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ORIGINAL ARTICLE

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# The functional *ALDH2* polymorphism is associated with breast cancer risk: A pooled analysis from the Breast Cancer Association Consortium

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**Abstract**

**Background:** Epidemiological studies consistently indicate that alcohol consumption is an independent risk factor for female breast cancer (BC). Although the aldehyde dehydrogenase 2 (*ALDH2*) polymorphism (rs671: Glu>Lys) has a strong effect on acetaldehyde metabolism, the association of rs671 with BC risk and its interaction with alcohol intake have not been fully elucidated. We conducted a pooled analysis of 14 case-control studies, with individual data on Asian ancestry women participating in the Breast Cancer Association Consortium.

**Methods:** We included 12,595 invasive BC cases and 12,884 controls for the analysis of rs671 and BC risk, and 2,849 invasive BC cases and 3,680 controls for the analysis of the gene-environment interaction between rs671 and alcohol intake for BC risk. The pooled odds ratios (OR) with 95% confidence intervals (CI) associated with rs671 and its interaction with alcohol intake for BC risk were estimated using logistic regression models.

**Results:** The Lys/Lys genotype of rs671 was associated with increased BC risk (OR = 1.16, 95% CI 1.03–1.30, $p = 0.014$). According to tumor characteristics, the Lys/Lys genotype was associated with estrogen receptor (ER)-positive BC (OR = 1.19, 95% CI 1.05–1.36, $p = 0.008$), progesterone receptor (PR)-positive BC (OR = 1.19, 95% CI 1.03–1.36, $p = 0.015$), and human epidermal growth factor receptor 2 (HER2)-negative BC (OR = 1.25, 95% CI 1.05–1.48, $p = 0.012$). No evidence of a gene-environment interaction was observed between rs671 and alcohol intake ($p = 0.537$).

**Conclusion:** This study suggests that the Lys/Lys genotype confers susceptibility to BC risk among women of Asian ancestry, particularly for ER-positive, PR-positive, and HER2-negative tumor types.

**KEYWORDS**

acetaldehyde, alcohol drinking, aldehyde dehydrogenase-2, breast cancer, single nucleotide polymorphism

## 1 | INTRODUCTION

Epidemiological studies consistently indicate that alcohol is an independent risk factor for female breast cancer (BC) (Singletary & Gapstur, 2001). The International Agency for Research on Cancer concluded that there is sufficient evidence to classify alcohol as a carcinogen for female BC (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2010). One hypothesized mechanism behind alcohol-related breast carcinogenesis is the involvement of acetaldehyde, a metabolite of ethanol. An impact of acetaldehyde on carcinogenesis for several types of alcohol-induced cancers has been shown in experimental models (Brooks & Theruvathu, 2005). Molecular epidemiological studies demonstrated a gene-environment interaction between a functional aldehyde dehydrogenase 2 (*ALDH2*) polymorphism (rs671: Glu>Lys, OMIM: 100650) and alcohol intake for esophageal and upper digestive tract cancers in East Asian countries (Matsuo et al., 2001; Oze et al., 2010), where rs671 is prevalent (Li et al., 2009). These studies support the hypothesis that acetaldehyde is a carcinogen. The Glu/Lys heterozygotes of rs671 have far less than half of ALDH2 activity of Glu/Glu homozygotes, and the Lys/Lys homozygotes have no detectable ALDH2 activity, which leads to high acetaldehyde concentrations upon alcohol intake in individuals harboring the Lys allele (Crabb, Edenberg, Bosron, & Li, 1989). Therefore, exploring the association of rs671 with BC risk and its interaction with alcohol intake is one approach to elucidate whether acetaldehyde is a causative agent for breast carcinogenesis. To date, evidence of an association of rs671 with BC risk is scarce; statistically significant associations have not been observed in case-control studies in Japan (456 cases and 912 controls) (Kawase et al., 2009) Korea (346 cases and 377 controls) (Choi et al., 2003) or Thailand (561 cases and 486 controls) (Sangrajrang et al., 2010). We conducted a pooled analysis of individual genetic and alcohol consumption data for women of Asian ancestry participating in studies in the Breast Cancer Association Consortium (BCAC) with at least 18 times larger sample size than previous studies.

## 2 | METHODS

### 2.1 | Study population

We used data from 14 case-control studies in the BCAC. Table 1 shows participating studies contributing to this pooled analysis. All study participants were of Asian ancestry and recruited from studies conducted in Asian countries, Canada, and the USA. Eight studies were hospital-based, five were population-based, and one included hospital-based cases and population-based controls. We included 12,595 BC cases and 12,884 controls for the analysis of rs671 and BC risk. For the analysis of the gene-environment interaction between rs671 and alcohol intake for BC risk, we included 2,849 BC cases and 3,680 controls after excluding participants with missing values for alcohol intake from seven studies. All studies were approved by their local ethics review boards, and all participants provided informed consent. This investigation was approved by a human research investigations committee at Aichi Cancer Center.

### 2.2 | Genotyping methods

Genotyping was carried out using the iCOGS array (http://ccge.medschl.cam.ac.uk/research/consortia/icogs/), or the OncoArray (https://support.illumina.com/downloads/infinium-oncoarray-500k-v1-0-product-files.html). Details of array design, genotyping, postgenotyping quality control, and imputation have been provided elsewhere (Michailidou et al., 2013, 2017). The rs671 SNP on *ALDH2* was a candidate SNP selected on the basis of specific hypotheses described above.

To adjust for potential population stratification, principal components analyses (PCA) were carried out separately for Asian subgroups. Briefly, PCA was performed based on a subset of 37,000 uncorrelated SNPs for the iCOGS data and based on 33,661 uncorrelated SNPs for the OncoArray data. For the present analyses, we used two Asian principal components for the iCOGS dataset and 10 Asian principal components for the OncoArray dataset as covariates. Further details have been provided in previous articles (Michailidou et al., 2013, 2017).

### 2.3 | Alcohol assessment

Each study ascertained alcohol intake via self-reported questionnaire. Daily alcohol intake in grams was determined by summing the product of frequency of consumption of specified alcoholic beverages (beer, wine, and other alcoholic beverages) by the alcohol content of each beverage using national estimates of alcohol content for that country. The exposure period was the year preceding recruitment. A multistep harmonization procedure was used to reconcile differences in individual study questionnaires.

### 2.4 | Statistical analysis

To assess the associations of rs671 with BC risk, we estimated odds ratios (ORs) with 95% confidence intervals (CIs) by unconditional logistic regression models using the Glu/Glu genotype as reference. This was done separately for iCOGS and OncoArray datasets, and results were combined by a fixed-effects meta-analysis. The ORs were adjusted for age, Asian principal components, and study. We also evaluated the associations by tumor characteristics (estrogen receptor, ER; progesterone receptor, PR; human epidermal growth factor receptor 2, HER2) and tumor subtypes (luminal [either ER or PR positive, HER2 negative], triple positive [ER, PR, HER2 positive], HER2 enrich [ER, PR negative, HER2 positive], triple negative [ER, PR, HER2 negative]) using cases with these specific characteristics. Heterogeneity by tumor characteristics and between studies was assessed using Cochran's Q test. We assessed the gene-environment interaction between rs671 and alcohol intake by including an interaction term. Alcohol intake was classified in three ways: 1) two categories (none, any alcohol intake); 2) three categories (none, <15 g ethanol/day, ≥15 g ethanol/day); and 3) four categories (none, <15 g ethanol/day, 15–30 g ethanol/day, ≥30 g ethanol/day). We also performed stratified analyses by menopausal status: women with missing menopausal status were considered premenopausal if they were ≤50 years or postmenopausal if >50 years. All statistical analyses were performed using Stata version 15.1 (Stata Corp., College Station, TX, USA), with a P value <0.05 considered to be statistically significant.

## 3 | RESULTS

Demographic characteristics of participants are shown in Table 2. The median age was 50 years for both cases and controls, with a higher proportion of women in the oldest age groups for cases. The proportion of nondrinkers and heavy drinkers (≥15 g ethanol/day) was higher among controls than cases, possibly due to the smaller number of unknown category in controls (71.4%) than in cases (77.4%). The distributions of tumor characteristics among cases were 7,648 ER positive (60.7%), 6,308 PR positive (50.1%), and 3,054 HER2 positive (24.3%) for participants included in the analysis of rs671 alone and, 1,871 ER positive (65.7%), 1,620 PR positive (56.9%), and 552 HER2 positive (19.4%) for those in the analysis of gene-environment interaction, respectively.

Table 3 presents the associations of rs671 with BC risk. Overall, the Lys/Lys genotype was associated with increased BC risk, with OR of 1.16 (95% CI = 1.03–1.30, $p$ = 0.014) relative to Glu/Glu genotype. According to tumor characteristics, we observed an association of the Lys/Lys genotype with ER-positive BC (OR = 1.19, 95% CI 1.05–1.36, $p$ = 0.008),

**TABLE 1** List of participating studies and number of participants

| Study acronym | Study name | Study design | Country | Subjects of analysis for rs671 | | | | Subjects of analysis for GE interaction | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Case | Control | Lys allele frequency among cases (%) | Lys allele frequency among controls (%) | Case | Control | Lys allele frequency among cases (%) | Lys allele frequency among controls (%) |
| ACP | Asia Cancer Program | Hospital based case-control study | Thailand | 830 | 1,060 | 8.9 | 8.0 | — | — | — | — |
| CBCS | Canadian Breast Cancer Study | Population-based case-control study | Canada | 252 | 170 | 28.6 | 20.0 | — | — | — | — |
| HERPACC | Hospital-based Epidemiologic Research Program at Aichi Cancer | Hospital-based case-control study | Japan | 792 | 1,659 | 29.9 | 28.3 | 783 | 1,632 | 30.1 | 28.6 |
| HKBCS | Hong Kong Breast Cancer Study | Hospital-based case-control study | China | 466 | 451 | 32.1 | 28.4 | — | — | — | — |
| KOHBRA | Korean Hereditary Breast Cancer Study | Population-based case-control study | Korea | 1,251 | 665 | 17.1 | 15.9 | 413 | 601 | 6.8 | 15.4 |
| LAABC | Los Angeles County Asian-American Breast Cancer Case-Control Study | Population-based case-control study | USA | 808 | 990 | 24.9 | 27.5 | 808 | 990 | 24.9 | 27.5 |
| MYBRCA | Malaysian Breast Cancer Genetic Study | Hospital-based case-control study | Malaysia | 1,408 | 1,866 | 24.5 | 22.6 | — | — | — | — |
| NC-BCFR | Northern California Breast Cancer Family Registry | Population-based case-control study | USA | 446 | 52 | 21.4 | 21.2 | 400 | 46 | 22.4 | 23.9 |

(Continues)

**TABLE 1** (Continued)

| Study acronym | Study name | Study design | Country | Subjects of analysis for rs671 | | | | Subjects of analysis for GE interaction | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Case | Control | Lys allele frequency among cases (%) | Lys allele frequency among controls (%) | Case | Control | Lys allele frequency among cases (%) | Lys allele frequency among controls (%) |
| NGOBCS | Nagano Breast Cancer Study | Hospital-based case-control study | Japan | 366 | 366 | 25.4 | 23.6 | 366 | 365 | 25.4 | 23.7 |
| SBCGS | Shanghai Breast Cancer Genetic Study | Population-based case-control study, cohort study | China | 1,644 | 1,827 | 24.9 | 23.9 | 5 | 46 | 10.0 | 7.6 |
| SEBCS | Seoul Breast Cancer Study | Hospital-based case-control study | Korea | 2,129 | 2,236 | 16.9 | 15.1 | 74 | — | 2.7 | — |
| SGBCC | Singapore Breast Cancer Cohort | Hospital based breast cancer cohort and population-based controls | Singapore | 775 | 798 | 20.8 | 23.6 | — | — | — | — |
| TBCS | IARC-Thai Breast Cancer Study | Hospital-based case-control study | Thailand | 138 | 253 | 6.9 | 11.7 | — | — | — | — |
| TWBCS | Taiwanese Breast Cancer Study | Hospital-based case-control study | Taiwan | 1,290 | 491 | 27.8 | 31.5 | — | — | — | — |
| Total | | | | 12,595 | 12,884 | 22.1 | 21.4 | 2,849 | 3,680 | 22.8 | 25.3 |

Abbreviation: GE interaction, gene-environment interaction.

**TABLE 2** Characteristics of cases and controls

| | Subjects of analysis for rs671 | | | | Subjects of analysis for GE interaction | | | |
|---|---|---|---|---|---|---|---|---|
| | **Cases (*N* = 12,595)** | **(%)** | **Control (*N* = 12,884)** | **(%)** | **Cases (*N* = 2,849)** | **(%)** | **Control (*N* = 3,680)** | **(%)** |
| Age (years) | | | | | | | | |
| Median (range) | 50 (20–91) | | 50 (15–92) | | 50 (20–81) | | 50 (19–86) | |
| ≦29 | 205 | 1.6 | 300 | 2.3 | 60 | 2.1 | 68 | 1.9 |
| 30–39 | 1,641 | 13.0 | 1,254 | 9.7 | 421 | 14.8 | 408 | 11.1 |
| 40–49 | 4,255 | 33.8 | 4,547 | 35.3 | 845 | 29.7 | 1,234 | 33.5 |
| 50–59 | 3,847 | 30.5 | 4,179 | 32.4 | 830 | 29.1 | 1,117 | 30.4 |
| 60–69 | 1,911 | 15.2 | 2,138 | 16.6 | 498 | 17.5 | 638 | 17.3 |
| ≧70 | 736 | 5.8 | 466 | 3.6 | 195 | 6.8 | 215 | 5.8 |
| Alcohol consumption[†] | | | | | | | | |
| g/day (mean ± *SD*) | 31.2 ± 91.2 | | 30.5 ± 83.0 | | 31.2 ± 91.2 | | 30.5 ± 83.0 | |
| Nondrinker | 1,746 | 13.9 | 2,348 | 18.2 | 1,746 | 61.3 | 2,348 | 63.8 |
| <15 g ethanol/day | 895 | 7.1 | 1,052 | 8.2 | 895 | 31.4 | 1,052 | 28.6 |
| ≥15 g ethanol/day | 208 | 1.7 | 280 | 2.2 | 208 | 7.3 | 280 | 7.6 |
| Unknown | 9,746 | 77.4 | 9,204 | 71.4 | | | | |
| ALDH2 Glu/Glu genotype | | | | | | | | |
| g/day (mean ± *SD*) | 42.4 ± 103.9 | | 44.8 ± 102.0 | | 42.4 ± 103.9 | | 44.8 ± 102.0 | |
| Nondrinker | 828 | 10.6 | 1,040 | 12.9 | 828 | 48.0 | 1,040 | 50.7 |
| <15 g ethanol/day | 719 | 9.2 | 774 | 9.6 | 719 | 41.7 | 774 | 37.8 |
| ≥15 g ethanol/day | 178 | 2.3 | 236 | 2.9 | 178 | 10. | 236 | 11.5 |
| Unknown | 6,056 | 77.8 | 5,988 | 74.5 | | | | |
| ALDH2 Glu/Lys genotype | | | | | | | | |
| g/day (mean ± *SD*) | 16.1 ± 68.5 | | 13.3 ± 43.0 | | 16.1 ± 68.5 | | 13.3 ± 43.0 | |
| Nondrinker | 745 | 18.3 | 1,076 | 25.8 | 745 | 78.6 | 1,076 | 77.1 |
| <15 g ethanol/day | 173 | 4.3 | 276 | 6.6 | 173 | 18.3 | 276 | 19.8 |
| ≥15 g ethanol/day | 30 | 0.7 | 44 | 1.1 | 30 | 3.2 | 44 | 3.2 |
| Unknown | 3,122 | 76.7 | 2,779 | 66.6 | | | | |
| ALDH2 Lys/Lys genotype | | | | | | | | |

(Continues)

**TABLE 2** (Continued)

| | Subjects of analysis for rs671 | | | | Subjects of analysis for GE interaction | | | |
|---|---|---|---|---|---|---|---|---|
| | **Cases (*N* = 12,595)** | **(%)** | **Control (*N* = 12,884)** | **(%)** | **Cases (*N* = 2,849)** | **(%)** | **Control (*N* = 3,680)** | **(%)** |
| g/day (mean ± *SD*) | 0.4 ± 3.4 | | 0.5 ± 5.1 | | 0.4 ± 3.4 | | 0.5 ± 5.1 | |
| Nondrinker | 232 | 99.2 | 173 | 98.3 | 232 | 99.2 | 173 | 98.3 |
| <15 g ethanol/day | 2 | 0.8 | 3 | 1.7 | 2 | 0.8 | 3 | 1.7 |
| ≥15 g ethanol/day | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Unknown | 0 | 0 | 0 | 0 | | | | |
| Menopausal status | | | | | | | | |
| Premenopausal | 3,690 | 29.3 | 5,234 | 40.6 | 836 | 29.3 | 1,393 | 37.9 |
| Postmenopausal | 4,287 | 34.0 | 4,830 | 37.5 | 879 | 30.9 | 1,246 | 33.9 |
| Unknown | 4,618 | 36.7 | 2,820 | 21.9 | 1,134 | 39.8 | 1,041 | 28.3 |
| ER status | | | | | | | | |
| Positive | 7,648 | 60.7 | | | 1,871 | 65.7 | | |
| Negative | 3,701 | 29.4 | | | 658 | 23.1 | | |
| Unknown | 1,246 | 9.9 | | | 320 | 11.2 | | |
| PR status | | | | | | | | |
| Positive | 6,308 | 50.1 | | | 1,620 | 56.9 | | |
| Negative | 3,776 | 30.0 | | | 865 | 30.4 | | |
| Unknown | 2,511 | 19.9 | | | 364 | 12.8 | | |
| HER2 status | | | | | | | | |
| Positive | 3,054 | 24.3 | | | 552 | 19.4 | | |
| Negative | 4,054 | 32.2 | | | 557 | 19.6 | | |
| Unknown | 5,487 | 43.6 | | | 1,740 | 61.1 | | |

Abbreviations: ALDH2, aldehyde dehydrogenase 2; ER, estrogen receptor; GE interaction, gene-environment interaction; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

[†]Exposure period was the year preceding recruitment.

PR-positive BC (OR = 1.19, 95% CI 1.03–1.36, $p = 0.015$), and HER2-negative BC (OR = 1.25, 95% CI 1.05–1.48, $p = 0.012$), but not with ER-negative BC (OR = 1.07, 95% CI 0.90–1.27, $p = 0.453$), PR-negative BC (OR = 1.13, 95% CI 0.95–1.34, $p = 0.176$), or HER2-positive BC (OR = 1.19, 95% CI 0.97–1.48, $p = 0.102$), although no statistically significant heterogeneity was observed by tumor characteristics. According to tumor subtypes, the Lys/Lys genotype was only associated with luminal BC (OR = 1.30, 95% CI 1.09–1.55, $p = 0.004$), and not with other subtypes (Table 4). No evidence of heterogeneity was also observed by menopausal status (Table S1).

Figure S1 and Figure S2 show the forest plots of study-specific ORs for the association between rs671 and BC risk. With regard to the association between the Glu/Lys genotype and BC risk, there was no evidence of between-study heterogeneity ($p$ for heterogeneity = 0.380). In contrast, significant between-study heterogeneity was observed for the association of the Lys/Lys genotype with BC risk ($p$ for heterogeneity = 0.003), which was mainly attributable to a strong positive association for CBCS and a strong inverse association for ACP and TWBCS. However, exclusion of these studies did not alter the significant association of the Lys/Lys genotype with BC risk (OR = 1.18, 95% CI 1.05–1.33, $p = 0.008$)

**TABLE 3** Association between ALDH2 genotype and breast cancer risk

| | ALDH2 genotype | | | *p* for heterogeneity between tumor characteristics | |
|---|---|---|---|---|---|
| | Glu/Glu | Glu/Lys | Lys/Lys | For Glu/Lys | For Lys/Lys |
| Overall | | | | | |
| Cases/controls | 7,781/8,038 | 4,070/4,175 | 744/671 | | |
| OR (95% CI)[†] | 1 (ref.) | 1.03 (0.97–1.08, $p = 0.350$) | 1.16 (1.03–1.30, $p = 0.014$) | | |
| ER status | | | | | |
| Positive | | | | | |
| Cases/controls | 4,636/8,038 | 2,531/4,175 | 481/671 | | |
| OR (95% CI)[†] | 1 (ref.) | 1.01 (0.95–1.08, $p = 0.669$) | 1.19 (1.05–1.36, $p = 0.008$) | 0.447 | 0.329 |
| Negative | | | | | |
| Cases/control | 2,321/8,038 | 1,187/4,175 | 193/671 | | |
| OR (95% CI)[†] | 1 (ref.) | 1.05 (0.97–1.14, $p = 0.257$) | 1.07 (0.90–1.27, $p = 0.453$) | | |
| PR status | | | | | |
| Positive | | | | | |
| Cases/controls | 3,842/8,038 | 2,066/4,175 | 400/671 | | |
| OR (95% CI)[†] | 1 (ref.) | 0.98 (0.92–1.05, $p = 0.591$) | 1.19 (1.03–1.36, $p = 0.015$) | 0.410 | 0.653 |
| Negative | | | | | |
| Cases/control | 2,333/8,038 | 1,238/4,175 | 205/671 | | |
| OR (95% CI)[†] | 1 (ref.) | 1.02 (0.95–1.11, $p = 0.545$) | 1.13 (0.95–1.34, $p = 0.176$) | | |
| HER2 status | | | | | |
| Positive | | | | | |
| Cases/control | 1,961/8,038 | 940/4,175 | 153/671 | | |
| OR (95% CI)[†] | 1 (ref.) | 1.02 (0.92–1.14, $p = 0.674$) | 1.19 (0.97–1.48, $p = 0.102$) | 1.000 | 0.720 |
| Negative | | | | | |
| Cases/control | 2,521/7,841 | 1,287/4,175 | 246/671 | | |
| OR (95% CI)[†] | 1 (ref.) | 1.02 (0.93–1.11, $p = 0.722$) | 1.25 (1.05–1.48, $p = 0.012$) | | |

Abbreviations: ALDH2, aldehyde dehydrogenase 2; CI, confidence intervals; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; OR, odds ratios; PR, progesterone receptor.

[†]ORs were adjusted for age (continuous), Asian principal components and study site.

**TABLE 4** Association between ALDH2 genotype and breast cancer risk by tumor subtypes

| | ALDH2 genotype | | | *p* for heterogeneity between tumor characteristics | |
|---|---|---|---|---|---|
| | Glu/Glu | Glu/Lys | Lys/Lys | For Glu/Lys | For Lys/Lys |
| Luminal | | | | | |
| Cases/controls | 1,950/8,038 | 979/4,175 | 198/671 | | |
| OR (95% CI)[†] | 1 (ref.) | 1.00 (0.92–1.10, $p = 0.916$) | 1.30 (1.09–1.55, $p = 0.004$) | 0.452 | 0.755 |
| Triple positive | | | | | |
| Cases/controls | 1,202/8,038 | 583/4,175 | 93/671 | | |
| OR (95% CI)[†] | 1 (ref.) | 1.03 (0.91–1.16, $p = 0.640$) | 1.19 (0.93–1.53, $p = 0.164$) | | |
| HER2 enrich | | | | | |
| Cases/controls | 694/8,038 | 322/4,175 | 55/671 | | |
| OR (95% CI)[†] | 1 (ref.) | 0.96 (0.83–1.11, $p = 0.557$) | 1.12 (0.83–1.51, $p = 0.453$) | | |
| Triple negative | | | | | |
| Cases/control | 546/8,038 | 310/4,175 | 46/671 | | |
| OR (95% CI)[†] | 1 (ref.) | 1.13 (0.97–1.32, $p = 0.108$) | 1.11 (0.81–1.53, $p = 0.519$) | | |

Abbreviations: ALDH2, aldehyde dehydrogenase 2; CI, confidence intervals; HER2, human epidermal growth factor receptor 2; OR, odds ratios.

[†]ORs were adjusted for age (continuous), Asian principal components and study site.

and there was no longer evidence of between-study heterogeneity ($p$ for heterogeneity = 0.133). Furthermore, when we repeated analyses using random effects meta-analyses to calculate summary study-specific estimates, the results did not change substantially (Table S2).

Stratified analyses by alcohol intake categories assessing a gene-environment interaction between rs671 and alcohol intake showed no evidence of interaction, although the sample size is small compared to the analysis of rs671 and BC risk (Table S3, $p$ for interaction = 0.537).

## 4 | DISCUSSION

In this study, we found that the Lys/Lys genotype of rs671 was associated with increased BC risk among women of Asian ancestry. No evidence of interaction was observed between rs671 and alcohol intake. This is the largest study to date to perform this evaluation quantitatively using high-quality individual-level data for Asian women.

Several epidemiological studies have reported a gene-environment interaction between rs671 and alcohol intake for several types of cancer (Hiraki et al., 2007; Ishioka et al., 2018; Masaoka et al., 2016; Matsuo et al., 2001, 2013; Oze et al., 2010). Our findings are not consistent with our hypothesis of gene-environment interaction between rs671 and alcohol intake. Considering the established impact of rs671 on cancer risk, this lack of interaction suggests that acetaldehyde may be less influential in breast carcinogenesis. Other biological mechanisms for alcohol-related breast carcinogenesis have been hypothesized, including increased circulating estrogens and androgens, enhancement of mammary gland susceptibility to carcinogenesis, increased mammary carcinogen DNA damage, interference of folate metabolism by alcohol, and greater potential for invasiveness into BC cells (Bernstein & Ross, 1993; Singletary & Gapstur, 2001; Singletary & McNary, 1994; Stolzenberg-Solomon et al., 2006). To better understand the etiologic nature of the effect of alcohol on breast carcinogenesis, further investigations are needed.

We observed an association of the Lys/Lys genotype with increased BC risk. Because individuals with the Lys/Lys genotype have no detectable ALDH2 activity and almost completely refrain from drinking due to severe adverse reactions caused by acetaldehyde (e.g., facial flushing, nausea and headache) (Matsuo et al., 2006), the observed genetic association suggests that the Lys/Lys genotype confers susceptibility to BC risk independently of alcohol intake. ALDH2 plays a key role in removal of not only ethanol-derived acetaldehyde, but also other toxic endogenous aldehydes such as 4-hydroxy-2-nonenal (4-HNE) and malondialdehyde (Chen, Ferreira, Gross, & Mochly-Rosen, 2014). These endogenous aldehydes have been reported to cause DNA damage and might be related to breast carcinogenesis (Chen et al., 2014; Garaycoechea et al., 2018). In addition, we did not find an association of the Glu/Lys genotype with BC risk. This suggest that

ALDH2 activity of the Glu/Lys homozygotes may be sufficient for detoxifying toxic endogenous aldehydes related to breast carcinogenesis. In contrast, the Lys/Lys homozygotes have no detectable ALDH2 activity, thus may not tolerate these endogenous aldehydes. Furthermore, the Lys/Lys genotype was associated with increased risk only in hormone receptor positive BC, and not in hormone receptor negative BC. These results suggest that the biological mechanism could be through a hormonal receptor mediated pathway (Zhang, Man, Zhao, Dong, & Ma, 2014). The evidence of an association of rs671 with BC risk is scarce and may warrant additional evaluation in future studies.

The strengths of this investigation include the analysis of individual-level data from a large sample of Asian women, allowing us to obtain stable, and precise summary estimates of the association of rs671 with BC risk. Other strengths are the uniform genotyping procedures and quality-control measures undertaken for the iCOGS and the OncoArray, respectively. We were also able to control for population stratification by including Asian principal components as a covariate to control for residual genetic heterogeneity. Furthermore, the Lys allele of rs671 is only prevalent in East Asia, and has not been found in Caucasians or Africans (Li et al., 2009). Thus, this analysis is unique and can be performed only among Asian women. Several limitations also warrant consideration. First, we could not evaluate the association between alcohol intake and BC risk because there were a lot of missing data on potential confounding factors (e.g., smoking, estrogen-related factors) and we were not able to control for them. However, genotypes are fixed at birth and these factors cannot influence genotypes; therefore, our results about rs671 and BC risk may be unbiased even though we did not adjust for these factors. Second, even though all study participants were of Asian ancestry, the heterogeneity across study populations, designs, and methods are potential limitations. Third, careful interpretation of results from the analysis of gene-environment interaction and stratified analyses is necessary because we had a limited number of participants in some sub-groups and did not adjust for multiple comparisons.

In conclusion, we observed an association between the Lys/Lys genotype of rs671 and increased BC risk. Among women of Asian ancestry, this study suggests that the Lys/Lys genotype confers susceptibility to BC risk, particularly for ER-positive, PR-positive, and HER2-negative tumor types. These findings warrant further investigation in future studies.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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