

Short CommunicationGenetic Variants of *GPX1* and *SOD2* and Breast Cancer Risk at the Ontario Site of the Breast Cancer Family Registry

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Abstract

There are several genes that code for enzymes, including various forms of superoxide dismutase and glutathione peroxidase, that protect the cell against oxidative damage that, in turn, can lead to carcinogenesis. There are a few common genetic polymorphisms in these genes that lead to altered proteins. Three that have been identified are *SOD2 Val-9Ala*, *GPX1 Pro198Leu*, and the *GPX1 GCG* repeat (three alleles with four, five, or six repeats). The *SOD2* variant has been associated with increased breast cancer risk in two studies. The *GPX1* variants have not been studied with respect to breast cancer, but *Pro198Leu* has been associated with lung cancer. We conducted a case-control study of these three polymorphisms in incident, invasive breast cancer in Caucasian women under 55. There were 399 cases and 372 controls genotyped, of whom 488 were premenopausal, 208 postmenopausal, and 75 of unknown menopausal status. We were unable to replicate the previously observed association with *SOD2 Val-9Ala* and also found no association between breast cancer and *GPX1 Pro198Leu*. However, the allele of *GPX1* containing four GCG repeats was significantly associated with breast cancer risk in premenopausal women (odds ratio, 1.55; 95% confidence interval, 1.04–2.30 for carriers versus noncarriers). There is a significant trend of increasing risk with increasing number of alleles with four GCG repeats ($P = 0.03$). This variant has not previously been reported to be associated with breast cancer.

Introduction

Oxidative stress from reactive oxygen species, which results in cellular and DNA damage, has been linked to cancer and other

diseases of aging (1–6). The group of enzymes responsible to a large degree for endogenous antioxidant defense in the cell includes superoxide dismutase, catalase, and glutathione peroxidase (GPX).

There is a polymorphism in the *SOD2* gene encoding manganese superoxide dismutase (MnSOD), which may have functional effects. This C to T substitution (at position 2734 of accession no. L34157) results in an amino acid change from valine to alanine at codon –9. This change occurs in the mitochondrial targeting sequence and likely affects transport of MnSOD to the mitochondria (7). The alanine variant has been found more frequently in both pre- and postmenopausal breast cancer patients compared with controls in a study in Caucasian women (266 cases and 295 controls; Ref. 8). This finding was replicated in a Finnish case-control study with 483 cases and 482 controls (9), but was not observed in another study with 261 cases and 370 controls (10).

The isoform of GPX that is found in the mitochondria and that functions in the same pathway as MnSOD is encoded by the *GPX1* gene. In this gene, variation in the number of GCG repeats (four, five, or six; at position 337 of accession no. NM_000581.1) has been identified resulting in a protein with a variable number of alanines (5, 6, or 7 because of a neighboring GCC codon; Refs. 11, 12). A substitution of C to T (at position 911 of accession no. NM_000581.1) in the *GPX1* gene has also been detected, corresponding to an amino acid change from proline to leucine at position 198 (initially incorrectly assigned to position 197; Ref. 13). In the limited number of case-control studies examining *GPX1* polymorphisms and cancer, no relationship was found between the GCG repeat and prostate cancer (267 cases and 260 controls; Ref. 14), but some evidence for an association between *Pro198Leu* genotype and lung cancer in smokers was observed (15).

We conducted a case-control study to consider whether three identified common polymorphisms leading to protein alteration in antioxidant enzymes are associated with breast cancer in Caucasian women under age 55. These variants are *SOD2 Val-9Ala*, *GPX1 Pro198Leu*, and the *GPX1 GCG* repeat polymorphism. These *GPX1* variants have not been previously studied with respect to breast cancer risk

Materials and Methods

A case-control study was conducted making use of the Ontario Familial Breast Cancer Registry (OFBCR) a participating site in the United States NIH Breast Cancer Family Registry. The OFBCR has been described more fully elsewhere (16). Cases of invasive breast cancer, pathologically confirmed, and diagnosed between 1996 and 1998 in the province of Ontario were identified from the Ontario Cancer Registry within ~6 months of diagnosis in most cases. All female cases under 55, a random sample of female cases ages 55–69, and all male cases under age 80 were identified. However, the present study was restricted to women under 55 for two reasons. The number of older women available for inclusion was limited, and it was

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hypothesized that genetic alterations would play a stronger role in younger women. The Ontario Cancer Registry uses a passive, voluntary system of cancer registration, but it is estimated that ~99% of all breast cancer diagnoses in Ontario residents are captured based on a recent field study.⁷ Physicians were contacted to obtain permission to contact patients, and permission was granted for 91% of cases (7668 of 8453). Only 1.7% (140) of the 8453 had died. Patients who could be contacted were then mailed a cancer family history questionnaire and 65% (4957) completed it (5% of the nonresponders had died). All of the respondents (excluding 1.6% who declined further contact or 0.4% who died after responding) who met a defined set of genetic risk criteria, and a random sample of 25% of those not meeting criteria, were selected to continue to participate in the OFBCR ($n = 2580$). This participation included completing a mailed risk factor questionnaire (completed by 72% of all eligible; $n = 1848$) and providing a blood sample (provided by 62% of all eligible; $n = 1601$). Only 3% had died or were otherwise unable to provide a blood sample. For the present study, we restricted the sample to those who self-identified as white only and had provided blood with or without a questionnaire. Also, because of the 25% random sample of those who did not meet genetic risk criteria, we randomly sampled 25% of those who did meet genetic risk criteria to create a more generally representative sample of cases. A total of 459 white cases with blood available were selected. After exclusion of those with insufficient DNA or who could not be genotyped for other reasons, 399 cases were genotyped, 347 of whom also had risk factor questionnaire data available (246 premenopausal, 98 postmenopausal, and 3 unknown). Because there was loss at each stage, we were concerned about potential bias, particularly related to family history. However, response by the participants at all stages was not related to family history of breast and ovarian cancer (16, 17). Race/ethnicity was a factor in response, but in general, Caucasians had higher response rates than non-Caucasians. In preliminary case-control analyses, increased risk has been observed with nulliparity and increased age at first birth as would be expected. Five-year survival after breast cancer diagnosis is high and very few potential participants were lost because of death.

Controls were identified by calling randomly selected residential telephone numbers from across the province of Ontario and were frequency-matched to all female OFBCR cases by 5-year age group. The number of telephone numbers was 14,653, but 1,101 (8%) were invalid and no contact could be made for 841 (6%). Of the 12,711 households contacted, 7,829 (62%) did not have an eligible individual. No information on eligibility was provided for 2,194 (17%) households. Of the 2,688 eligible individuals identified on the telephone, 1,726 (64%) completed the mailed risk factor questionnaire. Six hundred seventy-six women were asked to provide a blood sample; the women were randomly selected from those under 55 who had agreed to be approached about blood sampling (75% agreed), and blood samples were obtained from 419 (62%). Individuals who were not white were excluded from the analysis as were those with insufficient DNA or those subsequently found to be ineligible because of age. This left 372 controls (240 premenopausal, 110 postmenopausal, and 12 unknown) with genotypes available (370 for the *GPXI Pro198Leu* variant).

The *GPXI Pro198Leu* polymorphism was analyzed by

TaqMan 5' nuclease assay. Oligonucleotide primer sequences (accession no. NM_000581.1), *GPX-cd198TM4* (5'-TGTGCCCTACGCAGGTACA-3', position 831–850) and *GPX-cd198TM3* (5'-CCCCGAGACAGCAGCA-3', position 961–977) were taken from Ratnasinghe *et al.* (15). The dual-labeled allele-specific minor groove binder probes, *GPXI-cd198-C* (5'^{6FAM}CACAGCTGGGCCCTT^{MGBNQF}-3', position 905–919), and *GPXI-cd198-T* (5'^{VIC}CACAGCTGAGCCCTTG^{MGBNQF}-3', position 905–920) were designed using PrimerExpress version 2.0 (PE Biosystems). PCR reactions were performed in 96-well plates containing at least four control DNAs for each possible genotype. Genomic DNA (10 ng) was amplified in a total volume of 10 μ l in the presence of 3 mM MgCl₂, 100 μ M each dNTP, 3 pmol of each of the primers, 2 pmol of each dual-labeled probes, and 0.025 unit of Platinum TaqDNA Polymerase (Invitrogen). PCR cycling conditions consisted of 40 cycles of 94°C for 15 s, 69°C for 15 s, and 72°C for 15 s. The reactions were analyzed by ABI PRISM 7900HT Sequence Detection System (version 2.0).

The *GPXI CCG* repeat was analyzed by microsatellite analysis. Oligonucleotide primer sequences (accession no. NM_000581.1), *GPX-AlaI* (5'-AAACTGCCTGTGCCACGTGACC-3', position 205–228) and *GPX-AlaR* (5'-CGAGAGGCATACACCGACTGGGC-3', position 349–372), were taken from Moscow *et al.* (12). Genomic DNA (20 ng) was amplified in a total of 15- μ l reaction volume, in the presence of 500 μ M of MgCl₂, 42 μ M each cold dNTP, 2.5 pmol of each of the primers, 0.2 μ M Ci [α -³³P]dATP, and 0.5 unit of Platinum TaqDNA Polymerase (Invitrogen). PCR cycling conditions consisted of 30 cycles of 94°C for 30 s and 65°C for 60 s. The PCR products from specimens were run on 5% denaturing polyacrylamide (with 5% cross-linker) gels containing 7 M urea, at 75 W for 2–3 h.

The *SOD2 Val-9Ala* polymorphism was analyzed by SSCP analysis. Oligonucleotide primer sequences for (accession no. L34157), *MnSOD-F* (5'-CAGCCAGCCGTGCGTAG-3', position 2644–2661) and *MnSOD-R* (5'-CGCGTGTGCTTGCTGTG-3', position 2838–2855) were designed with Oligo 4.0 software. Genomic DNA (25 ng) was amplified in a total of 25 μ l of reaction volume, in the presence of 1.5 mM of MgCl₂, 15 μ M each cold dNTP, 7.5 pmol of each of the primers, 0.2 μ M Ci [α -³³P]dATP (PE Biosystems), and 0.5 unit of HotStar TaqDNA Polymerase (Qiagen). PCR cycling conditions consisted of an initial 15-min incubation at 95°C for the activation of HotStar enzyme, followed by 2 cycles of 94°C for 30 s, 65°C for 30 s, and 72°C for 30 s, and 2 cycles of 94°C for 30 s, 63°C for 30 s, and 72°C for 30 s, followed by 30 cycles of 94°C for 30 s, and 58°C for 60 s. The PCR products from specimens were analyzed on 1 \times molecular detection enhancement gels (BioWhittaker Molecular Applications) at room temperature, at 600 v for ~16 h. All gels were dried and subject to autoradiography.

A panel of samples, representing different genotypes of each variant, were amplified and subjected to sequencing analysis before the genotyping. The same set of primers used for sequencing were also used for genotyping the specimens. Positive control specimens with known genotypes and expected mobility patterns were included in each experiment for all of the polymorphisms studied. Multiple negative DNA control specimens were also used in each genotyping experiment to eliminate any false-positive results. For validation purposes, 10% of breast cancer cases and population controls were randomly selected and re-genotyped.

We analyzed the genotypes for all individuals combined and for premenopausal women separately. In the subgroup

⁷ Dr. Eric Holowaty, Director of the Ontario Cancer Registry, personal communication.

Table 1 Age, menopausal status, and family history distribution of genotyped cases and controls

	Controls (n = 372)	Cases (n = 399)
Age		
<30	7 (1.9%)	3 (0.8%)
30–34	23 (6.2%)	23 (5.8%)
35–39	40 (10.8%)	41 (10.3%)
40–44	77 (20.7%)	79 (19.8%)
45–49	110 (29.6%)	112 (28.1%)
50–55 ^a	115 (30.9%)	141 (35.3%)
Menopausal Status ^b		
Premenopausal	246 (69.1%)	242 (71.1%)
Postmenopausal	110 (30.9%)	98 (28.8%)
Family History ^c		
Yes	35 (9.4%)	80 (20.1%)
No	337 (90.6%)	319 (79.9%)

^a All are 50–54 except for two individuals age 55 in the control group.

^b Menopausal status was not available for all individuals.

^c Family history was defined as a first-degree relative with breast cancer.

analyses, women who did not complete the risk factor questionnaire or whose menopausal status could not be determined based on their responses were excluded. Menopause was defined as no periods for 1 year or complete oophorectomy. Women who had a hysterectomy without bilateral oophorectomy or who were having periods but who were taking hormone replacement for menopause were considered unknown status. Unconditional logistic regression was used to generate odds ratios (ORs) and 95% confidence intervals by genotype. The trend for an increasing number of a specific allele was tested by coding for the number of alleles carried (0, 1, or 2).

Results

The age distribution of cases and controls, as shown in Table 1, was quite similar as was the proportion who were premenopausal. As the number of postmenopausal women was relatively small leading to uncertain estimates, only results from all women combined (397 cases and 372 controls) as well as those who were known to be premenopausal (246 cases and 240 controls) are presented. Table 1 also shows the proportions of cases and controls with a first-degree relative with breast cancer. Approximately twice as many cases as controls have such a family history as would be expected.

Table 2 shows the results for the *SOD2 Val-9Ala* variant. Unlike two previous studies, we did not see an increased risk for breast cancer associated with the alanine allele. This was true of all women under 55 as well as the premenopausal subgroup. Similarly, no significant association was observed between the *GPXI Pro198Leu* variant and breast cancer (Table 2).

The variable number of GCG repeats in the *GPXI* gene leads to three alleles, 4, 5, or 6 repeats, and six possible genotypes (Table 3). Overall the genotypes including the four allele tended to be associated with estimates of higher risk, but this was not significant. When all carriers of the four alleles were combined and compared with all noncarriers, the confidence interval narrowed, but still included 1.00. However, this association was significant in premenopausal women in whom an OR of 1.55 (95% confidence interval, 1.04–2.03) was observed for carriers of fewer repeats. There was also evidence ($P = 0.03$) for a significant increasing trend with an increasing number of four alleles (0, 1, 2).

Discussion

Cellular defenses against oxidative damage are, like DNA repair, part of the available mechanisms preventing carcinogenesis. Of the genes coding for enzymes involved in this process, there are relatively few polymorphisms causing amino acid changes that have been identified. The *SOD2* gene that codes for MnSOD has received the most attention. Two published studies found a significant association between the A allele (alanine) and breast cancer (8, 9) in Caucasian populations. Although these studies appear to be consistent, there are dif-

Table 2 Odds ratios (ORs) and 95% confidence intervals (CIs) for *SOD2 Val-9Ala* and *GPXI Pro198Leu* in all women (n = 771) and in premenopausal women (n = 488)

Genotype	Controls, n (%)	Cases, n (%)	OR	95% CI
All				
<i>Val/Val</i>	90 (24)	107 (27)	1.00	
<i>Ala/Val</i>	195 (52)	187 (47)	0.81	0.57–1.14
<i>Ala/Ala</i>	87 (23)	105 (26)	1.02	0.68–1.51
<i>Ala/Val</i> or <i>Ala/Ala</i>	282 (76)	292 (73)	0.87	0.63–1.21
Premenopause				
<i>Val/Val</i>	61 (25)	68 (28)	1.00	
<i>Ala/Val</i>	130 (53)	111 (46)	0.77	0.50–1.18
<i>Ala/Ala</i>	55 (22)	63 (26)	1.03	0.62–1.70
<i>Ala/Val</i> or <i>Ala/Ala</i>	185 (75)	174 (72)	0.84	0.56–1.26
All				
<i>Pro/Pro</i>	169 (45)	192 (48)	1.00	
<i>Pro/Leu</i>	164 (44)	171 (43)	0.92	0.68–1.24
<i>Leu/Leu</i>	39 (10)	34 (9)	0.77	0.46–1.27
<i>Pro/Leu</i> or <i>Leu/Leu</i>	203 (55)	205 (52)	0.89	0.67–1.18
Premenopause				
<i>Pro/Pro</i>	121 (49)	121 (50)	1.00	
<i>Pro/Leu</i>	100 (41)	98 (41)	0.98	0.67–1.43
<i>Leu/Leu</i>	25 (10)	21 (9)	0.84	0.45–1.58
<i>Pro/Leu</i> or <i>Leu/Leu</i>	125 (51)	119 (50)	0.95	0.67–1.36

Table 3 Odds ratios (ORs) and 95% confidence intervals (CIs) for the *GPXI* GCG repeat in all women (n = 771) and in premenopausal women (n = 488)

Genotype	Controls, n (%)	Cases, n (%)	OR	95% CI
All				
6/6	21 (6)	19 (5)	1.00	
5/6	60 (16)	58 (15)	1.07	0.52–2.19
5/5	41 (11)	36 (9)	0.97	0.45–2.09
4/6	91 (24)	97 (24)	1.18	0.60–2.33
4/5	102 (27)	114 (29)	1.24	0.63–2.43
4/4	57 (15)	75 (19)	1.45	0.72–2.96
6/6 or 5/6 or 5/5	122 (33)	113 (28)	1.00	
4/6 or 4/5 or 4/4	250 (67)	286 (72)	1.24	0.91–1.68
Premenopause				
6/6	16 (7)	8 (3)	1.00	
5/6	40 (16)	30 (12)	1.50	0.57–3.96
5/5	26 (11)	21 (9)	1.62	0.58–4.50
4/6	63 (26)	62 (26)	1.97	0.79–4.93
4/5	60 (24)	70 (29)	2.33	0.93–5.83
4/4	41 (17)	51 (21)	2.49	0.97–6.39
6/6 or 5/6 or 5/5	82 (33)	59 (24)	1.00	
4/6 or 4/5 or 4/4	164 (67)	183 (76)	1.55	1.04–2.30

ferences in the results. The study by Ambrosone *et al.* (8) found the association was stronger in homozygotes than in heterozygotes and stronger in premenopausal (OR = 3.5) than in postmenopausal (OR = 1.7) women. In contrast, Mitrunen *et al.* (9), found little difference between homozygotes and heterozygotes and a slightly stronger effect in postmenopausal women (OR, 1.2 in premenopause; OR, 1.7 in postmenopause). In fact, the results for postmenopausal women are similar between the two studies, but results for premenopausal women differ. At least one other group has presented results that were negative for an association with this *SOD2* variant (10). If a small association occurs in postmenopausal women, our study would not have been able to identify this because the majority of women in our sample were premenopausal and all were under age 55. As with Mitrunen *et al.*, we did not find an association in this group.

Few studies have considered a relationship between *GPX1* variants and cancer, and none have considered these in breast cancer, although the enzyme plays an important role in the cellular antioxidant defenses. In our preliminary examination, we did not find a relationship between the *GPX1 Pro198Leu* variant and breast cancer. We did, however, observe a significantly increased risk of premenopausal breast cancer associated with the four GCG repeat allele compared with five or six repeats. The results were no longer significant when postmenopausal women were included. A test for trend associated with the increasing number of alleles with four repeats (2 or 1 *versus* 0) was also significant in premenopausal women ($P = 0.03$). As in Moscow *et al.* (12), we found that five GCG repeats always occurred with proline, forming a consistent haplotype, but this was not associated with altered breast cancer risk. Leucine occurred with both four and six GCG repeats, but only the instance of four repeats was associated with increased risk. Although located in the coding region, alanine repeats are not found in a known functional motif of the GPX protein sequence. However, different lengths of alanine repeats may potentially affect the folding or stability of this protein or its interaction with other proteins.

Although we restricted the sample to Caucasians, the possibility of persistent confounding (population stratification) cannot be entirely ruled out. However, it has been shown to be unlikely in North American Caucasians (18). Of greater concern is whether the loss of participants at various stages of the data and sample collection resulted in a biased sample. For the OR estimates to be biased, participation would have to be associated with the genotypes of interest. If the participation bias was nondifferential between cases and controls, this would likely lead to an underestimate of effect. Although this is possible, there is no obvious reason why response should be related to either of these genotypes in either cases or controls unless this variant contributed to a family history of cancer, which, in turn, was related to participation. In general, we have not found that family history was associated with response at any stage of data and sample collection in cases (16, 17). More complex scenarios are possible, including a relationship between response and an important, but unknown, interacting factor. Survival bias is not a major concern because very few eligible individuals died at each stage of the initial data and sample collection in the OFBCR.

In this particular sample, the number of postmenopausal women was too small and too selected to draw general conclusions. An association in premenopausal women is consistent with the concept that genetics will play a greater role in earlier-

onset disease. However, given the potential for bias in any single study, we consider the *GPX1* GCG repeat result to be preliminary and requiring replication.

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