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Alcohol, tobacco, and mammographic density: a population-based study

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ABSTRACT

Mammographic density (MD), or the proportion of the breast with respect to its overall area that is composed of dense tissue, is a strong risk factor for breast cancer. Studies support a positive association of mammographic density and alcohol drinking.

This was a cross-sectional multicenter study based on 3584 women, aged 45 to 68 years, recruited from seven screening centers within the Spanish Breast Cancer Screening Program network. The association between MD, alcohol consumption and tobacco use was evaluated by using ordinal logistic models with random center-specific intercepts.

We found a **weak** positive association between current alcohol intake and higher MD, with current alcohol consumption increasing the odds of high MD by 13% (OR=1.13; 95% CI 0.99-1.28) and high daily grams of alcohol being positively associated with increased MD (p for trend=0.045). There were no statistically significant differences in MD between smokers and non-smokers. Nevertheless, increased number of daily cigarettes and increased number of accumulated lifetime cigarettes were negatively associated with high MD (**p for trend 0.017 and 0.021**). The effect of alcohol on MD was modified by menopausal status and tobacco smoking: whereas alcohol consumption and daily grams of alcohol were positively associated with higher MD in postmenopausal women and in women who were not currently smoking, alcohol consumption had no effect on MD in premenopausal women and current smokers.

Our results support an association between recent alcohol consumption and high MD, characterized by a modest increase in risk at low levels of current consumption and a decrease in risk among heavier drinkers. Our study also shows how the effects of alcohol in the breast can be modified by other factors, such as smoking.

Keywords: mammographic density, alcohol, smoking, breast cancer, ordinal logistic models

LIST OF ABBREVIATIONS

MD: Mammographic density

FFQ: Food frequency questionnaire

BMI: Body mass index

HRT: Hormone replacement therapy

E2: Estradiol

IGF-1: Insulin-like growth factor 1

INTRODUCTION

Mammographic density (MD), or the proportion of the breast with respect to its overall breast area that is composed of dense tissue, is a strong risk factor for breast cancer. Over 40 studies have assessed this association and the majority have reported a 2- to 6-fold increased risk of breast cancer for the highest to lowest density categories (1).

Breast density is also associated with reproductive and anthropometric risk factors for breast cancer (2-13). However, the association between MD and breast cancer appears to be independent, and usually persists after adjustment for these factors. In addition, there is strong evidence of a genetic determinant of MD (14).

Although relatively few studies have examined the association between alcohol consumption and breast density, most nonetheless report higher MD among alcohol drinkers than abstainers (15-19). Whereas some of these studies support a weak, albeit significant, positive association between current alcohol intake and MD in both pre- and postmenopausal women, there is more limited and inconclusive data on the association between the timing of initiation of alcohol intake and MD (19,20).

Even less information is available on the effects of tobacco smoking on breast density. Some studies consistently report an inverse relationship between current smoking and MD (7,15,21,22), attributed to an antiestrogenic effect of tobacco smoke; others, in contrast, fail to observe any association (23,24).

Accordingly, we decided to investigate the association between alcohol consumption, smoking and adult MD using data from food frequency questionnaires (FFQs), risk factor data, and breast density measures from the Determinants of Mammographic Density in Spain study (*DDM-Spain*).

MATERIALS AND METHODS

Study population

This was a cross-sectional multicenter study based on 3584 women, aged 45 to 68 years, recruited from seven specific screening centers within the Spanish Breast Cancer Screening Program network. All women aged 50-65 years, regardless of nationality or legal status, are screened under these government-sponsored programs every two years, with the exception of women carrying BRCA1 or BRCA2 mutations who are generally screened by specific units. In some regions, women between 45-49 years of age are also included. Furthermore, the age range in all regional programs is currently being extended to cover women up to the age of 70 years.

Sampling procedure and data-collection

A minimum of 500 women per screening center were recruited from October 7, 2007 to July 14, 2008. Women previously diagnosed with breast cancer or some other malignant disease (except basal cell epitheliomas) were excluded, as were women who failed to respond to the questionnaire or presented with some physical inability that prevented a mammography from being performed. The DDM-Spain study protocol was formally approved by the Institutional Review Board at the Carlos III Institute of Health.

Women were interviewed at the screening center by purpose-trained interviewers. The questionnaire collected demographic information relating to the following: childhood and youth; family and personal background; gynecologic, obstetric and occupational history; household activities; current and lifetime alcohol consumption; current and lifetime tobacco use; current and past physical activity; and diet during the preceding year. Women's height and weight were measured twice by the interviewer, with a third

measurement being taken if the first two were in any way dissimilar. Average values were used to compute BMI.

The dietary section of the questionnaire ascertained the frequency of consumption and usual portion size of 117 food items (including alcoholic beverages), and was used to estimate daily intake of alcohol and calories. The standard servings of red wine [125ml], white wine [125ml], beer [200ml], sherry [50ml], hard cider [125ml], spirits [30ml], and brandy, gin, rum, whisky and vodka [40ml], were estimated to contain 13.25g, 12.63g, 6.15g, 3.06g, 7.80g, 7.40g, and 14.25g of ethanol, respectively. Daily calorie intake was estimated from a nutrient database developed by Vioque et al (25). The folate intake values comprised dietary sources and vitamin supplements.

Estimation of percent breast density

We measured MD from the craniocaudal mammogram of the left breast using Boyd's semiquantitative scale, **a visual scale that** rates density in 6 categories, namely: A (0%); B (<10%); C (10-25%); D (25-50%); E (50-75%); and F (>75%). Mammographic density was assessed on a blind, anonymous basis by a single, experienced radiologist.

Statistical analysis

The association between MD, alcohol consumption and tobacco use was evaluated by using ordinal logistic models with random center-specific intercepts (26). The main exposure variables, as well as the remaining adjustment factors, were regarded as fixed effects, so that their associated ORs were deemed to be the same for women at all screening centers. In addition, the ordinal logistic models included a random, center-specific intercept term that accounted for unexplained variations in the baseline odds of higher MDs across screening centers.

The Brant test was used to verify the proportional odds assumption. This assumption held for the effects of alcohol consumption and tobacco use in all fitted models, after the two lowest categories (A and B) of Boyd's classification had been combined. These categories are fairly similar in terms of reduced percentage of dense breast tissue (0 and <10%), and there were only 4.2% of women in the "no dense tissue" category. Hence, all logistic models included MD as an ordinal response variable with five categories (A+B, C, D, E, and F).

The main exposures of interest linked to alcohol consumption were: (a) current alcohol intake (yes or no); (b) lifetime alcohol drinking (never, past, or current drinker); (c) average alcohol intake during preceding year as reported in the FFQ (grams/day); and (d) age at which regular drinking had been initiated. Insofar as tobacco use was concerned, the exposures of interest were: (e) current smoking (yes or no); (f) lifetime tobacco smoking (never, past, or current smoker); (g) daily amount of cigarettes; (h) accumulated amount of cigarettes; and (i) age at which smoking had been initiated. All these exposures were analyzed as categorical variables, except for daily grams of alcohol, daily and accumulated amount of cigarettes, and age of initiation of alcohol and tobacco use, which were modeled both as predetermined categorical and continuous variables.

To further explore the association between amount of alcohol intake and MD without assuming a linear dose-response relationship, we used restricted quadratic splines for log-transformed alcohol intakes, with knots at 0.09, 3.3, and 33.1 g/day, corresponding to the 5th, 50th and 95th percentiles of alcohol consumption among drinkers, respectively. These spline models require the same number of parameters as the categorical analysis but can accommodate a wide variety of smoothed risk trends (27).

In addition, the above models were fitted with increasing levels of adjustment. First, we fitted a simple model adjusted for strong determinants of MD, i.e., age at mammography (continuous), BMI (restricted quadratic spline), and menopausal status. Second, we fitted an extended model, further adjusted for variables associated both with lifestyle and MD, including number of live births (continuous), current HRT use, current alcohol intake, and current smoking. Separate simple and extended models were constructed for pre- and postmenopausal women. Furthermore, the effect of alcohol consumption was separately assessed in current and noncurrent smokers.

All analyses were performed in Stata (StataCorp LP, College Station, TX), using the *gllamm* function to fit random-intercept ordinal logistic models (28), and R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Of the three thousand, five hundred, eighty-four (3584) women recruited and interviewed, MD assessment was completed for 3568. The average participation rate was 74.5% (64.7-84.0%). Women who developed breast cancer within 6 months of mammography were excluded from the analysis (n=10). Daily calorie intake below 800 calories or above 4000 was considered unrealistic, and the women concerned were also excluded (n=8) along with one woman who was being fed intravenously.

The overall proportion of Boyd mammographic density categories in the study population was as follows: A, n=150 (4.2%); B, n=722 (20.3%); C, n=732 (20.7%); D, n=1135 (32%); E, n=623 (17.5%); and F, n=187 (5.3%). Twenty-one percent of women were pre- or perimenopausal, and 79% were postmenopausal. With respect to alcohol consumption, 41.6% were abstainers, 41.1% currently drank up to 10g of alcohol/day, and only 17.3% consumed more than 10g of alcohol/day. In the case of tobacco use,

57.8% of participants had never smoked, 24.3% currently smoked, and 17.9% were ex-smokers.

In a simple analysis adjusted for age, BMI, menopausal status and screening program, higher MD was positively associated with never being pregnant, older age at first live birth, larger daily caloric intake and more years of education (Table 1). In contrast, higher MD was negatively associated with increased age; younger age at menopause, increased number of live births; being postmenopausal; having osteoporosis; and being very active between the ages of 36 and 50 years. Age at menarche, HRT use, folic acid intake and tobacco smoking were considered potential confounders, but in our study were not associated with MD.

After an extended analysis adjusted for age, screening program, BMI, menopausal status, number of live births, HRT use, current alcohol consumption and current tobacco use, osteoporosis and high levels of physical activity remained associated with decreased odds of being in high MD groups (OR=0.71; 95% CI 0.59-0.86 and OR=0.86; 95% CI 0.75-0.98, respectively), and daily calorie intake was associated with increased odds of being in high-density categories (highest versus lowest calorie intake OR=1.33; 95% CI 1.11-1.59; *p* for trend=0.003)(Table 1).

Alcohol was positively related with MD (Table 1). In the extended model, current alcohol drinking increased the odds of high MD by 13% (OR=1.13; 95% CI 0.99-1.28), with high daily grams of alcohol being positively associated with increased MD (*p* for trend=0.045; Table 1). Among drinkers, older age of initiation of alcohol consumption was only slightly associated with a higher probability of being in high MD categories, though the statistical test was not significant at *p*<0.05 (Table 1). In contrast, women who started drinking before menarche had a lower probability of being in higher density categories than did other women who also consumed alcohol. Further adjustment for

daily calorie intake, physical activity levels, and osteoporosis failed to change the magnitude of the associations (data not shown) and so these variables were not included in the final analysis.

There were no statistically significant differences in MD between smokers and non-smokers. Nevertheless, increased number of daily cigarettes and increased number of accumulated lifetime cigarettes were negatively associated with high MD in the extended adjusted model (p for trend 0.008 and 0.004, respectively). Age of smoking initiation had no influence on MD (Table 1).

Although formal testing showed no statistical interactions between menopausal status and variables linked to alcohol consumption and tobacco use (likelihood ratio test; $p > 0.05$), in view of the strong influence of ovarian hormones on MD and the reported estrogenic or antiestrogenic effects of alcohol and tobacco on the breast, extended models were constructed separately for pre- and postmenopausal women (Table 2).

In peri- and premenopausal women, alcohol consumption was not associated with MD and the dose-response curve was almost flat (Fig. 1). Increased age of initiation of alcohol consumption seemed to be associated with higher MD, though the number of women in the older age groups was small.

Among postmenopausal women, in contrast, alcohol consumption increased the odds of being in high MD categories by 15% relative to abstainers (OR=1.15; 95% CI 1.00-1.32). Raising daily alcohol consumption resulted in a dose-dependent increase in the likelihood of being in a high MD group (p for trend=0.022). In comparison with abstaining, drinking more than 10g of alcohol/day increased the probability of having MD by 26% (OR=1.26; 95% CI 1.03-1.53). Using restricted quadratic splines, we observed increased odds of being in high MD groups with increasing amounts of

alcohol but the relationship was not linear. Whereas moderate daily intake of alcohol (less than one glass of red wine) increased mammographic density, higher alcohol intake led to a lower probability of having high MD (Fig. 1).

Postmenopausal women displayed a negative association between the number of cigarettes -both current and accumulated over a lifetime- and the odds of being in high MD groups. Women who smoked more than 15 cigarettes/day were 32% less likely to be in high MD categories than were women who smoked 0-5 cigarettes/day (OR=0.68; 95% CI 0.46-0.99; p for trend=0.046); and similarly, women who had smoked more than 700 cigarettes in their lifetime were 30% less likely to be in high MD categories than were women who had smoked fewer than 300 cigarettes (OR=0.70; 95% CI 0.51-0.96; p for trend=0.053).

We found that an interaction test between alcohol and tobacco use with respect to their influence on mammographic density approached statistical significance (likelihood ratio test $p=0.075$). The effects of increasing tobacco consumption on MD were different depending on the level of alcohol intake. In the highest alcohol consumption group (women who drank more than 10g of alcohol/day), the odds of being in high MD categories decreased by 17% for every increase of 10 cigarettes/day ($p=0.037$) compared to women that do not drink. In women who drank less than 10g/day, however, the increased number of daily cigarettes showed no association with lower MD ($p=0.976$). Moreover, alcohol consumption and smoking are interrelated, in that heavy drinkers tend to smoke more than do light drinkers or abstainers. In the DDM-Spain study, while only 4% of abstainers smoked over 20 cigarettes a day, 9% of women in the highest alcohol intake levels (>20 g/day) smoked over 20 cigarettes a day.

Given the strong antiestrogenic effects reported for tobacco smoking, extended models for alcohol consumption were separately fitted for current and noncurrent smokers (Table 3). There was a positive association between increased daily grams of alcohol and high MD among noncurrent smokers (women who drank more than 10g of alcohol/day versus abstainers OR=1.25; 95% CI 1.02-1.53; p for trend 0.029). Increasing the amount of alcohol consumed raised the odds of being in a higher density group (p for trend=0.029). Whereas older age of alcohol initiation increased the probability of being in higher MD groups, starting to drink alcohol before menarche decreased the odds of being in high MD categories by 50% (OR=0.50; 95% CI 0.29-0.85). Among current smokers, in contrast, no association was observed between drinking alcohol, increased alcohol consumption or age of initiation into alcohol drinking and MD. The effects of alcohol on MD were observed solely for women who were not current smokers.

DISCUSSION

This paper reports a positive association between current alcohol intake and higher MD. The effect of alcohol on MD was mainly observed among postmenopausal women. Furthermore, whereas alcohol consumption and daily grams of alcohol were positively associated with higher MD among women who were not current smokers, alcohol consumption failed to show any effect on MD among current smokers.

In general, the positive association observed for current drinking is in line with much of the literature on alcohol and MD (15,17-20,29,30). Even though the interaction test between menopausal status and alcohol consumption was not statistically significant in our study, a different effect in pre- versus postmenopausal women has been described elsewhere (15,17). To our knowledge, no other study has yet reported an opposite effect of smoking and alcohol drinking on MD.

We failed to find a consistent association between age at which women started consuming alcohol and MD. However, our results suggest that the timing of exposure to alcohol affected MD in several different ways. First, later age of initiation of alcohol consumption was positively related (although not statistically significant) with a higher probability of being in high-density categories in premenopausal women versus women who started drinking at early ages. Conversely, women who started drinking alcohol before menarche were half as likely to be in high MD groups as women who started drinking after menarche. This is in agreement with reports showing that prepubertal estrogenic exposures reduce MD (31,32) while estrogenic exposures during adulthood increase it (2,33-35).

Thus, alcohol may have different effects on MD, depending on the time of exposure, i.e., whereas starting to drink during peripubertal years reduces the odds of being in high mammographic density groups, starting to drink during adulthood has no effect on MD unless it occurs close to the date of mammography. This agrees both with reports suggesting that drinking alcohol before age 21 years is inversely associated with mammary density (20), and with others showing that current rather than lifetime alcohol intake is more strongly associated with MD (19). In this regard, we created a variable representing the time elapsed between initiation of alcohol consumption and mammography, and found that the likelihood of being in a higher Boyd category of MD increased as initiation approached mammography, which suggests that starting to drink increases MD but that the initial effect of alcohol wanes over time. This is not the only estrogenic exposure with this paradoxical effect: one study has found that the effects of estrogen-plus-progestin therapy on MD persist but are attenuated after 2 years of treatment (33).

Our finding of a weak, negative association between current smoking and MD supports most (7,21,22) but not all (23,24,36) prior published reports, and is consistent with an antiestrogenic effect of cigarette smoking on breast tissue. While MD and daily number of cigarettes smoked were found to have an inverse relationship, neither age at initiation nor smoking duration displayed an association.

According to our results, the effects of both exposures -alcohol and tobacco- on MD may work in opposite directions, which could explain why the OR of the effect of alcohol consumption on MD among smokers was close to one and why there was a decrease in risk of high MD with increased number of daily cigarettes among heavy drinkers. An antagonistic effect would also explain the unexpected decline at the end of the dose-response curve of alcohol intake and MD in postmenopausal women. Alcohol consumption and smoking are interrelated, in that heavy drinkers tend to smoke more than do light drinkers or abstainers. However, women in the highest alcohol consumption group may have been different in other lifestyle aspects, and so residual confounding by unknown factors at high alcohol intake levels cannot be ruled out.

One potential limitation of this study is the error inherent in dietary assessment in such a large epidemiologic study. However, the semiquantitative FFQ was adapted from Willett et al. (37) for the Spanish population, and has demonstrated reasonable levels of reliability and validity in other studies (25). Further, we found that the association of MD with general reproductive variables such as age at first birth, number of live births, age at menarche and menopause (2,3), etc, as well as osteoporosis (38), level of physical activity (39,40) or daily caloric intake (41) were consistent with what is known about MD. These observed findings provide additional support for the validity of the questionnaire that was used in this study.

Low alcohol consumption and low prevalence of regular adolescent drinking among the study population constitute two further possible drawbacks of our study: only 17% of the women drank more than 10g of alcohol/day, and less than 19% of the women started drinking at age 18 years or before. Another potential limitation resides in the length of time between adolescence and recall of alcohol consumption later in life. Even though other studies have shown good reliability of reporting past alcohol consumption (42), recall of exposures during adolescence is likely to be imprecise and could result in attenuation of estimates.

Similarly, the measure of breast density was subjectively determined by only one radiologist. Nevertheless, the intra-observer reproducibility of the Boyd scale was good in our study, with a concordance between the first and second reading of 0.92 (43). Indeed, all disagreements corresponded to differences in only one category.

In summary, our results provide further support for an association between recent alcohol consumption and high mammographic density, characterized by a modest increase in risk at low levels of current consumption and a decrease in risk among heavier drinkers. Our study also suggests that the effects of alcohol in the breast can be modified by other factors, such as smoking. Yet, to what precise degree tobacco use may explain the lack of increased MD among women who drink alcoholic beverages daily is difficult to establish. Alcohol drinking is a modifiable behavior, and since moderate alcohol consumption is associated with a reduced risk of cardiovascular mortality and overall mortality among women, studies such as ours, which address the link between alcohol consumption and breast cancer risk, are critical for ascertaining the cost-benefit ratio of alcohol intake.

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FIGURE LEGENDS

Figure 1

Odds ratio of higher mammographic density (MD) according to alcohol intake in premenopausal (top) and postmenopausal women (bottom). Curves depict adjusted odds ratios (solid lines) and their 95% confidence intervals (dashed lines), based on restricted quadratic splines for log-transformed alcohol intakes with knots at 5th, 50th, and 95th percentiles among drinkers. The reference value (OR = 1) was set at 0.01 g/day (abstainers). Odds ratios were obtained from an ordinal logistic model with random program-specific intercepts, adjusted for age, BMI, current smoking status, number of live births, and current use of HRT (only for postmenopausal women). Bars represent the frequency distribution of alcohol intake among pre- and postmenopausal women.

TABLE 1. Characteristics of study population according to Boyd¹ mammographic density categories, associated ORs and 95% CIs for a higher B category.

VARIABLES	N	Boyd Scale (%)					Simple Model ¹				Extended Model ²		
		A+B <10%	C 10- 25%	D 25- 50%	E 50- 75%	F >75%	OR	95% CI	p	p for trend*	OR	95% CI	p
Age (y)													
< 50 y	547	10	13	35	31	11	1.00				1.00		
50-54 y	968	20	19	33	22	7	0.81	0.65- 1.02	0.071		0.83	0.66-1.04	0.119
55-59 y	1000	25	25	33	14	4	0.68	0.53- 0.87	0.002		0.72	0.55-0.93	0.011
60-64 y	939	37	22	29	10	2	0.45	0.35- 0.58	<0.001		0.49	0.37-0.64	<0.001
>65 y	95	38	23	24	12	3	0.41	0.26- 0.63	<0.001	<0.001	0.44	0.28-0.68	<0.001
BMI (kg/m²)													
<25	977	10	14	35	29	11	1.00				1.00		
25-30	1516	22	23	33	18	4	0.48	0.41-0.56	<0.001		0.49	0.42-0.57	<0.001
>30	1056	42	23	27	6	2	0.18	0.16-0.22	<0.001	<0.001	0.20	0.17-0.24	<0.001
Number of live births													
1	543	17	17	33	27	6	1.00				1.00		
2	1701	24	21	33	17	5	0.72	0.61- 0.86	<0.001		0.77	0.64-0.92	0.004
3	715	29	24	29	14	4	0.65	0.53- 0.80	<0.001		0.73	0.59-0.90	0.003
≥4	272	42	26	26	3	2	0.40	0.31- 0.53	<0.001		0.48	0.36-0.63	<0.001
Nulliparous	318	15	15	35	23	12	1.33	1.03- 1.72	0.029	<0.001	1.40	1.08-1.81	0.010
Age at 1st birth (y)													
<20	155	26	30	23	16	5	1.00				1.00		
20-24	1340	29	23	30	15	4	0.96	0.71- 1.29	0.771		0.88	0.65- 1.20	0.422

25-29 & nulliparous	1546	23	19	35	17	6	1.20	0.89- 1.62	0.231		0.94	0.69- 1.28	0.717
≥30	465	18	17	31	27	6	1.38	0.99- 1.92	0.060	0.053	1.04	0.74- 1.46	0.832
Education													
5 th grade	1203	31	23	31	11	3	1.00				1.00		
Below 8 th grade	1314	25	21	31	18	5	1.07	0.92- 1.24	0.379		1.03	0.89- 1.20	0.685
Below 12 th grade	664	18	19	31	25	6	1.21	1.01- 1.46	0.042		1.13	0.94- 1.36	0.202
University degree	362	17	15	38	22	9	1.25	1.00- 1.56	0.052	0.016	1.09	0.87- 1.37	0.475
Age at menarche													
≥14 y	1174	23	21	31	19	5	1.00				1.00		
12-13 y	1564	23	20	33	18	5	1.07	0.93- 1.23	0.350		1.05	0.91- 1.21	0.498
<12 y	802	29	22	30	14	5	0.94	0.80- 1.12	0.505	0.644	0.92	0.78- 1.09	0.336
Age at menopause													
50-54 y	1170	27	21	34	14	4	1.00				1.00		
≥55 y	250	39	24	26	10	1	0.83	0.64-1.07	0.151		0.82	0.63-1.06	0.136
≤45 y	496	28	26	29	12	5	0.81	0.67-0.99	0.039		0.83	0.68-1.01	0.060
45-49	854	26	23	32	15	4	0.88	0.75-1.04	0.140		0.89	0.75-1.05	0.159
Premenopausal	758	12	13	34	32	10	1.44	1.17-1.78	0.001	0.152	1.42	1.15-1.76	0.001
HRT													
Never	3043	24	21	32	18	5	1.00				1.00		
Current hormones	154	22	19	32	18	8	1.13	0.84- 1.53	0.420		0.98	0.72-1.32	0.882
Past hormones	301	30	21	32	14	4	0.86	0.69- 1.07	0.173		0.85	0.68-1.06	0.160
Raloxifen	51	27	27	35	6	4	0.70	0.42- 1.15	0.160		0.71	0.43-1.18	0.193
Osteoporosis													
No	3030	23	20	32	18	6	1.00				1.00		
Yes	463	34	22	29	12	3	0.70	0.58- 0.84	<0.001		0.71	0.59-0.86	<0.001
Daily calorie intake													
≤1750	1007	28	22	30	15	5	1.00				1.00		
1751-2000	714	26	21	33	16	4	1.02	0.86- 1.22	0.791		1.02	0.86- 1.22	0.806
2000-2400	1037	24	21	33	17	6	1.07	0.91- 1.26	0.424		1.08	0.92- 1.28	0.339
>2400	791	20	19	33	23	6	1.31	1.10- 1.56	0.003	0.005	1.33	1.11- 1.59	0.002
Daily folate intake													
200-399 µg	2415	25	21	32	18	5	1.00				1.00		
<200 µg	173	24	24	35	13	3	1.01	0.77- 1.33	0.943		1.00	0.76- 1.32	1.000
≥400 µg	961	24	20	31	18	7	1.08	0.94- 1.24	0.297	0.364	1.10	0.96- 1.27	0.169
Physical activity													
Moderate	1620	23	19	33	20	5	1.00				1.00		
Little	224	23	19	31	20	7	1.07	0.82- 1.38	0.625		1.00	0.77-1.30	0.978
Very active	1691	26	22	31	15	5	0.83	0.73- 0.95	0.005		0.86	0.75-0.98	0.026
ALCOHOL													
Current drinker													
No	1477	29	20	32	15	5	1.00				1.00		
Yes	2072	22	21	32	19	6	1.15	1.02- 1.31	0.025		1.13	0.99- 1.28	0.060
Daily g alcohol													
0 (non-drinker)	1477	29	20	32	15	5	1.00				1.00		
0- less than 10 g	1460	22	21	32	19	6	1.13	0.99- 1.30	0.069		1.11	0.97- 1.27	0.147
10 g or more	612	20	21	33	21	6	1.20	1.01- 1.43	0.040	0.023	1.18	0.99- 1.41	0.062
Lifetime alcohol use													
Never	1312	29	19	31	15	5	1.00				1.00		
Ex-drinker	165	23	23	35	16	3	1.01	0.75- 1.35	0.955		0.98	0.73- 1.32	0.912
Current	2072	22	21	32	19	6	1.15	1.01- 1.31	0.029		1.13	0.99- 1.28	0.075

Age of alcohol initiation ^a												
≤18 years old	603	17	22	33	21	7	1.00					1.00
19-24	540	24	19	31	22	5	0.99	0.80- 1.22	0.907			1.10 0.89- 1.37 0.374
25-40	508	20	21	35	18	6	0.99	0.80- 1.23	0.920			1.14 0.92- 1.42 0.232
>40 years old	146	21	20	32	23	5	1.05	0.75- 1.45	0.792	0.915		1.28 0.92- 1.79 0.149
Before/at 18 years	1194	22	20	33	20	5	1.00					1.00
After 18 years old	603	17	22	33	21	7	1.00	0.84- 1.20	0.958			0.88 0.73- 1.05 0.159
After menarche	1734	20	21	33	21	6	1.00					1.00
Before/at menarche	68	26	22	28	18	6	0.66	0.42- 1.02	0.063			0.66 0.42- 1.03 0.067
Before/at first pregn.	1060	22	21	31	21	5	1.00					1.00
After first pregnancy	463	22	22	35	16	5	1.00	0.82- 1.23	0.973			1.11 0.90- 1.36 0.324
SMOKING												
Current smoker												
No	2691	26	20	32	16	5	1.00					1.00
Yes	858	19	21	32	21	6	0.95	0.82- 1.09	0.476			0.91 0.79- 1.05 0.210
Daily cigarettes												
0-5	251	17	21	33	23	6	1.00					1.00
6-15	315	20	19	30	23	8	0.68	0.52- 0.88	0.004			0.83 0.61- 1.13 0.239
>15	292	20	24	35	17	4	0.78	0.48- 1.26	0.317	0.007		0.68 0.50- 0.93 0.017
Lifetime tobacco												
Never	2054	28	21	32	15	4	1.00					1.00
Ex-smoker	637	22	19	31	21	8	1.18	1.00- 1.40	0.053			1.08 0.91- 1.28 0.373
Current	858	19	21	32	21	6	0.99	0.85- 1.15	0.901			0.93 0.80- 1.08 0.353
Accumulated												
≤300	606	17	19	33	24	7	1.00					1.00
301-500	308	24	19	27	21	9	0.78	0.60- 1.00	0.049			0.76 0.59- 0.99 0.038
501-700	246	19	17	37	19	7	0.90	0.68- 1.18	0.436			0.88 0.67- 1.16 0.370
>700	230	24	27	29	17	2	0.72	0.54- 0.95	0.021	0.031		0.70 0.53- 0.93 0.014
Age tobacco initiation ^a												
≤18 years old	871	16	21	32	24	8	1.00					1.00
19-24	317	25	19	32	19	5	0.84	0.65-1.07	0.154			0.82 0.65-1.06 0.128
25-40	174	31	18	29	18	4	0.94	0.68-1.30	0.701			0.96 0.70-1.33 0.819
>40 years old	34	26	18	38	15	3	1.00	0.52-1.89	0.983	0.486		1.14 0.60-2.19 0.679
Before/at 18 years	871	16	21	32	24	8	1.00					1.00
After 18 years old	525	27	19	31	18	5	0.84	0.71-1.08	0.220			0.88 0.71-1.09 0.249
After menarche	1332	20	20	32	21	7	1.00					1.00
Before/at menarche	72	11	21	33	25	10	1.11	0.72-1.70	0.632			1.15 0.75- 1.76 0.524
Before/at first pregn.	1374	19	18	32	23	8	1.00					1.00
After first pregnancy	174	30	23	29	14	4	0.84	0.62-1.13	0.245			1.06 0.78- 1.46 0.683

¹ Simple model adjusted for age at mammography, BMI, menopausal status, and screening program. ² Extended model adjusted for age at mammography, BMI, menopausal status, and screening program, plus number of live births, HRT use, current smoker, and current alcohol drinker status. *To calculate trends, variables were modeled as continuous variables; ^a Variables linked to age of alcohol and smoking initiation were analyzed only in drinkers and smokers/ex-smokers.

TABLE 2. Associated ORs and 95% CIs for a higher Boyd category.

VARIABLES	PRE & PERIMENOPAUSAL ¹					POSTMENENOPAUSAL ²				
	N	OR	95% CI	<i>p</i>	<i>p for trend</i>	N	OR	95% CI	<i>p</i>	<i>p for trend</i>
ALCOHOL DRINKING										
Current drinker										
No	301	1.00				1174	1.00			
Yes	499	1.04	0.79- 1.36	0.801		1573	1.15	1.00- 1.32	0.058	0.058
Daily g alcohol										
0 (non-drinker)	301	1.00				1174	1.00			
0- less than 10	373	1.07	0.80- 1.42	0.656		1087	1.10	0.94- 1.29	0.223	
10 or more	126	0.95	0.65- 1.40	0.790	0.925	486	1.26	1.03- 1.53	0.023	0.022
Lifetime alcohol use										
Never	263	1.00				1047	1.00			
Ex-drinker	38	0.65	0.35- 1.23	0.185		127	1.13	0.81- 1.58	0.470	
Current	499	0.98	0.74- 1.30	0.887		1573	1.16	1.00- 1.35	0.043	
Age of alcohol initiation^a										
≤18 years old	225	1.00				378	1.00			
19-24	123	1.03	0.69- 1.55	0.870		417	1.10	0.85- 1.42	0.477	
25-40	101	1.03	0.67- 1.57	0.893		407	1.13	0.87- 1.46	0.366	
>40 years old	21	2.57	1.06- 6.26	0.038	0.258	125	1.12	0.78- 1.62	0.534	0.381
Before/at 18 years old	245	1.00				949	1.00			
After 18 years old	225	0.91	0.65- 1.26	0.564		378	0.90	0.72- 1.12	0.336	
After menarche	451	1.00				1283	1.00			
Before/at menarche	20	0.49	0.21- 1.14	0.098		48	0.70	0.41- 1.19	0.189	
Before/at first pregn	300	1.00				760	1.00			
After first pregnancy	100	1.04	0.68- 1.59	0.853		363	1.12	0.89- 1.41	0.342	
SMOKING										
Current smoker										
No	549	1.00				2141	1.00			
Yes	251	0.86	0.65- 1.13	0.278		606	0.93	0.79- 1.10	0.415	0.415
Daily cigarettes										
0-5	73	1.00				178	1.00			
6-15	92	1.01	0.57- 1.79	0.970		223	0.81	0.56- 1.19	0.285	
>15	86	0.80	0.45- 1.42	0.442	0.434	205	0.68	0.46- 0.99	0.046	0.046
Lifetime tobacco										
Never	342	1.00				1712	1.00			
Ex-smoker	207	1.06	0.77- 1.47	0.721		429	1.10	0.90- 1.34	0.366	
Current	251	0.88	0.65- 1.19	0.398		606	0.95	0.80- 1.13	0.579	
Accumulated cigarettes life										
≤300	215	1.00				391	1.00			
301-500	106	0.88	0.57- 1.35	0.555		202	0.73	0.53- 1.01	0.054	
501-700	87	0.82	0.52- 1.30	0.400		157	0.92	0.65- 1.29	0.628	
>700	37	0.72	0.37- 1.40	0.337	0.238	193	0.70	0.51- 0.96	0.028	0.053
Age of smoking initiation^a										
≤18 years old	350	1.00				519	1.00			
19-24	70	0.66	0.40-1.08	0.098		247	0.92	0.69- 1.22	0.557	
25-40 (or ≥25 in prem.)	26	0.81	0.37-1.66	0.590	0.177	153	0.96	0.67- 1.37	0.824	
>40 years old						29	1.36	0.67-2.80	0.396	0.920
Before/at 18 years old	350	1.00				519	1.00			
After 18 years old	76	0.71	0.46- 1.09	0.119		429	0.95	0.74- 1.22	0.700	
After menarche	411	1.00				919	1.00			
Before/at menarche	36	1.36	0.73- 2.53	0.333		36	1.00	0.55- 1.83	0.992	

Before/at 1st pregn	453	1.00			919	1.00			
After 1st pregnancy	25	1.04	0.48-2.27	0.915	149	0.95	0.68-1.33	0.779	
¹ In pre- and perimenopausal women, the model was adjusted for age at menopause, menopause status, hormone therapy use, HRT use, and current smoker status. ² In postmenopausal women, the model was adjusted for the same variables as well as HRT use. ³ Complete p trends, variables were modeled as continuous variables; ^a Variables linked to age of alcohol use, smoking initiation were only analyzed in drinkers and smokers/ex-smokers.									
Current drinker									
No	1169	1.00			308	1.00			
Yes	1522	1.15	0.99- 1.32	0.063	550	1.06	0.82- 1.37	0.672	
Daily g alcohol									
0 (non-drinker)	1169	1.00			308	1.00			
0- less than 10	1079	1.11	0.95- 1.29	0.207	381	1.09	0.82- 1.44	0.562	
10 or more	443	1.25	1.02- 1.53	0.034	169	1.00	0.70- 1.41	0.984	0.916
Lifetime alcohol use									
Never	1058	1.00			254	1.00			
Ex-drinker	111	0.92	0.64- 1.32	0.650	54	1.15	0.67- 1.97	0.601	
Current	1522	1.14	0.98- 1.32	0.089	550	1.09	0.82- 1.43	0.562	
Age of alcohol initiation ^a									
≤18 years old	426	1.00			177	1.00			

19-24	375	1.13	0.87- 1.46	0.354		165	1.04	0.70- 1.55	0.843
25-40	366	1.13	0.87- 1.47	0.357		142	1.14	0.75- 1.73	0.533
>40 years old	114	1.33	0.91- 1.95	0.136	0.146	32	1.06	0.51- 2.19	0.873 0.595
Before/at 18 years old	855	1.00				339	1.00		
After 18 years old	426	0.87	0.70- 1.08	0.192		177	0.92	0.66- 1.30	0.647
After menarche	1234	1.00				500	1.00		
Before menarche	52	0.50	0.29- 0.85	0.010		16	1.52	0.63- 3.65	0.347
Before first pregnancy	752	1.00				308	1.00		
After first pregnancy	343	1.12	0.88- 1.42	0.361		120	1.09	0.73- 1.62	0.669

¹Model adjusted for age at mammography, BMI, menopausal status, and screening program, in addition of number of live births, HRT use and current drinker. *To calculate *p* trends, variables were modeled as continuous variables; ^a Variables linked to age of alcohol and smoking initiation were only analyzed in drinkers and smokers/ex-smokers.

