Genetic polymorphisms in DNA repair and oxidative stress pathways may modify the association between body size and postmenopausal breast cancer

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Abstract

Purpose—Obesity is associated with increased bioavailability of estrogen, hyperinsulemia and chronic inflammation, all of which may promote tumor growth. Given DNA repair and oxidative stress pathways may work together with these mechanisms to influence carcinogenesis, we

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hypothesized that genetic variation in these pathways may modify the obesity-postmenopausal breast cancer association.

Methods—Resources from a population-based case-control study (990 cases/970 controls) were used to construct logistic regression models. Body mass index (BMI, weight kg/height m^2) was assessed 1-year prior to reference date. We characterized interactions between BMI and 29 genetic polymorphisms in oxidative stress and DNA repair pathways.

Results—Age-adjusted odds ratios (95% confidence intervals) for postmenopausal breast cancer were 1.24 (1.00–1.52) and 1.35 (1.09–1.71) for 25 BMI<30 and BMI 30, respectively. We observed multiplicative interactions (p 0.05) for eight gene polymorphisms in DNA repair and oxidative stress pathways. For example, among *MPO* variant allele carriers, obesity was associated with a two-fold increased risk of postmenopausal breast cancer [2.13 (1.35–3.36)]; however in wild-type homozygotes, the relationship was less pronounced [1.33 (0.93–1.89)]. Our findings were no longer significant after Bonferroni correction.

Conclusions—Obesity may be particularly deleterious for postmenopausal breast cancer development in the presence of biologically plausible DNA repair or oxidative stress genotypes.

Keywords

Introduction

Obesity is a major public health problem and is a risk factor for several chronic disorders including heart disease, type 2 diabetes, and certain cancers [1]. The National Center for Health Statistics reports that approximately 35.8% of the US adult female population is obese [2]. Given the growing prevalence of obesity and its strong links to postmenopausal breast cancer (BC), it is critical to understand the mechanisms driving the association. Several factors produced by adipose tissue are thought to both directly and indirectly promote tumor growth. Increased bioavailability of estrogens resulting from the conversion of androgens to estradiol in peripheral adipose tissue, systemic reductions in sex hormone–binding globin (SHBG), and obesity related hyperinsulemia have been hypothesized as central contributors [3, 4]. Obesity mediated inflammation may also be an important biologic process in the link between obesity and postmenopausal BC. Adipose tissue is known to produce inflammatory cytokines and prostaglandins, leading to localized inflammation [5]. Chronic inflammation can promote changes in the cellular microenvironment causing increased proliferation and free radical production [6]. Cytokine induced oxidative stress could potentially lead to carcinogenesis.

We hypothesized that decreased DNA damage repair is an important pathologic mechanisms in the obesity-postmenopausal BC association, and that polymorphisms in nucleotide excision repair (NER), mismatch repair (MMR) and base excision repair (BER) may modify this association. Given oxidatively induced DNA damage is repaired primarily by the BER pathway, potential modification of the obesity-postmenopausal BC association by polymorphisms in the oxidative stress pathway were also of interest. We posit that genotypes related to reduced antioxidant enzyme expression, detoxification of oxidized

molecules, or DNA repair capacity may work in synergy with obesity to enhance the risk of postmenopausal BC. This study reports on potential interactions between body size and polymorphisms in genes related to DNA repair (*ERCC1*, *MGMT*, *MLH1*, *MSH2*, *MSH3*, *OGG1*, *XPA*, *XPC*, *XPD*, *XPF*, *XPG* and *XRCC1*) and genes involved in oxidative stress (*CAT*, *COMT, GPX*, *GSTA1*, *GSTM1*, *GSTP1*, *GSTT1* and *MPO*) with respect to the risk of developing BC. Few studies have assessed this hypothesis [7–9], and only one [9] focused on interactions among postmenopausal women, where we hypothesize that modification will be most relevant [10].

Materials and Methods

We used existing genetic and questionnaire data from the case-control component of the Long Island Breast Cancer Study Project (LIBCSP), a population-based study. Details of the parent study have been reported previously [11]. Institutional Review Board approval was obtained by all participating institutions.

Study population

LIBCSP study participants were drawn from English-speaking female residents of Nassau and Suffolk counties, Long Island, New York. LIBCSP case women were aged 20–98 years and newly diagnosed with a first primary *in-situ* or invasive BC between August 1, 1996 and July 31, 1997. Case women were identified through daily or weekly contact with local hospital pathology departments. Population-based controls, without a personal history of BC, were identified from among residents of the same two Long Island counties using random digit dialing for women under age 65 and Health Care Finance Administration rosters for women ages 65 and older. LIBCSP controls were frequency matched to the expected age distribution of case women by 5-year age groups. Distributions by race were similar for cases and controls (94% white, 4% black, and 2% other), and are consistent with the resident populations for these counties [11].

Written informed consent was obtained from all participants prior to the study interview, Interviews were completed within about 3 months of diagnosis (reference date) for 82.1% (N=1508) of eligible cases and within 5 ½ months of identification (reference date) for 62.8% (N=1556) of controls. Respondents were more likely to be older (median age = 57 years in cases and 56 years in controls), postmenopausal (classified as participants whose last menstrual period was more than 6 months prior to reference date or who had both ovaries removed before reference date), and white (93.4% white, which reflects the underlying distribution of the source population). Among the women who completed an interview, 73.1% of cases and 73.3% of controls donated a blood sample. Among blood donors, genotyping was unavailable for 4.4% of cases and 3.4% of controls primarily due to insufficient DNA quantity. After excluding participants without body size data, our final sample of postmenopausal women includes 990 cases and 970 controls. Inconsistencies in sample size by gene polymorphism are due to varying genotyping success rates.

Single Nucleotide Polymorphism (SNP) Selection and Genotyping

We selected 20 polymorphisms representing 12 genes in BER, NER and MMR pathways to assess interactions with obesity: *ERCC1* (rs3212986), *MGMT* (rs12917, rs2308321 and rs2308327), *MLH1* (rs1799977and rs2286940), *MSH2* (rs2303428, rs3732182 and rs4583514), *MSH3* (rs1650663), *OGG1* (rs1052113), *XPA* (rs1800975), *XPC* (rs2228000 and rs2228001), *XPD* (rs1799793 and rs13181), *XPF* (rs1800067), *XPG* (rs17655), *XRCC1* (rs1799782 and rs25487). In addition, we identified 9 SNPs from 8 genes in the oxidative stress pathway to assess interactions with body size: *COMT* (rs4680 and rs737865), *CAT* (rs1001179), *GPX* (rs1050450), *GSTA1* (rs3957356), *GSTM1* (gene deletion), *GSTP1* (rs1695), *GSTT1* (gene deletion), and *MPO* (rs2333227). Polymorphisms in DNA repair and oxidative stress pathways were identified through the BC literature and the SNPinfo web server [12]. The associations between all polymorphisms and BC risk have previously been reported in the LIBCSP study population [8, 13–23].

A non-fasting 40 mL blood sample was obtained from participants at time of interview and shipped at room temperature, overnight, for processing. Genomic DNA was extracted from mononuclear cells in whole blood separated by Ficoll (Sigma Chemical Co., St. Louis, Missouri). Pelleted cells were frozen at −80°C until DNA isolation by standard phenol, and chloroform isoamyl alcohol extraction and RNase treatment were performed [11]. SNP genotyping was performed using several high-throughput methods, which have varied over the course of the study. The fluorescence polarization (FP) method, as described by Chen and colleague's [24], was used to genotype *ERCC1, MGMT, OGG1, XPC, XPD* (rs13181) and *XRCC1*. Taqman assays (Applied Biosystems, Foster City, CA) with 384-well plates were used to genotype *XPA, XPD* (rs1799793), *CAT* (rs4756146, rs2284365 and rs480575) and SNPs in MMR pathway genes. Genotyping for *XPF, XPG, CAT* (rs1001179)*, GPX, GSTA1, GSTP,* and *MPO* was performed by using Sequenom's high-throughput matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, while *GSTM1* and *GSTT1* deletions were analyzed by multiplex polymerase chain reaction by Biotechnologies (Laurel, MD), as described previously [15, 17]. Controls for genotype and two non-template controls were included on each plate. Samples that were outside the variables defined by the controls were identified as non-informative and retested. For quality control, 10% of samples were distributed throughout the DNA samples as blinded duplicates. Laboratory personnel were blinded to case-control status, and all genotyping results were reviewed manually.

Body Size and Covariate Assessment

The interviewer-administered structured questionnaire lasted approximately 101 minutes, and was completed on average within 3 months of diagnosis for cases, and 5.5 months of study identification for controls. As part of this questionnaire participants were asked about their demographic characteristics; reproductive, menstrual, environmental, and medical histories (including family history of BC); cigarette smoking and alcohol use; use of exogenous hormones; participation in recreational physical activity, and body size. Specifically, participants self-reported height to the nearest inch and weight to the nearest pound at age 20 and 1-year prior to reference date. Body mass index (BMI, weight kg/height m^2) at age 20 and 1-year prior to reference date were calculated for each participant based

on the following formula: weight (in kilograms)/height (in meters squared), and used as our measures of body size. We categorized BMI using the standard World Health Organization classifications (<25.0 kg/m^2; 25.0–29.9 kg/m^2; and 30 kg/m^2). The association between BMI and the risk of developing BC has been previously reported among all women [11]; this association among postmenopausal women only is reported here.

Statistical Methods

All analyses were conducted using SAS 9.1 (Cary, NC). Odds ratios (ORs) and corresponding 95% confidence intervals (CI's) for the association between BMI and postmenopausal BC risk, as well as the joint effects of genetic variants and body size, were estimated by unconditional logistic regression [25]. SNPs' effects were assessed using a dominant genetic model (at least one variant allele vs. no variant alleles) due to sparse data among women with the homozygous variant genotype. Among women with complete genotype data we conducted DNA repair and oxidative stress pathway-based analysis by combining pathway-specific genotypes to estimate the association between BMI and postmenopausal breast cancer risk within strata of low, intermediate and high number of variant alleles as described by [26]. The cutoffs for low, intermediate and high number of variant alleles were 0–7, 8–13, and 14 for the DNA repair pathway and 0–4, 5–8, and 9 for the oxidative stress pathway.

We identified potential confounders based on the analysis of causal diagrams [27]. For DNA repair and oxidative stress variants potential confounders included first degree family history of BC (yes/no), race (categorical), and religion (categorical). For body size, potential covariates included education (categorical), family history of BC (yes/no), history of benign breast disease (yes/no), income (categorical), lactation history (ever/never), use of oral contraceptives (ever/never), parity (categorical), recreational physical activity (ever/never) and smoking history (never, current, former). Confounders were included in the final model if their inclusion changed the exposure estimate by greater than 10% [28]. None of the covariates met our criterion. Final models were therefore adjusted only for 5-year age group and departures from the multiplicative null were assessed using the likelihood ratio test, comparing a model with and without the interaction term [29, 30].

Results

BMI and Postmenopausal BC

In the LIBCSP, among women who were overweight (BMI between 25–29.5kg/m^2), the OR (95% CI) for postmenopausal BC was 1.24 (1.00, 1.52). For women classified as obese (BMI 30kg/m^2), the corresponding OR (95% CI) was 1.36 (1.09, 1.71) (Table 1).

Polymorphisms and Postmenopausal BC

As previously described [8, 13–23], effect estimates for the associations between SNP-specific genes in the DNA repair and oxidative stress pathways and postmenopausal BC risk were largely null.

DNA Repair-BMI Interactions and Postmenopausal BC

In the DNA repair pathway, consistent with our *a priori* hypotheses, we found several multiplicative interactions (p 0.05) between body size and gene polymorphisms including: *MGMT* (rs12917), *MSH2* (rs3732182 and rs4583514), *MSH3* (rs1650663), *XPG* (rs17655), and *XRCC1* (rs25487) (Table 2). Overall, we observed substantial increases in BC risk among obese women who harbored at least one minor allele while associations among obese women homozygous for the major allele were less in magnitude. For example, postmenopausal women who were heterozygous or homozygous for the minor C allele in *MSH3* (rs1650663) and classified as obese 1-year prior to reference date experienced a greater than two-fold increase in BC risk [2.04 (1.37, 3.05)]. In addition, overweight variant allele carriers were also at elevated BC risk [1.55 (1.07, 2.25)] relative to women with BMI $<25 kg/m^2$. In contrast, the effect of body size among women homozygous for the major allele was less pronounced; the corresponding ORs (95% CIs) were 0.99 (0.69, 1.43) and 1.26 (0.85, 1.89), for overweight and obese women, respectively. Similar patterns of association were observed for *MGMT, MSH2, XPG* and *XRCC1*. When we assessed the association between BMI and postmenopausal breast cancer risk within strata of low, intermediate and high number of variant alleles we found no interactions ($p < 0.05$, data not shown).

Oxidative Stress-BMI Interactions and Postmenopausal BC

Significant multiplicative interactions (p 0.05) were observed between body size and two gene polymorphisms in the oxidative stress pathway, namely *GSTT1* and *MPO* (Table 3). The effect modification noted for *MPO* (rs2333227) was consistent with our *a priori* hypotheses, whereas the interaction finding for *GSTT1* (gene deletion) was not. For example, we observed an 84% increased risk for carrying any *MPO* variant among women classified as overweight [1.84 (1.21, 2.78)] and a greater than two-fold risk among women classified as obese [2.13 (1.35, 3.36)] relative to women with BMI $<25 kg/m^2$ (p for multiplicative interaction = 0.024). In contrast, the pattern among women homozygous for the major allele, was less pronounced; for overweight participants the common *MPO* genotype (CC) was associated with a very modest 5% increased risk [1.05 (0.76, 1.46)] while among obese women the OR was only increased by 33% [1.33 (0.93, 1.89)] relative to women with BMI $<25 kg/m^2$. We found no interactions ($p < 0.05$) between BMI and postmenopausal breast cancer risk within strata of low, intermediate and high number of variant alleles (data not shown).

Upon adjusting for multiple comparisons none of our associations were significant at the 0.001 significance level.

Discussion

In this population-based study, we observed a significant 24 to 36% increase in the risk of postmenopausal BC in relation to overweight and obesity. However, our results suggest that genotypes in DNA repair and oxidative stress pathways modify this association. Obese women with a BMI 30kg/m2 who carried at least one minor allele in MGMT, MSH2 (rs3732182 and rs4583514), MSH3, XPG, XRCC1 or MPO experienced significant

increases in postmenopausal BC risk (excess risk ranging from 79% to greater than 2-fold) while obese women without the variant allele experienced only modest increases (excess risk between 17% and 37%). Our findings suggest that postmenopausal obesity could be particularly deleterious in the presence of specific, biologically plausible DNA repair or oxidative stress genotypes.

The positive association between elevated BMI (e.g. >25kg/m2) and postmenopausal BC risk is well-documented [10]. In a 2008 review, Pichard and colleagues report risk ratios ranging from 1.26 to 2.52, which are consistent with our findings [31]. Elevated levels of circulating estrogens are proposed to underlie this positive association and are thought to result from aromatase mediated conversion of androgens to estradiol in peripheral adipose tissue, reductions in sex hormone–binding globin, and obesity related hyperinsulemia [3, 4].

However, the underlying mechanisms for the BMI-BC association are complex and remain unclear [32]. In addition to circulating estrogens, obesity may influence postmenopausal BC risk through an inflammatory pathway [5]. Adiposity is associated with a state of chronic inflammation and produces a pro-inflammatory oxidative environment [33, 34]. In this environment, adipocytes express highs levels of pro-inflammatory cytokines including tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), and decreased anti-inflammatory markers, such as adiponectin [35, 36]. Chronic inflammation is likely to lead to changes in the cellular microenvironment, increased proliferation and oxidative stress [6]. Cytokine induced free radical production can cause damage to DNA, and if unrepaired may lead to deregulated normal cell development increasing the propensity for breast malignancy [37]. We therefore hypothesized that both decreased DNA damage repair and increased oxidative stress are important pathologic mechanisms in the obesity-BC association and may be modified by polymorphisms in these pathways.

Few studies have assessed interactions between obesity and DNA repair polymorphisms, particularly among postmenopausal women, where the obesity-BC association is most relevant [10]. Investigators from a 2005 hospital-based case-control study conducted in Korea [7] reported a borderline significant interaction between a single DNA repair SNP in ERCC4 and BMI, although stratified estimates were not provided. Women with BMI 25 kg/m2 and who carried the variant C allele were at a 1.7-fold (0.96, 2.93) increased risk of BC risk compared to women with BMI < 25kg/m2 and who were homozygous for the G allele. Another investigation, conducted using our own LIBCSP study population [8], showed increased ORs for BC among women with BMI 25 kg/m2 who also harbored the variant G allele for two SNPs in OGG1 [7143A/G: 1.47(1.10, 1.96) and 11657A/G: 1.41(1.05, 1.88)], relative to women with BMI<25 kg/m2 and the common genotype. This study showed no evidence of interaction between BMI and the Ser326Cys polymorphism, however, modification was importantly not assessed within strata of menopausal status.

Similarly, there are few population-based studies that have considered potential interaction between body size and oxidative stress gene polymorphisms. For example, in the LIBCSP, we previously considered interactions between body size and genetic polymorphisms in MnSOD, but found no evidence to support interaction on the multiplicative scale [9]. Some studies have estimated associations between urinary F2-isoprostanes (IsoP), secondary end

products of lipid peroxidation, and BC risk examining potential modification by BMI. In the LIBCSP we found similar associations among women in the highest quartile of 15-F2t-IsoP levels compared with the lowest quartile irrespective of body size (BMI<25 and BMI 25) [38]. In contrast, findings from the Shanghai Women's Health Study indicate the association between 15-F2t-IsoP and BC may be modified by BMI [39]. While 15-F2t-IsoP and its metabolite 15-F2t-IsoPM were inversely associated with BC risk among women with a BMI<25, the association was positive among women with a BMI 25. The magnitude of these associations became stronger among women with a higher BMI, although the estimates were imprecise. These data suggest that although 15-F2t-IsoP is the most frequently used biomarker of oxidative stress, it may not accurately reflect interactions with obesity.

Related findings from other studies, in conjunction with our own, also lend support to our hypothesis that obesity may differentially impact women with certain DNA repair or oxidative stress genotypes. For example, in human lymphocytes, the MGMT (Leu84Phe) polymorphism results in suboptimal repair of genetic damage [40]. Women who carry the variant T allele may therefore not be able to effectively repair damage caused by obesity mediated reactive oxygen species resulting in augmented BC risk. While these findings are suggestive of enhanced risk among obese women with deficient antioxidant or repair capacity, the functional significance of many of the polymorphisms evaluated remains to be resolved [41, 42]. Our findings should therefore be interpreted with caution.

Our study has potential limitations, which should be considered during the interpretation of our results. In the LIBCSP, blood donation varied by both age and race [11]. Although genotype may be associated with race, given the small number of non-white women included in the study, potential racial variation in blood donation is likely negligible. We were unable to explore potential variation by BC subtype given our limited study power and low proportion of women with HER2-tumors. We assessed BMI 1-year prior to reference date to account for any changes in weight that may occur with chemotherapy initiation. However, this time point may not represent the etiologically relevant time period for breast carcinogenesis. It is also plausible that there was differential recall of body size with respect to case status. However, neither cases nor controls were aware of their genotype at the time of interview and it is unlikely that systematic differences in recall persist across strata of genotype [23]. We therefore do not anticipate that any misclassification of body size would bias our interaction parameter estimates. While the number of tests may have led to chance findings, it is unlikely that we would find evidence of interaction for more than 25% of the polymorphisms assessed based on chance alone. Although we recognize that correction for multiple comparisons is important and have included Bonferroni adjusted results, this correction may be unduly conservative. Our study hypotheses were based on strong biologic rationale and we employed a targeted candidate-gene approach. Given this is one of the first studies to assess potential modification of the BMI-postmenopausal BC association by genotypes in these two pathways, we were primarily interested in estimating effects and corresponding CIs without adjusting for multiple comparisons. These data may provide rational for future investigation and replication. Finally, the pathways selected for investigation represent a small proportion of a number of proposed mechanisms through which obesity may influence postmenopausal BC risk [43]. Other pathways (e.g., sex-

steroid) were not considered and we were unable to simultaneously examine multiple pathways using higher level modeling (e.g. hierarchical) due to limited power. These potential limitations should be explored in future investigations.

Conclusions

This study found evidence of interaction between BMI and six variants in DNA repair and two SNPs in the oxidative stress, respectively. The observed multiplicative interaction supports our biologically plausible hypothesis that obesity may be associated with a pro-inflammatory oxidative environment, and that insufficient antioxidant capacity or DNA repair could result in damage to cellular constituents (e.g., DNA) and enhanced postmenopausal BC risk. While we detected interactions across multiple gene polymorphisms, the limited functional data in these SNPs limits our ability to make strong conclusions. Replication of our results, in addition to new mechanistic data, will further enhance our understanding and negate any suggestions of chance discovery.

Acknowledgments

Abbreviations

BC	breast cancer
BER	base excision repair
BMI	body mass index
CI	confidence interval
FP	fluorescence polarization
ICR	interaction contrast ratio
IL-6	interleukin-6
IsoP	isoprostanes
LIBCSP	Long Island breast cancer study project
MMR	mismatch repair
NER	nucleotide excision repair
OR	odds ratio
SHBG	sex hormone binding globulin
SNP	single nucleotide polymorphism
TNF-α	tumor necrosis factor-α

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TABLE 1

Age-adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between body mass index (BMI) and postmenopausal breast cancer risk, Long Island Breast Cancer Study Project (1996–1997).

BMI[c]	Ca[a]/Co[b]	OR	95% CI
<25kg/m2	386/439	1.00	Reference
25–29.9kg/m2	340/309	1.24	(1.00–1.52)
30kg/m2	264/222	1.36	(1.09–1.71)

[a]Cases;

[b]Controls;

[c]1-year prior to reference date

TABLE 2

Age-adjusted odds ratios (OR) and 95% confidence intervals (CI) for the interactions between DNA repair genes polymorphisms and body mass index (BMI) in association with postmenopausal breast cancer risk, Long Island Breast Cancer Study Project (1996–1997).

Gene (rs) major/minor alleles BMI[a]	Homozygous for major allele			At least one copy of minor allele			Multiplicative p
	Ca[b]/Co[c]	OR	95% CI	Ca/Co	OR	95% CI	
ERCC1 (rs3212986) C/A							
<25kg/m2	134/182	1.00	reference	128/135	1.00	reference	0.056
25–29.9kg/m2	115/123	1.28	(0.90, 1.80)	116/87	1.43	(0.97, 2.09)	
30kg/m2	108/77	1.90	(1.30, 2.76)	82/72	1.24	(0.82, 1.88)	
MGMT (rs12917) C/T							
<25kg/m2	195/223	1.00	reference	68/84	1.00	reference	0.049
25–29.9kg/m2	170/156	1.32	(0.98, 1.77)	65/56	1.37	(0.83, 2.25)	
30kg/m2	134/117	1.37	(0.99, 1.89)	57/30	2.52	(1.43, 4.44)	
MGMT (rs2308321) A/G							
<25kg/m2	198/235	1.00	reference	66/82	1.00	reference	0.742
25–29.9kg/m2	186/163	1.35	(1.01, 1.80)	49/49	1.36	(0.79, 2.33)	
30kg/m2	152/113	1.59	(1.16, 2.18)	38/33	1.51	(0.84, 2.72)	
MGMT (rs2308327) A/G							
<25kg/m2	204/242	1.00	reference	61/75	1.00	reference	0.580
25–29.9kg/m2	195/169	1.37	(1.03, 1.82)	40/44	1.35	(0.75, 2.42)	
30kg/m2	161/120	1.60	(1.18, 2.18)	31/29	1.57	(0.83, 2.97)	
MLH1 (rs1799977) A/G							
<25kg/m2	127/157	1.00	reference	129/149	1.00	reference	0.508
25–29.9kg/m2	98/94	1.29	(0.89, 1.87)	119/114	1.23	(0.86, 1.75)	
30kg/m2	95/70	1.72	(1.16, 2.56)	90/77	1.42	(0.95, 2.12)	
MLH1 (rs2286940) C/T							
<25kg/m2	90/100	1.00	reference	165/207	1.00	reference	0.376
25–29.9kg/m2	59/52	1.25	(0.77, 2.04)	154/156	1.26	(0.92, 1.71)	
30kg/m2	65/39	1.87	(1.13, 3.09)	118/108	1.43	(1.02, 2.01)	
MSH2 (rs2303428) T/C							
<25kg/m2	208/249	1.00	reference	41/51	1.00	reference	0.589

Gene (rs) major/minor alleles BMI[a]	Homozygous for major allele			At least one copy of minor allele			Multiplicative p
	Ca[b]/Co[c]	OR	95% CI	Ca/Co	OR	95% CI	
25–29.9kg/m2	173/171	1.22	(0.92, 1.62)	36/33	1.59	(0.81, 3.12)	
30kg/m2	160/131	1.53	(1.13, 2.08)	19/15	1.36	(0.60, 3.10)	
MSH2 (rs3732182) G/T							
<25kg/m2	138/164	1.00	reference	111/140	1.00	reference	0.028
25–29.9kg/m2	116/109	1.34	(0.94, 1.92)	97/100	1.26	(0.86, 1.85)	
30kg/m2	91/91	1.23	(0.84, 1.81)	93/56	2.09	(1.36, 3.21)	
MSH2 (rs4583514) A/G							
<25kg/m2	97/113	1.00	reference	159/193	1.00	reference	0.021
25–29.9kg/m2	94/75	1.56	(1.02, 2.39)	123/135	1.12	(0.80, 1.55)	
30kg/m2	65/64	1.18	(0.75, 1.87)	119/83	1.79	(1.25, 2.56)	
MSH3 (rs1650663) T/C							
<25kg/m2	125/141	1.00	reference	128/166	1.00	reference	0.034
25–29.9kg/m2	108/119	0.99	(0.69, 1.43)	107/89	1.55	(1.07, 2.25)	
30kg/m2	88/80	1.26	(0.85, 1.89)	97/65	2.04	(1.37, 3.05)	
OGG1 (rs1052133) C/G							
<25kg/m2	154/186	1.00	reference	129/101	1.00	reference	0.069
25–29.9kg/m2	132/127	1.22	(0.87, 1.70)	80/98	1.59	(1.06, 2.39)	
30kg/m2	120/80	1.80	(1.25, 2.58)	64/67	1.36	(0.87, 2.12)	
XPA (rs1800975) G/A							
<25kg/m2	123/138	1.00	reference	140/175	1.00	reference	0.276
25–29.9kg/m2	103/99	1.19	(0.81, 1.74)	130/111	1.47	(1.04, 2.08)	
30kg/m2	79/66	1.36	(0.90, 2.07)	111/82	1.72	(1.18, 2.48)	
XPC (rs2228000) C/T							
<25kg/m2	151/173	1.00	reference	112/143	1.00	reference	0.221
25–29.9kg/m2	132/125	1.19	(0.85, 1.66)	101/86	1.48	(0.99, 2.20)	
30kg/m2	96/85	1.38	(0.95, 2.00)	94/62	1.80	(1.19, 2.74)	
XPC (rs2228001) A/C							
<25kg/m2	78/103	1.00	reference	185/211	1.00	reference	0.352
25–29.9kg/m2	79/71	1.50	(0.96, 2.34)	153/140	1.23	(0.90, 1.68)	
30kg/m2	71/52	1.82	(1.14, 2.92)	119/95	1.49	(1.06, 2.11)	

Gene (rs) major/minor alleles BMI[a]	Homozygous for major allele			At least one copy of minor allele			Multiplicative p
	Ca[b]/Co[c]	OR	95% CI	Ca/Co	OR	95% CI	
XPD (rs1799793) G/A							
<25kg/m2	105/137	1.00	reference	157/178	1.00	reference	0.920
25–29.9kg/m2	94/94	1.30	(0.88, 1.94)	139/116	1.33	(0.95, 1.86)	
30kg/m2	86/73	1.64	(1.08, 2.49)	103/74	1.61	(1.10, 2.35)	
XPD (rs13181) A/C							
<25kg/m2	100/137	1.00	reference	160/178	1.00	reference	0.352
25–29.9kg/m2	88/83	1.48	(0.99, 2.22)	143/129	1.20	(0.87, 1.67)	
30kg/m2	73/65	1.56	(1.01, 2.41)	118/80	1.72	(1.19, 2.48)	
XPF (rs1800067) G/A							
<25kg/m2	220/258	1.00	reference	36/46	1.00	reference	0.076
25–29.9kg/m2	187/167	1.31	(0.99, 1.74)	35/37	1.08	(0.55, 2.10)	
30kg/m2	149/125	1.42	(1.05, 1.93)	36/18	2.46	(1.16, 5.24)	
XPG (rs17655) G/C							
<25kg/m2	141/150	1.00	reference	106/148	1.00	reference	0.050
25–29.9kg/m2	135/129	1.09	(0.77, 1.54)	83/74	1.56	(1.03, 2.37)	
30kg/m2	94/81	1.26	(0.85, 1.85)	88/62	2.00	(1.31, 3.06)	
XRCC1 (rs1799782) C/T							
<25kg/m2	235/277	1.00	reference	30/39	1.00	reference	0.649
25–29.9kg/m2	206/189	1.28	(0.98, 1.68)	29/24	1.64	(0.75, 3.58)	
30kg/m2	167/131	1.55	(1.16, 2.09)	24/17	1.88	(0.81, 4.35)	
XRCC1 (rs25487) G/A							
<25kg/m2	106/113	1.00	reference	159/204	1.00	reference	0.045
25–29.9kg/m2	97/84	1.28	(0.85, 1.94)	138/129	1.35	(0.98, 1.87)	
30kg/m2	68/67	1.17	(0.75, 1.84)	124/82	1.93	(1.35, 2.75)	

[a] 1-year prior to reference date;

[b] Cases;

[c] Controls

TABLE 3

Age-adjusted odds ratios (OR) and 95% confidence intervals (CI) for the interaction between oxidative stress genes polymorphisms and body mass index (BMI) and postmenopausal breast cancer risk, Long Island Breast Cancer Study Project (1996–1997).

Gene (rs) major/minor alleles BMI[a]	Ca[b]/Co[c]	Homozygous for major allele OR	95% CI	Ca/Co	At least one copy of minor allele OR	95% CI	Multiplicative p
CAT (rs1001179) C/T							
<25kg/m2	153/199	1.00	reference	106/116	1.00	reference	0.572
25–29.9kg/m2	139/132	1.34	(0.97, 1.86)	85/76	1.23	(0.81, 1.86)	
30kg/m2	116/98	1.60	(1.13, 2.28)	116/98	1.74	(1.09, 2.77)	
COMT (rs4680) G/A							
<25kg/m2	64/85	1.00	reference	197/228	1.00	reference	0.086
25–29.9kg/m2	67/49	1.88	(1.13, 3.13)	163/160	1.15	(0.86, 1.55)	
30kg/m2	59/39	2.12	(1.24, 3.64)	129/108	1.39	(1.00, 1.92)	
COMT (rs737865) T/C							
<25kg/m2	131/148	1.00	reference	126/164	1.00	reference	0.347
25–29.9kg/m2	107/94	1.28	(0.88, 1.86)	118/114	1.32	(0.92, 1.90)	
30kg/m2	88/72	1.33	(0.89, 2.00)	98/76	1.74	(1.18, 2.57)	
GPX (rs1050450) C/T							
<25kg/m2	118/147	1.00	reference	144/165	1.00	reference	0.346
25–29.9kg/m2	102/112	1.15	(0.80, 1.67)	121/98	1.39	(0.98, 1.99)	
30kg/m2	86/66	1.67	(1.10, 2.52)	103/79	1.54	(1.06, 2.25)	
GSTA1 (rs3957356) G/A							
<25kg/m2	89/115	1.00	reference	173/200	1.00	reference	0.364
25–29.9kg/m2	71/66	1.39	(0.88, 2.19)	153/143	1.21	(0.88, 1.65)	
30kg/m2	62/44	1.88	(1.14, 3.09)	128/102	1.47	(1.05, 2.06)	
GSTP1 (rs1695) A/G							
<25kg/m2	121/152	1.00	reference	135/154	1.00	reference	0.133
25–29.9kg/m2	119/97	1.56	(1.08, 2.26)	105/106	1.09	(0.76, 1.58)	
30kg/m2	95/64	1.93	(1.28, 2.91)	89/80	1.26	(0.85, 1.86)	
GSTM1 (gene deletion)							
<25kg/m2	123/152	1.00	reference	120/135	1.00	reference	0.527

Gene (rs) major/minor alleles BMI[a]	Homozygous for major allele			At least one copy of minor allele			Multiplicative p
	Ca[b]/Co[c]	OR	95% CI	Ca/Co	OR	95% CI	
25–29.9kg/m2	103/104	1.32	(0.91, 1.91)	111/82	1.46	(0.99, 2.15)	
30kg/m2	98/84	1.56	(1.06, 2.29)	80/51	1.73	(1.11, 2.69)	
GSTT1 (gene deletion)							
<25kg/m2	193/231	1.00	reference	49/57	1.00	reference	*0.017*
25–29.9kg/m2	183/141	1.58	(1.18, 2.13)	35/48	0.85	(0.47, 1.56)	
30kg/m2	131/107	1.52	(1.09, 2.11)	47/31	1.87	(1.01, 3.48)	
MPO (rs2333227) G/A							
<25kg/m2	173/178	1.00	reference	88/136	1.00	reference	*0.024*
25–29.9kg/m2	136/133	1.05	(0.76, 1.46)	90/77	1.84	(1.21, 2.78)	
30kg/m2	113/91	1.33	(0.93, 1.89)	75/55	2.13	(1.35, 3.36)	

[a] 1-year prior to reference date;

[b] Cases;

[c] Controls