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Polymorphisms in DNA Repair Genes, Recreational Physical Activity and Breast Cancer Risk

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Abstract

The mechanisms driving the inverse association between recreational physical activity (RPA) and breast cancer risk are complex. While exercise is associated with increased reactive oxygen species production it may also improve damage repair systems, particularly those that operate on single-strand breaks including base excision repair (BER), nucleotide excision repair (NER) and mismatch repair (MMR). Of these repair pathways, the role of MMR in breast carcinogenesis is least investigated. Polymorphisms in MMR or other DNA repair gene variants may modify the association between RPA and breast cancer incidence. We investigated the individual and joint effects of variants in three MMR pathway genes (*MSH3*, *MLH1* and *MSH2*) on breast cancer occurrence using resources from the Long Island Breast Cancer Study Project. We additionally characterized interactions between RPA and genetic polymorphisms in MMR, BER and NER pathways. We found statistically significant multiplicative interactions ($p<0.05$) between *MSH2* and *MLH1*, as well as between postmenopausal RPA and four variants in DNA repair (*XPC*-Ala499Val, *XPF*-Arg415Gln, *XPG*-Asp1104His and *MLH1*-lle219Val). Significant risk reductions were observed among highly active women with the common genotype for *XPC* (OR=0.54; 95% CI, 0.36–0.81) and *XPF* (OR=0.62; 95% CI, 0.44–0.87), as well as among active women who carried at least one variant allele in *XPG* (OR=0.46; 95% CI, 0.29–0.77) and *MLH1*

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(OR=0.46; 95% CI, 0.30–0.71). Our data show that women with minor alleles in both *MSH2* and *MLH1* could be at increased breast cancer risk. RPA may be modified by genes in the DNA repair pathway, and merit further investigation.

Keywords

Breast Cancer; Epidemiology; DNA Repair; Mismatch Repair; Physical Activity

Introduction

Damage to DNA may occur through a variety of endogenous or exogenous processes including oxidative damage through the generation of reactive oxygen species (ROS) (1). If these compounds are not neutralized by endogenous antioxidants they have the capacity to react with biomolecules causing damage. The integrity of DNA is primarily maintained by four repair pathways that operate on impaired DNA: base excision repair (BER), double strand break (DSB) repair, nucleotide excision repair (NER) and mismatch repair (MMR) (2). Of these, MMR is the least studied in breast carcinogenesis. MMR improves replication fidelity by correcting DNA polymerase-mediated replication errors (2, 3). MMR gene dysfunction is proposed to occur through one of two mechanisms: epigenetic gene silencing or genetic mutations in one of six genes associated with MMR (4–6). These changes may lead to increased mutations of oncogenes, tumor suppressor genes, and loss of DNA damage-induced apoptosis, therefore facilitating carcinogenesis (7).

Microsatellite instability (MSI), characterized as simple sequence repeats in DNA, is closely associated with MMR deficiency (2, 8) and is reported to be present in some breast tumors (9–10). Moreover, there is accumulating evidence that reduced tumor expression of *MSH2* and *MLH1* are related to breast tumor progression and invasion (11–12). While these data suggest a potential role for MMR in breast cancer susceptibility there are few epidemiologic studies examining associations between germline polymorphisms in MMR and breast cancer incidence (13–17). These data are mixed and previous investigations have been limited by small samples or less than optimal designs making additional studies warranted.

Polymorphisms in MMR or other DNA repair genes may interact with environmental exposures to influence carcinogenesis (18), even if the main effect of repair variants on breast cancer risk is small or null. Physical activity (PA) is known to be associated with breast cancer risk, particularly among postmenopausal women, but the complex physiological effects of exercise make the mechanisms driving the inverse association difficult to disentangle. While PA is an important contributor to ROS production, regular exercise may improve damage repair systems (19–22), particularly those that operate on single-strand breaks induced by oxidation (i.e. BER, NER and MMR). Animal and clinical studies have shown that several DNA repair enzymes are up-regulated with long term exercise (23–27). These changes likely result in increased resistance to oxidative damage, diminished DNA impairment and a lower probability of initiating events. This could be tested through epidemiologic analyses assessing the joint effects of low PA and reduced

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DNA repair capacity on breast cancer incidence, but to date no study has considered this approach despite the biologic plausibility.

We hypothesized that MMR variants related to reduced repair capacity may be associated with increased breast cancer risk. We also anticipate that genotypes associated with reduced DNA repair act synergistically with low levels of PA to increase the risk of breast cancer greater than would be expected by their individual effects. In this report, we aimed to: (1) examine the main effect of variants in MMR on breast cancer risk; (2) examine two-way interactions between single nucleotide polymorphisms (SNPs) in the MMR pathway and breast cancer incidence; and (3) examine the joint effects of recreational physical activity (RPA) and variants in DNA repair genes from the BER, NER and MMR pathways on breast cancer risk. Secondary aims were to evaluate associations between MMR polymorphisms and breast cancer with cases categorized according to tumor hormone receptor status, as well as to examine the combined effect of MMR SNPs on breast cancer incidence using a pathway-based approach.

Materials and Methods

Resources for this project were drawn from the Long Island Breast Cancer Study Project (LIBCSP), a population-based investigation conducted on Long Island, New York. Details of the case-control study have been previously described (28). This study was approved by the Institutional Review Board of the collaborating institutions.

Study population

LIBCSP case women were English speaking residents of Nassau and Suffolk counties in New York (NY), aged 20–98 years and newly diagnosed with a first primary *in-situ* or invasive breast cancer between August 1, 1996 and July 31, 1997. Population-based controls, without a personal history of breast cancer, were randomly selected from the same two counties using random digit dialing for women under age 65 and rosters from the Health Care Finance Administration for women ages 65 and older. 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 NY counties (28).

Exposure and covariate data were obtained through an interviewer-administered structured questionnaire. Interviews were completed for 82.1% (n=1508) of eligible cases and 62.8% (n=1556) of controls. Among the women who completed an interview, blood samples were donated by 73.1% and 73.3% of cases and controls, respectively. Women who donated a blood sample differed somewhat from non-blood donors on key characteristics including age and race; blood donors more likely to be younger in age and white (28). Genotyping was unavailable for 4.4% of cases and 3.4% of controls primarily due to insufficient DNA quantity. Thus, the final sample includes 1053 case and 1102 control women.

Single Nucleotide Polymorphism Selection and Genotyping

We selected five tag SNPs (*MSH3*: rs1650663; *MLH1*: rs2286940; *MSH2*: rs2303428, rs3732182 and rs4583514) and one functional variant (*MLH1*: rs1799977, a single non-

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synonymous base pair change affecting splicing regulation) from three genes in the MMR pathway for genotyping. A tagging strategy was employed to maximize our ability to capture genetic variation across the each gene. The National Institute of Environmental Health Service SNPinfo database (29) was used to select Tag SNPs based on data from phase I and II of the International HapMap Project (30). The CEU population (30 Utah trios with ancestry from northern and western Europe) was selected as the reference panel given the racial homogeneity of the LIBCSP population with DNA available for analyses (93.4% White and 6.6% Non-White) (31). SNP selection procedures were based on a minor allele frequency (MAF) cutoff value of 5% and r^2 threshold minimum of 0.80 as well as a combination of factors including SNP location, MAF and bin size. In addition to the aforementioned MMR SNPs, we selected 14 presumed functional variants from 9 genes in BER and NER pathways to assess interactions with RPA: *ERCC1* (rs3212986), *MGMT* (rs12917, rs2308321 and rs2308327), *OGG1* (rs1052113), *XPA* (rs1800975), *XPC* (rs2228000 and rs2228001), *XPD* (rs1799793 and rs13181), *XPF* (rs1800067), *XPG* (rs17655), *XRCC1* (rs1799782 and rs25487). The main effects of these SNPs have previously been reported.

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° centigrade until DNA isolation by standard phenol, and chloroform/isoamyl alcohol extraction and RNase treatment (28). Genotyping of newly selected MMR SNPs was accomplished using Taqman assays (Applied Biosystems, Foster City, CA) with 384-well plates. For the remaining SNPs genotyping was performed using several high-throughput genotyping methods, which have varied over the course of the study. The fluorescence polarization (FP) method, as described by Chen and colleague's (32), was used to genotype *ERCC1, MGMT, OGG1, XPC, XPD* (rs13181) and *XRCC1*. *XPA* and *XPD* (rs1799793) were genotyped using Taqman assays described above. Genotyping for *XPF* and *XPG* was accomplished using Sequenom's high-throughput matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, previously reported by Ahn and colleagues (33). 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. Ten percent of samples were distributed throughout the DNA samples for quality control and laboratory personnel blinded to case-control status.

RPA and Covariate Assessment

Other data for this project comes from the interviewer-administered LIBCSP questionnaire and, for cases, medical record abstraction. The comprehensive questionnaire lasted approximately 101 minutes, and was completed on average within 3 months of diagnosis for cases, and 6 months of study identification for controls. Study participants were asked about their demographic characteristics; reproductive, medical and environmental histories; cigarette smoking and alcohol use; use of exogenous hormones; energy intake; participation in RPA, and select anthropometric measurements. RPA was assessed using a modified instrument developed by Bernstein and colleagues (34). Women were screened for RPA participation by replying to the question: "Have you ever participated in any activities or

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exercises on a regular basis – that is, for at least 1 hour per week for 3 months or more in any year?" Women answering negatively were classified as having no RPA while subjects answering positively were further queried about their involvement. For these women the activity name, the ages the activity was started and stopped, and the number of hours per week and months per year the activity was performed were obtained. Activity data was summed across all activities for each year of a woman's life, providing a composite score of exercise duration from menarche (left truncated) to reference date. In this analysis we assessed the interaction between variants in DNA repair genes and two PA variables for which the effects for breast cancer were strongest in the LIBCSP population (35): average hours per week of postmenopausal and lifetime RPA. Our findings showed little or no heterogeneity by RPA-intensity (35).

Among case women, clinical data (including hormone receptor [HR] status of the first primary breast cancer) were obtained from abstracting medical records.

Statistical Methods

All analyses were conducted using SAS 9.1 (Cary, NC). Evaluation of Hardy-Weinberg equilibrium (HWE) was conducted using observed genotype frequencies among White controls and X^2 test with 1 degree of freedom (36). Odds ratios (ORs) and corresponding 95% CIs for the independent effects of MMR SNPs, their interactions, and the joint effect of DNA repair variants and RPA were estimated by unconditional logistic regression (37). SNPs effects were assessed using a dominant genetic model because of the low prevalence of the homozygous recessive genotype among MMR SNPs.

Main effects of MMR variants on breast cancer risk were assessed among all women combined, and within strata of menopausal status (pre vs. post) when the Breslow-Day p for homogeneity was <0.10 (38). Effects were also evaluated by breast cancer subtype according to HR status, by stratifying cases into two HR groups using information on estrogen receptor (ER) and progesterone receptor (PR) status. Women who were ER or PR positive were classified as HR+ (which is consistent with considering luminal A and B intrinsic subtypes as a single group), while women with tumors that were negative for both ER and PR receptors were classified as HR- (39).

Two-way interactions between MMR genes and breast cancer risk were assessed using a likelihood ratio test (LRT): the difference of the −2LogL values of logistic models calculated with and without the interaction terms for SNP1 and SNP2 (40). For our MMR pathway-based analysis we combined MMR genotypes, and calculated age-adjusted ORs for breast cancer stratifying on the number of 'variant' genotypes: 0–3, 4–7, ≥8 using methods previously described by Mohrenweiser (41).

Additive and multiplicative gene by environment interactions were assessed using indicator terms for women with the genotype only, exposure only, and both the genotype and exposure of interest. A dominant genetic model was used for all SNPs. Among physically active women, participants were classified into categories based on the median average hours per week among controls creating three levels of RPA: no, low (< control medium), and high (≥ control median) RPA. Departures from the multiplicative null were assessed

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using the LRT, comparing a model with and without the interaction terms (38). Departures from the additive null were estimated by the interaction contrast ratio (ICR) based on the formula: ICR= OR11–OR01–OR10+1 (40).

Covariates considered as potential confounders for MMR variants were first degree family history of breast cancer (yes/no), race (categorical), and religion (categorical). For RPA, potential covariates included education (categorical), family history of breast cancer (yes/no), history of benign breast disease (yes/no), income (categorical), lactation history (ever/never), use of oral contraceptives (ever/never), parity (categorical), and smoking history (never, current, former) and were included in the final model if their inclusion changed the exposure estimate by > 10% (42). None of these altered the estimate by greater than 10%. Final models were adjusted only for 5-year age group.

Results

Hardy Weinberg Equilibrium

Genotype frequencies for polymorphisms in *MSH3* (rs1650663) *MLH1* (rs1799977, rs2286940) and *MSH2* (rs2303428, rs3732182, rs4583514) are reported in Table 1. All genotypes were consistent with HWE.

Main SNP Effects

There was no evidence of a main effect for any of the individual MMR minor alleles on breast cancer risk (Table 1), and these findings did not change materially with menopausal status (data not shown). When we restricted these analyses to Whites only, results were similar to those observed among the entire study population. For some variants (*MLH1* rs1799977, *MLH1* rs2286940, and *MSH2* rs2303428) there was suggestion of heterogeneity by HR status (data not shown). We observed moderate risk reductions for the minor alleles of rs1799977, rs2286940, and rs2303428 among HR negative cases (OR; 95% CI = 0.77; 0.52–1.12, 0.69; 0.46–1.01 and 0.71; 0.39–1.27, respectively) and approximately null or slightly increased risk among HR positive cases (OR; 95% CI = 1.11; 0.89–1.37, 0.99; 0.78–1.24 and 1.15; 0.86–1.54, respectively). There was no evidence of tumor heterogeneity by HR status for the remaining MMR polymorphisms (data not shown).

Gene-Gene (GxG) Interactions

We evaluated all potential 2-way multiplicative interactions among MMR genes and found one significant effect between *MLH1* (rs1799977) and *MSH2* (rs2303428) (*p* for multiplicative interaction = 0.045). The modest decrease in breast cancer risk among minor allele carriers of the *MLH1* (OR=0.81; 95% CI, 0.58–1.14) or *MSH2* (OR=0.94; 95% CI, 0.77–1.14) was antagonistically reversed among women who carried at least one minor allele in both genes (OR=1.25; 95% CI, 0.88–1.76) compared with women who were homozygous dominant for both *MLH1* and *MSH2*, although the effect was not statistically significant.

We found little or no association with breast cancer upon combining genotypes across MMR pathway (data not shown).

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Gene-Environment (GxE) Interactions

The main effects of RPA, NER and BER genes on breast cancer risk have been published previously in the LIBCSP study population, although no study had previously reported DNA repair SNP-RPA interactions. In the LIBCSP, the effect estimate of moderate postmenopausal RPA (<9.24 hrs/wk) was near null (OR=0.99; 95% CI: 0.77–1.26), while high postmenopausal RPA (≥ 9.24 hrs/wk) was associated with reduced risk of postmenopausal breast cancer (OR=0.77; 95% CI: 0.60–0.99) (35). When we restricted these analyses to women with data available for genotyping we found similar, but more pronounced, effects for moderate and high postmenopausal RPA. SNP-specific main effects for the genes of interest showed no significant association with breast cancer risk. These data are summarized in Table 2 to facilitate understanding of SNP-RPA interactions shown in Table 3 and reported below.

Our models did not support the presence of additive interactions between RPA and DNA repair genotypes (data not shown). However, when we considered multiplicative interactions, significant results ($p \leq 0.05$) were observed for lifetime RPA among all women and women carrying variants in *MGMT*, *OGG1*, *XPC*, *XPF*, and *XPG* (supplemental table 1). The interaction between *MLH1* and lifetime RPA was near significant (p=0.051).

Effect estimates were stronger and more consistent once we restricted our models to postmenopausal participants only. As shown in Table 3, we found statistically significant multiplicative interactions between postmenopausal RPA and several DNA repair gene polymorphisms including: *XPC* Ala499Val (rs2228000, p=0.048), *XPF* Arg415Gln (rs1800067, p=0.012), *XPG* Asp1104His (rs17655, p=0.022) and *MLH1* lle219Val (rs1799977, p=0.010). Postmenopausal women homozygous for the major alleles *XPC* Ala499Val or *XPF* Arg415Gln who engaged in greater than 9.23 hrs/wk of RPA from menopause to reference date experienced statistically significant reductions in breast cancer risk (OR=0.54; 95% CI, 0.36–0.81 and OR=0.62; 95% CI, 0.44–0.87, respectively) compared to women homozygous for the major alleles who were inactive (<0.01 hrs/wk). Postmenopausal women with minor alleles in *XPG* Asp1104His and *MLH1* lle219Val and were active during the postmenopausal years also experienced significant breast cancer risk reductions (OR=0.46; 95% CI, 0.29–0.77 and OR=0.46; 95% CI, 0.30–0.71, respectively) compared to inactive women who harbored at least one minor allele.

Discussion

In the current study, we found no association between MMR variants and breast cancer risk. There was evidence of a significant gene-gene interaction on the multiplicative scale for *MLH1* (rs1799977) and *MSH2* (rs2303428); women who harbored minor alleles in both genes were at greater risk of breast cancer than women who carried no minor alleles or minor alleles in only one gene. Given both genes are necessary components for the MMR complex our finding of interaction on the multiplicative scale is biologically plausible (4). When we assessed the combined effects of MMR genes by counting the number of minor alleles, we found no indication of association with breast cancer risk.

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Our study also provides some evidence for modification of DNA repair genotype effect by postmenopausal activity level. Highly active women homozygous for the major allele in *XPC* Ala499Val and *XPF* Arg415Gln or who carried at least one minor allele in *XPG* Asp1104His and *MLH1* lle219Val experienced significant breast cancer risk reductions compared to inactive women with the same genotype. Our findings suggest that the beneficial effects of RPA may be isolated to women who carry a specific genotype.

While there are several studies that assess the association between MMR variants and cancer risk, particularly for colorectal cancer, few investigations have been reported for breast cancer. Previous breast cancer studies (13–17) have reported significant associations with minor alleles in MMR SNPs, which may vary by menopausal status. But results are inconsistent, conducted among different international populations with varying genetic profiles, and based on small, select samples. In our larger population-based study conducted among primarily white women on Long Island, NY, we found little evidence for associations between MMR polymorphisms and breast cancer, even when we considered menopausal status. These findings warrant additional investigation in larger studies with diverse populations as our data were suggestive of differences by HR status.

Although previous studies indicate modest effects of DNA repair variants on breast cancer outcomes, it is possible that associations between some DNA repair variants and cancer risk may be apparent only in the presence of DNA damaging/repairing agents. Several investigations of breast cancer, including our own, have been suggestive of interactions between DNA repair polymorphisms and cigarette smoking, alcohol drinking, radiation exposure, body mass, intake of fruits, vegetables and antioxidant micronutrients (15, 43–44). Data from animal and clinical studies show that DNA repair could be up-regulated with long term exercise, but to our knowledge our report is the first epidemiologic study to consider interactions between PA, DNA repair and breast cancer risk among women.

PA has consistently been shown to increase the formation of reactive oxygen and nitrogen species (50), which may influence carcinogenesis. Regular exercise training can also result in improvement of damage repair systems (19–22). A 2002 study by Radak and colleagues (25) showed that regular exercise decreased the accumulation oxidative stress-induced 8-oxodeoxyguanosine (8-oxo-dG) lesions in the skeletal muscle of exercised rats. These lesions are excised exclusively by 8-oxoguanine DNA glycosylase, the enzyme encoded by *OGG1* (46). Similarly, investigators found that 8-oxo-dG repair, measured by the excision of ^{32}P-labeled damaged oligonucleotide, increased in the muscle of exercising animals as did the chymotrypsin-like activity of the proteasome complex, a repair enzyme important in the degradation of proteins modified by oxidative stress (25). Clinical studies have shown that trained cyclist (27) and marathon runners (26) exhibit up-regulation of DNA excision repair enzymes NESP and RAD23A (27), as well as OGG1 (26).

We hypothesized that up-regulation of DNA repair enzymes might be an important part of the exercise induced adaptation process and that these changes could reduce the likelihood of initiating events in breast carcinogenesis. Our study results lend support to this hypothesis, as we found significant multiplicative interactions between variants in several DNA repair genes and both lifetime and postmenopausal RPA. The observed results show

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that women who engage in high levels of RPA may only experience breast cancer risk reductions if they harbor specific genotypes. While these findings may suggest enhanced risk reduction for RPA in the presence of augmented DNA repair capacity, the functional significance of many DNA repair gene polymorphisms is largely unknown (47, 48). Determining functional status of variants is challenging because of differences in study population characteristics, variations in assay used between studies, and limited ability to detect changes in DNA repair capacity based on single SNP analysis (49). Both replication and additional mechanistic data are necessary to fully understand the PA, DNA repair, breast cancer association.

Our study has several limitations. In the LIBCSP, blood donation varied by both age and race (28). While genotype is likely associated with race, given the small number of non-white women included in the study racial variations in blood donation is likely negligible. Moreover, when we restricted our analyses to White women, we observed little change in effect estimates. While our ability to generalize findings to non-white racial groups is limited, we believe that this study may provide clues about the underlying biologic mechanisms of DNA repair and RPA, which likely do not vary by race. Inaccurate recall of exposure variables may have biased our study results. However, neither cases nor controls were aware of their genotype at the time of the interview. Although exposure information on RPA may be differentially recalled by cases and controls, this misclassification would not likely be differential by genotype. Finally, even with a sample size of 2000+ women, we were limited in our ability to detect modest GxE associations. Our results will therefore need to be confirmed in larger studies with similarly detailed assessment of RPA but expanded genetic data to capture additional variability in the MMR pathway. Multiple comparisons is a consideration in this study, as there were no a priori evidence for the association exists between PA, DNA repair variants and breast cancer. Given we selected genes based on their biologic relevance to breast cancer and PA, we were primarily interested in estimating effect estimates and corresponding 95% confidence intervals without adjusting for multiple comparisons. However, this approach could result in chance findings. Finally, DNA repair represents a single mechanism through which PA may influence breast cancer risk. Other mechanisms (e.g. inflammation and oxidative stress) and their interactions were not considered. The population-based study design, hypothesis-driven DNA repair SNP selection and testing, and detailed exposure assessment, are strengths of this study.

In conclusion, we found little evidence to indicate that any of the six MMR polymorphisms investigated were associated with breast cancer risk. We did find evidence of an interaction between two SNPs in *MLH1* (rs1799977) and *MSH2* (rs2303428) and breast risk. These genes are central to all mismatch recognition and alterations in them have been shown to be the most common mechanism inducing cancer-related MSI (50). They may therefore play an important role in breast carcinogenesis. We previously reported significant inverse associations between RPA performed after menopause and postmenopausal breast cancer risk (35), and, in this report we find that this protection may be partially dependent upon DNA repair status, particularly *XPC* 499 C-allele, *XPF* 415 G-allele, *XPG* 1104 C-allele, and *MLH1* 219 G-allele status. Our findings may provide clues toward understanding the underlying role of DNA repair in the PA-breast cancer association. For example, our results

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may suggest that exercise could result in up-regulation of certain DNA repair enzymes lowering cancer risk. While the functional significance of many DNA repair polymorphisms with respect to breast cancer remains largely unknown, the observed associations are consistent across multiple indicators of physical activity and repair pathways reducing the likelihood that these findings are attributable to chance. However, replication of these findings is necessary to make strong conclusions about the validity and strength of these associations. Our results therefore and merit further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations Used

8-oxo-dG	8-oxodeoxyguanosine
BER	base excision repair
CI	confidence interval
DSB	double strand break
ER	estrogen receptor
FP	fluorescence polarization
HR	hormone receptor
HWE	Hardy Weinberg equilibrium
ICR	interaction contrast ratio
LIBCSP	Long Island Breast Cancer Study Project
LRT	likelihood ratio test
MAF	minor allele frequency
MMR	mismatch repair
NER	nucleotide excision repair
NY	New York
OR	odds ratio
PA	physical activity
PR	progesterone receptor
ROS	reactive oxygen species

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RPA	recreational physical activity
SNP	single nucleotide polymorphism

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Novelty and Impact

This is the first study to assess interaction between physical activity (PA) and DNA repair variants and is based on biologic evidence from animal and clinical literature. We found multiplicative interactions ($p<0.05$) between PA and four variants in DNA repair. Our data suggest that allelic variability in DNA repair may modify associations between PA and breast cancer. These data may help to identify women particularly susceptible to the beneficial effects of PA based on genetics.

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TABLE 1

Age Adjusted Odds Ratios and 95% Confidence Intervals for the Association between Mismatch Repair Genes and Breast Cancer Risk. The Long Island Breast Cancer Study Project (1996–1997).

		Cases (N=1053)		Controls (N=1102)		OR[a]	95% CI[b]
***Gene* (rs)**	**Genotype**	**N**	**%**	**N**	**%**		
MSH3 (rs1650663)	TT	497	49.35%	530	49.58%	1.00	Reference
	CT	412	40.91%	429	40.13%	1.02	(0.85, 1.22)
	CC	98	9.73%	110	10.29%	0.98	(0.72, 1.32)
	CT and CC	510	50.64%	539	50.42%	1.01	(0.85, 1.20)
MLH1 (rs1799977)	AA	503	49.75%	542	50.56%	1.00	Reference
	AG	410	40.55%	443	41.32%	0.98	(0.81, 1.17)
	GG	98	9.69%	87	8.12%	1.17	(0.85, 1.60)
	AG and GG	508	50.24%	530	49.44%	1.01	(0.85, 1.20)
MLH1 (rs2286940)	CC	340	33.83%	342	31.84%	1.00	Reference
	CT	467	46.47%	541	50.37%	0.85	(0.70, 1.04)
	TT	198	19.70%	191	17.87%	1.01	(0.79, 1.30)
	CT and TT	665	66.17%	732	68.24%	0.89	(0.74, 1.08)
MSH2 (rs2303428)	TT	828	83.98%	886	84.14%	1.00	Reference
	CT	150	15.21%	155	14.72%	1.07	(0.83, 1.36)
	CC	8	0.81%	12	1.14%	0.66	(0.27, 1.66)
	CT and CC	158	16.02%	167	15.86%	1.04	(0.81, 1.32)
MSH2 (rs3732182)	GG	542	54.36%	574	53.75%	1.00	Reference
	GT	375	37.61%	411	38.48%	0.98	(0.82, 1.18)
	TT	80	8.02%	83	7.77%	1.04	(0.74, 1.45)
	GT and TT	455	45.63%	494	46.25%	0.99	(0.83, 1.18)
MSH2 (rs4583514)	GG	394	39.01%	404	37.69%	1.00	Reference
	AG	485	48.02%	521	48.60%	0.96	(0.80, 1.16)
	AA	131	12.97%	147	13.71%	0.93	(0.70, 1.23)
	AG and AA	616	60.99%	668	62.31%	0.95	(0.80, 1.14)

[a]Odds Ratio

[b] Confidence Interval

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TABLE 2

Age Adjusted Odds Ratios and 95% Confidence Intervals for the Main Effects of DNA Repair Genes on Postmenopausal Breast Cancer Risk. The Long Island Breast Cancer Study Project (1996–1997).

SNPs for Gene-Environment Interactions	OR[a]	95% CI[b]
Gene Effect (Dominant Models)		
Gene (rs) major/minor alleles		
ERCC1 (rs3212986) C/A[c]	1.16	(0.93, 1.44)
MGMT (rs12917) C/T[d]	1.12	(0.88, 1.43)
MGMT (rs2308321) A/G[d]	0.89	(0.69, 1.15)
MGMT (rs2308327) A/G[d]	0.85	(0.65, 1.11)
OGG1 (rs1052133) C/G[e]	0.95	(0.76, 1.18)
XPA (rs1800975) G/A[c]	1.04	(0.84, 1.29)
XPC (rs2228000) C/T[f]	1.07	(0.86, 1.33)
XPC (rs2228001) A/C[f]	0.99	(0.79, 1.25)
XPD (rs1799793) G/A[c]	1.15	(0.92, 1.43)
XPD (rs13181) A/C[g]	1.16	(0.93, 1.44)
XPF (rs1800067) G/A[c]	1.03	(0.77, 1.40)
XPG (rs17655) G/C[c]	0.98	(0.78, 1.22)
XRCC1 (rs1799782) C/T[h]	1.00	(0.72, 1.38)
XRCC1 (rs25487) G/A[h]	0.99	(0.80, 1.24)
MSH3 (rs1650663) T/C	1.07	(0.86, 1.33)
MLH1 (rs1799977) A/G	1.00	(0.80, 1.24)
MLH1 (rs2286940) C/T	0.83	(0.66, 1.05)
MSH2 (rs2303428) T/C	1.00	(0.73, 1.36)
MSH2 (rs3732182) G/T	1.11	(0.89, 1.38)
MSH2 (rs4583514) A/G	1.00	(0.80, 1.24)

[a] Odds Ratio

[b] Confidence Interval

[c] Crew et al. Cancer Epidemiol Biomarkers Prev. (2007)

[d] Shen et al. Carcinogenesis. (2005)

[e] Rossner et al. Cancer Epidemiol Biomarkers Prev. (2006)

[f] Shen et al. Eur J. Cancer. (2008)

[g] Terry et al. Cancer Epidemiol Biomarkers Prev. (2004)

[h] Shen et al. Cancer Epidemiol Biomarkers Prev. (2005)

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TABLE 3

Age Adjusted Odds Ratios and 95% Confidence Intervals for Multiplicative Effects of DNA Repair SNPs and Recreational Physical Activity on Postmenopausal Breast Cancer Risk. The Long Island Breast Cancer Study Project (1996–1997).

	Homozygous for major allele			At least one copy of minor allele			
Gene (SNP) major/minor alleles Postmenopausal RPA	**Ca[a]/Co[b]**	**OR[c]**	**95% CI[d]**	**Ca/Co**	**OR**	**95% CI**	***p for interaction***
ERCC1 (rs3212986) C/A							
<0.01 hrs/wk	93/84	1.00	reference	82/71	1.00	reference	*0.466*
0.01–9.23 hrs/wk	128/116	0.94	(0.63, 1.40)	104/82	1.16	(0.75, 1.82)	
>9.23 hrs/wk	93/114	0.67	(0.44, 1.01)	92/98	0.78	(0.50, 1.21)	
MGMT (rs12917) C/T							
<0.01 hrs/wk	137/113	1.00	reference	40/40	1.00	reference	*0.129*
0.01–9.23 hrs/wk	163/141	0.94	(0.67, 1.33)	70/59	1.27	(0.70, 2.27)	
>9.23 hrs/wk	128/162	0.62	(0.43, 0.87)	58/50	1.04	(0.57, 1.91)	
MGMT (rs2308321) A/G							
<0.01 hrs/wk	141/125	1.00	reference	36/28	1.00	reference	*0.554*
0.01–9.23 hrs/wk	175/149	1.01	(0.73, 1.41)	58/50	0.89	(0.46, 1.72)	
>9.23 hrs/wk	143/159	0.74	(0.52, 1.03)	43/53	0.56	(0.28, 1.11)	
MGMT (rs2308327) A/G							
<0.01 hrs/wk	149/130	1.00	reference	29/25	1.00	reference	*0.752*
0.01–9.23 hrs/wk	186/156	1.02	(0.74, 1.41)	47/44	1.01	(0.49, 2.09)	
>9.23 hrs/wk	145/163	0.71	(0.51, 1.00)	42/50	0.73	(0.36, 1.50)	
OGG1 (rs1052133) C/G							
<0.01 hrs/wk	113/90	1.00	reference	64/61	1.00	reference	*0.177*
0.01–9.23 hrs/wk	128/122	0.86	(0.58, 1.25)	94/73	1.15	(0.71, 1.87)	
>9.23 hrs/wk	106/118	0.70	(0.48, 1.04)	75/91	0.66	(0.41, 1.08)	
XPA (rs1800975) G/A							
<0.01 hrs/wk	84/73	1.00	reference	93/81	1.00	reference	*0.131*
0.01–9.23 hrs/wk	110/83	1.15	(0.74, 1.78)	121/112	0.95	(0.63, 1.42)	
>9.23 hrs/wk	75/97	0.61	(0.39, 0.96)	112/115	0.77	(0.51, 1.17)	
XPC (rs2228000) C/T							
<0.01 hrs/wk	93/81	1.00	reference	71/67	1.00	reference	*0.048*

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	Homozygous for major allele			At least one copy of minor allele			
Gene (SNP) major/minor alleles Postmenopausal RPA	**Ca[a]/Co[b]**	**OR[c]**	**95% CI[d]**	**Ca/Co**	**OR**	**95% CI**	***p for interaction***
0.01–9.23 hrs/wk	121/112	0.84	(0.57, 1.24)	109/82	1.37	(0.86, 2.17)	
>9.23 hrs/wk	112/115	0.54	(0.36, 0.81)	91/86	1.01	(0.63, 1.61)	
XPC (rs2228001) A/C							
<0.01 hrs/wk	67/44	1.00	reference	110/108	1.00	reference	*0.077*
0.01–9.23 hrs/wk	75/65	0.74	(0.44, 1.25)	156/131	1.17	(0.81, 1.68)	
>9.23 hrs/wk	55/71	0.48	(0.28, 0.82)	131/142	0.83	(0.57, 1.20)	
XPD (rs1799793) G/A							
<0.01 hrs/wk	72/64	1.00	reference	105/90	1.00	reference	*0.066*
0.01–9.23 hrs/wk	92/95	0.83	(0.52, 1.32)	138/101	1.20	(0.82, 1.78)	
>9.23 hrs/wk	85/88	0.80	(0.50, 1.27)	101/125	0.66	(0.44, 0.98)	
XPD (rs13181) A/C							
<0.01 hrs/wk	66/68	1.00	reference	112/85	1.00	reference	*0.173*
0.01–9.23 hrs/wk	87/88	1.00	(0.62, 1.59)	141/108	0.99	(0.68, 1.46)	
>9.23 hrs/wk	75/82	0.86	(0.53, 1.38)	107/130	0.60	(0.40, 0.88)	
XPF (rs1800067) G/A							
<0.01 hrs/wk	150/119	1.00	reference	21/27	1.00	reference	*0.012*
0.01–9.23 hrs/wk	179/168	0.82	(0.59, 1.14)	43/25	2.29	(1.01, 5.17)	
>9.23 hrs/wk	150/175	0.62	(0.44, 0.87)	30/30	1.11	(0.49, 2.54)	
XPG (rs17655) G/C							
<0.01 hrs/wk	88/89	1.00	reference	80/57	1.00	reference	*0.022*
0.01–9.23 hrs/wk	126/111	1.13	(0.75, 1.68)	92/81	0.80	(0.50, 1.28)	
>9.23 hrs/wk	113/107	0.99	(0.66, 1.49)	65/96	0.46	(0.29, 0.75)	
XRCC1 (rs1799782) C/T							
<0.01 hrs/wk	166/135	1.00	reference	12/19	1.00	reference	*0.188*
0.01–9.23 hrs/wk	205/177	0.95	(0.70, 1.30)	28/22	1.69	(0.64, 4.46)	
>9.23 hrs/wk	160/186	0.68	(0.50, 0.94)	26/27	0.84	(0.31, 2.29)	
XRCC1 (rs25487) G/A							
<0.01 hrs/wk	64/65	1.00	reference	114/90	1.00	reference	*0.343*
0.01–9.23 hrs/wk	86/80	1.04	(0.64, 1.68)	147/120	0.97	(0.67, 1.41)	
>9.23 hrs/wk	69/78	0.84	(0.52, 1.38)	118/135	0.64	(0.44, 0.94)	

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	Homozygous for major allele			At least one copy of minor allele			
Gene (SNP) major/minor alleles Postmenopausal RPA	**Ca[a]/Co[b]**	**OR[c]**	**95% CI[d]**	**Ca/Co**	**OR**	**95% CI**	***p for interaction***
MSH3 (rs1650663) T/C							
<0.01 hrs/wk	97/79	1.00	reference	74/70	1.00	reference	*0.127*
0.01–9.23 hrs/wk	103/109	0.81	(0.53, 1.22)	114/83	1.21	(0.77, 1.89)	
>9.23 hrs/wk	83/97	0.66	(0.43, 1.01)	94/113	0.67	(0.43, 1.05)	
MLH1 (rs1799977) A/G							
<0.01 hrs/wk	72/81	1.00	reference	101/70	1.00	reference	*0.010*
0.01–9.23 hrs/wk	107/93	1.27	(0.82, 1.96)	110/99	0.77	(0.51, 1.18)	
>9.23 hrs/wk	93/96	1.06	(0.68, 1.64)	85/114	0.46	(0.30, 0.71)	
MLH1 (rs2286940) C/T							
<0.01 hrs/wk	50/47	1.00	reference	123/104	1.00	reference	*0.085*
0.01–9.23 hrs/wk	76/55	1.40	(0.81, 2.43)	138/139	0.82	(0.57, 1.18)	
>9.23 hrs/wk	62/59	1.00	(0.57, 1.74)	114/150	0.58	(0.40, 0.84)	
MSH2 (rs2303428) T/C							
<0.01 hrs/wk	140/125	1.00	reference	25/20	1.00	reference	*0.476*
0.01–9.23 hrs/wk	174/160	0.99	(0.71, 1.37)	36/31	0.81	(0.35, 1.84)	
>9.23 hrs/wk	152/176	0.73	(0.52, 1.01)	23/31	0.55	(0.22, 1.35)	
MSH2 (rs3732182) G/T							
<0.01 hrs/wk	98/82	1.00	reference	75/69	1.00	reference	*0.329*
0.01–9.23 hrs/wk	108/102	0.86	(0.57, 1.30)	102/90	1.03	(0.66, 1.61)	
>9.23 hrs/wk	95/121	0.57	(0.38, 0.86)	80/88	0.84	(0.53, 1.34)	
MSH2 (rs4583514) A/G							
<0.01 hrs/wk	73/61	1.00	reference	100/90	1.00	reference	*0.964*
0.01–9.23 hrs/wk	81/70	0.90	(0.55, 1.47)	135/124	0.97	(0.66, 1.42)	
>9.23 hrs/wk	71/80	0.65	(0.40, 1.06)	107/129	0.71	(0.48, 1.06)	

[a] Case

[b] Control

[c] Odds Ratio

[d] Confidence Interval

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A priori, criteria for interaction on the multiplicative scale is $p<0.05$