Research Article

Cancer Epidemiology, Biomarkers & Prevention

Postdiagnosis Alcohol Consumption and Breast Cancer Prognosis in the After Breast Cancer Pooling Project

Marilyn L. Kwan[1], Wendy Y. Chen[3,4], Shirley W. Flatt[2], Erin K. Weltzien[1], Sarah J. Nechuta[5], Elizabeth M. Poole[3], Michelle D. Holmes[3], Ruth E. Patterson[2], Xiao Ou Shu[5], John P. Pierce[2], and Bette J. Caan[1]

Abstract

Background: Alcohol consumption is an established risk factor for incident breast cancer. However, its role in breast cancer prognosis remains unclear.

Methods: We conducted an investigation of postdiagnosis alcohol consumption with recurrence and mortality among 9,329 breast cancer patients in the After Breast Cancer Pooling Project. Women were diagnosed from 1990 to 2006 with AJCC Stage I-III breast tumors from three prospective US cohorts. Alcohol intake was assessed at cohort entry (mean 2.1 years postdiagnosis) using a food frequency questionnaire. HR and 95% confidence intervals (CI) were estimated using delayed entry Cox proportional hazards models with adjustment for known prognostic factors.

Results: After a mean follow-up of 10.3 years, 1,646 recurrences and 1,543 deaths were ascertained. 5,422 women (58%) were considered drinkers (≥0.36 g/day of alcohol, ≥0.25 drinks/week) with a median of 5.3 g/day. Overall, compared with nondrinking, regular alcohol intake (≥6.0 g/day) was not associated with risk of recurrence (HR for 6 to less than 12 g/day, 1.03; 95% CI, 0.86–1.24; HR for 12 to less than 24 g/day, 1.12; 95% CI, 0.93–1.34; HR for ≥24 g/day, 1.04; 95% CI, 0.84–1.31). However, risk varied significantly by menopausal status (P for interaction < 0.05). Postmenopausal women who regularly consumed alcohol (≥6.0 g/day) had increased risk of recurrence (HR, 1.19; 95% CI, 1.01–1.40). Alcohol intake was not associated with mortality.

Conclusions: Regular alcohol consumption was not associated with breast cancer recurrence and total mortality overall, yet recurrence risk was only elevated in postmenopausal women.

Impact: The association between alcohol intake and recurrence may depend on menopausal status at breast cancer diagnosis. *Cancer Epidemiol Biomarkers Prev; 22(1); 32–41. ©2012 AACR.*

Introduction

In 2011, the estimated number of breast cancer survivors in the US was over 2.6 million, and the population continues to grow (1, 2). Many women living with breast cancer are keenly interested in how they can improve their prognosis and survival by making lifestyle changes after their diagnosis. One factor of particular interest is alcohol consumption, which is generally recognized to increase the risk of breast cancer (3–5). However, inconclusive results have emerged from the limited number of studies that have examined alcohol intake (primarily before diagnosis) and breast cancer-related outcomes.

Previous studies have reported increased (6–9) and decreased risks of death (10–13) with pre- and postdiagnosis alcohol consumption, as well as no association (14–24). Fewer studies have examined the association of alcohol on breast cancer recurrence, with mixed results (6, 13, 25, 26).

Overall, studies of alcohol and breast cancer prognosis have suffered from methodologic challenges, namely, varied endpoints, narrow exposure (drinking) range, prediagnosis rather than postdiagnosis assessment of intake, and failure to adjust for prognostic factors (27, 28). Alcohol might influence breast cancer risk and prognosis by increasing estrogen metabolism and endogenous estrogen levels, particularly in postmenopausal women (29–33). However, epidemiologic studies to date have not had adequate sample size to conduct subgroup analyses by estrogenic factors.

To address these limitations, we conducted one of the largest pooled investigations of postdiagnosis alcohol consumption and breast cancer recurrence and total mortality using data from 9,329 US breast cancer survivors in the After Breast Cancer Pooling Project (ABCPP). We also

Authors' Affiliations: [1]Division of Research, Kaiser Permanente Northern California, Oakland, California; [2]Cancer Prevention and Control Program, Moores UCSD Cancer Center, University of California, San Diego, California; [3]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [4]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts; and [5]Division of Epidemiology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee

Corresponding Author: Marilyn L. Kwan, 2000 Broadway, Oakland, CA 94612. Phone: 510-891-3521; Fax: 510-891-3761; E-mail: Marilyn.L.Kwan@kp.org

doi: 10.1158/1055-9965.EPI-12-1022

examined potential effect modification by *a priori* selected estrogenic factors including menopausal status, tumor estrogen receptor (ER) status, and obesity.

Materials and Methods

The After Breast Cancer Pooling Project

The ABCPP is an international collaboration of pooled data from 4 prospective studies of breast cancer survivors to examine the roles of physical activity, adiposity, dietary factors, supplement use, and quality of life in breast cancer prognosis. Details about cohort creation and characteristics have been published previously (34). Briefly, the ABCPP includes 18,333 breast cancer survivors diagnosed with stage I-IV invasive breast cancer from 4 population-based prospective cohort studies recruited from the US and Shanghai, China: the Shanghai Breast Cancer Survival Study (SBCSS; ref. 35), the Life after Cancer Epidemiology (LACE) Study (36), the Women's Healthy Eating and Living (WHEL) Study (37), and breast cancer patients from the Nurses' Health Study (NHS; ref. 38). Each cohort collected data on clinical and reproductive factors, family history of breast cancer, quality of life, medical history, anthropometry, smoking history, alcohol intake, supplement use, physical activity, and diet. In the ABCPP, these data have been harmonized into a common dataset. Individual studies received Institutional Review Board approval from their respective institution(s) to participate in this collaboration.

Alcohol intake

Data from WHEL, LACE, and NHS were included in this analysis, as almost no women in the SBCSS reported alcohol consumption. Postdiagnosis alcohol intake was collected from participants at baseline (entry into cohort for LACE and WHEL) or regular follow-up after diagnosis (NHS) using validated food frequency questionnaires (FFQ).

Alcohol was assessed at baseline (on average 2 years postdiagnosis) in WHEL using the Arizona Food Frequency Questionnaire (39, 40) and in LACE using the Fred Hutchinson Cancer Research Center Food Frequency Questionnaire (FHRCC-FQ; ref. 41). For wine, beer, and liquor, women reported their average frequency of consumption over the past 12 months, and a medium serving size was defined as 1 6-oz glass, 1 12-oz can or bottle, and 1 1.5-oz shot, respectively. For WHEL, other minor sources of alcohol (e.g., vanilla extract and bread) were included in calculations of alcohol intake. The NHS assessed dietary habits using a validated semi-quantitative FFQ approximately every 4 years since diagnosis (38). For wine, beer, and liquor, women reported their average frequency of consumption over the past 12 months, and single serving sizes were defined as 1 4-oz glass, 1 12-oz can or bottle, and 1 standard shot, respectively.

Servings per day in oz was converted to grams (g) per day of alcohol [one standard drink in the United States is commonly 12.0 to 14.0 g of pure alcohol depending on the alcohol by volume of the drink (42)] and categorized as none (<0.36 g/day, considered nondrinkers), 0.36 to less than 6.0 g/day (occasional drinkers), and 6.0 g/day or more (regular drinkers). Half a drink per day (6.0 g) was selected as the cutoff point, given that the median level of intake among drinkers in the combined cohorts was 5.3 g/day and the current guidelines for cancer prevention is 1 drink per day for women with no cancer history (3, 43). Higher categories of consumption were also created to examine dose response relationships among regular drinkers (6.0 to less than 12.0 g/day, 12.0 to less than 24.0 g/day, and $\geq$24.0 g/day).

Covariates

Sociodemographic and lifestyle factors. Data included race/ethnicity (non-Hispanic white, non-Hispanic black, Asian, Hispanic, and other), education (less than high school, high school, some college, and college graduate), smoking history at diagnosis (never, past, and current), and menopausal status at diagnosis (premenopausal, postmenopausal, and unknown). Postdiagnosis recreational physical activity in metabolic equivalents (MET-hours/week) was determined on average 2.4 years postdiagnosis (range: 1.4–4.0 years) from semiquantitative questionnaires and classified as meeting or not meeting the 2008 Physical Activity Guidelines of 10 MET-hours/week or more (44). Prediagnosis body mass index (BMI) was calculated from self-reported prediagnosis weight and height at baseline (entry into cohort for WHEL and LACE) or regular follow-up before diagnosis (NHS). The BMI measures from all 3 studies were between 1 and 2 years before breast cancer diagnosis (45).

Clinical characteristics. Data included age at diagnosis (years), AJCC stage (I, II, III, and IV), ER/progesterone receptor (PR) status (ER+/PR+, ER+/PR−, ER−/PR+, ER−/PR−), surgery (none, lumpectomy, and mastectomy), chemotherapy (no and yes), radiation therapy (no and yes), and hormonal therapy (no and yes). Any comorbidity history consisted of reporting at least one of the following conditions: diabetes, hypertension, myocardial infarction, and/or stroke.

Ascertainment of outcomes

All studies ascertained outcome events by self-report and regular linkage to electronic medical records and vital statistics registries. Reported events were verified by medical record review except self-reported recurrences in the NHS. Cause of death, including breast cancer and cardiovascular disease (CVD), was determined from death certificates and supplemented with medical records if necessary. Details of outcome ascertainment have been published (34).

Primary analytic outcomes were a new breast cancer event, defined as a first recurrence/metastasis or new primary breast cancer (hereafter referred to as recurrence), all-cause mortality, breast cancer mortality, and CVD mortality. New primary breast cancers were longitudinally recorded in all cohorts except the NHS. For NHS

participants who did not report a recurrence but died from breast cancer (7.2%), the recurrence date was set 2 years before the date of death (46).

Final analytic sample size

Women were excluded from the analysis if they were diagnosed before 1990 to ensure comparable diagnosis dates and treatment information across the cohorts (n = 2,965 NHS cases), had stage IV breast cancer (n = 126), or had no postdiagnosis alcohol data (n = 1,021) or follow-up time (n = 6). A total of 9,329 breast cancer survivors comprised the final cohort. For the analyses depending on the outcome of interest, we further excluded women with missing outcome data (n = 119 with no recurrence information; n = 19 with no cause of death information), missing covariate data (n = 4), and/or date of recurrence was before start of study follow-up (n = 55). A total of 9,151 observations were available for the recurrence analyses, 9,325 observations for the total mortality analyses, and 9,306 observations for the breast cancer and CVD mortality analyses.

Statistical analysis

Sociodemographic, lifestyle, and clinical characteristics of the pooled cohort and by category of postdiagnosis alcohol intake were summarized by frequency distributions for categorical variables and means with SD for continuous variables.

The multivariable analysis involved 3 steps. First, delayed entry Cox proportional hazards regression models were used to estimate study-specific adjusted HRs and 95% confidence intervals (CI) with time since diagnosis as the time scale (47). The entry date was the date of the first survey after breast cancer diagnosis. For models with breast cancer recurrence as the outcome, the exit date was date of recurrence or date of death (whichever was first), or date of last contact (i.e., date of last follow-up survey or date of last registry linkage, whichever occurred first) for women without an event. For models with mortality as the outcome, the exit date was the date of death or date of last contact. Second, a meta-analysis was conducted with study-specific HRs using inverse-variance weights in random-effects models (48). The Q test statistic was used to assess heterogeneity in risk estimates across studies (49). Evidence for heterogeneity was not observed (P > 0.05); hence, pooled analyses were conducted and presented herein for the alcohol-outcome associations of interest using delayed entry Cox proportional hazards regression models stratified by study (50). The proportional hazards assumption for all Cox models was assessed by Kolmogorov-type supremum tests. Tests for linear trend were conducted by modeling categorical variables on an ordinal scale. Statistical significance was considered as $P < 0.05$ or 95% CI not overlapping with 1.0.

Covariates for the final Cox models were chosen based on *a priori* determination from literature review or if a covariate produced a 10% change in the main effect estimate when the covariate was added individually to the Cox model (51). Age at diagnosis, AJCC stage, race/ethnicity, education, menopausal status at diagnosis, hormone receptor status, surgery, treatment, smoking, physical activity, prediagnosis BMI, and comorbidity were retained. All missing values for each covariate were included as dummy variables. To test for the impact of missing covariate information, we ran a complete case analysis, and results were similar to treating missing data as an indicator category. We also conducted a subgroup analysis excluding women who had an early recurrence within the first 2 years of their breast cancer diagnosis (n = 152) to rule out potential effects of reverse causality attributable to underlying disease.

Possible *a priori* effect modification was evaluated in the associations of alcohol consumption with recurrence and mortality by menopausal status (premenopausal vs. postmenopausal), ER status (ER+ vs. ER−), and obesity (obese vs. nonobese) in stratified analyses. Statistical significance of multiplicative interaction terms was assessed by a Wald test of the cross-product terms between the main exposure (3-level alcohol variable) and the potential effect modifier (dichotomous variable as described above) in the Cox models.

Results

Over a mean follow-up of 10.3 years in the entire cohort, a total of 1,646 recurrences and 1,543 deaths (156 related to CVD) were confirmed. Mean times (range) from index diagnosis to recurrence and death were 5.6 (0.1–16.6) years and 7.8 (1.0, 18.6) years among the women who had the events, respectively. Alcohol consumption was assessed on average 2.1 years postdiagnosis (range: 0.1–14.2 years).

Characteristics of the pooled cohort by nondrinkers, occasional drinkers, and regular drinkers (g/day of alcohol consumption) are given in Table 1. The mean age at breast cancer diagnosis was 58.8 years, and 70.9% were postmenopausal at diagnosis. The majority was non-Hispanic white (88.6%) and had at least some college education (89.7%). Most women (88.4%) were diagnosed with stage I or II tumors, and 83.1% of the tumors were ER+ and/or PR+. Compared with nondrinkers (41.9%), drinkers were more likely to be younger and premenopausal, more educated, diagnosed with earlier stage, hormone receptor positive breast cancer, and received radiation therapy or hormonal therapy. Drinkers also tended to be current or past smokers, more physically active, leaner, and with fewer comorbidities.

In the cohort, the mean (SD) g/day of alcohol consumption was 5.79 (11.15), whereas the median (range) was 1.00 (0–149.32; Table 2). Thus, the distribution of alcohol consumption was skewed by a small proportion of heavy drinkers. Among the drinkers (≥0.36 g/day), the mean (SD) consumption was 9.94 (13.14) g/day (median 5.30; range: 0.39–149.32).

Table 3 gives the associations between postdiagnosis alcohol intake (nondrinker, occasional, regular low,

Table 1. Characteristics of the After Breast Cancer Pooling Project (ABCPP) by postdiagnosis alcohol consumption

	Overall *n* = 9,329	Nondrinker (<0.36 g/day) *n* = 3,907	Occasional (0.36 to less than 6 g/day) *n* = 2,880	Regular (≥6 g/day) *n* = 2,542
Age at diagnosis (mean, SD)	58.8 (10.5)	59.8 (10.8)	57.4 (10.0)	58.7 (10.3)
Prediagnosis BMI (mean, SD)	26.5 (5.4)	27.6 (6.0)	26.2 (5.1)	25.0 (4.3)
	n (%)	*n* (%)	*n* (%)	*n* (%)
Race/ethnicity				
Non-Hispanic white	8,261 (88.6)	3,302 (84.5)	2,578 (89.5)	2,381 (93.7)
Non-Hispanic black	248 (2.7)	149 (3.8)	65 (2.3)	34 (1.4)
Asian	238 (2.5)	156 (4.0)	66 (2.3)	16 (0.6)
Hispanic	308 (3.3)	153 (3.9)	102 (3.5)	53 (2.1)
Other	272 (2.9)	146 (3.8)	69 (2.4)	57 (2.2)
Education				
Less than high school	113 (1.2)	65 (1.7)	29 (1.0)	19 (0.7)
High school	846 (9.1)	416 (10.7)	242 (8.4)	188 (7.4)
Some college	1,652 (17.7)	740 (18.9)	496 (17.2)	416 (16.4)
College grad or higher	6,714 (72.0)	2,685 (68.7)	2,113 (73.4)	1,916 (75.5)
Menopausal status at diagnosis				
Premenopausal	2,222 (23.8)	843 (21.6)	754 (26.2)	625 (24.6)
Postmenopausal	6,613 (70.9)	2,836 (72.6)	1,983 (68.8)	1,794 (70.6)
Unknown	494 (5.3)	228 (5.8)	143 (5.0)	123 (4.8)
AJCC stage				
I	4,699 (51.3)	1,867 (48.8)	1,430 (50.6)	1,402 (56.1)
II	3,392 (37.1)	1,504 (39.3)	1,063 (37.6)	825 (33.0)
III	1,062 (11.6)	453 (11.9)	335 (11.8)	274 (10.9)
Hormone receptor status				
ER+, PR+	5,746 (65.2)	2,361 (64.0)	1,751 (64.6)	1,634 (68.0)
ER−, PR+	276 (3.1)	113 (3.0)	100 (3.7)	63 (2.6)
ER+, PR−	1,302 (14.8)	570 (15.4)	380 (14.0)	352 (14.6)
ER−, PR−	1,484 (16.9)	648 (17.6)	481 (17.7)	355 (14.8)
Chemotherapy				
No	4,402 (47.9)	1,843 (47.9)	1,267 (44.6)	1,292 (51.4)
Yes	4,795 (52.1)	2,004 (52.1)	1,572 (55.4)	1,219 (48.6)
Radiation therapy				
No	3,595 (38.9)	1,576 (40.8)	1,093 (38.3)	926 (36.7)
Yes	5,649 (61.1)	2,290 (59.2)	1,764 (61.7)	1,595 (63.3)
Hormonal therapy				
No	2,416 (26.2)	1,036 (26.9)	769 (26.9)	611 (24.3)
Yes	6,808 (73.8)	2,815 (73.1)	2,087 (73.1)	1,906 (75.7)
Surgery type				
None	18 (0.2)	9 (0.2)	7 (0.2)	2 (0.1)
Lumpectomy	4,675 (50.6)	1,842 (47.7)	1,472 (51.5)	1,361 (54.0)
Mastectomy	4,553 (49.2)	2,014 (52.1)	1,381 (48.3)	1,158 (45.9)
Smoking history				
Never	4,472 (48.2)	2,244 (57.8)	1,375 (48.0)	853 (33.7)
Past	4,167 (44.9)	1,388 (35.7)	1,322 (46.1)	1,457 (57.5)
Current	646 (6.9)	253 (6.5)	169 (5.9)	224 (8.8)
Any comorbidity				
No	5,376 (61.4)	2,005 (54.4)	1,787 (66.0)	1,584 (67.1)
Yes	3,373 (38.6)	1,678 (45.6)	920 (34.0)	775 (32.9)
Met physical activity guidelines				
No	3,696 (48.9)	1,714 (55.0)	1,104 (45.9)	878 (42.9)
Yes	3,869 (51.1)	1,400 (45.0)	1,302 (54.1)	1,167 (57.1)

NOTE: Missing values for covariates were as follows: race/ethnicity (*n* = 2), education (*n* = 4), AJCC stage (*n* = 176), hormone receptor status (*n* = 521), chemotherapy (*n* = 132), radiation therapy (*n* = 85), hormonal therapy (*n* = 105), surgery type (*n* = 90), smoking history (*n* = 44), any comorbidity (*n* = 580), and met 2008 Physical Activity Guidelines of 10 MET-hours/week or more (*n* = 1,764; ref. 44).

Table 2. Alcohol consumption in the ABCPP

		Total alcohol consumption g/day		
	n (%)	Mean (SD)	Median	Range
Total cohort	9,329 (100)	5.79 (11.15)	1.00	0.00–149.32
Nondrinker (<0.36 g/day)	3,907 (41.88)	0.02 (0.05)	0.00	0.00–0.33
Drinker (≥0.36 g/day)	5,422 (100)	9.94 (13.14)	5.30	0.39–149.32
Occasional (0.36 to less than 6 g/day)	2,880 (53.12)	2.23 (1.49)	1.83	0.39–6.00
Regular (≥6 g/day)	2,542 (46.88)	18.67 (14.91)	13.80	6.00–149.32

NOTE: 0.36 and 6 g/day are approximately 0.25 and 3.5 drinks/week, respectively.

regular medium, and regular high) and breast cancer recurrence and mortality in the overall pooled cohort. Compared with no consumption, regular consumption of alcohol (≥6.0 g/day) was not associated with risk of recurrence at any level (HR for 6 to less than 12 g/day, 1.03; 95% CI, 0.86–1.24; HR for 12 to less than 24 g/day, 1.12; 95% CI, 0.93–1.34; HR for ≥24 g/day, 1.04; 95% CI, 0.84–1.31). Occasional drinking (0.36 to less than 0.6 g/day) was also not associated with recurrence risk (HR, 0.99; 95% CI, 0.87–1.12). No dose–response effect for increasing alcohol consumption was found. When excluding the $n = 152$ women who had an early recurrence within the first 2 years of their breast cancer diagnosis to examine the potential impact of reverse causality, all the associations remained nonsignificant with no dose–response effect.

Examining risk of overall mortality, breast cancer mortality, and CVD mortality, no significant associations were found for any amount of alcohol intake. However, a borderline statistically significant trend of increasing consumption with decreasing risk of CVD death was observed for regular consumption of 24 g/day or more (HR, 0.48; 95% CI, 0.21–1.12; P for trend $= 0.07$). A corresponding decreased risk of overall death was also found for regular consumption of 24 g/day or more (HR, 0.79; 95% CI, 0.63–1.00; P for trend $= 0.06$).

Table 4 gives stratified analyses of postdiagnosis alcohol consumption (nondrinker, occasional, and regular) and recurrence by menopausal status at diagnosis, ER status, and prediagnosis obesity. Significant effect modification was present for risk of recurrence by menopausal status (P for interaction $= 0.027$) and ER status (P for interaction $= 0.012$). Among postmenopausal women at diagnosis, increasing consumption of alcohol postdiagnosis was associated with an increased risk of recurrence (P for trend $= 0.04$), and the increased risk associated with regular consumption (≥6.0 g/day) was statistically significant (HR, 1.19; 95% CI, 1.01–1.40). In contrast, among premenopausal women at diagnosis, occasional drinking (0.36 to less than 0.6 g/day) postdiagnosis was associated with a decreased risk of recurrence (HR, 0.75; 95% CI, 0.59–0.94) with no apparent dose–response effect. While no associations were observed among ER+ women, occasional alcohol consumption (0.36 to less than 6.0 g/day) in ER− women was associated with decreased risk of recurrence (HR, 0.70; 95% CI, 0.53–0.92), whereas regular consumption (≥6.0 g/day) had no association with recurrence (HR, 1.03; 95% CI, 0.78–1.36). Associations were similar across the obese and nonobese groups with no evidence of effect modification (Table 4).

Stratified analyses of alcohol intake and mortality outcomes (total and breast cancer specific) by menopausal status, hormone receptor status, and obesity were not significant (data not shown).

Discussion

In this large pooled analysis of 9,329 US breast cancer survivors, alcohol consumption after a breast cancer diagnosis was not associated with increased risk of recurrence or total mortality in general, yet some varying risk associations were observed by estrogenic factors. Specifically, compared with no drinking, regular consumption of more than 3 drinks per week (approximately half a drink or more per day) was associated with an approximate 20% increased relative risk of recurrence among postmenopausal women. While not statistically significant yet consistent with previous studies, there was a suggestive inverse trend of alcohol intake with decreased cardiovascular-related mortality despite the limited number of CVD deaths in the cohort. These results suggest that alcohol intake is generally not associated with poor outcomes after a breast cancer diagnosis in the largest analytic sample size to date. However, alcohol might be associated with a modestly increased risk of recurrence in postmenopausal women, but this finding requires independent corroboration in other large studies.

A possible explanation as to why postdiagnosis alcohol intake was not associated with risk of breast cancer recurrence among all women yet associated with increased risk among postmenopausal women only is that the estrogenic effects of alcohol on circulating estrogens might vary depending on the endogenous estrogen environment (29, 33). Among postmenopausal women with breast cancer, sex hormone concentrations have been shown to be stable over time (52, 53), yet those in premenopausal women with breast cancer can fluctuate greatly because of treatment effects and age (53–55). Furthermore, women

Table 3. Association of alcohol consumption and recurrence and mortality in the ABCPP

		Total cohort[a]		Excluding early events (within 2 years of initial breast cancer diagnosis)[a]	
		***n* = 9,151 (1,487 events)**		***n* = 8,987 (1,335 events)**	
Recurrence	***n***	**Events**	**HR (95% CI)**	**Events**	**HR (95% CI)**
Nondrinker (<0.36 g/day)	3,829	624	Ref	549	Ref
Occasional (0.36 to less than 6 g/day)	2,816	454	0.99 (0.87–1.12)	415	1.02 (0.90–1.17)
Regular low (6 to less than 12 g/day)	1,002	160	1.03 (0.86–1.24)	146	1.08 (0.89–1.30)
Regular medium (12 to less than 24 g/day)	928	156	1.12 (0.93–1.34)	139	1.12 (0.93–1.36)
Regular high (≥24 g/day)	576	93	1.04 (0.84–1.31)	86	1.09 (0.86–1.37)
P for trend			0.32		0.21
		***n* = 9,325 (1,542 events)**		***n* = 9,286 (1,510 events)**	
Total mortality	***n***	**Events**	**HR (95% CI)**	**Events**	**HR (95% CI)**
Nondrinker (<0.36 g/day)	3,906	712	Ref	697	Ref
Occasional (0.36 to less than 6 g/day)	2,880	438	0.91 (0.81–1.03)	429	0.91 (0.81–1.04)
Regular low (6 to less than 12 g/day)	1,013	166	1.01 (0.84–1.20)	162	1.00 (0.84–1.20)
Regular medium (12 to less than 24 g/day)	945	140	0.89 (0.74–1.07)	137	0.89 (0.74–1.07)
Regular high (≥24 g/day)	581	86	0.79 (0.63–1.00)	85	0.80 (0.64–1.01)
P for trend			0.06		0.07
		***n* = 9,306 (911 events)**		***n* = 9,267 (885 events)**	
Breast cancer mortality	***n***	**Events**	**HR (95% CI)**	**Events**	**HR (95% CI)**
Nondrinker (<0.36 g/day)	3,900	402	Ref	390	Ref
Occasional (0.36 to less than 6 g/day)	2,875	276	0.94 (0.80–1.10)	268	0.94 (0.80–1.10)
Regular low (6 to less than 12 g/day)	1,009	102	1.06 (0.85–1.33)	98	1.05 (0.84–1.32)
Regular medium (12 to less than 24 g/day)	942	85	0.93 (0.73–1.18)	83	0.93 (0.73–1.19)
Regular high (≥24 g/day)	580	46	0.80 (0.59–1.09)	46	0.83 (0.60–1.13)
P for trend			0.29		0.36
		***n* = 9,306 (156 events)**		***n* = 9,267 (155 events)**	
CVD Mortality	***n***	**Events**	**HR (95% CI)**	**Events**	**HR (95% CI)**
Nondrinker (<0.36 g/day)	3,900	88	Ref	87	Ref
Occasional (0.36 to less than 6 g/day)	2,875	37	0.83 (0.56–1.23)	37	0.84 (0.57–1.24)
Regular low (6 to less than 12 g/day)	1,009	14	0.88 (0.49–1.58)	14	0.89 (0.50–1.60)
Regular medium (12 to less than 24 g/day)	942	11	0.72 (0.38–1.37)	11	0.73 (0.38–1.39)
Regular high (≥24 g/day)	580	6	0.48 (0.21–1.12)	6	0.48 (0.21–1.13)
P for trend			0.07		0.07

NOTE: 0.36, 6, and 12 g/day are approximately 0.25, 3.5, and 7 drinks/week, respectively.

[a]Adjusted for age at diagnosis, AJCC stage, race/ethnicity, education, menopausal status around diagnosis, hormone receptor status, surgery, treatment (radiation therapy, chemotherapy, and hormonal therapy), smoking, physical activity, prediagnosis BMI, and comorbidity.

who experience menopause resulting from treatment likely have higher estrogen levels than women who are already postmenopausal at diagnosis. Overall, more research is needed to elucidate the potentially differing biologic mechanisms of alcohol intake among premenopausal and postmenopausal women with breast cancer.

We report an increased risk of recurrence among women who were postmenopausal at breast cancer diagnosis and a corresponding decreased risk of recurrence among those who were premenopausal at diagnosis. Previous large studies on alcohol and incident breast cancer have reported an elevated risk among postmenopausal women

Table 4. Association of alcohol consumption and recurrence in the ABCPP, stratified by estrogen-related factors

	Premenopausal[a]			Postmenopausal[a]		
	n = 2,209 (447 events)			*n* = 6,456 (938 events)		
Menopausal status	***n***	**Events**	**HR (95% CI)**	***n***	**Events**	**HR (95% CI)**
Nondrinker (<0.36 g/day)[a]	838	188	Ref	2,765	389	Ref
Occasional (0.36 to less 6 g/day)	749	133	0.75 (0.59–0.94)	1,928	287	1.10 (0.94–1.29)
Regular (≥6 g/day)	622	126	0.91 (0.72–1.16)	1,763	262	1.19 (1.01–1.40)
P for trend			0.30			0.04
P for interaction = 0.027						
	ER negative[a]			**ER positive[a]**		
ER receptor status	*n* = 1,738 (328 events)			*n* = 7,027 (1,098 events)		
	n	**Events**	**HR (95% CI)**	***n***	**Events**	**HR (95% CI)**
Non-drinker (<0.36 g/day)	750	156	Ref	2,924	444	Ref
Occasional (0.36 to less than6 g/day)	575	87	0.70 (0.53–0.92)	2,116	348	1.09 (0.94–1.26)
Regular (≥6 g/day)	413	85	1.03 (0.78–1.36)	1,987	306	1.08 (0.92–1.26)
P for trend			0.76			0.31
P for interaction = 0.012						
	Obese (BMI ≥ 30 kg/m^2)[a]			**Nonobese (BMI < 30 kg/m^2)[a]**		
Prediagnosis BMI	*n* = 1,909 (318 events)			*n* = 7,107 (1,143 events)		
	n	**Events**	**HR (95% CI)**	***n***	**Events**	**HR (95% CI)**
Nondrinker (<0.36 g/day)	1,075	180	Ref	2,691	429	Ref
Occasional (0.36 to less than 6 g/day)	543	86	1.01 (0.77–1.32)	2,243	362	0.99 (0.85–1.14)
Regular (≥6 g/day)	291	52	1.15 (0.83–1.60)	2,173	352	1.07 (0.92–1.23)
P for trend			0.47			0.43
P for interaction = 0.94						

NOTE: 0.36 and 6 g/day are approximately 0.25 and 3.5 drinks/week, respectively.

[a]Adjusted for age at diagnosis, AJCC stage, race/ethnicity, education, surgery, treatment (radiation therapy, chemotherapy, and hormonal therapy), smoking, physical activity, prediagnosis BMI, and comorbidity while excluding menopausal status and hormone receptor status as appropriate depending on stratified model.

(56–58), and when we excluded the second primary breast cancers (n = 135) from our menopausal analysis, the recurrence findings were essentially unchanged. Furthermore, a linear increase in estrone sulfate levels (the most abundant, long-lasting estrogen in postmenopausal women) was previously observed across alcohol intakes of 0 to 30 g/day or more in the NHS (59).

While our results suggest a possible interaction of postdiagnosis alcohol intake by ER tumor status, because of the limited sample size of women with ER− tumors who had an event of interest, we cannot rule out chance and residual confounding. Nonetheless, alcohol has been found to increase the expression and proliferation of ERs in cultured human breast cancer cells (32, 60) and has been found to be associated with the development of incident ER+ breast cancer in postmenopausal women (61, 62). When we conducted a subgroup analysis among the 5,082 postmenopausal, ER+ women in our cohort, any level of alcohol intake was associated with a borderline significant, increased risk of recurrence (HR, 1.21; 95% CI, 0.99–1.45 for <6.0 g/day and HR, 1.19; 95% CI, CI: 0.99–1.45 for ≥6.0 g/day).

The 3 studies included in this pooled analysis have previously published individual analyses on alcohol and breast cancer prognosis, yet they either did not examine recurrence specifically (NHS) or were limited by sample size to adequately examine potential interactions by estrogen-related factors (all studies). This pooled analysis includes new analyses of recurrence, longer follow-up, and an expanded number of NHS women.

In the earlier WHEL study of 3,088 early-stage breast cancer survivors followed for 7.3 years, moderate (≥1

drink/day) alcohol intake postdiagnosis was associated with reduced overall mortality, particularly among nonobese women (13), yet was not associated with recurrence. In the NHS, moderate alcohol intake postdiagnosis was not associated with total mortality among 1,982 women diagnosed with invasive breast cancer and followed for 13.1 years (19). Similarly, in the LACE study of 1,897 women diagnosed with early-stage breast cancer and followed for 7.4 years, regular consumption of alcohol ($\geq$0.5 drink/day) after diagnosis was not associated with overall death (25). In agreement with this pooled analysis, an elevated risk of recurrence with alcohol intake was observed among postmenopausal women in LACE, whereas WHEL and NHS did not examine alcohol associations by menopausal status.

Strengths of this pooled study include being the largest to date of breast cancer survivors with data on postdiagnosis alcohol consumption, and having the ability to adjust for important prognostic and treatment-related factors, including BMI, smoking, menopausal status, cancer stage, hormone receptor status, and treatment. Our study population had a wide range of alcohol intake, allowing adequate exploration of higher levels of drinking and outcomes. The mean level in the pooled cohort among drinkers was 9.9 g/day (median 5.3), which is in agreement with mean levels reported in studies of healthy female drinkers (3.2–12.6 g/day; ref. 5). Pooling data also improved the statistical power to conduct stratified analyses by estrogen-related factors.

Of note, our analysis did not examine patterns of change in postdiagnosis alcohol consumption, as follow-up assessments across cohorts were not temporally uniform relative to baseline. However, most women (98%) remained in the same or adjacent category of intake at their subsequent follow-ups. Furthermore, change in alcohol consumption from prediagnosis to postdiagnosis may also be a contributing factor in associations of alcohol and mortality. Specifically, women who more regularly consumed alcohol before their breast cancer diagnosis and then substantially reduced or stopped their intake after diagnosis may have lower overall mortality compared with lifelong nondrinkers or low drinkers. While we do not have information on prediagnosis alcohol intake on the entire pooled cohort, perhaps this hypothesis explains, in part, the attenuated CVD mortality association observed in our analyses. We also relied on self-reported alcohol use, yet in NHS and WHEL, levels have been shown to be highly reproducible using food records and 24-hour recalls, respectively (13, 63).

In summary, we observed that alcohol consumption after a breast cancer diagnosis was generally not associated with risk of recurrence, or total or breast cancer-related mortality. A suggestive trend of alcohol intake and decreased risk of cardiovascular-related deaths was noted. However, regular drinking of more than 3 drinks per week (half a drink or more per day) was associated with higher risk of recurrence in postmenopausal women. Given that consuming alcohol is a potentially modifiable lifestyle factor following a breast cancer diagnosis, further confirmation is warranted in other large prospective studies of breast cancer survivors with long-term follow-up and detailed information on alcohol intake and estrogen-related covariates.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: M.L. Kwan, W.Y. Chen, X.-O. Shu, J.P. Pierce, B.J. Caan

Development of methodology: M.L. Kwan, W.Y. Chen, J.P. Pierce, B.J. Caan

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): W.Y. Chen, S. Nechuta, M. Holmes, J.P. Pierce, B. J. Caan

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.L. Kwan, W.Y. Chen, S.W. Flatt, E.K. Weltzien, S. Nechuta, R.E. Patterson, X.-O. Shu, B.J. Caan

Writing, review, and/or revision of the manuscript: M.L. Kwan, W.Y. Chen, S.W. Flatt, E.K. Weltzien, S. Nechuta, E.M. Poole, M. Holmes, R.E. Patterson, X.-O. Shu, J.P. Pierce, B.J. Caan

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.L. Kwan, S.W. Flatt, E.K. Weltzien, S. Nechuta, E.M. Poole

Study supervision: B.J. Caan

Grant Support

This work was supported by the National Cancer Institute (3R01CA118229-03S1). Funding for each individual cohort participating in the After Breast Cancer Pooling Project is as follows: The SBCSS was supported by the Department of Defense (DAMD 17-02-1-0607); and the National Cancer Institute (R01 CA118229). The WHEL Study was supported by the Susan G. Komen Foundation (#KG100988). The LACE Study was supported by the National Cancer Institute (R01 CA129059). The NHS was supported by the National Cancer Institute (P01 CA87969, T32 CA009001).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received September 4, 2012; revised October 22, 2012; accepted October 23, 2012; published OnlineFirst November 13, 2012.

References

1. SEER Cancer Statistics Review, 1975–2009 (Vintage 2009 Populations), National Cancer Institute. Bethesda, MD; 2012.
2. American Cancer Society. Breast Cancer Facts & Figures 2011–2012. Atlanta: American Cancer Society, Inc.
3. Kushi LH, Doyle C, McCullough M, Rock CL, Demark-Wahnefried W, Bandera EV, et al. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. CA Cancer J Clin 2012;62:30–67.
4. World Cancer Research Fund/American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington, D.C.: AICR; 2007.
5. Smith-Warner SA, Spiegelman D, Yaun SS, van den Brandt PA, Folsom AR, Goldbohm RA, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. Jama 1998;279:535–40.
6. Hebert JR, Hurley TG, Ma Y. The effect of dietary exposures on recurrence and mortality in early stage breast cancer. Breast Cancer Res Treat 1998;51:17–28.

7. Jain MG, Ferrenc RG, Rehm JT, Bondy SJ, Rohan TE, Ashley MJ, et al. Alcohol and breast cancer mortality in a cohort study. Breast Cancer Res Treat 2000;64:201–9.
8. McDonald PA, Williams R, Dawkins F, Adams-Campbell LL. Breast cancer survival in African American women: is alcohol consumption a prognostic indicator? Cancer Causes Control 2002;13: 543–9.
9. Allemani C, Berrino F, Krogh V, Sieri S, Pupa SM, Tagliabue E, et al. Do pre-diagnostic drinking habits influence breast cancer survival? Tumori 2011;97:142–8.
10. Barnett GC, Shah M, Redman K, Easton DF, Ponder BA, Pharoah PD. Risk factors for the incidence of breast cancer: do they affect survival from the disease? J Clin Oncol 2008;26:3310–6.
11. Pierce JP, Stefanick ML, Flatt SW, Natarajan L, Sternfeld B, Madlensky L, et al. Greater survival after breast cancer in physically active women with high vegetable-fruit intake regardless of obesity. J Clin Oncol 2007;25:2345–51.
12. Reding KW, Daling JR, Doody DR, O'Brien CA, Porter PL, Malone KE. Effect of prediagnostic alcohol consumption on survival after breast cancer in young women. Cancer Epidemiol Biomarkers Prev 2008; 17:1988–96.
13. Flatt SW, Thomson CA, Gold EB, Natarajan L, Rock CL, Al-Delaimy WK, et al. Low to moderate alcohol intake is not associated with increased mortality after breast cancer. Cancer Epidemiol Biomarkers Prev 2010;19:681–8.
14. Harris HR, Bergkvist L, Wolk A. Alcohol intake and mortality among women with invasive breast cancer. Br J Cancer 2012;106:592–5.
15. Dal Maso L, Zucchetto A, Talamini R, Serraino D, Stocco CF, Vercelli M, et al. Effect of obesity and other lifestyle factors on mortality in women with breast cancer. Int J Cancer 2008;123:2188–94.
16. Ewertz M, Gillanders S, Meyer L, Zedeler K. Survival of breast cancer patients in relation to factors which affect the risk of developing breast cancer. Int J Cancer 1991;49:526–30.
17. Franceschi S, Dal Maso L, Zucchetto A, Talamini R. Alcohol consumption and survival after breast cancer. Cancer Epidemiol Biomarkers Prev 2009;18:1011–2; author reply 2–3.
18. Holm LE, Nordevang E, Hjalmar ML, Lidbrink E, Callmer E, Nilsson B. Treatment failure and dietary habits in women with breast cancer. J Natl Cancer Inst 1993;85:32–6.
19. Holmes MD, Stampfer MJ, Colditz GA, Rosner B, Hunter DJ, Willett WC. Dietary factors and the survival of women with breast carcinoma. Cancer 1999;86:826–35.
20. Rohan TE, Hiller JE, McMichael AJ. Dietary factors and survival from breast cancer. Nutr Cancer 1993;20:167–77.
21. Zhang S, Folsom AR, Sellers TA, Kushi LH, Potter JD. Better breast cancer survival for postmenopausal women who are less overweight and eat less fat. The Iowa Women's Health Study. Cancer 1995;76:275–83.
22. Goodwin PJ, Ennis M, Pritchard KI, Koo J, Trudeau ME, Hood N. Diet and breast cancer: evidence that extremes in diet are associated with poor survival. J Clin Oncol 2003;21:2500–7.
23. Beasley JM, Newcomb PA, Trentham-Dietz A, Hampton JM, Bersch AJ, Passarelli MN, et al. Post-diagnosis dietary factors and survival after invasive breast cancer. Breast Cancer Res Treat 2011;128: 229–36.
24. Hellmann SS, Thygesen LC, Tolstrup JS, Gronbaek M. Modifiable risk factors and survival in women diagnosed with primary breast cancer: results from a prospective cohort study. Eur J Cancer Prev 2010;19: 366–73.
25. Kwan ML, Kushi LH, Weltzien E, Tam EK, Castillo A, Sweeney C, et al. Alcohol consumption and breast cancer recurrence and survival among women with early-stage breast cancer: the life after cancer epidemiology study. J Clin Oncol 2010;28:4410–6.
26. Saxe GA, Rock CL, Wicha MS, Schottenfeld D. Diet and risk for breast cancer recurrence and survival. Breast Cancer Res Treat 1999;53: 241–53.
27. Bandera EV, August DA. Alcohol consumption and breast cancer survival. J Clin Oncol. 2009;27:1727; author reply 8.
28. Holmes MD. Challenge of balancing alcohol intake. J Clin Oncol 2010;28:4403–4.
29. Dorgan JF, Baer DJ, Albert PS, Judd JT, Brown ED, Corle DK, et al. Serum hormones and the alcohol-breast cancer association in postmenopausal women. J Natl Cancer Inst 2001;93:710–5.
30. Dumitrescu RG, Shields PG. The etiology of alcohol-induced breast cancer. Alcohol 2005;35:213–25.
31. Seitz HK, Maurer B. The relationship between alcohol metabolism, estrogen levels, and breast cancer risk. Alcohol Res Health 2007; 30:42–3.
32. Singletary KW, Gapstur SM. Alcohol and breast cancer: review of epidemiologic and experimental evidence and potential mechanisms. Jama 2001;286:2143–51.
33. Reichman ME, Judd JT, Longcope C, Schatzkin A, Clevidence BA, Nair PP, et al. Effects of alcohol consumption on plasma and urinary hormone concentrations in premenopausal women. J Natl Cancer Inst 1993;85:722–7.
34. Nechuta SJ, Caan BJ, Chen WY, Flatt SW, Lu W, Patterson RE, et al. The After Breast Cancer Pooling Project: rationale, methodology, and breast cancer survivor characteristics. Cancer Causes Control 2011;22:1319–31.
35. Shu XO, Zheng Y, Cai H, Gu K, Chen Z, Zheng W, et al. Soy food intake and breast cancer survival. Jama 2009;302:2437–43.
36. Caan B, Sternfeld B, Gunderson E, Coates A, Quesenberry C, Slattery ML. Life After Cancer Epidemiology (LACE) Study: a cohort of early stage breast cancer survivors (United States). Cancer Causes Control 2005;16:545–56.
37. Pierce JP, Faerber S, Wright FA, Rock CL, Newman V, Flatt SW, et al. A randomized trial of the effect of a plant-based dietary pattern on additional breast cancer events and survival: the Women's Healthy Eating and Living (WHEL) Study. Control Clin Trials 2002;23:728–56.
38. Colditz GA, Hankinson SE. The Nurses' Health Study: lifestyle and health among women. Nat Rev Cancer 2005;5:388–96.
39. Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. Am J Epidemiol 1986;124:453–69.
40. Ritenbaugh C, Aickin M, Taren D, Teufel N, Graver E, Woolf K, et al. Use of a food frequency questionnaire to screen for dietary eligibility in a randomized cancer prevention phase III trial. Cancer Epidemiol Biomarkers Prev 1997;6:347–54.
41. Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP, Agurs-Collins T. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. Ann Epidemiol 1999;9:178–87.
42. Centers for Disease Control and Prevention. http://www.cdc.gov/alcohol/fact-sheets/alcohol-use.htm [Accessed July 15, 2012].
43. Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin 2012;62:243–74.
44. 2008 Physical Activity Guidelines for Americans. http://www.health.gov/paguidelines/ [Accessed June 28, 2012].
45. Kwan ML, Chen WY, Kroenke CH, Weltzien EK, Beasley JM, Nechuta SJ, et al. Pre-diagnosis body mass index and survival after breast cancer in the After Breast Cancer Pooling Project. Breast Cancer Res Treat 2011;132:729–39.
46. Ernst MF, van de Poll-Franse LV, Roukema JA, Coebergh JW, van Gestel CM, Vreugdenhil G, et al. Trends in the prognosis of patients with primary metastatic breast cancer diagnosed between 1975 and 2002. Breast 2007;16:344–51.
47. Hosmer DW, Lemeshow S. Applied survival analysis: regression modeling of time to event data. New York: John Wiley & Sons, Inc.; 1999.
48. Smith-Warner SA, Spiegelman D, Ritz J, Albanes D, Beeson WL, Bernstein L, et al. Methods for pooling results of epidemiologic studies: the Pooling Project of Prospective Studies of Diet and Cancer. Am J Epidemiol 2006;163:1053–64.
49. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
50. Therneau TM, Grambsch PM. Modeling survival data: extending the Cox model. New York: Springer-Verlag; 2000.
51. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. Am J Epidemiol 1989;129:125–37.

52. Emond JA, Patterson RE, Natarajan L, Laughlin GA, Gold EB, Pierce JP. Sex hormone concentrations and the risk of breast cancer recurrence in postmenopausal women without hot flashes. Cancer Epidemiol Biomarkers Prev 2011;20:939–45.
53. Jordan VC, Fritz NF, Tormey DC. Endocrine effects of adjuvant chemotherapy and long-term tamoxifen administration on node-positive patients with breast cancer. Cancer Res 1987;47:624–30.
54. Jordan VC, Fritz NF, Langan-Fahey S, Thompson M, Tormey DC. Alteration of endocrine parameters in premenopausal women with breast cancer during long-term adjuvant therapy with tamoxifen as the single agent. J Natl Cancer Inst 1991;83:1488–91.
55. Ravdin PM, Fritz NF, Tormey DC, Jordan VC. Endocrine status of premenopausal node-positive breast cancer patients following adjuvant chemotherapy and long-term tamoxifen. Cancer Res 1988;48: 1026–9.
56. Chen WY, Rosner B, Hankinson SE, Colditz GA, Willett WC. Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. Jama 2011;306:1884–90.
57. Hiatt RA, Klatsky AL, Armstrong MA. Alcohol consumption and the risk of breast cancer in a prepaid health plan. Cancer Res 1988;48: 2284–7.
58. Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Hennekens CH, Speizer FE. Moderate alcohol consumption and the risk of breast cancer. N Engl J Med 1987;316:1174–80.
59. Hankinson SE, Willett WC, Manson JE, Hunter DJ, Colditz GA, Stampfer MJ, et al. Alcohol, height, and adiposity in relation to estrogen and prolactin levels in postmenopausal women. J Natl Cancer Inst 1995; 87:1297–302.
60. Fan S, Meng Q, Gao B, Grossman J, Yadegari M, Goldberg ID, et al. Alcohol stimulates estrogen receptor signaling in human breast cancer cell lines. Cancer Res 2000;60:5635–9.
61. Deandrea S, Talamini R, Foschi R, Montella M, Dal Maso L, Falcini F, 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.
62. 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.
63. Giovannucci E, Colditz G, Stampfer MJ, Rimm EB, Litin L, Sampson L, et al. The assessment of alcohol consumption by a simple self-administered questionnaire. Am J Epidemiol 1991;133:810–7.