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Alcohol Consumption and Prognosis and Survival in Breast Cancer Survivors: The Pathways Study

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- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
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Conflict of Interest
The authors have no conflicts to disclose.

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The study was approved by the KPNC institutional review board. Written informed consent was obtained from study participants.

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Abstract

Background: The impact of alcohol consumption on breast cancer (BC) prognosis remains unclear.

Methods: We examined short-term alcohol intake in relation to recurrence and mortality in 3,659 women diagnosed with Stage I-IV BC from 2005–2013 in the Pathways Study. Alcohol drinking in the past 6 months was assessed at cohort entry (mean=2 months post-diagnosis) and 6 months later using a food frequency questionnaire. Study endpoints were recurrence and death due to BC, cardiovascular disease (CVD), and all causes. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using multivariable Cox proportional hazards models.

Results: Over an average follow-up of 11.2 years, 524 recurrences and 834 deaths (369 BC-specific and 314 CVD-specific) occurred. Compared with non-drinkers (36.9%), drinkers were more likely younger, more educated, and current or past smokers. Overall, alcohol consumption was not associated with recurrence or mortality. However, women with higher body mass index (BMI≥30 kg/m^2) had lower risk of overall mortality with increasing alcohol consumption for occasional (HR=0.71; 95% CI: 0.54–0.94) and regular drinking (HR=0.77; 95% CI: 0.56–1.08) around diagnosis, along with six months later, in a dose-response manner ($p<.05$). Women with lower BMI<30 kg/m^2 were not at higher risk of mortality but possibly higher, yet non-significant, risk of recurrence for occasional (HR=1.29; 95% CI: 0.97–1.71) and regular drinking (HR=1.19; 95% CI: 0.88–1.62).

Conclusions: Alcohol drinking around and up to six months after BC diagnosis was associated with lower risk of all-cause mortality in obese women. A possible higher risk of recurrence was observed in non-obese women.

Precis

Alcohol consumption around and up to six months after breast cancer diagnosis was associated with lower risk of all-cause mortality in women with obesity in the Pathways Study. A potential association of alcohol intake with increased risk of recurrence in women without obesity was suggested.

Keywords

alcohol; ethanol; estrogen; breast cancer; recurrence; mortality; prognosis

Introduction

Many women with a history of breast cancer are interested in how to improve their prognosis and survival by making lifestyle changes after diagnosis. Alcohol consumption is of high interest and generally recognized to increase risk of breast cancer.[1–3] The most common hypothesized mechanisms for greater risk are increased alcohol metabolism resulting in high circulating levels of the carcinogen acetaldehyde, particularly in premenopausal women, and alcohol elevating endogenous estrogen levels and upregulating estrogen receptors under certain hormonal conditions in pre- and postmenopausal women.[4–9]

Current cancer prevention guidelines recommend avoiding alcohol intake or limiting consumption to no more than 1 drink per day for women.[1,10] However, no specific guideline exists for cancer survivors, other than following the cancer prevention guidelines to reduce the risk of a second cancer.[10] A modest number of studies have examined alcohol consumption (primarily before diagnosis) and outcomes after breast cancer diagnosis with inconclusive results. The most recent systematic review on this topic reported some evidence that alcohol intake increases the risk of breast cancer recurrence, specifically in postmenopausal women.[11] Further, moderate alcohol intake has been associated with reduced risk of cardiovascular death, which is a major cause of mortality second to breast cancer in breast cancer survivors.[12,13] Overall, studies of alcohol and breast cancer prognosis have suffered from methodological challenges, namely varied disease endpoints, narrow ranges of exposure to alcohol, pre-diagnosis rather than post-diagnosis exposure assessment, and failure to adjust for important prognostic factors.[11,14,15]

We conducted a comprehensive investigation of peri-diagnosis and early post-diagnosis alcohol consumption and breast cancer recurrence and mortality in 3,659 breast cancer survivors in the Pathways Study. This is the largest analysis from a single prospective cohort study of women with breast cancer on short-term alcohol intake and prognosis. We also examined potential effect modification by *a priori* estrogenic factors including menopausal status, estrogen receptor status, and obesity.

Materials and Methods

The Pathways Study

The Pathways Study is a prospective cohort study of 4,504 female breast cancer survivors diagnosed with invasive breast cancer from 2005 to 2013 at Kaiser Permanente Northern California (KPNC).[16] Eligibility criteria included being female; aged 21 years or older at diagnosis; KPNC member; speaking English, Spanish, Cantonese, or Mandarin; living within a 65-mile radius of a field interviewer; diagnosis of first invasive breast cancer; and no prior history of other invasive cancers. The study was approved by the

KPNC institutional review board, and written informed consent was obtained from study participants.

Alcohol Consumption

Alcohol consumption was collected from participants at enrollment into the cohort and six months later using an expanded version of the Block 2005 Food Frequency Questionnaire (FFQ) consisting of 139 food items.[17] Women reported their average frequency of consumption over the past six months for wine, beer, and liquor. A medium serving size was defined as one 6-ounce (oz) glass, one 12-oz can or bottle, or one 1.5-oz shot. Baseline assessment captured the period just before and around the time of breast cancer diagnosis (peri-diagnosis), while the six-month assessment captured the early period after breast cancer diagnosis (post-diagnosis).

Servings per day of each alcoholic beverage were converted to grams (g) per day of alcohol (one standard drink in the U.S. is about 12.0–14.0 g of pure ethanol[18]), and respondents were categorized as non-drinker (<0.36 g/day), occasional drinker (0.36-<6.0 g/day), and regular drinker (≥6.0 g/day). Half a drink per day (6.0 g) represented the cutpoint for regular drinker, as the median level of intake among drinkers in the cohort was 5.5 g/day and the current cancer prevention guidelines advise no more than one drink per day for women with no history of cancer.[2,10] Higher consumption categories were also created to examine dose response relationships in regular drinkers: regular low (6.0-<12.0 g/day), regular medium (12.0-<24.0 g/day), and regular high (≥24.0 g/day).

Covariates

Sociodemographic and lifestyle factors.—The baseline questionnaire included questions on self-reported race and ethnicity (Non-Hispanic White, Non-Hispanic Black, Asian/Pacific Islander, Hispanic, American Indian/Alaska Native), education (high school or less, some college, college graduate, post-graduate), menopausal status at diagnosis (premenopausal, postmenopausal), nulliparity at diagnosis (no, yes), and smoking history at diagnosis (never, past, current). Moderate-vigorous physical activity in minutes per week in the past six months at baseline was determined from the validated Arizona Activity Frequency Questionnaire[19] and classified as meeting or not meeting the 2018 Physical Activity Guidelines of at least 150 minutes per week or more of moderate-vigorous intensity aerobic activity.[20] Body mass index (BMI) at diagnosis was determined from the electronic health record (EHR) and supplemented with baseline self-report if EHR data were not available (<5%). A census block group-level composite measure of neighborhood socioeconomic status (nSES) was derived.[21,22]

Clinical and treatment characteristics.—Data were obtained from the KPNC Cancer Registry and electronic databases including the Virtual Data Warehouse.[23] Characteristics included age at cancer diagnosis (years), AJCC stage 7th edition (I, II, III, IV), estrogen receptor (ER)/progesterone receptor (PR) status (ER+/PR+, ER+/PR-, ER-/PR+, ER-/PR-), human epidermal growth factor receptor 2 (Her2) status (negative, positive), chemotherapy (no, yes), radiation therapy (no, yes), endocrine therapy (no, yes), surgery type (none,

lumpectomy, mastectomy), comorbidity status (Charlson comorbidity index), and history of alcohol dependence at baseline (ICD-9 303, ICD-10 F10.2).

Study Outcomes

Study outcomes included breast cancer recurrence, breast cancer mortality, cardiovascular disease (CVD) mortality, and all-cause mortality. Recurrences were ascertained during follow-up interviews at 6, 12, 24, 48, 72, and 96 months, and biennially thereafter with participants, and from monthly algorithmic searches of KPNC electronic databases. All recurrences were confirmed by EHR chart review. Deaths and primary causes of death were identified from periodic linkages with vital statistics data from the state of California, the Social Security Administration, and the National Death Index. Death information was also obtained from KPNC sources and relatives of deceased participants during routine follow-up interviews, and then confirmed by EHR chart review.

Final Samples

For analyses of alcohol consumption peri-diagnosis, 845 women with a missing baseline FFQ were excluded from the full cohort, leaving a final sample size of 3,659 for analysis. For analyses of alcohol consumption during the six months post-diagnosis, 1,741 women with a missing six-month follow-up FFQ were excluded from the full cohort, leaving a final sample size of 2,763 for analysis. A total of 2,576 women were included in both analytic cohorts.

Statistical Analysis

Sociodemographic, lifestyle, and clinical characteristics, overall and by category of baseline alcohol intake, were summarized by frequency distributions for categorical variables and means with standard deviations (SD) for continuous variables.

Cox proportional hazards regression models estimated cause-specific adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) with time since diagnosis as the time scale.[24] The entry date was the date of Pathways Study enrollment (signified by completion of the baseline interview). For recurrence, censoring was first of health plan disenrollment or study drop-out, death, or end of study (12/31/2021). Women with Stage IV breast cancer were not at risk of recurrence and thus excluded (n=56). For breast cancer mortality, censoring was on first of health plan disenrollment or study drop-out, death from other causes, or end of study. For CVD mortality, censoring was on first of death from other causes or end of study. For all-cause mortality, censoring was at end of study. The proportional hazards assumption was assessed by Schoenfeld residuals. Tests for linear trend were performed by modeling the continuous alcohol intake variable. Statistical significance was considered as $p<.05$ or 95% CI not overlapping with 1.0.

Covariates were chosen *a priori* from literature review. Age at diagnosis, AJCC stage, race and ethnicity, education, nSES, menopausal status at diagnosis, nulliparity at diagnosis, ER/PR status, surgery, treatment (radiation therapy, chemotherapy, endocrine therapy), smoking history at diagnosis, physical activity at diagnosis, BMI at diagnosis, comorbidity at diagnosis, and alcohol dependence at diagnosis were retained.

Possible *a priori* effect modification was evaluated in associations of alcohol consumption (3-level alcohol variable) with recurrence and all-cause mortality by menopausal status (premenopausal vs. postmenopausal), ER status (ER+ vs. ER-), and obesity (obese vs. non-obese) 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 described above) in the Cox models. Statistical significance was considered as p<.10.

Results

Over a mean follow-up of 11.2 years, 524 recurrences and 834 deaths (369 breast cancer-specific and 314 CVD-specific) were confirmed. Mean time (range) from breast cancer diagnosis was 4.9 (0.5–15.3) years to recurrence and 6.9 (0.3–15.0) years to death. Alcohol consumption was assessed at baseline, on average 2.3 months post-diagnosis (range: 0.7–18.7), and at six-month follow-up, on average 8.4 months post-diagnosis (range: 6.1–23.9). The time difference between these two assessments was mean 6.1 (range: 2.9–12.0) months.

Cohort characteristics by categories of alcohol consumption (g/day) of non-drinkers, occasional drinkers, and regular drinkers are shown in Table 1. Mean age at breast cancer diagnosis was 59.7 years, and 71.1% were postmenopausal at diagnosis. The racial and ethnic distribution was 68.1% non-Hispanic white, 6.6% non-Hispanic Black, 13.0% Asian/Pacific Islander, 10.3% Hispanic, and 2.1% American Indian/Alaska Native. Most women (85.0%) had at least some college education, 89.1% were diagnosed with Stage I or II tumors, and 84.2% of the tumors were ER+ and/or PR+. Compared with non-drinkers (36.9%), 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 endocrine therapy. Drinkers also tended to be current or past smokers, more physically active, leaner, and with fewer comorbidities.

The mean (SD) g/day of alcohol (ethanol) consumption at baseline was 7.1 (12.8) while the median was 1.0 (interquartile [IQ] range: 168.1) (Supplemental Table 1). 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 for occasional drinkers was 2.0 (1.6) g/day (median 1.3; IQ range: 5.6) and regular drinkers was 21.4 (15.9) g/day (median 16.7; IQ range: 162.1). At the six-month follow-up, drinking levels were lower. The mean (SD) was 5.7 (11.1) g/day. Among the drinkers (≥0.36 g/day), the mean (SD) consumption for occasional drinkers was 1.8 (1.5) g/day and regular drinkers was 20.1 (14.1) g/day.

Table 2 shows the associations between alcohol consumption peri-diagnosis and post-diagnosis and study endpoints of recurrence, all-cause mortality, breast cancer mortality, and CVD mortality. For peri-diagnosis consumption, compared with no consumption, occasional (0.36-<0.6 g/day) and regular consumption of alcohol (≥6.0 g/day) were not associated with any outcomes. No significant dose-response effect for increasing consumption was found. For alcohol drinking post-diagnosis, all the associations were non-significant, including for all-cause mortality, with no significant dose-response effects observed. Across all models, type of alcohol, including wine, beer, and liquor, was not associated with any outcome,

except for beer consumed at follow-up was associated with higher risk of breast cancer mortality (HR=1.47; 95% CI: 1.06–2.03).

Stratified analyses for risk of recurrence and alcohol consumption at peri-diagnosis in Table 3 and post-diagnosis in Table 4 are shown by menopausal status at diagnosis, ER status, and obesity status at diagnosis. Effect modification by obesity was observed for peri-diagnosis (p for interaction=.09) and post-diagnosis drinking (p for interaction=.07). Specifically, in non-obese women, occasional (HR for 0.36-<0.6 g/day=1.29; 95% CI: 0.97–1.71) and regular drinking (HR for ≥6.0 g/day=1.19; 95% CI: 0.88–1.62) at peri-diagnosis were associated with non-statistically significant increased risk of recurrence, whereas in obese women, no associations were apparent for occasional (HR for 0.36-<0.6 g/day=0.96; 95% CI: 0.68–1.36) and regular drinking (HR for ≥6.0 g/day=0.90; 95% CI: 0.58–1.40). For six-months post-diagnosis drinking, the HRs were in the same direction and not statistically significant, yet they were stronger in magnitude for the non-obese women (p for trend=.06).

Similarly, stratified analyses for risk of all-cause mortality and alcohol consumption at peri-diagnosis and post-diagnosis are shown in Table 5 and Table 6, respectively. Effect modification by obesity was present for all-cause mortality risk for peri-diagnosis (p for interaction=.05) and post-diagnosis drinking (p for interaction=.02). For obese women, increasing peri-diagnosis consumption of alcohol was associated with decreased risk of all-cause mortality (p for trend=.04) with a statistically significant decreased risk for occasional drinking (HR for 0.36-<0.6 g/day=0.71; 95% CI: 0.54–0.94) but not significant for regular drinking (HR for ≥6.0 g/day=0.77; 95% CI: 0.56–1.08). In contrast, for non-obese women, occasional (HR for 0.36-<0.6 g/day=1.22; 95% CI: 0.97–1.53) and regular drinking (HR for ≥6.0 g/day=1.03; 95% CI: 0.81–1.31) were not associated with risk of all-cause mortality with no dose-response effect (p for trend=.80). For consumption at post-diagnosis, results were similar yet attenuated compared with peri-diagnosis consumption. In obese and non-obese stratified models of risk of breast cancer mortality (Supplemental Table 2) and CVD mortality (Supplemental Table 3), a similar pattern of lower risks in the obese women but not non-obese women was observed for peri-diagnosis and post-diagnosis drinking for CVD mortality (p for trend=.04 and .20) but not breast cancer mortality (p for trend=.73 and 0.29).

Finally, associations were similar and non-significant across the subgroups of menopausal status and ER status with no effect modification (Tables 5 and 6).

Discussion

In this analysis of 3,659 breast cancer survivors in the Pathways Study, alcohol consumption around and up to six months after breast cancer diagnosis was, in general, not associated with risk of recurrence or death. However, the risk associations varied by BMI. Specifically, in obese women, compared with no drinking, occasional consumption of two or more drinks per week (approximately one-quarter to one-half drink or more per day) was associated with a decreased risk of overall death, contributed in part by decreased risk of CVD death. Also, occasional consumption was possibly associated with an increased risk of recurrence in non-obese women. These results, in the largest prospective cohort to date of female breast cancer survivors, suggest that occasional, short-term alcohol consumption is generally not

associated with poor outcomes after breast cancer diagnosis. Instead, moderate intake might be associated with improved survival in obese women.

Light to moderate alcohol consumption might reduce overall mortality in healthy cohorts due to possible beneficial effects on risk of CVD,[25–29] yet we did not observe overall inverse associations in our breast cancer cohort. Instead, we appear to be the first to report that obese women experienced improved survival with moderate alcohol consumption, which was not observed in non-obese women. While we are unsure how to explain this finding, 693 obese women consumed alcohol compared with 529 obese women who did not, and they appeared more educated and physically active. This profile appears counterintuitive yet might reflect a healthier lifestyle contributing to better overall survival. Further, higher levels of alcohol consumption could lead to improvement in insulin sensitivity and reduction in insulin-like growth factor-I (IGF-I), as observed in an alcohol feeding trial of 63 healthy postmenopausal women.[30,31] Reduced fasting insulin concentrations and lower IGF-I levels are associated with decreased risk of type 2 diabetes, CVD, and cancer. Finally, the pharmacokinetics of alcohol could be important to consider given that the volume of distribution of alcohol depends on age, sex, and degree of adiposity.[32] Specifically, it can decrease with increasing BMI,[33] which might limit the adverse health effects of alcohol due to lower levels of distribution from the plasma to other tissues. This phenomenon might also explain the possible increased, rather than decreased, risk of recurrence that we observed in the non-obese women.

Alcohol has been found to increase the expression and proliferation of estrogen receptors in cultured human breast cancer cells[8,34] and has been associated with the development of incident ER-positive breast cancer in postmenopausal women.[35,36] However, we did not observe any interactions of alcohol intake by ER status and menopausal status on risk of recurrence. The trends were consistent across both groups. Interestingly, while not statistically significant, additional analyses in postmenopausal women with ER+ breast cancer suggest possible higher risk of recurrence for those who continue to drink up to six months after diagnosis (Supplemental Table 4).

Study strengths include being the largest cohort of breast cancer survivors with data on post-diagnosis alcohol consumption and sufficient follow-up time, and having the ability to adjust for important prognostic and treatment-related factors. Our study population had a reasonably wide range of alcohol intake, allowing exploration of higher levels of drinking and outcomes, and variability in types of alcohol consumed compared with previous cohort studies. The mean consumption in drinkers at baseline was 11.2 g/day (median 5.5), which is consistent with mean levels reported in studies of healthy female drinkers (3.2–12.6 g/day).[3]

Of note, our analysis did not examine patterns of change in post-diagnosis alcohol consumption, as we examined separate effects of peri-diagnosis and early post-diagnosis (up to six months) exposure on outcomes. Change in alcohol consumption from pre-diagnosis to early post-diagnosis may be a contributing factor in associations of alcohol and mortality. However, most women (84.4%) remained in the same or adjacent category of intake at follow-up. Our data also did not allow us to determine the timing of alcohol consumption during the day or week, the quantity consumed per drinking occasion, or whether alcohol

was consumed alone or with a meal.[32,37,38] We also relied on self-reported alcohol use, which can be prone to recall bias; however, alcohol levels have been shown to be highly reproducible using food records and 24-hour recalls.[39,40] Finally, while we adjusted for multiple confounders related to alcohol exposure and the study outcomes, including abstainer bias, residual confounding cannot be completely ruled out.

In summary, we found that short-term alcohol consumption immediately before and up to six months after breast cancer diagnosis was generally not associated with risk of recurrence or mortality. However, in obese women, drinking more than two drinks per week (one-quarter to one-half a drink or more per day) was associated with lower risk of all-cause mortality, especially CVD mortality. Risk of recurrence was possibly greater in non-obese women who drink. Given that consuming alcohol is a potentially modifiable lifestyle factor after breast cancer diagnosis, further confirmation is warranted in other large prospective studies of breast cancer survivors with detailed exposure assessment and focus on body size.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon request.

Abbreviations

KPNC	Kaiser Permanente Northern California
EHR	electronic health record
FFQ	Food Frequency Questionnaire
BMI	body mass index
nSES	neighborhood socioeconomic status
MET	metabolic equivalents
AJCC	American Joint Committee on Cancer
ER	estrogen receptor
PR	progesterone receptor

HER2	human epidermal growth factor receptor 2
SD	standard deviation
HR	hazard ratio
CI	confidence interval
CVD	cardiovascular disease
IQ	interquartile
IGF-I	insulin-like growth factor-I

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Table 1.

Baseline characteristics of the Pathways Study (n=3659) by alcohol consumption around breast cancer diagnosis

	Overall		Non-drinker (<0.36 g/day)		Occasional (0.36-<6 g/day)		Regular (≥6 g/day)	
	n=3659		n=1352		n=1211		n=1096	
Age at diagnosis, years (mean, SD)	59.68 (11.9)		60.30 (12.2)		59.02 (11.9)		59.65 (11.5)	
BMI at diagnosis, kg/m^2(mean, SD)	28.46 (6.7)		29.31 (7.2)		28.89 (6.8)		26.94 (5.7)	
Total folate intake, mcg/day (median, range)	329.96 (1215.2)		316 (1215.2)		337.75 (1060.3)		339.53 (975.0)	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Race/Ethnicity								
Non-Hispanic White	2490	(68.1)	757	(56)	805	(66.5)	928	(84.7)
Non-Hispanic Black	240	(6.6)	114	(8.4)	83	(6.9)	43	(3.9)
Asian/Pacific Islander	475	(13.0)	287	(21.2)	141	(11.6)	47	(4.3)
Hispanic	378	(10.3)	161	(11.9)	154	(12.7)	63	(5.8)
American Indian/Alaska Native	76	(2.1)	33	(2.4)	28	(2.3)	15	(1.4)
Education								
High school or less	547	(15.0)	278	(20.6)	160	(13.2)	109	(10.0)
Some college	1244	(34.0)	463	(34.3)	431	(35.6)	350	(32.0)
College grad	1024	(28.0)	381	(28.2)	337	(27.9)	306	(28.0)
Post grad	842	(23.0)	230	(17.0)	282	(23.3)	330	(30.1)
Neighborhood SES [a]								
Quintile 1	148	(4.2)	74	(5.7)	51	(4.3)	23	(2.2)
Quintile 2	409	(11.6)	189	(14.4)	141	(12.0)	79	(7.5)
Quintile 3	717	(20.3)	282	(21.5)	242	(20.6)	193	(18.3)
Quintile 4	1043	(29.5)	387	(29.6)	340	(28.9)	316	(30.0)
Quintile 5	1222	(34.5)	377	(28.8)	402	(34.2)	443	(42.0)
Menopausal Status at Diagnosis								
Premenopausal	1059	(28.9)	388	(28.7)	355	(29.3)	316	(28.8)
Postmenopausal	2600	(71.1)	964	(71.3)	856	(70.7)	780	(71.2)
Nulliparity at Diagnosis								
No	2944	(80.5)	1135	(84.0)	1000	(82.6)	809	(73.9)
Yes	713	(19.5)	217	(16.1)	210	(17.4)	286	(26.1)
AJCC Stage 7thEdition								
I	2007	(54.9)	714	(52.8)	656	(54.2)	637	(58.1)
II	1250	(34.2)	471	(34.8)	428	(35.3)	351	(32.0)
III	346	(9.5)	145	(10.7)	106	(8.8)	95	(8.7)
IV	56	(1.5)	22	(1.6)	21	(1.7)	13	(1.2)
Hormone Receptor Status								

	Overall		Non-drinker (<0.36 g/day)		Occasional (0.36-<6 g/day)		Regular (≥6 g/day)	
	n=3659		n=1352		n=1211		n=1096	
ER+/PR+	2341	(64.1)	841	(62.4)	761	(62.8)	739	(67.4)
ER+/PR-	729	(20.0)	281	(20.9)	243	(20.1)	205	(18.7)
ER-/PR+	6	(0.2)	1	(0.1)	2	(0.2)	3	(0.3)
ER-/PR-	579	(15.8)	225	(16.7)	205	(16.9)	149	(13.6)
Chemotherapy								
No	1940	(53.2)	716	(53.0)	616	(51.0)	608	(55.8)
Yes	1708	(46.8)	634	(47.0)	592	(49.0)	482	(44.2)
Radiation Therapy								
No	1940	(53.2)	716	(53.0)	616	(51.0)	608	(55.8)
Yes	1708	(46.8)	634	(47.0)	592	(49.0)	482	(44.2)
Endocrine Therapy								
No	2038	(55.7)	802	(59.3)	683	(56.4)	553	(50.5)
Yes	1621	(44.3)	550	(40.7)	528	(43.6)	543	(49.5)
Surgery Type								
None	118	(3.2)	45	(3.3)	54	(4.5)	19	(1.7)
Lumpectomy	2177	(59.5)	747	(55.3)	712	(58.8)	718	(65.5)
Mastectomy	1362	(37.2)	558	(41.3)	445	(36.8)	359	(32.8)
Smoking History								
Never	2091	(57.2)	885	(65.5)	725	(60.0)	481	(44.0)
Past	1408	(38.5)	414	(30.6)	441	(36.5)	553	(50.6)
Current	154	(4.2)	53	(3.9)	42	(3.5)	59	(5.4)
Any Comorbidity at Diagnosis								
No	3283	(89.7)	1166	(86.2)	1098	(90.7)	1019	(93.0)
Yes	376	(10.3)	186	(13.8)	113	(9.3)	77	(7.0)
History of Alcohol Dependence at Diagnosis								
No	3620	(98.9)	1337	(98.9)	1203	(99.3)	1080	(98.5)
Yes	39	(1.1)	15	(1.1)	8	(0.7)	16	(1.5)
Met 2018 Physical Activity Guidelines for Americans at Diagnosis								
No	1149	(31.4)	551	(40.8)	363	(30.0)	235	(21.5)
Yes	2506	(68.6)	800	(59.2)	848	(70.0)	858	(78.5)

NOTE: Missing values for covariates were as follows: race/ethnicity (n=0), education (n=2), neighborhood SES (n=120), menopausal status (n=0), nulliparity (n=2), AJCC stage (n=0), hormone receptor status (n=4), chemotherapy (n=11), radiation therapy (n=0), hormonal therapy (n=25), surgery type (n=2), smoking history (n=6), any comorbidity (n=0), history of alcohol dependence (n=0), and met 2018 Physical Activity Guidelines for Americans of 150 minutes per week of moderate-vigorous physical activity (n=4)

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

[a]Derived from principal component analysis based on seven factors: median household income, Liu education index, percent below 200% of poverty line, proportion with blue collar occupation, proportion without a job, median rent, and median house value[21,22]

Table 2.

Associations of alcohol consumption around breast cancer diagnosis and 6 months post-breast cancer diagnosis and recurrence and mortality in the Pathways Study

	Alcohol Consumption Around Breast Cancer Diagnosis						Alcohol Consumption 6 months Post-Breast Cancer Diagnosis				
Recurrence	**n=3659 (524 events)**						**n=2763 (372 events)**				
	n	**events**	**HR[a,b]**	**95% CI**			**n**	**events**	**HR[a,b]**	**95% CI**	
Non-drinker (<0.36 g/day)	1352	186	Ref	Ref	Ref		1183	168	Ref	Ref	Ref
Occasional (0.36-<6 g/day)	1211	191	1.14	0.92	1.42		878	112	1.06	0.81	1.39
Regular (≥6g/day)	1096	147	1.07	0.84	1.36		702	92	1.26	0.94	1.69
p for trend			.52						.13		
Non-drinker (<0.36 g/day)	1352	186	Ref	Ref	Ref		1183	168	Ref	Ref	Ref
Occasional (0.36-<6 g/day)	1211	191	1.14	0.92	1.42		878	112	1.06	0.81	1.39
Regular low (6-<12 g/day)	356	51	1.05	0.76	1.47		259	37	1.35	0.91	2.00
Regular medium (12-<24 g/day)	414	55	1.11	0.80	1.54		241	29	1.09	0.70	1.69
Regular high (≥24 g/day)	326	41	1.04	0.73	1.50		202	26	1.35	0.87	2.11
p for trend			.71						.15		
Continuous 6 g/day	3659	524	1.00	0.99	1.01		2763	372	1.01	1.00	1.02
Wine											
No	1273	188	Ref	Ref	Ref		1099	149	Ref	Ref	Ref
Yes	2386	336	0.91	0.73	1.14		1664	223	1.11	0.85	1.45
Beer											
No	2356	333	Ref	Ref	Ref		1924	254	Ref	Ref	Ref
Yes	1303	191	1.09	0.88	1.35		839	118	1.24	0.96	1.62
Liquor											
No	2724	395	Ref	Ref	Ref		1771	241	Ref	Ref	Ref
Yes	935	129	1.05	0.84	1.30		992	131	1.04	0.81	1.34
All-Cause Mortality	**n=3659 (834 events)**						**n=2763 (594 events)**				
	n	**events**	**HR[a,c]**	**95% CI**			**n**	**events**	**HR[a,c]**	**95% CI**	
Non-drinker (<0.36 g/day)	1352	342	Ref	Ref	Ref		1183	287	Ref	Ref	Ref
Occasional (0.36-<6 g/day)	1211	268	0.97	0.82	1.15		878	163	0.89	0.72	1.10
Regular (≥6g/day)	1096	224	0.89	0.74	1.08		702	144	0.95	0.76	1.19
p for trend			.25						.54		

	Alcohol Consumption Around Breast Cancer Diagnosis						Alcohol Consumption 6 months Post-Breast Cancer Diagnosis				
Recurrence	**n=3659 (524 events)**						**n=2763 (372 events)**				
	n	**events**	**HR[a,b]**	**95% CI**			**n**	**events**	**HR[a,b]**	**95% CI**	
Non-drinker (<0.36 g/day)	1352	342	Ref	Ref	Ref		1183	287	Ref	Ref	Ref
Occasional (0.36-<6 g/day)	1211	268	0.97	0.82	1.15		878	163	0.89	0.72	1.10
Regular low (6-<12 g/day)	356	69	0.87	0.66	1.15		259	52	0.97	0.69	1.35
Regular medium (12-<24 g/day)	414	89	1.02	0.79	1.31		241	47	0.85	0.61	1.19
Regular high (≥24 g/day)	326	66	0.78	0.58	1.03		202	45	1.05	0.75	1.48
p for trend			.18						.78		
Continuous 6 g/day	3659	834	1.00	0.99	1.00		2763	594	1.00	1.00	1.01
Wine											
No	1273	326	Ref	Ref	Ref		1099	257	Ref	Ref	Ref
Yes	2386	508	0.96	0.82	1.14		1664	337	1.00	0.82	1.23
Beer											
No	2356	569	Ref	Ref	Ref		1924	442	Ref	Ref	Ref
Yes	1303	265	1.00	0.84	1.18		839	152	1.01	0.81	1.26
Liquor											
No	2724	661	Ref	Ref	Ref		1771	414	Ref	Ref	Ref
Yes	935	173	0.87	0.72	1.04		992	180	0.94	0.76	1.16
Breast Cancer Mortality	**n=3659 (369 events)**						**n=2763 (246 events)**				
	n	**events**	**HR[a,d]**	**95% CI**			**n**	**events**	**HR[a,d]**	**95% CI**	
Non-drinker (<0.36 g/day)	1352	141	Ref	Ref	Ref		1183	122	Ref	Ref	Ref
Occasional (0.36-<6 g/day)	1211	132	1.04	0.81	1.35		878	74	1.08	0.78	1.50
Regular (≥6g/day)	1096	96	0.95	0.71	1.27		702	50	1.12	0.77	1.62
p for trend			.77						.53		
Non-drinker (<0.36 g/day)	1352	141	Ref	Ref	Ref		1183	122	Ref	Ref	Ref
Occasional (0.36-<6 g/day)	1211	132	1.04	0.81	1.35		878	74	1.08	0.78	1.50
Regular low (6-<12 g/day)	356	31	0.89	0.59	1.35		259	22	1.40	0.86	2.29
Regular medium (12-<24 g/day)	414	38	1.12	0.76	1.64		241	16	0.91	0.52	1.61
Regular high (≥24 g/day)	326	27	0.83	0.53	1.30		202	12	1.03	0.55	1.92

	Alcohol Consumption Around Breast Cancer Diagnosis						Alcohol Consumption 6 months Post-Breast Cancer Diagnosis				
Recurrence	**n=3659 (524 events)**						**n=2763 (372 events)**				
	n	**events**	**HR[a,b]**	**95% CI**			**n**	**events**	**HR[a,b]**	**95% CI**	
p for trend			.66						.81		
Continuous 6 g/day	3659	369	1.00	0.99	1.01		2763	246	1.00	0.99	1.02
Wine											
No	1273	140	Ref	Ref	Ref		1099	114	Ref	Ref	Ref
Yes	2386	229	0.97	0.75	1.25		1664	132	0.98	0.71	1.35
Beer											
No	2356	240	Ref	Ref	Ref		1924	173	Ref	Ref	Ref
Yes	1303	129	1.03	0.80	1.34		839	73	1.47	1.06	2.03
Liquor											
No	2724	297	Ref	Ref	Ref		1771	173	Ref	Ref	Ref
Yes	935	72	0.82	0.62	1.09		992	73	0.86	0.62	1.20
CVD Mortality	**n=3659 (314 events)**						**n=2763 (234 events)**				
	n	**events**	**HR[a,e]**	**95% CI**			**n**	**events**	**HR[a,e]**	**95% CI**	
Non-drinker (<0.36 g/day)	1352	139	Ref	Ref	Ref		1183	116	Ref	Ref	Ref
Occasional (0.36-<6 g/day)	1211	95	0.96	0.73	1.27		878	60	0.83	0.59	1.18
Regular (≥6g/day)	1096	80	0.89	0.66	1.22		702	58	0.96	0.67	1.38
p for trend			.49						.71		
Non-drinker (<0.36 g/day)	1352	139	Ref	Ref	Ref		1183	116	Ref	Ref	Ref
Occasional (0.36-<6 g/day)	1211	95	0.96	0.73	1.27		878	60	0.83	0.59	1.18
Regular low (6-<12 g/day)	356	23	0.85	0.52	1.36		259	18	0.87	0.49	1.54
Regular medium (12-<24 g/day)	414	28	0.84	0.54	1.30		241	20	0.91	0.54	1.54
Regular high (≥24 g/day)	326	29	1.00	0.65	1.56		202	20	1.11	0.67	1.86
p for trend			.64						.94		
Continuous 6 g/day	3659	314	1.00	0.99	1.01		2763	234	1.01	1.00	1.02
Wine											
No	1273	122	Ref	Ref	Ref		1099	99	Ref	Ref	Ref
Yes	2386	192	1.04	0.79	1.37		1664	135	1.03	0.73	1.44
Beer											
No	2356	216	Ref	Ref	Ref		1924	176	Ref	Ref	Ref
Yes	1303	98	1.13	0.85	1.50		839	58	1.18	0.82	1.69

	Alcohol Consumption Around Breast Cancer Diagnosis						Alcohol Consumption 6 months Post-Breast Cancer Diagnosis				
Recurrence	**n=3659 (524 events)**						**n=2763 (372 events)**				
	n	**events**	**HR[a,b]**	**95% CI**			**n**	**events**	**HR[a,b]**	**95% CI**	
Liquor											
No	2724	252	Ref	Ref	Ref		1771	168	Ref	Ref	Ref
Yes	935	62	0.79	0.59	1.07		992	66	0.88	0.63	1.24

[a]Adjusted for age at diagnosis, AJCC stage, race/ethnicity, education, menopausal status at diagnosis, nulliparity at diagnosis, hormone receptor status, surgery, treatment (radiation therapy, chemotherapy, endocrine therapy), smoking status at diagnosis, physical activity at diagnosis, BMI at diagnosis, comorbidity at diagnosis, neighborhood SES, and history of alcohol dependence at diagnosis.

[b]For recurrence models, censored at first of KPNC health plan disenrollment or Pathways Study drop-out, death, or end of study (December 31, 2021).

[c]For all-cause mortality models, censored at end of study (December 31, 2021).

[d]For breast cancer mortality models, censored at first of KPNC health plan disenrollment or Pathways Study drop-out, death from other causes, or end of study (December 31, 2021).

[e]For CVD mortality models, censored at death from other causes or end of study (December 31, 2021).

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

Table 3.

Associations of alcohol consumption around breast cancer diagnosis and recurrence in the Pathways Study, stratified by estrogen-related factors

	Premenopausal						Postmenopausal				
	n=1059 (162 events)						n=2600 (362 events)				
	n	events	HR[a,b]	95% CI			n	events	HR[a,b]	95% CI	
Non-drinker (<0.36 g/day)	388	55	Ref	Ref	Ref		964	131	Ref	Ref	Ref
Occasional (0.36-<6 g/day)	355	63	1.18	0.79	1.75		856	128	1.13	0.87	1.46
Regular (≥6 g/day)	316	44	1.13	0.71	1.77		780	103	1.05	0.78	1.40
p for trend			.58						.71		
p for interaction=.97											
Continuous 6 g/day	1059	162	1.00	0.98	1.02		2600	362	1.00	0.99	1.01
	ER-negative						ER-positive				
	n=586 (105 events)						n=3071 (419 events)				
	n	events	HR[a,b]	95% CI			n	events	HR[a,b]	95% CI	
Non-drinker (<0.36 g/day)	227	39	Ref	Ref	Ref		1123	147	Ref	Ref	Ref
Occasional (0.36-<6 g/day)	207	40	0.92	0.57	1.50		1004	151	1.18	0.93	1.51
Regular (≥6 g/day)	152	26	0.90	0.51	1.59		944	121	1.11	0.85	1.46
p for trend			.71						.38		
p for interaction=.88											
Continuous 6 g/day	586	105	1.00	0.98	1.02		3071	419	1.00	0.99	1.01
	Obese (BMI≥30 kg/m^2)						Non-obese (BMI<30 kg/m^2)				
	n=1222 (192 events)						n=2437 (332 events)				
	n	events	HR[a,b]	95% CI			n	events	HR[a,b]	95% CI	
Non-drinker (<0.36 g/day)	529	88	Ref	Ref	Ref		823	98	Ref	Ref	Ref
Occasional (0.36-<6 g/day)	430	69	0.96	0.68	1.36		781	122	1.29	0.97	1.71
Regular (≥6 g/day)	263	35	0.90	0.58	1.40		833	112	1.19	0.88	1.62
p for trend			.65						.27		
p for interaction=.09											
Continuous 6 g/day	1222	192	1.00	0.99	1.02		2437	332	1.00	0.99	1.01

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

[b]For recurrence models, censored at first of KPNC health plan disenrollment or Pathways Study drop-out, death, or end of study (December 31, 2021).

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

Table 4.

Associations of alcohol consumption at 6 months post-breast cancer diagnosis and recurrence in the Pathways Study, stratified by estrogen-related factors

	Premenopausal						Postmenopausal				
	n=725 (107 events)						n=2038 (265 events)				
	n	events	HR[a,b]	95% CI			n	events	HR[a,b]	95% CI	
Non-drinker (<0.36 g/day)	320	47	Ref	Ref	Ref		863	121	Ref	Ref	Ref
Occasional (0.36-<6 g/day)	244	35	1.03	0.62	1.71		634	77	1.12	0.82	1.53
Regular (≥6 g/day)	161	25	1.66	0.92	2.99		541	67	1.16	0.82	1.63
p for trend			.12						.38		
p for interaction=.32											
Continuous 6 g/day	725	107	1.03	1.01	1.06		2038	265	1.00	0.99	1.01
	ER-negative						ER-positive				
	n=431 (76 events)						n=2330 (296 events)				
	n	events	HR[a,b]	95% CI			n	events	HR[a,b]	95% CI	
Non-drinker (<0.36 g/day)	209	36	Ref	Ref	Ref		973	132	Ref	Ref	Ref
Occasional (0.36-<6 g/day)	133	25	1.10	0.61	2.00		744	87	1.05	0.78	1.42
Regular (≥6 g/day)	89	15	0.96	0.47	1.94		613	77	1.32	0.96	1.83
p for trend			.96						.11		
p for interaction=.90											
Continuous 6 g/day	431	76	0.99	0.96	1.02		2330	296	1.01	1.00	1.02
	Obese (BMI≥30 kg/m^2)						Non-obese (BMI<30 kg/m^2)				
	n=882 (125 events)						n=1881 (247 events)				
	n	events	HR[a,b]	95% CI			n	events	HR[a,b]	95% CI	
Non-drinker (<0.36 g/day)	437	75	Ref	Ref	Ref		746	93	Ref	Ref	Ref
Occasional (0.36-<6 g/day)	290	30	0.66	0.40	1.07		588	82	1.35	0.96	1.88
Regular (≥6 g/day)	155	20	1.26	0.72	2.21		547	72	1.41	0.98	2.02
p for trend			.97						.06		
p for interaction=.07											
Continuous 6 g/day	882	125	1.01	0.99	1.03		1881	247	1.01	1.00	1.02

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

[b]For recurrence models, censored at first of KPNC health plan disenrollment or Pathways Study drop-out, death, or end of study (December 31, 2021).

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

Table 5.

Associations of alcohol consumption around breast cancer diagnosis and all-cause mortality in the Pathways Study, stratified by estrogen-related factors

	Premenopausal						Postmenopausal[1]				
	n=1059 (150 events)						n=2600 (684 events)				
	n	events	HR[a,b]	95% CI			n	events	HR[a,b]	95% CI	
Non-drinker (<0.36 g/day)	388	58	Ref	Ref	Ref		964	284	Ref	Ref	Ref
Occasional (0.36-<6 g/day)	355	57	1.17	0.78	1.75		856	211	0.94	0.78	1.13
Regular (≥6 g/day)	316	35	0.93	0.58	1.50		780	189	0.89	0.72	1.09
p for trend			.87						.25		
p for interaction=.42											
Continuous 6 g/day	1059	150	0.99	0.97	1.01		2600	684	1.00	0.99	1.00
	ER-negative						ER-positive				
	n=586 (155 events)						n=3071 (679 events)				
	n	events	HR[a,b]	95% CI			n	events	HR[a,b]	95% CI	
Non-drinker (<0.36 g/day)	227	64	Ref	Ref	Ref		1123	278	Ref	Ref	Ref
Occasional (0.36-<6 g/day)	207	59	0.97	0.65	1.43		1004	209	0.97	0.80	1.17
Regular (≥6 g/day)	152	32	0.72	0.43	1.18		944	192	0.94	0.77	1.16
p for trend			.23						.56		
p for interaction=.39											
Continuous 6 g/day	586	155	0.98	0.96	1.00		3071	679	1.00	0.99	1.00
	Obese (BMI≥30 kg/m^2)						Non-obese (BMI<30 kg/m^2)				
	n=1222 (321 events)						n=2437 (513 events)				
	n	events	HR[a,b]	95% CI			n	events	HR[a,b]	95% CI	
Non-drinker (<0.36 g/day)	529	164	Ref	Ref	Ref		823	178	Ref	Ref	Ref
Occasional (0.36-<6 g/day)	430	100	0.71	0.54	0.94		781	168	1.22	0.97	1.53
Regular (≥6 g/day)	263	57	0.77	0.56	1.08		833	167	1.03	0.81	1.31
p for trend			.04						.80		
p for interaction=.05											
Continuous 6 g/day	1222	321	0.99	0.98	1.00		2437	513	1.00	0.99	1.00

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

[b]For all-cause mortality models, censored at end of study (December 31, 2021).

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

Table 6.

Associations of alcohol consumption 6 months post-breast cancer diagnosis and all-cause mortality in the Pathways Study, stratified by estrogen-related factors

	Premenopausal						**Postmenopausal**				
	n=725 (96 events)						**n=2038 (498 events)**				
	n	**events**	**HR[a,b]**	**95% CI**			**n**	**events**	**HR[a,b]**	**95% CI**	
Non-drinker (<0.36 g/day)	320	55	Ref	Ref	Ref		863	232	Ref	Ref	Ref
Occasional (0.36-<6 g/day)	244	26	0.58	0.34	1.00		634	137	0.98	0.78	1.24
Regular (≥6 g/day)	161	15	0.96	0.50	1.86		541	129	0.97	0.76	1.24
p for trend			.47						.82		
p for interaction=.10											
Continuous 6 g/day	725	96	1.00	0.97	1.04		2038	498	1.00	1.00	1.01
	ER-negative						**ER-positive**				
	n=431 (106 events)						**n=2330 (488 events)**				
	n	**events**	**HR[a,b]**	**95% CI**			**n**	**events**	**HR[a,b]**	**95% CI**	
Non-drinker (<0.36 g/day)	209	53	Ref	Ref	Ref		973	234	Ref	Ref	Ref
Occasional (0.36-<6 g/day)	133	35	0.98	0.60	1.60		744	128	0.85	0.67	1.08
Regular (≥6 g/day)	89	18	0.76	0.40	1.45		613	126	0.95	0.75	1.22
p for trend			.46						.57		
p for interaction=.96											
Continuous 6 g/day	431	106	0.99	0.96	1.01		2330	488	1.01	1.00	1.01
	Obese (BMI≥30 kg/m^2)						**Non-obese (BMI<30 kg/m^2)**				
	n=882 (231 events)						**n=1881 (363 events)**				
	n	**events**	**HR[a,b]**	**95% CI**			**n**	**events**	**HR[a,b]**	**95% CI**	
Non-drinker (<0.36 g/day)	437	134	Ref	Ref	Ref		746	153	Ref	Ref	Ref
Occasional (0.36-<6 g/day)	290	61	0.67	0.47	0.94		588	102	1.04	0.79	1.38
Regular (≥6 g/day)	155	36	0.75	0.49	1.16		547	108	1.12	0.84	1.48
p for trend			.05						.46		
p for interaction=.02											
Continuous 6 g/day	882	231	1.00	0.98	1.01		1881	363	1.00	1.00	1.01

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

[b]For all-cause mortality models, censored at end of study (December 31, 2021).

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