

Fiber intake modulates the association of alcohol intake with breast cancer

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Novelty and impact

Alcohol intake increases the risk of breast cancer, while fiber intake has a protective effect. In this prospective study analysis of women enrolled in the European Prospective Investigation into Cancer and Nutrition, a significant interaction was observed between alcohol and fiber intakes,

women with high alcohol intake and low fiber intake had the highest risk for breast cancer. This result supports a modulating effect of fiber intake on the adverse effect of alcohol intake.

Abstract

Alcohol intake has been related to an increased risk of breast cancer (BC) while dietary fiber intake has been inversely associated to BC risk. A beneficial effect of fibers on ethanol carcinogenesis through their impact on estrogen levels is still controversial. We investigated the role of dietary fiber as a modifying factor of the association of alcohol and breast cancer using data from the European Prospective Investigation into Cancer and Nutrition (EPIC). This study included 334,850 women aged 35-70 years at baseline enrolled in the ten countries of the EPIC study and followed up for 11.0 years on average. Information on fiber and alcohol intake at baseline and average lifetime alcohol intake were calculated from country-specific dietary and lifestyle questionnaires. Hazard ratios (HR) of developing invasive breast cancer according to different levels of alcohol and fiber intake were computed. During 3,670,439 person-years, 11,576 incident breast cancer cases were diagnosed. For subjects with low intake of fiber (<18.5 g/day), the risk of BC per 10g/day of alcohol intake was 1.06 (1.03-1.08) while among subjects with high intake of fiber (>24.2 g/day) the risk of BC was 1.02 (0.99-1.05) (test for interaction $p=0.011$). This modulating effect was stronger for fiber from vegetables. Our results suggest that fiber intake may modulate the positive association of alcohol intake and BC.

Introduction

A consistent association has been observed between alcohol intake and breast cancer (BC) among pre- and postmenopausal women ¹. We recently reported in the EPIC cohort that for each 10g/day increase in alcohol intake the HR increased by 4.2% (95% CI, 2.7% -5.8%) ². Taking 0 to 5g/day as a reference, alcohol intake of >5 to 15 g/day was related to a 5.9% increase of breast cancer risk (95% CI, 1% -11%). A significant increasing trend was observed between alcohol intake for different types of tumor receptors status (ER+/PR+, ER-/PR-, HER2- and ER-/PR-/HER2-) tumors. While it is widely accepted that dietary fiber intake inversely correlates to BC risk, ³ a beneficial effect on ethanol carcinogenesis through their impact on estrogen levels, ⁴ is still controversial ⁵. It is therefore important to evaluate the association of alcohol intake and BC phenotypes and the potential modulating role of fiber intake.

Material and Methods

EPIC is a large prospective cohort study conducted in 23 centers in Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, the Netherlands, and the United Kingdom. EPIC recruited a total of 367,993 women, aged 35-70 years who gave informed consent and completed questionnaires on diet, lifestyle, and medical history ⁶. Women with prevalent cancers other than non-melanoma skin cancer at recruitment (n= 19,853), missing diagnosis or censoring date (n= 2,892), missing dietary or lifestyle information (n= 3,339), in the top and bottom 1% of the ratio of energy intake to estimated energy requirement, calculated from age, sex, body weight and height (n= 6,753) were excluded from the analysis. Only first primary BC cases were retained in the analysis (217 non-primary BCs excluded). The EPIC study was approved by the IARC Ethics Committee and by the local ethics committees of the participating centers.

Dietary assessment and alcohol intake

For the present study, intake of alcoholic beverages at baseline was calculated from dietary questionnaires which have been previously validated for alcohol intake ^{6, 7}. Subjects reported the number of standard glasses of beer, cider, wine, sweet liquor, distilled spirits or fortified wines consumed per day/week during the 12 months prior to recruitment. 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 ^{8, 9}. Among 76% of the participants with available information, average lifetime alcohol intake was determined ². Estimation of dietary fiber intake has been described previously ¹⁰. In brief, dietary fiber was defined by the AOAC (Association of Official Agricultural Chemists) gravimetric method for Total Dietary Fiber, ¹¹ and includes soluble and insoluble forms (including lignin) of non-starch polysaccharides and resistant starch ^{10, 11}. The dietary fiber variable used in this work was obtained using the EPIC Nutrient Data Base (ENDB) in which the dietary fiber composition of foods was harmonized across the participating European countries to take into account the different analytical methods used ¹².

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 ¹³. 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 ^{14, 15}.

Outcome assessment

Incident BC cases were identified through population cancer registries (Denmark, Italy (all centers but Naples), the Netherlands, Norway, Spain, Sweden and United Kingdom) or by a combination of methods including health insurance records, cancer and pathology registries and active follow-up (France, Germany, Naples and Greece). Subjects were followed up from study entry and until cancer diagnosis (except for non-melanoma skin cancer cases), death, emigration or until the end of the follow-up period (varying from 2004 and 2010 depending on the center), whichever occurred first. Information on ER, Progesterone Receptor (PR) and Human Epidermal Growth Factor Receptor 2 (HER2) was provided by each center using the same techniques to collect incident BC cases.

Menopausal status was determined as previously reported in the EPIC study. ^{16, 17}.

Statistical analysis

Cox proportional hazards regression models were used to quantify the association between alcohol intake and the risk of BC. Age was the primary time variable, and the Breslow method was adopted for handling ties ¹⁸. Analyses were conducted for all women as well as by receptors status. Systematic adjustments were made for menopausal status, weight, height, smoking status (never, former, smoker and unknown), education, physical activity and energy intake from non-alcohol sources. In addition, the following variables were included in the models: age at menarche, age at birth of first child, age at menopause, whether the contraceptive pill was ever used, and whether menopausal hormone therapy was ever used. Analyses were stratified by study center to control for differences in questionnaires, follow-up procedures and other center-specific effects. To further control for the possible confounding effect of age, models were stratified by age at recruitment in 1-year categories ¹⁹.

Alcohol intake (baseline as well as averaged intake over lifetime) was modelled using continuous and categorical (<5, 5-15, >15 g/day) variables and the association was expressed for an increase in 10g of alcohol intake per day ². Dietary fiber intake was modelled as continuous and categorical (low, medium and high intake according to distribution in the controls) for total fiber intake as well as for fiber sources (vegetables, fruits and cereals). Multivariate hazard ratios for breast cancer according to the combined effects of dietary fibers (g/day) and alcohol (drink/week) were explored. 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 dietary fiber intake (continuous) and the value of alcohol intake at recruitment as well as averaged lifetime intake (continuous). Similar analyses were carried out according to estrogen receptor status. For all models, the proportional hazards assumption was satisfied, and was evaluated via inclusion into the disease model of interaction terms between exposure and attained age (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).

Results

During an average of 11.0 years of follow up (3,670,439 person-years) of 334,850 study participants, the EPIC study documented 11,576 invasive incident BC cases. The mean age at

recruitment was 50.8 years, and the mean age at BC diagnosis was 59.4 years. Among them the distribution was as follows: 35.2% were premenopausal, 43.1% postmenopausal (18.8% of women were unknown and 2.9% reported bilateral ovariectomy). ER, PR and HER2 status was available only in 63%, 52% and 20% of cancer cases, respectively, and were distributed as follows, 80% ER⁺ tumors and 20% ER⁻, 64% PR⁺ tumors and 36% PR⁻, 25% HER2⁺ and 75% HER2⁻.

Table 1 presents the amount of fiber intake and mean intake of alcohol according to tertiles of fiber intake for total fiber, fiber from vegetables, fruits and cereals. The mean alcohol intake in the first tertile (lowest) of total fiber intake was 8.06 grams/day, 7.32 gr/day in the second tertile and 6.76 gr/day in the third (highest) tertile of fiber intake. Regarding specific types of fiber intake, the mean alcohol intake was 8.68 gr/day in the first tertile of fibers from fruit intake, 7.30gr/day in the second tertile and 6.70 gr/day in the third tertile. Alcohol intake was slightly lower among women with the highest total fiber intake ($p<.0001$).and with the highest fibers from fruit intake ($p<.0001$). No significant difference in alcohol intake was observed among tertiles of fiber from vegetables or cereals. (alcohol intake in gr/day within tertiles of fiber intake: 7.26,7.55 and 7.28 gr/day for fiber from vegetables and 7.52 ,7.68,7.39gr/day for fiber from cereals).

Alcohol consumption was significantly related to breast cancer among women with low total fiber intake ($<18.5\text{g/day}$) with an increased risk of 5.7% (95% CI 3.2% to 7.9%) per 10g/alcohol per day (equivalent to 1 drink per day). However, among women with high fiber intake ($>24.2\text{g/day}$) the risk was not significant (1.2% 95% CI -0.6% to 4.9%). We observed a significant interaction between alcohol and fiber intake on breast cancer risk ($p=0.011$). When data were stratified by estrogen receptor status, we observed similar results in ER⁺ and ER⁻ tumors with a significant increased risk of BC with alcohol consumption among women with low fiber intake. The test for interaction between alcohol and fiber intake was marginally significant for ER⁺ tumors ($p=0.10$) and the small number of ER⁻, tumors precluded definite conclusion.

We explored the effect of different sources of fiber and observed that fiber from vegetable sources had the strongest protective effect on overall BC. Among women with low vegetable fiber intake ($<3.2\text{g/day}$) the increased risk of BC per 10g/day of alcohol consumption was 6.3%

(3.7 to 9.0%) while among women with a high intake of fiber (>5.5g/day) the risk was non-significant (2.3% 95% CI -0.2% to 4.8%). A significant interaction between alcohol and fiber intake was observed ($p=0.0033$). For fiber from other sources, no significant protective effect was observed although BC risk was consistently lower among women with high fiber intake from fruits and cereals (Table 2).

Figure 1 presents the HRs associated to categories of alcohol intake and fiber intake (tertiles). Compared to women with low alcohol (<5g/day or 2 dr/week) and high fiber (>24g/day) intakes (as reference category), women with a high alcohol (>15g/day or >10 dr/week) and low fiber (<18.5g/day) intakes had a 35% (95% CI, 23%-48%) increased BC risk. Among women with high alcohol intake and high fiber, the increased risk was 12% (95% CI, 2% -23%; test of heterogeneity $p=0.005$) while among women with low alcohol intake and low fiber the increased risk was 8% (95% CI, 0% -18%). When both alcohol and fiber intakes were considered as continuous variables we observed a significant interaction ($p=0.01$).

Additional analyses using averaged lifetime intake instead of baseline alcohol consumption ($n=9,025$) or restricting cases to those occurring at least 2 years after baseline recruitment ($n=9,916$), provided similar results as presented above.

Discussion

In this prospective study of 334,850 women and 11,576 incident invasive BC cases, fiber intake appeared to modulate the adverse effect of ethanol on BC risk. This effect was most apparent for fiber from vegetables sources.

Our findings are in accordance with a recent result from the SUVIMAX cohort suggesting a modulating effect of fiber intake on the adverse effect of alcohol intake on breast cancer although no significant interaction was observed. However, this study included only a small number of breast cancer cases ($n=158$)²⁰.

Alcohol has been shown to increase sex hormone levels²¹ and a reduction of circulating estrogen and androstenedione has been observed in epidemiological and intervention studies in relation to fiber intake³. Fiber may bind estrogen in the colon thus increasing the fecal excretion of estrogens. In addition, dietary fiber may reduce the hydrolysis of conjugated estrogen resulting in

less reabsorption ³. The modulating effect that we observed for fibers supports both the notion that fiber-rich foods may counteract the enhanced estrogen responsiveness due to alcohol drinking and that different dietary habits may confound the association of alcohol drinking with BC ⁴. However, plausible anti-cancer mechanisms and explanations exist for dietary fibers from different food sources (including an array of phytochemicals such as antioxidants and phytoestrogens, the glycemic/insulinemic control, the substitutive effect of foods associated with high BC risks). It is largely unclear what specific biological mechanisms may underlie observed differences in the associations of fruit, vegetable and cereal fibers with BC in the present analysis. In addition, the biological mechanism underlying the differential associations of risk factors with hormone-receptor positive and negative BC remains to be fully characterized ²²⁻²⁴. So far, epidemiological evidence suggests that factors linked to estrogen metabolism are more strongly related to ER⁺ tumors, while ER⁻ might be more susceptible to non-hormonal factors, including diet ²²⁻²⁴.

In our population 30% of women had fiber intake in accordance with the current recommendation of 25g/day ²⁵. With regards to cancer risk, the lowest level of alcohol intake has been recommended ²⁶. The mean alcohol intake in our population was 9 g/day, 48.5% consumed less than 5 g/day, 32% between 5 and 15 g/day and 19.5% more than 15g/day (excluding the non consumers).

Major strengths of our study include the prospective and population-based design, a large sample size, detailed information on alcohol intake at different periods of life, data on HR status of the breast tumors, excellent follow-up and larger numbers of cases which provided 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 ^{7, 27} and the prospective setting of our study minimizes recall bias on baseline and average lifetime alcohol intake. Residual confounding by misreporting of alcohol intake cannot be ruled out. Women with poor diet with a low fiber intake may report differentially (underreport) alcohol intake leading to a higher RR per 10 g/day of alcohol among women with low fiber intake, therefore overestimating a potential protective effect of fiber. However, the fact that the modulating effect of fiber intake is observed mostly for vegetables sources support a true association. In addition, the multi-centric nature of

the EPIC study made it possible to evaluate this association based on a large variation of dietary exposure, with total fiber ranging between 16 to 27 g/day, depending on the center. Further adjustment of our model for folate intake as marker of healthy diet and life style did not affect our results supporting the protective effect of fiber. Among the main limitations of the study, it should be noted that diet was assessed at recruitment only, no information was available on soluble or insoluble sub-types of dietary fiber, and on cancer histology.

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The results of this study suggest that dietary fiber intake, especially from vegetable sources may modulate the adverse effect of alcohol consumption on the risk of breast cancer. The beneficial effect observed in our study deserves further investigation in future studies to better assess the mechanisms and specific protective effect of sources of fibers on tumor subtypes.

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Table 1. Levels of fiber and alcohol intakes by tertiles of total fiber and fiber from different sources

	Tertiles of total fibers		Tertiles of fibers from vegetables		Tertiles of fibers from fruits		Tertiles of fibers from cereals	
	Total fibers ⁽¹⁾	Alcohol ⁽²⁾	Fibers from vegetables ⁽¹⁾	Alcohol ⁽²⁾	Fibers from fruits ⁽¹⁾	Alcohol ⁽²⁾	Fibers from cereals ⁽¹⁾	Alcohol ⁽²⁾
Low	14.94 (11.18-17.92)	8.06 (0.13-21.61)	2.24 (1.28-3.05)	7.26 (0.11-19.62)	1.78 (0.58-2.76)	8.68 (0.13-23.57)	3.80 (2.11-5.24)	7.52 (0.12-20.38)
Medium	21.23 (19.04-23.50)	7.32 (0.13-19.52)	4.26 (3.44-5.15)	7.55 (0.15-19.94)	4.15 (3.22-5.09)	7.30 (0.14-19.19)	7.14 (5.90-8.51)	7.68 (0.13-20.31)
High	29.72 (24.84-36.35)	6.76 (0.13-18.29)	7.74 (5.72-10.56)	7.28 (0.13-19.62)	8.38 (5.75-12.06)	6.70 (0.12-18.12)	12.17 (9.38-15.95)	7.39 (0.14-19.82)

¹ country-adjusted means and 10th-90th percentile values of fiber intake

² country-adjusted means and 10th-90th percentile values of baseline alcohol intake

Table 2. HR estimates of 10 g/day increase of alcohol intake associated to BC risk by tertiles of total dietary fiber intake and fiber from different sources.

		N cases	Total Fibers ¹	Inter ²	Fibers from vegetables ¹	Inter ²	Fibers from fruits ¹	Inter ²	Fibers from cereals ¹	Inter ²
Fiber cutpoints (g/day)			18.5 - 24.2		3.2 - 5.5		3.0 - 5.4		5.6 - 9.0	
All cases	Low	3855	1.06 (1.03-1.08)	0.011	1.06 (1.04-1.09)	0.003	1.05 (1.02-1.07)	0.13	1.05 (1.03-1.08)	0.19
	Medium	3810	1.04 (1.01-1.07)		1.04 (1.02-1.07)		1.04 (1.02-1.07)		1.05 (1.02-1.07)	
	High	3911	1.02 (0.99-1.05)		1.02 (1.00-1.048)		1.04 (1.01-1.06)		1.03 (1.00-1.05)	
ER-	Low	482	1.06 (1.00-1.13)	0.84	1.08 (1.01-1.16)	0.52	1.02 (0.96-1.09)	0.93	1.05 (0.99-1.12)	0.50
	Medium	458	1.05 (0.98-1.12)		1.05 (0.98-1.12)		1.09 (1.02-1.16)		1.07 (1.00 -1.14)	
	High	498	1.02 (0.95-1.10)		1.03 (0.96-1.09)		1.03 (0.96-1.11)		1.02 (0.95-1.09)	
ER+	Low	1913	1.05 (1.02-1.08)	0.10	1.06 (1.03-1.10)	0.08	1.05 (1.01-1.08)	0.42	1.06 (1.03-1.09)	0.24
	Medium	1921	1.05 (1.01 -1.08)		1.03 (0.99-1.06)		1.04 (1.00 -1.08)		1.04 (1.00-1.07)	
	High	1996	1.03 (0.99-1.07)		1.05 (1.02-1.08)		1.05 (1.01-1.08)		1.03 (1.00-1.07)	

¹Multivariate model 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), hormone replacement therapy use (yes/no), height (continuous), weight (continuous), interaction menopause and weight, smoking status (never, ex, current), educational level (primary/no schooling, technical/professional/secondary, longer education.), physical activity (inactive, moderately active, moderately inactive, active), age at first menses (≤ 12 , 13-14, 15+.), age at first full term pregnancy (nulliparous, ≤ 21 , 22-30, >30 .), age at menopause (<50 , ≥ 50 .) and energy intake without alcohol intake.

²p for interactions was assessed using likelihood ratio tests based on the models with and without the interaction terms of dietary fiber and alcohol intake at recruitment (both in continuous).

