

Summit Meeting on Breast Cancer among African-American Women

Supplement to Cancer

Environmental Risk Factors for Breast Cancer among African-American Women

Mary S. Wolff, Ph.D.¹
Julie A. Britton, Ph.D.¹
Valerie P. Wilson, Ph.D.²

¹ Department of Community and Preventative Medicine, Mount Sinai School of Medicine, New York, New York.

² Center for Bioenvironmental Research, Tulane University, New Orleans, Louisiana.

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There are few unequivocally established environmental carcinogens for breast cancer in women. Nevertheless, environmental factors are believed to explain much of the international variation in breast cancer risk and possibly differences among racial/ethnic groups. Along with lifestyle, some adverse exposures may be higher in minority racial/ethnic groups and in underserved populations that experience higher ambient contamination. Associations have been found between environmental agents and breast cancer in subgroups of women who can be identified by common susceptibility traits as well as by timing of exposures at certain milestones of reproductive life. Susceptibility can be defined by social, environmental, and genetic modalities—factors that may predominate in certain racial/ethnic groups but that also transcend racial/ethnic boundaries. For example, genes involved in transcription and estrogen metabolism have rapid variants that are more prevalent among African-Americans, yet risk accompanying metabolic changes from these genes will prevail in all racial/ethnic groups. Lack of reliable exposure assessment remains a principal obstacle to elucidating the role of environmental exposures in breast cancer. Resources must be identified and consolidated that will enable scientists to improve exposure assessment and to assemble studies of sufficient size to address questions regarding exposure, susceptibility, and vulnerability factors in breast cancer. Breast cancer studies should be expanded to examine combinations of chemicals as well as competing or complementary exposures such as endogenous hormones, dietary intake, and behavioral factors. *Cancer* 2003;97(1 Suppl):289–310.

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Other than radiation and alcohol, few environmental exposures to our knowledge have been associated clearly with breast cancer etiology in any racial/ethnic group. Nevertheless, environmental etiologies have been invoked to explain the failure of known risk factors to account entirely for the occurrence of breast cancer. Based on studies of twins and of families with cancer in Sweden, recent estimates indicate that > 60% of breast cancer risk has an environmental component.^{1,2} Environmental factors, including diet, also are believed to account for some of the disparity in breast cancer rates noted among racial/ethnic groups. African-American and white women in the U.S. are reported to have similar overall rates of breast cancer. However, compared with white women, African-American women have a higher incidence of breast cancer before age 40 years, and their prognosis after a diagnosis of breast cancer is reported to be

TABLE 1
Mechanistic Framework for the Action of Environmental Agents in Breast Cancer

Gene-regulated process with potential for environmental modulation	Step in carcinogenesis	Examples of putative environmental exposure	Possible temporal window
Mammary cell development and differentiation	Susceptibility to premalignant changes	Chemicals in utero	Perinatal
Oxidation, cell turnover	Formation of procarcinogen	Modulation of gene expression PAH epoxide, viral damage	Peripubertal
Detoxification	Gene mutation (DNA adduct)	PAH epoxide, free radicals	Lifetime
DNA repair	Clonal expansion, oncogene mutation	Modulation of gene expression <i>P53</i> mutations by PAH	Lifetime
Growth, tumor promotion	Tumor growth, tumor recurrence	DDT, phorbol esters, DES?	Young adult
Tumor progression	Tumor aggressivity, metastasis Metastasis	Modulation of hormone metabolism Dieldrin?	Middle age

PAH: polycyclic aromatic hydrocarbons; DDT: bis (4-chlorophenyl)-1,1,1 trichloroethane; DES: diethylstilbestrol.

poorer across all ages.³ Differences in breast cancer incidence among racial/ethnic groups within in the U.S., along with wide international variability, suggest that environmental factors contribute to the etiology of the disease. Among African-American women within the U.S., breast cancer mortality also appears to vary geographically.⁴

Furthermore, it has been suggested that disparate exposures in conjunction with different genetic susceptibility may make African-Americans more vulnerable than white individuals to the insults of exogenous carcinogens.⁴ Therefore, the investigation of environmental exposures that may have a differential impact on breast cancer etiology in African-American women should be considered, and studies should seek to identify risk factors that might reduce or even eliminate these disparities in incidence and mortality. Of particular urgency is the failure to understand the higher incidence of breast cancer reported among young African-American women, which may be attributable to risk factors other than established reproductive endpoints.⁵

The biologic basis for the investigation of breast cancer and environment is broad (Table 1). First, as mutagens or tumor promoters, environmental chemicals may influence carcinogenesis at many junctures in its pathway; they also may modulate the metabolic processes that activate and detoxify these pathways. In addition, environmental contaminants, acting as hormone mimics, may affect breast development and cell differentiation in early life. Therefore, to qualify as a mammary carcinogen, an environmental exposure should have the potential to operate within this proposed scheme. Environmental factors may be relevant to particular characteristics of breast cancer occurring in African-Americans: early onset, poor prognosis, and early life events such as a younger age at menarche.

This temporal framework of reproductive events is described elsewhere in this supplement to *Cancer*.

Members of the Conference Workshop on Environmental Issues and Breast Cancer in African-American Women argued that although subgroups at increased breast cancer risk may be more readily identifiable in racial/ethnic groups, such entities are just as likely to exist across race and ethnicity. Examples include women with a high body mass index (BMI), variants in *BRCA1/BRCA2*, and low socioeconomic status (SES). Race/ethnicity does not imply that individuals are "genetically homogenous"; thus it is necessary to consider criteria other than just skin color to classify "at-risk" susceptible subgroups. For instance "blacks" of various ancestry (i.e., African and Caribbean) residing within the U.S. are genetically heterogenous and therefore for some scientific hypotheses it would be methodologically inappropriate to consider these groups together.

Environmental Exposures That May Be Relevant for Breast Cancer Etiology and Progression

Based on laboratory studies, a number of potential breast cancer carcinogens have been identified that also are known environmental contaminants (Table 2). More than 30 mammary carcinogens in animals and at least twice that many human carcinogens have been characterized to date.⁶⁻⁸ Many of these chemicals are more likely to be encountered in an industrial environment than in settings that most women experience daily. With the advent of the so-called "endocrine disruptor" phenomenon,⁹ hormonally active environmental chemicals have been targeted as potential risk factors for reproductive toxicity, including breast cancer. In a recent survey, 86 potential mammary toxins were identified and measured in household dust and air, including 9 known mammary

TABLE 2
Known Mammary Carcinogens in Rodents

Benzene, butadiene	Mutagenic agents
3-MC, DMBA, aromatic amines	
EDB, VC, CCl ₄ , CH ₂ Cl ₂	
MNU and analogs	Hormonal agents
DES, E2	

3-MC: 3-methylcholanthrene; DMBA: dimethylbenzanthracene; EDB: ethylene dibromide; VC: vinyl chloride; CCl₄: carbon tetrachloride; CH₂Cl₂: dichloromethane; MNU: methylnitrosourea; DES: diethylstilbestrol; E2: estradiol.

Adapted from: Huff J. Breast cancer risks from environmental chemicals. *Eur J Oncol*. 2000;5:127-132; Dunnick JK, Elwell MR, Huff J, Barrett JC. Chemically induced mammary gland cancer in the National Toxicology Program's carcinogenesis bioassay. *Carcinogenesis*. 1995;16:173-179; and Wolff MS, Weston A. Breast cancer risk and environmental exposures. *Environ Health Perspect*. 1997;105(Suppl 4):891-896.

carcinogens and 77 hormonally active agents or closely related compounds. Of these, > 30% were detected at least once in a pilot study of 3 homes (7 samples).¹⁰ A study of occupational exposure to these compounds found approximately 30% of women to have hormonally active exposures in their workplace.¹¹

The carcinogenic polycyclic aromatic hydrocarbons (PAH; e.g., 3-methylcholanthrene and dimethylbenzanthracene [DMBA]) and heterocyclic amines (HAA) are ubiquitous in the environment and arise from many ambient and food sources. In addition, a large variety of compounds currently in commerce (e.g., styrene, chlorinated alkanes and alkenes, and pesticides) are analogs of the chemicals listed in Table 2; relatively few have been tested for carcinogenic potential. Other chemicals (bis(4-chlorophenyl)-1,1,1-trichloroethane [DDT], polychlorinated biphenyls [PCBs], and atrazine) that are not acknowledged breast carcinogens are known to enhance or inhibit tumor growth.^{12,13} The organochlorines (OCs), including DDT, PCB, 2,3,7,8-tetrachlorodibenzodioxin (TCDD), polybrominated biphenyls (PBB), and phenoxy acids as well as solvents, may reduce cell-mediated immune function.¹⁴ A number of environmental agents have been investigated in epidemiologic studies with respect to their potential influence on breast cancer risk. However, few of these have been examined in terms of their specific relation to breast cancer risk in African-American women. The quality of the exposure assessments in studies conducted to date varies greatly, and few or no data are available regarding exposures to the majority of these chemicals. Therefore, obtaining better exposure information is perhaps the most challenging part of environmental cancer research.

Occupational exposures to chemicals usually are

higher than those in other surroundings, providing the opportunity to determine cancer risk among workers, either by identifying work-related exposures within specific cancer types or by enumerating cancer occurrence within jobs that have known chemical or physical contamination. Studies have investigated the incidence or mortality of all cancer types in specific occupations, and some results support an environmental etiology for breast cancer in both African-American and white women workers. However, there are limitations to such studies (see Goldberg et al.¹⁵ for a discussion of these issues). Of primary concern in many of the studies are the imprecise or poorly classified exposures or disease status, the examination of breast cancer mortality rather than incidence, and the lack of information regarding confounders. Furthermore, occupational cohorts often have too few women diagnosed with breast cancer, whereas case-control studies often have too few women within a given occupational group available for analyses. Either situation reduces statistical power to examine hypotheses. Poor assessment of exposure or disease is likely to result in attenuated risk estimates, whereas failure to consider confounders can overestimate or underestimate study findings. Finally, conclusions drawn from mortality studies of breast cancer often can be misleading with regard to understanding etiology because approximately 67% of women who survive the disease are excluded. However, such research often points the way to more carefully designed analytical studies.

In occupational research, evidence that chemical exposures may increase the risk for breast cancer incidence or mortality is most consistent among school teachers and managerial personnel.¹⁶⁻¹⁸ However, it is not obvious that these jobs would have high carcinogenic exposures, and it is possible that other risk factors such as reproductive history were not assessed adequately.^{19,20} Among the multiethnic occupational studies is a large-scale retrospective analysis that included approximately 4000 breast cancer deaths among African-Americans; both African-American and white women were found to have a higher risk of mortality from breast cancer if they had experienced higher levels of various metal exposures.²¹ In addition, solvents and styrene posed an increased breast cancer mortality risk in this study. Among women who had worked in chemical, pharmaceutical, printing, or electrical equipment manufacturing industries in New Jersey, the risk of death from breast cancer among African-American women, but not white women, was elevated.²² A recent study of hairdressers and barbers, who are exposed to a variety of genotoxic and mutagenic chemicals, included 19,980 deaths among white women and 3602 deaths among African-American

women.²³ Slight elevations in the risk of breast cancer mortality were found (mortality odds ratio [OR] of 1.10 [95% confidence interval (95% CI), 1.03–1.17] for whites and a mortality OR of 1.15 [95% CI, 0.98–1.36] for African-Americans). Other occupational studies, although not including minority women, have supported the association between an elevated breast cancer risk and potentially carcinogenic chemical exposures in the workplace. These reports include exposures to PAH and benzene exposures,²⁴ to solvents and pesticides,¹⁶ among dry-cleaning, auto repair, gas station workers,²⁵ and textile and apparel jobs.²⁶

Female farmers generally have a lower risk of breast cancer compared with nonfarmers, possibly because of protective reproductive factors such as a late age at menarche or vigorous physical activity.^{18,27} For example, in a recent population-based case-control study, female farmers exhibited an overall lower risk of breast cancer than women who did not work on a farm. However, in this population, female farmers exposed to pesticides were at greater risk of developing breast cancer.²⁸ This study, the Carolina Breast Cancer Study (CBCS), is the only study published to date that has reported extensively on environmental risk factors for breast cancer incidence among a sizeable number of African-American women. Enrollment recently was completed for the study, which includes > 800 cases and a similar number of population-based controls; currently published articles include approximately 600 African-Americans (300 cases and > 300 controls; R.C. Millikan, personal communication). Another potential population will be derived from a large-scale prospective follow-up study of 64,000 African-American women that is still underway. A major goal is to assess risk factors for breast cancer, of which incident cases are identified every 2 years through follow-up questionnaires. Limited information regarding environmental exposures will be available.²⁹

Individual Environmental Agents, Suspected to Be Mammary Carcinogens, and Reported Risks in African-American Women

Ionizing radiation is the most well established environmental risk factor for breast cancer. Based on information from groups with very high exposure, it is known that nearly all the excess risk occurs among women who were exposed during adolescence and who are diagnosed with breast cancer at a relatively early age.^{30,31} In a study of survivors of childhood cancer, 68% of whom received radiation therapy, breast cancer was found to be the most common of all second malignancies regardless of gender.³² It also had the longest latency of all second tumors (a median of 16 years after diagnosis of the first cancer). The

CBCS found a modest, nonsignificant risk among women exposed to ionizing radiation between ages 10–19 years (OR of 1.6; 95% CI, 0.4–7.8); these data were adjusted for race, but separate analyses were not conducted for African-Americans.³³ The majority of studies of workers exposed to low levels of radiation (e.g., weapons facilities), generally over an extended time period, reportedly have not observed an increased breast cancer risk even in the higher ranges of such exposure.¹⁵ Admittedly, the failure to detect associations may be attributable to methodologic limitations in these studies.¹⁵ Pilots and flight attendants have been studied for cancer risk related to excess high-altitude radiation exposure. There were suggestive increases of breast cancer among flight attendants,^{34,35} but it has been noted that other factors such as parity may account for these findings.³⁶

Another environmental exposure that has been examined frequently in relation to breast cancer is electromagnetic fields (EMF). In several studies of male breast cancer, an elevated risk was observed among men employed in either electrical,^{37,38} telephone,³⁹ or railroad⁴⁰ occupations that have been linked with higher EMF exposure. Some studies of female workers also support an association between EMF and breast cancer risk,^{41–43} yet the majority do not appear to (as reviewed by Caplan et al.⁴⁴). Furthermore, the inconsistent results of studies examining other sources of EMF exposure such as residential proximity to power lines^{45–52} or electric blanket use^{52–57} do not appear to corroborate a harmful relation between EMF and breast cancer risk. Thus, to date, the reported findings have not shown a consistent link between EMF and breast cancer risk. However, as a recent comprehensive review concluded, the verdict is still not in given that methodologic limitations may explain the variation in findings from these studies.⁴⁴

Cigarette smoking is not an acknowledged breast cancer risk factor, but there has been sustained interest in its evaluation because chemicals in cigarette smoke are potent mammary carcinogens in rodents and are human carcinogens for other organs (e.g., lung, bladder, and lymphatic system).⁵⁸ The majority of studies examining smoking alone as a breast cancer risk factor do not support an overall association,^{58–61} including two studies examining this association in African-American women.^{5,62} Failure to detect an association may be due to the fact that tobacco smoke has been hypothesized to have dual influences on breast cancer risk. It may increase risk by either acting directly as a genotoxic agent or by acting as a promoter, but may reduce risk through its antiestrogenic properties.^{60,63} These contradictory influences on risk

may be dependent on the age of the individual or the time period of exposure to tobacco smoke.⁶⁴ Nevertheless, both would be of relevance to breast cancer etiology among African-American women. Genotoxic exposures derived from tobacco use are most likely to be carcinogenic to the breast during early life; this finding would apply mainly to activity of chemical components as primary carcinogens, as with ionizing radiation. Animal and in vitro studies strongly support this idea (i.e., that mammary cells at an early stage of development are more susceptible to PAH-induced tumorigenesis).^{65–67} Epidemiologic studies that have investigated the question have found some hints of elevated breast cancer risk among women who report smoking as teenagers,^{33,58} as well as among women exposed to passive smoke at younger ages⁶⁴ or who actively smoked during their first pregnancy.⁶⁸

At later stages of tumorigenesis, smoking may exert an effect by acting as a promoter or by causing mutations in genes related to tumor suppression and progression (Table 1). Postmenopausal women in the CBCS exhibited higher risk if they had been smokers in the past (OR of 1.5; 95% CI, 1.0–2.4) or in the recent past (OR of 3.4; 95% CI, 1.4–8.1, adjusted for race and age).⁶⁹ In the interim between tumor initiation and progression to malignancy, cigarette smoke may exert its antiestrogenic effects, thereby reducing a woman's risk of breast cancer.⁶⁴ Thus, ignoring the timing of exposure may obscure the underlying relation between tobacco smoke and breast cancer risk. Likewise, Morabia et al. observed a positive association between tobacco smoke exposure and breast cancer when the reference group was restricted to women that not only had never actively smoked but who also had never been exposed to passive smoke,⁷⁰ suggesting that previous studies may have failed to detect an association as a result of unrecognized exposures within their referent group.^{71–73} Genetic modulation of tobacco smoke exposures is considered below.

PAH and HAA compounds are among the putative carcinogens in cigarette smoke, and they also are present in foods cooked at a high temperature, smoked foods, charcoal-broiled meats, and air pollution. HAA exposures may be derived predominantly from cooked meat. A number of recent studies have examined relations between the intake of cooked meat and breast cancer risk; some^{74,75} but not all^{76,77} studies reported significant associations.

PAH themselves are prototypical mammary carcinogens in rodents,⁷⁸ but links between PAH exposures and breast cancer, and indeed with other malignancies, in humans are not definitive. As with smoking, the possible mechanisms are complex; PAH and their metabolites can be agonists or antagonists in

hormonal pathways, making the epidemiologic characterization of risk even more difficult.^{60,79} PAH exposure can be estimated via questionnaire or biologic measures. Questionnaire assessment of exposure relies on recall of experiences that occurred in the distant past. Unlike HAA, PAHs are found in many pollution sources, making accurate exposure assessment complicated. Conversely, the ability to measure the genotoxic agent (PAH-DNA adducts) in target tissue presents an excellent opportunity for more precise, objective exposure assessment. However, the lifetime of such adducts is relatively short, requiring the assumption either that the current measure of exposure is indicative of the individual's exposure at the time of carcinogenesis or that exposures are related to late-stage advancement of tumor development. Alternatively, it has been argued that higher levels of such adducts in an individual serve as a biomarker of greater susceptibility.⁸⁰

Two separate studies, not conducted among African-Americans, found no relation between PAH-DNA adducts in breast tissue and a history of smoking, food intake, or P53 expression.^{81,82} Such findings suggest a lack of specificity between these sources of exposure and the biomarker of exposure. Two studies that included African-Americans quantified PAH-DNA or aromatic-DNA adducts in breast tissue, but no significant differences in adduct levels were reported based on race/ethnicity.^{82,83} Nor were case-control differences between PAH-DNA adducts in breast tissue found to be significant when adjusted for race, although there was a positive association with breast cancer risk.⁸³ One of these investigations found more adducts in breast adipose than epithelial cells, which may have a bearing on the presumed mechanism of action (i.e., paracrine action [across cell types] vs. autocrine function [direct changes within the cell]).⁸²

PAH-related mutations have been identified in the tumor suppressor gene *P53*, which may inactivate the gene's tumor suppressor function and augur for poor prognosis. One of these mutations has been reported to be more common among African-Americans than whites and to have greater geographic variability,^{84,85} suggesting an environmental origin.⁴ However, in the largest study of P53 expression in tumors among African-Americans published to date, no differences among three ethnic groups, including whites and Hispanics, were found.⁸⁶

In addition to assessment issues, repair systems for PAH damage in biologic systems are efficient, and thus the associations between PAH-DNA adducts and cancer may be very weak or may be limited to small subgroups of susceptible individuals.

OCs are neutral, persistent, lipid-soluble agents

TABLE 3
Comparison of Organochlorine Levels in African-Americans versus Whites

	African-American			White			Basis	Reference
	DDE	PCB	No.	DDE	PCB	No.		
FL, 1960s ^a	13	-	70	8.2	-	64	Whole	Davies et al., 1969 ⁹³
SC, 1968-rural ^a	11	0.3	> 100	3	2.3	> 100		Finklea et al., 1972 ⁹⁵
SC, 1968-urban ^a	6	1.9	> 100	3	3.1	> 100		
CA, 1964-1971 ^b	43	4.5	50	35	4.2	50	Whole	Krieger et al., 1994 ⁹⁷
NC, 1993-1996 ^b	1690	510	270	760	380	389	Lipid	Millikan et al., 2000 ⁹¹
NYC, 1994-1997 ^b	1000	800	69	550	650	193	Lipid	Wolff et al., 2000 ⁹⁸
CT, 1994-1997 ^b	1930	-	< 100	917	-	< 100	Lipid	Zheng et al., 1999 ⁹⁶

DDE: bis(4-chlorophenyl)-1,1 dichloroethene; PCB: polychlorinated biphenyls.

^a Parts per billion, means or geometric means, among noncancer subjects in recent studies.

^b Parts per billion, means or geometric means, among control subjects in recent studies.

Lipid basis is approximately 200. OR × OR whole serum in the majority of reports.

that have been widely used as pesticides or electrical insulating fluids. They have the potential to enhance or inhibit hormonal actions. As such, they may influence tumor development or growth.^{12,13,87-89} Because OCs are not complete carcinogens, any significant increases in risk conferred by OC exposure may require the presence of other risk factors. Interactions between hormonally related risk factors (reproductive history, BMI, and progression) and OCs as reported in several studies⁹⁰⁻⁹² could be explained as late-stage promoting activity by these compounds, the type of activity they exhibit in biologic models.^{12,14} Similarly, modulation of cytochrome P450 enzymes (or their *CYP* genes) by OCs leads to alterations in hormone metabolism and to oxidative damage that may contribute to tumor development throughout its time-course.

Studies over the past 30 years consistently have found OC compounds to be present at higher levels in African-Americans compared with whites,⁹³⁻⁹⁵ and this pattern appears to continue. Levels of bis(4-chlorophenyl)-1,1-dichloroethene (DDE) in African-Americans are reported to be approximately twice as high as those found in whites, with somewhat similar trends reported for PCBs (Table 3).^{91,96-98} Hispanic women also were found to have higher levels of OCs compared with whites in some reports. In various studies, levels of OCs in white women have reportedly declined approximately 10-fold since 1970, but this finding was not apparent in African-American women. The 10-fold decline is consistent with approximately three half-lives of elimination accompanied by no further exposure; therefore, African-Americans may continue to be exposed and they also may have longer clearance times that are attributable to both metabolic capacity and a higher BMI. Therefore, if there is a

threshold dose for breast cancer risk with OCs, then the low levels currently reported among white women may fall below that, whereas risk may yet be discernible in African-American women.

A great many reports currently exist regarding the relation between OC exposures and breast cancer risk, mainly with regard to DDE and PCBs, which have been measured in bodily fluids at the time of diagnosis or not long before. The first study to consider African-American women found a nonsignificantly elevated risk with higher DDE or PCB exposure.⁹⁷ However, DDE and PCB levels in this study were highest among African-Americans, and the association between OCs and breast cancer risk also were strongest, compared with white and Asian women, albeit in a relatively small sample size. The CBCS found that both DDE and PCBs were associated with an elevated breast cancer risk among 292 African-American cases and 270 controls (the OR for PCB was statistically significant at 1.7 with a 95% CI of 1.0-3.0). There was no apparent association between 456 white cases and 389 controls.⁹¹ Again, in this study levels of DDE and PCBs were higher among African-American women. The majority of the case-control studies with the largest sample sizes (> 300 cases) have been comprised primarily of white women, and found no significant associations between individual OC residues measured in blood or adipose tissue and breast cancer risk in the overall population.⁹⁹⁻¹⁰² Similarly, a pooled analysis of 1400 cases from 5 studies, primarily white individuals, found no increased risk of breast cancer with exposure to DDE or PCB when adjusted for race.¹⁰² Nevertheless, some studies have reported increased risks between one or more OC compounds and breast cancer onset¹⁰⁴⁻¹⁰⁸ or poorer prognosis.^{92,101}

Associations have been found between OCs and

breast cancer risk within subgroups that may be related to hormonal factors, including women who had not breastfed,⁹⁰ postmenopausal women,¹⁰⁹ and women with the rapid CYP1A1 genotype.¹¹⁰ In the CBCS, in which both DDE and PCBs were associated with risk among African-Americans, higher levels of exposure to specific OC compounds were found to be associated with an increased breast cancer risk in certain subgroups of women, including African-American women in the upper tertile of BMI (PCB: OR of 4.9; 95%CI, 1.6–14.8) and African-American women in the lowest tertile of BMI (DDE: OR of 3.8; 95% CI, 0.98–15.1), as well as African-American and white women who were parous but had never breastfed (for both DDE and PCB).⁹¹ Given these observations among African-American women in the CBCS, and their consistency with other studies,⁹⁰ further investigation may be warranted regarding the effect of OC exposure on breast cancer risk with respect to reproductive milestones, including pregnancy, menopause, and pubertal development.^{111,112} In addition, the higher levels of OCs among African-Americans and their poorer prognosis would warrant the investigation of breast cancer incidence, recurrence, and survival with regard to hormonally active xenobiotics such as these. Finally, OCs possess a range of hormonal activity (estrogenic, antiandrogenic, antiestrogenic, etc.). Therefore, specific mechanisms may be relevant to African-American women, whose hormonal profiles have been shown in some studies to differ from white women at different times of life.^{113–116}

Other Exposures

Certain solvents and related small molecules including the chloroethylenes are reported to be carcinogens in animals and some are mammary carcinogens (Table 2).^{8,117} Many of these substances commonly are found in the ambient environment, in public water supplies, and around hazardous waste sites. A few ecologic studies have assessed risk for breast cancer with such exposures, although some initial associations subsequently have been suggested to be the result of confounding factors.¹¹⁸ In North Carolina, halomethanes in drinking water (chlorination byproducts of water treatment) were quantified by zip code but were not found to be associated significantly with breast cancer in either African-American or white women.¹¹⁹ Nitrates in water, an indicator of mutagenic exposures, were quantified on a community basis in Iowa, and associations with some malignancies were found, but not with breast cancer.¹²⁰ In another study, atrazine (a hormonally active herbicide) was quantified at the county level and was found to be associated with breast cancer risk.¹²¹ A study of

women on Long Island, New York, in which the addresses of women in a case-control study of breast cancer were linked with proximate high-traffic sites or chemical facilities having carcinogenic emissions, found a higher risk among postmenopausal women living closer to the sources of exposure.¹²² In Massachusetts, case-control studies of breast cancer have investigated estrogenic chemical exposures that occurred in previous occupations and tetrachloroethylene contamination of municipal water supplies; no significant associations were found, but there were suggestions of positive associations with tetrachloroethylene.^{11,123} However, these studies suffer many of the same shortcomings as occupational studies, including difficulty in adjusting for confounding factors such as reproductive history. In addition, the ecologic studies cannot quantify exposures on an individual basis, leading to imprecisely characterized risk. However, many chemicals, including solvents, are short-lived in the body and historic assessments can be the only way to estimate exposures.

Factors That Act in Concert with Exposures to Link Environment with Breast Cancer Etiology and Progression

The majority of environmental exposures today either exist at concentrations too low or have carcinogenic potential too weak to be easily identified as risk factors, in contrast with very strong associations between smoking and lung cancer or between radiation and various cancers. Therefore, modifying factors that make some women more susceptible to the effects of environmental agents must be identified to elucidate any role of the environment in breast cancer. Exposure assessments and factors that create or influence susceptibility can be examined within several contexts, an approach that may benefit research among African-American women but that would encompass susceptible women of any racial/ethnic group. Four contexts were envisioned by this Workshop as being central to the investigation of environmental agents and exposure modifiers in breast cancer.

Context 1. Environment/environment interactions

Mammary carcinogens may interact with other exposures to increase risk above and beyond the risk associated with each individual exposure. Therefore, epidemiologic research and laboratory investigations must ascertain effects of multiple as well as single exposures, thereby advancing the understanding of joint effects. Exposures interacting with one another can have a direct and/or a modifying effect on disease risk. Combinations of exposures have not been well studied because of biologic as well as epidemiologic

study design complexities. A major obstacle to the study of joint exposures is the need for large numbers of participants with complete risk factor assessments.

Some information concerning the resultant effect of multiple exposures can be gleaned from laboratory studies with the OCs, in which a combination of chemicals has been administered, usually at staggered timepoints, to assess promoter or initiator potential in animal models. The timing of tumor-promoting, tumor-inhibiting, or tumor initiating exposures is critical.¹²⁴ Examples include dioxin (TCDD; an antiestrogenic chemical), DDT, and PCBs as tumor promoters and PAH or MNU as tumor initiators.^{12,13,87} Many *in vitro* studies have found effects to be additive.^{125–127}

Environment/environment interactions may occur between exposures of very different origins, such as chemicals and viruses. Solvents, DDT, TCDD, and PCBs are immunotoxic,¹²⁸ and some chemicals of this kind have been implicated as cofactors in hematopoietic malignancies that have a viral etiology,^{14,129} including PCBs and non-Hodgkin lymphoma.^{130,131} Given the recently revived interest in viral etiologies for breast cancer,^{132–134} investigation of cofactors such as OCs that may be secondary to viral immunosuppression could be relevant. Also, by compromising T-cell immune function, OCs and other such immunotoxic exposures may serve as late-stage promoters of cancers that originate through other mechanisms.

The examination of joint exposures should take into account endogenous hormones, which are considered carcinogens and may act as mutagens as well as transcription factors. Hormone levels can be affected by many factors including BMI, alcohol intake, and diet. Examples can be found in the study of OCs in relation to breast cancer risk. Associations between OCs and breast cancer risk in the CBCS differed according to BMI among African-American and white women.⁹¹ BMI has been reported to have a major influence on the disposition and metabolism of persistent OCs.^{135–137} Furthermore, BMI and weight gain have been reported to be associated independently with postmenopausal breast cancer risk,^{138–142} possibly through the elevation of steroid hormones synthesized in peripheral adipose.¹⁴³ Weight at the time of breast cancer diagnosis¹⁴⁴ and weight gain after diagnosis^{145,146} also have been linked to increased breast cancer mortality and recurrence. Moreover, BMI is related to reproductive development, including puberty and age at menarche,¹⁴⁷ which in turn have been reported to be associated with breast cancer risk.¹⁴⁸ Therefore, BMI may affect the bioavailability of OCs as well as hormones in women.

Clearly, research on environment and breast cancer must be incorporated into a larger picture of the

complex hormonal milieu that is critical for the development of breast cancer. An individual's hormonal profile is determined by an array of factors encompassing both genetic and environmental influences. Such factors are hypothesized to account for the majority of the differences between premenopausal and postmenopausal breast cancer risk, as well as for breast cancer related to family history and early age at diagnosis; risk likely will be better explained by a combination of these factors.¹⁴⁹ Environmental/lifestyle risk factors can confer risk that varies among subgroups classified according to hormonal factors. For instance, a stronger protective effect for breast cancer has been reported for a higher (versus lower) intake of fruits and vegetables among 1) premenopausal compared with postmenopausal women, 2) women who consume more alcohol compared with those who consume less, and 3) among women with a family history compared with those without.^{150–153} It is possible that African-American women, and especially those who are at high risk for breast cancer, possess an elevated hormonal profile that may enhance or reduce their response to certain environmental insults, derived from both exposures and from modifying genes.¹⁵⁴

Context 2. Environment/gene interactions

Environment-gene interactions have the potential to alter the course of carcinogenesis at many steps along the way by mutagenesis and gene regulation. Environment-gene interactions include 1) genes that control the Phase I enzymes responsible for converting environmental exposures to mutagenic metabolites; 2) genes that control Phase II enzymes that convert metabolites of environmental toxins to inactive forms; 3) genes responsible for DNA repair; 4) oncogenes and tumor suppressor genes. Environmental exposures can also act as hormone mimics and thus as transcription factors to alter the expression of genes, or that can induce gene expression including that of Phase I enzymes.^{155,156} A schematic example is shown in the Figure 1 for metabolizing genes.

Inherited genetic capacity for metabolism is believed to explain wide interindividual variations in biologic measures of dose, such that even people with comparable exposures can have quite different internal or target-organ levels. Differences in metabolic capacity may provide quite different susceptibility patterns among African-American women exposed to environmental carcinogens when compared with other racial/ethnic groups. Unlike the rare genetic variants (e.g., *BRCA1* mutations) typically associated with a high risk for cancer, the genome contains numerous more common genetic variants (present at > 1–50%), including genes that govern bodily “house-

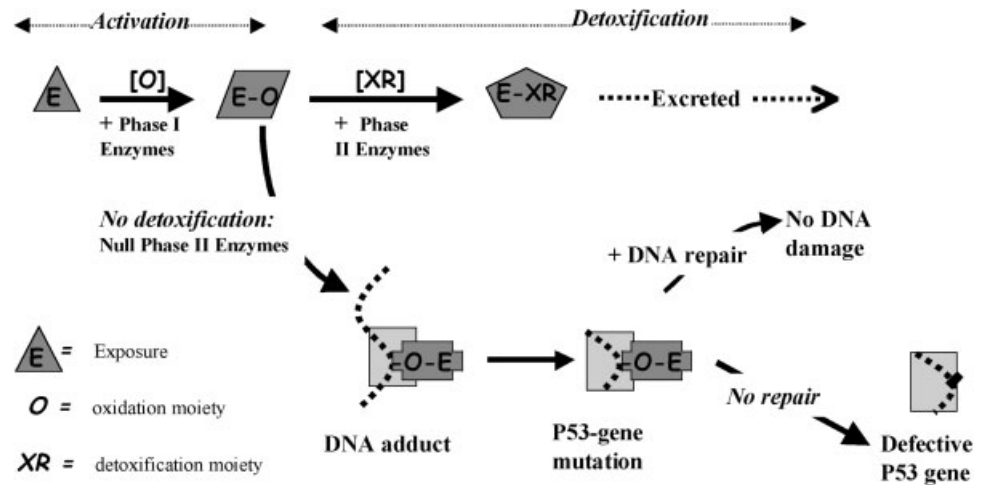


FIGURE 1. Schematic for damage to DNA by the electrophilic metabolite of an enzymatically oxidized environmental toxin, resulting in a *P53* mutation.

keeping" functions or that indirectly influence metabolic capacity. The idea of individual susceptibility is aptly illustrated by the example of smokers, who do not all experience lung cancer, whereas smoking accounts for much of lung cancer risk. An additional example is that of *BRCA* gene mutation carriers, among whom it has been estimated that 30% will never suffer from cancer.¹⁵⁷

BRCA1/BRCA2 and other high-penetrance genes may have low-prevalence variant alleles that carry a very great risk for subsequent cancer, but they appear to account for little of the overall attributable risk for the disease because inherited mutations exist in altogether < 10% of the population. When a mutation in one copy of the *BRCA1/BRCA2* (or *P53* or *AT*) gene is inherited, cancer is believed to ensue only if a somatic mutation occurs in the second copy of the gene, resulting in reduced function as a tumor suppressor or in DNA repair. Because these genes are such powerful guardians of the genome, damage may result in short latency (time between exposures and clinically detectable disease) and a young age at the time of diagnosis of cancer. Thus, even high-penetrance genes that pose a greatly increased cancer risk may undergo mutations from environmental toxins; protective exposures may prevent these changes.

Studies of genetic variants in metabolizing genes, including the examples shown in Table 4, generally have reported few or no consistent increases in breast cancer risk with the gene variant alone.^{110,158} This is not surprising given that the gene variants under study are quite common and may affect risk over a long latent period by acting in concert with relevant exposures, including hormones.¹⁵⁹ Compared with the more straightforward and strong (monogenic) risks accompanying *BRCA1/BRCA2* mutations, carcinogenesis evolving from metabolic pathways requires cumu-

lative, multiple steps, a process that has been termed polygenic.^{159,160} Studies that have found increased risks with gene variants alone will be discussed along with the gene exposure findings.

Susceptibility: variability in metabolizing enzymes

Phase I metabolizing enzymes. The majority of the susceptibility genes that have been investigated with regard to environmental exposures can be implicated in cellular oxidative damage that may contribute to the carcinogenic process. Oxidized species, or reactive molecules, are created by Phase I enzyme activation of exogenous agents (Table 2), from endogenous hormones, and from other free radical sources, such as fatty acid oxidation. Many of the genes controlling this process have a higher frequency of the at-risk variant in African-Americans (Table 4). A general marker of genotoxicity is oxidative damage to DNA (e.g., levels of 8-OHdG and 5HMDU in the blood, urine, or tissues). Biomarkers of this kind have shown a much wider variation among African-American women compared with white women.¹⁶¹ A well studied research area of oxidative damage involves exposure to PAH, which can be metabolized to the genotoxic PAH diol-epoxide metabolites by cytochrome P450 (*CYP*) enzymes; higher levels of the diol-epoxide are found with the more rapid metabolizing Phase I genotype.¹⁶² HAAs are similarly activated by N-acetyl transferase (*NAT*). Therefore, if African-American women have high adverse exposures in combination with a greater prevalence of the related adverse genotype(s) then excess risk may ensue; this might be manifest in measures of primary oxidative DNA damage (ODD), of tissue damage, or in other diseases related to similar damage. Enzymes of this kind also are involved in the uptake and delivery of pain medications, chemotherapy

TABLE 4
Examples of Genes that Modulate Environmental Agents: Prevalence (%) of Variants

		Reference	African-American Range of reported values	White Range of reported values
Phase I metabolizing genes	<i>CYP1A1</i> , MSPI (wt/var; wt/var)	158, 170, 180	13–31%; 3–5.8%	21–39%; 2–5%
	<i>CYP1A1</i> , Ile-Val (wt/var; wt/var)	170, 179, 180	3.7–4.4%; 0%	9–15%; 1.1%
	<i>CYP1A1</i> , MSPI-AA (wt/var; wt/var)	170, 179	15–20%; 0–1.9%	0%; 0%
	<i>CYP2E1</i> (2 sites, allele frequency)	244	0.02–0.09	0.02–0.08
	<i>CYP1B1</i> rapid, gene frequency	174, 175	70–75%	35–40%
	<i>NAT1</i> * 10 rapid	245	76%	38%
Phase II conjugation/detoxification genes	<i>NAT2</i> ^o (null; 4–7 alleles)	245–247	40–64%	56–74%
	<i>GSTM</i> ^o (null)	158, 244, 245	13–41%	52–62%
	<i>GSTT</i> ^o (null)	158, 244, 245, 248	17–29%	16–27%
	<i>GSTP</i> (val/val)	245	23%	11%
	<i>XRCC1</i> (cod399 gln allele frequency)	207	0.14	0.36
DNA repair gene				
	Tumor suppressor, repair, etc.	<i>P53</i> 2-1-2 haplotype	249	37%
		1-2-1 haplotype	32%	9%

wt/var: wild type/variant; val/val: valine/valine; NAT: n-acetyl transferase; GST: glutathione-S-transferase.

Data from breast cancer studies were from controls for whom information was available.

drugs, and hormones that may be substrates for several enzymes (e.g., CYP1A1 and CYP1A2). Such variability has been proposed to explain how tamoxifen metabolism differs among racial/ethnic groups, in a way that adversely affects the response to tamoxifen among African-Americans.¹⁶³

Phase ii metabolizing enzymes. Phase II detoxification or deactivating enzymes conjugate genotoxic oxidation products from environmental exposures into readily eliminated metabolites including sulfates, glucuronides, and acetates. If deactivation mechanisms were lower in a subgroup with excessive oxidative damage, then this subgroup might be at an increased risk for a number of diseases. A number of examples demonstrate how Phase II enzymes alter individual levels of biomarkers of exposure. Oxidative damage measured as 8-OHdG was reported to be highest in urine from neonates whose mothers were both exposed to tobacco smoke and null glutathione-S-transferase (*GST*); levels were successively lower in nontobacco-exposed women with null *GST* and tobacco-exposed women with *GST*, and were lowest among those with no tobacco smoke exposure who had *GST* activity.¹⁶⁴ In addition, women with breast cancer who carried the *GST*-null genotype were found to have higher PAH-DNA adducts in tissue compared with controls,¹⁶⁵ a finding that parallels experiments in cell lines.¹⁶⁶ *NAT*, which can activate HAAs, can also detoxify electrophilic intermediates. To illustrate the role of *NAT2* detoxification, persons with slow *NAT2* phenotypes accumulated higher levels of 3-aminobiphe-

nyl-hemoglobin adducts; among racial/ethnic groups, the average adduct levels were directly proportional to the *NAT2* slow phenotype, which varied 4-fold: 14% slow (Asians; the lowest adduct levels), 34% slow (African-Americans), and 54% (whites).¹⁶⁷ These relations were independent of racial/ethnic status. The combination of *GSTM*-null with the *NAT*-slow phenotype also was found to be related directly to adduct level.¹⁶⁸ With the possible exception of *GSTP*, African-Americans appear to have a higher proportion of null genes for conjugating activity compared with whites (Table 4).

In epidemiologic studies, more significant findings for the gene variant alone with breast cancer risk have been reported for the Phase II deactivating enzymes compared with Phase I pathways. One explanation could be that there is a temporal advantage in their assessment at later stages of carcinogenesis, for example if oxidative damage affects late-stage tumor promotion or tumor suppression. However, there are multiple metabolic pathways that control oxidation processes. Deficiencies in DNA-repair genes plus a lower intake of dietary antioxidants also would be adverse for risks related to oxidative damage.

Genes that control metabolizing enzymes

The majority of genes related to metabolism (Table 4) are expressed primarily in the liver, so that a carcinogenic effect on mammary epithelium would require that active metabolites be transported to the breast, unless they have an indirect effect such as to raise or lower systemic hormone levels. *GST* and *CYP1A1* are

expressed in breast tissue, although the isoforms do not necessarily reflect the known gene variants.^{168–170}

Phase I metabolizing genes. Chemicals of particular interest to breast cancer, including PCBs, DDT, PAH, cigarette smoke, and HAA, can induce some of these enzymes and can be substrates for their own transformation. CYP2D6 and CYP2E1 also may be up-regulated by or may catalyze the metabolism of environmental agents, including cigarette smoke components, alcohol, and small molecules such as those shown in Table 2. The at-risk variants in both *CYP2D6* and *CYP2E1* are uncommon (< 10%, Table 4 and reference 172). Because the prevalence of the known gene variants is low, current epidemiologic studies are too small to detect a gene effect that yields a relative risk below 2.¹⁷³ Pooled analysis of epidemiologic studies indicated that relative risk from the gene variant alone would be < 1.5 for *CYP1A1*, *NAT1/2*, *CYP2D6*, *CYP2E1*, and *GSTT*.¹⁷³ Hormone synthesis and metabolism also are governed by several Phase I enzymes that can be induced or inhibited by environmental exposures.¹⁵⁹ In a mammary tumor model, PAH increased levels of both CYP1B1 and CYP1A1 in normal tissue but only CYP1B1 was increased in tumor tissue.⁷⁹ Thus xenobiotics may be able to alter the hormone sensitivity of tumors. CYP1B1 metabolizes estrogen (as well as PAH) and the rapid variant is more common among African-American women compared with white women.^{174,175} The variant was associated with increased risk of breast cancer among Chinese women (allele frequency of 53%),¹⁷⁶ but not among African-American or white women in another small study.¹⁷⁵

Among the Phase I enzymes, CYP1A1 is the most well studied. There are four *CYP1A1* variants that have been scrutinized in epidemiologic studies; genotoxic potential is suspected for minor variants that code for more rapid metabolism and that are inducible by various exposures. Two of the identified variants are more prevalent among whites than African-Americans. Another variant is specific to African-Americans (MSPI-AA) and has been reported to be more common in African-American women with breast cancer and to be associated with higher levels of adverse estrogen metabolites.^{158,177} However, the number of patients studied was very small, and the findings have not yet been reproduced in other populations of African-Americans. The MSPI variant is more common among Asian women and was found to be associated with higher risk of breast cancer in a study in Taiwan^{178,179} whereas the wild-type genotype was found to be associated with early-onset breast cancer in whites.¹⁸⁰ The *CYP1A1*4* variant was found to confer a higher risk in another study, especially among postmeno-

pausal women.¹⁸¹ Other U.S. studies (mainly of white women) have found associations for breast cancer among women who smoked before age 18 years and who also had 2 *CYP1A1* variants.¹⁸² The Ile-Val variant was associated with risk among long-time smokers¹⁸³ and among women with higher PCB exposures.¹¹⁰

Phase III metabolizing genes: NAT. The *NAT* gene family can N-oxidize HAA and related compounds, rendering the rapid form as the at-risk genotype. However, the NATs also conjugate, or deactivate, oxidative intermediates; slow metabolizers would be at risk if this were the exposure of interest. Therefore, findings regarding environment-gene interactions with the N-acetyl transferases are conflicting, but this is not remarkable given the complex, multiple pathways through which these genes may act. The *NAT2* and *NAT1*10* rapid genotypes were reported to confer a higher risk for breast cancer among recent smokers in the CBCS (race-adjusted risk estimates); just as the null genotype is rarer, the rapid genotypes are more common in African-Americans than in other ethnic groups (Table 4).⁶⁹ A study of whites found a higher risk of breast cancer among smokers with the rapid *NAT1*11* genotype.¹⁸⁴ Two studies among white women found higher risk for smokers who also had low activity *NAT2* compared with nonsmokers.^{185,186} One of these studies also found a higher risk among women smokers who had rapid *NAT2* genotypes.¹⁸⁶ A third study found a nonsignificantly increased risk for smokers with low-activity *NAT2*.^{187,188}

Because the NAT enzymes activate HAA, they have been investigated in relation to reported dietary intake of cooked meat, although not specifically among African-Americans. One study has found an association between rapid *NAT2* or rapid *NAT1*11* and the intake of meat or well-done meat.^{184,189} The same study found an increased risk of breast cancer with low-activity sulfotransferase alone or with two high-activity alleles and a higher meat intake.¹⁹⁰ Three other reports found no risk associated with *NAT2* and meat intake.^{76,77,191} In a case-control study performed in Taiwan, slow acetylators were at higher risk for breast cancer, and this finding was found to be significant among postmenopausal but not premenopausal women.¹⁹²

Another environment-gene example of Phase II metabolism that deserves further attention is the higher risk observed for breast cancer occurring among postmenopausal white women with the inactive *MnSOD* genotype, especially those with a lower intake of fruit, vegetables, and antioxidants, consistent with higher oxidative damage.¹⁹³ This association was not found in a preliminary report from the CBCS,

which included African-Americans; furthermore, the frequency of low-activity *MnSOD* was reported to be similar in African-Americans and whites.¹⁹⁴ Protection by dietary intake of antioxidants or increased risk from oxidative exposures may have to be taken into account in addition to the reduced activity genotype for both Phase I and Phase II enzymes.

Phase II metabolizing genes: GST. The GST family of enzymes conjugates electrophilic substances to their glucuronide metabolites, which are biologically inactive and are excreted readily. The at-risk genotype lacks GST activity; known *GST*-null genotypes are reported to be less common in African-Americans compared with whites (Table 4). *GST*-null genotypes themselves in the majority of studies reportedly have shown no or weak associations with breast cancer risk, both among African-Americans^{158,195} and whites.^{183,195-197} In the CBCS, *GSTM* and *GSTT* null genotypes were found to be associated with increased risk among women diagnosed at an earlier age (adjusted for race) or those with a family history.¹⁹⁵ Among whites, one study found null *GSTM1* to be associated significantly with breast cancer risk, whereas *GSTT* and *GSTP* null demonstrated positive but nonsignificantly increased risk.¹⁹⁸ Elevated risk was found for *GSTP1* null, but not for *GSTM1*-null, among women with a family history.¹⁹⁹ There also was an increased risk for *GSTM1*-null among older patients in two studies^{200,201} and a slightly lower risk of early-onset breast cancer in two studies.^{180,197} However, a pooled analysis indicated that alone, *GSTM1* and *GSTP* null variants confer a modest (less than twofold) increased risk of breast cancer.¹⁷³ Thus in vulnerable subgroups *GST*-null may pose a risk for breast cancer, perhaps in conjunction with the age at onset of cancer or with a family history among women with relevant exposures.

Of particular interest for African-Americans, who are reported to have a poorer prognosis after a diagnosis of breast cancer, *GSTM* and *GSTT* null genotypes were reported to be related to longer survival in a study of 240 cases of white women,²⁰² although not in a smaller study.²⁰³ Moreover, the null variant may be protective against disease recurrence by improving response to chemotherapies that result in oxidative damage.²⁰⁴ Because of the lower frequency of null *GSTM1* among African-Americans, more rapid progression of breast cancer in this population potentially may be related to these genes. Conversely, studies of GST expression in tissue have been reported to find no correlation with survival.^{170,171} Nevertheless, these associations are consistent with a possible effect of GST on reducing oxidative damage or opposing other hormonally related oxidative pathways throughout life. In addition, early onset, family history, and poor survival

are risk patterns that are significant for African-American women, but these profiles also may be common to a risk subgroup that responds poorly to oxidative damage; such a group may be able to be characterized in part by null *GST*, along with other dysfunctional deactivating enzyme profiles, regardless of ethnicity.

DNA repair. Genetic susceptibility to breast cancer after radiation exposure as well as other genotoxic exposures may be related to rare gene variants including germline mutations in *BRCA1/BRCA2* and the *AT* gene.^{205,206} Studies of these highly penetrant genes among African-Americans are discussed elsewhere in this supplement. Because the variants in these genes are so rare, research is limited with regard to their interactions with environmental factors. In contrast, a common variant exists in the *XRCC1* base excision repair gene, which was reported to be associated with increased breast cancer risk among African-American women who had the rare allele (codon 399 gln)²⁰⁷ Among African-Americans, breast cancer risk also was found to be elevated for women with the homozygous *XRCC1* wild-type gene who had a history of smoking, whereas among white women the wild-type gene was found to be associated with breast cancer only among those women with a past exposure to ionizing radiation. The *XRCC1* wild-type gene was associated with a higher prevalence of deletions in the *P53* gene in breast tumors among African-American women with radiation exposure and more *P53* transversions among women who smoked. A number of mutations in the *P53* gene have been attributed to environmental exposures,²⁰⁸ and these findings suggest a series of mutations that can arise from environment-gene processes.

Oncogenes and tumor suppressor genes

P53 is overexpressed in approximately 40% of breast tumors, with approximately 20% having mutations in the gene; these rates are similar among African-Americans, Hispanics, and whites.^{86,98,209,210} *P53* has many functions in development, DNA repair, apoptosis, cell cycle regulation, and transcription and as a tumor suppressor.²⁰⁸ Environmental genotoxins have been linked to specific mutations, or hotspots, along the *P53* gene, with some being characteristic of environmental mutagens such as PAH. The resulting *P53* mutational spectrum appears to vary with ethnicity and geographic distribution, which is consistent with an environmental etiology.^{4,210} Furthermore, as many as 10 inherited variants have been found in the *P53* gene; these differ by race/ethnicity and possibly are associated with a risk of breast cancer.^{173,210-212} Potential evidence of an environmental influence on *P53* inac-

tivation includes the observation that P53 overexpression in tumors is associated with a history of smoking, which is consistent with a genotoxic effect of smoking on P53.²⁰⁹ In addition, evidence from the CBCS suggested different P53 alterations were found with smoking versus radiation exposures.²⁰⁷

The rare HRAS alleles are associated with breast cancer, an association that may be stronger in African-Americans.²¹³ Moreover, some polymorphisms in the HRAS gene are more common among African-Americans than whites.²¹² Environmental exposures have been implicated in HRAS mutations.^{212,214} A significant positive association between HRAS mutations and breast cancer risk also was observed in a pooled analysis of nine studies.²¹²

Transcriptionally active genes

Estrogen receptor (ER)-negative breast tumors are implicated in the poor prognosis of breast cancer occurring among African-American women.⁴ Limited but inconclusive evidence suggests that gene variants in the ER are associated with the risk of breast cancer,¹⁷¹ although studies of these variants have not been reported among African-Americans. There are at least two ERs (ER- α and ER- β) that potentially are highly relevant to environmental exposures and are expressed in different tissues.^{215,216} Hormones and environmental agents have different affinities for ER- α and ER- β . The action of many compounds, including the OCs as transcription factors, is believed to be mediated through the ER or other hormone receptors (e.g. the androgen receptor).²¹⁷

Another transcriptionally active gene (*UGT1A1*) appears to have a more potent variant among African-Americans; in the CBCS, an elevated risk of breast cancer was found among premenopausal African-American women who possessed this variant, with a suggestion of a higher risk among those women with ER-negative breast cancer.²¹⁸

In addition, levels of hormone synthesizing and metabolizing enzymes may be induced by environmental substances and thereby alter levels of other exposures. One example is the up-regulation of P450 enzymes by drugs, dioxin, or broccoli, shifting the ratio of estrogen metabolites in favor of 2-hydroxyestronone over 16 α hydroxyestronone.^{156,219}

Summary of environment-gene interactions

Individual genes and their targeted substrates have been studied with regard to breast cancer risk, but few studies published to date have included African-American women. Nevertheless, the majority of genetic variants exist in all populations, albeit in different proportions. Therefore, the average metabolic

profile of racial/ethnic subgroups may be shifted to the degree that variant alleles predominate. Regardless of race, a combined effect of environmental exposures, metabolizing genes, and hormone synthesis and metabolism on breast cancer risk is suggested by evidence from both experimental and epidemiologic research; compared with other racial/ethnic groups, African-Americans appear to have different distributions of a number of the genes controlling these processes, in particular *NAT2*- and *CYP1B1*-rapid alleles. The phenotypic potential, or the overall distribution of such genotypes, appears to hold great promise for identifying an environment gene or profile associated with breast cancer risk. Future research also should attempt to incorporate a pharmacokinetic-based compartmental approach to exposure assessment that would incorporate pharmacogenetics (i.e., dose-time-gene models) and provide an integrated (time-relevant) dose picture over a woman's lifetime. Dietary intake also is important to consider with metabolizing enzymes, particularly antioxidants, which, with detoxifying enzymes, may reduce oxidative damage and thereby alter both the transcriptional and mutagenic effects of environmental agents.

Concept 3. Environment/social interactions

Environmental epidemiologic research generally has disregarded the fact that environmental exposures are entwined intimately with social, behavioral, and psychosocial factors. Statistical models usually include SES and race/ethnicity, but SES is measured rather crudely (e.g., by annual income or educational level). Research has suggested that SES accounts for much of the racial/ethnic variability in breast cancer incidence or mortality.²²⁰ Both factors should be considered to obtain a more complete picture of breast cancer risk in the U.S.²²¹ Other investigators believe that geographic differences in breast cancer mortality can be explained by reproductive factors and lifestyle variations across various regions in the U.S.^{113,222} Furthermore, it has been proposed that two socially influenced factors play an important role in breast cancer risk: tissue susceptibility brought on by reproductive factors such as early menarche and higher exposures to carcinogens.²²³

The concept of environmental justice has emphasized the idea that higher exposures to carcinogens often exist in underserved populations and that these populations also contain a disproportionate number of minority groups, including African-Americans.²²⁴ An environmental justice approach would suggest that SES and reproductive factors may be responsible for the higher levels of OCs reported in African-Americans and Hispanics.²¹⁴ Type of housing, its upkeep, and geographic loca-

tion can dictate the type, number, and level of exposure. In addition, stress can arise from poverty and other inadequacies with regard to quality-of-life issues, and these may render such individuals more vulnerable to the adverse effects of exogenous exposures.²²⁵ For example, stress may compromise immune function through a psychophysiological mechanism or secondary to infectious diseases that arise from psychosocial stress or indigence.^{226,227} This, in turn, may increase the risk for breast cancer from environmental exposures that lower immune response. It has been theorized that the type of tumor may represent socioenvironmental exposure.¹⁵⁴ Therefore, the environment–social context into which environmental exposures are incorporated can describe a biobehavioral environmental model for breast cancer risk, and this context would include socially vulnerable subgroups regardless of racial/ethnic status.²²⁵

Context 4. Temporal effects, or timing of environmental risk factors

The biologic sequence of events leading to cancer no doubt coincides with certain times of vulnerability during life and latency for cancer (Table 1). Much epidemiologic and experimental evidence suggests the need to investigate mutagenic exposures that occur early in a woman's life, even in utero.²²⁸ Studies of breast cancer suggest that the intrauterine environment, age at menarche, and age at first birth as well as the interval between these latter two events may be critical periods in the development of breast cancer.^{229,230} For example, being a twin or being heavier at birth appears to increase breast cancer risk whereas maternal preeclampsia or breastfeeding has been reported to decrease the risk in the daughter.²³⁰ To reiterate examples given earlier in this article, ionizing radiation and cigarette smoke are purported to exert a primary carcinogenic effect relatively early in life, whereas immunotoxic or tumor-promoting activity may support later stages of tumorigenesis.

Russo et al. have argued that the peripubertal and early postpartum periods are highly likely periods for tumor initiation to occur.^{65,124} It also has been suggested that exposures after menarche but prior to first pregnancy are more detrimental because the breast cells are undergoing differentiation and proliferation during this interval and therefore are more vulnerable to carcinogenic exposure.²³¹ Experimental research has established that tumor initiation is most effective during early breast development.^{65,124,214,232} In vitro studies further suggest that mammary epithelial cells from virgin rats produce more mutagenic PAH metabolites than do cells from pregnant rats.⁶⁷ In addition, in laboratory studies, perinatal exposures can alter ductal and lobular development within the breast.²³³

However, little research in humans has been performed in this area.

Age at puberty is approximately 1 year earlier among African-Americans,²³⁴ and age at menarche has been consistently younger compared with that of whites during this century by approximately 6 months.^{113,234} This finding potentially has great impact for cancer risk, because early menarche may explain, in part, the higher rates of premenopausal breast cancer among African-American women compared with white women in the U.S.^{113,235} As suggested earlier, a younger age at puberty and menarche could provide a longer period of vulnerability to insult by environmental carcinogens on the breast tissue. Studies have identified some environmental exposures that influence age at puberty and/or menarche as well as other factors believed to be associated with reproductive function (such as cyclicity and fecundity). In animals, a large number of chemical exposures may alter the onset of puberty (vaginal opening).^{236,237} In support of this experimental data, Gladen et al.¹¹² reported a positive association among girls with in utero exposures to PCBs and weight gain during puberty, although no association was found with pubertal stage. White girls exposed to higher versus lower levels of PBBs in utero reportedly experienced an earlier age at menarche.¹¹¹ To our knowledge, no comparable data exist for nonwhite children. Chemical exposures also have been reported to be associated with menstrual function during the reproductive years.²³⁸ In addition, cyclicity and age at menopause have been linked to stress as well as smoking and this finding has been observed in African-American women.²³⁹ Rogan et al. observed a shortened duration of lactation among women with the highest exposures to DDE.^{240,241} Because a long duration of lactation may be protective for later breast cancer, these findings offer an additional mechanism by which environmental exposures may alter a woman's risk for breast cancer many years before breast cancer diagnosis.

We believe more research is needed to identify environmental exposures experienced in early life that may affect breast cancer risk.⁴ These exposures may affect tumorigenesis only indirectly, making risk ascertainment very difficult. Therefore, research efforts should be directed toward determining how environmental exposures may alter known risk factors, including timing of puberty/menarche, menstrual function, fecundity, lactation, and age at menopause. As reviewed elsewhere in the current supplement, early life and other reproductive factors among African-American women, as well as among other racial/ethnic groups, confer a risk for breast cancer (generally less than twofold). Because breast cancer risk may

vary depending on the timing of exposure, the future examination of environmental risk factors should take into consideration the age or time period in a woman's life during which these exposures occur.

RESOURCES ARE NEEDED TO BE ABLE TO LINK ENVIRONMENT WITH BREAST CANCER ETIOLOGY AND PROGRESSION EFFECTIVELY

Efforts must be made to identify resources for undertaking research concerning the role of environment in the development of breast cancer, both with regard to populations available for study and methodologies used to assess multiple risk factors. Opportunities should be developed that will enable research to be undertaken within the contexts of the environmental etiologies discussed earlier. A number of general as well as specific opportunities were suggested by the Environmental Working Group.

Large populations can be combined to enhance existing studies. Future studies must include African-American women or must identify susceptible or vulnerable subgroups. Attempts to pool existing and future data, biologic samples, or other population resources should be made to elucidate risks that affect African-American women. Newly funded studies should collaborate in the early stages of the research so that data collected can be combined effectively in later analyses.

Studies should be undertaken among highly exposed or uniquely exposed women, including those working in occupations and industries with intense exposures to carcinogens or hormonally active agents; migrant groups so that research can elucidate the role of migration and acculturation; uniquely exposed groups such as migrant farm workers (pesticides) and populations living on or near environmental justice/superfund sites; and in the case of male breast cancer to determine risk factors among blacks.²⁴²

Focus groups may help to identify new exposures and appropriate contexts for the assessment of risk.

Groups of women with early-onset breast cancer would enable researchers to assess differing risk factors in such women, but it also would be possible to then examine risk in sisters, mothers, and daughters (and sons!) of the affected women.

Registries of affected persons exist already for special studies; environmental assessment could be added on to existing studies of African-American women (at least five or six such efforts were identified by the Workshop).

Research should be encouraged that will develop better tools for exposure assessment and for ecologic, occupational, cohort, and case-control studies.

In keeping with the theme that etiologic and prog-

nostic factors are useful only in so far as they are generalizable, newly identified population resources must preserve the ability to study individual populations while enabling the results to be linked with other research. Efforts must continue to implement existing recommendations that are particular to breast cancer that develops in African-American women. Examples include recent reports from the Institute of Medicine on Cancer in Minorities and on Gender Differences in Susceptibility to Environmental Factors.²⁴³

Conclusions

Evidence suggests that environmental factors and genetic susceptibility are associated with breast cancer risk, although there is a paucity of research among African-Americans. Compared with white women, African-American women as well as women of other racial/ethnic minorities may have higher levels of exposures to certain environmental agents that have been implicated in increasing the risk of breast cancer. They also may have greater genetic susceptibility to the biologic effects of such exposures. When possible, future studies should include women of all racial/ethnic backgrounds to elucidate environment-gene as well as social factors in breast cancer etiology. In addition, research should consider how genetic, social, and environmental factors act within the complex hormonal milieu that leads to the development of breast cancer.

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