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Hypothesis

Exposure, susceptibility, and breast cancer risk:

A hypothesis regarding exogenous carcinogens, breast tissue development, and social gradients, including black/white differences, in breast cancer incidence

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Summary

At present, known risk factors account for only one-third of breast cancer cases diagnosed in the United States. They explain an even smaller fraction of the ten-fold variation in international breast cancer incidence rates. The low population-attributable risk of these identified risk factors, plus the existence of phenomena that cannot be easily explained by current etiologic hypotheses (such as the higher rate of breast cancer among black as compared to white women under age 40 within the United States), suggests that unidentified risk factors contribute substantially to breast cancer causation. This paper summarizes evidence to propose that two socially-conditioned factors determine a society's breast cancer incidence and its social gradients in risk: 1) the extent of exposure to exogenous carcinogens, and 2) breast tissue susceptibility to these exposures. It is further hypothesized that breast tissue susceptibility is inversely related to breast tissue differentiation, and that socially-mediated reproductive patterns (involving both early-terminated and full-term pregnancies) affect susceptibility both by altering (via hormonally-mediated mechanisms) the number and ratio of undifferentiated and differentiated cells, and by stimulating the growth of initiated and transformed cells. This view is presented in contrast to hypotheses that propose exposure to endogenous hormones as the major determinant of breast cancer risk.

Abbreviations: BBD – Benign Breast Disease, DDE – Dichlorodiphenyl Dichloroethene, ETP – Early-Terminated Pregnancy, FETP – First Early-Terminated Pregnancy, FFTP – First Full-Term Pregnancy, FTP – Full-Term Pregnancy, OC – Oral Contraceptive, PCB – Polychlorinated Biphenyl, RR – Relative Risk, SES – Socioeconomic Status, TDLU – Terminal Ductal-Lobular Unit

Introduction

Breast cancer is the most prevalent type of cancer among women both worldwide and within the United States, and its incidence, while varying geographically, has been rising internationally for at least the past two decades [1–4]. At present, the U.S. age-adjusted incidence of breast cancer is among the world's highest [4], and breast cancer now ranks second only to lung cancer as the leading cause of U.S. female cancer mortality [3]. In 1987, an estimated 130,000 women in the U.S. will have

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been diagnosed with breast cancer, constituting one in every four new female cancer cases, while another 41,000 will have died of this disease [3].

Extensive epidemiological research conducted during the past twenty-five years has uncovered several important breast cancer risk factors, including early age at menarche, late age at first full-term pregnancy (FFTP), nulliparity, absence of premenopausal bilateral ovariectomy, late age at menopause, single marital status, and high socioeconomic status (SES) [5–10]. Conversely, early age at FFTP consistently has emerged as the strongest protective factor [5–12]. Other more controversial risk factors identified in some, but not all, studies include: high levels of dietary fat [13–16], increased alcohol consumption [16–22], a history of benign breast disease [5–7, 23–25], use of oral contraceptives (OC) (especially prior to FFTP) [26–29], first trimester abortion [29–32], low parity [33–35], and failure to have lactated [36]. The only well-accepted exogenous carcinogen, albeit with a low population attributable risk, is ionizing radiation [6–9]. In contrast, other suspected exogenous substances, such as cigarettes [21, 37], hair dye [38], and caffeine plus related methylxanthines [39], have failed to show any significant association with increased breast cancer risk.

To explain the apparently pronounced role of reproductive risk factors in breast cancer epidemiology, numerous researchers have proposed that endogenous sex hormones are the major determinant of breast cancer risk (Fig. 1) [5–10, 40–44]. According to this view, long-term changes in the levels of progesterone, estrogens, prolactin, and perhaps other hormones, are postulated to increase risk by acting as genotoxic or epigenetic carcinogens (*i.e.*, agents that convert normal cells to latent tumor cells by altering genetic material, and substances that facilitate proliferation of such cells [45]); genetic susceptibility and non-hormonal exogenous exposures that could provoke or enhance tumorigenesis (*e.g.*, radiation and perhaps dietary fat) are accorded a secondary role. Noting how hormonal explanations apparently link major breast cancer risk factors into a coherent and concise ensemble, Henderson *et al.* have further inferred that primary prevention of breast cancer 'will probably depend on modification of factors which affect the secretion and metabolism of the responsible hormones, rather than control of exposure to classical exogenous initiators' [43].

Additional observations, however, suggest that non-hormonal factors must also be integral to breast cancer causation. A recently completed 10-year prospective study conducted on 13,000 women in the U.S., for example, observed little difference in the endogenous reproductive hormone levels of women who did and did not develop breast cancer [46]. Similarly, few consistent differences have been found by case-control investigations designed to detect variations in hormone profiles among women with and without breast cancer [47–51], and also among women presumed to be at low and high risk for breast cancer on account of either their family or reproductive histories [52–55]. Moreover, extensive experiments performed upon both rats and mice repeatedly have demonstrated that hormones alone cannot explain breast cancer occurrence; also needed are exogenous genotoxic agents and/or heightened genetic sensitivity to hormonal exposures [6–7, 56–58]. Finally, at a population level, increasing evidence indicates that reproductive and other known risk factors account for only one-quarter to one-third of breast cancer cases within the U.S. [59–60], and explain an even smaller fraction of the ten-fold or more variation in breast cancer rates between countries [4, 61].

Perhaps the most striking challenge to current hormonal hypotheses, however, stems from U.S. data regarding black/white differences in the age-specific incidence of breast cancer [1–2, 62–66]. The three studies to date specifically examining breast cancer risk factors for black women in the U.S. have found them to be equivalent to those affecting whites [67–69]. Present knowledge therefore would predict breast cancer incidence to be higher among white women for two intertwined reasons: 1) the SES of whites generally is higher than that of blacks, and 2) wealthier women tend to delay childbearing, have fewer children, and consume higher fat diets, thereby elevating breast cancer risk [5–8, 69–73]. Apparently in agreement with this reasoning, the U.S. age-adjusted breast cancer incidence rate among white women consistently

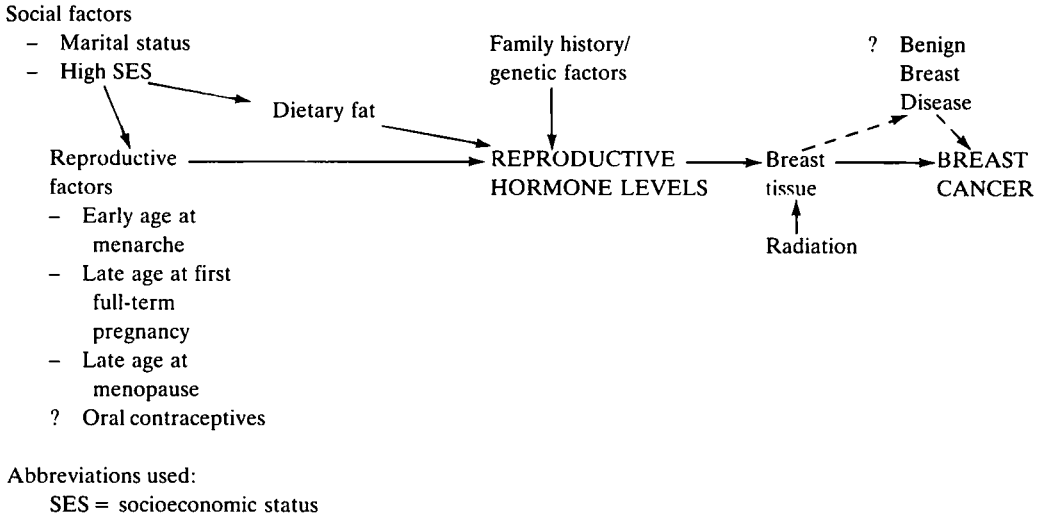

Fig. 1. Current hormonal model incorporating major known risk factors for breast cancer pathogenesis.

has exceeded that among blacks at least since the First National Cancer Survey of 1937–1939 [1–2, 62–64]. Moreover, utilizing data collected in the Third National Cancer Survey of 1969–1971, Devesa and Diamond found that most of the 25% excess of breast cancer among white women over age 40 could be ascribed to such social factors as the overall higher SES of the white women and the correspondingly younger age of black women at FFTP [69].

Yet, in contrast to the hormonal hypotheses' prediction regarding higher white breast cancer rates, among women under age 40, commencing with the Third National Cancer Survey, the incidence of breast cancer among black women has exceeded and risen more quickly than that of whites, and in 1980 was 30% higher (Table 1) [1, 64]. Suggesting that unanticipated factors associated with low SES contribute to these trends, a recent study utilizing data from a population-based cancer registry in Washington state found that the incidence of breast cancer between 1974 and 1984 rose most rapidly among young women who were black and/or from low-income census tracts [66]. These results, moreover, could not be explained either by increased reporting of breast cancer cases or by underestimates of the female population ages 25 to 44.

To reconcile the existence of this racial crossover in breast cancer incidence rates with the leading hormonal hypotheses, Gray *et al.* initially surmised that the higher incidence among younger black women might be due to a slightly earlier age at menarche among blacks; this factor, however, accounted for at most only 7% of the observed difference [65]. Alternatively, White *et al.* suggested that the Washington state data might be explained by a cohort effect involving increasing rates of delayed childbirth among women born after 1930 and a lessening difference between black and white reproductive patterns; in an unspecified manner, they further speculated that higher abortion rates among black and low-income women might also increase risk [66]. National data indicate, however, that the secular rise in late age at FFTP chiefly reflects the experience of whites, not blacks [74–77]. Moreover, even though the incidence of teen pregnancy since 1970 has declined more among blacks than whites, the black rate still is twice that of whites [76, 78–79], and the proportion of black women having a first child by the age of 18 among women born in the birth cohorts of 1930–1934 and 1950–1954 was 2.6 and 3.3 times higher, respectively, than that of white women from the same cohorts [77, 80].

The seemingly anomalous finding of higher and

rising breast cancer incidence among young black women, combined with the low attributable risk of most known risk factors for breast cancer, therefore suggests that causative factors not identified by current hormonal hypotheses must also be at work. This paper accordingly seeks to present an alternative approach to breast cancer etiology and epidemiology, one that explores the socially-mediated relationship between exposure and susceptibility in determining breast cancer risk.

Alternative hypothesis

Toward a social and biological hypothesis linking exposure and susceptibility

According to this alternative hypothesis, two socially-conditioned factors determine a society's breast cancer incidence and its social gradients in risk: 1) the extent of exposure to exogenous carcinogens, and 2) breast tissue susceptibility to these exposures (Fig. 2). Proposing that breast tissue susceptibility is inversely related to breast tissue differentiation, this hypothesis further posits that socially-mediated reproductive patterns (involving both early-terminated as well as full-term pregnancies) affect susceptibility primarily by altering (via hormonally-mediated mechanisms) the number and ratio of undifferentiated and differentiated cells, and also by stimulating the growth of initiated and transformed cells.

Two core biological and social premises underlie this hypothesis. Biologically, this alternative approach postulates that breast tissue is most vulnerable to both genotoxic and epigenetic carcinogens when composed chiefly of rapidly-growing and relatively undifferentiated epithelial cells, and grows increasingly refractory as breast cells differentiate into terminal ductal-lobular units (TDLU) and secretory cells [81–85]. Socially, this hypothesis proposes that women's level of exposure to exogenous carcinogens and their reproductive patterns are jointly determined and necessarily linked by their society's degree of economic development and social relations (principally those involving class, race, nationality, and gender). The extent to which a society is industrialized affects not only the types and amounts of carcinogens present, but also people's dietary patterns and the relative contribu-

Table 1. Average annual age-specific and age-adjusted breast cancer incidence rates for black and white women, United States, 1969–1981 (per 100,000) [1,64]

Age (years)	Race	1969–1971 Rate	RR*	1973–1977 Rate	RR*	1978–1981 Rate	RR*	Percent change: 1969–1981
20–24	Black	2.5	2.3	1.8	1.6	2.2	2.0	− 12.0
	White	1.1		1.1		1.1		0.0
25–29	Black	10.7	1.2	9.9	1.2	12.9	1.7	+ 20.6
	White	8.7		8.1		7.5		− 13.8
30–34	Black	29.3	1.3	37.8	1.5	34.8	1.4	+ 18.8
	White	22.5		24.8		24.8		+ 10.2
35–39	Black	55.6	1.1	61.9	1.1	69.5	1.2	+ 25.0
	White	52.5		56.7		59.1		+ 12.6
Age** Adjusted:								
<40	Black	8.8	1.2	9.9	1.2	10.7	1.3	+ 21.6
	White	7.5		8.1		8.2		+ 9.3
≥40	Black	143.1	0.7	178.4	0.8	179.3	0.8	+ 25.3
	White	193.3		226.1		221.1		+ 14.4
Total	Black	57.6	0.8	71.2	0.8	71.9	0.8	+ 24.8
	White	75.1		87.3		85.6		+ 14.0

* RR = Relative Risk of blacks compared to whites

** Adjusted to the 1970 US Standard

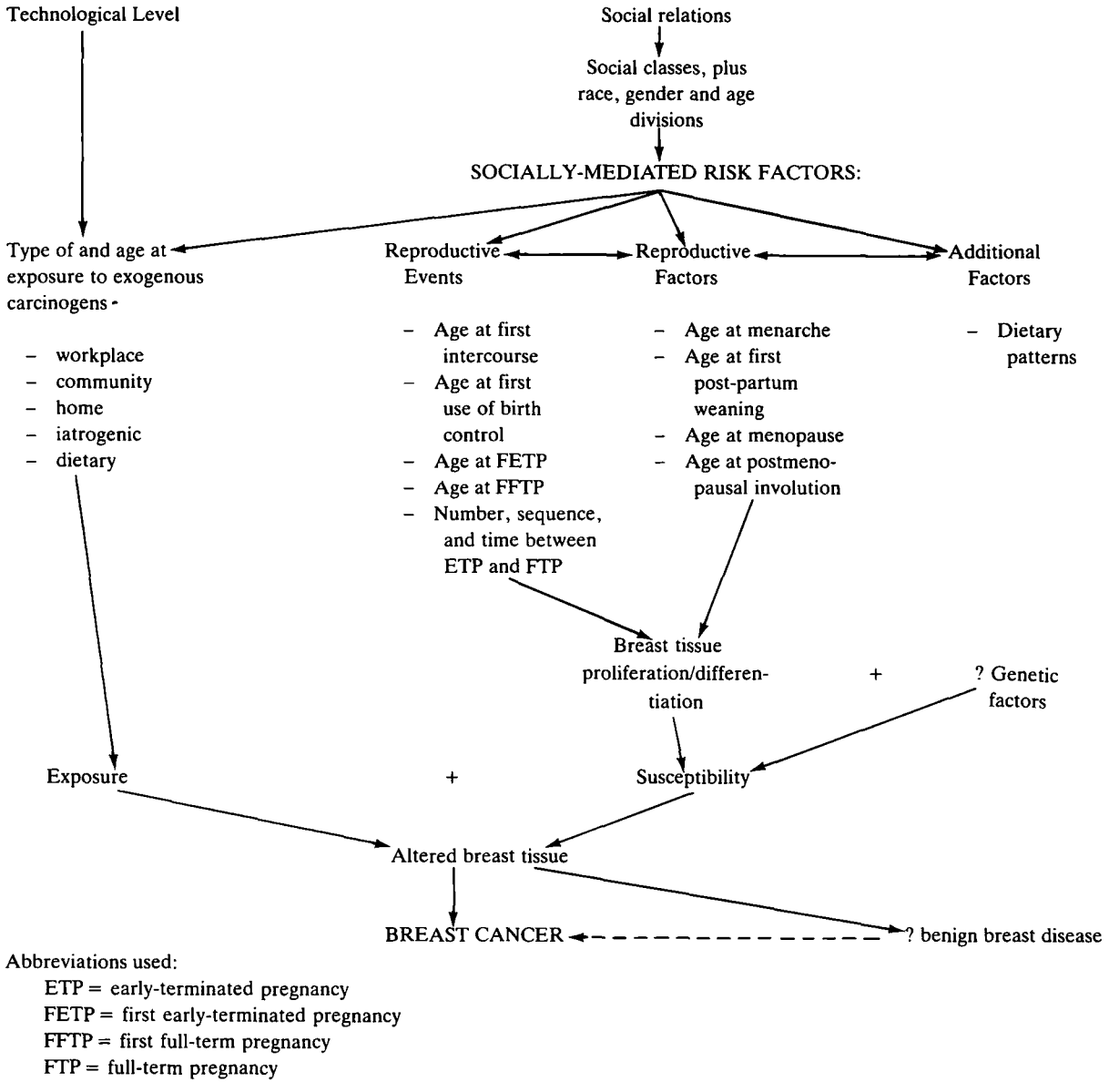

Fig. 2. Alternative social model of breast cancer pathogenesis.

tion of female and child labor to a family's survival; simultaneously, its social relations determine which women are most likely to be exposed to these carcinogens (whether at work or at home), what constitutes their typical diet, and whether or not they bear many children beginning at an early age [86–90]. Additionally, wars and economic recessions may also affect exposure and susceptibility by altering employment patterns, modifying diets, and reducing fertility rates [75, 86–89].

Before elaborating this alternative hypothesis, however, it is helpful first to review current knowledge regarding human breast development, the susceptibility of replicating DNA and undifferentiated cells to carcinogens, and the presumed histologic origins of breast cancer. Although the dynamics of breast development remain incompletely understood, numerous studies have established that girls' breasts undergo massive levels of ductal growth during puberty (with ducts extending into

the breasts' fat pads), that breast cell growth and elimination (apoptosis) fluctuate with the menstrual cycle, and that all women's breasts (including those of nulliparous women) undergo differentiation as a function of age and involution as a function of menopause [84, 91–94]. It is also well known that the second major round of breast tissue growth occurs during the first trimester of a women's first pregnancy, that full development of this tissue into secretory cells requires a full-term pregnancy (FTP), that pregnancy promotes the vascularization of breast tissue, and that a women's breast is qualitatively transformed by her FFTP, resulting in a much higher ratio of differentiated to undifferentiated cells; this latter change is spurred by the action of maternal, placental, and fetal hormones (especially prolactin and human chorionic somatomammotropin) [91–94].

Suggesting an inverse relationship between differentiation and susceptibility, numerous experiments have demonstrated that undifferentiated cells undergo mitosis more frequently than differentiated cells and that DNA is most vulnerable to carcinogenic mutations (or least able to repair them) when replicating, but least susceptible when resting [45, 81, 85]. Other investigations have found that a cell's degree of differentiation may affect susceptibility through influencing the level of receptors and/or substrates with which diverse carcinogens interact [81, 91]. Recent studies on human breast cell kinetics also have shown that the rate of DNA synthesis is greatest in the cells of young as compared to older women [83–84], and that within any given breast, it is highest in TDLU, intermediate in duct cells, and lowest in alveoli, *i.e.*, the rate peaks in regions with greatest growth [83]. Moreover, additional investigations have indicated that breast cancer in women originates in the TDLU and that numerous tumors typically appear simultaneously in TDLU throughout both breasts [95–96]. Together, these findings imply that breast cancer in women occurs as a generalized response to systemic carcinogens operating within the breasts' most active tissue.

In light of these observations, this alternative approach proposes that genotoxic carcinogens would exert their greatest effect when a large number of undifferentiated breast cells are present and/or replicating. Given sufficient exposure to such agents, the likelihood of a tumor developing and its type would probably depend on four factors:

1) the location of the induced mutation,
2) the level of differentiation and physical location of the exposed cells (*i.e.*, TDLU, duct, or alveoli, with the most aggressive tumors arising from the least differentiated cells) [97–98],
3) whether the altered cells are retained or removed (via the menstrually-induced cyclic deletion of cells or possibly by lactation) [94], and
4) whether the potential tumor encounters conditions favorable for proliferation, such as pregnancy-induced vascularization [93] or additional epigenetic carcinogenic exposures [99].

At different stages of the breast's development, the probability of tumorigenesis might be modified further by additional factors, such as overall health status and genetic constitution. Family history of breast cancer, however, might also reflect familial continuity in exposure and reproductive risk factors.

Linking exposure and susceptibility in this manner, the proposed hypothesis therefore suggests that exposures increasing the risk of breast cancer conceivably could begin at birth. Infants and children consuming milk or food contaminated with fat-soluble carcinogens potentially could accumulate these substances in their breasts' adipose tissue, thus elevating the chance of subsequent malignant transformation of adjacent breast epithelial cells. Girls would be most susceptible to these and other early-stage carcinogens around puberty, due to the onset of massive ductal proliferation [91–93]; the absence of a comparable growth spurt in boys' breasts perhaps may partially explain the much lower rates of breast cancer in men.

After puberty, monthly fluctuations of breast cell growth induced by the menstrual cycle [84, 93–94] could sustain a woman's susceptibility to exogenous genotoxic carcinogens (present in the home, community, or workplace [100]). Initiated cells could then later be transformed into malignant cells by post-pubertal exposures to additional epigenetic carcinogens, including endogenous reproductive hormones. Absent pregnancy, the

three factors most likely to offset the risk of both initiation and transformation would be:

1) the deletion of altered cells by apoptosis [94],
2) the gradual differentiation of breast epithelium contingent upon the aging process itself [94, 99], and
3) menopause-induced involution (further reducing the number of undifferentiated cells and also the amount of breast fat [91–92], hence adjacent fat-soluble carcinogens).

According to this hypothesis, an early FFTP would provide the greatest protection against breast cancer by drastically reducing, early on, the presence of undifferentiated and hence vulnerable breast cells, thereby decreasing the risk of subsequent transformation. Moreover, lactation and post-weaning involution might also reduce risk, primarily through the excretion or removal of fat-soluble carcinogens and initiated or transformed cells. Finally, increased parity following an early FFTP also would be expected to reduce risk by inducing additional differentiation.

Other types of pregnancies, however, might increase risk of breast cancer. If a woman's first pregnancy resulted in a first trimester abortion, the dramatic rise in undifferentiated cells that takes place during the first trimester would not be followed by the marked differentiation occurring during the second and third trimesters. The consequent sharp increase in the number of vulnerable cells would thus elevate breast cancer risk. Abortions occurring shortly before a woman's FFTP, however, might not increase risk, since most of the newly-produced undifferentiated cells would soon undergo differentiation. Similarly, abortions occurring after a woman's FFTP or any subsequent FTP also might have little effect, because the number of undifferentiated cells eligible to proliferate would be markedly smaller, due to the prior pronounced breast development induced by each FTP.

Additionally, a late FFTP conceivably could increase breast cancer risk by spurring the growth of previously transformed cells or 'latent' tumors in several ways. For example, pregnancy-induced elevated levels of estrogens could increase not only the mitotic activity of breast cells, but also, via enhancing vascularization of the breast, the likelihood of small tumors obtaining sufficient nutrients to reach 'critical mass'. Such factors could account for why nulliparous women are at higher risk for breast cancer than women with an early FFTP but at a lower risk than women with a late FFTP. Presumably, both nulliparous women and those with a late FFTP would accumulate many more transformed (or even malignant) cells than women with an early FFTP, thus putting both at increased risk; the late FFTP of the latter, however, would raise the risk even further by provoking these otherwise 'silent' tumors to grow.

This alternative hypothesis consequently implies that the presumed joint determinants of breast cancer incidence – exposure and susceptibility – cannot be examined statically, but instead must be considered in relation to each other at every stage in a woman's life. Just as the same exogenous exposure might have dramatically different effects on breast cancer risk (depending on the exposed breasts' level of development and the type of cell affected), so too might similar reproductive patterns yield different results (with women subjected to high exposures at greater risk than those experiencing low exposures). Analogously, women with different carcinogenic exposures and different reproductive histories might nonetheless be at similar risk of breast cancer, because high-risk reproductive patterns among women with low exposures may well be equivalent to low-risk patterns among women with high exposures. A comprehensive account of breast cancer epidemiology would therefore require specifying not only the biological mechanisms through which breast development and carcinogenesis occur, but also the social factors that affect risk by shaping both exposure and susceptibility throughout the course of women's lives.

Evidence supporting this alternative hypothesis

Numerous epidemiological and animal studies buttress the interpretation of breast cancer risk offered by this alternative approach, as do analyses of social gradients in disease. Although none offer definitive proof, all suggest that exogenous non-hormonal exposures may play the primary role in de-

termining the baseline risk of breast cancer observed among women and animals who have low-risk reproductive histories, with endogenous hormones secondarily affecting susceptibility to genotoxic agents.

Perhaps the best human evidence for this alternative hypothesis derives from data pertaining to female survivors of the nuclear destruction of Hiroshima and Nagasaki. The highest risk for radiation-induced breast cancer occurred in women who were 1–9 and 10–19 years old at the time the bombs were dropped (with a latency period of approximately 15 years); risk, moreover, was inversely related to increasing age and parity [101]. Similar modifying effects of age and parity on breast cancer risk also have been found in studies examining fluoroscopy-induced breast cancer [102]. Additionally, migration studies have shown that when women have moved to the U.S. from regions with low breast cancer incidence, such as Poland, Japan, and Central or South America, breast cancer risk was highest among those who migrated prior to adulthood and increased only slightly among first-generation immigrants; risk then rose markedly in the next and subsequent generations and could not be accounted for simply by changes in reproductive patterns [61, 103–105].

Further bolstering this alternative approach are several studies designed to detect exogenous substances directly within breast tissues or fluids [106–109]. One recent case-control study, for example, detected significantly higher levels of carcinogenic trace elements in the breast tissue of women with breast cancer, with concentrations in excess of those observed in the blood (implying that the breast may accumulate these substances) [107]. Similarly, several investigations have documented biologically significant levels of pesticide metabolites (such as dichlorodiphenyl dichloroethene [DDE]) and other halogenated hydrocarbons (such as polychlorinated biphenyls [PCBs]) in breast milk [108–109]. Higher concentrations occurred not only among poor as compared to affluent women and among black as compared to white women, but also in women who were nursing for the first time and in earlier samples from a given lactation [108–109]. The observed association of both time spent breast feeding and total number of breast-fed children with declines in both the breast milk concentration of pesticide metabolites [109] and maternal risk of breast cancer [36, 106] suggests lactation may help rid the breast of accumulated fat-soluble carcinogens, while at the same time exposing the nursing infant to these substances.

Also in accord with this proposed hypothesis, current epidemiological research has indicated that increased parity among women with an early FFTP, but not a late FFTP, may be a protective factor [33–35], and that first trimester abortions prior to, but not after, a woman's FFTP might elevate breast cancer risk [29–32]. In one recent cohort study conducted among women with only one FTP at the time of entry, those reporting one or more spontaneous abortions prior to this pregnancy were 3.5 times more likely to develop breast cancer than women who had no spontaneous abortions (95% confidence interval = [1.7, 4.2], adjusted for age at FFTP, age at menarche, and estrogen use during pregnancy) [31]. A population-based case-control study examining all incident cases of breast cancer in Denmark, diagnosed between March 1983 and February 1984, has also found that, among women with no FTP, the relative risk of breast cancer was 2.83 times greater among those who had at least one abortion as compared to women who had no abortions (95% confidence interval = [1.32, 6.07], adjusted for age and rural/urban status) [32]. Among women with at least one FTP, however, the relative risk associated with abortion either prior to or after the FFTP dropped to 1.2 and was not statistically significant.

Together, these results provide additional evidence regarding a link between abortion and breast cancer risk that was hinted at by numerous international investigations conducted in the 1960s and 1970s, but blurred by the fact that most did not distinguish between abortions occurring before and after a woman's FFTP [110–113]. A similar disregard for the sequence of and/or interval between women's abortions and first or subsequent FTP may also mar the analyses of several of the more recent studies finding no association [33–34, 113–116].

Negative evidence concerning exposure to exogenous hormones and to dietary fat also strengthens this alternative approach. Most epidemiological studies, for example, have found no significant association between noncontraceptive estrogen use and breast cancer risk [6–7, 116–117], and have also failed to link exposure to OCs with either increased or decreased breast cancer risk (even allowing for a 15-year latency period) [5–7, 118–123]. Concomitantly, laboratory data indicate that the mitotic activity of breast tissue in OC users equals that of non-users [84, 94, 124]. Moreover, among those studies which have linked OC use and breast cancer, increased risk was confined to women with prolonged OC use prior to FFTP [26, 29], implying that the effect of OCs on risk, if any, is modified by the breast's degree of development. Additionally, although many researchers have interpreted the high international correlation between per capita fat consumption and breast cancer incidence as evidence supporting fat-mediated tumor promotion and/or the hormonal hypothesis (*i.e.*, high fat diets lead to earlier menarche and increased adiposity, thus elevating secretion of adrenal steroids and intensifying their conversion to estrogens) [4–8], most case-control and cohort studies have failed to detect a consistent risk [13–15, 125].

More importantly, despite the existence of many *in vitro* experiments demonstrating hormonal acceleration and retardation of the growth and development of both normal and malignant breast cells [91–93, 126], epidemiological research conducted during the past two decades has yielded little definitive evidence linking endogenous hormone levels to breast cancer risk [5–7, 10, 46–55]. Many of the initial suggestive studies, moreover, have subsequently been criticized for several reasons, including insufficiently taking into account the periodicity of hormonal secretion, assuming that hormone concentrations measured after the onset of disease provide etiological clues, and presuming that plasma or urine levels accurately reflect breast tissue exposure [6, 51, 91]. New evidence indicates not only that breast tissue selectively concentrates and perhaps even synthesizes endogenous hormones [51, 91–92, 127], but also that undifferentiated and differentiated breast cells apparently exhibit different levels of hormone receptors [91], in turn implying that the same hormonal exposure at different stages in a breast cell's development may yield different results.

Tying together the diverse clues offered by human data, extensive experiments conducted on rats clearly demonstrate the relationship between exposure and susceptibility in determining breast cancer risk [57, 82]. Breast tissue growth dramatically accelerates around the time of the rat's first estrous cycle and then declines with increasing age; breast differentiation is spurred chiefly by pregnancy but also by increasing age [82, 128]. Researchers have invoked these features of rat breast development to explain why, among rats exposed to identical levels of the same genotoxic carcinogen at the same age, the highest to lowest rates of breast cancer occurred among: 1) rats that underwent 'first trimester' abortion (alone, and prior to FFTP), 2) rats that had a 'delayed' FFTP, 3) virgin rats, and 4) rats that had an early FFTP [57, 82, 128–134]. Likewise, among similarly-aged mice given identical levels of the same carcinogen, those exposed prior to their FFTP developed more tumors than mice exposed after their FFTP [135].

Lastly, the contention that the degree of exposure to carcinogens and types of reproductive patterns present within any given society reflect its level of industrialization as well as social relations is borne out by numerous analyses [86–89, 100]. Within the U.S., historical and current evidence show that poor and working class communities, as compared to more affluent groups, typically confront more noxious environmental and occupational carcinogenic exposures [70, 86, 100, 109, 136–143] and also are more likely to commence childbearing while young [75–76, 80, 143]. These patterns are most evident in the black community, due to its disproportionate concentration among the poor [75–76, 79, 89–90, 144], and are expressed through excess black morbidity (including higher incidence rates for most types of cancer) [70, 142–143] and higher fertility rates at younger ages [75–76, 79–80, 143]. Unfortunately, virtually no studies to date report whether community-based or occupational carcinogenic exposures contribute to breast cancer occurrence [5–7]. Nevertheless, data

regarding other types of cancer support the view that social gradients in incidence chiefly reflect socially-mediated variations in exogenous exposures [70, 138, 142–143].

Interpreting unresolved issues using this alternative approach

Juxtaposing exposure and susceptibility in the manner proposed by this alternative hypothesis potentially may shed light on several controversial risk factors, including OC use, benign breast disease (BBD), and dietary fat. For example, international variation in abortion patterns [145–146] might help explain why only a handful of studies have found prolonged OC use to be a risk factor [26–29] when most have not [118–122]. If OC users in some countries more frequently utilized abortion as a back-up for contraceptive failure, and if different control groups not only used OCs less but also were less sexually active and hence at less risk for abortion, then this alternative approach would suggest that OC use might emerge as a risk factor if studies failed to control for variations in abortion patterns.

Additionally, confounding due to the heterogeneity of conditions termed 'BBD' may help explain why, despite many shared risk factors, only certain types of BBD (such as atypical hyperplasia and proliferative disease without atypia) are consistently associated with an elevated risk of breast cancer, whereas other types of BBD are not [23–25]. At issue may be two causal pathways: direct (with proliferative types of BBD representing actual preneoplastic lesions arising from initiated, relatively undifferentiated tissue) and indirect (with other types of BBD resulting from comparable exposures affecting more differentiated cells [96]). If so, and if the latency period for non-proliferative BBD were also shorter than that for cancer, then the truly benign types of BBD would appear to lead to breast cancer *only* among women in whom more susceptible cells had also been exposed and undergone initiation. Among women whose breasts were chiefly composed of relatively differentiated cells at the time of exposure, however, these benign types of BBD would not appear to be associated with breast cancer risk.

A failure to account for differential exposures to exogenous carcinogens may likewise illuminate why few case-control studies have found elevated dietary fat to be a risk factor, despite high international correlations between fat consumption and breast cancer incidence. If, for example, the exposure in question were the extent to which fats are contaminated by fat-soluble carcinogens, rather than the quantity of fat consumed, then the observed dietary link would be indirect, reflecting international variation in carcinogenic exposures, as opposed to causation per se [147–148]. It is important to stress, however, that the high international correlations may instead be spurious, and in fact be due to ecologic fallacy [149–154]. This would occur if the actual risk factor(s) in question not only had no direct relation to fat but also were differentially distributed by the grouping variable (*i.e.*, 'nation'). Such would be the case if the conditions leading to elevated breast cancer risk were mediated by each country's particular level of technological development and set of social relations and involved exposure to non-fat-soluble carcinogens and/or reproductive patterns affecting breast tissue susceptibility.

Joint consideration of exposure and susceptibility factors may also render more comprehensible several trends in breast cancer incidence not easily explained by current hormonal hypotheses. For example, despite sharing comparable low-risk reproductive profiles, low fat diets, and internationally low age-adjusted breast cancer incidence rates, women in Latin America nonetheless are more likely to develop breast cancer than women living in Asian countries [4]. Similarly, second-generation Latinas and Japanese women in the U.S. are at higher risk for breast cancer than first-generation immigrants, despite similar reproductive histories [61, 103, 105]. In both cases, greater exposure to unidentified exogenous carcinogens might help account for these discrepancies.

Lastly, in view of the overall excess cancer rates among blacks in the U.S. and their likely link to higher levels of socially-mediated exogenous exposures, this alternative hypothesis suggests that the

puzzling question 'why do black premenopausal breast cancer rates exceed those of whites?' perhaps should be changed to 'why should age-specific breast cancer rates ever be lower among blacks?' Phrased this way, the question highlights the fact that impoverished conditions rarely afford protection against the vast majority of diseases, except through premature mortality [86–90].

Although the paucity of breast cancer studies examining genotoxic carcinogens means that discussions regarding exogenous exposures and breast cancer risk among black and white women must remain speculative, it nonetheless is possible to highlight several trends potentially affecting exposure and susceptibility that could influence the breast cancer risk of women born in the U.S. after 1945. First, use of petrochemical products in agriculture, industrial workplaces, and the home has increased [100, 147], as has domestic consumption of high-fat and pesticide-contaminated foods [108–109, 147]; presumably, women born after 1945 would experience higher rates of pre-pubertal, adolescent, and early adult exposures than prior generations. Second, black residence in metropolitan regions has grown enormously, with the proportion of the black population living in cities rising from under 50% in 1940 to over 80% by 1970 [75, 79, 155–156]. This shift in part resulted from the major wave of black urban migration that commenced with World War II, one which also spurred a rise in industrial employment among both black women and men [75, 144, 155–156]. Moreover, the black urban communities created during this migration disproportionately have been located adjacent to both industrial areas and hazardous waste dumps [75, 141, 155].

Additionally, the concurrent trend of increasing labor force participation of both black and white women (with economic necessity keeping the former consistently higher than the latter [75, 144, 156]) may also have elevated breast cancer risk. This shift not only has increased occupational exposures [100], but also has prompted declining fertility rates in each group (with black rates nonetheless consistently higher than those of whites) [75, 79, 143, 156]; elevated workforce participation may also underlie the lower rates of breast feeding among minority and low-income women [157–158]. Moreover, the legalization of abortion in 1973 enhanced two demographic transitions in abortion patterns that might also affect breast cancer occurrence. In contrast to earlier cohorts in which white and relatively affluent women were more likely to obtain therapeutic and induced abortions [146, 159–160], between 1973 and 1981 the abortion rate among black and white women 15 to 44 years old rose, respectively, from 41 to 57 per 1000 and from 16 to 24 per 1000 [145, 161–162]. Secondly, post-1973 abortion rates also climbed most rapidly among adolescents, such that U.S. teen abortion rates now rank among the world's highest [78, 145]. Reflecting these changes, black and/or low-income women under the age of 25 currently are at least twice as likely to obtain an abortion as are similarly aged white and/or higher-income women [76, 78, 145, 161–162]; they also remain more prone to spontaneous abortions [76, 161–162].

That the incidence of breast cancer is now higher among black as compared to white women *only* under the age of 40 could therefore be explained by shifting combinations of exposure and susceptibility patterns in successive cohorts (Table 2). The higher teen abortion rate among black women could conceivably heighten black teenagers' susceptibility to potentially excessive and increasing exogenous carcinogenic exposures, thereby contributing (along with lower breast feeding rates) to higher rates of premenopausal breast cancer. Young white women's presumed lower exposure and lower susceptibility would, in turn, yield a lower early breast cancer risk. In contrast, older black women's lower average age at FFTP, higher parity, and higher rates of hysterectomies [163] (hence earlier menopause), would, despite their higher exposures, reduce risk for developing breast cancer at a later age. Lastly, the breast cancer incidence rate among older white women would reflect the combination of high-risk reproductive patterns with baseline societal exposures.

In sum, this alternative hypothesis would predict that the observed racial cross-over in age-specific breast cancer incidence rates represents a complex class-based phenomenon shaped by race relations, and also that breast cancer rates among young

white women would correlate inversely with SES. Similarly, it would suggest that the overall high incidence of breast cancer among U.S. black and white women of all ages, as compared to women in other nations, most likely would stem from comparatively high society-wide exposures to currently unidentified exogenous genotoxic carcinogens. Finally, such ubiquitous exposures also could account for why factors affecting susceptibility, such as reproductive variables, rather than exogenous carcinogens, have emerged as key predictors of breast cancer occurrence [164].

Implications for future research and prevention

To ascertain whether the proposed hypothesis is valid and whether it improves understanding of phenomena that either contradict or cannot easily be explained by current hormonal hypotheses of breast cancer causation, it will be necessary to conduct additional research regarding the role of exogenous carcinogens and breast tissue susceptibility in determining breast cancer risk. Specific refutable predictions that could be tested in a variety of laboratory and epidemiological investigations include:

1. Less differentiated breast tissue is more susceptible to genotoxic and epigenetic carcinogens than is more differentiated tissue, particularly during periods of substantial growth.

2. Reproductive events that contribute to marked increases in undifferentiated cells include onset of menarche and first trimester abortions that either are not followed by or occur substantially prior to a FFTP; reproductive events that lead to delayed or reduced breast tissue differentiation include late age at FFTP, nulliparity, and late age at menopause.

Corollaries of predictions 1 and 2:

a) The greatest susceptibility to genotoxic carcinogens occurs during: the initial stages of menarche, the subsequent interval preceding FFTP, and the first trimester of a woman's first and subsequent pregnancies; initiated cells that are least differentiated are also most susceptible to epigenetic carcinogens.
b) First trimester abortions occurring substantially prior to or not followed by a FFTP elevate breast cancer risk; abortions in any trimester occurring shortly prior to or after a woman's FFTP pose little increased risk of breast cancer.
c) Breast cancer and proliferative BBD originate most frequently in regions of the breast containing the least differentiated and most actively growing cells; non-proliferative BBD more typically arises in more differentiated and less actively growing cells.

3. Among women with similar reproductive histories, higher concentrations of exogenous carcinogens (and most likely fat-soluble carcinogens) exist or have existed in the breast tissue of those

Table 2. Proposed relation of exposure and susceptibility to genotoxic agents in determining black/white differences in age-specific breast cancer incidence within the United States

		Susceptibility to genotoxic agents	
		High	Low
Exposure to genotoxic agents	High	Younger Black women	Older Black women
	Low	Older white women	Younger white women

with as compared to those without breast cancer; these exposure differences will be especially evident in the interval spanning onset of menarche to FFTP, and may be less discernible at the time of diagnosis, depending on the degree to which the breast accumulates or excretes these carcinogens.

4. Among women with similar exposure histories, those with higher risk reproductive patterns will be at greatest risk for breast cancer.

Corollaries of predictions 3 and 4:

a) If genotoxic carcinogens that affect breast cancer tissue are widely dispersed throughout a given society, reproductive events that augment the proliferation of undifferentiated breast cells will be powerful determinants of breast cancer risk, while reproductive events that enhance early differentiation will be strong protective factors.
b) If these genotoxic carcinogens are unevenly distributed, then the same reproductive factors will exhibit smaller associations with breast cancer risk in regions of low as compared to high exposure.

In light of these predictions, studies demonstrating marked differences in breast cancer risk among women with similar reproductive histories and hormonal profiles, but divergent exposures to exogenous carcinogens (particularly during times of greatest susceptibility), would constitute critical evidence in refuting the hypothesis that exposure to endogenous hormones is the primary determinant of breast cancer risk.

Tests of predictions regarding the relationship between differentiation, growth, and susceptibility could be addressed at a cellular level by experiments that seek to replicate and expand not only work comparing the mitotic and labeling indices of breast cells at different stages of development [82–84, 94, 124], but also studies investigating whether known genotoxic carcinogens preferentially bind to the DNA of less differentiated breast epithelial cells [82]. New research should focus especially on discerning how diverse reproductive events (such as menarche, pregnancy, abortions, and menopause) affect breast tissue proliferation and differentiation. Additional investigations should also attempt to determine if any of the direct-acting genotoxic agents or procarcinogens and their metabolites already detected in human breast tissue, breast milk, and nipple aspirate fluid [106–109] are capable of acting as initiators within breast tissue. Moreover, future pathological research should seek to identify more precisely the histologic origins of the diverse types of BBD, as well as breast cancer, thereby testing the hypothesis that proliferative and malignant disease more frequently originate in the breasts' least differentiated regions.

Secondly, at an epidemiological level, a new priority should be investigations designed to detect (by gas chromatography or other appropriate techniques) the presence of exogenous carcinogens in human breast fluids and breast tissue (both epithelial and adipose). This could be accomplished by comparing malignant versus benign biopsy specimens, and also the breast milk of lactating women (or the nipple aspirate fluid of non-lactating women) with and without breast cancer. Differences in baseline carcinogenic exposures among women from countries with low and high breast cancer incidence rates likewise would be worth examining. Because the most appropriate measurements of exposure levels, however, may be in the time period extending from onset of menarche to FFTP, it would be important to conduct retrospective cohort studies where possible. For example, it may be feasible to assess the breast cancer risk of teenage girls and young women for whom serum and urine pesticide levels, as well as reproductive histories, were obtained in the Second National Health and Nutrition Examination Survey [165]. Another way to address concerns regarding the timing of exposures might be through studies that compare differences in exposure status and reproductive histories of first- and second-generation immigrants. Studies to evaluate potential carcinogenic contaminants in dietary fat consumed in countries with low and high rates of breast cancer incidence potentially could prove informative as well.

Important new information concerning reproductive risk factors might also be obtained if studies

sought to clarify the association between breast cancer and first trimester abortions, including whether it matters if the abortion precedes or follows a woman's FFTP, and by what length of time. Controlling for abortion patterns might also help resolve some of the ambiguities concerning the status of OCs as a risk factor for breast cancer.

In addition, given the proposed hypothesis that social gradients in breast cancer risk most likely reflect socially-mediated differences in exposure and susceptibility, the most fruitful epidemiological studies may be well be those which seek to analyze such unexplained phenomena as the higher and rising incidence of breast cancer among young black women in the United States. An initial step, for example, might be determining whether the observed racial cross-over stems from a more general social class cross-over in age-specific breast cancer incidence. If so, it would then be important to identify, through a case-control study, potential reproductive and exposure factors (including both abortion patterns and community- or home-based carcinogenic exposures) that could lead to a higher incidence of breast cancer among young working class women. Once hypotheses are refined through these and other types of epidemologic investigations, it may then be necessary to implement a 'Framingham'-type study [166], in which lifetime histories regarding both exposure and susceptibility risk factors can be monitored simultaneously in selected communities (such as those covered by population-based cancer registries).

Finally, this alternative hypothesis suggests that primary prevention of breast cancer might not only be possible but also increasingly necessary, especially given the minimal decline in U.S. breast cancer mortality rates during the past two decades [1–2, 167–168]. The conjoint trends of women's rising labor force participation and delayed childbearing augur future increases in breast cancer occurrence [74]. Since reversing societal changes in fertility patterns is unlikely, reducing risk will require minimizing exposures. The urgency of this task is further highlighted by the fact that even women with low-risk reproductive profiles in the U.S. are currently at high risk for developing breast cancer [59–60]. Moreover, if abortion substantially prior to FFTP is implicated as a risk factor, then additional interventions to ensure access to safe and effective contraceptives, especially for teenagers, also will be important.

Conclusion

The proposed alternative social approach to analyzing breast cancer etiology and epidemiology hypothesizes that breast cancer risk is primarily determined by exposures to exogenous genotoxic carcinogens and secondarily influenced by epigenetic factors (including hormones) that affect susceptibility either by altering the ratio of undifferentiated to differentiated breast cells or by accelerating the growth of initiated or transformed cells. It further posits that the incidence of breast cancer in any given society does not simply represent the sum of the risks of individual women as determined by changes in each woman's hormonal profile, but instead necessarily reflects the ways in which a society's level of technological development and social relations simultaneously shapes both exposure and susceptibility. Consequently, this approach predicts that social gradients in age-specific breast cancer rates – chiefly along the lines of social class, race, nationality, and gender – must necessarily exist to the extent these social relations influence risk. Finally, it illustrates how endeavors to explain race and class gradients in U.S. breast cancer epidemiology can provide not only important tests of accepted hypotheses but also new impetus for public health interventions geared toward eliminating socially-determined gradients in disease.

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