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Alcohol intake and breast cancer in the European prospective investigation into cancer and nutrition

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Key words: alcohol consumption, breast cancer, prospective study

Abbreviations: BC: breast cancer; BMI: body mass index;; CI: confidence interval; EPIC: European prospective investigation into cancer and nutrition; ER: estrogen receptor; FFQ: food-frequency questionnaire; FFTP: first full-term pregnancy; HER2: human epidermal growth factor receptor; HR: hazard ratio; PR: progesterone receptor

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Alcohol intake has been associated to breast cancer in pre and postmenopausal women; however results are inconclusive regarding tumor hormonal receptor status, and potential modifying factors like age at start drinking. Therefore, we investigated the relation between alcohol intake and the risk of breast cancer using prospective observational data from the European Prospective Investigation into Cancer and Nutrition (EPIC). Up to 334,850 women, aged 35–70 years at baseline, were recruited in ten European countries and followed up an average of 11 years. Alcohol intake at baseline and average lifetime alcohol intake were calculated from country-specific dietary and lifestyle questionnaires. The study outcomes were the Hazard ratios (HR) of developing breast cancer according to hormonal receptor status. During 3,670,439 person-years, 11,576 incident breast cancer cases were diagnosed. Alcohol intake was significantly related to breast cancer risk, for each 10 g/day increase in alcohol intake the HR increased by 4.2% (95% CI: 2.7–5.8%). Taking 0 to 5 g/day as reference, alcohol intake of >5 to 15 g/day was related to a 5.9% increase in breast cancer risk (95% CI: 1–11%). Significant increasing trends were observed between alcohol intake and ER+/PR+, ER−/PR−, HER2− and ER−/PR−HER2− tumors. Breast cancer risk was stronger among women who started drinking prior to first full-time pregnancy. Overall, our results confirm the association between alcohol intake and both hormone receptor positive and hormone receptor negative breast tumors, suggesting that timing of exposure to alcohol drinking may affect the risk. Therefore, women should be advised to control their alcohol consumption.

What's new?

Although it is now established that alcohol consumption increases breast cancer risk, many questions remain. Using a prospective study design with 11,576 incident breast cancer cases across 10 European countries, the authors confirmed the increased risk of alcohol on breast cancer development. They further show that women who started drinking before their first full-term pregnancy have a higher risk than women who started afterwards. These effects were observed in hormone-receptor positive and –negative tumors pointing to non-hormonal pathways that need to be further investigated.

A consistent association has been observed between alcohol intake and breast cancer (BC) among both pre and postmenopausal women,[1] with a linear dose-response increase ranging from 2%[2] to 12%[3] for each additional drink per day (equivalent to about 10 g/day). While the association is firmly established, some questions such as the association with specific tumor subtypes, the impact of the age at start drinking and a potential window of susceptibility, remain unanswered. Mechanistic evidences show that ethanol stimulates both cell proliferation and estrogen receptor (ER) signaling in the mammary gland.[4–6] Most epidemiological studies report an impact of ethanol on ER+ tumors.[7] However a recent meta-analysis showed an increased risk in both hormone receptor positive and negative tumors.[8] The consumption of alcoholic beverages may interact with other BC risk factors such as hormonal status or first full-term pregnancy (FFTP),[9,10]and thus differentially modulate breast cancer risk over a woman's lifetime.[11] Recent studies report that low to moderate alcohol intake between menarche and first pregnancy is associated with BC risk.[12] It is, therefore, important to evaluate the association of alcohol intake and BC phenotypes in light of a potential modulating effect of age at start drinking.

Material and Methods

The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort consists of approximately 370,000 women and 150,000 men, aged 35–69, recruited between 1992 and 1998 in 23 research centers across 10 Western European countries, Denmark (Aarhus and Copenhagen), France, Germany (Heidelberg and Potsdam), Greece, Italy (Florence, Varese, Ragusa, Turin, and Naples), Norway, Spain (Asturias, Granada, Murcia, Navarra, and San Sebastian), Sweden (Malmö and Umeå), the Netherlands (Bilthoven and Utrecht) and the United Kingdom (Cambridge and Oxford). The design and methodology has been published elsewhere.[13] Eligible men and women were invited to participate; those who accepted gave informed consent and compiled questionnaires on diet, lifestyle, and medical history. EPIC recruited 367,993 women, aged 35–70 years. Women with prevalent cancers at any site at recruitment ($n = 19{,}853$) or with missing diagnosis or censoring date ($n = 2{,}892$) were excluded. A total of 3,339 subjects with missing dietary or lifestyle information, and 6,753 women in the top and bottom 1% of the ratio of energy intake to estimated energy requirement, calculated from age, sex, body weight and height, were excluded from the analysis. In addition, 217 nonfirst breast cancer cases were excluded. Thus, the analysis was performed in 334,850 EPIC women with complete exposure information. Within this group, 11,576 women with invasive breast cancer (including 1,227 carcinoma *in situ*) were identified after a median follow-up of 11.0 years. Information on lifetime alcohol consumption was missing for Sweden, Norway, Naples and Bilthoven, 24.1% were then excluded from the subanalyses on lifetime alcohol intake. The study was approved by IARC ethical committee and the local ethical committees of the participating centers.

Dietary assessment, lifestyle and alcohol consumption

Dietary and lifestyle questionnaires were completed by participants at enrolment when anthropometric measurements were taken.[13] Past-year physical activity (PA) in occupational and recreational domains was assessed at baseline with a self-administered questionnaire. For occupational activity, both employment status as well as the level of physical activity done during work was recorded as: nonworker, sedentary, standing, manual, heavy manual and unknown (for which duration and frequencies were not recorded). Recreational time physical activity included walking, cycling and sport activities. The duration and frequency of recreational activity were multiplied by the intensity assigned by metabolic equivalent values (METs) for the different activities. A total PA index, the "Cambridge PA Index" was estimated by crosstabulating occupational with recreational PA. This index is based on occupational, cycling and sport activities.

Information on alcohol use at the time of enrolment into the study was based on a dietary assessment of usual consumption of alcoholic beverages and types of alcoholic beverage (*i.e.,* wine, beer, spirits and liquors) during the past 12 months. In each country, intake was calculated based on the estimated average glass volume and ethanol content for each type of alcoholic beverage, using information collected in highly standardized 24-hr dietary recalls from a subset of the cohort.[14] Information on past alcohol consumption (available for 75.9% of participants) was assessed as glasses of different beverages consumed per week at 20, 30, 40 and 50 years of age. Average lifetime alcohol intake was determined as a weighted average of intake at different ages, with weights equal to the time of individual exposure to alcohol at different ages. To determine which women had started drinking prior to FFTP, we used information on alcohol consumption at different ages and the age of FFTP reported by the women in the questionnaire.

Anthropometric measurements

Weight and height were measured at baseline, while the subjects were not wearing shoes, to the nearest 0.1 kg, or to the nearest 0.1, 0.5 or 1.0 cm, depending on the center.[15] In France, Norway and Oxford, height and weight were self-reported on a questionnaire. The procedures used to account for procedural differences between centers in the collection of anthropometric measurements are described elsewhere.[16]

Perspective ascertainment of breast cancer cases, coding of receptor status and determination of menopausal status

Incident BC cases were identified through population cancer registries (Denmark, Italy, the Netherlands, Norway, Spain, Sweden and United Kingdom) or by active follow-up (France, Germany, Naples and Greece). The active follow-up procedure used a combination of methods, including health insurance records, cancer and pathology registries and contacts

with participants and their next-of-kin. Subjects were followed up from study entry and until cancer diagnosis (except for nonmelanoma skin cancer cases), death and emigration or until the end of the follow-up period, whichever occurred first. The end of follow-up period was: December 2004 (Asturias), December 2006 (Florence, Varese, Ragusa, Granada and San Sebastian), December 2007 (Murcia, Navarra, Oxford, Bilthoven, Utrecht and Denmark), June 2008 (Cambridge), December 2008 (Turin, Malmo, Umea and Norway). For study centers with active follow-up, the last follow-up contact was: December 2006 for France, December 2009 for Greece, June 2010 for Heidelberg, December 2008 for Potsdam and December 2006 for Naples. Cancer incidence data were classified according to the International Classification of Diseases for Oncology, Second Revision (ICDO-2).

Information on tumor receptor status, on the available laboratory methods and on quantification descriptions used to determine receptor status, were collected by 20 centers. Information on ER, progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) was provided by each center based on pathology reports. To standardize the quantification of receptor status among the EPIC centers, the following criteria for a positive receptor status were used: $\geq$10% cells stained, any "plus-system" description, $\geq$20 fmol/mg, an Allred score of $\geq$3, an IRS $\geq$2 or an H-score $\geq$10.[17–21]

Women were considered as premenopausal when reporting regular menses over the past 12 months, or when aged $<$46 years at recruitment. Women were considered as postmenopausal when not reporting any menses over the past 12 months, or having received bilateral ovariectomy. Women with missing or incomplete questionnaire data or with previous hysterectomy, were considered postmenopausal only if older than 55 years of age. Women were considered with unknown menopausal status when aged between 46 and 55 years and had missing or incomplete questionnaire data, or reported previous hysterectomy (without ovariectomy).[22,23]

Statistical analysis

Cox proportional hazards regression models were used to quantify the association between alcohol consumption and breast cancer risk. Age was the primary time variable and the Breslow method was adopted for handling ties.[24] Time at entry was age at recruitment; time at exit was age at cancer diagnosis, death, loss to follow-up, or end of follow-up, whichever came first. Models were stratified by center to control for differences in questionnaire design, follow-up procedures and other center effects. Further stratification by age at recruitment (1-year categories) was used. Systematic adjustments were made for menopausal status (dichotomized as postmenopausal or women that underwent an ovariectomy *vs.* other), weight and height (all continuous), smoking (never, former, and current), educational attainment (five categories of schooling) as a proxy variable for socioeconomic status, physical activity (inactive, moderately inactive, moderately active, active). In addition, the following variables were included in the models: age at menarche ($\leq$12, 12–14, $>$14 years), age at birth of first child (nulliparous, $\leq$21, 21–30, $>$30 years), and age at menopause ($\leq$50, $>$50 years), ever use of contraceptive pill and ever use of replacement hormones, energy intake without alcohol consumption and adjustment for interaction "menopause, weight."

Alcohol consumption was modeled as both continuous and categorical variable (none, 0.1–5, 5.1–15, 15.1–30, $>$30 g/day). Both baseline consumption and lifetime consumption were studied. Correlation between both estimations was high ($r = 0.80$). *P*-trend values were obtained by modeling a score variable (from 1 to 5) category-specific level of alcohol at baseline. In addition, the shape of the dose-response curve between alcohol consumption and breast cancer risk was evaluated with fractional polynomials of order two,[25] using 3 g/day as reference value and after exclusion of former consumers at baseline. Nonlinearity was tested comparing the difference in log-likelihood of a model with fractional polynomials with a model with a linear term only to a chi-square distribution with three degrees of freedom.[25] For all models, the proportional hazards assumption was satisfied, evaluated *via* inclusion into the disease model of interaction terms between exposure and attained age (data not shown). Statistical heterogeneity of associations across countries or receptor status, was based on a χ^2 statistics, computed comparing country-specific coefficients to an overall coefficient. Stratified analyses were conducted according to the time at start drinking (prior of after FFTP) and interaction term was tested using alcohol intake as continuous variable in multivariate models. Models were run with the exclusion of the first 2 years of follow-up, but the results did not differ from those including the entire cohort (data not shown).

Statistical tests were two sided, and *p*-values $<$0.05 were considered significant. All analyses were performed using SAS version 9.2 (SAS Institute, 1999) and STATA (Stata Statistical Software: Release 12 (2011) StataCorp.,College Station, TX: StataCorp LP).

Results

During an average of 11.0 years of follow-up (3,670,43940 person-years) of 334,850 study participants, the EPIC study documented 11,576 incident BC cases (e-Table 1). The overall percentage of women drinking over 15 g/day at baseline was 16.3% (e-Table 1).

The mean age at recruitment was 50.8 years, and the mean age at BC diagnosis was 59.4 years. Table 1 presents the baseline alcohol intake according to the distribution of major baseline demographic and lifestyle characteristics. At baseline, 35.2% of women were premenopausal and 43.1% postmenopausal (the menopausal status of 18.8% of women was not defined, and 2.9% reported bilateral ovariectomy; Table 1). No drinkers at baseline were less likely to ever have used exogenous hormones and less likely to have ever smoked, were more moderately active and attained less education at baseline than drinkers at baseline (Table 1).

Table 1. Demographic and lifestyle characteristics according to breast cancer status and alcohol intake at baseline

Demographic and lifestyle characteristics[1]	Breast cancer cases	Noncases	Average daily alcohol intake (g/day)				
			0	0.1–5	5.1–15	15.1–30	>30
Participants (*N*)	11,576	323,274	54,907	135,599	89,694	35,460	19,190
Age at recruitment (years) (mean, SD)	52.2 (8.8)	50.8 (10.2)	52.2 (9.0)	50.9 (9.8)	50.1 (9.5)	50.2 (9.0)	50.2 (9.0)
Breast cancer cases (*N*, %)	11,576	—	1,626 (2.96)	4,280 (3.16)	3,261 (3.64)	1,475 (4.16)	934 (4.87)
Receptor status (*N*, %)							
ER+/PR+	3,653 (31.6)	—	527 (0.98)	1,367 (1.03)	970 (1.11)	472 (1.37)	317 (1.71)
ER+/PR−	1,133 (9.8)	—	177 (0.33)	404 (0.31)	303 (0.35)	162 (0.47)	87 (0.42)
ER−/PR−	1,050 (9.1)	—	131 (0.25)	441 (0.33)	252 (0.29)	132 (0.39)	94 (0.51)
HER−	1,764 (75.6)	—	246 (0.46)	662 (0.50)	457 (0.53)	238 (0.70)	161 (0.87)
HER+	570 (24.4)	—	88 (0.16)	231 (0.18)	132 (0.15)	81 (0.24)	38 (0.21)
ER−/PR−/HER−	226 (2.0)	—	25 (0.05)	84 (0.06)	62 (0.07)	29 (0.09)	26 (0.14)
Menopausal status (%)							
Premenopausal	24.4	35.2	31.4	37.2	35.5	32.5	29.1
Perimenopausal	22.0	18.8	17.3	18.8	19.2	20.3	20.6
Postmenopausal	50.7	43.1	47.3	41.4	42.7	44.5	47.1
Surgical postmenopausal	2.8	2.9	4.0	2.6	2.6	2.7	3.2
Reproductive factors							
Age at menarche (years) (mean, SD)	12.95 (1.51)	13.01 (1.75)	13.03 (1.57)	12.98 (1.68)	13.01 (1.65)	13.02 (1.55)	12.99 (1.56)
Age at menopause (years) (mean, SD)[2]	49.52 (4.72)	49.03 (5.85)	48.80 (4.96)	49.09 (5.29)	49.20 (5.27)	49.17 (4.89)	49.07 (4.91)
Nulliparous (%)	13.7	15.2	10.8	14.5	17.3	17.2	18.7
N of full-term pregnancies (mean, SD, range)	1.90 (1.17) (0–9)	1.99 (1.37) (0–17)	2.05 (1.21) (0–17)	2.01 (1.30) (0–14)	1.94 (1.28) (0–13)	1.90 (1.20) (0–12)	1.86 (1.20) (0–11)
Ever breastfed (%)	71.7	72.2	75.3	73.4	71.1	68.8	67.1
Exogenous hormone use (%)							
Ever-used HRT[2]	54.1	42.2	28.6	42.4	48.0	48.8	50.9
Ever-used OC	58.8	58.7	40.7	58.5	65.2	65.0	68.9
Duration of OC use	6.56 (6.95)	6.48 (9.15)	6.11 (7.08)	6.32 (8.18)	6.66 (8.06)	6.82 (7.27)	7.23 (7.21)
Anthropometric factors							
Height (cm) (mean, SD)	161.62 (5.89)	161.08 (6.82)	160.48 (6.06)	160.94 (6.58)	161.42 (6.39)	161.70 (6.02)	162.02 (6.03)
Weight (kg) (mean, SD)	66.20 (11.22)	65.70 (13.01)	66.60 (11.57)	65.96 (12.56)	64.99 (12.19)	64.88 (11.49)	65.38 (11.51)

Table 1. Demographic and lifestyle characteristics according to breast cancer status and alcohol intake at baseline (Continued)

Demographic and lifestyle characteristics[1]	Breast cancer cases	Noncases	Average daily alcohol intake (g/day)				
			0	0.1–5	5.1–15	15.1–30	>30
Waist-to-hip ratio (mean, SD)	0.80 (0.06)	0.80 (0.08)	0.80 (0.07)	0.80 (0.07)	0.79 (0.07)	0.80 (0.07)	0.80 (0.07)
BMI (mean, SD)[3]	25.40 (4.08)	25.37 (4.73)	25.91 (4.20)	25.50 (4.56)	25.00 (4.42)	24.87 (4.17)	24.97 (4.18)
Obese (BMI $\geq$30 kg/m^2) (%)	11.4	12.7	22.3	13.1	8.9	7.8	8.1
Smoking status (%)							
Never smoker	56.0	57.0	67.2	58.8	54.8	49.5	39.2
Former smoker	25.0	23.0	14.8	22.3	26.3	27.5	29.3
Current smoker	19.0	20.0	18.1	19.0	18.9	23.0	31.5
Total physical activity (%)							
Inactive	17.8	16.0	9.0	15.5	20.0	20.1	22.1
Moderately inactive	41.3	37.1	32.3	37.3	39.0	39.7	41.8
Moderately active	34.4	39.1	51.4	38.8	33.6	33.2	29.5
Active	6.6	7.8	7.3	8.4	7.4	7.0	6.6
Highest education level (%)							
None or primary school	26.1	29.7	52.5	28.8	22.1	21.8	17.4
Secondary/technical/ professional school	48.6	46.8	34.7	50.1	49.2	47.1	49.5
University	25.3	23.5	12.9	21.2	28.7	31.1	33.1
Dietary intake (mean, SD)							
Total energy intake (kcal/day)	1,976 (512)	1962 (594)	1,868 (522)	1,926 (567)	1,993 (550)	2,086 (519)	2206 (520)
Total energy without alcohol (kcal/day)	1,918 (505)	1909 (586)	1,868 (521)	1,913 (566)	1,928 (549)	1,939 (518)	1902 (519)
Total dietary fiber (g/day)	22.1 (7.1)	22.1 (8.2)	22.1 (7.3)	22.4 (8.0)	22.2 (7.7)	21.6 (7.3)	20.6 (7.3)

Note: Unknown values were excluded from the calculations. HRT: hormone replacement therapy; OC: oral contraceptives; SD: standard deviation; BMI: body mass index; All p values $<$0.0001, except for age at menarche (not significant); Trend test for continuous variables; Cochran–Armitage test for trend for categorical variables and global χ^2 test.
Missing data in the total cohort were: 3.2% for age at menarche; 4.6% for parity; 2.5% for oral contraceptive; 2.3% for smoking status; 15.3% for physical activity; 7.7% for diabetes; 14.4% for hypertension; 28.4% for waist-to-hip ratio; 3.9% for education level; in postmenopausal women: 5.3% for HRT and 24.3% for age at menopause.
[1]Continuous variables are presented as means and standard deviations (SD), adjusted by age at recruitment and center (except age, which is adjusted by center only).
[2]Among postmenopausal women only.
[3]Weight (kg)/height (m)^2.

Alcohol intake showed a significant positive dose-response relation with BC ($p < 0.0001$, Table 2). BC hazard ratio (HR) was increased by 6% (95% CI: 1–11%), 12% (95% CI: 6–19%) and 25% (95% CI: 17–35%) for the consumption of 5–15 g/day, 15–30 g/day and >30 g/day, respectively, compared to the 0.1–5 g/day category of intake. For each additional 10 g/day the HR increased by 4% (95% CI: 3–6%). Figure 1 shows the relation between alcohol intake and BC risk, fractional polynomial of order 2 using 3 g/day as reference. A statistically significant relation was observed ($p < 0.0001$), while the test for nonlinearity was compatible with a linear trend ($p = 0.100$).

When the associations were evaluated according to hormone receptor status, for each additional 10 g/day the HR significantly increased by 4% (95% CI: 1–6%) in ER+/PR+, by 5% (95% CI: 0–10%) in ER−/PR−, by 5% (95% CI: 2–9%) in HER2− and by 12% (95% CI: 3–23%) in ER−/PR−/HER2− breast tumors (Table 2). Test for heterogeneity between alcohol consumption and hormone receptor status was not significant ($p = 0.26$). No significant association was observed for ER+/PR−, ER−/PR+ and HER2+. When using lifetime alcohol intake slightly lower estimates were observed (see eTable2). Similar results were observed for pre and postmenopausal women, although, given the smaller sample size among premenopausal women, statistically significance was reached only in the overall analysis. There was no heterogeneity in results between pre and postmenopausal women (p interaction = 0.48). No interaction was observed with body mass index (BMI) or use of exogenous hormones either. Since statistical adjustment for smoking can be difficult, analyses in nonsmokers at baseline were carried out and results remained virtually similar (data not shown).

Age at start drinking according to FFTP, was positively related to BC risk among women who start drinking prior to FFTP. Stronger associations were observed for ER−, PR−, ER−/PR− and ER−/PR−/HER2− tumors (Table 3). In a multivariable model, an increase of 10 g of alcohol/day was related to an 8% (95% CI: 2–14%) increased risk of ER− tumors in women who start drinking prior to FFTP, while no association could be detected among women who start drinking after FFTP (p for interaction = 0.047), and a 9% (95% CI: 2–16%) increased risk of ER−/PR− tumors in women who start drinking prior to FFTP (p for interaction = 0.10). When using lifetime alcohol intake slightly lower estimates were observed (see eTable3). We were not able to evaluate the amount of alcohol consumed prior to FFTP.

BC hazard ratios, with data stratified according to the median period between menarche and FFTP (13 years) among women who start drinking prior to FFTP, was of 5.6% (95% CI: 2.6–8.8%) among women with longer median period and of 2.6% (95% CI: 1.0–6.2%) among their counterpart. These data suggest that a longer time between menarche and FFTP may modulate BC risk among women who start drinking prior to FFTP. However, the test for interaction was not significant ($p = 0.23$) (data not shown).

Discussion

In this prospective study of 334,850 women and 11,576 incident BC cases, an increased intake of 10 g of alcohol/day was related to a 4.2% increased BC risk (95% CI: 2.7–5.8%). This was observed for both ER+/PR+ and ER−/PR− tumor subtypes with the largest risk observed for triple negative tumors (ER−/PR−/HER2−). No interaction was observed with BMI and use of hormones. Women who started drinking before their FFTP appeared to be at higher risk for BC than women who started drinking after their FFTP.

Most studies published to date have reported an increased BC risk with increasing alcohol intake.[1] A previous analysis within the EPIC cohort on a smaller number of BC cases ($n = 4,285$), reported a 3% increase in BC incidence for each additional 10 g/day of alcohol.[26] Our results, based on [mt]11,000 incident BC cases, confirm our previous results and suggest a slightly stronger association. We did not observe strong differences in estimates across tumor receptor status (triple negative tumors showed the strongest risk, however, the sample size in this category was small). Although most of prior studies have reported a higher risk for ER+ and/or PR+ tumors compared to ER− and/or PR− tumors in particular, for the highest *versus* the lowest alcohol intake group,[9,27–33] an increased risk for hormone receptor negative tumors was also reported.[8,34,35] This inconsistency of results across studies might be partially due to the smaller number of BC cases with negative hormone receptor status. The very large number of both hormone receptor positive and hormone receptor negative tumors in our study increased our power on the association. Nonhormonal pathways such as DNA damage are likely to be involved in the incidence of receptor negative tumors.[8] The effect of alcohol appears linear, suggesting that there is no safe level of intake for BC risk.

A limited number of studies have investigated the presence of a window of susceptibility to alcohol carcinogenesis in the breast. Some epidemiological studies suggest that drinking alcohol during adolescence or early adulthood has a strong impact on BC risk.[36] Results from the Nurses' Health Study II show that low to moderate alcohol intake during adolescence and early adulthood is dose-dependently associated with an increased risk of proliferative benign breast disease, which may lead to invasive BC later in life.[37] More recent results support the effect of drinking alcohol between menarche and FFTP on BC risk (RR = 1.11 per 10 g/day intake; 95% CI: 1.00–1.23) and on proliferative benign breast disease (RR = 1.16 per 10 g/day intake; 95% CI: 1–1.02).[11] In addition, the association between drinking before FFTP and development of breast neoplasia appeared to be stronger with longer menarche to first pregnancy intervals. These results are consistent with the hypothesis that alcohol carcinogens may preferentially act during mammary development.[38] We observed a stronger effect of alcohol intake prior to FFTP, with a significant interaction for receptor negative tumors. Our findings suggest that starting drinking before FFTP might be a more sensitive period, even if we cannot exclude the

Table 2. Breast cancer risk by hormonal subtypes according to alcohol consumption at baseline

N cases/ person-years	Average daily alcohol intake at baseline (g/day)					*p* values (trend)[2]	HR (95% CI) per 10 g/day	*p*-value[3]
	0[1]	0.1–5	5.1–15	15.1–30	>30			
All cases	1,626/605,217	4,280/1,488,055	3,261/983,711	1,475/387,280	934/206,177		11,576/3,670,440	
	1.04 (0.98–1.10)	1.00 (ref)	1.06 (1.01–1.11)	1.12 (1.06–1.19)	1.25 (1.17–1.35)	<.001	1.04 (1.03–1.06)	<.001
ER+/PR+	527/598,625	1,367/1,470,607	970/969,575	472/381,199	317/202,569		3,653/3,622,575	
	1.06 (0.95–1.18)	1.00 (ref)	1.09 (1.00–1.18)	1.11 (0.99–1.23)	1.30 (1.15–1.48)	0.001	1.04 (1.01–1.06)	0.003
ER+/PR−	177/596,367	404/1,464,086	303/965,046	162/379,089	87/200,949		1,133/3,605,537	
	1.18 (0.98–1.42)	1.00 (ref)	1.13 (0.97–1.31)	1.22 (1.01–1.47)	1.13 (0.88–1.43)	0.41	1.04 (0.99–1.09)	0.09
	27/595,288	88/1,461,768	53/963,248	35/378,194	14/200,458		217/3,598,956	
ER−/PR+	0.93 (0.59–1.45)	1.00 (ref)	1.06 (0.74–1.51)	1.37 (0.90–2.07)	1.03 (0.57–1.86)	0.26	1.05 (0.95–1.17)	0.34
ER−/PR−	131/596,019	441/1,464,103	252/964,537	132/378,867	94/200,964		1,050/3,604,490	
	0.89 (0.73–1.10)	1.00 (ref)	0.92 (0.78–1.08)	1.03 (0.84–1.26)	1.28 (1.01–1.61)	0.06	1.05 (1.00–1.10)	0.03
HER2−	246/597,134	662/1,466,665	457/966,684	238/379,950	161/201,697		1,764/3,612,130	
	1.11 (0.95–1.29)	1.00 (ref)	1.09 (0.96–1.23)	1.14 (0.98–1.34)	1.41 (1.17–1.68)	0.007	1.05 (1.02–1.09)	0.004
HER2+	88/595,882	231/1,463,254	132/964,054	81/378,655	38/200,712		570/3,602,557	
	1.14 (0.87–1.49)	1.00 (ref)	0.89 (0.72–1.12)	1.18 (0.90–1.54)	0.97 (0.68–1.39)	0.83	0.98 (0.92–1.06)	0.68
ER−/PR−/HER2−	25/595,363	84/1,461,973	62/963,514	29/378,261	26/200,594		226/3,599,705	
	1.09 (0.68–1.74)	1.00 (ref)	1.18 (0.84–1.66)	1.20 (0.77–1.86)	1.97 (1.23–3.16)	0.03	1.12 (1.03–1.23)	0.01

[1]Includes both never and former drinkers.
[2]Test for a trend in HRs by categories of alcohol intake were computed by assigning consecutive scores (1, 2, 3, 4, 5) to the categories.
[3]Test of trend for alcohol intake continuous.
Note: Stratified by center and age at recruitment (1-year interval), and adjusted for menopausal status (pre/peri *vs*.postmenopausal women), oral contraceptive use (yes/no/missing), hormone replacement therapy use (yes/no/missing), height (continuous), weight (continuous), interaction menopause and weight, smoking status (never, ex, current and missing), educational level (primary, no schooling, technical or professional or secondary, longer education, missing), physical activity (inactive, moderately active, moderately inactive, active and unknown), age at first menses (≤ 12, 13–14, 15+, missing), age at first full term pregnancy (nulliparous, ≤21, 22–30, >30, missing), age at menopause (<50, ≥50, missing) and energy intake without alcohol intake.

possibility that the stronger association between alcohol intake and BC in women who started drinking before FFTP might be the consequence of longer duration and amount of drinking.

In our study, demographic characteristic, lifestyle and alcohol intake of women with available hormone receptor status could have differed from women with unavailable status. However, we did not observe such differences among cases with known and unknown ER status and sub analyses of these groups led to similar overall results. Similar strategies were adopted to inspect BC cases with and without available information on PR and HER2 status. In addition, a bias due to the influence of preclinical disease on alcohol intake is unlikely, given that similar results were obtained after exclusion of samples from the first 2 years of follow-up. However, we conducted multiple comparison analyses based on hormonal status and chance findings cannot be excluded.

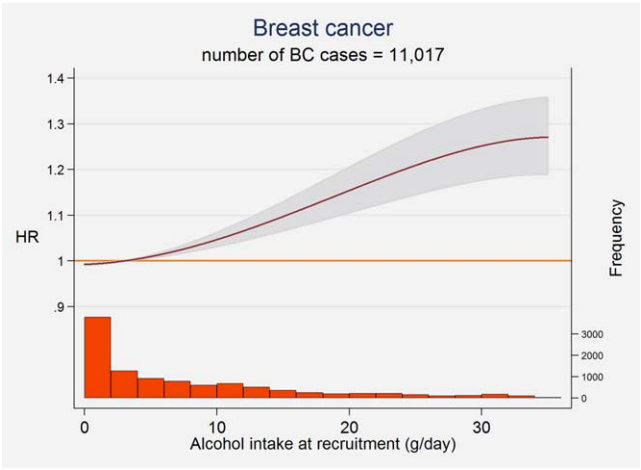

Figure 1. – Dose-response curve of BC risk with alcohol intake at recruitment. The dose-response curve is displayed up to 35 g/day, corresponding to the 99th percentile of the alcohol intake distribution. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Major strengths of our study include the prospective and population based design, the large sample size, detailed information on alcohol intake at different period of life, age at start drinking and types of beverage, data on hormone receptor status, excellent follow-up and large number of cases, which provided us with good power for subgroups analyses. Information on alcohol intake was self-reported and potential misclassification may have underestimated the effect of alcohol intake. Still, assessment of alcohol intake has been shown to be reliable in the EPIC cohort[39,40] and the prospective setting of our study minimizes recall bias on age at start drinking and lifetime alcohol intake. We were unable to determine the amount of alcohol consumed before FTTP and while consumption both at baseline and over lifetime was

Table 3. Breast cancer risk among parous women with alcohol intake at baseline by age at start drinking before/after first full-term pregnancy

		Average daily alcohol intake at baseline			
	Age at start drinking	*N* cases/person-years	HR (95% CI) for 10 g/day	*p*-value	Interaction *p*-value[1]
All cases	Before FFTP	4,104/1,216,204	1.04 (1.02–1.06)	≤.001	0.14
	After FFTP	2,747/793,546	1.02 (0.99–1.05)	0.26	
ER+	Before FFTP	2,221/1,205,111	1.04 (1.01–1.07)	0.005	0.16
	After FFTP	1,460/786,197	1.02 (0.98–1.07)	0.32	
PR+	Before FFTP	1,375/1,199,890	1.04 (0.99–1.07)	0.06	0.40
	After FFTP	987/783,211	1.01 (0.96–1.07)	0.60	
ER+/PR+	Before FFTP	1,286/1,199,505	1.04 (1.00–1.08)	0.04	0.39
	After FFTP	924/782,918	1.01 (0.96–1.07)	0.65	
ER−	Before FFTP	552/1,194,218	1.08 (1.02–1.14)	0.009	0.05
	After FFTP	371/778,873	0.97 (0.88–1.06)	0.49	
PR−	Before FFTP	776/1,196,034	1.06 (1.02–1.11)	0.009	0.05
	After FFTP	545/780,237	0.98 (0.91–1.06)	0.66	
ER−/PR−	Before FFTP	383/1,193,437	1.09 (1.02–1.16)	0.01	0.10
	After FFTP	261/778,358	0.97 (0.88–1.09)	0.65	
ER−/PR−/HER2−	Before FFTP	99/1,191,822	1.17 (1.04–1.31)	0.007	0.24
	After FFTP	50/777,139	0.97 (0.75–1.24)	0.78	

[1]Age start prior to first full-term pregnancy (FFTP), was defined based on the information on 'Age at start drinking alcohol' and 'Age at first full-term pregnancy'. Results of stratified analyses by age start prior/after FFTP are displayed. Significance of interaction term was tested including in a multivariate model using alcohol as continuous variable and age start prior/after FFTP as categorical variable.
Note: Adjustments are the same as in Table 2. The statistical significance of interactions was assessed using likelihood ratio tests based on the models with and without the interaction terms formed by the product of age at start drinking alcohol before or after first pregnancy and the value of alcohol intake at recruitment.

associated with a stronger adverse effect among women who start drinking prior to FFTP than among their counterpart, our results should be interpreted with caution.

In conclusion, findings from the EPIC cohort confirm the carcinogenic effect of alcohol intake on both receptor positive and negative breast tumors. Starting to drink prior to FFTP appears to have a larger adverse effect than after FTTP. No interaction with body fatness and use of hormone was observed. Alcohol has been shown to act through the estrogen pathway, however our results suggest that nonhormonal pathways are likely to act and need to be further investigated.

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