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Review Article

Oxidants and Antioxidants in Breast Cancer

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ABSTRACT

Although a number of risk factors have been identified for breast cancer, mechanisms by which they increase risk of the disease are not clear. Breast cancer etiology could, in part, be related to oxidative stress. Recognized risk factors for breast cancer include a family history of the disease. BRCA1 is needed for post-transcriptional repair of oxidative damage, indicating that oxidative stress may be an important risk factor for women with a family history of the disease. Reproductive and hormonal factors that result in greater exposure to circulating estrogens also increase risk, and steroid hormones are metabolized to reactive quinones and hydroquinones, which can directly damage DNA. Alcohol consumption is associated with increased risk, and the metabolism of alcohol results in production of DNA-damaging reactive oxygen species (ROS). Finally, the inverse relationship noted with consumption of fruits and vegetables could be related to their being a source of antioxidant vitamins. Endogenous factors may play an equally important role in the effects of oxidative stress on breast carcinogenesis. Genetic variability in enzymes that result in increased production of ROS and those that protect the cell from oxidative stress could also have an impact for risk of the disease. In this review, a rationale is given for linking breast cancer risk factors to oxidative stress. The possible role of genetic polymorphisms in a number of enzymes that may be important in affecting levels of ROS to which the cell is exposed, as well as those that protect the cell from oxidative stress, is discussed. Antiox. Redox Signal. 2, 903–917.

EPIDEMIOLOGY OF BREAST CANCER

DESPITE FOCUSED EFFORTS over the last few decades to understand further the causes of breast cancer, little new information has been gained regarding breast cancer etiology. Risk factors that are 'known' explain approximately 40% of the variability in incidence (Madigan *et al.*, 1995); the remaining risks for breast cancer remain unknown. The traditional risk factors, excepting presence of breast cancer in a first-degree relative, are primarily related to hormonal and reproductive events (Kelsey and Bernstein, 1996). Characteristics or behaviors that result in prolonged exposure to circulating estrogens, such as early age at menarche, no or few children, late first full-term pregnancy, and late age at menopause, are all associated with increased breast cancer risk. Higher body mass index also increases risk for postmenopausal women. It is thought that the mechanism responsible for this association is the production of estrogens in peripheral adipose tissue. Regarding dietary factors, the presumed relationship between dietary fat and breast cancer risk has not been supported in epidemiologic studies (Hunter *et al.*, 1996), although there is strong support from ecologic and laboratory studies for this hypothesis. There is consistent evidence indicating that alcohol consumption, even moderate use, increases risk of breast cancer (Schatzkin and Longnecker, 1994). Finally, there are somewhat consistent data that consumption of fruits and

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vegetables will decrease risk, as well as specific dietary sources of antioxidants such as ascorbic acid, α-tocopherol, and carotenoids (Steinmetz and Potter, 1996).

There are primarily two paradigms proposed to link the above risk factors to breast carcinogenesis. The historically older model, which has predominated until recently, is that of two-stage carcinogenesis. Based on rodent experiments, this is a model of initiation and promotion: cells that develop mutations through DNA damage replicate and immortalize that damage. In the case of breast cancer, replication would be driven by the mitotic stimulation of circulating steroid hormones. Although we now know that there are likely multiple 'hits' that damage DNA, and multiple genetic events occurring over a number of years, this model of DNA damage and cell replication is still plausible. There are a number of factors that could initiate DNA damage, including spontaneous errors in replication, chemical carcinogens, and reactive oxygen species (ROS) that could be generated through a number of processes. The role of estrogen as a mitogen in breast carcinogenesis is clearly established, and could be sufficient and necessary breast carcinogens through this function alone.

The second paradigm of carcinogenesis in hormonally responsive tissue is that of steroid hormones as complete carcinogens, which is related to endogenously produced estrogen metabolites as well as the mitotic role of estrogens. Biosynthesis and metabolism of estrogens is mediated by a number of enzymes, many which are polymorphic. Some estrogen metabolites, namely the 4-hydroxy catechol estrogen, have been shown to bind to DNA and cause mutations (Cavalieri *et al.*, 1997; Liehr, 1997). In this scenario, estrogens would act as both the DNA damaging agent and the mitotic stimulator. The catechol estrogens also result in formation of hydroxy radicals through redox cycling. Thus, in both paradigms of carcinogenesis, ROS may play a major role.

OXIDATIVE STRESS AND BREAST CANCER

The term "oxidative stress" is generally used to refer to the total burden of potentially harmful reactive biochemical species that are present in tissue as a consequence of the routine cellular oxidative metabolism of both endogenous and exogenous compounds (Nathan and Chaudhuri, 1998). ROS, including the superoxide radical, hydrogen peroxide (H_2O_2), and the hydroxyl radical, are continuously produced within the cell as a result of the mitochondrial electron transfer processes (Loft and Poulsen, 1996). ROS can be formed as a result of metabolism of xenobiotics by cytochrome p450 enzymes, or exposure to other environmental factors (Hayes and McLellan, 1999b), and ROS and compounds generating ROS are ubiquitous in the environment and present in inhaled smoke, polluted, air and ingested goods (Frei *et al.*, 1991; Nagashima *et al.*, 1995).

When ROS are produced as a consequence of normal metabolism and in an environment where there is sufficient antioxidant power and repair capacity, there are presumably few deleterious effects. However, when there is excessive production of ROS due to exposure to toxic agents or to pathologic processes, or 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 (Halliwell and Gutteridge, 1989; Schwartz *et al.*, 1993; Cerutti, 1994; Emerit, 1994; Esterbauer and Jurgens, 1993).

Damage to DNA includes a number of oxidized purines and pyrimidines, as well as strand breaks (reviewed by Loft and Poulsen, 1996). The hydroxyl radical induces DNA modifications that include single-base deletions, base ring opening (primarily adenine and guanine), single- and double-strand breakage, and adduction of bases to form chiefly 5-OH-cytosine, 8-OH-guanine, and 8-OH-adenine (Malins, 1993; Wagner *et al.*, 1992). The most damaging ROS, the hydroxyl radical, can cause almost any DNA modification, including 8-oxodG. 8-Oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG), which is an indicator of oxidative DNA modifications that can be mutagenic (Ribeiro *et al.*, 1994; Toyokuni *et al.*, 1994), is often used in etiologic and intervention studies as a biomarker of oxidative stress, and is markedly elevated in some studies of breast cancer (Malins and Haimanot, 1991; Malins *et*

al., 1993, 1996). It has also been linked to G::C to T::A transversion mutations (Ribeiro *et al.*, 1994; Toyokuni *et al.*, 1994), and transversion mutations of p53 have been observed in human breast cancers (Callahan *et al.*, 1992). In fact, Cerutti's group has shown mutagenesis in p53 directly by oxy-radicals (Hussain *et al.*, 2000).

Studies of breast cancer have found that DNA from invasive ductal carcinomas contains extensive modifications linked to oxidative stress. These include hydroxyl radical adducts of adenine, guanine, and cytosine, as well as single- and double-strand breaks (Malins and Haimanot, 1991; Malins *et al.*, 1993, 1996). Wang *et al.* (1996) 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 urine of women with mammographic breast dysplasia (Boyd and McGuire, 1991). Damage resulting from hydroxyl radicals has also been directly linked to the progression of human breast cancer (Malins *et al.*, 1996). Oxidative damage has been reported to be higher in women with breast cancer, compared to controls, although studies to date remain small (Djuric *et al.*, 1996; Musarrat *et al.*, 1996), and these levels vary with the consumption of meats, vegetables, and fruits (Djuric *et al.*, 1998).

LINKAGE OF BREAST CANCER RISK FACTORS TO OXIDATIVE STRESS

Family history of breast cancer

Perhaps the most consistent risk factor for breast cancer is diagnosis of the disease in a first-degree relative. A positive family history of breast cancer may or may not imply genetic susceptibility, however. It may also be due to similar environments or lifestyle habits or other less penetrant, but more prevalent, inherited factors. Among women with a family history of breast cancer, a proportion of them carry mutant alleles in *BRCA1* or *BRCA2*, which confer a high lifetime risk of breast cancer. Only a small proportion of the population of women with breast cancer carry *BRCA* mutations (<3%), but the two genes are believed to be responsible for most truly hereditary breast cancers, particularly early-onset breast cancer. Although this mutation is present in families with hereditary breast cancer, it was also found in 10% of a population-based cohort of women diagnosed with breast cancer before the age of 35 (Langston *et al.*, 1996). Recently, it was found that *BRCA1* in embryonic mouse stem cells is required for the transcription-coupled repair of oxidative damage (Gowen *et al.*, 1998). Thus, poor repair due to mutations in *BRCA1*, combined with normal or higher levels of oxidative stress, could link these inherited mutations to breast cancer risk.

Reproductive and hormonal factors

Risk related to reproductive and hormonal factors could be due to the metabolism of estradiol to reactive hydroxy radicals through redox cycling of the catechol estrogens (Yager and Liehr, 1996). The semiquinone radicals have been shown to damage protein (Winter and Liehr, 1986) and to induce kidney tumors (Kirkman, 1959) in hamsters treated with estradiol. Evidence that these effects are through an oxidative stress mechanism comes from the observation that when hamsters were treated with estradiol, products of lipid peroxidation more than doubled in the kidney, and increases were noted in glutathione and glutathione peroxidase in the target tissue (Roy and Liehr, 1989). Recently, Mobley *et al.* (1999) showed that treatment of calf thymus DNA with hydroxy estradiol resulted in damage (8-oxo-2'-deoxyguanosine), and that the presence of endogenous antioxidants such as glutathione, superoxide dismutase (SOD), and catalase dramatically reduced the amount of DNA damage induced by the catechol estrogens. The authors note that extremely high levels of catechol estrogens were needed for observed DNA damage. However, Yoshie and Ohshima (1998) found that DNA strand breakage occurred when plasmid DNA was incubated with both a catechol estrogen and a nitric oxide (NO)-releasing compound, both of which are formed in the human breast. Therefore, lower amounts of catechol estrogens used by Mobley *et al.* would likely result in DNA damage in the presence of a NO-releasing compound. Estrogens have also been shown to have antioxidant capabilities (Subbiah *et al.*, 1993). The net effect (oxidant and antioxidant) may be dependent

upon levels of catechol estrogens (determined, in part, by catechol *O*-methyl transferase [COMT]) or other enzymatic activities.

Diet

Alcohol: Alcohol consumption could increase breast cancer risk through the generation of DNA-damaging reactive species (Wright *et al.*, 1998). Ethanol can be converted to acetate through the combined activities of alcohol dehydrogenase (ADH) and xanthine oxidoreductase (XOR) and/or aldehyde oxidase (AOX). Both XOR and AOX can generate ROS. Studies of acute alcohol toxicity of the liver have noted that metabolism of alcohol produces ROS, resulting in oxidative damage to DNA, including strand breakage (Rajasinghe *et al.*, 1990). Studies from the liver and pancreas have also shown that the ROS generated are from the combined activity of XOR and AOX (Rajasinghe *et al.*, 1990; Shaw and Jayatilleke, 1992; Nordback *et al.*, 1994; Mira *et al.*, 1995). ADH and XOR are present in human breast tissue (Saleem *et al.*, 1984; Ishii *et al.*, 1995). It has been suggested that alcohol-derived ROS could have an impact on breast carcinogenesis at several stages (Wright *et al.*, 1998): they could act as initiators of tumors, or at later stages of progression and transformation. They may also affect cell proliferation.

Dietary fat: Dietary fat intake has long been hypothesized to be associated with breast cancer risk (Willett, 1989) on the basis of animal studies (Cave, 1994), ecologic studies (Armstrong and Doll, 1975; Caroll *et al.*, 1986), and studies of migrants from areas with low fat intake to those with high fat intake (Dunn, 1975). However, many analytic epidemiologic studies have not shown an effect of fat, including the results of a pooled analysis of seven cohort studies (Hunter *et al.*, 1996). Recently, it has been suggested that diet in childhood and at the time of puberty may be of importance (Potischman *et al.*, 1998). Evidence from animal studies suggests that only fat intake before the first pregnancy affects risk (Ip, 1993). It is possible that the failure to identify an association of fat intake with breast cancer in epidemiologic studies may be because intake early in life, rather than recent consumption, is most important. Failure to detect an association may also be due to fact that there is not enough variability in fat consumption within populations (*i.e.*, there are too few individuals with low intakes) (Goodwin and Boyd, 1987), or because of measurement error inherent in dietary questionnaires (Bingham *et al.*, 1994). It may also be that specific types of dietary fat are more important than total fat, and investigators have not been evaluating the proper variables.

If there is an association with dietary fat and breast cancer, it could be through a mechanism of its oxidation to ROS and stimulation of lipid peroxidation. For example, autoxidized linolenic and linoleic acids can form 8-hydroxy-2′-deoxyguanosine in DNA (Kasai and Nishimura, 1988). In fact, in an intervention study, Djuric *et al.* (1991) found that regardless of the diet arm, there was a significant linear regression relationship between total fat intake and DNA damage levels. In fact, level of oxidized DNA bases was an important marker for dietary compliance to a low-fat diet. Caloric intake, however, may be even more important in generation of oxidative stress and breast cancer risk than fat consumption (Simic and Bergtold, 1991).

Fruits and vegetables: Numerous nutritional epidemiologic studies have noted associations between dietary antioxidants and decreased breast cancer risk (AICR, 1997, pp. 274–276), although not all studies support such an association (Byers, 1994). The evidence for a protective effect appears to be more abundant for fruits than for vegetables (AICR, 1997, p. 281). The mechanistic relationship of these putative risk factors, however, has not been elucidated. Fruits and vegetables are sources of a number of nutrients, including antioxidant vitamins such as carotenoids, the tocopherols, vitamin C, and flavonoids, and the inverse relationships with consumption of fruits and vegetables could be tied in through their antioxidant properties. One hypothesis is that dietary antioxidants affect oxidative stress and the production of ROS by altering the balance between prooxidant cellular activity and antioxidant defenses.

Environmental contaminants: The interaction of xenobiotics with numerous enzyme systems has been shown to result in the metabolism of chemicals to free radical intermediates, some of which, in turn, can also activate molecular oxy-

gen via univalent reduction to superoxide (Mason, 1982; Trush and Kensler, 1991). Because of temporal and demographic trends, there has been growing interest in the role of chemical carcinogens in relation to breast cancer, and there is evidence that enzymes involved in oxidative pathways could affect these associations.

In the past several years, a number of epidemiologic studies have been conducted to evaluate possible associations between exposure to environmental factors, including organochlorines and risk of breast cancer. Results from the studies of breast cancer are inconsistent, but there have also been findings of elevated risk among specific subsets of the population. For example, Moysich, Ambrosone, and colleagues (Moysich *et al.*, 1998) found that, while there was no overall increased risk of breast cancer associated with higher serum levels of polychlorinated biphenyls (PCBs) and 1,1-dichloro-2,2-*bis*(*p*-chlorophenyl)ethylene (DDE), or with specific PCB congeners, risk was increased among women with higher levels who had never lactated, a major form of excretion of lipid-soluble organochlorines. We also found that in women with levels of PCBs above the median, the presence of at least one *CYP1A1* isoleucine-to-valine substitution allele increased risk almost three-fold. CYP1A1 is an enzyme that is highly induced by organochlorines and metabolizes some of the less persistent PCBs (Moysich *et al.*, 1999). In women with lower body burden of organochlorines, no association between *CYP1A1* genotype and breast cancer risk was observed.

In addition to PCBs and DDE, other lipid-soluble organochlorines could also be associated with breast cancer risk, although they have not been studied to the same extent that PCBs and DDE have. In a Danish cohort study, Hoyer *et al.* (1998) found that higher levels of dieldrin, a highly toxic persistent pesticide, were associated with significantly increased breast cancer risk [adjusted odds ratio (OR) for fourth quartile = 2.05, 95% confidence interval (CI = 1.17–3.57)]. There was also a nonsignificant increase in risk with higher levels of β-hexachlorocyclohexane.

Interestingly, for both PCBs and dieldrin, a mechanism of induced oxidative stress in breast carcinogenesis has been proposed. Amaro *et al.* (1996) have shown that PCBs can be metabolically activated to catechols and hydroquinones. These species can be further activated by peroxidases, including myeloperoxidase, to species that are capable of binding to DNA (Ariyoshi *et al.*, 1993; Oakley *et al.*, 1996b). Hydroxylated metabolites of PCBs were shown to be retained in human plasma (Bergman *et al.*, 1994), and Oakley *et al.* (1996a) investigated the hypothesis that PCBs may impact breast cancer risk by increased oxidative DNA damage due to metabolites via enzymatic and nonenzymatic mechanisms. They found that peroxidase-mediated oxidation of PCB dihydroxy metabolites results in oxidative DNA damage, using 8-oxodG as a marker.

There is also accumulating evidence that possible associations between exposure to dieldrin and cancer risk are through oxidative stress. Klaunig's group (Bachowski *et al.*, 1998) has shown that the selective toxicity of dieldrin in mouse liver, but not rat, is due to dieldrin's ability to induce oxidative stress in the liver of mice, but not in rats. Furthermore, vitamin E supplementation in mice with dieldrin-induced tumors resulted in inhibition of hepatic focal lesion growth (Kolaja *et al.*, 1998). Another chlorinated pesticide, lindane, has been shown to reduce superoxide dismutase and catalase activity in both rat and mouse liver, while increasing peroxidase and P450 activity, leading to an increased oxidative load (Junqueira *et al.*, 1986). Clearly, associations between organochlorines and breast cancer risk need to be evaluated in relation to metabolic variability in enzymes that produce and prevent oxidative stress.

ENDOGENOUS GENERATION OF AND RESPONSE TO ROS

Variability in exposure to factors that could increase levels of ROS, through exogenous routes or by variability in endogenous processes, as well as cellular responses to ROS, will ultimately determine levels of oxidative stress in the breast. ROS are generated by numerous enzymes, *e.g.*, myeloperoxidase, or regulatory processes such as those stimulated by tumor necrosis factor-α. Endogenous defenses against ROS include glutathione peroxidase, catalase,

and SOD, of which there are three known forms: the cytosolic and extracellular copper/zinc SODs and the mitochondrial manganese SOD (MnSOD). These enzymes form the first line of defense against superoxide and hydrogen peroxide (H_2O_2). The resultant secondary oxidation products may still damage DNA, proteins, and lipid, and require further detoxification. This second line of defense against ROS is provided by enzymes such as glutathione peroxidase and the glutathione *S*-transferases. Many of these enzymes are polymorphic and breast cancer risk related to oxidative stress could be impacted by this interindividual variability.

Polymorphic enzymes related to oxidative stress: generation of ROS

Myeloperoxidase (MPO): MPO is thought to function as an antimicrobial agent by catalyzing a reaction between hydrogen peroxide, produced by NADPH oxidase, and chloride to generate hypochlorous acid (HOCl), a toxic oxidizing agent. HOCl further reacts with other biological molecules to generate secondary radicals, including highly reactive hydroxyl ions (Klebanoff, 1980). The enzyme is present in neutrophils, which invade inflamed tissues, including the breast, to combat infection and presumably to protect breast milk during lactation (Josephy, 1996). In addition to its presence in human breast milk, detection with immunohistochemistry has demonstrated the presence of MPO in breast tissue from women with cancer (Samoszuk *et al.*, 1996), and *MPO* gene coamplification was observed with c-*erbB-2* in human breast carcinomas (Coene *et al.*, 1997). A functional polymorphism has been identified that decreases expression of *MPO*, apparently, by destroying a binding site for the SP1 transcription factor (Piedrafita *et al.*, 1996). In a study of lung cancer, London *et al.* (1997) found that 8% of the Caucasian population in the study ($n = 459$) were homozygous for the allele (A) that reduces transcription of the myeloperoxidase gene, and 31% were heterozygotes. In that study, lung cancer risk was decreased among individuals who inherited two copies of the A allele. A small study (Reynolds *et al.*, 1999) was also conducted of the relationship between the *MPO* genetic polymorphism and risk for Alzheimer's disease, in which oxidizing radicals are implicated (Cross *et al.*, 1987; Multhaup *et al.*, 1997; Smith, 1998). In that study, it was found that the allele associated with higher expression of *MPO* increased risk of Alzheimer's disease among women, but not among men. The authors suggest that the gender difference in risk may be related to the possible effects of sex hormones on *MPO* gene expression. Because of the presence of MPO in the breast, and its ability to generate ROS, the polymorphism may be important in an oxidative stress pathway in human breast cancer.

Tumor Necrosis Factor-α (TNF-α): The cytokine, TNF-α triggers receptor-mediated processes, yielding ROS and causing oxidative stress in mitochondria. TNF-α was discovered through its antitumor activity, but it has been implicated in the pathophysiology of diabetes and cardiovascular disease due to its physiologic involvement in oxidative stress. In fact, one of the mechanisms of TNF-α cytotoxicity is thought to be damage from ROS (Luster, 1999). A G-to-A transition in the gene at position 308 directly affects the regulation of TNF-α, and the variant allele is associated with higher constitutive and inducible levels of TNF-α (Wilson, 1994). In a study of TNF-α, genetic polymorphisms in relation to both lymphoma and breast cancer in a Tunisian population (Choucane, 1997), Chouchane found that heterozygosity for the variant allele significantly increased cancer risk. In this population, 32% of the controls were homozygous or heterozygous for the variant alleles, cited as only slightly higher than in a European population (28%). Higher levels of TNF-α could result in more ROS in the mitochondrion, causing oxidative stress and resultant DNA damage; conversely, low levels could be protective.

Polymorphic enzymes related to oxidative stress: response to ROS

Endogenous defenses against ROS include glutathione peroxidase, catalase, and SOD. There are three known forms of SOD: the cytosolic and extracellular copper/zinc SODs and the mitochondrial manganese SOD (MnSOD).

MnSOD: This SOD is synthesized in the cytosol and modified post-transcriptionally for transport into the mitochondrion (Wispe *et al.*, 1989; Shimoda-Matsubayashi *et al.*, 1996). In the mitochondrion, it catalyzes the dismutation of two superoxide radicals, producing H_2O_2 and oxygen. MnSOD is induced with free radical challenge (Rohrdanz and Kahl, 1998a) and cigarette smoke (Gilks *et al.*, 1998). Recently, two genetic variants of the *MnSOD* gene were identified (Shimoda-Matsubayashi *et al.*, 1996). A structural mutation, a T-to-C substitution in the mitochondrial-targeting sequence, was found and changes an amino acid. The investigators who identified the polymorphism (Shimoda-Matsubayashi *et al.*, 1996) predicted that the resulting amino acid change would alter the secondary structure of the protein. Rosenblum and colleagues (Rosenblum *et al.*, 1996) suggest that the alteration might 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. We hypothesized that the polymorphism in the *MnSOD* gene would result in higher levels of ROS, and that in women whose diets were low in fruits and vegetables, this polymorphism would increase risk of breast cancer. Interestingly, we found this to be the case, particularly for premenopausal women (Ambrosone *et al.*, 1999a). Those who were homozygous for the variant allele had a four-fold increase in breast cancer risk in comparison to those with who were homozygous or heterozygous for the common allele (OR = 4.3, 95% CI, 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. These data support the hypothesis that MnSOD and oxidative stress play a significant role in breast cancer risk, particularly in premenopausal women. Interestingly, there is a link between TNFa and MnSOD in the breast. When MCF-7 cells were treated with TNF, there was a five-fold increase in MnSOD activity (Siemankowski *et al.*, 1999).

Extracellular SOD (EC-SOD): This is the principal enzymatic scavenger of superoxide in the extracellular space. Molecular genetic studies have shown that a single base substitution causing substitution of glycine for Arg213 in the heparin-binding domain of this enzyme causes the extremely high plasma level of EC-SOD (Yamada *et al.*, 1995; Marklund *et al.*, 1997). In a study of 242 healthy volunteers in Australia (Adachi and Wang, 1998), serum EC-SOD levels were found to be distributed in two discrete groups of low level (29.9–152.1 μg/liter) and high level (940.2–1,798 μ/liter). All of individuals within the high-level group (3.3%) carried the R213G mutation, whereas none of the low-level EC-SOD volunteers did. Similar distribution of phenotype was observed in a large cohort (n = 4,925) in Sweden (Marklung *et al.*, 1997), where 4% had eight-fold higher plasma levels of EC-SOD. All but one of the individuals in this group carried the R213G polymorphism. It is likely that those with high EC-SOD were likely to be homozygous for the variant allele.

SOD works in conjunction with two other antioxidant proteins, catalase and glutathione peroxidase. These enzymes remove the toxic H_2O_2 produced by the SODs, by converting them into water.

Catalase (CAT): CAT is a heme enzyme that has a predominant role in controlling H_2O_2 concentration in human cells, by converting H_2O_2 into H_2O and O_2. Catalase induction was elicited by H_2O_2 in hamster tracheal epithelial cells (Shull *et al.*, 1991) and human retinal pigment epithelial cells (Tate *et al.*, 1995), indicating a key role for catalase in antioxidant defense. It was also found to be inducible in both primary rat hepatocytes and rat hepatoma cell lines (Rohrdanz and Kahl, 1998b). Acatalasemic mice that have blood and tissue levels of catalase that are approximately one-tenth that of normal mice (Ishii *et al.*, 1996) and females are susceptible to spontaneous mammary carcinoma. Because a preventive effect of vitamin E on human breast cancer is controversial, Ishii and colleagues used the acatalasemic mouse to test whether carcinogenesis could be prevented by vitamin E. In this study,

acatalasemic mice developed mammary tumors after 9 months after vitamin E deprivation, and 14 months after supplementation. Normal mice did not develop mammary tumors, regardless of diet. These data indicate that there could be important implications for the study of variability in CAT in relation to dietary and supplemental antioxidants and human breast cancer risk.

Glutathione-associated metabolism is a major mechanism for cellular protection against agents that generate oxidative stress. Glutathione participates in detoxification at several different levels, and may scavenge free radicals, reduce peroxides, or be conjugated with electrophilic compounds, providing the cell with multiple defenses against ROS and their reactive toxic products (Hayes and McLellan, 1999a).

Glutathione peroxidases: The glutathione peroxidases are a family of enzymes that catalyze the reduction of H_2O_2 and organic hydroperoxides to water and alcohols, respectively. Se-dependent glutathione peroxidase (GPX1) is present in the cytosol and in mitochondria (Ursini *et al.*, 1986). Knockout mice studies have shown that GPX1 is of critical importance in protection against oxidative stress generated by H_2O_2 (deHaan *et al.*, 1998). GPX1 is transcriptionally up-regulated as an adaptive response to oxidative stress. An amino acid substitution in the *GPX1* gene was identified by searching the human expressed sequence tags (EST) database (Forsberg *et al.*, 1999), followed by PCR and DNA sequencing. Restriction analyses of 25 individuals showed 13 homozygotes for Pro, 3 homozygotes for Leu, and 9 heterozygotes. The polymorphism in *GPX1* was evaluated in 18 populations that were endemic for malaria in relation to polymorphisms in hemoglobin β-chain (Destro-Bisol *et al.*, 1999). These investigators found that the erythrocytes of those heterozygous for the variant allele were more efficient in sheltering the cell membrane from irreversible oxidation and binding of hemoglobin caused by the oxidant stress exerted by the malaria parasite. An in-frame variable polyalanine (GCG) repeat polymorphism has been described, and the 6-alanine (ALA6) repeat allele also has a nucleotide substitution associated with a proline-leucine substitution (Moscow *et al.*, 1994). Measurement of 8-hydroxydeoxyguanosine (8OHdG), a marker of oxidative damage, in DNA from normal lung tissue revealed a trend of less 8OHdG associated with one or two copies of the ALA6 allele (Hardie *et al.*, 2000), indicating that the variant may protect DNA from ROS damage. This difference could be relevant for breast cancer associated with oxidative stress.

Phase II enzymes: Phase II enzymes, which include the glutathione S-transferases (GSTs), are involved in the detoxication of many reactive species and are the second line of defense after SOD, CAT, and GPX. The GSTs detoxify not only lipid peroxidation products and oxidized bases (Hayes and McLellan, 1999b), but also other endogenous oxidation products, including *o*-quinones formed from catecholamines and estrogen-3,4-quinones (Yager and Liehr, 1996; Cavalieri *et al.*, 1997). The cytosolic glutathione transferases comprise four classes, alpha, mu, pi, and theta, of which at least three are represented in both normal and breast tumor tissue (Forrester *et al.*, 1990). Although glutathione transferases appear to have a fundamental role in the detoxication of electrophilic xenobiotics by conjugation to glutathione, several enzymes possess limited glutathione-dependent peroxidase activity (Hayes and Pulford, 1995). Of these classes, the alpha class appears to possess the greatest peroxidase activity, but enzymes of this class are expressed at low levels in both normal and breast tumor tissue. Therefore, GSTM1-1, which is expressed at higher levels, may make a significant contribution to Se-independent glutathione peroxidase activity in breast (Forrester *et al.*, 1990). Of the glutathione transferases, *GSTM1* is of particular interest because it shows a null polymorphism that results in lack of the enzyme in approximately 50% of the population (Brockmoller *et al.*, 1992). As reviewed by Rebbeck (1997), studies have shown that individuals who possess the homozygous null allele are at increased risk of lung and bladder cancer, both of which are associated with exposure to chemical carcinogens. However, studies of possible associations between *GSTM1* and breast cancer risk have yielded inconsistent results (Zhong *et al.*, 1993; Kelsey *et al.*, 1997; Bailey *et al.*, 1998; Helzlsouer *et al.*, 1998). Although we did not find an association between GSTM1 and breast

cancer in the western New York study (Ambrosone *et al.*, 1995, 1999b), Helzlsouer noted a more than two-fold increased risk with the null allele (Helzlsouer *et al.*, 1998).

Oxidative stress through hormone metabolism

The secondary metabolism of 17β-estradiol involves *O*-methylation by catechol *O*-methyltransferase (COMT), conjugation to glucuronides and sulfates, and clearance of reactive semiquinones and quinones, reported to involve catechol oxidation coupled to glutathione conjugation (Zhu and Conney, 1998).

Catechol-O-methyl transferase: *COMT* is one of several phase II enzymes involved in the conjugation and inactivation of the catechol estrogens (Guldberg and Marsden, 1975). Because of the potential for the catechol estrogens, particularly the 4-hydroxy catechol, to bind to DNA and result in DNA damage (Liehr, 1997; Cavalieri *et al.*, 1997), and to undergo redox cycling to damaging quinones and semiquinones, the possible role of variable activity in the enzyme in relation to breast cancer risk is important. An amino acid change (valine to methionine) at position 158/108 in the membrane-bound/cytosolic form of the protein has been linked to decreased methylation activity of COMT (Lachman *et al.*, 1996). The polymorphism is believed to be closely associated with the observed trimodal distribution of COMT enzyme activity in the human population associated with high ($COMT^{Val/Val}$), intermediate ($COMT^{Val/Met}$), and low ($COMT^{Met/Met}$) COMT activity (Goldstein and Leiberman, 1992; Price-Evans, 1993). The role of the *COMT* genetic polymorphism in relation to breast cancer risk has been evaluated by three groups to date in the United States, all with conflicting results (Lavigne *et al.*, 1997; Millikan *et al.*, 1998; Thompson *et al.*, 1998). Results from a recent study in Taiwan (Huang *et al.*, 1999) indicated that *COMT* low-activity alleles increased breast cancer risk and that combined 'high-risk' genotypes for *COMR*, *CYP17*, and *CYP1A1* inferred the greatest risk of all.

UDP-glucuronsyltransferases (UGTs): These are also phase II enzymes that render polarity to reactive species, making them more water soluble and more easily excreted. The UGTs are involved not only in the metabolism of many drugs and xenobiotics, but also are important in the biotransformation of important endogenous substrates, including estradiol (deWildt *et al.*, 1999). Three human liver UGTs (UGT2B7, 1A1, 1A3) have been shown to catalyze the glucuronidation of catechol estrogens and lead to their enhanced elimination (Cheng *et al.*, 1998). UGT2B7 was shown to react with higher efficiency toward 4-hydroxyestrogenic catechols, whereas UGT1A1 showed higher activities toward 2-hydroxyestrogens (Cheng *et al.*, 1998). Both of these enzymes are polymorphic. There are variable numbers of TA repeats in the promoter TATA box of UGT1A1, and they are inversely related to levels of gene expression (Hall *et al.*, 1999). Hall *et al.* (1999) found that two *UGT1A1* alleles are present in Caucasian Europeans; between 9% and 16% are homozygous for the variant allele (7) and heterozygotes range from 44 to 51% of European Caucasian populations. Variability in expression of UGT1A1 could have important effects on ultimate effects of catechol estrogens.

A polymorphism has also been identified in UGT2B7, in which a C-to-T transversion at nucleotide 802 results in a tyrosine to histidine substitution (Jin *et al.*, 1993), with allele frequencies for His268 and Tyr268 calculated at 0.52 and 0.48, respectively.

SUMMARY

As mechanisms of carcinogenesis become more fully elucidated, the complexity of cancer etiology becomes more and more obvious, particularly for hormone-responsive diseases. Moreover, epidemiologic and laboratory studies show that the manner in which risk factors relate to disease incidence is not well understood. It is now clear that breast cancer is multifactorial, and that some relevant exposures may be those that occur before puberty. Molecular epidemiologic studies may be useful for unraveling some of that etiologic complexity. By evaluating genetic variability that contributes to ultimate effects of factors to which women are exposed, relationships may be more clearly observed. If only "sensitive" subgroups are evaluated, based upon their genetic

metabolic profiles, more precise risk estimates may be calculated. The study of variability in genes that are involved in the generation of ROS and protection from oxidative stress may elucidate pathways of carcinogenesis in the breast that are clearly linked to an imbalance between prooxidant and antioxidant forces.

ABBREVIATIONS

8-oxo-dG, 8-Oxo-7,8-dihydro-2′-deoxyguanosine; ADH, alcohol dehydrogenase; AOX, aldehyde oxidase; CAT, catalase; COMT, catechol *O*-methyltransferase; CYP1A1, cytochrome P450 1A1; DDE, 1,1-dichloro-2,2-*bis*(*p*-chlorophenyl)ethylene; EC-SOD, extracellular superoxide dismutase; GST, glutathione *S*-transferase; GPX1, glutathione peroxidase; H_2O_2, hydrogen peroxide; MnSOD, manganese superoxide dismutase; MPO, myeloperoxidase; PCBs, polychlorinated biphenyls; ROS, reactive oxygen species; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-α; XOR, xanthine oxidoreductase; UGT, UDP-glucuronsyltransferase.

REFERENCES

AICR. (1997). *Food, Nutrition and the Prevention of Cancer: A Global Perspective.* (American Institute for Cancer Research, Washington, DC).

ADACHI, T., and WANG, X.L. (1998). Association of extracellular-superoxide dismutase phenotype with the endothelial constitutive nitric oxide synthase polymorphism. FEBS Lett. **433,** 166–168.

AMARO, A.R., OAKLEY, G.G., BAUER, U., SPIELMANN, H.P., and ROBERTSON, L.W. (1996). Metabolic activation of PCBs to quinones: reactivity toward nitrogen and sulfur nucleophiles and influence of superoxide dismutase. Chem Res Toxicol. **9,** 623–629.

AMBROSONE, C.B., FREUDENHEIM, J.L., GRAHAM, S., MARSHALL, J.R., VENA, J.E., BRASURE, J.R., LAUGHLIN, R., NEMOTO, T., MICHALEK, A.M., and HARRINGTON, A. (1995). Cytochrome P4501A1 and glutathione S-transferase (M1) genetic polymorphisms and postmenopausal breast cancer risk. Cancer Res. **55,** 3483–3485.

AMBROSONE, C.B., FREUDENHEIM, J.L., THOMPSON, P.A., BOWMAN, E.D., VENA, J.E., MARSHALL, J.R., GRAHAM, S., LAUGHLIN, R., NEMOTO, T., and SHIELDS, P.G. (1999a). Manganese superoxide dismutase (MnSOD) genetic polymorphisms, dietary antioxidants and risk of breast cancer. Cancer Res. **59,** 602–606.

AMBROSONE, C.B., COLES, B.F., FREUDENHEIM, J.L., and SHIELDS, P.G. (1999b). Glutathione S-transferase (GSTM1) genetic polymorphisms do not affect human breast cancer risk, regardless of dietary antioxidants. J. Nutr. **129,** 565S–568S.

ARIYOSHI, N., YOSHIMURA, H., and OGURI, K. (1993). Identification of in vitro metabolites of 2,4,5,2′,4′,6′-Hexachlorobiphenyl from phenobarbital-treated dog liver microsomes. Biol. Pharm. Bull. **16,** 852–857.

ARMSTRONG, B., and DOLL, R. (1975). Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. Int. J. Cancer **15,** 617–631.

BACHOWSKI, S., XU, Y., STEVENSON, D.E., WALBORG, E.F., and KLAUNIG, J.E. (1998). Role of oxidative stress in the selective toxicity of dieldrin in the mouse liver. Toxicol. Appl. Pharmacol. **150,** 301–309.

BAILEY, L.R., ROODI, N., VERRIER, C.S., YEE, C.J., DUPONT, W.D., and PARL, F.F. (1998). Breast cancer and *CYP1A1*, *GSTM1*, and *GSTT1* polymorphisms: evidence of a lack of association in Caucasians and African Americans. Cancer Res. **58,** 65–70.

BERGMAN, A., KLASSON-WEHLER, E., and KUROKI, H. (1994). Selective retention of hydroxylated PCB metabolites in blood. Env. Health Persp. **102,** 464–469.

BINGHAM, S.A., GILL, C., WELCH, A., DAY, K., CASSIDY, A., KHAW, K.T., SNEYD, M.J., and KEY, T.J.A. (1994). Comparison of dietary assessment methods in nutritional epidemiology: weighted records v. 24h recalls, food frequency questionnaires and estimated diet records. Br. J. Nutr. **72,** 643.

BOYD, N.F., and MCGUIRE, V. (1991). The possible role of lipid peroxidation in breast cancer risk. Free Radical Biol. Med. **10,** 185–190.

BROCKMOLLER, J., GROSS, D., KERB, R., DRAKOULIS, N., and ROOTS, I. (1992). Correlation between transstilbene oxide-glutathione conjugation activity and the deletion mutation in the glutathione S-transferase class Mu gene detected by polymerase chain reaction. Biochem. Pharmacol. **43,** 647–650.

BYERS, T. (1994). Nutritional risk factors for breast cancer. Cancer **74,** 288–295.

CALLAHAN, R., CROPP, C.S., MERLO, G.R.L.D.S., CAPPA, A.P.M., and LIDEREAU, R. (1992). Somatic mutations and human breast cancer. Cancer **69,** 1582–1588.

CAROLL, K.K., BRADEN, L.M., BELL, J.M., and KALAMEGHAM, R. (1986). Fat and cancer. Cancer **58,** 1818–1825.

CAVALIERI, E.L., STACK, D.E., DEVANESAN, P.D., TODOROVIC, R., DWIVEDY, I., HIGGINBOTHAM, S., JOHANSSON, S.L., PATIL, K.D., GROSS, M.L., GOODEN, J.K., RAMANATHAN, R., CERNY, R.L., and ROGAN, E.G. (1997). Molecular origin of cancer: Catechol estrogen-3-4-quinones as endogenous tumor initiators. Proc. Natl. Acad. Sci. USA **94,** 10937–10942.

CAVE, W.T. (1994). Dietary fat effects on animal models of breast cancer. In *Diet and Breast Cancer.* E.K. Weisburger, ed. (Plenum Press, New York).

CERUTTI, P.A. (1994). Oxy-radicals and cancer. Lancet **344,** 862–863.

CHENG, Z., RIOS, G.R., KING, C.D., COFFMAN, B.L., GREEN, M.D., MOJARRABI, B., MACKENZIE, P.I., and TEPHLY, T.R. (1998). Glucuronidation of catechol estrogens by expressed human UDP-glucuronosyltransferases (UGTs) 1A1, 1A2 and 2B7. Toxicol. Sci. **45,** 52–57.

COENE, E.D., SCHELFHOUT, V., WINKLER, R.A., SCHELFHOUT, A.M., VANROY, N., GROOTECLAES, M., SPELEMAN, F., and DEPOTTER, C.R. (1997). Amplification units and translocation at chromosome 17q and c-erbB-2 overexpression in the pathogenesis of breast cancer. Virchows' Archiv. **430,** 365–372 (Abstract).

CROSS, C.E., HALLIWELL, B., BORISH, E.T., PRYOR, W.A., AMES, B.A., SAUL, R.L., MCCORD, J.M., and HARMAN, D. (1987). Oxygen radicals and human disease. Ann. Intern. Med. **107,** 526–545 (Abstract).

DEHAAN, J.B., BLADIER, C., GRIFFITHS, P., KELNER, M., O'SHEA, R.D., CHEUNG, N.S., BRONSON, R.T., SILVERSTRO, M.J., WILD, S., ZHENG, S.S., BEART, P.M., HERTZOG, P.J., and KOLA, I. (1998). Mice with a homozygous null mutation for the most abundant glutathione peroxidase, Gpx1, show increased susceptibility to the oxidative stress-inducing agents paraquat and hydrogen peroxide. J. Biol. Chem. **273,** 22528–22536.

DESTRO-BISOL, G., VIENNA, A., BATTAGGIA, C., PAOLI, G., and SPEDINI, G. (1999). Testing a biochemical model of human genetic resistance to falciparum malaria by the analysis of variation at protein and microsatellite loci. Hum. Biol. **71,** 315–332.

DEWILDT, S.N., KEARNS, G.L., LEEDER, J.S., and VAN DEN ANKER, J.N. (1999). Glucuronidation in humans—pharmacogenetic and developmental aspects., Clin. Pharmacokinet. **36,** 439–452.

DJURIC, Z., HEILBRUN, L.K., READING, B.A., BOOMER, A., VALERIOTE, F.A., and MARTINO, S. (1991). Effects of a low-fat diet on levels of oxidative damage to DNA in human peripheral nucleated blood cells. J. Natl. Cancer Inst. **83,** 766–769.

DJURIC, Z., HEILBRUN, L., SIMON, M.S., SMITH, D., LUONGO, D.A., LORUSSO, P.M., and MARTINO, S. (1996). Levels of 5-hydroxymethyl-2′-deoxyuridine in DNA from blood as a marker of breast cancer. Cancer **77,** 696.

DJURIC, Z., DEPPER, J.B., UHLEY, V., SMITH, D., LABABIDI, S., MARTINO, S., and HEILBRUN, L. (1998). Oxidative DNA damage levels in blood from women at high risk for breast cancer are associated with dietary intakes of meats, vegetables, and fruits. J. Am. Diet Assoc. **98,** 524–528.

DUNN, J.E. (1975). Breast cancer among American Japanese in the San Francisco bay area. J. Natl. Cancer Inst. Monogr. **47,** 157–160.

EMERIT, I. (1994). Reactive oxygen species, chromosome mutation and cancer: possible role of clastogenic factors in carcinogenesis. Free Rad. Biol. Med. **16,** 99–109.

ESTERBAUER, H., and JURGENS, G. (1993). Mechanistic and genetic aspects of susceptibility of LDL to oxidation. Curr. Opin. Lipidol. **4,** 114–124.

FORRESTER, L.M., HAYES, J.D., MILLIS, R., BARNES, D., HARRIS, A.L., SCHLAGER, J.J., POWIS, G., and WOLF, C.R. (1990). Expression of glutathione S-transferases and cytochrome P450 in normal and tumor breast tissue. Carcinogenesis **11,** 2163–2170.

FORSBERG, L., DEFAIRE, U., and MORGENSTERN, R. (1999). Low yield of polymorphisms from EST blast searching: analysis of genes related to oxidative stress and verification of the P197L polymorphism in GPX1. Hum. Mutat. **13,** 294–300.

FREI, B., FORTE, T.M., AMES, B.N., and CROSS, C.E. (1991). Gas phase oxidants of cigarette smoke induce lipid peroxidation and changes in lipoprotein properties in human blood plasma. Biochem. J. **277,** 133–138.

GILKS, C.B., PRICE, K., WRIGHT, J.L., and CHURG, A. (1998). Antioxidant gene expression in rat lung after exposure to cigarette smoke. Am. J. Pathol. **152,** 269–278.

GOLDSTEIN, M., and LEIBERMAN, A. (1992). The role of the regulatory enzymes of catecholamine synthesis in Parkinson's disease. Neurology **12,** 822–825.

GOODWIN, P.J., and BOYD. N.F. (1987). Critical appraisal of the evidence that dietary fat intake is related to breast cancer risk in humans. J. Natl. Cancer Inst. **79,** 473–485.

GOWEN, L.C., AVRUTSKAYA, A.V., LATOUR, A.M., KOLLER, B.H., and LEADON, S.A. (1998). BRCA1 required for transcription-coupled repair of oxidative DNA damage. Science **281,** 1009–1012.

GULDBERG, H.C., and MARSDEN, C.A. (1975). Catechol-O-methyltransferase: pharmacological aspects and physiological role. Pharmacol. Rev. **27,** 135–206.

HALL, D., YBAZETA, G., DESTRO-BISOL, G., PETZL-ERLER, M.L., and DIRIENZO, A. (1999). Variability at the uridine diphosphate glucuronosyltransferase 1A1 promoter in human populations and primates. Pharmacogenetics **9,** 591–599.

HALLIWELL, B., and GUTTERIDGE, J.M.C. (1989). *Free Radicals in Biology and Medicine.* (Oxford University Press, Oxford).

HARDIE, L.J., BRIGGS, J.A., DAVIDSON, L.A., ALLAN, J.M., KING, R.F., WILLIAMS, G.I., and WILD, C.P. (2000). The effect of hOGG1 and glutathione peroxidase I genotypes and 3p chromosomal loss on 8-hydroxydeoxyguanosine levels in lung cancer. Carcinogenesis **21,** 167–172.

HAYES, J.D., and MCLELLAN, L.I. (1999a). Glutathione and glutathione-dependent enzymes represent a co-ordinately regulated defence against oxidative stress. Free Rad. Res. **31,** 273–300.

HAYES, J.D., and MCLELLAN, L.I. (1999b). Glutathione and glutathione-dependent enzymes represent a co-ordinately regulated defence against oxidative stress. Free Rad. Res. **31,** 273–300.

HAYES, J.D., and PULFORD, D.J. (1995). The glutathione S-transferase supergene family: regulation of GST and the contribution of the isoenzymes to cancer chemoprotection and drug resistance. Crit. Rev. Biochem. Mol. Biol. **30,** 445–600.

HELZLSOUER, K.J., SELMIN, O., HUANG, H.-Y., STRICKLAND, P.T., HOFFMAN, S., ALBERG, A.J., WATSON, M., COMSTOCK, G.W., and BELL, D.A. (1998). Association between glutathione S-transferase M1, P1, and T1 genetic polymorphisms and development of breast cancer. J. Natl. Cancer Inst. **90,** 512–518.

HOYER, A.P., GRANDJEAN, P., JORGENSEN, T., BROCK, J.W., and HARTVIG, H.B. (1998). Organochlorine exposure and risk of breast cancer. Lancet **352,** 1816–1820.

HUANG, C.-S., CHERN, H.-D., CHANG, K.J., CHENG, C.-W., HSU, S.-M., and SHEN, C.Y. (1999). Breast cancer risk associated with genotype polymorphism of the estrogen-metabolizing genes CYP17, CYP1A1, and COMT: a multigenic study on cancer susceptibility. Cancer Res **59,** 4870–4875.

HUNTER, D.J., SPIEGELMAN, D., ADAMI, H.O., BEESON, L., VAN DEN BRANDT, P.A., FOLSOM, A.R., FRASER, G.E., GOLDBOHM, R.A., GRAHAM, S., HOWE, G.R., KUSHI, L.H., MARSHALL, J.R., MCDERMOTT, A., MILLER, A.B., SPEIZER, F.E., WOLK, A., YAUN, S., and WILLETT, W. (1996). Cohort studies of fat intake and the risk of breast cancer—a pooled analysis. N. Engl. J. Med. **334,** 356–361.

HUSSAIN, S.P., AGUILAR, F., AMSTAD, P., and CERUTTI, P.A. (2000). Oxy-radical induced mutagenesis of hotsot codons 248 and 249 of the human p53 gene. Oncogene **9,** 2277–2281.

IP, C. (1993). Controversial issues of dietary fat and experimental mammary carcinogenesis. Prev. Med. **22,** 728–737.

ISHII, K., ZHEN, L.X., WANG, D.H., FUNAMORI, Y., OGAWA, K., and TAKETA, K. (1996). Prevention of mammary tumorigenesis in acatalasemic mic by vitamin E supplementation. Japanese J. Cancer Res. **87,** 680–684.

ISHII, T., AOKI, N., NODA, A., ADACHI, T., NAKAMURA, R., and MATSUDA, T. (1995). Carboxy terminal cytoplasmic domain of mouse butyrophilin specifically associated with a 150kDa protein of mammary epithelial cells and milk fat globule membrane. Biochem. Biophys. Acta **1245,** 285–292.

JIN, C., MINERS, J.O., LILLYWHITE, K.J., and MACKENZIE, P.I. (1993). Complementary deoxyribonucleic acid cloning and expression of a human liver uridine diphosphate-glucuronosyltransferase glucuronidating carboxylic acid-containing drugs. J. Pharm. Exp. Therapeut. **264,** 475–479.

JOSEPHY, P.D. (1996). The role of peroxidase-catalyzed activation of aromatic amines in breast cancer. Mutagenesis **11,** 3–7.

JUNQUEIRA, B.C.V., SIMIZU, K., VIDELA, L.A., and BARROS, S.B. (1986). Dose dependent study of the effects of acute lindane administration on rat lever superoxide anion production, antioxidant enzyme activities and lipid peroxidation. Toxicology **41,** 198–204.

KASAI, H., and NISHIMURA, S. (1988). Formation of 8-hydroxydeoxyguanosine in DNA by auto-oxidized unsaturated fatty acids. In *Medical, Biochemical, and Chemical Aspects of Free Radicals*. O. Hayaishi, ed. (Elsevier, New York) pp. 1021–1023.

KELSEY, J.L., and BERNSTEIN, L. (1996). Epidemiology and prevention of breast cancer. Annu. Rev. Public Health **17,** 47–67.

KELSEY, K.T., HANKINSON, S.E., COLDITZ, G.A., SPRINGER, K., GARCIA-CLOSAS, M., SPIEGELMAN, D., MANSON, J.E., GARLAND, M., STAMPFER, M.J., WILLETT, W.C., SPEIZER, F.E., and HUNTER, D.J. (1997). Glutathione S-transferase μ deletion polymorphism and breast cancer: results from prevalent *versus* incident cases. Cancer Epidemiol. Biomarkers Prev. **6,** 511–515.

KIRKMAN, H. (1959). Estrogen induced tumors of the kidney. III: growth characteristics in the syrian hamster. Natl. Cancer Inst Monogr. **1,** 1–57.

KLEBANOFF, S.J. (1980). Oxygen metabolism and the toxic properties of phagocytes. Ann. Intern. Med. **93,** 480–489 (Abstract).

KOLAJA, K.L., XU, Y., WALBORG, E.F., STEVENSON, D.E., and KLAUNIG, J.E. (1998). Vitamin E modulation of dieldrin-induced hepatic focal lesion growth in mice. J. Toxicol. Environ. Health **53,** 479–492.

LACHMAN, H.M., PAPOLOS, D.F., SAITO, T., YU, Y.M., SZUMLANSKI, C.L., and WEINSHILBOUM, R.M. (1996). Human catechol-*O*-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics **6,** 243–250.

LANGSTON, A.A., MALONE, K.E., THOMPSON, J.D., DALING, J.R., and OSTRANDER, E.A. (1996). BRCA1 mutations in a population-based sample of young women with breast cancer. N. Engl. J. Med. **334,** 137–142

LAVIGNE, J.A., HELZLSOUER, K.J., HUANG, H.-Y., STRICKLAND, P.T., BELL, D.A., SELMIN, O., WATSON, M.A., HOFFMAN, S., COMSTOCK, G.W., and YAGER, J.D. (1997). An association between the allele coding for a low activity variant of catechol-O-methyltransferase and the risk for breast cancer. Cancer Res. **57,** 5493–5497.

LIEHR, J.G. (1997). Hormone-associated cancer: mechanistic similarities between human breast cancer and estrogen-induced kidney carcinogenesis in hamsters. Environ Health Perspect. **105,** 565–569.

LOFT, S., and POULSEN, H.E. (1996). Cancer risk and oxidative damage in man. J. Mol. Med. **74,** 297–312.

LONDON, S.J., LEHMAN, T.A., and TAYLOR, J.A. (1997). Myeloperoxidase genetic polymorphism and lung cancer risk. Cancer Res. **57,** 5001–5003.

LUSTER, M.P., SIMEONOVA, P., GALLUCCI, R., and MATHESON, J. (1999). Tumor necrosis factor alpha and toxicology. Crit. Rev. Toxicol. **29,** 491–511.

MADIGAN, M.P., ZIEGLER, R.G., BENICHOU, J., BYRNE, C., and HOOVER, R.N. (1995). Proportion of breast cancer cases in the United States explained by well-established risk factors. J. Natl. Cancer Inst. **87,** 1681–1685.

MALINS, D.C. (1993). Identification of hydroxyl radical-induced lesions in DNA base structure: biomarkers

with a putative link to cancer development. J. Toxicol. Environ. Health **40,** 247–261.

MALINS, D.C., and HAIMANOT, R. (1991). Major alterations in the nucleotide structure of DNA in cancer of the female breast. Cancer Res. **51,** 5430–5432.

MALINS, D.C., HOLMES, E.H., POLISSAR, N.L., and GUNSELMAN, S.J. (1993). The etiology of breast cancer. Cancer **71,** 3036–3043.

MALINS, D.C., POLISSAR, N.L., and GUNSELMAN, S.J. (1996). Progression of human breast cancers to the metastatic state is linked to hydroxyl radical-induced DNA damage. Proc. Natl. Acad. Sci. USA **93,** 2557–2563.

MARKLUND, S.L., NILSSON, P., ISRAELSSON, K., SCHAMPI, I., PELTONEN, M., and ASPLUND, K. (1997). Two variants of extracellular-superoxide dismutase: relationship to cardiovascular risk factors in an unselected middle-aged population. J. Intern. Med. **242,** 5–14.

MASON, R. (1982). Free radical intermediates in the metabolism of toxic chemicals. In *Free Radicals in Biology,* W.A. Pryor, ed. vol. 5. (Academic Press, New York) pp. 161–122.

MILLIKAN, R.C., PITTMAN, G.S., TSE, G.S., DUELL, E., NEWMAN, B., SAVITZ, D., MOORMAN, P.G., BOISSY, R., and BELL, D.A. (1998). Catechol-O-methyltransferase and breast cancer risks. Carcinogenesis **19,** 1943–1947.

MIRA, L., MAIA, L., BARREIRA, L., and MANSO, C.F. (1995). Evidence for ROS generation due to NADH oxidation by aldehyde oxidase during ethanol metabolism. Arch. Biochem. Biophys. **318,** 53–58.

MOBLEY, J.A., BHAT, A.S., and BRUEGGEMEIER, R.W. (1999). Measurement of oxidative DNA damage by catechol estrogens and analogues in vitro. Chem. Res. Toxicol. **12,** 270–277.

MOSCOW, J.A., SCHMIDT, L., INGRAM, D.T., GNARRA, J., JOHNSON, B., and COWAN, K.H. (1994). Loss of heterozygosity of the human cytosolic glutathione peroxidase I gene in lung cancer. Carcinogenesis **15,** 2769–2773.

MOYSICH, K.B., AMBROSONE, C.B., VENA, J., MENDOLA, P., MARSHALL, J.R., GRAHAM, S., LAUGHLIN, R., SHIELDS, P.G., KOSTYNIAK, P., GREIZERSTEIN, H., SCHISTERMAN, E.F., and FREUDENHEIM, J.L. (1998). Environmental organochlorine exposure and postmenopausal breast cancer risk. Cancer Epidemiol. Biomarkers Prev. **7,** 181–188.

MOYSICH, K.B., SHIELDS, P.G., FREUDENHEIM, J., VENA, J.E., KOTAKE, T., GRENBERG-FUNES, R.A., SCHLAGER, J.J., MARSHALL, J.R., GRAHAM, S., and AMBROSONE, C.B. (1999). Polychlorinated biphenyls, cytochrome P4501A1 polymorphism, and postmenopausal breast cancer risk. Cancer Epidemiol. Biomarkers Prev. **8,** 41–44.

MULTHAUP, G., RUPPERT, T., SCHLICKSUPP, A., HESSE, L., BEHER, D., MASTERS, C.L., and BEYREUTHER, K. (1997). Reactive oxygen species and Alzheimer's disease. Biochem. Pharmacol. **54,** 533n539 (Abstract).

MUSARRAT, J., AREZINA-WILSON, J., and WANI, A.A. (1996). Prognostic and aetiological relevance of 8-hydroxyguanosine in human breast carcinogenesis. Eur. J. Cancer **32A,** 1209–1214.

NAGASHIMA, M., KASAI, H., YOKOTA, J., NAGAMACHI, Y., ICHINOSE, T., and SAGAI, M. (1995). Formation of an oxidative DNA damage, 8-hydroxydeoxyguanosine, in mouse lund DNA after intratracheal instillation of diesel exhaust particles and effects of high dietary fat and beta-carotene on this process. Carcinogenesis **16,** 1441–1445.

NATHAN, L., and CHAUDHURI, G. (1998). Antioxidant and prooxidant actions of estrogens: potential physiological and clinical implications. Sem. Reprod. Endocrinol. **16,** 309–314.

NORDBACK, I.H., OLSON, J.L., CHAKO, V., and CAMERON, J.L. (1994). Detailed characterization of experimental acute alcoholic pancreatitis. Surgery **117,** 41–49.

OAKLEY, G.G., DEVANABOYINA, U., ROBERTSON, L.W., and GUPTA, R.C. (1996a). Oxidative DNA damage induced by activation of polychlorinated biphenyls (PCBs): implications for PCB-induced oxidative stress in breast cancer. Chem. Res. Toxicol. **9,** 1285–1292.

OAKLEY, G.G., ROBERTSON, L.W., and GUPTA, R.C. (1996b). Analysis of polychlorinated biphenyl-DNA adducts by 32P-postlabeling., Carcinogenesis **17,** 109–114.

PIEDRAFITA, F.J., MOLANDER, R.B., VANSANT, G., ORLOVA, E.A., PFAHL, M., and REYNOLDS, W.F. (1996). An Alu element in the myeloperoxidase promoter contains a composite SP1-throid hormone-retinoic acid response element., J. Biol. Chem. **271,** 14412–14420 (Abstract).

POTISCHMAN, N., WEISS, H.A., SWANSON, C.A., COATES, R.J., GAMMON, M.D., MALONE, K.E., BROGAN, D., STANFORD, J.L., HOOVER, R.N., and BRINTON, L.A. (1998). Diet during adolescence and risk of breast cancer among young women. J. Natl. Cancer Inst. **90,** 226–233.

PRICE-EVANS, D.A. (1993). Genetic Factors in Drug Therapy: Clinical and Molecular Pharmacogenetics. (Cambridge University Press, Cambridge).

RAJASINGHE, H., JAYATILLEKE, E., and SHAW, S. (1990). DNA cleavage during ethanol metabolism: role of superoxide radicals and catalytic iron. Life Sci. **47,** 807–814.

REBBECK, T.R. (1997). Molecular epidemiology of the human glutathione S-transferase genotypes GSTM1 and GSTT1 in cancer susceptibility. Cancer Epidemiol. Biomarkers Prev. **6,** 733–743.

REYNOLDS, W.F., RHEES, J., MACIEJEWSKI, D., PALADINO, T., SIEBURG, H., MAKI, R.A., and MASLIAH, E. (1999). Myeloperoxidase polymorphism is associated with gender specific risk for Alzheimer's disease. Exp. Neurol. **155,** 31–41 (Abstract).

RIBEIRO, D.T., OLIVEIRA, R.C.D., MASCIO, P.D., and MENCK, C.F.M. (1994). Singlet oxygen induces predominantly G to T transversions on a single stranded shuttle vector replicated in monkey cells. Free Radic. Res. **21,** 75–83.

ROHRDANZ, E., and KAHL, R. (1998a). Alterations of antioxidant enzyme expression in response to hydrogen peroxide. Free Radic. Biol. Med. **24,** 27–38.

ROHRDANZ, E., and KAHL, R. (1998b). Alterations of antioxidant enzyme expression inresponse to hydrogen peroxide. Free Radic. Biol. Med. **24,** 27–38.

ROSENBLUM, J.S., GILULA, N.B., and LERNER, R.A. (1996). On signal sequence polymorphisms and diseases of distribution. Proc. Natl. Acad. Sci. USA **93,** 4471–4473.

ROY, D., and LIEHR, J.G. (1989). Changes in activities of free radical detoxifying enzymes in kidneys of male syrian hamsters treated with estradiol. Cancer Res. **49,** 1475–1480.

SALEEM, M.M., AL-TAMER, Y.Y., SKURSKY, L., and AL-HABBAL, Z. (1984). Alcohol dehydrogenase activity in human tissues. Biochem. Med. **31,** 1–9.

SAMOSZUK, M.K., NGUYEN, V., GLUZMAN, I., and PHAM, J.H. (1996). Occult deposition of eosinophil peroxidase in a subset of human breast carcinomas. Am. J. Pathol. **148,** 701–706 (Abstract).

SCHATZKIN, A., and LONGNECKER, M.P. (1994). Alcohol and breast cancer. Cancer **74,** 1101–1110.

SCHWARTZ, J.L., ANTONIADES, D.Z., and ZHAO, S. (1993). Molecular and biochemical reprogramming of oncogenesis through the activity of prooxidants and antioxidants. Ann. NY Acad. Sci. **686,** 262–278.

SHAW, S., and JAYATILLEKE, E. (1992). The role of cellular oxidases and catalytic iron in the pathogenesis of ethanol induced liver injury. Life Sci. **50,** 2045–2052.

SHIMODA-MATSUBAYASHI, S., MATSUMINE, H., KOBAYASHI, T., NAKAGAWA-HATTORI, Y., SHIMIZU, Y., and MIZUNO, Y. (1996). Structural dimorphism in the mitochondrial targeting sequence in the human manganese superoxide dismutase gene. A predictive evidence for conformational change to influence mitochondrial transport and a study of allelic association in Parkinson's disease. Biochem. Biophys. Res. Commun. **226,** 561–565.

SHULL, S., HEINTZ, N.H., PERIASAMY, M., MANOHAR, M., JANSSEN, Y.M.W., MARSH, J.P., and MOSSMAN, B.T. (1991). Differential regulation of antioxidant enzymes in response to oxidants. J. Biol. Chem. **266,** 24398–24403.

SIEMANKOWSKI, L.M., MORREALE, J., and BRIEHL, M.M. (1999). Antioxidant defenses in TNF-reated MCF-7 cells: selective increase in MnSOD. Free Radic. Biol. Med. **26,** 919–924.

SIMIC, M.G., and BERGTOLD, D.S. (1991). Dietary modulation of DNA damage in human. Mutat. Res. **250,** 17–24.

SMITH, M.A. (1998). Alzheimer's disease. Int. Rev. Neurobiol. **4,** 21–54 (Abstract).

STEINMETZ, K.A., and POTTER, J.D. (1996). Vegetables, fruit, and cancer prevention: a review. J. Am. Diet. Assoc. **96,** 1027–1039.

SUBBIAH, M.T., KESSEL, B., AGRAWAL, M., RAJAN, R., ABPLANALP, W., and RYMASZEWSKI, Z. (1993). Antioxidant potential of specific estrogens on lipid peroxidation. J. Clin. Endocrinol. Metab. **77,** 1095–1097.

TATE, D.J., MICELI, M.V., and NEWSOME, D.A. (1995). Phagocytosis and H_2O_2 induce catalase and metallothionein gene expression in human retinal pigment epithelial cells. Invest. Ophthalm. Vis. Sci. **36,** 1271–1279.

THOMPSON, P.A., SHIELDS, P.G., FREUDENHEIM, J.L., STONE, A., VENA, J.E., MARSHALL, J.R., GRAHAM, S., LAUGHLIN, R., NEMOTO, T., KADLUBAR, F.F., and AMBROSONE, C.B. (1998). Genetic polymorphisms in catechol-O-methyltransferase, menopausal status, and breast cancer risk. Cancer Res. **58,** 2107–2110.

TOYOKUNI, S., MORI, T., and DIZDAROGLU, M. (1994). DNA base modification in renal chromatin of Wistar rats treated with a renal carcinogen ferric nitriloacetate. Int. J. Cancer **57,** 123–128.

TRUSH, M.A., and KENSLER, T.W. (1991). An overview of the relationship between oxidative stress and chemical carcinogenesis. Free Radic. Biol. Med. **10,** 201–209.

URSINI, F., MAIORINO, M., and GREGOLIN, C. (1986). Phospholipid hydroperoxide glutathione peroxidase. Tissue React. **8,** 99–103.

WAGNER, J.R., HU, C.-C., and AMES, B.N. (1992). Endogenous oxidative damage of deoxycytidine in DNA. Proc. Natl. Acad. Sci. USA **89,** 3380–3384.

WANG, M., DHINGRA, K., HITTLEMAN, W.N., LIEHR, J.G., DE ANDRADE, M., and LI, D. (1996). Lipid peroxidation-induced putative malondialdehyde-DNA adducts in human breast tissues. Cancer Epidemiol. Biomarkers Prev. **5,** 705–710.

WILLETT, W.C. (1989). The search for the causes of breast and colon cancer. Nature **338,** 389–394.

WILSON, A.G., SYMONS, J.A., MCDOWELL, T.L., DI-GIOVINE, F.S., and DUFF, G.W. (1994). Effects of a tumor necrosis factor (TNF-alpha) promotor base transition on transcriptional activity. Br. J. Rheumatol. **33,** 89–98.

WINTER, M.L., and LIEHR, J.G. (1986). Free radical-induced carbonyl content in protein of estrogen-treated hamsters assayed by sodium boro[^{3}H]hydride reduction. J. Biol. Chem. **266,** 14446–14462.

WISPE, J.R., CLARK, J.C., BURHANS, M.S., DROPP, K.E., KORFHAGEN, T.R., and WHITSETT, J.A. (1989). Synthesis and processing of the precursor for human mangano-superoxide dismutase. Biochim. Biophys. Acta **994,** 30–36.

WRIGHT, R.M., MCMANAMAN, J.L., and REPINE, J.E. (1998). Alcohol-induced breast cancer: a proposed mechanism. Free Radic. Biol. Med. **26,** 348–354.

YAGER, J.D., and LIEHR, J.G. (1996). Molecular mechanisms of estrogen carcinogenesis. Annu. Rev. Pharmacol. Toxicol. **36,** 203–232.

YAMADA, H., YAMADA, Y., ADACHI, T., GOTO, H., OGASAWARA, N., FUTENMA, A., KITANO, M., HIRANO, K., and KATO, K. (1995). Molecular analysis of

extracellular superoxide dismutase gene associated with high level in serum. Jpn. J. Hum. Genet. **40,** 177–184.

YOSHIE, Y., and OHSHIMA, H. (1998). Synergistic induction of DNA strand breakage by catechol-estrogen and nitric oxide: implications for hormonal carcinogenesis. Free Radic. Biol. Med. **24,** 341–348.

ZHONG, S., WYLLIE, A.H., BARNES, D., WOLF, C.R., and SPURR, N.K. (1993). Relationship between the GSTM1 genetic polymorphism and susceptibility to bladder, breast and colon cancer. Carcinogenesis **14,** 1821–1824.

ZHU, B.T., and CONNEY, A.H. (1998). Functional role of estrogen metabolism in target cells: review and perspectives. Carcinogenesis **19,** 1–27.

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2. Ping-Ping Bao, Xiao-Ou Shu, Ying Zheng, Hui Cai, Zhi-Xian Ruan, Kai Gu, Yinghao Su, Yu-Tang Gao, Wei Zheng, Wei Lu. 2012. Fruit, Vegetable, and Animal Food Intake and Breast Cancer Risk by Hormone Receptor Status. *Nutrition and Cancer* **64**:6, 806-819. [CrossRef]
3. Manuela Marron, Paolo Boffetta, Henrik Møller, Wolfgang Ahrens, Hermann Pohlabeln, Simone Benhamou, Christine Bouchardy, Pagona Lagiou, Areti Lagiou, Alena Slámová, Miriam Schejbalová, Franco Merletti, Lorenzo Richiardi, Kristina Kjaerheim, Antonio Agudo, Xavier Castellsague, Tatiana Victorovna Macfarlane, Gary John Macfarlane, Renato Talamini, Luigi Barzan, Cristina Canova, Lorenzo Simonato, Anne-Marie Biggs, Peter Thomson, David Ian Conway, Patricia Ann McKinney, Ariana Znaor, Claire Marie Healy, Bernard Eugene McCartan, Paul Brennan, Mia Hashibe. 2012. Risk of upper aerodigestive tract cancer and type of alcoholic beverage: a European multicenter case–control study. *European Journal of Epidemiology* **27**:7, 499-517. [CrossRef]
4. Yun-Ji Yang, Se-Kwon Kim, Sun-Joo Park. 2012. An Anti-inflammatory Peptide Isolated from Seahorse Hippocampus kuda bleeler Inhibits the Invasive Potential of MG-63 Osteosarcoma Cells. *Fisheries and aquatic sciences* **15**:1, 29-36. [CrossRef]
5. Dai-Hua Fang, Cong-Hai Fan, Qiang Ji, Bo-Xiang Qi, Juan Li, Lu Wang. 2012. Differential effects of paraoxonase 1 (PON1) polymorphisms on cancer risk: evidence from 25 published studies. *Molecular Biology Reports* . [CrossRef]
6. Yousri M. Hussein, Amal F. Gharib, Rasha L. Etewa, Wael H. ElSawy. 2011. Association of L55M and Q192R polymorphisms in paraoxonase 1 (PON1) gene with breast cancer risk and their clinical significance. *Molecular and Cellular Biochemistry* **351**:1-2, 117-123. [CrossRef]
7. Naushad Shaik Mohammad, Rupasree Yedluri, Pavani Addepalli, Suryanarayana Raju Gottumukkala, Raghunadha Rao Digumarti, Vijay Kumar Kutala. 2011. Aberrations in one-carbon metabolism induce oxidative DNA damage in sporadic breast cancer. *Molecular and Cellular Biochemistry* **349**:1-2, 159-167. [CrossRef]
8. Ying Qu, Jinhua Wang, Partha S. Ray, Hua Guo, Jian Huang, Miyung Shin-Sim, Bolanle A. Bukoye, Bingya Liu, Adrian V. Lee, Xin Lin, Peng Huang, John W. Martens, Armando E. Giuliano, Ning Zhang, Ning-Hui Cheng, Xiaojiang Cui. 2011. Thioredoxin-like 2 regulates human cancer cell growth and metastasis via redox homeostasis and NF-#B signaling. *Journal of Clinical Investigation* **121**:1, 212-225. [CrossRef]
9. Miroslava Spanova, Günther Daum. 2011. Squalene - biochemistry, molecular biology, process biotechnology, and applications. *European Journal of Lipid Science and Technology* n/a-n/a. [CrossRef]
10. Jia Hu, Guo-Wu Zhou, Ning Wang, Ya-Jie Wang. 2010. GPX1 Pro198Leu polymorphism and breast cancer risk: a meta-analysis. *Breast Cancer Research and Treatment* **124**:2, 425-431. [CrossRef]
11. Jelena Kasapovi#, Snežana Peji#, Vesna Stojiljkovi#, Ana Todorovi#, Ljiljana Radoševi#-Jeli#, Zorica S. Sai#i#, Snežana B. Pajovi#. 2010. Antioxidant status and lipid peroxidation in the blood of breast cancer patients of different ages after chemotherapy with 5-fluorouracil, doxorubicin and cyclophosphamide. *Clinical Biochemistry* **43**:16-17, 1287-1293. [CrossRef]
12. Naima Badid, Fatima Zohra Baba Ahmed, Hafida Merzouk, Slimane Belbraouet, Nassima Mokhtari, Sid Ahmed Merzouk, Riad Benhabib, Djalloul Hamzaoui, Michel Narce. 2010. Oxidant/Antioxidant Status, Lipids and Hormonal Profile in Overweight Women with Breast Cancer. *Pathology & Oncology Research* **16**:2, 159-167. [CrossRef]
13. Ying Qu, Jinhua Wang, Myung-Shin Sim, Bingya Liu, Armando Giuliano, James Barsoum, Xiaojiang Cui. 2010. Elesclomol, counteracted by Akt survival signaling, enhances the apoptotic effect of chemotherapy drugs in breast cancer cells. *Breast Cancer Research and Treatment* **121**:2, 311-321. [CrossRef]
14. Michael Phillips, Renee N Cataneo, Christobel Saunders, Peter Hope, Peter Schmitt, James Wai. 2010. Volatile biomarkers in the breath of women with breast cancer. *Journal of Breath Research* **4**:2, 026003. [CrossRef]

15. Fernando Warleta, María Campos, Yosra Allouche, Cristina Sánchez-Quesada, Jesús Ruiz-Mora, Gabriel Beltrán, José J. Gaforio. 2010. Squalene protects against oxidative DNA damage in MCF10A human mammary epithelial cells but not in MCF7 and MDA-MB-231 human breast cancer cells. *Food and Chemical Toxicology* **48**:4, 1092-1100. [CrossRef]
16. Y. Li, C. B. Ambrosone, M. J. McCullough, J. Ahn, V. L. Stevens, M. J. Thun, C.-C. Hong. 2009. Oxidative stress-related genotypes, fruit and vegetable consumption and breast cancer risk. *Carcinogenesis* **30**:5, 777-784. [CrossRef]
17. Aref Hosseinian Amiri, Mohammad Javad Tarrahi, Alireza Rafiei. 2009. Clinical Finding and Outcome in Suicidal Attempt Due to Intravenous Injection of Kerosene. *Pakistan Journal of Biological Sciences* **12**:5, 439-442. [CrossRef]
18. Chunyan He, Rulla M. Tamimi, Susan E. Hankinson, David J. Hunter, Jiali Han. 2009. A prospective study of genetic polymorphism in MPO, antioxidant status, and breast cancer risk. *Breast Cancer Research and Treatment* **113**:3, 585-594. [CrossRef]
19. Jelena Kasapovic, Snezana Pejic, Ana Todorovic, Vesna Stojiljkovic, Ljiljana Radosevic-Jelic, Snezana Pajovic. 2009. Antioxidant status in breast cancer patients of different ages after radiotherapy. *Archives of Biological Sciences* **61**:1, 23-28. [CrossRef]
20. Jelena Kasapovic#, Snez#ana Pejic#, Ana Todorovic#, Vesna Stojiljkovic#, Snez#ana B. Pajovic#. 2008. Antioxidant status and lipid peroxidation in the blood of breast cancer patients of different ages. *Cell Biochemistry and Function* **26**:6, 723-730. [CrossRef]
21. Vineeta Singh, Christobel Saunders, Liz Wylie, Anita Bourke. 2008. New diagnostic techniques for breast cancer detection. *Future Oncology* **4**:4, 501-513. [CrossRef]
22. Bayram Yilmaz, John Ssempebwa, Carl R. Mackerer, Kathleen F. Arcaro, David O. Carpenter. 2007. Effects of Polycyclic Aromatic Hydrocarbon-Containing Oil Mixtures on Generation of Reactive Oxygen Species and Cell Viability in MCF-7 Breast Cancer Cells. *Journal of Toxicology and Environmental Health, Part A* **70**:13, 1108-1115. [CrossRef]
23. Vidya Akhileshwar, Samir P. Patel, Surendra S. Katyare. 2007. Diabetic cardiomyopathy and reactive oxygen species (ROS) related parameters in male and female rats: A comparative study. *Indian Journal of Clinical Biochemistry* **22**:1, 84-90. [CrossRef]
24. Wen-Sheng Wu. 2007. The signaling mechanism of ROS in tumor progression. *Cancer and Metastasis Reviews* **25**:4, 695-705. [CrossRef]
25. Samir P. Patel, Surendra S. Katyare. 2006. A comparative study of reactive oxygen species (ROS) related parameters in rat tissues. *Indian Journal of Clinical Biochemistry* **21**:1, 48-53. [CrossRef]
26. Jaanus Kruusma, Adam M. Benham, J. A. Gareth Williams, Ritu Kataky. 2006. An introduction to thiol redox proteins in the endoplasmic reticulum and a review of current electrochemical methods of detection of thiols. *The Analyst* **131**:4, 459. [CrossRef]
27. Mia M. Gaudet, Marilie D. Gammon, Regina M. Santella, Julie A. Britton, Susan L. Teitelbaum, Sybil M. Eng, Mary Beth Terry, Jeannette T. Bensen, Jane Schroeder, Andrew F. Olshan, Alfred I. Neugut, Christine B. Ambrosone. 2005. MnSOD Val-9Ala Genotype, Pro- and Anti-oxidant Environmental Modifiers, and Breast Cancer Among Women on Long Island, New York. *Cancer Causes & Control* **16**:10, 1225-1234. [CrossRef]
28. R DUMITRESCU, P SHIELDS. 2005. The etiology of alcohol-induced breast cancer. *Alcohol* **35**:3, 213-225. [CrossRef]
29. Beena P. Patel, Upendra M. Rawal, Pankaj M. Shah, Jayesh A. Prajapati, Rakesh M. Rawal, Tina K. Dave, Prabhudas S. Patel. 2005. Study of Tobacco Habits and Alterations in Enzymatic Antioxidant System in Oral Cancer. *Oncology* **68**:4-6, 511-519. [CrossRef]
30. Susan A. Nowell, Jiyoung Ahn, Christine B. Ambrosone. 2004. Gene-Nutrient Interactions in Cancer Etiology. *Nutrition Reviews* **62**:11, 427-438. [CrossRef]
31. Jane Higdon, Balz FreiVitamin C, Vitamin E, and b-Carotene in Cancer Chemoprevention **20041296**, . [CrossRef]
32. Magda Morad, John Digiovanni, Melissa Bondy, Amr Soliman, Suryanarayana Vulimiri, Heather Kleiner, Jianjun Shen, Saad Eissa, Donghui LI, Dennis Johnston, Serrine Lau, Hala Taha, Herng-Hsang Lo, Farzana Lukmanji.

2004. High levels of oxidative DNA damage in lymphocyte DNA of premenopausal breast cancer patients from Egypt. *International Journal of Environmental Health Research* **14**:2, 121-134. [CrossRef]

33. Keith W. Singletary, Sean L. Barnes, Richard B. van Breemen. 2004. Ethanol inhibits benzo[a]pyrene-DNA adduct removal and increases 8-oxo-deoxyguanosine formation in human mammary epithelial cells. *Cancer Letters* **203**:2, 139-144. [CrossRef]
34. Zora Djuric, Samir Lababidi, Virginia E. Uhley, Lance K. Heilbrun. 2004. Levels of 5-hydroxymethyl-2#-deoxyuridine in DNA from women participating in an intervention trial of low-fat and low-energy diets. *Biomarkers* **9**:1, 93-101. [CrossRef]
35. X. Steven Wan, Zhaozong Zhou, Ann R. Kennedy. 2003. Adaptation of the Dichlorofluorescein Assay for Detection of Radiation-Induced Oxidative Stress in Cultured Cells. *Radiation Research* **160**:6, 622-630. [CrossRef]
36. Michael Phillips, Renee N. Cataneo, Beth Ann Ditkoff, Peter Fisher, Joel Greenberg, Ratnasiri Gunawardena, C. Stephan Kwon, Farid Rahbari-Oskoui, Cynthia Wong. 2003. Volatile Markers of Breast Cancer in the Breath. *The Breast Journal* **9**:3, 184-191. [CrossRef]
37. Snezana Pajovic, Snezana Pejic, Jelena Kasapovic, Marija Radojcic, Nenad Borojevic, Ljiljana Radosevic-Jelic. 2003. Role of superoxide dismutase in individualization of breast cancer radiation therapy protocols. *Archive of oncology* **11**:3, 191-192. [CrossRef]