Published in final edited form as:
Cancer Causes Control. 2011 May ; 22(5): 775–783. doi:10.1007/s10552-011-9750-7.

Smoking and alcohol consumption in relation to risk of triple-negative breast cancer in a cohort of postmenopausal women

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Financial disclosures: none

Conflicts of interest: none

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Abstract

Purpose—Little is known about risk factors for triple negative breast cancer (TNBC), which has a worse prognosis compared to hormone receptor-positive breast cancer. We examined the association of smoking and alcohol intake with TNBC and estrogen receptor-positive (ER+) breast cancer.

Methods—Among 146,985 women enrolled in the Women's Health Initiative, 300 TNBC cases and 2,479 ER+ cases were identified over a median of 8.0 years of follow-up. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI).

Results—Cigarette smoking was not associated with TNBC, whereas drinkers had reduced risk compared to never drinkers. In contrast, both exposures showed slight positive associations with ER+ breast cancer: for women with ≥40 pack-years of smoking, the HR was 1.24, 95% CI 1.06–1.44; for women consuming ≥7 servings of alcohol per week the HR was 1.26, 95% CI 1.06–1.50. Intakes of wine and hard liquor were also significantly positively associated with ER+ breast cancer.

Conclusions—These findings from a large cohort of postmenopausal women suggest that smoking and alcohol consumption are not associated with increased risk of TNBC, but may be modestly associated with increased risk of ER+ breast cancer.

Keywords

breast neoplasms; triple-negative; estrogen receptor-positive; cigarette smoking; alcohol consumption; postmenopausal women

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Breast cancer is the most common cancer and the leading cause of cancer death in women worldwide [1]. It is now widely recognized that breast cancer is a heterogeneous disease at the molecular, pathologic, and clinical levels [2, 3]. Triple negative breast cancer (TNBC) is characterized by the absence of protein expression of the estrogen receptor (ER) and progesterone receptor (PR) and lack of over-expression of human epidermal growth factor receptor 2 (HER2) [4]. Triple-negative breast cancers account for between 10% and 25% of all breast cancers in western countries [4] and occur disproportionately in younger women (< 50 years) [4–9], in African-American women [10, 11], and in carriers of BRCA1 [4]. A large proportion (~70%) are basal-like and almost all are high-grade tumors, and they have a more aggressive pathology and a worse prognosis compared to other subtypes [4–12]. However, to date relatively few studies have examined risk factors for TNBC [13–19].

Alcohol consumption has been consistently, although modestly, associated with breast cancer risk overall [20–22], whereas the association of cigarette smoking with breast cancer risk remains unresolved [21, 23, 24]. Few studies have examined the association of these exposures with risk of TNBC. The four previous studies that have reported on the association of smoking and alcohol intake with TNBC [16–19] have been limited in their assessment and inconsistent in their findings. We used data from the Women's Health Initiative to examine the association of cigarette smoking and alcohol consumption with the risk of TNBC. For the purpose of qualitative comparison, we also assessed associations with ER+ breast cancer.

Materials and Methods

The Women's Health Initiative is a large, multi-faceted study designed to extend our understanding of the determinants of major chronic diseases in women. It is composed of a Clinical Trial component (CT) and an Observational Study (OS) component [25]. The CT component included randomized controlled clinical trials to test the effects of a low-fat dietary pattern, calcium plus vitamin D supplementation, and administration of postmenopausal estrogen alone or estrogen plus progestin on the risk of coronary heart disease, breast cancer, colorectal cancer, and fractures [25]. Women between the ages of 50 and 79 were recruited from the general population at 40 clinical centers throughout the United States between 1993 and 1998. Details of the design and reliability of the baseline measures have been published [26, 27]. All participants provided informed consent using material approved by institutional review boards at each center.

Data Collection

Information was collected at study entry on demographics, medical, reproductive and family history, and dietary and lifestyle factors, including smoking history and current intake of alcoholic beverages. Clinical outcomes (including cancer diagnosis) were updated semi-annually in the CT by mailed or telephone questionnaires and annually in the OS [28]. Breast cancer diagnoses reported by participants were verified locally by WHI physician adjudicators. Medical records and pathology reports were forwarded to the WHI Clinical Coordinating Center for central adjudication and coding of ER, PR, and HR2 status. As of September 12, 2005 (close-out date), a total of 329 triple-negative breast cancer cases had been identified in the entire WHI cohort (199 in the OS and 130 in the CT). Information on smoking habits at baseline included: whether subjects had ever smoked (at least 100 cigarettes) and, among those who had ever smoked, age at initiation of regular smoking, current smoking status, age at quitting, typical number of cigarettes smoked per day, and number of years of smoking. In order to characterize alcohol consumption, information obtained in two different questionnaires was combined. In a health habits questionnaire administered at baseline, women were asked whether they had ever consumed at least 12 drinks of any alcoholic beverage over their lifetime and whether they still drank alcohol. In addition, in the food frequency questionnaire (FFQ) women were asked about their intake of beer, wine, and hard liquor during the past three months. Frequency categories for number of servings were: never or less than once per month, 1–3 per month, 1 per week, 2–4 per week, 5–6 per week, 1 per day, 2–3 per day, 4–5 per day, and 6+ per day. Serving size was also queried. A medium serving was defined as a 12 oz can or bottle of beer, 6 oz glass of wine, or 1 shot (1.5 oz) of hard liquor. The Pearson correlation coefficient between alcohol intake assessed by the FFQ versus 8-day dietary intake diary (four 24-hour recalls and a 4-day food record) was 0.89 in a validation study carried out in a sub-sample of 113 participants [29]. Based on information from the two questionnaires, two variables were created to describe frequency of total alcohol intake: a categorical variable (non-drinker, past drinker, <1 drink per month, <1 drink per week, 1–<7 drinks per week, and ≥7 drinks per week) and a continuous variable (alcoholic drinks per week). In addition, we analyzed intake of specific alcoholic beverages.

Over 8.0 years of follow-up, 5,430 cases of invasive breast cancer were identified within the cohort. The proportion of cases with clear-cut results for ER, PR, and HER2 were as follows: 89.6%, 87.7%, and 59.7, respectively. The breakdown of ER+ cases by PR and HER2 status was as follows: PR+/HER2+ (N = 315); PR+/HER2- (N = 1,661); PR-/HER2+ (N = 107); and PR-/HER2- (N = 352). In addition, 1,420 ER+ cases were missing information on HER2 status.

Of 161,808 WHI participants, we excluded 8,735 women with a history of breast cancer or a mastectomy, 690 women missing information on breast cancer as an outcome; 2,263 breast cancer cases who did not have definite marker status (i.e., positive or negative) for ER, PR, and/or HER2, 1,773 women missing smoking status, and 318 women missing alcohol consumption data. After making these exclusions, 148,030 women were available for analysis, among whom 300 had TNBC and 2,479 had ER+ breast cancer (and were not missing HER2 status).

Statistical Analysis

Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CI) for the associations between smoking-related variables and alcohol intake and risk of TNBC and ER+ breast cancer. Each case group was contrasted with non-cases in separate models. In these analyses, cases contributed person-time to the study from their date of enrollment until the date of diagnosis of their breast cancer, and non-cases contributed person-time from their date of enrollment until the end of follow-up (date of close-out, date of death, or date of withdrawal from the study, whichever occurred first).

Each of five smoking variables (smoking status, number of cigarettes smoked per day, age started smoking, duration of smoking, and pack-years) was assessed in separate models. Pack-years of cigarette smoking were computed by multiplying the midpoint of the smoking frequency interval by the midpoint of the duration interval and dividing the product by 20. We classified women according to frequency of overall alcohol intake at baseline. In addition, we separately examined the intake of beer, wine, and hard liquor (0 servings per week, >0 and <3 servings per week, and ≥3 servings per week.) Tests for trend were performed by assigning the median value to each category and modeling this variable as a continuous variable.

Both age-adjusted and multivariable-adjusted results were generated. In the full multivariable model, we included variables that were significantly associated with breast cancer in the WHI cohort as well as several additional variables that were not significantly associated with breast cancer risk in WHI but that show consistent associations with breast cancer in the literature. The full model included: age (continuous), age at menarche (continuous), age at first full-term pregnancy (nulliparous, <20, 20–29, ≥30), parity (continuous), age at menopause (<50, ≥50), body mass index (kg/m^2 – continuous), waist circumference (cm – continuous), use of oral contraceptives (never/ever), use of hormone therapy (never, estrogen alone, estrogen plus progesterone, both), history of breast biopsy (never, ever), family history of breast cancer in a first-degree relative (absent, present), mammogram in past two years (no, yes), physical activity (metabolic equivalents per week - continuous), education (less than high school graduate, high school graduate/some college, college graduate, post-college), ethnicity (white, black, other), and study arm assignment in each of the clinical trials or the observational study. Models evaluating the effects of smoking included alcohol (servings/week – continuous variable), and models evaluating the effect of alcohol included pack-years of smoking (0, <20, 20–<40, ≥40). All statistical tests were two-sided.

In addition to our primary analysis, we conducted several sub-analyses and sensitivity analyses. To complement our extensive multivariable model, we constructed a parsimonious model which included only those variables that were significantly associated with the outcome (TNBC or ER+ breast cancer) in the full multivariable analysis ($p < 0.05$), in addition to the exposures of interest. For TNBC, this parsimonious model included: age, ethnicity, family history of breast cancer, and history of breast biopsy. The parsimonious model for ER+ breast cancer included: age, age at menarche, age at first birth, age at

menopause, waist circumference, hormone therapy, family history of breast cancer, history of breast biopsy, physical activity, and education.

Results

TNBC cases differed little from non-cases on most baseline characteristics, including age, body mass index, parity, age at menopause, and ever use of hormone therapy, but were more likely to have had an early menarche, to have a family history of breast cancer in a first degree relative, to have ever had a breast biopsy, and were less likely to be of non-Hispanic white ethnicity (Table 1). Compared to ER+ cases, TNBC cases were younger, had greater parity, were less likely to have had a first birth at age ≥30, less likely to have ever used hormone therapy and to have post-college education, and to be non-Hispanic white. TNBC and ER+ cases did not differ by stage of disease; however, TNBC cases were more likely to have poorly differentiated and anaplastic tumors compared to ER+ cases.

Neither smoking status nor other smoking parameters were associated with risk of TNBC (Table 2). Indices of smoking showed only weak and inconsistent positive associations with ER+ breast cancer. Former smokers, but not current smokers, were at slightly increased risk. There was a suggestion of increased risk with increasing cigarettes smoked per day, early age at initiation, duration, and pack-years; however, the magnitude of the increase was small, and there were no clear gradients. The results of the parsimonious models (for TNBC and ER+) did not differ from those of the corresponding full models (data not shown).

Risk of TNBC was lower among alcohol consumers than non-drinkers, and was significantly reduced among consumers of ≥7 drinks per week (HR 0.57, 95% CI 0.34–0.95) (Table 3), but there was no clear trend with recency or amount of alcohol intake. In contrast, consumers of ≥7 drinks per week had a significantly increased risk of ER+ breast cancer (HR 1.26, 95% CI 1.06–1.50). When considered separately, intake of beer, wine, and liquor were not associated with TNBC (Table 3); however, intake of wine and liquor each showed small but statistically significant positive associations with ER+ breast cancer. Again, the results of the parsimonious models regarding history of alcohol use did not differ from those of the full models for either TNBC or ER+ breast cancer (data not shown).

Discussion

Given that alcohol consumption and smoking are both modifiable risk factors for breast cancer, it is important to understand their associations with specific breast cancer subtypes. In this prospective cohort study of postmenopausal women, smoking was not associated with risk of TNBC, whereas consumers of alcohol had reduced risk. In contrast, both smoking and alcohol intake at baseline showed weak, positive associations with ER+ breast cancer.

Of four previous studies that have reported on the associations of smoking and alcohol intake with TNBC [17–19] or “basal-like” breast cancer [16], three found little evidence of an association of either smoking or drinking with risk TNBC [16–18]. In contrast, Trivers et al [19] reported that, compared to never smokers, former smokers had an increased risk of TNBC (odds ratio 1.56, 95% CI 1.14–2.14), whereas current smokers had reduced risk (odds ratio 0.53, 95% CI 0.34–0.82); alcohol consumption showed no association with risk [19]. All four studies presented only limited detail on the extent of smoking and alcohol consumption history.

Whether cigarette smoking is associated with increased risk of breast cancer overall is unresolved [21, 23, 24, 30]. Many studies have shown no association of smoking status (being a current or former smoker vs. never having smoked) or other aspects of smoking

with increased risk [21, 24, 31–37], whereas other studies have indicated that greater intensity, early age of initiation, and longer duration of smoking are associated with increased risk [38–43]. Li et al. [43] and others [23] proposed that studies examining the association of smoking with breast cancer in older populations tend to report positive associations compared to studies conducted across a wider, or younger, age range due to a cohort effect: that is, older women have smoked for longer durations than younger women. Few studies, however, have examined the association with attention to hormone receptor status [43–50], and those that have show conflicting results. Our results suggesting a slight increase in risk of ER+ breast cancer with greater intensity of smoking, younger age at initiation, longer duration, and greater number of pack-years are consistent with the results of several [43, 44, 46, 47, 50], but not all [45–48], previous studies.

In the present study, consumers of alcohol had a reduced risk of TNBC, which reached statistical significance in women with an intake of ≥7 drinks/week at baseline. However, because there was no clear trend with recency or amount of alcohol consumed and because the number of cases in the highest intake category (N = 27), the inverse association is difficult to interpret. In three previous studies, alcohol intake was not associated with TNBC [17, 18] or basal-like breast cancer [16]. Similar to our finding for TNBC, Trivers et al. [19] reported reduced odds ratios for drinkers of <7 drinks/week (OR = 0.72, 95% CI 0.50–1.10) and >7 drinks/week (OR = 0.72, 95% CI 0.44–1.17). Our finding of a modest positive association of alcohol intake with all ER+ breast cancer but not with TNBC is consistent with the results of a number of studies [19, 51–54], which generally show positive associations with ER+/PR+, ER+/PR− tumors but not with ER-/PR− or ER-/PR+. There is some overlap between the breast cancer cases included in the present analysis and those in the analysis by Li et al. [54]; however, Li et al. restricted their analysis to the WHI OS and they did not classify their cases by HER2 status.

The observed association of alcohol consumption with ER+ breast cancer but not with TNBC may indicate that alcohol acts through a hormonal pathway, since alcohol intake appears to increase endogenous steroid hormone levels [55, 56]. However, it is possible that a number of non-hormonal pathways may be involved [51].

Strengths of this study include the relatively large number of TNBC cases (previous studies had 135 [19], 187 [17], 225 [16], and 288 [18] cases), the prospective nature of the WHI, the completeness of participant follow-up, the centralized adjudication of breast cancer diagnosis, and the availability of extensive information on breast cancer risk factors. In particular, the comprehensive nature of WHI questionnaire items on tobacco and alcohol use allowed us to explore these potential risk factors in far greater detail than previous studies on this question [16–19].

Our study also has some limitations. Our analysis was limited to exposure information obtained at baseline, and smoking and drinking habits could have changed over the follow-up period. Additionally, as women in the WHI were relatively light drinkers, we were not able to explore associations with heavy drinking in great detail. Nevertheless, a significant association was seen for ER+ breast cancer in women in the highest intake category of total alcohol, as well as those for wine and liquor. Furthermore, because we did not have information to characterize TNBC cases as basal-like according to cytokeratin 5/6 and/or epidermal growth factor [EGFR] status, heterogeneity among TNBC cases could reduce the power to detect associations; however, given that these two markers are rarely tested for in clinical settings, the triple-negative phenotype may be more clinically relevant. Finally, 40% of cases were missing HER2 status, and these cases were excluded from our analysis. Cases lacking HER2 status did not differ from cases with HER2 status with respect to their distribution by exposures or covariates.

In conclusion, in this cohort study of postmenopausal women, cigarette smoking was not associated with risk of TNBC, whereas consumers of alcohol at baseline had reduced risk compared to non-drinkers. In contrast, both risk factors showed modest positive associations with ER+ breast cancer. The different pattern of association of smoking and drinking with TNBC and ER+ breast cancer adds to accumulating evidence suggesting that etiologic factors may differ between different breast cancer subtypes.

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Table 1

Baseline characteristics of TNBC cases, ER+ cases, and non-cases in the Women's Health Initiative observational study and clinical trial combined.

Characteristic	TNBC cases (N = 300)	ER+ cases (N = 2,479)	Non-cases (N = 148,030)
Age at randomization/enrollment	62.2 ± 7.3	63.8 ± 7.0	63.1 ± 7.2
Body mass index[a]	28.5 ± 6.0	28.3 ±5.8	28.0 ± 5.9
Parity	2.8 ± 1.6	2.3 ± 1.7	2.6 ± 1.7
Age at menopause, years	47.5 ± 6.5	48.4 ± 6.6	47.2 ± 6.7
Alcohol intake (servings/week)	1.9 ± 4.3	2.9 ± 5.3	2.3 ± 4.9
Physical activity (MET-hrs[b]/week)	11.3 ± 12.7	11.3 ± 12.6	11.9 ± 13.7
Age ≤11 years at menarche (%)	25.8	24.2	21.9
Age ≥30 years at first birth (%)	6.7	12.2	8.9
Ever use of oral contraceptives (%)	44.2	40.2	41.8
Ever use of hormone therapy (%)	54.5	61.7	56.5
Breast cancer in first degree relative (%)	27.2	22.1	17.0
Ever had breast biopsy (%)	26.7	29.8	20.8
Had mammogram in last 2 years (%)	85.8	87.1	83.3
Post-college education (%)	26.3	33.9	28.3
Non-hispanic white ethnicity (%)	78.5	89.2	83.3
Smoking status (%)			
Never	51.5	47.8	51.2
Former	41.1	46.1	41.8
Current	7.4	6.1	7.1
Clinical variables			
Stage (%)			
Localized	70.1	72.9	
Regional	26.9	24.9	
Distant	2.0	0.8	
Unknown	1.0	1.4	
Grade (%)			
Well-differentiated	5.0	29.7	
Moderately differentiated	17.7	42.0	
Poorly differentiated	64.6	17.8	
Anaplastic	7.4	1.7	
Unknown	5.4	8.8	

Abbreviations: MET, metabolic equivalent task; SE, standard error.

[a] Weight (kg)/height (m)^2

[b] Defined as caloric need per kilogram of body weight per hour of activity divided by the caloric need per kilogram of body weight per hour at rest, per hour per week.

Table 2

Association of cigarette smoking with risk of TNBC and ER+ breast cancer in the Women's Health Initiative observational study and clinical trial combined

Variable	TNBC			ER+		
	No. cases	MV-adjusted		No. cases	MV-adjusted	
		HR[a]	95% CI		HR[a]	95% CI
Smoking status						
Never	155	1.00	reference	1185	1.00	reference
Former	123	0.91	0.70–1.16	1144	1.14	1.05–1.24
Current	22	1.09	0.69–1.72	150	1.05	0.88–1.25
Amount (cigarettes/day)						
Never smoker	155	1.00	reference	1185	1.00	reference
>0–4	31	0.89	0.60–1.33	257	1.03	0.90–1.19
5–14	50	1.07	0.77–1.48	380	1.11	0.98–1.25
15–24	37	1.00	0.69–1.43	365	1.20	1.07–1.36
≥25	21	0.74	0.44–1.23	220	1.09	0.94–1.27
Missing data	6				72	
P*trend*		*0.30*			*0.02*	
Age started smoking, years						
Never smoker	155	1.00	reference	1185	1.00	reference
<20	85	0.95	0.72–1.26	756	1.16	1.05–1.28
≥20	60	0.92	0.67–1.25	530	1.07	0.96–1.19
Missing data	0				8	
Duration of smoking, years						
Never	155	1.00	reference	1185	1.00	reference
<20	66	0.93	0.69–1.26	558	1.09	0.99–1.21
20–29	24	0.65	0.41–1.04	270	1.09	0.95–1.25
≥30	49	1.10	0.78–1.54	402	1.14	1.01–1.28
Missing data	6				64	
P*trend*		*0.91*			*0.03*	
Pack-years of smoking						
Never smoker	155	1.00	reference	1185	1.00	reference

Variable		TNBC			ER+	
	No. cases	MV-adjusted		No. cases	MV-adjusted	
		HR[a]	95% CI		HR[a]	95% CI
<20	90	0.98	0.75–1.29	722	1.10	1.00–1.22
20–<40	26	0.77	0.50–1.19	276	1.06	0.92–1.21
≥40	23	0.95	0.58–1.54	223	1.24	1.06–1.44
Missing data	6				73	
P*trend*		*0.47*			*0.01*	

[a]Adjusted for the following variables: age (continuous), education (3 levels), ethnicity (3 levels), body mass index (kg/m^2 -- continuous), waist circumference (cm – continuous), oral contraceptive use (never, ever), hormone therapy (never, estrogen only, estrogen plus progestin, both), age at menarche (continuous), age at first birth (4 levels), age at menopause (3 levels), alcohol (servings per week – continuous), family history of breast cancer (no, yes), history of breast biopsy (never, ever, missing), mammogram with past 2 years (no, yes), physical activity (METs/week - continuous), and treatment/control arm assignment in the estrogen alone, estrogen plus progestin,, calcium plus vitamin D, and dietary modification trials.

Table 3

Association of alcohol intake and intake of specific beverages with risk of TNBC and ER+ breast cancer in the Women's Health Initiative observational study and clinical trial combined

	TNBC cases (N = 300)				ER+ cases (N = 2,479)			
	N cases (%)		HR[a]	95% CI	N cases (%)		HR[a]	95% CI
Alcohol intake at baseline								
Never drank	44	(14.7)	1.00	reference	239	(11.1)	1.00	reference
Past drinker	59	(19.7)	0.72	0.48–1.08	427	(18.7)	0.99	0.84–1.57
<1 drink/month	27	(9.0)	0.47	0.29–0.78	264	(10.7)	0.87	0.73–1.05
<1 drink/week	70	(23.3)	0.78	0.53–1.16	499	(20.2)	0.98	0.83–1.14
1–6 drinks/week	73	(24.4)	0.68	0.46–1.02	666	(27.0)	1.00	0.86–1.17
≥7 drinks/week	27	(9.1)	0.57	0.34–0.95	376	(15.2)	1.26	1.06–1.50
Missing	0				8			
Beer intake at baseline								
0	239	(79.7)	1.00	reference	1935	(78.1)	1.00	reference
<3 servings/week	53	(17.7)	0.93	0.68–1.27	502	(20.3)	1.04	0.94–1.15
≥3 servings/week	8	(2.7)	1.60	0.79–3.26	42	(1.7)	1.01	0.73–1.38
P for trend			*0.74*				*0.51*	
Wine intake at baseline								
0	159	(53.2)	1.00	reference	1119	(45.2)	1.00	reference
<3 servings/week	116	(38.7)	0.95	0.73–1.22	1019	(41.1)	1.00	0.91–1.09
≥3 servings/week	25	(8.4)	0.75	0.48–1.17	341	(13.8)	1.16	1.02–1.32
P for trend			*0.25*				*0.08*	
Liquor intake at baseline								
0	220	(73.3)	1.00	reference	1750	(70.6)	1.00	reference
<3 servings/week	68	(22.7)	1.07	0.81–1.43	528	(21.3)	0.95	0.86–1.05
≥3 servings/week	12	(4.0)	0.84	0.47–1.52	201	(8.1)	1.36	1.17–1.58
P for trend			*0.93*				*0.02*	

[a]Adjusted for the following variables: age (continuous), education (3 levels), ethnicity (3 levels), body mass index (kg/m^2 -- continuous), waist circumference (cm – continuous), oralcontraceptive use (never, ever), hormone therapy (never, estrogen only, estrogen plus progestin, both), age at menarche (continuous), age at first birth (4 levels), age at menopause (3 levels), alcohol (servings per week –

continuous), pack-years of smoking (0, <20, 20–<40, ≥40), family history of breast cancer (no, yes), history of breast biopsy (never, ever, missing), mammogram with past 2 years (no, yes), physical activity (METs/week - continuous), and treatment/control arm assignment in the estrogen alone, estrogen plus progestin, calcium plus vitamin D, and dietary modification trials.