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Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk

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Abstract

Context—Multiple studies have linked alcohol consumption to breast cancer risk, but the risk of lower levels of consumption has not been well quantified. In addition, the role of drinking patterns (i.e. frequency of drinking and “binge” drinking) and consumption at different times of adult life are not well understood.

Objective—To evaluate the association of breast cancer with alcohol consumption during adult life, including quantity, frequency, and age at consumption.

Design, Setting, and Participants—Prospective observational study of 105,986 women enrolled in the Nurses’ Health Study followed from 1980 until 2008 with early adult and eight updated alcohol assessments during this time.

Main Outcome Measures—Relative risks of developing invasive breast cancer.

Results—7690 cases developed during 2.4 million person-years of follow-up. Increasing alcohol consumption was associated with increased breast cancer risk that was statistically significant at levels as low as 5.0-9.9 gm/day, equivalent to 3-6 drinks/week (RR 1.15 (95% CI 1.06-1.24) 332 cases/100,000 person-years). After controlling for cumulative alcohol intake, binge drinking, but not frequency of drinking, was associated with breast cancer risk. Alcohol intake both earlier and later in adult life was independently associated with risk.

Conclusion—Low levels of alcohol consumption were associated with a small increase in breast cancer risk, with the most consistent measure being cumulative alcohol intake throughout adult life. Alcohol intake both earlier and later in adult life was independently associated with risk.

In many studies, higher consumption of alcohol has been associated with an increased risk of breast cancer.[1-3] However, the impact of low levels of drinking as is common in the

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United States has not been well quantified. A few studies showed increased risk [1, 4], but in most no significant association was observed.[2, 3, 5-11] Many of these studies did not regularly update assessments of alcohol intake, which may change over a person's lifetime and obscure the ability to detect an effect. In addition, most lacked information on drinking patterns, such as regularity of drinking and heavy episodic ("binge") drinking. Finally, because some breast cancer risk factors, for example first full-term pregnancy[12] and ionizing radiation[13], have different effects depending upon the ages at exposure, it is important to evaluate the role of alcohol intake at different times in a woman's life.

METHODS

The Nurses' Health Study (NHS) cohort was established in 1976, when 121,700 female registered nurses aged 30 to 55 years completed a baseline questionnaire including items on risk factors for cancer and cardiovascular disease. Every 2 years, follow-up questionnaires have been sent to update risk factor information and disease development. Based upon self-report, the NHS population is predominantly White (93.7% White, 2% Black, 0.7% Asian, and 3.6% other/unknown) reflecting the demographics of registered nurses in the United States in 1976. Follow-up has been extremely high with 4.4% of person-time lost to follow-up. We routinely search the National Death Index every two years for non-responders.[14] In 1976, written informed consent was not required; instead, return of completed questionnaires was considered consent to enroll on the study. The Institutional Review Board of the Brigham and Women's Hospital reviewed and approved the study protocol.

Population for Analysis

For the main analysis, the analytic period began in 1980 when alcohol intake was first assessed. From the initial cohort of 121,700 women enrolled in 1976, after excluding those who died or developed cancer before 1980 (n=5565) or did not return any alcohol assessments (n=10149), 105,986 women entered the analysis beginning in 1980. Women who developed any type of cancer (except non-melanoma skin cancer) were censored at the time of their diagnosis. For analyses of drinking patterns and drinking during early adult life, follow up began with the 1988 questionnaire and included the 74, 854 participants who answered questions regarding their current and past drinking patterns.

Measurement of Alcohol Consumption

Information on alcohol consumption was first collected in 1980 when participants completed a semi-quantitative food frequency questionnaire and reported their average frequency of consumption of specific food and beverage items during the previous twelve months. Consumption of beer, wine, and liquor was ascertained as separate items. Alcohol consumption in grams per day was calculated as the sum of the daily number of drinks multiplied by the average alcohol content per type of alcoholic beverage (12.8 g of alcohol per 12 oz serving of beer, 11.0 g per 4 oz serving of wine, and 14.0 g per standard serving of liquor). [15] Alcohol intake measured by the food frequency questionnaire was highly correlated with intake calculated from detailed food diaries completed by a sample of study participants (Spearman rank-correlation coefficient = 0.90) and with high-density lipoprotein levels (r=0.40). [16] Data on current alcohol consumption were updated in 1984, 1986, 1990, 1994, 1998, 2002, and 2006.

Cumulative average alcohol intake was calculated by averaging alcohol use over time beginning in 1980. For example, cumulative average alcohol use in 1986 was obtained by averaging the daily consumption reported in 1980, 1984, and 1986. If a participant was missing alcohol consumption for a certain year, the measurements from the available years were averaged. For analyses of current alcohol use, alcohol intake was updated at each

alcohol questionnaire, without accounting for prior use. For current alcohol analyses, person-time for people missing alcohol consumption during a specific questionnaire cycle was excluded, but they could re-enter the analysis when alcohol intake data became available.

To maintain the prospective nature of the study, analyses on drinking patterns began with the 1988 questionnaire when participants were first asked the usual number of days alcohol was consumed in a typical week and largest number of alcoholic drinks consumed in one day in a typical month (none, 1-2, 3-5, 6-9, 10-14, or 15+). These questions were updated in 1996, 2000, and 2004. For alcohol consumption at different times of life, analyses also began in 1988 when participants were asked about the usual number of alcoholic drinks per week at three different age periods (age 18-22 years, 25-30, and 35-40). This information was not updated.

Identification of Breast Cancer Cases

The primary endpoint was the diagnosis of invasive breast cancer. On each questionnaire, we asked whether breast cancer had been diagnosed and, if so, the date of diagnosis. We search the National Death Index routinely for deaths among women who did not respond to the questionnaires; the last search was conducted in December 2010. We asked all women who reported breast cancer (or next of kin for those who died) for permission to review the pertinent medical records for confirmation. Pathology reports, obtained in 96% of the cases, showed a 99.4% confirmation rate. Carcinomas in situ were excluded. Estrogen- and progesterone receptor (ER/PR) status was abstracted from pathology reports.

Statistical Analyses

For this analysis, follow-up time began in 1980 and terminated with the diagnosis of any type of cancer, death, or June 1, 2008, whichever came first. Cox proportional hazards models were used to compute hazard ratios as estimates for age-adjusted and multivariable-adjusted RR and 95% CI's. The underlying time variables for the Cox model are questionnaire year and age. Additional covariates in the model were chosen to represent possible confounders and commonly accepted breast cancer risk factors and included menopausal status, age at menarche, parity, age at first birth , body mass index, family history of breast cancer in a first-degree relative, breastfeeding, cigarette smoking, and self-report of benign breast disease . All variables except age at menarche and breastfeeding were updated from follow-up questionnaires. For postmenopausal women, terms were also included for age at menopause, type of menopause, and duration/type of hormone therapy use. We included dummy variables for missing covariate data, which comprised less than 5% of total person-time (except for missing breastfeeding which was 9.5%). Tests for trend were calculated using alcohol consumption as a continuous variable. Tests for interaction were performed using the Wald test for the cross-product interaction term. The proportional hazards assumption was not violated. All analyses were performed using SAS software, version 9.1 with a two-sided significance p-value <0.05.

RESULTS

From 1980 until 2008, 7690 cases of invasive breast cancer were diagnosed among 2.4 million years of person-time. Table 1 illustrates the characteristics of the study population according to cumulative average alcohol intake in 1994, the midpoint of the follow-up period. Breast cancer risk factors were distributed fairly evenly across the groups except that higher alcohol consumers were more likely to have had natural menopause, have a lower body mass index, and be current smokers. Although tumor characteristics, current use of hormone therapy and compliance with mammography/clinical breast exams did vary slightly

across groups, none of these variables nor any other of the standard breast cancer risk factors displayed a consistent linear trend across categories of increasing alcohol use.

For the primary analyses, relative risks (RR) were calculated using average cumulative alcohol consumption since baseline (1980). Initially, analyses were also performed using baseline intake and simple current updating of alcohol use (i.e. consumption updated with the return of each questionnaire and therefore past use would not be carried forward). Although the relationship with baseline and current alcohol use closely approximated that of cumulative average intake (Table 2), cumulative average use provided the most linear and consistent associations suggesting that this represents the most accurate measure over time and also provided more statistical power by utilizing assessments throughout all follow-up periods. Notably, our assessment of cumulative average alcohol intake reflects predominantly alcohol intake in mid to later adult life, since we first began assessing alcohol use in 1980 when the participants were aged 34-59. Even a low level of alcohol consumption was modestly but significantly associated with breast cancer risk (for 5-9.9 grams/day (equivalent to 3-6 glasses of wine per week) multivariate (MV) RR 1.15 (95% CI 1.06-1.24) 332 cases/100,000 person-years). In addition, women who consumed at least 30 grams/alcohol daily on average (at least 2 drinks per day) had a greater risk of breast cancer (RR 1.51 (95% CI 1.35-1.70) 413 cases/100,000 person-years)compared to those who never consumed alcohol. The percent attributable risk (PAR) for each alcohol category in the study population is still low (1-3%) given the low prevalence of higher levels of alcohol consumption, but the PAR for alcohol overall was 10%.

When stratified by menopausal status, the association with alcohol appeared stronger among postmenopausal women, but the interaction was not significant (p=0.74) (eTable 1). We also evaluated whether the associations varied by type of alcohol and found little difference (RR per 10 gms/day for wine 1.12 (95% CI 1.07-1.18), beer 1.09 (95% CI 1.03-1.15) and liquor 1.09 (95% CI 1.05-1.13)).

Because one potential mechanism for alcohol's impact on breast cancer risk involves hormonal effects[17], we examined the association by ER/PR status of the tumor (Table 3). For this analysis, we excluded 1620 cases with unknown ER and/or PR status. Alcohol consumption seemed to be more strongly associated with risk of ER+and//orPR+, but the p for interaction was not significant. Results were similar for ductal and lobular histology (eTable 2).

In 1988, we first asked about drinking patterns including frequency of drinking and quantity of drinking. Heavy episodic or binge drinking is not consistently defined across studies, but one commonly used definition in the United States is 4 or more drinks at one time for a female.

When cumulative alcohol use was not included in the model, both regularity of drinking and binge drinking were strongly associated with breast cancer risk (Table 4). However, once cumulative alcohol consumption was added to the model, there was still an association with binge drinking, but not with frequency of drinking.

Finally, we examined associations with alcohol consumption at different periods of life. For this analysis, follow-up also began with the 1988 questionnaire cycle when questions on alcohol consumption at ages 18-22, 25-30, and 35-40 years were asked. Based upon these answers, we calculated the cumulative average intake between the ages of 18-40 as a representation of drinking during early adult life and cumulative intake after age 40 as representing intake later in life. When examined separately, alcohol consumption at ages 18-40 and after age 40 were both strongly associated with breast cancer risk (Table 5). The

association with drinking in early adult life still persisted even after controlling for alcohol intake after age 40.

DISCUSSION

In this large prospective cohort study, we observed an association between even low levels of alcohol consumption and breast cancer risk. The most relevant measure was cumulative average alcohol consumption over long periods of time, and both drinking earlier and later in adult life were independently associated with breast cancer risk. We also saw an association with binge drinking, but not frequency of drinking.

Prior studies have consistently demonstrated a linear dose-response relation between alcohol consumption and breast cancer risk, with an increased risk mainly observed among women who consumed the equivalent of at least one alcoholic beverage daily, but power was limited at the lower levels of alcohol consumption to determine whether there was a lower threshold. [2, 3, 5-11] Our data demonstrated that even consumption of alcohol as low as 5-9.9 gms/day (3 to 6 glasses of wine per week) may be associated with a modest increase in risk. We observed a 10% increase in risk with each 10 gm/day of alcohol intake, which is somewhat stronger than the risk reported in a previous large meta-analysis that used a single measure of alcohol intake at baseline (RR for each 10 gm per day = 1.07).[1] Consistent with other studies, we did not find any difference by type of alcoholic beverage (i.e. beer, wine, or liquor).[2, 3, 18, 19]

Although the exact mechanism for the alcohol and breast cancer association is not known, one probable explanation would involve alcohol's effects on circulating estrogen levels. Most other large studies have shown a stronger association with ER+ breast cancers.[8, 9, 20-24] In short-term feeding studies, moderate levels of alcohol consumption increased circulating sex hormone levels in both pre- and postmenopausal women. [25, 26] Cross-sectional studies also support a positive association between alcohol consumption and plasma sex hormone levels.[27, 28] Alcohol may increase sex hormone levels in several ways: increased aromatase activity [29], decreased hepatic catabolism of androgens[30] or effects on adrenal steroid production[26]. In vitro studies have demonstrated that alcohol can increase the transcriptional activity of ER-α[31] (which may influence breast tissue's sensitivity to estrogens) and preferentially enhance proliferation and ER-α content in ER+ cell lines.[32]

To our knowledge, this is the first study to evaluate breast cancer risk in relation to both frequency of drinking and binge drinking. Two other prospective studies have evaluated regularity of drinking and did not find a difference between less and more frequent drinking, but they had fewer breast cancer cases and used less detailed measures.[10, 11] In terms of binge drinking, a prospective study showed a non-linear association with the highest risk among those who consumed 4-5 drinks per weekday or 16-21 drinks per weekend and lower risks for those who drank more, but they had few cases in the highest categories and contrary to most studies, non-drinkers had an increased risk of breast cancer.[33] A case-control study found a non statistically significant increased risk associated with binge drinking limited to high alcohol consumers.[34] After controlling for cumulative average intake, we observed an association with binge drinking, but not frequency of drinking. However, there may still be some residual confounding with the higher cumulative alcohol intake among binge drinkers.

Several other studies have evaluated drinking at different time periods in adult life and most did not identify an association with alcohol consumption in early adult life.[3, 5, 11, 21, 35-37] A meta-analysis found that studies with shorter duration of follow-up reported higher relative risks than studies with longer follow-up, suggesting that recent, rather than early, alcohol

intake is more strongly associated with breast cancer risk.[38] Alternatively, for studies that do not obtain updated assessments through a person's lifetime, there may be increasing misclassification of alcohol consumption as dietary patterns change with age. Our study had greater statistical power than previous studies to evaluate the effect of drinking in early adult life. We found an association of similar magnitude for early and late life, even when mutually adjusted. Our study underscores the importance of considering the totality of a woman's exposure to alcohol over her lifetime as the best measure, rather than those from one specific time period. This type of temporal relationship for alcohol intake over longer periods parallels those of hormonal influences and breast cancer risk in which the broadest consideration of hormonal influences over a lifetime most accurately reflects risk.[39]

The strengths of this study include the large number of cases, length of follow-up, and detailed prospective and updated assessments of alcohol consumption across different age periods affording the most comprehensive evaluation of the effect of alcohol consumption throughout a woman's life. Limitations include that this was an observational study, so alcohol use was not randomly assigned to women. However, it is unlikely that such a long-term randomized trial will ever be performed. We relied upon self-reported alcohol use, but this has previously been shown to be highly reproducible within our cohort and strongly correlated with HDL levels.[16] We have also previously demonstrated that measurement error does not strongly affect our estimates of the alcohol association.[40] Compared to some studies done in Europe, we do not have as many women with higher levels of alcohol consumption. However, the distribution of alcohol intake in NHS is fairly similar to that of US women.[41] Our study population was predominantly White, but the limited available data suggest that the associations between alcohol and breast cancer does not differ by ethnicity.[42] The referent group was women who completely abstained from alcohol. Although this may represent a unique group, there was a linear association with increasing alcohol consumption, rather than an immediate jump from the referent group. Finally, PAR's can provide a sense of the potential public health impact of alcohol, but they are dependent upon the distribution of alcohol consumption in the population and also assume causality and this is an observational study. Also, PAR's do not account for the overall disease burden and with an estimated 172,000 new cases of invasive breast cancer in the US, a PAR of 10% would translate to 17,200 cases prevented annually.[43]

In summary, our study provides a comprehensive assessment of the relationship between alcohol intake and breast cancer risk in terms of timing, frequency, quantity, and types of alcohol in a large prospective cohort with detailed information on breast cancer risk factors. We did find an increased risk at low levels of use, but the risk was quite small. We found independent associations with drinking in early and later adult life with the strongest associations seen with cumulative drinking assessed over multiple decades. Our results highlight the importance of considering lifetime exposure when evaluating the impact of alcohol, and probably other dietary factors, on the carcinogenesis process. However, an individual will need to weigh the modest risks of light to moderate alcohol use on breast cancer development against the beneficial effects on cardiovascular disease[44] to make the best personal choice regarding alcohol consumption.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Hamajima N, Hirose K, Tajima K, et al. Alcohol, tobacco and breast cancer--collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. Br J Cancer. 2002; 87:1234–45. [PubMed: 12439712]
2. Smith-Warner SA, Spiegelman D, Yaun S-S, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. JAMA. 1998; 279:535–40. [PubMed: 9480365]
3. Tjonneland A, Christensen J, Olsen A, et al. Alcohol intake and breast cancer risk: the European Prospective Investigation into Cancer and Nutrition (EPIC). Cancer Causes Control. 2007; 18:361–73. [PubMed: 17364225]
4. Dumeaux V, Lund E, Hjartaker A. Use of oral contraceptives, alcohol, and risk for invasive breast cancer. Cancer Epidemiol Biomarkers Prev. 2004; 13:1302–7. [PubMed: 15298950]
5. Longnecker MP, Newcomb PA, Mittendorf R, et al. Risk of breast cancer in relation to lifetime alcohol consumption. J Natl Cancer Inst. 1995; 87:923–9. [PubMed: 7666482]
6. Rohan TE, Jain M, Howe GR, Miller AB. Alcohol consumption and risk of breast cancer: a cohort study. Cancer Causes Control. 2000; 11:239–47. [PubMed: 10782658]
7. Mattisson I, Wirfalt E, Wallstrom P, Gullberg B, Olsson H, Berglund G. High fat and alcohol intakes are risk factors of postmenopausal breast cancer: a prospective study from the Malmo diet and cancer cohort. Int J Cancer. 2004; 110:589–97. [PubMed: 15122593]
8. Suzuki R, Ye W, Rylander-Rudqvist T, Saji S, Colditz GA, Wolk A. Alcohol and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status: a prospective cohort study. J Natl Cancer Inst. 2005; 97:1601–8. [PubMed: 16264180]
9. Li CI, Malone KE, Porter PL, Weiss NS, Tang MT, Daling JR. The relationship between alcohol use and risk of breast cancer by histology and hormone receptor status among women 65-79 years of age. Cancer Epidemiol Biomarkers Prev. 2003; 12:1061–6. [PubMed: 14578143]
10. Tjonneland A, Thomsen BL, Stripp C, et al. Alcohol intake, drinking patterns and risk of postmenopausal breast cancer in Denmark: a prospective cohort study. Cancer Causes Control. 2003; 14:277–84. [PubMed: 12814207]
11. Horn-Ross PL, Canchola AJ, West DW, et al. Patterns of alcohol consumption and breast cancer risk in the California Teachers Study cohort. Cancer Epidemiol Biomarkers Prev. 2004; 13:405–11. [PubMed: 15006916]
12. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. Am J Epidemiol. 2000; 152:950–64. [PubMed: 11092437]
13. Hancock SL, Tucker MA, Hoppe RT. Breast cancer after treatment of Hodgkin's disease. J Natl Cancer Inst. 1993; 85:25–31. [PubMed: 8416252]
14. Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the National Death Index and Equifax Nationwide Death Search. Am J Epidemiol. 1994; 140:1016–9. [PubMed: 7985649]
15. United States Department of Agriculture ARS. USDA Nutrient Database for Standard Reference; 1997. Report No.: Release 11-1
16. Giovannucci E, Colditz G, Stampfer MJ, et al. The assessment of alcohol consumption by a simple self-administered questionnaire. Am J Epidemiol. 1991; 133:810–7. [PubMed: 2021148]
17. Hankinson SE, Willett WC, Manson JE, et al. Alcohol, height, and adiposity in relation to estrogen and prolactin levels in postmenopausal women. J Natl Cancer Inst. 1995; 87:1297–302. [PubMed: 7658481]
18. Allen NE, Beral V, Casabonne D, et al. Moderate alcohol intake and cancer incidence in women. J Natl Cancer Inst. 2009; 101:296–305. [PubMed: 19244173]
19. Li Y, Baer D, Friedman GD, Udaltsova N, Shim V, Klatsky AL. Wine, liquor, beer and risk of breast cancer in a large population. Eur J Cancer. 2009; 45:843–50. [PubMed: 19095438]

20. Enger SM, Ross RK, Paganini-Hill A, Longnecker MP, Bernstein L. Alcohol consumption and breast cancer oestrogen and progesterone receptor status. Br J Cancer. 1999; 79:1308–14. [PubMed: 10098777]
21. Terry MB, Zhang FF, Kabat G, et al. Lifetime alcohol intake and breast cancer risk. Ann Epidemiol. 2006; 16:230–40. [PubMed: 16230024]
22. Deandrea S, Talamini R, Foschi R, et al. Alcohol and breast cancer risk defined by estrogen and progesterone receptor status: a case-control study. Cancer Epidemiol Biomarkers Prev. 2008; 17:2025–8. [PubMed: 18708394]
23. Lew JQ, Freedman ND, Leitzmann MF, et al. Alcohol and risk of breast cancer by histologic type and hormone receptor status in postmenopausal women: the NIH-AARP Diet and Health Study. American Journal of Epidemiology. 2009; 170:308–17. [PubMed: 19541857]
24. Li CI, Chlebowski RT, Freiberg M, et al. Alcohol consumption and risk of postmenopausal breast cancer by subtype: the women's health initiative observational study. Journal of the National Cancer Institute. 2010; 102:1422–31. [PubMed: 20733117]
25. Reichman ME, Judd JT, Longcope C, et al. Effects of alcohol consumption on plasma and urinary hormone concentrations in premenopausal women. J Natl Cancer Inst. 1993; 85:722–7. [PubMed: 8478958]
26. Dorgan JF, Baer DJ, Albert PS, et al. Serum hormones and the alcohol-breast cancer association in postmenopausal women. J Natl Cancer Inst. 2001; 93:710–5. [PubMed: 11333294]
27. Onland-Moret NC, Peeters PH, van der Schouw YT, Grobbee DE, van Gils CH. Alcohol and endogenous sex steroid levels in postmenopausal women: a cross-sectional study. J Clin Endocrinol Metab. 2005; 90:1414–9. [PubMed: 15572431]
28. Rinaldi S, Peeters PH, Bezemer ID, et al. Relationship of alcohol intake and sex steroid concentrations in blood in pre- and post-menopausal women: the European Prospective Investigation into Cancer and Nutrition. Cancer Causes Control. 2006; 17:1033–43. [PubMed: 16933054]
29. Purohit V. Can alcohol promote aromatization of androgens to estrogens? A review. Alcohol. 2000; 22:123–7. [PubMed: 11163119]
30. Sarkola T, Adlercreutz H, Heinonen S, von Der Pahlen B, Eriksson CJ. The role of the liver in the acute effect of alcohol on androgens in women. J Clin Endocrinol Metab. 2001; 86:1981–5. [PubMed: 11344195]
31. Fan S, Meng Q, Gao B, et al. Alcohol stimulates estrogen receptor signaling in human breast cancer cell lines. Cancer Res. 2000; 60:5635–9. [PubMed: 11059753]
32. Singletary KW, Frey RS, Yan W. Effect of ethanol on proliferation and estrogen receptor-alpha expression in human breast cancer cells. Cancer Lett. 2001; 165:131–7. [PubMed: 11275361]
33. Morch LS, Johansen D, Thygesen LC, et al. Alcohol drinking, consumption patterns and breast cancer among Danish nurses: a cohort study. Eur J Public Health. 2007
34. Kinney AY, Millikan RC, Lin YH, Moorman PG, Newman B. Alcohol consumption and breast cancer among black and white women in North Carolina (United States). Cancer Causes Control. 2000; 11:345–57. [PubMed: 10843445]
35. Swanson CA, Coates RJ, Malone KE, et al. Alcohol consumption and breast cancer risk among women under age 45 years. Epidemiology. 1997; 8:231–7. [PubMed: 9115015]
36. Tjonneland A, Christensen J, Thomsen BL, et al. Lifetime alcohol consumption and postmenopausal breast cancer rate in Denmark: a prospective cohort study. J Nutr. 2004; 134:173–8. [PubMed: 14704313]
37. McDonald JA, Mandel MG, Marchbanks PA, et al. Alcohol exposure and breast cancer: results of the women's contraceptive and reproductive experiences study. Cancer Epidemiol Biomarkers Prev. 2004; 13:2106–16. [PubMed: 15598768]
38. Ellison RC, Zhang Y, McLennan CE, Rothman KJ. Exploring the relation of alcohol consumption to risk of breast cancer. Am J Epidemiol. 2001; 154:740–7. [PubMed: 11590087]
39. Colditz GA, Rosner BA, Chen WY, Holmes MD, Hankinson SE. Risk factors for breast cancer according to estrogen and progesterone receptor status. J Natl Cancer Inst. 2004; 96:218–28. [PubMed: 14759989]

40. Rosner BA. Measurement error models for ordinal exposure variables measured with error. Stat Med. 1996; 15:293–303. [PubMed: 8643887]

41. Midanik LT, Clark WB. The demographic distribution of US drinking patterns in 1990: description and trends from 1984. Am J Public Health. 1994; 84:1218–22. [PubMed: 8059875]

42. Suzuki R, Iwasaki M, Inoue M, et al. Alcohol consumption-associated breast cancer incidence and potential effect modifiers: the Japan Public Health Center-based Prospective Study. International Journal of Cancer. 2010; 127:685–95.

43. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin. 2011; 61:212–36. [PubMed: 21685461]

44. Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ. 2011; 342:d671. [PubMed: 21343207]

Table 1

Demographic characteristics

Cumulative average daily alcohol (gms/day) *	**0**	**0.1-4.9**	**5-9.9**	**10-19.9**	**≥ 20**
N	18967	37700	11559	10212	6192
Age (mean(SD))	61.2(7.2)	60.0 (7.2)	60.2(7.1)	60.8(6.9)	61.5(6.8)
Age at menarche (mean(SD))	12.4(1.8)	12.4(1.8)	12.5(1.8)	12.5(1.7)	12.5(1.8)
Body mass index (mean(SD))	27.6(5.8)	27.0(5.3)	25.7(4.5)	25.1(4.2)	25.1(4.3)
Premenopausal (%)	10.4	10.5	10.8	10.6	9.3
Nulliparous (%)	5.2	4.8	5.8	6.3	7.7
Benign breast disease (%)	18.9	19.0	18.7	17.8	17.2
Family history (%)	9.2	10.0	10.2	10.5	10.3
Tobacco use					
Never (%)	62.2	45.7	35.0	27.5	20.4
Past (%)	27.8	41.4	51.0	54.3	53.0
Current (%)	9.8	12.7	13.8	18.1	26.5
For parous women only, total duration breastfeeding in months **					
N	17614	35267	10699	9412	5623
None (%)	32.2	34.4	33.0	31.7	32.1
0.1-11mths (%)	38.9	42.0	42.3	44.3	45.0
12+ mths (%)	19.2	17.2	18.0	16.8	16.2
For postmenopausal women only					
N	17183	32032	9931	9125	5805
Current hormone therapy use (%)	35.7	40.3	43.4	44.3	4.5
Natural menopause (%)	56.8	60.1	62.4	62.0	63.7
Age at menopause (mean(SD))	49.5(6.5)	49.4(5.8)	49.5(5.8)	49.7(5.9)	49.6(6.0)
For women at least 50 years of age					

Cumulative average daily alcohol (gms/day)*	**0**	**0.1-4.9**	**5-9.9**	**10-19.9**	**≥ 20**
N	18182	35831	11078	10019	6195
Mammogram or clinical breast exam in past 2 years (%)	71.6	79.8	81.2	79.3	76.6
Mammogram and clinical breast exam in past 2 years (%)	61.1	69.8	72.3	70.0	67.5
Tumor	1669	3143	1063	1091	724
Characteristics***					
Stage I	42.4(707)	44.5(1399)	49.0(521)	48.3(527)	46.1(334)
Stage II	24.8(413)	25.6(806)	22.9(243)	24.0(262)	25.4(184)
Stage III	10.4(174)	10.9(341)	9.4(100)	9.8(107)	10.9(79)
Stage IV	2.2(36)	1.9(58)	1.2(13)	1.6(17)	2.2(16)
Missing stage information	20.3(339)	17.2(539)	17.5(186)	16.3(178)	15.3(111)

*All variables except for age and tumor characteristics are age-standardized. Demographic characteristics for study population based upon alcohol consumption in 1994.

**Numbers do not add up to 100% because breast feeding duration was missing for 9.5% of total person-time (ranging from 7 to 10% within each alcohol category).

***Alcohol categories for tumor characteristics based upon consumption immediately prior to breast cancer diagnosis. Please note that most women missing stage information were confirmed via either cancer registry or death certificate data which provide confirmation of invasive cancer but do not provide sufficient information to assign a TNM stage or were diagnosed in the early 1980's when only limited data were available on pathology report.

Table 2

Alcohol consumption and risk of invasive breast cancer by alcohol intake

Different measures of alcohol intake										
	Baseline intake (1980)			Current updated intake*			Cumulative intake**			
Alcohol (gms/day)****	Cases	Incidence rate per 100,000 person-years	RR(95%CI)***	Cases	Incidence rate per 100,000 person-years	RR(95%CI)***	Cases	Incidence rate per 100,000 person-years	RR (95% CI)***	Percent attributable risk for cumulative intake
0	1776	312	1.0 (ref)	2475	323	1.0 (ref)	1669	281	1.0 (ref)	
0.1-4.9	2016	331	1.07 (1.00-1.14)	1930	314	1.04 (0.98-1.11)	3143	309	1.06 (0.99-1.12)	2
5-9.9	723	363	1.15 (1.06-1.26)	692	333	1.11 (1.01-1.20)	1062	332	1.15 (1.06-1.24)	2
10-19.9	1020	370	1.15 (1.06-1.27)	863	340	1.11 (1.03-1.21)	1092	351	1.22(1.13-1.32)	3
20-29.9	246	412	1.28 (1.12-1.47)	208	370	1.21 (1.05-1.40)	362	356	1.20 (1.07-1.35)	1
≥ 30	413	476	1.50 (1.34-1.67)	350	403	1.34 (1.19-1.50)	362	413	1.51 (1.35-1.70)	2
RR per 10 gm increase	6194	344	1.09 (1.07-1.11)	6518	328	1.07 (1.05-1.10)	7690	316	1.10 (1.07-1.12)	10
P for trend			<0. 001			<0.001			< 0.001	

* For current intake, person-time for women missing alcohol intake during a specific questionnaire cycle were excluded, resulting in fewer cases for the analysis of current intake compared to that for cumulative use.

** Cumulative intake calculated from baseline (1980) forward.

*** Controlled for age, questionnaire year, ages at menarche and menopause, family history of breast cancer in first degree relative, benign breast disease, body mass index, parity and age at first full term birth, hormone therapy use, total duration of breastfeeding (months), and cigarette smoking.

**** A four-ounce glass of wine contains 11 grams of alcohol. The number of glasses of wine per week corresponding to the alcohol categories are 1-3 glasses per week for 0.1-4,9 gms/day, 3-6 glasses/wk for 5-9.9, 6-13 glasses/wk for 10-19.9, 13-19 glasses/wk for 20-29.9, and ≥19 glasses/wk for ≥ 30 gms/day.

Table 3

Alcohol and breast cancer risk by estrogen and progesterone receptor (ER/PR) status

Alcohol (gms/day)	ER+/PR+		ER-/PR-		ER+/PR-		ER-/PR+	
	Cases	Multivariate RR (95% CI)*	Cases	Multivariate RR (95% CI)*	Cases	Multivariate RR (95% CI)	Cases	Multivariate RR (95% CI)
0	806	1.0 (ref)	222	1.0 (ref)	209	1.0 (ref)	33	1.0 (ref)
0.1-4.9	1569	1.03 (0.94-1.12)	447	1.14 (0.97-1.34)	435	1.15 (0.97-1.36)	72	1.30 (0.86-1.97)
5-9.9	541	1.14 (1.02-1.28)	151	1.25 (1.01-1.54)	129	1.07 (0.856-1.34)	29	1.49 (0.89-2.50)
10-19.9	565	1.27 (1.14-1.42)	135	1.17 (0.94-1.46)	140	1.19 (0.95-1.48)	24	1.30 (0.76-2.23)
20-29.9	185	1.20 (1.02-1.47)	40	1.05 (0.75-1.49)	57	1.39 (1.03-1.88)	7	1.45 (0.67-3.17)
≥30	181	1.58 (1.34-1.86)	38	1.24 (0.87-1.76)	43	1.35 (0.96-1.89)	12	2.59 (1.33-5.07)
P for trend	3847	<0. 001	1033	0.23	1011	0.04	177	0.02

*Same covariates as Table 2. Cases that were ER and/or PR unknown (N=1620) were excluded.

Table 4

Drinking patterns and breast cancer risk

Number of days consumed alcohol in typical week					Largest number of alcoholic drinks in one day in typical month				
Days	**Cases/person years**	**Incidence rate per 100,000 person-years**	**MV RR (95% CI), model 1***	**MV RR (95% CI), model 2****	**Drinks**	**Cases/person-years**	**Incidence rate per 100,000 person-years**	**MV RR (95% CI), model 1***	**MV RR (95% CI), model 2****
0	2382/654064	364	1.0 (ref)	1.0 (ref)	0	1736/476522	364	1.0 (ref)	1.0 (ref)
1-2	1441/385233	372	1.05 (0.99-1.13)	1.03 (0.95-1.11)	1-2	2559/653056	392	1.08 (1.02-1.16)	1.07 (0.99-1.15)
3-4	500/132420	378	1.05 (0.93-1.16)	0.97 (0.86-1.09)	3-5	905/233786	387	1.16 (1.07-1.27)	1.08 (0.97-1.20)
5-7	961/217546	442	1.20 (1.10-1.30)	1.05 (0.93-1.18)	≥ 6	131/31614	414	1.33 (1.11-1.59)	1.21 (0.99-1.47)
P for trend	5284/1385420	380	<0.001	0.29	P for trend	5331/1394978	382	<0. 001	0.04

* Covariates same as Table 2. Analyses begin in 1988 when drinking patterns were first assessed. Model 1 does not control for cumulative alcohol intake. Model 2 does control for cumulative alcohol intake.

Table 5

Alcohol consumption in earlier and later adult life and breast cancer risk

	All Invasive Breast Cancers							
	18-40 years				Cumulative >40 years			
Alcohol (gm/day)	Cases/person-years	Incidence rate per 100,000 person-years	RR (95%CI) Model 1*	RR (95%CI) Model 2**	Cases/person-years	Incidence rate per 100,000 person-years	RR (95%CI) Model 1*	RR (95%CI) Model 2**
0	816/235246	347	1.0 (ref)	1.0 (ref)	976/283346	344	1.0 (ref)	1.0 (ref)
0.1-4.9	3028/828044	366	1.06 (0.97-1.14)	1.02 (0.93-1.12)	2162/606120	357	1.03 (0.95-1.11)	1.02 (0.93-1.10)
5-9.9	748/189544	395	1.13 (1.02-1.26)	1.05 (0.93-1.18)	703/185850	378	1.09 (0.99-1.20)	1.07 (0.96-1.19)
10-19.9	322/74250	434	1.25 (1.09-1.43)	1.15 (0.99-1.33)	691/99266	426	1.20 (1.09-1.33)	1.17 (1.04-1.31)
≥ 20	42/97968	429	1.33 (0.97-1.82)	1.21 (0.88-1.67)	424	429	1.23 (1.09-1.39)	1.18 (1.03-1.34)
RR per 10 gm increase	4956/1336212	371	1.16 (1.08-1.25)	1.10 (1.02-1.20)	4956/1336212	371	1.08 (1.05-1.12)	1.07 (1.03-1.11)
P for trend			<0.001	0.02			<0.001	<0.001

* Model lanalyses begin with 1988 follow-up period when drinking in earlier adult life was first assessed. For cumulative alcohol intake after age 40, cumulative intake was calculated from baseline (1980) going forward for nurses 40 or older at baseline and from the time the nurse turned 40 for those younger than 40 at baseline. All relative risks were controlled for same variables as Table 2.

** Model 2 is the same as Model 1, but both alcohol intake at ages 18 – 40 and cumulative alcohol intake are included in the same model

eTable 1

Alcohol consumption and breast cancer risk by menopausal status at diagnosis

	Menopausal Status*					
	Postmenopausal			Premenopausal		
Alcohol (gms/day)	Cases	Incidence rate per 100,000 person-years	RR(95%CI)	Cases	Incidence rate per 100,000 person-years	RR (95% CI)
0	1348	317	1.0	221	172	1.0
0.1-4.9	2630	350	1.08 (1.01-1.16)	367	181	0.97 (0.82-1.15)
5-9.9	880	374	1.17 (1.08-1.28)	143	223	1.15 (0.93-1.43)
10-19.9	904	399	1.27 (1.17-1.38)	137	211	1.11 (0.89-1.38)
20-29.9	314	404	1.27 (1.12-1.44)	34	189	0.96 (0.66-1.39)
≥30	298	462	1.56 (1.37-1.76)	44	260	1.35 (0.97-1.88)
P for trend	6374	358	<0.0001	946	191	0.03
P for interaction = 0.74						

*Premenopausal women who had a simple hysterectomy without bilateral oophorectomy were considered to have a “dubious” menopausal status and were excluded from the menopausal status analyses until the age when natural menopause had occurred in 90% of the cohort (54 years for current cigarette smokers and 56 years for nonsmokers).

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eTable 2

Alcohol consumption and breast cancer risk by histology*

	Ductal			Lobular		
Alcohol (gms/day)	**Cases**	**Incidence rate per 100,000 person-years**	**RR(95%CI)**	**Cases**	**Incidence rate per 100,000 person-years**	**RR (95% CI)**
0	1283	216	1.0	150	25	1.0
0.1-4.9	2396	236	1.06 (0.99-1.13)	310	31	1.10 (0.90-1.33)
5-9.9	803	250	1.13 (1.04-1.24)	116	37	1.33 (1.04-1.71)
10-19.9	830	267	1.22 (1.12-1.33)	112	36	1.36 (1.15-2.24)
20-29.9	287	282	1.25 (1.10-1.42)	46	46	1.61 (1.15-2.24)
≥30	275	314	1.49 (1.30-1.70)	38	44	1.81 (1.26-2.60)
P for trend	5874	242	<0.0001	772	32	<0.0001

*Only cases that were considered pure ductal or pure lobular were included in this analysis.