The Role of Nutrition in Preventing and Treating Breast and Prostate Cancer

Maternal and Prepubertal Diet, Mammary Development and Breast Cancer Risk$^{1,2}$

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Although diet has been implicated as playing a major role in breast cancer, we do not know what dietary factors are responsible for initiating and promoting breast cancer. Until recently, a high intake of dietary fat was believed to contribute to the high incidence of breast cancer in the Western world. However, results obtained in cohort studies indicate that this may not be the case (Hunter et al. 1996). Another dietary component that has been linked to breast cancer is soy. High soy intake has been suggested to lower breast cancer incidence in Asian countries (Adlercreutz et al. 1996). However, a meta-analysis of results obtained in case-control and cohort studies indicates that high soy intake does not reduce cancer risk, at least in postmenopausal women (Trock et al. 2000). A consensus exists that high vegetable intake reduces breast cancer risk, but none of the suspected components in vegetables appear to explain their protective effect. Thus, the dilemma is that although diet is estimated to contribute to at least 50% of newly diagnosed breast cancers, the specific dietary components associated with breast cancer etiology remain unknown.

Estrogen exposure and breast cancer risk

One factor contributing to the current confusion regarding diet and breast cancer is that the same dietary component might have a different—even opposing—effect on breast cancer risk, depending on the timing of exposure. In the case of estrogens, where the evidence strongly indicates that they increase breast cancer risk, timing of exposure is important. Estrogens stimulate the growth of human breast cancer cells in vitro (Dickson and Russo 2000), and estrogen exposure increases breast cancer risk, at least in postmenopausal women (Hankinson et al. 1998). Further, several reproductive factors indicating an increased exposure to estrogens also increase breast cancer risk (Hulka and Stark 1995), whereas reduction in ovarian estrogen levels by bilateral ovariectomy markedly reduces breast cancer risk (Kreiger et al. 1999). However, circulating estrogen levels during the reproductive years are not associated with a risk of developing premenopausal breast cancer (Key et al. 1996). A modest reduction in circulating estrogens, such as that produced by unilateral ovariectomy (Parazzini et al. 1997), or oral contraceptive (Romieu et al. 1990) or contraceptive depot use (Paul et al. 1989) (both inhibit ovulation and ovarian estrogen production) actually increases rather than reduces breast cancer risk. Further, a 10-fold increase in circulating estrogens during pregnancy (Yuan et al. 1988), a short menstrual cycle length (increased exposure to ovarian estrogens) (Titus-Ernstoff et al. 1998) or a high body mass index (BMI)$^a$ (increased exposure to adipose tissue–derived estrogens) reduces the risk for developing premenopausal breast cancer.

In utero estrogen exposure and breast cancer risk

It has been suggested that the higher the in utero estrogenicity, the greater the subsequent risk of developing breast cancer (Trichopoulos 1990). This hypothesis is supported by data obtained in epidemiologic studies (Ekbom et al. 1992, Michels et al. 1996, Weiss et al. 1997). Animal studies indicate that a maternal exposure to an elevated estrogenic environment, as induced by an administration of either estradiol (Hilakivi-Clarke et al. 1997b) or the synthetic estrogen diethylstilbestrol (DES) (Walker 1984), significantly increases breast cancer risk in female offspring.

The concept that a high in utero estrogenicity increases breast cancer risk has been challenged recently by clinical findings showing that circulating estrogen levels are significantly higher in pregnant Asian women, who exhibit low breast cancer risk, than in Caucasian women, who exhibit high breast cancer risk (Lipworth et al. 1999). Because nonpregnant Asian women have ~40% lower serum estrogen levels than do Caucasian women (Goldin et al. 1986), it is

$^a$ Abbreviations used: BMI, body mass index; DES, diethylstilbestrol; DMBA, 7,12-dimethylbenz[a]anthracene; EGF, epidermal growth factor; ER, estrogen receptor; LAU, lobuloalveolar units; PUFA, polyunsaturated fatty acids; TEB, terminal end buds; TGF-α, transforming growth factor α.
essential to determine why the reverse occurs during pregnancy. Our animal studies (Cabanes et al., unpublished data) suggest that soy and fish oil, both typical to Asian diets, increase circulating estrogen levels during pregnancy, whereas they have an opposite effect on offspring (i.e., adult female offspring of dams who consumed a high soy diet during pregnancy exhibit reduced estrogen levels).

Maternal diet and offspring's breast cancer risk

We have studied the effect of maternal diets on mammary tumorigenesis in female rat offspring. The diets were those with high or low amounts of (n-6) polyunsaturated fatty acids (PUFA) (Hilakivi-Clarke et al. 1997b), genistein (Hilakivi-Clarke et al. 1999) or soy (Cabanes et al., unpublished data). The source of the (n-6) PUFA was corn oil, and it significantly increased circulating estradiol levels in pregnant rats (Hilakivi-Clarke et al. 1996 and 1997b). Genistein is a phytoestrogen and the component believed to mediate soy’s effects on the breast; however, it binds and activates the estrogen receptor (ER) and therefore stimulates the growth of normal and malignant mammary cells both in vitro and in vivo (Bouker and Hilakivi-Clarke 2000).

The results indicate that high amounts of (n-6) PUFA and genistein both increase the offspring’s mammary tumorigenesis if exposed through a pregnant rat dam (Hilakivi-Clarke et al. 1997b and 1999). The carcinogen used to induce tumors was 7,12-dimethylbenz[a]anthracene (DMBA) administered to offspring as a single oral 10-mg dose. Maternal soy intake did not increase offspring’s risk of developing mammary tumors (Cabanes et al., unpublished data), although the soy diet contained high levels of genistein. The soy diet also increased pregnancy estrogen levels. These results indicate that soy must contain some additional components, which reverse the effects of genistein on offspring’s breast cancer risk when administered in utero.

Prepubertal estrogen exposure

Little is known about estrogenicity during childhood and its effect on later breast cancer risk. In a unique study with rats, daily exposure to estradiol between postnatal d 0 and 30 effectively reduced susceptibility to carcinogen-induced mammary tumorigenesis (Nagasawa et al. 1974). However, alterations in reproductive parameters were also noted, which could potentially affect fertility. We recently found that a shorter exposure (between postnatal d 7 and 20) at lower estradiol concentrations also reduced carcinogen-induced mammary tumorigenesis in rats without causing alterations in the reproductive system (Cabanes et al., unpublished data).

In humans, the effect of childhood exposure to estrogens has been studied indirectly by investigating associations among BMI, height and dietary fat intake. Obese girls have more adipose tissue than thin girls, and adipose tissue is the site of the conversion of adrenal androgens to estrogens. Four recent studies, including our cohort study, indicate that women who had a high BMI between ages 7 and 13 y exhibit significantly reduced breast cancer risk (Berkey et al. 1999, Hilakivi-Clarke et al. 2000, Le Marchand et al. 1998, Magnusson et al. 1998). Breast cancer risk is also reported not to be affected or reduced in women who consumed a high fat diet around the time of puberty (Hilaiopol et al. 1986, Potter-Chun et al. 1998). Height in childhood is linked directly with later breast cancer risk; that is, if a girl is tall at age 7 y, her risk of developing breast cancer is significantly increased (Hilakivi-Clarke et al. 2000). Childhood height is inversely linked to circulating estrogen levels (Jacklin et al. 1994). These findings support the data obtained in animal studies indicating that an exposure to estrogens in childhood reduces later breast cancer risk.

Prepubertal diet and breast cancer risk

As indicated above, human studies suggest that high fat intake at puberty does not increase breast cancer risk but rather reduces it. To our knowledge, no animal studies exist that have examined the effects of an exposure to dietary fat before weaning on mammary tumorigenesis. We are currently performing such a study in rats that were exposed to high (n-6) PUFA diet between postnatal d 7 and 21.

Our group (Hilakivi-Clarke et al. 1998) and the group of Dr. Lamartiniere (Murrill et al. 1996) have been studying the effects of prepubertal exposure to genistein on DMBA-induced mammary tumorigenesis. We (Hilakivi-Clarke et al. 1998) also have studied the effects of prepubertal exposure to another phytoestrogen, zearalenone—a contaminant in grains, corn, potato, rice and other similar farm products that effectively activates the ER. Exposure to either of these two phytoestrogens between postnatal d 7 and 20 effectively reduced carcinogen-induced mammary tumor incidence.

Mechanisms mediating in utero estrogenic exposures of the breast

Mammary gland morphology. Estrogenic exposures in early life play a central role in the development of the normal mammary gland. The effects in rodents and humans appear markedly similar, perhaps reflecting the many structural, functional and endocrinologic similarities between the mammary glands in these species (Russo et al. 1990). In rodents (as well as in humans), the rudimentary mammary gland develops in utero and is characterized by growth of the primary branch from the nipple with subsequent limited secondary branching. This process depends on transplacental maternal hormones of pregnancy, including estrogens (Dickson and Russo 2000).

We have found that in utero exposure to estradiol, high (n-6) PUFA or genistein alters normal mammary gland development. The glands exposed to estrogenic compounds in utero contain persistent terminal end buds (TEB), exhibit reduced differentiation to lobuloalveolar units (LAU) or both (Hilakivi-Clarke et al. 1997a and 1997b). TEB play a central role in mammary gland development. They are the most actively growing epithelial structures and contain cap cells that are interpreted to represent a pluripotent stem cell population (Russo and Russo 1996). These cap cells are located on the basal surface of the TEB beneath the basal lamina. The TEB are known to be the sites of malignant transformation in the rodent mammary gland and possibly also in the human breast (Russo and Russo 1996). These data clearly support the hypothesis that perinatal exposure to estrogenic compounds can alter mammary gland development, which in turn might be associated with increased susceptibility to develop breast cancer.

Epigenetic mechanisms. The ER is a likely mediator of the effects of in utero estrogenic exposures on mammary tumorigenesis. Two ER subtypes have been identified in the mammary gland, i.e., the classical ER-α and a novel ER-β (Kuiper et al. 1996). ER-α is known to be associated with increased cell proliferation and breast cancer risk, but it is not clear whether activation of ER-β has similar or different effects on cells than activation of ER-α. Some evidence suggests that activation of ER-β may prevent epithelial cell proliferation,
including the proliferative effects resulting from activation of ER-α, and thus protect the gland (Paech et al. 1997, Saji et al. 2000). Further, ER-β levels are highest in normal breast tissue and lowest in malignant tumors (Leygue et al. 1998), suggesting that low ER-β levels are associated with increased risk to develop breast cancer.

Earlier studies measured ER levels in the mammary glands of rodents exposed to estrogenic manipulations in utero using a ligand binding assay that determines total ER binding (including both ER-α and ER-β). The data indicate that a maternal exposure to DES reduces total ER binding sites in the offspring's mammary gland or tumors (Bern et al. 1985, Verhoven et al. 1982). Because ER-β levels are higher than ER-α levels in the virgin rat mammary gland (Saji et al. 2000), the decrease in total ER binding sites after DES exposure may reflect a reduction in ER-β levels. This would allow ER-α to induce cell proliferation without being opposed by ER-β. In support of this view, our preliminary data obtained in female rat offspring whose mothers were fed a diet high in (n-6) PUFA during pregnancy indicate that their mammary glands contained increased levels of ER-α protein and reduced levels of ER-β protein (Cabanes et al., unpublished data). Further, it has been noted that neonatal estrogenization of male rats, which increases susceptibility to estrogen-induced carcinogenesis of the urogenital tract, leads to increased expression of ER-α but decreased expression of ER-β in the adult prostate (Prins et al. 1998).

We have found that a maternal exposure to genistein, in contrast, increases mammary ER binding sites in the offspring (Hilakivi-Clarke et al. 1999). This increase may reflect up-regulation of ER-α, again causing an increase in unopposed cell proliferation. The latter interpretation is supported by the observation that genistein preferentially binds to (and perhaps down-regulates) ER-β (Kuiper et al. 1997) and thus may up-regulate ER-α as a consequence of in utero exposure. Because in utero exposure to a high fat diet, DES or genistein increases carcinogen-induced mammary tumorigenesis, changes in either ER-α or ER-β might be critical in terms of determining the susceptibility to breast cancer.

Mechanisms mediating prepubertal estrogen exposures on the breast

Mammary gland morphology. During puberty, ductal elongation and branching occur in the mammary gland, and ovarian estrogens participate in regulating this process. In particular, estrogens induce the growth of mammary ducts, and estrogen-induced progesterone induces lobuloalveolar growth (Russo and Russo 1996). There is some dispute concerning whether estrogens can directly mediate mitogenic effects on the mammary gland or whether they occur through estrogen-induced stimulation of growth factors, such as epidermal growth factor (EGF) and transforming growth factor α (TGF-α) (Dickson and Russo 2000). In normal mammary epithelial cells, the ER is not located in cells that proliferate but in cells immediately next to them. Therefore, the proliferation of normal mammary epithelial cells that are exposed to estrogens probably occurs via estrogen-induced stimulation of, for example, TGF-α, which is located in the TEB of proliferating cells (Snedeker et al. 1991). We (Hilakivi-Clarke et al. 1998) and others (Murrill et al. 1996) have noted that prepubertal exposure to genistein causes changes in the mammary gland that become apparent a few weeks after the cessation of prepubertal exposure. These changes can be characterized as increased differentiation of TEB to LAU. The differentiated mammary gland exhibits low or no susceptibility to carcinogen-induced malignancies, whereas nondifferentiated gland containing high levels of TEB is particularly prone to develop malignancies if exposed to carcinogens (Russo et al. 1990).

Epigenetic mechanisms. A complex interplay among various hormones, growth factors and other pathways is likely to be responsible for the differentiation of the mammary epithelial tree. Lamartiniere’s group (Brown et al. 1998) showed that prepubertal exposure to genistein modulates expression of estrogen-regulated growth factors such as TGF-α, EGF and EGF receptor in the mammary gland. We have found that ER-α and ER-β protein levels are altered in the mammary glands of rats exposed to estradiol during the prepubertal period (Cabanes et al., unpublished data). Specifically, loss of ER-α protein expression and an almost fourfold increase in ER-β protein levels occur in the mammary glands of rats exposed prepubertally to estradiol. These findings suggest that a reduction in ER-α and estrogen-mediated growth factor pathways is linked to reduced mammary tumorigenesis. Further, an increase in ER-β protein levels in the mammary gland of rats exposed to estradiol during prepuberty may be associated with reducing their risk for developing mammary tumors.

SUMMARY

At present, we do not know what causes sporadic breast cancer. Environmental factors, particularly diet, appear to explain at least 70% of newly diagnosed breast cancers, but it is not clear what these factors are. We propose that the lack of progress in this area is due to a lack of considering the effects of timing of environmental and dietary exposures on the breast. The evidence provided above suggests that an in utero exposure to an estrogenic environment—including that caused by diet [high (n-6) PUFA or genistein]—increases breast cancer risk. This increase may be mediated by an increased presence of TEB in the mammary epithelial tree and increased ER-α levels, reduced ER-β levels or both. Prepubertal estrogen exposure, in contrast, reduces later risk of developing breast cancer. The protective effect of estrogens may be mediated by early epithelial differentiation, reduced presence of ER-α and increased levels of ER-β in the mammary gland. The challenge we are now facing is to determine whether the data obtained mainly through the use of animal models is relevant to women and if so, how we might be able to modulate pregnancy and childhood estrogen exposure by appropriate dietary modifications to reduce breast cancer risk in women.

LITERATURE CITED


