Protection against breast cancer with genistein: a component of soy¹⁻³

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ABSTRACT  Breast cancer is the most common cancer in women. Because genetics is believed to account for only 10–15% of breast cancer cases, the environment, including nutrition, is thought to play a significant role in predisposing women to this cancer. Studies of Asian women suggest that those who consume a traditional diet high in soy products have a lower incidence of breast cancer, but that among emigrants to the United States, the second generation, but not the first, loses this protection. These findings suggest a possible common mechanism of action for breast cancer protection from early, specific nutritional exposure. Genistein, an isoflavone found in soy, has been reported to have weak estrogenic and antiestrogenic properties, to be an antioxidant, to inhibit topoisomerase II and angiogenesis, and to induce cell differentiation. In studies of the mammary glands of immature rats, we showed that genistein up-regulates the expression of the epidermal growth factor receptor shortly after treatment, which may be responsible for the increased cell proliferation seen at that age. We hypothesize that the early genistein action promotes cell differentiation that results in a less active epidermal growth factor signaling pathway in adulthood that, in turn, suppresses the development of mammary cancer. We speculate that breast cancer protection in Asian women consuming a traditional soy-containing diet is derived from early exposure to soybean products containing genistein. We believe that early events are essential for the benefits of cancer protection. Am J Clin Nutr 2000;71(suppl):1705S–7S.

KEY WORDS  Genistein, breast cancer, soy, epidermal growth factor receptor, women, isoflavones

INTRODUCTION
Cancer of the breast is the most common cancer in women. More than 50% of breast cancers occur in developed countries; high-risk areas include North America and Europe, whereas Asia has the lowest risk. Risk factors are nulliparity, late age at first pregnancy, late natural menopause, exposure to ionizing radiation, and inheritance of mutations in specific genes, including BRCA1 and BRCA2 (1). Because genetics is believed to account for only 10–15% of all breast cancer cases (2), the environment, including chemicals, nutrition, and lifestyle, is thought to play a significant role in predisposing women to this disease. In general, epidemiologic studies do not support a relation between total dietary fat intake and breast cancer (3, 4). A closer look at the relative amounts of fatty acid intake, however, suggests that consumption of n–6 polyunsaturated fatty acids (which include linoleic and arachidonic acids) is correlated with breast cancer incidence (4). Conversely, eicosapentaenoic and docosahexaenoic acids, both of which are n–3 polyunsaturated fatty acids concentrated in fish oils, may confer protection against breast cancer. Other studies suggest that olive oil, an essentially monounsaturated oil, may have beneficial effects for both cardiovascular health and protection against breast cancer (5). Except for reports that women aged 15–19 y are more susceptible to ionizing radiation (6, 7), epidemiologic studies of the role of environmental chemicals in causing breast cancer have yielded conflicting results (8).

Findings that radiation can cause cancer during adolescence (6, 7) and that early but not late pregnancy protects against breast cancer (1) suggest that events early in a woman’s life are crucial for predisposing her to, or protecting her from, breast cancer. Such findings are consistent with the development of the breast and the differentiation of breast cells; although most developmental changes occur perinatally, the mammary tissue continues to undergo maturation even during early adulthood. In rats, at birth and during the first week postpartum, the mammary gland is composed of a single primary or main lactiferous duct that branches into 3–5 secondary ducts (9). During the second week, further sprouting of ducts occurs up to the sixth generation. This sprouting of ducts markedly increases the density of terminal end buds, which reach their maximum number during puberty. Terminal end buds are the growing fringe of the mammary gland, with lateral buds branching dichotomously to form branches more proximal to the nipple. A portion of the terminal end buds differentiates in response to each estrous cycle, giving rise to alveolar buds that comprise lobules.

Laboratory studies have confirmed the role of early exposure to estrogen and progesterone in causing differentiating effects on the mammary tissue and in reducing subsequent susceptibility to chemically induced mammary cancer (10, 11). But do we

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really want to advocate early pregnancy or early use of estrogens to protect against breast cancer? Are other alternatives available to achieve the same end?

In 1991 Lee et al (12) reported that Asian women who consumed a traditional diet (high in soy products) had a low incidence of breast cancer. Yuan et al (13), however, reported no protection against breast cancer from soy consumption. In a third investigation, Wu et al (14) reported a correlation between tofu intake and a reduced rate of mammary cancer in a population-based case-control study of breast cancer among Chinese American, Japanese American, and Filipino American women. Adjustment for migration rates showed that the second generation, but not the first, lost this protection (15). This finding suggests that there may be a common mechanism of action for protection against breast cancer from early, specific nutritional exposure and from exposure to hormones of pregnancy early in life.

EXPERIMENTAL STUDIES IN RATS

In 1992, while investigating the potential developmental toxicity of diethylstilbestrol, we observed that neonatal diethylstilbestrol treatment reduced the incidence of spontaneous development of mammary tumors (16). Because we did not wish to advocate the use of this synthetic estrogen to protect against breast cancer, we investigated the potential of other agents to exert a similar chemopreventive effect without exposing women to significant toxicity. One such agent was genistein, an isoflavone found in soy; genistein has been reported to have weak estrogenic and antiestrogenic activity (24). On the other hand, analysis for EGF receptor mRNA and protein in mammary glands of 50-d-old female rats (24). On the other hand, analysis for EGF receptor mRNA and protein in mammary glands of 50-d-old animals showed no change from treatment with genistein before puberty. On further analysis (by immunohistochemical methods), we found that in 50-d-old rats treated prepubertally with genistein, EGF receptor expression was specifically reduced in the epithelial cells of the terminal end buds in comparison with the rest of the mammary gland. The mechanism of action of genistein appears to be different in the mammary gland of female rats than in the prostate of male rats, but the end effect is similar: reduced EGF receptor mass in the target tissue of adult animals, an effect that could alter signal transduction, mammary gland differentiation, and cell proliferation.

Because the perinatal period is the most sensitive for developmental and reproductive tract alterations, we investigated a variety of measures in animals exposed to genistein from conception until 21 d postpartum (21). We found no significant effect on the rate of fertility in dams fed 25 or 250 mg genistein/kg diet. In addition, the offspring had no significant effect on the number of males or females, anogenital distances, time of vaginal opening or testes descent, body weights at all ages, or the percentage of time spent in the phases of the estrous cycle or of follicular development. Histomorphologic analysis did not show any significant alterations of the female reproductive tract (ovaries, uterus, and vagina). We conclude that perinatal exposure of rats to physiologic concentrations of genistein does not cause any significant toxicity.

SUMMARY

We recently completed an investigation of the potential of feeding genistein to rats perinatally at physiologic concentrations to protect against DMBA-induced mammary cancer in their offspring. We found that 25 and 250 mg genistein/kg diets (AIN-76A; Harlan Texland, Madison, WI) reduced the number of mammary tumors by 20% and 50%, respectively (21). These data are consistent with our earlier data from studies using pharmacologic doses of genistein (17–20). Thus, it appears that perinatal exposure of rats to physiologic concentrations of genistein can exert a permanent protective effect against breast cancer.

Giving genistein to prepubertal rats increased uterine weights at day 21 postpartum, but at day 50 there was no significant difference between treated and control rats in uterine weight (21). Thus, genistein also mimics an estrogen in the uterus. In addition, inhibition of tyrosine kinases by genistein has been reported in vitro (22) but not in vivo.

The epidermal growth factor (EGF) signaling pathway functions via tyrosine kinase action. Recently, we investigated the potential of genistein to modulate the EGF receptor in the rat prostate and found that it could inhibit the expression of the receptor mass but not of the specific tyrosine phosphorylation of the receptor (23). Hence, we thought that the same effect might occur in the rat mammary gland. However, using reverse transcription and polymerase chain reaction as well as western blot analysis we found that prepubertal genistein treatment up-regulated the expression of the EGF receptor messenger RNA (mRNA) and protein in mammary glands of 21-d-old female rats (24). On the other hand, analysis for EGF receptor mRNA and protein in mammary glands of 50-d-old animals showed no change from treatment with genistein before puberty. On further analysis (by immunohistochemical methods), we found that in 50-d-old rats treated prepubertally with genistein, EGF receptor expression was specifically reduced in the epithelial cells of the terminal end buds in comparison with the rest of the mammary gland. The mechanism of action of genistein appears to be different in the mammary gland of female rats than in the prostate of male rats, but the end effect is similar: reduced EGF receptor mass in the target tissue of adult animals, an effect that could alter signal transduction, mammary gland differentiation, and cell proliferation.

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Because the perinatal period is the most sensitive for developmental and reproductive tract alterations, we investigated a variety of measures in animals exposed to genistein from conception until 21 d postpartum (21). We found no significant effect on the rate of fertility in dams fed 25 or 250 mg genistein/kg diet. In addition, the offspring had no significant effect on the number of males or females, anogenital distances, time of vaginal opening or testes descent, body weights at all ages, or the percentage of time spent in the phases of the estrous cycle or of follicular development. Histomorphologic analysis did not show any significant alterations of the female reproductive tract (ovaries, uterus, and vagina). We conclude that perinatal exposure of rats to physiologic concentrations of genistein does not cause any significant toxicity.
at that age. We hypothesize that the early genistein action promotes cell differentiation, resulting in a less active EGF-signaling pathway in adulthood that, in turn, suppresses the development of mammary cancer. We speculate that breast cancer protection in Asian women consuming a traditional soy-containing diet is derived from early exposure to soybean products containing genistein. We believe that early events are essential for cancer-protection benefits.

REFERENCES


