



Letter to the editor

Changes in Dietary Iodine Explains Increasing Incidence of Breast Cancer with Distant Involvement in Young Women

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The incidence of breast cancer with distant involvement at diagnosis is increasing in young women, age 25-39, possibly at an accelerating rate, as previously demonstrated by Johnson et al.¹ This disturbing trend was also observed in women age 40-54, albeit to a lesser extent. Understanding the causes for these changes in cancer demographics is particularly important in view of the young age of these women, as well as the poor survival rate for women with distant metastatic breast disease. There have been explanations proposed in several letters, including vaccination², advanced-age at first pregnancy³ as well as folate supplementation⁴, however these explanations have not been particularly satisfying. In response, the original authors⁵ suggested causal association need explain: 1) why a proposed agent or risk factor would cause advanced disease, 2) why it would preferentially affect the youngest women, and 3) how temporal trends in the proposed causative agent have changed since the mid-1970s⁵. The hypothesis that iodine deficiency in the United States, plays a role in the increased incidence of breast cancer with distant involvement, is discussed here in the context of these three factors.

1) Pathogenesis: Iodine deficiency has been proposed to play a causative role in the development of breast cancer^{6,7}. Dietary iodine has also been previously proposed to play a protective role in breast cancer⁸, to a large degree based on the increased iodine consumption of dietary iodine in Japanese women, having an exceptionally low incidence of

breast cancer⁹. Furthermore, emigration of Japanese women¹⁰ and adopting a western diet¹¹ is associated with higher breast cancer rates. Iodine is taken up by the sodium/iodide symporter in the breast and its role is important in promoting the development of normal versus neoplastic breast tissue development¹². In animal models of breast cancer, iodine in supplement or seaweed form, has demonstrated beneficial effects in suppressing breast cancer cell and tumor growth¹². The mechanism of action of iodine's anticancer effect may be complex, and roles as an antioxidant, promoting differentiation and apoptosis related to breast cancer have been proposed¹³.

Iodine deficiency is an important cause of thyroid deficiency; the potential linkage between thyroid disease and breast cancer has been a matter of considerable interest^{7,14-16} and has been extensively reviewed¹⁷⁻²⁰. In contrast, one study suggested hypothyroidism actually reduces the risk of breast cancer²¹, however, this study was done in older, mostly postmenopausal women and thus, this conclusion may not be relevant to the population of younger women (age 25-39) at risk for increased invasive breast cancer discussed here. Studies implanting human breast cancer as well as hepatocellular carcinoma cells in nude mice demonstrate that hypothyroidism reduces tumor growth, but at the same time enhances invasiveness and metastasis²². These findings provide a potential explanation for increased distant breast tumors at time of diagnosis. Since iodine deficiency is a major cause of hypothyroidism, breast cancer with distant

metastasis may be promoted in part by reduced thyroid function, where slower tumor growth (precluding earlier diagnosis), yet increased invasiveness could be consequential. Iodine deficiency, therefore, may contribute to breast cancer and its progression directly within breast tissue, and secondarily by decreased thyroid function leading to metastasis. The importance of iodine in breast cancer is further emphasized by the adjuvant effects of iodine (I_2) supplementation in combination with doxorubicin for breast cancer treatment²³. In these studies, iodine treatment resulted in reduced tumor size and proliferating cell nuclear antigen (PCNA) expression.

2) Population Iodine Deficiency: Increased iodine demand in women is likely due to the increased uptake of iodine in breast tissue, in addition to the thyroid gland, where iodine plays a role in the development and maintenance of healthy breast tissue (expanding after puberty) and in breast remodeling during lactation, and pregnancy¹². Young women and to a greater extent pregnant women, have lower urinary iodine levels than men of similar age. According to the CDC's 2012 Second National Report of Biochemical Indicators of Diet and Nutrition in the U.S. Population (www.cdc.gov/nutritionreport/report.html), women of childbearing age exhibited the lowest urinary iodine levels of any age group.

Iodine deficiency is associated with fibrocystic breast disease, which can be effectively treated or prevented with iodine supplementation²⁴. Fibrocystic breast disease affects at least 50% of women of child-bearing age and is associated with an increased risk of developing breast cancer²⁵. In women with atypia, there was twice the risk of developing breast cancer among women under age 45 in this study, relative to women age 55 or older, possibly reflecting a relationship between hormonal considerations and cancer risk. While the issue of metastasis was not investigated in this study, the increased risk in developing cancer in the ipsilateral and contralateral breast tissue might suggest metastasis or alternatively the presence of cancerous precursors as proposed by the authors. A previous study demonstrated atypia among the consequences of iodine deficiency in human and animal models²⁶.

Studies in rats have previously demonstrated that iodine deficiency results in "hyperresponsiveness" to estradiol, resulting in increased alveolar cell proliferation, abnormal changes within nuclei, and increased uptake of iodine within vacuoles, in estradiol stimulated mammary glands²⁷. These aforementioned studies provide a potential basis for the increased iodine requirements for women of childbearing age, as well as the

predisposition of this age group to the development of breast cancer.

Whether fibrocystic breast disease leads to metastatic breast disease at diagnosis is unclear, however, fibrocystic changes appear to be prognostically significant in patients with small, node-negative invasive breast cancer²⁸. The average age of women in this study was older, so it remains unclear if an increased risk for metastatic breast cancer can be attributed to previous fibrocystic breast disease in the age group (20-39) discussed. Nevertheless, the prognostic association of fibrocystic breast disease with metastatic breast cancer, as well as the association of fibrocystic breast disease with premenopausal women provides a plausible mechanism for disease progression.

3) Temporal Changes in Body Iodine: Comparisons of the National Health and Nutrition Examination Surveys (NHANES) showed a significant decrease in urinary iodine levels in the overall population during the period 1988-1994 as compared to the period 1971-1974²⁹. The initial urinary iodine levels (median 320 $\mu\text{g/L}$) were reduced by more than half during the period 1988-1994 (median 145 $\mu\text{g/dl}$; $P < 0.0001$). Accordingly, the percentage of total persons with iodine deficiency, (below 50 $\mu\text{g/L}$), increased from 2.6% during the period 1971-1974, to 14.5% in 1988-1994, representing a 5.6-fold increase²⁹. Females showed a higher frequency of iodine deficiency than males (15.1 versus 8.1%) with lower median iodine levels for females. For young women of child bearing age, age 15-44, there was a 3.8-fold increase in iodine insufficiency, with a 6.9-fold increase in the number of pregnant women also fitting this definition²⁹.

Blacks had lower levels of iodine than whites during both time periods (1971-1974 and 1988-1994)²⁹. During the period 2003-2006, blacks continued to exhibit lower urinary iodine levels than whites, with black women in the 20-39 age group having the lowest geometric mean levels of urinary iodine (www.cdc.gov/nutritionreport/report.html). Iodine deficiency is defined as levels below 50 μg iodine/liter urine or adjusted for creatinine, UI/Cr), where UI/Cr $< 50 \mu\text{g/g}$ creatinine is considered deficient. During this period 2003-2006, the geometric means of UI/Cr in white and black women in this age group was 128 (116-142, 95% confidence interval) and 74.9 (64.2-87.5), respectively. Lower UI levels in black relative to white women may also explain the greater increase in frequency of distant breast cancer in black women, as well as the growing health disparities gap³⁰. More recent studies including data between 2009 and 2014 demonstrate that breast cancers among black and white women with distant disease in the under-40 age

group continue to increase³¹. Black women remain at greater risk for breast cancer with distant disease, relative to white women or all women combined, and furthermore, the annual percentage increase of such cases among black women is larger (almost double that of white women)³¹.

According to the nutritional survey reports during the period 2005-2008, pregnant women had median urinary iodine levels of 125 µg/liter, and 56.9 percent had levels less than the 150-249 µg/liter urinary iodine recommended by the World Health Organization³². Thus, although potentially stabilized, the inadequate iodine levels observed in young women persists, with black women and pregnant women especially at risk. In addition to the potential risk for breast cancer, even mild iodine insufficiency appears to correlate with neurocognitive impairments in children³³. Thus, iodine insufficiency represents a major health issue for women of childbearing age as well as developing fetuses.

The observed drop in urinary iodine in young women as well as in the general population, since the 1970s, is presumably due to removal of iodine from bread and substitution with bromine as flour conditioner during this period of time, due in a large part to previous concerns about excess iodine as well as the preferences of commercial bakers for brominated flour. Bromine, a suspected carcinogen, may further exacerbate iodine insufficiency since bromine competes for iodine uptake by the thyroid gland³⁴ and potentially other tissues (i.e. breast).

The annual increase in distant breast cancer diagnosis since the mid- 1970s may reflect the time of exposure to decreased iodine and increased dietary bromine. Studies in countries where brominated flour and brominated vegetable oil are banned (i.e. the Canada and the European Union), may not necessarily show parallel increases in metastatic breast cancer in young women as occurring in the United States. New U.S. Government Dietary Recommendations (January 7th 2016) may also have impact since reduction in dietary salt intake from 3,440 to 2,300 mg per day may further reduce the intake of iodine from iodized salt. Such recommendations for universal salt restriction (i.e. for the benefit of salt-sensitive hypertension), should be balanced with the iodine needs of young women of childbearing age, particularly black women, to support breast and thyroid health, potentially cancer prevention, and the needs of the developing fetus during pregnancy.

In conclusion, dietary iodine insufficiency represents a plausible explanation for the increasing incidence of breast cancer in young women with distant metastasis. In view of the established

reduction in iodine levels in US women of childbearing age since the mid 70s, this group would be most vulnerable to increased breast cancer risk. The increased sensitivity of breast tissue to estradiol induced proliferative changes in the setting of dietary iodine insufficiency, provides a plausible mechanistic explanation for the increasing incidence of breast cancer with distant involvement in this age group. Based on the importance of iodine in thyroid and breast health, fetal brain development, as well as deficits in nutritional trends among younger women, iodine testing and management may be considered as a potentially important aspect for clinical practice.

Competing Interests

The author has declared that no competing interest exists.

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