



Published in final edited form as:

Cancer Prev Res (Phila). 2025 February 03; 18(2): 73–83. doi:10.1158/1940-6207.CAPR-24-0208.

Alcohol consumption does not modify the polygenic risk score-based genetic risk of breast cancer in postmenopausal women: Atherosclerosis Risk in Communities study

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Abstract

High genetic risk and alcohol consumption ≥ 1 drink/day are associated with increased breast cancer risk. However, the interaction between alcohol and genetics on breast cancer risk is poorly understood, including in populations not enriched with daily drinkers. We prospectively studied 5651 White and Black postmenopausal women in the Atherosclerosis Risk in Communities study. Alcohol intake was assessed by food frequency questionnaire. 313-SNPs polygenic risk score (PRS) was calculated. Breast cancer cases were ascertained primarily by cancer registry linkage through 2015. Multivariable Cox regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association of PRS and current ethanol intake with breast cancer, and their interaction. 50.6% were current drinkers, and of them 50.8% drank < 1 drink/week and 12.8% drank > 7 drinks/week. Higher PRS was associated with higher breast cancer risk among White (HR_{1-SD}:1.48, 95%CI:1.34–1.65) and Black (HR_{1-SD}:1.15, 95%CI:0.96–1.38) women. Positive associations were not observed between current ethanol intake and breast cancer risk (White, HR_{13g/week}:1.00, 95%CI:0.98–1.03; Black, HR:0.83, 95%CI:0.69–1.00). Among both White and Black women, PRS generally appeared to be positively associated with risk in drinkers

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Conflict of Interest Disclosure Statement

The authors declare no potential conflicts of interest.

and non-drinkers. There was no evidence of an PRS-ethanol intake interaction in White or Black women. Patterns in Black women were similar when using an 89-SNP PRS developed among African-ancestry women. In conclusion, in a prospective analysis of White and Black postmenopausal women in a study population not enriched with daily drinkers, our findings suggest that alcohol drinking does not modify PRS-based genetic risk of breast cancer.

Keywords

Breast cancer; alcohol; polygenetic risk score; gene-environment interaction; risk

Introduction

Breast cancer is one of the most common cancers and the second leading cause of cancer death among women in the United States [1], and it is a complex disease resulting from a combination of genetic, environmental, and reproductive factors [2–4].

Studies have shown that women with a positive family history have a higher lifetime risk of breast cancer, in part, indicating an inherited risk of breast cancer [5–6]. The heritability of breast cancer is estimated to be about thirty percent from twins' studies [7–8]. Pathogenic variants in genes, such as *BRCA1* and *BRCA2*, contribute to a relatively high lifetime risk of breast cancer compared to the general population [9]. However, these variants are rare and account for only a small proportion of breast cancer [10]. One approach to discovering common gene variants that are modestly associated with breast cancer risk is to use genome-wide association studies (GWAS). Although each of the validated single nucleotide polymorphism (SNP) individually contributes only to a small risk, they are common in the general population and thus their overall contribution to breast cancer is estimated to be greater than known high penetrate genes [11–12]. In 2015, the first polygenic risk score (PRS) assessing the joint contribution of 77 common single nucleotide polymorphisms (SNPs) on breast cancer risk was developed [13]. In the study, women in the highest 1% of the PRS had a three times higher risk of breast cancer compared with women in the middle quintile. In 2019, an updated PRS of 313 SNPs was developed and validated in women of European ancestry [11]. The results showed that women in the highest 1% of the PRS have a 4.04 times higher risk of breast cancer, compared to those in the middle quintile. This study suggested that this PRS is a discriminatory and calibrated method for predicting breast cancer risk. While the 313-SNP PRS is positively associated with breast cancer risk in women of African ancestry [14], in 2024, an 89-SNP PRS (PRS_{AFR}) was developed in women with African ancestry that had better risk prediction performance [15].

Besides genetic factors and reproductive factors, various well-established environmental factors are associated with breast cancer risk [2–3], including alcohol consumption. Alcohol is a known human carcinogen that is associated with an elevated risk of several types of cancer [16]. Systematic reviews have found a positive association between alcohol drinking and breast cancer risk [17–18]. For every 10 g of ethanol consumed daily, the relative risk of breast cancer increases by approximately 10%. Potential mechanisms include the differences

in people's ability to metabolize acetaldehyde and the impact of alcohol on estrogen levels, enzymatic activities, and oxidative stress [17,19–21].

However, the interaction between alcohol consumption and genetic factors on breast cancer development is poorly understood, including among lower drinking populations. To our knowledge, only four studies have attempted to assess the interaction between PRS and alcohol on breast cancer risk. A population-based, nested case-control study in Korea (390 cases, 36290 controls) found a positive quantitative interaction between alcohol intake and a 4-SNP estrogen-related PRS on breast cancer risk [22]. The association between high PRS and breast cancer risk was more robust in women with moderate alcohol consumption than those with no or mild alcohol consumption. A nested case-control study among White women included in 8 prospective cohorts (17171 cases, 19862 controls) from the Breast and Prostate Cancer Cohort Consortium in the U.S. found no interaction between alcohol consumption and a 24-SNP PRS on breast cancer risk [23]. Another analysis (28239 cases, 30445 controls) that included participants of European ancestry in 20 case-control studies from the Breast Cancer Association Consortium (BCAC), both prospective and retrospective, found a significant sub-multiplicative interaction between a 77-SNP PRS and alcohol consumption on breast cancer risk ($OR_{\text{interaction}} = 0.90$ (0.82–0.98), P-value: 0.016) [24]. However, a further study using data from women of European ancestry from 46 studies (72284 cases, 80354 controls) included in BCAC showed no statistically significant interaction between a 313-SNP PRS and alcohol intake [25]. Additional support for the hypothesis that lifestyle factors may interact with PRS on breast cancer risk comes from a British study of women in the UK Biobank [2]. The study found an additive but not multiplicative interaction between overall environmental factors, as measured by the Healthy Lifestyle Index, and the genetic factors, as measured by a 304-SNP PRS, on breast cancer risk. However, another similar study examining overall lifestyle factors and a 305-SNP PRS in women in the UK Biobank found no significant interaction between the lifestyle index and genetic risk groups for breast cancer risk [26]. The overall environmental factors in these latter two studies included alcohol, but they did not separately evaluate the alcohol-PRS association.

Given the inconsistent findings described above and the importance of determining whether the genetic risk of breast cancer can be modified through lifestyle interventions, more research is needed to evaluate this interaction. Therefore, in an analytic cohort of postmenopausal women not enriched with daily drinkers, we evaluated whether alcohol consumption modifies the association between the genetic risk of postmenopausal breast cancer as measured by PRS. Since alcohol affects the risk of cancer in multiple ways through a variety of pathways, we assessed genetic risk across the whole genome using PRS, rather than restricting to SNPs in alcohol metabolism genes. In the main analysis, we used the 313-SNP PRS for both White and Black participants, and confirmed the findings using the PRS_{AFR} [15] and a PRS (PRS_{hybrid}) that was built from SNPs selected for women of African ancestry and the 313-SNP PRS [14]. We hypothesized that there is a multiplicative interaction between alcohol consumption and PRS for breast cancer risk even at lower levels of alcohol consumption.

Materials and Methods

Study Population

The Atherosclerosis Risk in Communities (ARIC) Study (RRID:SCR_021769) is a prospective cohort study consisting of 15,792 participants aged 45 to 65 years at the time of recruitment (1987–1989) from one of the four ARIC communities (Washington County, MD; Forsyth County, NC; Jackson, MS; and Minneapolis, MN) [27]. The ARIC study protocol was approved by the Institutional Review Boards (US Common Rule) of all participating centers. Written informed consent was obtained from each study participant.

Our study population was women enrolled in ARIC, at risk for first primary breast cancer, with genetic information and who consented to their data being used for studies on genetics and chronic diseases including cancer. As shown in the flowchart (Figure 1), we excluded participants with male sex; who died or were lost to follow up while premenopausal; had a premenopausal breast cancer diagnosis; had prevalent breast cancer at baseline; had a breast cancer diagnosis or were lost to follow up before the second visit (1990–1992); missing information on any of the main covariates.

Alcohol Consumption Assessment

Information on alcohol consumption status was obtained by interview at Visit 2. Alcohol drinking status was classified into three groups “current drinker”, “former drinker”, and “never drinker” based on the self-reported responses to the following two questions “Do you presently drink alcoholic beverages?”, and “Have you ever consumed alcoholic beverages?”. Alcohol consumption was quantified in grams of ethanol intake per week (g/wk) based on the self-reported numbers of glasses of wine per week (4 oz., 10.8 grams), bottles/cans of beer per week (12 oz., 13.2 grams), drinks of hard liquor per week (1.5 oz., 15.1 grams). For former and never drinkers, this value was set to zero. Because of the relatively large number of White participants, we further grouped White current drinkers into the following three categories: current drinker with less than 1 drink per week, current drinker with 1 drink or more but less than 7 drinks per week, and current drinker with 7 drinks or more per week, based on conventional guidelines that recommend women limit their intake to 1 drink or less per day [28]. One drink of total alcohol was defined as 13 grams of ethanol intake in our study.

Polygenic Risk Score calculation

Eligible participants were genotyped using DNA extracted from buffy coat (majority of samples were from Visit 2) by the Affymetrix 6.0 array [29]. For all participants, the 313-SNPs polygenic risk score (PRS) for breast cancer was calculated by summing the product of the number of risk alleles for each of the 313 SNPs and their corresponding per-allele log odds ratio for breast cancer [11]. The PRS was then categorized into lower 10th percentile ($\leq 10\%$), middle 80th percentile ($> 10\%$ to $\leq 90\%$), and upper 10th percentile ($> 90\%$) separately for women who are White and Black for calculating baseline characteristics. For the main analysis for White women, PRS was categorized into seven categories: $\leq 10^{\text{th}}$, $> 10^{\text{th}}$ to $\leq 30^{\text{th}}$, $> 30^{\text{th}}$ to $\leq 50^{\text{th}}$, $> 50^{\text{th}}$ to $\leq 70^{\text{th}}$, $> 70^{\text{th}}$ to $\leq 90^{\text{th}}$, and $> 90^{\text{th}}$ percentiles, as well as two categories: lower 50th ($\leq 50^{\text{th}}$) and upper 50th ($> 50^{\text{th}}$) percentiles. For Black

women, due to the smaller sample size, PRS was categorized into two categories, lower 50th and upper 50th percentiles, for the main analysis.

For participants who are Black, we calculated two additional PRSs. The first PRS, developed by Jia et al., is an 89-SNP PRS built using data from women of African ancestry (PRS_{AFR}) [15]. The second PRS, developed by Gao et al., is a 29,569-SNP PRS built from SNPs identified in both women of African ancestry and European ancestry (PRS_{hybrid}) [14]. PRS_{AFR} and PRS_{hybrid} were categorized into two categories, lower 50th and upper 50th percentiles.

PRS, PRS_{AFR} and PRS_{hybrid} were scaled to have a mean of 0 and a standard deviation (SD) of 1.

Outcome Ascertainment

The outcome was first primary female, post-menopausal, invasive breast cancer, ascertained starting after Visit 2 or the first visit at which they were postmenopausal through 2015. Breast cancer cases were ascertained by linking to the cancer registries, abstracting archived hospital discharge summaries, medical records, and death certificates (underlying cause) [30]. Breast cancer was identified using the following ICD codes: ICD-O-1: 174.0–174.9; ICD-O-2: 50.0–50.9; ICD-O-3: 50.0–50.9; ICD-8 & 9: 174.0–174.9; ICD-10: 50.0–50.9.

Measurement of Covariates

Covariates were obtained at Visit 2, unless otherwise specified. Main covariates included race (White/Black; Visit 1), age at recruitment (years; Visit 1), height at recruitment (inches; Visit 1), body mass index (kg/m²), waist-hip ratio, education level (basic education, intermediate education, advanced education), physical activity (minutes per week; Visit 1), cigarette smoking status (current smoker, former smoker, never smoker), total energy intake (kcal; Visit 1), folic acid intake (micrograms; Visit 1), diabetes status (diabetes, at risk for diabetes, normal glycemia), age at menarche (years; Visit 1), ever taken hormone replacement therapy (yes/no), ever used oral contraceptives (yes/no; Visit 1), breast-feeding status (never, less than one year, one year or more; Visit 3).

Other covariates included parity (nulliparous/parous; Visit 3), age at first live birth (less than 35 years old/ 35 years or older; Visit 3), ever had a mammogram (yes/no; Visit 3), mother had breast cancer (yes/no; Visit 3), frequency of routine examinations (less than one ever five years/at least once every five year), health insurance status (yes/no).

Statistical analyses

For women who were postmenopausal at Visit 2 (the first available visit with genetic information for the majority of the participants), follow-up began at Visit 2 (n=5616, 99.4%). For women who were premenopausal at Visit 2 (n=35, 0.6%), follow-up began at the first visit at which they were postmenopausal.

We initially used the 313-SNPs PRS [11], and performed the entire analysis stratified by race given the difference in predictive performance of the PRS by race [14–15, 31]. For Black women, we repeated the main analyses using the PRS_{AFR} and PRS_{hybrid} to

confirm the findings when using the 313-SNP PRS. We estimated the age-adjusted and fully-adjusted hazard ratio (HR) and 95% confidence intervals (CI) for the association between continuous PRS (scaled) and breast cancer incidence using multivariable Cox proportional hazards models; we reported HRs per 1 SD increase of the scaled PRS. Age-adjusted model included PRS and age (continuous) as independent variables, while the fully-adjusted models additionally included height, body mass index (BMI), waist-hip ratio, education level, physical activity, cigarette smoking status, total calories intake, folic acid intake, diabetes status, age at menarche, ever taken hormone replacement therapy, ever used oral contraceptives, and breast-feeding status as independent variables. We used the last observation carried forward method to handle missing data on alcohol drinking status, ethanol intake, cigarette smoking status, BMI, waist-hip ratio, parity, and we created missing indicator for breast-feeding status and physical activity. We then examined whether the association between continuous 313-SNP PRS and breast cancer incidence was linear on the natural logarithm scale using the likelihood ratio test comparing the model with continuous PRS and the model with penalized spline (P-spline) terms with 4 degrees of freedom for PRS [32–34]. The proportional hazards assumption was checked by visualizing the time-dependent coefficient of the PRS to determine if the line was horizontal. No violation of proportional hazards assumption was found (Supplementary Figure S1).

We estimated the age-adjusted and fully-adjusted HR and 95% CI for the association between continuous current ethanol intake and breast cancer incidence using multivariable Cox proportional hazards models, and examined whether the association was linear on the natural logarithm scale using a similar method. Time-dependent coefficient for the association between current ethanol intake and breast cancer risk was plotted. There was no violation of the proportional hazards assumption among White women, while the sample size was too small for Black women to determine if the proportional hazards assumption holds (Supplementary Figure S2)

We evaluated whether alcohol modified the association between PRS and breast cancer by estimating fully-adjusted HRs of breast cancer incidence for continuous PRS within each stratum of alcohol consumption using Cox proportional hazards models. To test for gene-alcohol interaction, likelihood ratio tests were conducted comparing the fully-adjusted model with terms for alcohol consumption categories and continuous PRS to the model additionally including interaction terms for the product of alcohol consumption categories and continuous PRS. For each alcohol consumption categories, we also ran Cox models for PRS using P-spline with 4 degrees of freedom and plotted the log HR for the P-spline PRS terms.

Additionally, we evaluated whether PRS modified the alcohol and breast cancer association by estimating fully-adjusted HRs of continuous current ethanol intake on breast cancer incidence within each PRS stratum. Likelihood ratio tests were conducted comparing model with and without interaction terms.

We conducted three sensitivity analyses. 1. We stratified the age-adjusted model for PRS by maternal history of breast cancer (collected at Visit 3), given that PRS and family history of breast cancer may be capturing the same underlying genetic susceptibility. 2. In the analysis

of PRS-breast cancer association stratified by alcohol consumption categories, we excluded participants with extreme current ethanol intake using various cut points (ranging from >180 g/wk to >500 g/wk) to define an extreme intake, and modeled the alcohol as a continuous and as well as a binary variable (less than 1 drink per week vs. at least 1 drink per week; less than 7 drinks per week vs. at least 7 drinks per week). 3. To further study ethanol-breast cancer association, we restricted participant to those with health insurance, and stratified by routine examinations frequency and by mammogram status.

Statistical significance was set at P-value < 0.05 for two-sided test. All analyses were performed using R version 4.2.2 (RRID:SCR_001905).

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request (https://aric.csc.unc.edu/aric9/publications/policies_forms_and_guidelines)

Results

Study population

Our final analytic dataset consisted of 5651 participants, of which 4055 were of European ancestry and 1596 were of African ancestry (Figure 1). Among White women, 61.1% were current drinkers, and of them 50.7% of them drank <1 drink/week and 13.8% drank >7 drinks/week, whereas among Black women, 23.7% were current drinkers, and of them 51.6% drank <1 drink/week and 10.1% drank >7 drinks/week. Baseline characteristics for participants by alcohol intake category are shown in Supplementary Tables S1a (White) and S1b (Black). In general, current drinkers were younger, more educated, leaner, and more active, less likely to have diabetes, and more likely to take birth control pills, but had lower folic acid intake compared with never and former drinkers, in both White and Black participants. Across the three 313-SNP PRS groups, the distributions of covariates were relatively even (Supplementary Table S1c [White], S1d [Black]).

313-SNP PRS and breast cancer risk

Among White women, the fully-adjusted HR of breast cancer for a 1 SD increase in PRS was 1.48 (95% CI: 1.34–1.64, P-value < 0.001), whereas among Black women, the HR was 1.15 (95% CI: 0.96–1.38, P-value = 0.13) (Table 1). These associations were linear on the natural logarithm scale (p-linearity: 0.25 [Whites] and 0.20 [Blacks]; Supplementary Figure S3).

Ethanol intake and breast cancer risk

Positive associations were not found between current ethanol intake and breast cancer risk among White (per 13 g/week fully adjusted HR: 1.00, 95% CI: 0.98–1.03), and Black (HR: 0.83, 95% CI: 0.69–1.00) women (Table 2; Supplementary Figure S4A and S4B).

Interaction between 313-SNP PRS and ethanol intake for breast cancer risk

Higher PRS was associated with higher breast cancer risk in non-drinkers and in each of the alcohol consumption categories among White women (Table 3). The HR of breast cancer for a 1 SD increase in PRS (HR: 1.63, 95% CI: 1.10–2.41) was highest among the “≥ 7 drinks/wk” category, while the HR of breast cancer for a 1 SD increase in PRS (HR: 1.40, 95% CI: 1.12–1.73) was lowest among the “≥ 1 to < 7 drinks/wk” category. However, these differences in the HRs for the association between PRS and breast cancer across the alcohol consumption categories were not statistically significant (P-interaction=0.81). Within each of the five alcohol consumption categories, the natural logarithm of the HR of breast cancer generally increased as the PRS increased (Supplementary Figure S5).

Among Black women, the HRs of breast cancer for a 1 SD increase PRS were 1.30 (95% CI: 0.97–1.74), 1.05 (95% CI: 0.76–1.46), 1.25 (95% CI: 0.80–1.97) for never, former, and current drinkers, respectively (Table 3; Supplementary Figure S6). These estimates did not statistically differ across alcohol consumption categories (P-interaction=0.61).

Among White women, current ethanol intake was not associated with breast cancer risk across PRS categories, and there was no interaction between continuous ethanol intake and PRS categories for breast cancer risk (Table 4). However, for Black women, the HRs of breast cancer for a 13-gram increase in ethanol per week were 0.72 (95% CI: 0.51–1.04) and 0.88 (95% CI: 0.71–1.08) for the lower and upper 50% PRS group, respectively (Table 4).

PRS_{AFR} and PRS_{hybrid}, Alcohol, and Breast Cancer Risk in Black Women

Among Black women, the fully-adjusted HR of breast cancer for a 1 SD increase in PRS_{AFR} was 1.12 (95% CI: 0.93–1.35, P-value = 0.22), and for PRS_{hybrid}, was 1.22 (95% CI: 1.02–1.46, P-value = 0.03) (Table 5). The HRs of breast cancer for a 1 SD increase in PRS_{AFR} were 1.08 (95% CI: 0.82–1.40), 1.38 (95% CI: 0.94–2.00), 1.02 (95% CI: 0.68–1.54) for never, former, and current drinkers, respectively. For PRS_{hybrid}, the corresponding HRs were 1.40 (95% CI: 1.05–1.86), 1.11 (95% CI: 0.79–1.58), and 1.16 (95% CI: 0.77–1.75). The HRs of breast cancer for a 13-gram increase in current ethanol intake per week were similar across the lower and upper 50% of PRS_{AFR}, whereas the HRs were 0.91 (95% CI: 0.75–1.12) and 0.70 (95% CI: 0.46–1.06) in the lower and upper 50% group of PRS_{hybrid} (Table 5). No statistically significant interactions between PRS and ethanol intake were observed, with all P-interaction values >0.05 (Table 5).

Sensitivity analyses

Among White women, the association between PRS and breast cancer risk appeared similar between those whose mother had breast cancer (HR: 1.53, 95% CI: 1.09–2.13) and those whose mother did not have breast cancer (HR: 1.47, 95% CI: 1.32–1.64; Supplementary Table S2). Among Black women, the HR for those whose mothers had breast cancer was 1.36 (95% CI: 0.59–3.15) albeit based on small numbers, while the HR was 1.17 (95% CI: 0.96–1.41) among those whose mothers did not have breast cancer.

After excluding extreme values of current ethanol intake, association between continuous ethanol intake and breast cancer risk was consistently null for Whites, while the association

was inverse and borderline significant for Blacks (Supplementary Table S3). Drinking at least 1 drink per week (vs. <1 per week), or at least 7 drinks per week (vs. <7 per week) was not associated with higher breast cancer risk among Whites, while drinking at least 1 drink per week (vs. <1 per week) was associated with a borderline significant lower breast cancer risk among Blacks, although there were few cases among those who drank at least 1 drink per week.

The association between current ethanol intake and cancer risk remained unchanged after restricting to those with health insurance, and after stratifying by frequency of routine physical examinations and by ever had a mammogram status (Supplementary Table S4–S6).

Discussion

In this prospective cohort study in ARIC, we found that a 313-SNP PRS was associated with breast cancer risk among both White and Black women, as was the PRS_{AFR} and PRS_{hybrid} in Black women. We found no evidence that alcohol intake was associated with breast cancer risk among White women, whereas alcohol intake was inversely associated with breast cancer risk among Black women. We did not observe a multiplicative interaction between PRS and ethanol intake on breast cancer risk in either White or Black women. Our findings suggest that alcohol drinking does not modify PRS-based genetic risk of breast cancer among White and Black women with lower alcohol intake. Nevertheless, women should consider limiting alcohol consumption as a general cancer prevention strategy as indicated in dietary guidelines [28].

We explored the association between the 313-SNP PRS and breast cancer risk among White and Black women separately. While the PRS was positively associated with higher breast cancer risk among both White and Black women, the HR per 1 SD increase in PRS was smaller in Black women. Using a PRS developed among women with African ancestry [15], the HR for breast cancer per 1 SD increase in PRS_{AFR} was similar to using 313-SNP PRS among Black women. However, using a PRS built from SNPs selected for Black women and the 313-SNP PRS [14], the HR for a 1 SD increase in PRS_{hybrid} was larger than for either PRS_{AFR} or 313-SNP in Black women.

Overall, our study population was not enriched with women who drank daily (6.5%). There were fewer current drinkers among Black women compared to White women in our study, which is consistent with previous finding of differential drinking patterns among racial groups [35–37]. We did not find an association between alcohol intake and breast cancer risk in White women. The results remain unchanged after excluding extreme values of current alcohol intake. Explanations for the difference in findings for White women in ARIC and other cohort studies are not clear. We found a consistent inverse association between alcohol intake and breast cancer in Black women. According to World Cancer Research Fund and American Institute for Cancer Research, there is strong evidence that alcohol is a risk factor for postmenopausal breast cancer [38]. However, the studies included were conducted primarily among White populations, and results reported did not differentiate between racial groups. A population-based case-control study found null association between alcohol intake and breast cancer among Black and White women in the Carolina Breast Cancer Study [35],

while an update on the study found that drinking ≥ 7 drinks/week was associated with an increased risk of invasive breast cancer among Black women [36]. A case-control study among Black women found that low to moderate alcohol consumption was associated with reduced breast cancer risk [37], while another case-control study conducted in the African American Breast Cancer Epidemiology and Risk consortium found that drinking ≥ 7 drinks/week was associated with an increased risk of breast cancer [39]. Given the inconsistent findings, future studies should consider examining the association between alcohol intake and breast cancer separately by racial group, and pooling cohort studies to be able to address different levels of alcohol consumption and breast cancer risk among Black women.

Taken together, the previous four studies and our study on gene-alcohol interaction on breast cancer have conflicting results. In our study, using the 313-SNP PRS and stratified by racial groups or using the PRS_{AFR} and PRS_{hybrid} among Black women, we did not find a multiplicative interaction between alcohol drinking and PRS on breast cancer risk. Our findings are consistent with the two studies that did not find a statistically significant interaction [23, 25]. The other two studies both reported statistically significant interactions; the large consortium study that reported a positive multiplicative interaction [24] and the Korean study, using a 4-SNP PRS, reported a positive multiplicative interaction [22]. This inconsistency among the studies may be due to differences in the PRS used, study population ancestries, and differences in prevalences of non-drinking and daily drinking in the study populations. The Korean study used an estrogen-related PRS, whereas the other studies used PRS assessing genome-wide genetic risk, and only one of the previous studies, aside from ours, used the 313 SNPs PRS, (4/24/77 vs 313 SNPs). The ability to metabolize alcohol differs among populations of different ancestry [40], and these PRSs do not include those alcohol metabolic genes. With respect to alcohol intake, the four previously published studies reported alcohol consumption in non-comparable ways, although none of these had a study population enriched with daily drinkers. Further studies should consider assessing the interaction of the most up to date PRS and alcohol consumption on breast cancer risk among both higher and lower drinking populations of diverse ancestries.

There are some limitations to this study: 1) The sample size of our study is limited. We are not able to further categorize current drinkers among Black women, and we are not powered to be able to detect an interaction between multiple categories of PRS and alcohol. 2) The PRS we used in our main analysis was developed in European ancestry women, and previous study found that the PRS underperforms in African ancestry women compared with women of European ancestry [14, 31]. However, when using a PRS developed in African ancestry women and another developed using SNPs from both African and European ancestry women, our findings remained robust across different PRSs derived from women of different ancestries. 3) We do not have complete information on receptors for all cases of breast cancer, and thus, did not report associations by receptor status. Black women have higher risk of developing estrogen receptor negative and triple negative breast cancer, compared to White women [36, 41]. Additionally, the 313-SNP PRS we used in our main analysis was developed in ER-negative and ER-positive women, with evidence suggesting that prediction is better for ER-positive than ER-negative disease [11]. Given the impact of alcohol on estrogen levels and hormone metabolism [17,19–21, 42], as well as variation in PRS performance across different breast cancer subtypes, the gene-alcohol interaction

may differ across subtypes of breast cancer. 4) It is possible that only excessive alcohol consumption or binge drinking has a more pronounced effect on breast cancer risk, but we were not able to assess this due to limited study power, characteristics of the study population, and not having collected information on pattern of drinking. 5) Since our hypothesis is about ethanol intake, we analyzed the total amount of ethanol intake without investigating the associations for different types of alcohol. However, a meta-analysis reported different dose-responses by type of alcoholic beverage on breast cancer [43]. Thus, it is possible that the effect of alcohol on breast cancer differs across the type of beverages, and hence the gene-alcohol interaction could exist only for some beverages but not for others. 6) Our study population is restricted to postmenopausal women (due the small number of pre-menopausal women), and it is unknown whether our findings results are generalizable to premenopausal women. 7) Our study population consists of White and Black women. Therefore, it is also unknown whether the study results are generalizable to women of other ancestries.

The first strength of this study is that we have a more diverse study population compared to previous studies and we are able to examine the gene-alcohol interaction among White and Black women. Secondly, while most previous studies have been case-control or a combination of prospective and retrospective studies, our study is a prospective study. Thirdly, we adjusted for known or purported confounders of the association between alcohol drinking and breast cancer, and performed sensitivity analyses for variables that could lead to detection bias. Lastly, ARIC participants had similar prevalence of major cancer risk factors, cancer incidence, and cancer mortality rates in the same age, race, and sex groups, compared to the US population [30]. Therefore, our findings are likely to be generalizable to similar populations in the US.

In summary, our findings suggest that alcohol drinking does not modify PRS-based genetic risk of breast cancer among White and Black women in a study population not enriched for daily drinkers. Larger cohorts or pooled cohort analyses of women of diverse ancestry and with different levels of alcohol consumption are needed to investigate both the association for alcohol drinking and breast cancer risk, and whether the genetic risk of breast cancer is modified by alcohol consumption.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank the staff and participants of the ARIC study for their important contributions. Cancer data was provided by the Maryland Cancer Registry, Center for Cancer Prevention and Control, Maryland Department of Health, with funding from the State of Maryland and the Maryland Cigarette Restitution Fund. The collection and availability of cancer registry data are also supported by the Cooperative Agreement NU58DP007114, funded by the Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services.

The Atherosclerosis Risk in Communities study has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contract nos. (75N92022D00001, D.J. Couper, 75N92022D00002, J. Coresh, 75N92022D00003,

P.L. Lutsey, 75N92022D00004, T.H. Mosley, 75N92022D00005, L.E. Wagenknecht). Studies on cancer in ARIC are also supported by the National Cancer Institute (U01 CA164975, E.A. Platz). Funding was also supported by R01HL087641, E.A. Boerwinkle and R01HL086694, A. Chakravarti; National Human Genome Research Institute contract U01HG004402, E.A. Boerwinkle; and National Institutes of Health contract HHSN268200625226C, Broad Institute. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research. The content of this work is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. C.A. Zahnow was supported by the John Fetting Fund for Breast Cancer Prevention.

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Prevention Relevance Statement:

While our findings suggest that alcohol drinking does not modify PRS-based genetic risk of breast cancer among White and Black women with lower alcohol intake, nevertheless, women should consider limiting alcohol consumption as a general cancer prevention strategy as indicated in dietary guidelines.

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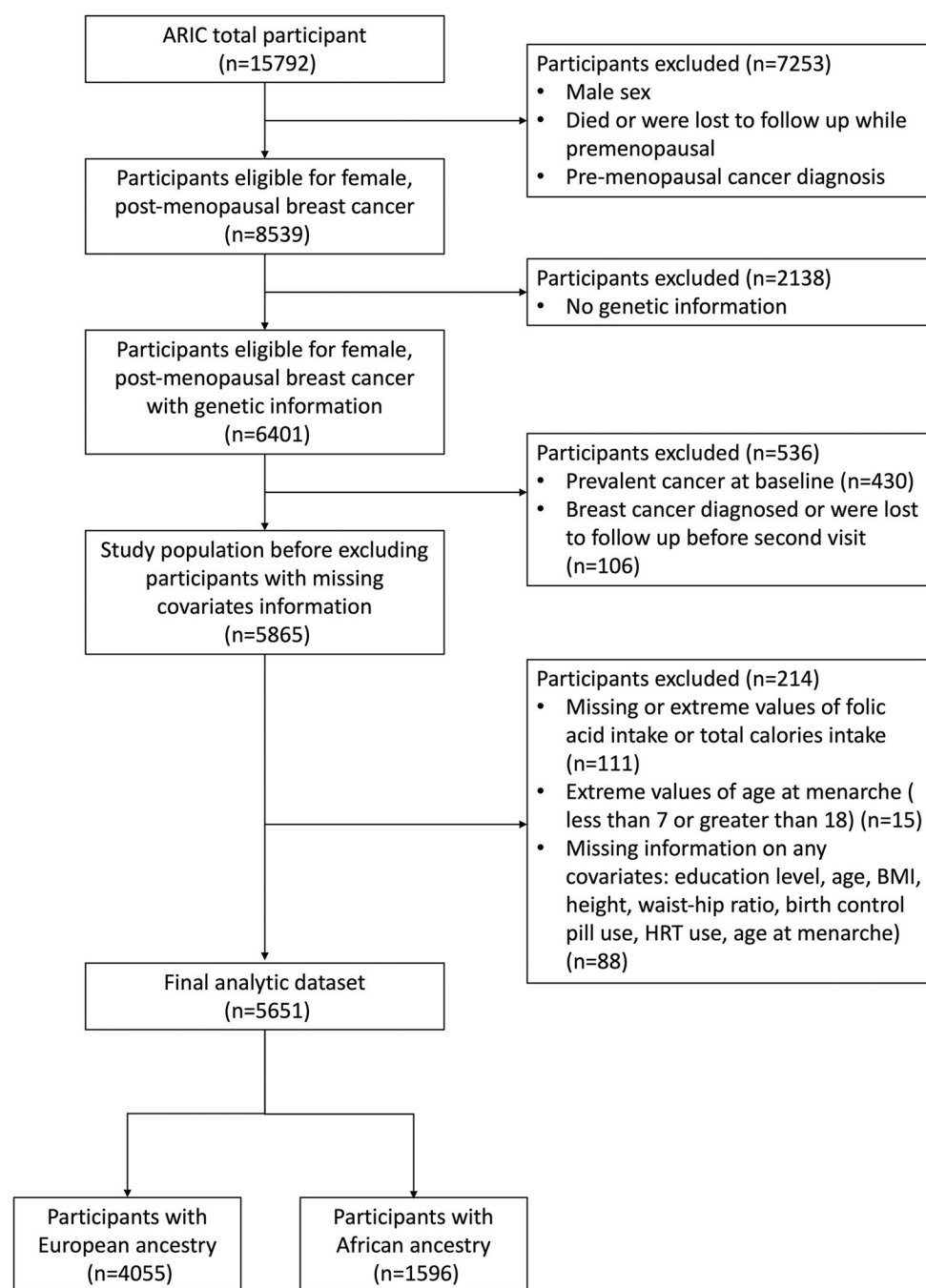


Figure 1. Flow chart of inclusion and exclusion of participants.

This figure presents the step-by step determination of eligibility for the analytic population, detailing the total number of participants in the ARIC study, specific reasons for exclusions, the number excluded at each step, and the final number of participants from the ARIC study who were included in analytic population.

Table 1.

The association between 313-SNPs PRS and breast cancer incidence, stratified by race in ARIC (1990–2015)

	Number of Cases (Person-years)	Model	Hazard Ratio ^a	95% CI	P value
White	358 (80501)	Age-adjusted	1.48	1.34–1.64	<0.001
		Fully-adjusted ^b	1.48	1.34–1.64	<0.001
Black	115 (30504)	Age-adjusted	1.17	0.97–1.40	0.10
		Fully-adjusted ^b	1.15	0.96–1.38	0.14

^a Estimated hazard ratio of breast cancer per 1 standard deviation increase in PRS

^b Adjusted for age at recruitment, height at recruitment, body mass index, waist-hip ratio, education level, physical activity, cigarette smoking status, total calories intake, folic acid intake, diabetes status, age at menarche, ever taken hormone replacement therapy, ever used oral contraceptives, breast-feeding status

Table 2.

The association between current ethanol intake and breast cancer incidence, stratified by race in ARIC (1990–2015)

Number of Cases (Person-years)		Model	Hazard Ratio ^a	95% CI	P value
White	358 (80501)	Age-adjusted	1.00	0.97–1.03	0.90
		Fully-adjusted ^b	1.00	0.98–1.03	0.75
Black	115 (30504)	Age-adjusted	0.88	0.74–1.04	0.14
		Fully-adjusted ^b	0.83	0.69–1.00	0.05

^aEstimated hazard ratio of breast cancer per 13 grams/week increase in ethanol intake

^bAdjusted for age at recruitment, height at recruitment, body mass index, waist-hip ratio, education level, physical activity, cigarette smoking status, total calories intake, folic acid intake, diabetes status, age at menarche, ever taken hormone replacement therapy, ever used oral contraceptives, breast-feeding status

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Table 3.

The association between 313-SNP PRS and breast cancer incidence, stratified by alcohol consumption category in ARIC (1990–2015)

Alcohol composition category ^a		Number of Cases (Person-years)	Hazard Ratio ^a	95% CI	P value
White ^b	Never drinker	95 (19593)	1.47	1.20–1.81	< 0.001
	Former drinker	41 (11107)	1.54	1.12–2.14	0.008
	< 1 drink/week	117 (25175)	1.60	1.33–1.93	< 0.001
	Current drinker ≥ 1 to < 7 drinks/week	77 (18131)	1.40	1.12–1.73	0.003
	≥ 7 drinks/week	28 (6495)	1.63	1.10–2.41	0.015
Black ^c	Never drinker	52 (14815)	1.30	0.97–1.74	0.08
	Former drinker	38 (8308)	1.05	0.76–1.46	0.75
	Current drinker	25 (7380)	1.25	0.80–1.97	0.31

^aEstimated hazard ratio of breast cancer per 1 standard deviation increase in PRS, adjusted for age at recruitment, height at recruitment, body mass index, waist-hip ratio, education level, physical activity, cigarette smoking status, total calories intake, folic acid intake, diabetes status, age at menarche, ever taken hormone replacement therapy, ever used oral contraceptives, breast-feeding status

^bP-value for likelihood ratio test comparing null model (including alcohol consumption categories, continuous PRS, and main covariates) to full model (including alcohol consumption categories, continuous PRS, main covariates, and interaction terms for the product of continuous PRS and alcohol consumption categories) was 0.81 for White women

^cP-value for likelihood ratio test comparing null model (including alcohol consumption categories, continuous PRS, and main covariates) to full model (including alcohol consumption categories, continuous PRS, main covariates, and interaction terms for the product of continuous PRS and alcohol consumption categories) was 0.61 for Black women

Table 4.

The association between current ethanol intake and breast cancer incidence, stratified by 313-SNP PRS category in ARIC (1990–2015)

	PRS category (percentiles)	Number of Cases (Person-years)	Hazard Ratio ^a	95% CI	P value	P-interaction ^b
White	≤ 10 th	16 (8434)	0.99	0.82–1.19	0.88	0.82
	>10 th – ≤ 30 th	43 (16335)	0.99	0.91–1.08	0.84	
	>30 th – ≤ 50 th	72 (15876)	1.01	0.94–1.08	0.81	
	>50 th – ≤ 70 th	76 (16231)	0.98	0.92–1.05	0.61	
	>70 th – ≤ 90 th	92 (15777)	0.99	0.93–1.04	0.61	
	> 90 th	59 (7848)	1.00	1.00–1.01	0.16	
Black	≤ 50 th	131 (40645)	1.00	0.96–1.05	0.85	0.91
	> 50 th	227 (39856)	1.00	1.00–1.00	0.95	
	≤ 50 th	49 (15398)	0.72	0.51–1.04	0.08	0.59
	> 50 th	66 (15106)	0.88	0.71–1.08	0.22	

^aEstimated hazard ratio of breast cancer per 13 grams/week increase in ethanol intake, adjusted for age at recruitment, height at recruitment, body mass index, waist-hip ratio, education level, physical activity, cigarette smoking status, total calories intake, folic acid intake, diabetes status, age at menarche, ever taken hormone replacement therapy, ever used oral contraceptives, breast-feeding status

^bP-value for likelihood ratio test comparing null model (including continuous ethanol intake, PRS categories, and main covariates) to full model (including continuous ethanol intake, PRS categories, main covariates, and interaction terms for the product of continuous ethanol intake and PRS categories)

Table 5.

The association of PRS_{AFR}, PRS_{hybrid}, and their interaction with ethanol intake interaction on breast cancer incidence among African-ancestry women in ARIC (1990–2015)

Number of Cases (Person-years)			Model ^a	Hazard Ratio	95% CI	P value
PRS and breast cancer risk						
PRS _{AFR}	115 (30504)		Age-adjusted	1.12 ^b	0.93–1.34	0.24
			Fully-adjusted	1.12 ^b	0.93–1.35	0.22
PRS _{hybrid}	115 (30504)		Age-adjusted	1.23 ^b	1.03–1.47	0.02
			Fully-adjusted	1.22 ^b	1.02–1.46	0.03
PRS and breast cancer risk, stratified by alcohol consumption category						
PRS _{AFR} ^c	Never drinker	52 (14815)	Fully-adjusted	1.08 ^b	0.82–1.40	0.58
	Former drinker	38 (8308)	Fully-adjusted	1.38 ^b	0.94–2.00	0.10
	Current drinker	25 (7380)	Fully-adjusted	1.02 ^b	0.68–1.54	0.92
PRS _{hybrid} ^d	Never drinker	52 (14815)	Fully-adjusted	1.40 ^b	1.05–1.86	0.02
	Former drinker	38 (8308)	Fully-adjusted	1.11 ^b	0.79–1.58	0.54
	Current drinker	25 (7380)	Fully-adjusted	1.16 ^b	0.77–1.75	0.47
Current ethanol intake and breast cancer incidence, stratified by PRS category						
PRS _{AFR} ^e	≤ 50 th	52 (15690)	Fully-adjusted	0.83 ^g	0.63–1.08	0.16
	> 50 th	64 (14814)	Fully-adjusted	0.80 ^g	0.61–1.06	0.12
PRS _{hybrid} ^f	≤ 50 th	49 (15386)	Fully-adjusted	0.91 ^g	0.75–1.12	0.39
	> 50 th	66 (15117)	Fully-adjusted	0.70 ^g	0.46–1.06	0.09

^aFully-adjusted models adjusted for racial group, age at recruitment, height at recruitment, body mass index, waist-hip ratio, education level, physical activity, cigarette smoking status, total calories intake, folic acid intake, diabetes status, age at menarche, ever taken hormone replacement therapy, ever used oral contraceptives, breast-feeding status

^bEstimated hazard ratio of breast cancer per 1 standard deviation increase in PRS

^cP-value for likelihood ratio test comparing null model (including alcohol consumption categories, continuous PRS, and main covariates) to full model (including alcohol consumption categories, continuous PRS, main covariates, and interaction terms for the product of continuous PRS and alcohol consumption categories) was 0.49 for 89-SNP PRS (PRS_{AFR})

^dP-value for likelihood ratio test comparing null model (including alcohol consumption categories, continuous PRS, and main covariates) to full model (including alcohol consumption categories, continuous PRS, main covariates, and interaction terms for the product of continuous PRS and alcohol consumption categories) was 0.44 for 29569-SNP PRS (PRS_{hybrid})

^eP-value for likelihood ratio test comparing null model (including continuous ethanol intake, PRS categories, and main covariates) to full model (including continuous ethanol intake, PRS categories, main covariates, and interaction terms for the product of continuous ethanol intake and PRS categories) was 0.88 for 89-SNP PRS (PRS_{AFR})

^fP-value for likelihood ratio test comparing null model (including continuous ethanol intake, PRS categories, and main covariates) to full model (including continuous ethanol intake, PRS categories, main covariates, and interaction terms for the product of continuous ethanol intake and PRS categories) was 0.20 for 29569-SNP PRS (PRS_{hybrid})

^gEstimated hazard ratio of breast cancer per 13 grams/week increase in current ethanol intake

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