Manganese Superoxide Dismutase (MnSOD) Genetic Polymorphisms, Dietary Antioxidants, and Risk of Breast Cancer

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ABSTRACT

Oxidative stress, resulting from the imbalance between prooxidant and antioxidant states, damages DNA, proteins, cell membranes, and mitochondria and seems to play a role in human breast carcinogenesis. Dietary sources of antioxidants (chemical) and endogenous antioxidants (enzymatic), including the polymorphic manganese superoxide dismutase (MnSOD), can act to reduce the load of oxidative stress. We hypothesized that the valine-to-alanine substitution that seems to alter transport of the enzyme into the mitochondrion, changing its efficacy in fighting oxidative stress, was associated with breast cancer risk and that a diet rich in sources of antioxidants could ameliorate the effects on risk. Data were collected in a case-control study of diet and breast cancer in western New York from 1986 to 1991. Caucasian women with incident, primary, histologically confirmed breast cancer were frequency-matched on age and county of residence to community controls. Blood specimens were collected and processed from a subset of participants in the study (266 cases and 295 controls). Using a RFLP that distinguishes a valine (V) to alanine (A) change in the −9 position in the signal sequence of the protein for MnSOD, we characterized MnSOD genotypes in relation to breast cancer risk. We also evaluated the effect of the polymorphism on risk among low and high consumers of fruits and vegetables. Premenopausal women who were homozygous for the A allele had a 4-fold increase in breast cancer risk in comparison to those with 1 or 2 V alleles (odds ratio, 4.3; 95% confidence interval, 1.7–10.8). Risk was most pronounced among women below the median consumption of fruits and vegetables and of dietary ascorbic acid and α-tocopherol, with little increased risk for those with diets rich in these foods. Relationships were weaker among postmenopausal women, although the MnSOD AA genotype was associated with an almost 2-fold increase in risk (odds ratio, 1.8; confidence interval, 0.9–3.6). No appreciable modification of risk by diet was detected for these older women. These data support the hypothesis that MnSOD and oxidative stress play a significant role in breast cancer risk, particularly in premenopausal women. The finding that risk was greatest among women who consumed lower amounts of dietary antioxidants and was minimal among high consumers indicates that a diet rich in sources of antioxidants may minimize the deleterious effects of the MnSOD polymorphism, thereby supporting public health recommendations for the consumption of diets rich in fruits and vegetables as a preventive measure against cancer.

INTRODUCTION

The preponderance of data from epidemiological studies indicates that, aside from a family history of breast cancer, most breast cancer risk factors are related to reproductive characteristics and hormonal factors including high body mass index in postmenopausal women (1).

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3 The abbreviations used are: ROS, reactive oxygen species; SOD, superoxide dismutase; MnSOD, manganese SOD; OR, odds ratio; CI, confidence interval.

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3. The preponderance of data from epidemiological studies indicates that, aside from a family history of breast cancer, most breast cancer risk factors are related to reproductive characteristics and hormonal factors including high body mass index in postmenopausal women (1).

2. The role of the consumption of alcoholic beverages and sources of dietary fat in breast carcinogenesis has also been considered, although there is controversy in the field regarding these factors (3–6). There also are relatively consistent data to support an association between fruit and vegetable intake and risk, as well as inverse associations with increased consumption of dietary sources of antioxidants including ascorbic acid, α-tocopherol, and carotenoids (7, 8). The mechanistic relationship of these putative risk factors, however, has not been elucidated. One hypothesis is that they affect oxidative stress and the production of ROS by altering the balance between prooxidant cellular activity and antioxidant defenses. These ROS are produced by normal cellular respiration and as a result of inflammation and cellular stress (9).

When ROS are produced as a consequence of normal metabolism and in an environment in which there is sufficient antioxidant power and repair capacity, there are presumably few deleterious effects. However, when there is excessive production of ROS because of exposure to toxic agents or to pathological processes, or when there are insufficient in vivo defense mechanisms, oxidative stress may occur. This results in damage to DNA including breakage, as well as lipid peroxidation, protein modification, membrane disruption, and mitochondrial damage (10–14). ROS also may be generated through the metabolism of estradiol and a variety of xenobiotics, in which superoxide anions are produced via redox cycling of quinones and semiquinones, and other intermediates (15). Catechol estrogens and nitric oxide, which produces ROS, synergistically increase DNA damage (16). Finally, ROS may result from peroxidation of polyunsaturated fatty acids (17).

Together, these data indicate that oxidative stress may be related to human breast etiologies. Oxidative stress has been shown to result in tumor formation in laboratory animal models, and there is other support for a role in human breast tumorigenesis (10, 18–22). Recently, it was found that BRCA1 in embryonic mouse stem cells is required for the transcription-coupled repair of oxidative damage (23). Oxidative damage has been reported to be higher in women with breast cancer compared with controls, although studies to date remain small (24, 25), and these levels vary with the consumption of meats, vegetables, and fruits (26).

Endogenous defenses against ROS include glutathione peroxidase, catalase, and SOD (9). There are three known forms of SOD: (a) the cytosolic copper/zinc SOD; (b) the extracellular copper/zinc SOD; and (c) the mitochondrial MnSOD. MnSOD is synthesized in the cytosol and posttranscriptionally modified for transport into the mitochondrion (27, 28). In the mitochondrion, it catalyzes the dismutation of two superoxide radicals, producing H2O2 and oxygen. MnSOD is induced with free radical challenge (29) and cigarette smoke (30).

Recently, two genetic variants of MnSOD were identified (28). A structural mutation, a T to C substitution in the mitochondrial targeting sequence, was found that changes the amino acid codon at −9 position in the signal peptide from valine (GTG) to alanine (GCT).
Using a Chou Fasman analysis, Shimodo-Matsubayashi (28) predicted that the resulting amino acid change would alter the secondary structure of the protein from an α-helical structure to a β-sheet conformation. Rosenblum et al. (31) suggest that the alteration may affect the cellular allocation of the enzyme and mitochondrial transport of MnSOD into the mitochondrion, where it would be biologically available. They further suggest that inefficient targeting of MnSOD could leave mitochondria without their full defense against superoxide radicals, which could lead to protein oxidation as well as mitochondrial DNA mutations. It is becoming increasingly clear that the mitochondrion plays a crucial role in controlling cell life and death. Apoptosis may be driven in the mitochondria by several mechanisms including disruption of electron transport, activation of caspase family proteases, and alteration of cellular reduction-oxidation potential (32). It has been reported that the depletion of mitochondrial DNA can affect the tumorigenic phenotype of cultured breast tumor cells (33). Perhaps even more importantly, overexpression of MnSOD: (a) decreases the malignant phenotypes of various types of cancer including breast cancer (34, 35); (b) decreases the resistance for cytotoxicity from tumor necrosis factor α in breast cancer (36, 37); (c) increases apoptosis (38); and (d) improves apoptosis after hydrogen peroxide challenge (38). Induction of MnSOD also increases catalase (39). It is also possible that mitochondrial MnSOD could impact on oxidative damage in nuclear DNA, which would be one plausible mechanism for increased risk from a genetic polymorphism in MnSOD, although the effects on the mitochondrion alone could be sufficient for its impact on carcinogenesis. Thus, there are a number of ways that affecting the cellular distribution of MnSOD might affect breast cancer risk.

To date, the frequency of this polymorphism has not been reported in Caucasians, but the frequency of the alanine and valine alleles in Japanese is 12 and 88%, respectively (28). This is the only study to date that has investigated a disease outcome related to this MnSOD polymorphism. In a study of 83 patients with Parkinson’s disease and 140 controls, cases were more likely to have the alanine variant (28).

The investigators hypothesized that Parkinson’s disease may be related to mitochondrial stress.

Because ROS, including those generated by xenobiotics, estrogens, polyunsaturated fatty acids, ethanol, and caloric metabolism, may be involved in breast carcinogenesis, and because MnSOD is a major scavenger of ROS, we hypothesized that the MnSOD A allele could be related to breast cancer risk by having an altered capacity to reduce oxidative stress. We previously reported (40, 41) a 2-fold decrease in risk with higher consumption of fruits and vegetables, as well as with specific sources of the antioxidants ascorbic acid, carotenoids, and α-tocopherol. Thus, we were also interested in evaluating the role of the MnSOD polymorphism in environments both rich and poor in antioxidant defenses.

**MATERIALS AND METHODS**

**Study Population.** These analyses are based on a subset from a study of diet and breast cancer in western New York that has been described in depth elsewhere (40–42). From 1986 to 1991, women with primary, incident, histologically confirmed breast cancer were identified from all of the major hospitals in Erie and Niagara counties. They were frequency-matched by age and county of residence to community controls who were identified from lists of the Department of Motor Vehicles (<= age 65) and the Health Care Finance Administration (> age 65). The protocol for the study was reviewed by the institutional review boards of the State University of New York at Buffalo and of all of the participating hospitals. Informed consent was received from all participants for interview and medical record review. The personal interview included a detailed, validated food frequency questionnaire, with information gathered on portion size and frequency of consumption for 72 foods 2 years before the interview. Grams of total fruit and vegetable intake were calculated and units of ascorbic acid, α-tocopherol, and carotenoids computed using nutrient composition data from United States Department Agriculture data tapes and published food composition data. At the time of the interview, women were asked to provide a blood specimen: approximately 45% of premenopausal and 63% of postmenopausal women consented to phlebotomy.

**Laboratory Analysis.** Genomic DNA (50 ng) was extracted from blood clots (42) and amplified using 40 pmol of primers (5′-ACCGAGCGACG-GGCCGCGC-3′ and 5′-GGGTGTAGTGTGAGGTTCCAG-3′) in reaction buffer [10 mM Tris-HCl buffer (pH 8.3), 50 mM KCl, and 1.0 mM MgCl2], and AmpliTaq DNA polymerase (1.25 units; Perkin-Elmer, Norwalk, CT) with 2′′-deoxynucleoside-3′-triphosphates (1.87 mM; Pharmacia, Piscataway, NJ) in a 50.1 reaction volume. A mutation was introduced by a primer mismatch to create a restriction cut site for Cac81 in the –9Ala codon. The alanine/valine polymorphism occurs at amino acid 16, which is toward the COOH terminus of the 24-residue mitochondrial signal sequence, at nt 47, counting from the adenosine of the initiation methionine codon (31). The PCR reaction had an initial melting temperature of 95°C (5 min) followed by 35 cycles of melting (95°C; 1 min), annealing (61°C; 1 min), and extension (72°C; 2 min). An extension period of 7 min at 72E C followed the final cycle. PCR product (10 μl) was digested with Cac81 (3 units; 37°C, 16 h; New England Biolabs, Beverly, MA). Digested products (87 or 93 bp) were visualized on a 4% metaphor gel (FMC Bioproducts, Rockland, ME) stained with ethidium bromide. Assay results were interpreted by two independent investigators (E. B., P. G. S.) who were blinded to case-control status; 20% of the samples were repeated for quality control to ensure that no coding errors occurred. The assay was validated by confirming polymorphic Mendelian inheritance patterns in seven human family cell lines (n = 134), encompassing three generations each (data not shown; National Institute of General Medical Sciences, Human Genetic Mutant Cell Repository, Coriell Institute, Camden, NJ). In addition, PCR product from a –9Ala and a –9Val sample underwent direct fluorescence sequencing.

**Statistical Analysis.** χ2 analyses were used to determine the differences in distribution of the MnSOD genotype between cases and controls. ORs and 95% CIs were calculated using unconditional logistic regression to evaluate associations between MnSOD genotypes and breast cancer risk separately for premenopausal and postmenopausal women. Two models were used; one was adjusted for age and education only, and another model also included: (a) age at menarche; (b) age at first pregnancy; (c) reported family history of breast cancer; (d) body mass index; (e) total caloric intake; and (f) age at menopause for postmenopausal women. For these analyses, consumption of total fruit and vegetables and dietary antioxidants, not including supplements, was divided at the median to categorize women into high and low consumption of each factor. Separate analyses were performed to evaluate effects of the MnSOD genotype on risk within users and nonusers of supplemental antioxidants (vitamins C and E). MnSOD genotypes were collapsed into a dichotomous variable to prevent extremely small cells in stratified analyses. There was little effect on risk with one A allele; thus, women who were homozygous for the V allele were grouped with heterozygotes as the referent category. The effect of the MnSOD A/A vs A/A polymorphism was then evaluated within groups of women with high and low
consumption of dietary sources of specific antioxidants and vitamin supplements as well as total fruits and vegetables.

RESULTS

Fig. 1 shows results for selected genotyping assays. Genotype data for MnSOD were available for 266 women with breast cancer and 295 community controls. For the most part, associations between putative risk factors for breast cancer (i.e., those for which logistic models were initially adjusted) were similar within the larger data set and the subset for which MnSOD data were available. Values for cases and controls within each group, by menopausal status are, shown in Table 1. MnSOD allele frequencies among cases and controls are shown in Table 2. Among controls, the A allele was present in 50% of the chromosomes evaluated, but the frequency of the A allele was higher in both pre- and postmenopausal women with breast cancer. The relationship between the MnSOD polymorphism and breast cancer risk among premenopausal and postmenopausal women is shown in Table 3. Among premenopausal women, those with at least one A allele had a higher increased risk of breast cancer in comparison to women homozygous for the V alleles. Premenopausal women who were homozygous for the A allele, however, had a 4-fold increase in risk (adjusted OR, 4.3; 95% CI, 1.7–10.8) in comparison with those with V alleles.

The association between MnSOD genotype and breast cancer risk was weaker among postmenopausal women (Table 3). There was little to no increase in risk with one A allele, but those who were homozygous for the A allele had an almost 2-fold increase in risk, although the CI included unity (OR, 1.8; 95% CI, 0.9–3.6). When genotypes were dichotomized (MnSOD Val/Val and MnSOD Val/Ala combined as referent), both pre- and postmenopausal women who were homozygous for the alanine allele were at significantly increased risk of breast cancer, although, again, risk was greatest for premenopausal women.

When women were dichotomized at the median into lower and higher consumers of fruits and vegetables and sources of dietary antioxidants, we observed that the deleterious effect of the MnSOD A polymorphism was most pronounced among premenopausal women who consumed lower amounts of total fruits and vegetables (OR, 6.0; CI, 2.0–18.2; Table 4). The effect was weaker, although still elevated, among premenopausal women who had diets rich in fruits and vegetables (OR, 3.2; CI, 1.2–8.2). Similar trends were noted for sources of ascorbic acid and α-tocopherol, with the MnSOD polymorphism conferring increased risk primarily among women with diets poorer in these antioxidants. However, for the carotenoids, the MnSOD polymorphism increased risk regardless of dietary intake. Among postmenopausal women, few clear differences were observed between low and high consumers of diets rich in antioxidants, except that, among women with diets poor in sources of α-tocopherol, the MnSOD polymorphism conferred a more than 2-fold risk of breast cancer with no association observed among those with higher intake of sources of α-tocopherol.

Similar associations were noted among users of vitamin supplements. Risk associated with the MnSOD AA genotype was observed only among premenopausal women who did not take supplements of vitamin C (OR, 4.8; 95% CI, 2.1–11.0) and α-tocopherol (OR, 3.8; 95% CI, 1.8–8.2). For those taking these supplements, the MnSOD AA genotype did not confer increased risk.

DISCUSSION

In these data, we observed an association between the MnSOD genetic polymorphism and breast cancer risk. The effect was strongest among premenopausal women, particularly those who were homozygous for the A allele. Furthermore, it appeared that risk associated with this MnSOD polymorphism was greatest among premenopausal women who consumed low amounts of fruits and vegetables and other sources of dietary antioxidants. Although the mechanisms are not clearly elucidated, these data indicate that ROS may be important in breast carcinogenesis, and that MnSOD activity or distribution may play a key role in the prevention of human breast cancer.

There is support in the literature for an association between oxidative stress and breast cancer risk. DNA damage and strand breaks are clearly linked to oxidative stress (18), and recent work by Wang et al. (21) identified DNA-malondialdehyde adducts, markers of oxidative stress due to lipid peroxidation, in human breast tissue. Higher levels of malondialdehyde have also been noted in the urine of women with mammographic breast dysplasia (20). Supported by indications that most breast cancer risk factors may be related to oxidative damage and that risk is reduced by the consumption of fruits and vegetables,
it is plausible that SOD, the major enzyme involved in preventing oxidative stress in the mitochondrion, would also be associated with breast cancer risk. The fact that risk associated with the MnSOD polymorphism was greatest among premenopausal women who consumed low amounts of fruits and vegetables and specific sources of dietary antioxidants is consistent with their functions and that of SOD (43). One could assume that disruption of the cellular distribution of MnSOD would have the most deleterious effects in an environment that was also low in other antioxidants.

It is unclear why effects should be strongest among premenopausal women. It may be possible that oxidative stress plays a larger role in breast carcinogenesis among these younger women, and that risk factors among postmenopausal women are less impacted by antioxidant processes. It is interesting to note that BRCA1 is required for transcription-coupled repair of oxidative DNA damage (23). This form of breast cancer is most often seen in younger women, and the fact that the effects of the MnSOD polymorphism were greatest among premenopausal women may be driven, to some degree, by less efficient DNA repair. Although we do not have information on the frequency of BRCA1 mutations among participants in this study, we did evaluate relationships with family history of breast cancer. Among postmenopausal women, associations between breast cancer and MnSOD did not differ by family history. However, among premenopausal women, associations between breast cancer and MnSOD did not differ by family history. Among postmenopausal women, associations between breast cancer and MnSOD did not differ by family history. Among postmenopausal women, associations between breast cancer and MnSOD did not differ by family history. Among postmenopausal women, associations between breast cancer and MnSOD did not differ by family history. Among postmenopausal women, associations between breast cancer and MnSOD did not differ by family history. Among postmenopausal women, associations between breast cancer and MnSOD did not differ by family history.

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<tr>
<th>Table 3</th>
<th>Risk of breast cancer associated with genetic polymorphisms in MnSOD</th>
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<tr>
<td></td>
<td>Case, n (%)</td>
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<tr>
<td>Premenopausal</td>
<td>MnSOD Val/Val</td>
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<td>MnSOD Val/Ala</td>
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<td>MnSOD Ala/Val</td>
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<td>MnSOD Val/Val and MnSOD Val/Ala</td>
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<td></td>
<td>MnSOD Ala/Ala</td>
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<tr>
<td>Postmenopausal</td>
<td>MnSOD Val/Val</td>
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<td>MnSOD Val/Ala</td>
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<td>MnSOD Val/Val and MnSOD Val/Ala</td>
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<td>MnSOD Ala/Ala</td>
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* ORs and 95% CIs calculated by unconditional logistic regression, adjusted for age and education.

* ORs and 95% CIs calculated by unconditional logistic regression, adjusted for age, education, age at menarche, age at first pregnancy, body mass index, family history of breast cancer, total caloric intake, and age at menopause for postmenopausal women.

** Table 4 | Risk associated with the MnSOD polymorphisms among premenopausal and postmenopausal women consuming low and high diets rich in antioxidants |
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<td>Low consumptiona</td>
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<td>ca/cob</td>
<td>ca/cob</td>
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<tr>
<td>Premenopausal</td>
<td>Total fruit and vegetables</td>
<td>32/40</td>
<td>37/47</td>
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<td></td>
<td>MnSOD Val/Val and MnSOD Val/Ala</td>
<td>24/16</td>
<td>21/17</td>
<td>3.2 (1.2–8.2)</td>
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<td></td>
<td>Carotenoids</td>
<td>38/43</td>
<td>31/44</td>
<td>1.0</td>
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<td>MnSOD Val/Val and MnSOD Val/Ala</td>
<td>27/12</td>
<td>18/11</td>
<td>3.6 (1.3–10.5)</td>
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<td>MnSOD Val/Val and MnSOD Val/Ala</td>
<td>27/38</td>
<td>42/49</td>
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<td></td>
<td>Ascorbic acid</td>
<td>26/15</td>
<td>19/16</td>
<td>2.2 (0.9–5.6)</td>
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<td>MnSOD Val/Val and MnSOD Val/Ala</td>
<td>32/37</td>
<td>37/50</td>
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<td></td>
<td>MnSOD Ala/Ala</td>
<td>25/12</td>
<td>20/14</td>
<td>2.3 (0.9–5.8)</td>
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<tr>
<td>Postmenopausal</td>
<td>Total fruit and vegetables</td>
<td>57/74</td>
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<td>MnSOD Val/Val and MnSOD Val/Ala</td>
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<td>1.8 (0.9–3.6)</td>
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<td></td>
<td>Carotenoids</td>
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<td>22/17</td>
<td>23/23</td>
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<td></td>
<td>Ascorbic acid</td>
<td>60/72</td>
<td>47/73</td>
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<td>MnSOD Val/Val and MnSOD Val/Ala</td>
<td>17/20</td>
<td>20/20</td>
<td>2.0 (1.0–4.1)</td>
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<td></td>
<td>α-tocopherol</td>
<td>56/74</td>
<td>51/71</td>
<td>1.0</td>
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<td></td>
<td>MnSOD Val/Val and MnSOD Val/Ala</td>
<td>13/16</td>
<td>22/24</td>
<td>1.1 (0.5–2.3)</td>
</tr>
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a Low and high consumption per day based on median values for sample pre- and postmenopausal, respectively; total fruit and vegetables, 764 and 797 gm; carotenoids, 294 and 290 g; ascorbic acid, 155 and 161 mg; α-tocopherol 7.5 and 7.5 mg.
b Number of cases (ca) and controls (co).

c ORs and 95% CIs calculated by unconditional logistic regression, adjusted for age and education, age at menarche, age at first pregnancy, body mass index, family history of breast cancer, total caloric intake, and age at menopause for postmenopausal women.
To our knowledge, this is the first study to evaluate the prevalence of the MnSOD polymorphism in a Caucasian population or to examine the association between the polymorphism and risk of cancer. The MnSOD genetic polymorphism was only recently identified, and, clearly, there is a need for biochemical studies to evaluate the effects of the polymorphism on the activity and distribution of SOD in the mitochondrion, possible effects on the cell, and sensitivity to damage by ROS. Although genotype is unalterable, it is encouraging to note that the effects of the MnSOD polymorphism were noted primarily among women who consumed low amounts of fruits and vegetables and other sources of dietary antioxidants and that risk was reduced with increased consumption. If these findings are corroborated, they will not only further elucidate breast cancer etiology but also reinforce public health recommendations for consumption of diets rich in fruits, vegetables, and other sources of antioxidants as a measure of cancer prevention.

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