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Joint associations of a polygenic risk score and environmental risk factors for breast cancer in the Breast Cancer Association Consortium

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Key Words: breast cancer, genetic susceptibility, gene-environment interactions, risk prediction, epidemiology

Joint associations of a polygenic risk score and environmental risk factors for breast cancer in the Breast Cancer Association Consortium

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ABSTRACT

Background: Polygenic risk scores (PRS) for breast cancer can be used to stratify the population into groups at substantially different levels of risk. Combining PRSs and environmental risk factors will improve risk prediction; however, integrating PRS into risk prediction models requires evaluation of their joint association with known environmental risk factors.

Methods: Analyses were based on data from 20 studies, datasets analyzed ranged from 3,453 to 23,104 invasive breast cancer cases and similar numbers of controls, depending on the analyzed environmental risk factor. We evaluated joint associations of a 77-single nucleotide polymorphism (SNP) PRS with reproductive history, alcohol consumption, menopausal hormone therapy (MHT), height and body mass index (BMI). We tested the null hypothesis of multiplicative joint associations for PRS and each of the environmental factors, and performed global and a tail-based goodness-of-fit tests in logistic regression models. The outcomes were breast cancer overall and by estrogen receptor (ER) status.

Results: The strongest evidence for a non-multiplicative interaction with the 77-SNP PRS was for alcohol consumption (P-interaction=0.009), adult height (P-interaction =0.025) and current use of combined MHT (P-interaction =0.038) in ER-positive disease. Risk associations for these factors by percentiles of PRS did not follow a clear dose-response. In addition, global and tail-based goodness of fit tests showed little evidence for departures from a multiplicative risk model, with alcohol consumption showing the strongest evidence for ER-positive disease (P=0.013 for global and 0.18 for tail-based test).

Conclusions: The combined effects of the 77-SNP PRS and environmental risk factors for breast cancer are generally well described by a multiplicative model. Larger studies are required to confirm possible departures from the multiplicative model for individual risk factors, and assess models specific for ER-negative disease.

Key words: breast cancer, genetic susceptibility, gene-environment interactions, risk prediction, epidemiology

Key Messages

- The combined effects of a polygenic risk score (PRS) derived from 77 single nucleotide polymorphisms (SNPs) and environmental risk factors for ER-positive breast cancer were generally well described by a multiplicative risk model.
- Analyses suggested non-multiplicative interactions of the 77-SNP PRS with alcohol consumption, height and menopausal hormone therapy (MHT) that did not follow a clear dose-response.
- Larger studies are required to confirm possible departures from the multiplicative model for individual risk factors, and assess models specific for ER-negative disease.

INTRODUCTION

Both inherited genetic factors and “environmental” factors, broadly defined as reproductive events (menarche, pregnancy, breast feeding and menopause), modifiable lifestyle (overweight/obesity, alcohol consumption, and physical activity); exogenous hormone medications (oral contraceptive pill and hormone replacement therapy) and medical history, play important roles in breast cancer etiology.[1] Genome-wide association studies have identified more common, low risk single nucleotide polymorphisms (SNPs) that in combination can substantially influence the risk of developing breast cancer.[2, 3] We previously described a 77-SNP polygenic risk score (PRS) for breast cancer; women in the top 1% of the PRS were at three-fold increased risk of developing the disease compared with women in the middle quintile.[4] This PRS explained ~12.6% of the familial relative risk (FRR) of breast cancer. The strength of the association (as measured by the relative risk per standard deviation) between the 77-SNP PRS and breast cancer risk decreased with increasing age. The association was similar in women with and without a family history, suggesting a multiplicative joint association of the PRS and other familial factors.[4]

In combination with environmental risk factors, the polygenic risk defined by the PRS and the residual FRR not explained by the PRS could result in substantial improvements in our ability to distinguish women at different levels of breast cancer risk in the general population, which could then be used to improve prevention and screening strategies for breast cancer.[5-8] Previous studies have indicated that established genetic and environmental risk factors are likely to combine multiplicatively in their associations with breast cancer risk.[9-12] A recent report evaluated interactions between a 24-SNP PRS and multiple environmental risk factors.[5] This study showed a good fit of a multiplicative risk model but had limited power to detect interactions, particularly at the extremes of the PRS. We have extended this study to evaluate the joint associations of the 77-SNP PRS and environmental risk factors for breast cancer using data from a larger multi-center study comprising 28,239 cases and 30,445 controls from 20 studies in the Breast Cancer Association Consortium (BCAC). Given that both environmental and genetic risk factors have been shown to differ by disease subtypes defined by estrogen receptor (ER) status,[13-15] analyses were performed for overall disease and separately for ER-positive and ER-negative disease. This study has immediate relevance as the 77 SNP PRS is currently being incorporated into risk prediction models for genetic counselling.

MATERIALS AND METHODS

Study sample

The study sample comprised 28,239 cases and 30,445 controls of European ancestry from 20 studies: two case-control studies nested in prospective cohorts, 8 population-based case-control and 10 non-population based case-control studies, all participating in the Breast Cancer Association Consortium (BCAC) (**Supplementary Tables 1 and 2**). Eligible studies had at least 200 cases and 200 controls with genotype data and information on at least one of the environmental risk factors of interest. Studies that oversampled cases with family history of breast cancer were excluded.

We excluded participants if they were male, were not of European descent (as defined by genome-wide genotype data), or had a missing value for age (age at diagnosis or interview for cases or controls, respectively). Statistical models included subjects with complete data on the specific environmental variable of interest and the adjustment variables. The number of participants available for analysis, therefore, varied by the investigated environmental factor. We also excluded prevalent cases from the cohort studies (date of diagnosis before baseline questionnaire) and cases from case-control studies interviewed more than five years after their diagnosis.

The relevant ethics committees approved individual studies and all study subjects gave written informed consent.

Data harmonization and variable definitions

Data from different studies were harmonized according to a common data dictionary. A quality assurance procedure was applied that included range and logic checks and comparisons of variable distributions within and between studies. Time-dependent variables were assessed at a reference date defined as the date of diagnosis for cases and the date of interview for controls in case-control studies. For cohort studies (MCCS and UKBGS), the reference date was the date of last follow-up questionnaire if data were available; otherwise date of baseline questionnaire was used as the reference.[9] The median time between the dates of last interview and diagnosis for cohort study participants was 2.0 years for UKBGS and 7.5 years for MCCS. Because we did not have data on menopausal status, we used the median age (54 years) as a surrogate: women aged <54 years were considered premenopausal and women aged ≥54 years postmenopausal.[9]

Seven risk factors for breast cancer were considered: age at menarche, ever being parous, age at first full-term pregnancy (AFTP), adult body mass index (BMI) in postmenopausal women, adult body height, current use of estrogen-progesterone menopausal hormone therapy (MHT), and lifetime average intake of alcohol. Current use of estrogen-progesterone MHT was defined as use within 6 months prior to the reference date. For case-control studies, BMI was calculated based on usual adult weight or weight one year prior to the reference date, if available (studies ABCFS, BREOGAN, CECILE, GENICA, MARIE, MCBCS, PBCS, SASBAC). If this variable was not available, body weight in early adulthood was used as a surrogate (studies ESTHER, pKARMA, SEARCH). Weight reported at the time of diagnosis or interview in case-control studies was not used to avoid disease effects on weight. For the two prospective cohort studies (MCCS, UKBGS), we used weight reported at the baseline interview (prior to diagnosis). Continuous variables (i.e. age at menarche, AFTP, alcohol, height and BMI) were modelled both as continuous and categorical variables; categories are shown in **Supplementary Table 3**.

Genotyping and Imputation

The rsnumbers for the 77 SNPs included in this report are shown in **Supplementary Table 4**. Genotype data for 76 of the 77 SNPs included in the PRS were generated as part of the Collaborative Oncological Gene-environment Study (COGS; www.nature.com/icogs) using an Illumina iSelect array (iCOGS) in all studies except BREOGAN. One SNP (rs78540526) was not genotyped but imputed using SHAPEIT and IMPUTEv2, using 5Mb non-overlapping intervals, as previously described.[16] Genotyping methods and quality control criteria have also been previously described.[17] Briefly, SNPs were excluded if the call rate was <95%, *P* for Hardy-Weinberg-Equilibrium test $<10^{-7}$, the concordance rate in duplicate samples was <98%, or if the SNP was monomorphic. Study participants were excluded from analyses if the overall genotyping call rate was <95% over the whole iCOGS array or if heterozygosity deviated from that expected in the general population (either lower or higher, $P < 10^{-6}$).

Genotyping for BREOGAN was performed at the Spanish National Genotyping Center (CeGen-ISCIII), using the Sequenom MassARRAY Genotyping system (technology iPLEX GOLD) following the manufacturer's instructions. The SNPs were analyzed using 4 assays (Assay Design v4 software) and genotyping calls were generated using the software Typer analyzer v4.0.20. The quality criteria described above were applied. The assay for rs7726159 failed and imputation of genotypes could not be conducted for this SNP or rs78540526 because of lack of other genotypes in BREOGAN. Therefore, only data on 75 SNPs were available for this study.

Statistical Methods

We investigated interactions between environmental risk factors for breast cancer and the PRS as a measure of the combined effects of 77 established SNPs on breast cancer risk. The calculation of the PRS for overall breast cancer and the PRS specific for ER-positive and ER-negative disease has been previously described.[4] Briefly, the PRS was derived for each study subject using the formula:

$$\text{PRS}=\beta_1 x_1+\beta_2 x_2+\ldots\beta_\kappa x_\kappa\ldots.+\beta_n x_n$$

where β_k was the per-allele log odds ratio (OR) for breast cancer associated with the minor allele for SNP *k*, x_k was the number of alleles for that same SNP (0, 1 or 2), and n=77 was the total number of SNPs (except for BREOGAN where we derived a 75 SNP PRS). To derive the ER-positive PRS, allele counts were weighted by ER-positive specific effect estimates; likewise, ER-negative specific effect estimates were used to derive the ER-negative PRS. The log ORs for each of the SNPs used to calculate the PRS were estimated using data in this report and are provided in **Supplementary Table 4**. These estimates are very close to those in our previous report,[4] which is expected given the large overlap in study populations.

ORs and 95% confidence intervals (CIs) were estimated using logistic regression models for overall breast cancer risk and by ER status of the tumor. Initial analyses included all studies with available data, regardless of study design, and considered each environmental variable one at a time. Models were adjusted for study (indicator variables), age and seven ancestry-informative principal components (for models including PRS). All models also included an interaction term between study design (population-based/cohort vs non-population based; see **Supplementary Table 1**) and the environmental variable of interest, to account for potential heterogeneity of main effects by design. Because estimates of main effects of environmental variables from non-population-based designs are prone to bias, we only reported results from population-based/cohort studies. However, interaction estimates and statistical tests of interaction (see below) are based on data from all studies. In models including current use of combined (estrogen-progesterone) MHT, users of combined MHT were compared with never users of any MHT and were further adjusted for use of MHT preparations other than combined therapy. MHT analyses were restricted to postmenopausal women. To assess interaction, we used a likelihood ratio test (LRT) comparing models with and without interaction terms for the PRS as a continuous variable and each of the environmental variables (modelled as continuous variables when appropriate).[12] Separate models were fit for each PRS and environmental risk factor combination.

To assess the goodness of fit of a multiplicative model, we also performed, for each risk factor, a global goodness of fit test and a recently developed tail-based goodness of fit test to assess deviations from logistic models at the extremes of the risk distribution.[18] For goodness of fit tests, analyses were restricted to population-based/cohort studies to remove the contribution of non-population based studies to the main effect estimates of environmental risk factors as these are more prone to biases. The goodness of fit tests were not fit for ER-negative disease, as the number of controls and the number of cases available for analysis was too small to provide reliable estimates, particularly in the tails.

The statistical analysis was conducted using SAS 9.3 and R (version 3.0.2). All tests performed were two-sided.

RESULTS

A total of 28,241 cases and 30,445 controls from 20 studies contributed data to at least one analysis. The numbers of cases and controls from each of the studies are shown in **Supplementary Table 2.** The associations between the 77-SNP PRS for overall and subtype specific breast cancer are shown in **Supplementary Figure 1**. As shown previously using a similar study population as in this report,[4] associations were stronger for ER-positive than ER-negative disease.

Associations of environmental risk factors in relation to overall and ER-positive breast cancer risk, based on data from population-based or cohort studies were of the expected magnitude and direction (**Supplementary Table 3**). Associations for nulliparity and MHT use differed by ER status of the tumor (P_{het}<0.003) and none of the environmental risk factors showed test for associations with ER-negative disease with P<0.05. Because of the relatively small number of ER-negative cases, we focused the presentation of interaction analyses on all breast cancers or ER-positive breast cancer.

Results from our primary analyses of interaction between PRS and individual environmental risk factors are shown in **Table 1**. The strongest evidence for non-multiplicative joint associations in ER-positive disease, as assessed by a trend in the OR by PRS level, was for alcohol consumption (LRT P = 0.009 based on 3,453 cases and 3,708 controls with available data), adult height (LRT P=0.025 based on 20,417 cases ad 18,412 controls) and current use of MHT (LRT P=0.038 based on 5,201 cases and 5,697 controls; **Table 1**). These interaction analyses were based on a study sample ranging from 3,453 cases and 3,708 controls for average lifetime intake of alcohol, to 23,104 cases and 25,914 controls for parity, and multiplicative interaction parameters showed no evidence for heterogeneity between population-based/cohort and non-population-based study designs (**Supplementary Table 5)**. We found no evidence for interactions in ER-negative disease (**Table 1**). **Figure 1** shows the estimated ORs (95%CI) for the risk of ER-positive breast cancer and each of the environmental risk factors stratified by percentiles of the PRS (see **Supplementary Figure 2** for results for overall breast cancer and by ER status). It should be noted that interaction tests in **Table 1** considered PRS as a continuous variable rather than in percentile categories as shown in the Figures. Estimated ORs by PRS percentiles for the three environmental factors in **Table 1** did not show clear dose-response relationships, particularly for alcohol consumption and adult height (**Figure 1**): the interaction for alcohol was mainly driven by the relatively large OR estimate for the lowest percentile of the PRS; the OR estimates for height were stronger for the middle categories of PRS; and the ORs for MHT showed more of a dose-response pattern, although not entirely consistent across categories of PRS.

Global and tail-based goodness of fit tests for models including the 77-SNP PRS and each of the environmental factors were performed in population-based or cohort studies only. These analyses did not show substantial evidence for departures from the multiplicative model, except alcohol consumption in ER-positive disease (P=0.013 for global and 0.18 for tail based tests; **Table 2**).

DISCUSSION

Our analyses indicate that the combined effects of the 77-SNP PRS and environmental risk factors (reproductive history, MHT use, adult height, BMI and alcohol intake) for breast cancer are generally consistent with a multiplicative model on the relative risk scale. An important consequence of the multiplicative model is that the absolute risk associated with each environmental factor would be larger among women at high genetic risk; this could be relevant to counselling and intervention studies. The observed evidence for non-multiplicative joint associations of PRS and alcohol intake, height and MHT use requires confirmation in larger studies.

Previous reports have shown that most SNPs and environmental risk factors, considered pairwise, combine multiplicatively.[9-12, 19] It is plausible, however, that groups of susceptibility variants could in combination interact with environmental risk factors. We therefore evaluated the joint association with a PRS summarizing the risk conferred from 77 SNPs (a straightforward and efficient approach, since there is little evidence for non-multiplicative interactions among SNPs).[4] This is relevant since models combining multiple SNPs in the form of PRSs are being used in risk prediction models that integrate genetic and environmental factors.[5, 8, 20, 21] A recent report evaluated interactions between a 24-SNP PRS and environmental risk factors (age at first birth, parity, age at menarche, height, menopausal status, age at menopause, BMI, MHT use, alcohol consumption and smoking status) based on analyses of data from 17,171 cases and 19,862 controls sampled from eight prospective cohort studies in the Breast and Prostate Cancer Cohort Consortium (BPC3).[5] This study found no evidence for departures from the multiplicative model for any of the risk factors evaluated, which is generally consistent with the goodness-of-fit test performed in population-based studies in this report. The BPC3 findings do not support the observed interactions between the 77-SNP PRS and alcohol consumption, height and MHT use in our report. Although it is possible that interactions are evident with the extended 77-SNP PRS but not the 24-SNP PRS used in BPC3, they need to be replicated in independent studies with appropriate study designs, particularly in view of the lack of a clear dose-response pattern for the interactions in our report. Our result should also be interpreted with caution because of multiple hypothesis testing and the relatively low power (as reflected by the wide confidence intervals in estimates of interaction parameters) that can lead to a higher probably of false positive findings for a given significance level.[22]

The 77 SNP PRS in our analysis is more predictive than the 24 SNP PRS evaluated in the BPC3 report since it includes all 24 SNPs plus additional SNPs identified in subsequent genome-wide association studies. However, the 77-SNP PRS could be over-fitted since our study population largely overlaps with populations in genome wide association studies that lead to the discovery of most of known SNPs.[17, 23] Nevertheless, over-fitting of the PRS is unlikely to bias the assessment of interactions with environmental risk factors.

A strength of our study is the large total sample size; however, data for some risk factors, particularly alcohol consumption and use of MHT, was only available from a subset of studies or was missing for a substantial number of participants. In addition, our report includes studies with different study designs: ten of 20 studies were non-population-based case-control studies that are prone to biases in assessing associations with environmental risk factors. To address this limitation, we included an interaction term for the environmental exposure and study design (population-based (including cohorts) versus non-population-based), and used only main effects estimates from population-based studies. In contrast, we used all data available for estimation of multiplicative interaction parameters since they are less susceptible to differential measurement error in case-control studies than main effect parameters,[24] and showed no evidence for heterogeneity across study designs.

Interactions with environmental risk factors, such as benign breast disease, mammographic breast density, oral contraceptive use or physical activity, are possible but could not be evaluated in this report due to sparse or lack of available data. A recent report based on a 76-SNP PRS and Breast Imaging Reporting and Data System (BI-RADS) breast density did not show evidence for non-multiplicative joint associations, albeit in a relatively small study including 1,643 cases and 2,397 controls.[21] Larger studies are needed to further evaluate the joint associations between PRS and these factors. More data than that included in this report will also be required to assess the joint effects for ER-negative disease, where the sample sizes and effect sizes for some factors are smaller.

In summary, our results provide support for the assumption of multiplicative joint associations between PRS and environmental risk factors in the development of risk prediction models for breast cancer; however, small departures are possible and require further investigation. Risk prediction tools based on validated models that can be easily implemented in clinical practice will be needed for the evaluation and ultimate adoption of risk-stratification-based strategies in breast cancer prevention and screening.

TABLES AND FIGURES

Table 1. Odds ratios and 95% confidence intervals for multiplicative interaction between polygenic risk score and environmental risk factors of breast cancer, for all and ER-positive breast cancers, based on population-based and non-population-based studies.

Table 2. Goodness of fit test p-values for overall breast cancer and estrogen receptor positive breast cancer, based on population-based studies.

Figure 1. Odds ratios and 95% confidence intervals for breast cancer risk factors by percentiles of the 77-SNP polygenic risk score (PRS) specific for ER-positive breast cancer, based on population-based and non-population-based studies. FFTP: First full-term pregnancy.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Description of BCAC studies included in the analysis of multiplicative interaction between environmental risk factors and 77-SNP polygenic risk score (PRS).

Supplementary Table 2. List of participating studies and number of subjects of European descent included in at least one GxE analysis.

Supplementary Table 3. Associations of environmental risk factors with breast cancer risk, overall and by ER status of the tumor, based on population-based studies.

Supplementary Table 4. SNPs included in polygenic risk score and effect sizes for association with breast cancer or subtypes of the disease.

Supplementary Table 5. Odds ratios and 95% confidence intervals for multiplicative interaction between 77-SNP polygenic risk score (PRS) and environmental risk factors of breast cancer by study design category.

Supplementary Figure 1. Odds ratios and 95% confidence intervals for percentiles of the 77-SNP polygenic risk score (PRS), for all, ER-positive breast cancer and ER-negative breast cancer, based on population-based and non-population-based studies.

Supplementary Figure 2. Odds ratios and 95% confidence intervals for breast cancer risk factors by percentiles of the 77-SNP polygenic risk score (PRS) for all, ER-positive breast cancer and ER-negative breast cancer, based on population-based and non-population-based studies.

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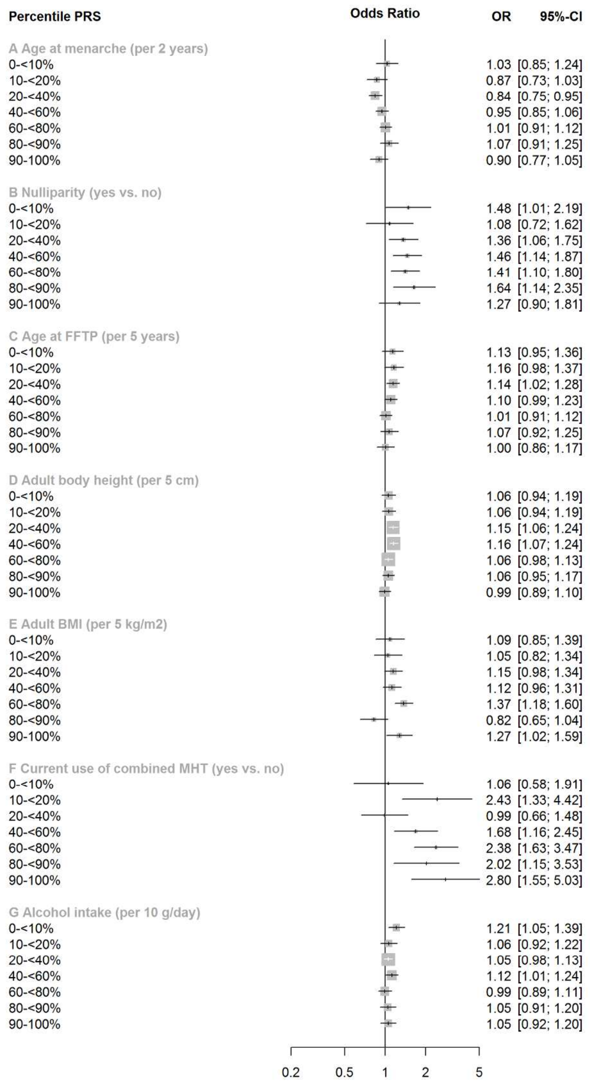

Odds ratios and 95% confidence intervals for breast cancer risk factors by percentiles of the 77-SNP polygenic risk score (PRS) specific for ER-positive breast cancer, based on population-based and non-population-based studies. FFTP: First full-term pregnancy.

190x381mm (200 x 200 DPI)

Table 1. Odds ratios and 95% confidence intervals for multiplicative interaction between polygenic risk score and environmental risk factors of breast cancer, for all, ER-positive breast cancer and ER-negative breast cancer, based on population-based and non-population-based studies

Environmental Factor	**N Studies**	**N cases / controls**	**$\mathrm{OR}_{\mathrm{int}}$ (95% CI)[1]**	***Pint***	**N cases / control**	**$\mathrm{OR}_{\mathrm{int}}$ (95% CI)[1]**	***Pint***	**N cases / control**	**$\mathrm{OR}_{\mathrm{int}}$ (95% CI)[1]**	***Pint***
		All breast cancers			**ER positive breast cancer**			**ER negative breast cancer**		
Age at menarche (per 2 years)	17	18175 / 20366	1.02 (0.96 - 1.08)	0.50	12664 / 20366	1.02 (0.96 - 1.08)	0.62	2995 / 20366	1.00 (0.88 - 1.14)	0.98
Nulliparity (yes vs. no)	19	23104 / 25914	1.05 (0.93 - 1.19)	0.45	16293 / 25914	1.04 (0.92 - 1.18)	0.55	3719 / 25914	1.11 (0.84 - 1.45)	0.48
Age at first full-term pregnancy (per 5 years)	16	15523 / 17623	0.96 (0.91 - 1.01)	0.10	10807 / 17623	0.96 (0.91 - 1.01)	0.15	2557 / 17623	0.92 (0.81 - 1.03)	0.14
Alcohol consumption (per 10g/day)	5	3453 / 3708	0.90 (0.82 - 0.98)	0.016	2661 / 3708	0.89 (0.82 - 0.97)	0.009	538 / 3708	1.16 (0.92 - 1.47)	0.22
Adult height (per 5 cm)	18	20417 / 18412	0.96 (0.92 - 0.99)	0.012	14525 / 18412	0.96 (0.92 - 0.99)	0.025	3389 / 18412	0.97 (0.90 - 1.04)	0.41
Adult BMI (per 5 kg/m^2)	12	8188 / 6717	0.96 (0.88 - 1.05)	0.45	6007 / 6717	0.97 (0.89 - 1.06)	0.48	1229 / 6717	0.92 (0.77 - 1.10)	0.35
Current use of combined MHT (yes vs. never)2	7	5201 / 5697	1.27 (0.95 - 1.70)	0.10	4147 / 5697	1.34 (1.02 - 1.77)	0.038	763 / 5697	0.95 (0.50 - 1.79)	0.87

[1] Adjusted for reference age, study, ancestry-informative principal components and an interaction term between environmental factor and study design (population-based vs. non-population-based). Models used to assess association with use of combined MHT have been further adjusted use of other MHT preparations.

[2] Postmenopausal women only

ER: estrogen receptor; $\mathrm{OR}_{\mathrm{int}}$: odds ratio for interaction; CI: confidence interval

Table 2. Goodness of fit test p-values for overall breast cancer and estrogen receptor positive breast cancer, based on population-based studies.

	Overall breast cancers				ER positive breast cancer			
Variables included in models	**N Studies**	**N cases / controls**	**Tail-based goodness-of-fit test**	**Global goodness-of-fit test**	**N Studies**	**N cases / controls**	**Tail-based goodness-of-fit test**	**Global goodness-of-fit test**
Single risk factor models with 77-SNP PRS								
Age at menarche	10	6209 / 6207	0.758	0.776	10	4320 / 6207	0.869	0.563
Nulliparity	10	6507 / 6578	0.639	0.888	10	4517 / 6578	0.540	0.085
Age at first full-term pregnancy [2]	9	5060 / 5317	0.760	0.562	9	3505 / 5317	0.445	0.306
Alcohol consumption	5	3453 / 3708	0.763	0.565	5	2661 / 3708	0.175	0.013
Adult body height	10	6462 / 6522	0.923	0.875	10	4476 / 6522	0.917	0.219
Adult BMI	8	2958 / 3343	0.956	0.933	8	2099 / 3343	0.563	0.352
MHT [3]	11	5060 / 5208	0.773	0.606	11	3636 / 5208	0.354	0.489
Multiple risk factor models with 77- SNP PRS								
Adult BMI + MHT + BMI*MHT [3]	5	2065 / 2417	0.205	0.655	5	1556 / 2417	0.386	0.494
All environmental factors with BMI*MHT + age + family history	3	1012 / 1161	0.179	0.251	3	847 / 1161	0.679	0.476

[1] always adjusted for study

[2] in parous women only

[3] Menopausal hormone therapy (MHT) categorized as follows: category 1: premenopausal women, irrespective of MHT use; category 2: postmenopausal women who never used MHT; category 3: postmenopausal women who used any kind of MHT in the time period up to six month before reference age; category 4: postmenopausal women who used estrogen-progestogen therapy (EPT) in the last six month before reference age; category 5: postmenopausal women who used any other kind of MHT despite EPT in the last six month before reference age

Age, age at menarche, age at first full time pregnacy, alcohol, height, BMI are in categories