1.13, 4.42	0.36
High	646	105	1.00		1.46	0.84, 2.54	0.79	0.36, 1.73	1.17	0.57, 2.38	
ER status											
ER^+	1,951	142	1.00		1.40	0.84, 2.33	1.01	0.53, 1.94	1.60	0.92, 2.79	0.79
ER^-	500	80	1.00		1.82	0.91, 3.66	1.26	0.50, 3.17	1.99	0.90, 4.37	
Adult BMI (kg/m^2)											
<22.8	1,221	101	1.00		1.69	0.91, 3.12	1.05	0.46, 2.39	2.08	1.07, 4.07	0.52
≥22.8	1,176	117	1.00		1.07	0.62, 1.85	0.70	0.34, 1.45	1.14	0.58, 2.24	
HRT use											
Yes	1,161	65	1.00		1.21	0.53, 2.77	1.03	0.38, 2.75	1.90	0.82, 4.38	0.30
No	1,295	158	1.00		1.76	1.13, 2.73	0.85	0.46, 1.56	1.67	0.96, 2.90	
Smoking status											
Never	1,334	125	1.00		1.19	0.71, 1.99	0.59	0.28, 1.24	1.52	0.80, 2.90	0.19
Ever	1,122	98	1.00		2.71	1.31, 5.62	2.90	1.24, 6.81	2.87	1.35, 6.13	

CI confidence interval, *ERPR* estrogen receptor/progesterone receptor, *HR* hazard ratio, *HRT* hormone replacement therapy

The models were stratified by age at diagnosis and study center, and adjusted for tumor size, nodal status, metastases, tumor grade, ERPR status, radiotherapy, HRT use at diagnosis, mode of detection

Table 6 Summary of studies on pre- and post-diagnostic alcohol consumption and breast cancer-specific mortality

First author, year, country (ref.)	Study population, BC deaths (% of total deaths)	Questionnaire	Follow-up time	Alcohol	Menopausal status	HR (95 % CI)	Adjustment factors
Rohan, 1993, Australia [24]	412 (no info on stage), 112 BC deaths (91 %)	FFQ mean 4.8 months after diagnosis	1982/84–1989 median 5.5 years	Pre-diagnostic alcohol (≥10 vs. 0 g/days)	Pre + post	0.86 (0.51, 1.47)	Energy, age at menarche, BMI
Hebert, 1998, US [12]	469 stage I–IIIa, 73 BC deaths (84 %)	Q at time of diagnosis	1982/84–1991 range 8–10 years	Pre-diagnostic beer (drinks/days)	Pre + post Pre Post	1.58 (1.00, 2.78) 2.33 (1.35, 4.00) NS	Tumor stage, age, BMI, meat butter/margarine/lard, menopausal status
McDonald, 2002, US [13]	125 local—distant BC, 33 BC deaths (73 %)	Q after diagnosis on lifetime alcohol consumption	1989/94–1998 median 5.4 years	Pre-diagnostic alcohol (≥1 vs. <1 drink/week)	Post	2.7 (1.3–5.8)	Tumor stage, radiation therapy, smoking
Goodwin, 2003, Canada [26]	477 stage I–III, 50 BC deaths (96 %)	FFQ 9 week after diagnosis over last 12 months	1989/1996–? median 6.1 years	Pre-diagnostic alcohol (continuous)	Pre + post	NS	Total energy, age, tumor stage, nodal stage, adjuvant hormone therapy, adjuvant therapy
Borugian, 2004, Canada [25]	603 stage 0–III, 112 BC deaths (77 %)	Q mean 2 months after diagnosis	1991/1992–2001 median 8 years	Pre-diagnostic alcohol (1 % increase in energy %)	Pre + post Pre Post	0.99 (0.94, 1.04) 0.96 (0.90, 1.04) 1.00 (0.93, 1.07)	Age, stage at diagnosis, energy intake
Dal Maso, 2008,/ Franceschi, 2009, Italy [14, 15]	1,453 stage I–IV, 398 BC deaths (79 %)	FFQ over 1–2 years before diagnosis	1991/94–2006 median 12.6 years	Pre-diagnostic alcohol (≥2 drinks/d vs. never)	Pre + post	1.10 (0.83, 1.46)	Region of residence, age at diagnosis, year of diagnosis, tumor stage, ERPR status Region of residence, age at diagnosis, year of diagnosis, tumor stage, ERPR status, BMI, smoking
Reding, 2008, US [22]	1,277 local—distant BC, 335 BC deaths (92 %)	Q over 5 years period before diagnosis	1983/92–2002	Pre-diagnostic alcohol (≥7 drinks/week vs. non)	Pre	0.7 (0.5, 0.9)	Age, year of diagnosis, mammography (further adjustment for tumor stage, histologic grade, and treatment did not change results)
Hellmann, 2009, Denmark [16]	420 local—metastatic BC 178 BC deaths	Q on average 6.7 years before diagnosis	1976–2007 median 7.8 years	Pre-diagnostic alcohol (>14 vs. <1 drinks/week)	Pre + post	1.39 (0.77, 2.52)	Smoking, physical activity, BMI, HRT, age, tumor stage, menopausal status, parity, education, adjuvant treatment

Table 6 continued

First author, year, country (ref.)	Study population, BC deaths (% of total deaths)	Questionnaire	Follow-up time	Alcohol	Menopausal status	HR (95 % CI)	Adjustment factors
Allemani, 2011, Italy [18]	264 stage I–IV	Q over year prior to recruitment	1987/ 2001–2005 median 7.0 years	Pre-diagnostic alcohol (>13 vs. 0 g/days)	Pre + post	RER 4.32 (1.80, 10.4)	Age, tumor stage, tumor subtype, BMI
Harris, 2012, Sweden [20]	3,146 stage I–IV, 385 BC deaths (45 %)	FFQ over 6 months/year prior to recruitment, average 12 years before diagnosis	1987/ 2008–2008 mean 8.2 years	Pre-diagnostic alcohol (≥10 vs. 0 g/days)	Pre + post Post	1.36 (0.82, 2.26) Similar results	Age, energy intake, education level, marital status, menopausal status at diagnosis, BMI, year of diagnosis, tumor stage, treatment
Holm, 2012, Denmark [21]	1,052 early stage, 106 BC deaths (60 %)	FFQ over year prior to recruitment	1993/ 2006–2008 median 6.3 years	Pre-diagnostic alcohol (>2 vs. ≤1 unit/day)	Pre + post	1.10 (0.67, 1.82)	Age at diagnosis, tumor size, lymph node status, receptor status, grade, BMI, smoking, menopausal status, HRT use, education level, physical activity, total folate intake
Flatt, 2010, US [23]	3,088 stage I–IIIa, 262 BC deaths (83 %)	FFQ over past 3 months and 4 24 h recalls during 3 week (highest of 2 estimates), mean 2 years after diagnosis	1995/ 2000–2006 median 7.3 years from cohort entry	Post-diagnostic alcohol (>300 vs. <10 g/months)	Pre + post	0.70 (0.48, 1.02)	Tumor stage, grade, years between diagnosis and study entry, physical activity, ethnicity, smoking, education, parity, BMI
Kwan, 2010, US [17]	1,897 stage I–IIIa, 154 BC deaths (56 %)	FFQ over past year at cohort entry, mean 2 years after diagnosis	2000/ 2002–2009 mean 7.4 years from cohort entry	Post-diagnostic alcohol (≥6 vs. ≤0.5 g/day)	Pre + post Pre Post	1.51 (1.00, 2.29) 1.25 (0.61, 2.54) 1.51 (1.05, 2.19)	Age at diagnosis, pre-diagnosis BMI, total folate intake, tumor stage, ERPR status, tamoxifen use, treatment, positive lymph nodes
Beasley, 2011, US [19]	4,441 local—regional BC, 137 BC deaths (26 %)	FFQ over past year, 1–16 years after diagnosis	1998/ 2001–2005 mean 5.5 years from cohort entry	Post-diagnostic alcohol [quintile 5 (med 15 % kcal) vs. quintile 1 (med 0 % kcal)]	Pre + post	1.27 (0.76, 2.14) *P* trend = 0.50	Age, state of residence, menopausal status, smoking, tumor stage, history of HRT use, interval between diagnosis and diet assessment, energy intake, treatment, BMI, physical activity

BC breast cancer, *BMI* body mass index, *CI* confidence interval, *ERPR* estrogen receptor/progesterone receptor, *FFQ* food frequency questionnaire, *HR* hazard ratio, *HRT* hormone replacement therapy, *pre* premenopausal, *post* postmenopausal, *Q* questionnaire, *RER* relative excess risk within 10 years of diagnosis

Only a limited number of studies investigated the association of alcohol consumption with breast cancer recurrence. In line with our results, three other studies showed no association with pre-diagnostic [9, 27] and post-diagnostic [23] alcohol consumption. Further, one study reported an increased risk with pre-diagnostic beer consumption in premenopausal but not in postmenopausal women [12], and two studies found an increased risk with pre-diagnostic [21] and post-diagnostic [17] alcohol consumption.

Strengths of our study are the relatively large sample size, the population-based design, the restriction to postmenopausal women, and the high completeness of follow-up (100 % for mortality and 98 % for recurrence). The FFQ has been previously validated for alcohol consumption and showed a high correlation with 12 24 h dietary recalls ($r = 0.88$) [29, 30]. However, measurement errors in and subsequent misclassification of alcohol consumption cannot be ruled out. Also, potential changes in alcohol consumption after diagnosis, which could have contributed to survival, cannot be accounted for in this analysis. This also implies that we cannot draw any conclusions about whether post-diagnostic alcohol consumption among breast cancer patients influences prognosis. Although we collected and assessed data on many potential confounding factors (i.e., tumor characteristics, therapy, lifestyle factors), we cannot exclude residual or uncontrolled confounding. Further, we had a limited sample size for subgroup analyses and these results must therefore be interpreted with caution.

In conclusion, we observed that alcohol consumption before diagnosis is associated with an increased risk of breast cancer-specific mortality and a non-significantly decreased risk of mortality due to other causes. No association with breast cancer recurrence and overall mortality was found. Due to the limited evidence thus far, further larger studies are needed to confirm these findings, to differentiate between pre- and post-diagnostic alcohol consumption, and to assess whether associations are restricted to specific subgroups of patients.

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Conflict of interest The authors declare that they have no conflict of interest.

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