FLUORIDE INTERACTIONS WITH IODINE AND IODIDE: IMPLICATIONS FOR BREAST HEALTH

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SUMMARY: The combination of iodide (or iodine) deficiency and the current widespread exposure to fluoride (F), often in uncontrolled doses, potentially affects the health and function of the mammary glands, which require elemental iodine (I_2) for normal architecture and function. Understanding the pathways by which F interferes with iodine transport and metabolism may help avoid breast mastopathies such as fibrocystic breast disease and breast cancer. Appreciation of these pathways may also assist in understanding the potential of F to affect thyroid hormone function and the transport of the essential nutrient iodide ion (I^-) to the developing fetus during critical windows of its development and postnatally to the suckling infant.

Keywords: Breast cancer; Breast iodine; Deiodinases; Fibrocystic disease; Fetal fluoride; Fluoride and thyroid; Iodine; Iodolactones; Sodium Iodide Symporter; Thyroid function.

INTRODUCTION

Described as an "endocrine disruptor" in a recent U.S. National Research Council (NRC) 2006 Review,[1a] fluoride (F, as the F^- anion) has the potential to disrupt the function of the many tissues that require iodine (I_2) or iodide (I^-). The NRC Review goes on to state that; "Intake of nutrients such as calcium and iodine often is not reported in studies of fluoride effects. The effects of fluoride on thyroid function, for instance, might depend on whether iodine intake is low, adequate, or high, or whether dietary selenium is adequate."[1b] Iodine deficiency is therefore due to many causes, including insufficient dietary intake,[5-9] lack of adequate nutritional co-factors,[1,5a,c,10,11] and the ubiquitous presence of inhibitors of iodine transport and utilization, such as thiocyanate, perchlorate, bromide, and F.[1,2] A combination of iodine deficiency with uncontrolled doses of such inhibitors of iodine transport and function potentially amplifies the incidence of iodine deficiency diseases.

Some of the cells and tissues that are known to concentrate the various forms of iodide against a concentration gradient include thyrocytes, brain cells and choroid plexus, white blood cells, salivary and lacrimal glands, the ciliary body of the eye, renal cortex, adrenal cortex, pancreas, fat tissue, liver, intestinal mucosa, nasopharynx, skin, hair, lungs, prostate, mammary gland, placenta, uterus, ovary, and kidney.[2] Mammary and thyroid glands are also involved in the conversion of iodide ion into organoiodide compounds or complexes—the process of attaching iodide to organic molecules such as proteins (e.g., casein in breast milk[3]) and fats

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(e.g., iodolactones[4] derived from polyunsaturated fats). Organoiodides are involved as storage vehicles, releasing iodide to tissues on demand with the help of enzymes, e.g., deiodinases.

This review examines some of the pathways by which fluoride may interfere with iodine function in animals and humans, with special reference to the mammary gland.

"IS IODINE A GATEKEEPER OF THE INTEGRITY OF THE MAMMARY GLAND?"[12]

A growing volume of research demonstrates an association between breast mastopathies and iodine deficiency. For centuries,[13] use of foods containing large amounts of iodine/iodide such as seaweed[14,15] for cyclical mastalgia,[8] fibrocystic breast disease[6,7] and breast cancer,[2,4-10,12-18] in both animal models and humans, has demonstrated the importance of iodine in human health and the prevention and treatment of these diseases. Iodine seems to accomplish the following:

1. Iodine desensitizes estrogen receptors in the breast[9c] and reduces estrogen production in overactive ovaries.[6]
2. Iodine increases progesterone production.[6]
3. Iodine reduces or eliminates fibrocystic breast disease in women, as demonstrated in three human trials.[6-8] It is purported that fibrocystic breast disease precedes breast cancer.[5,9]
4. Iodine provides anticancer effects at the promotional level, which causes cell death (apoptosis) and exerts anti-proliferative effects in a dose-dependent manner, only on tumoral cells.[4,17] These effects are more potent than from the chemotherapy drug 5-Fluorouracil.[14c]
5. Iodine prevents laboratory animals from getting cancer when they were fed the breast cancer-causing toxins 7,12-dimethyl-benz(a)anthracene (DMBA) or N-methyl-N-nitrosourea.[9,10,14]
6. Iodine triggers cell cycle differentiation, moving the cell cycle away from the undifferentiated characteristic of cancer.[4,18]
7. Iodine decreases lipoperoxidation and acts as an antioxidant.[12,16]
8. Iodine supplementation markedly increases urinary excretion of F, mercury, and bromide.[5b]

NEED FOR AND MECHANISMS OF IODINE TRANSFER FROM MOTHER TO CHILD

In female mammals, the breasts are a major storage site of iodine. The levels of iodine in the milk of a variety of animal species are ten- to thirty-fold higher than those present in the maternal plasma.[3] A mother delivers iodine to the developing egg in the ovary during the follicular phase of her cycle; she delivers iodine to the fetus via the placenta; she delivers iodocaseins during lactation to the suckling offspring.[3,4b,12] These iodine concentrating mechanisms can be considered, on teleological grounds, to have the function of ensuring an adequate supply for the developing fetus and newborn infant.[3,19] By implication, anything that interferes

with adequate uptake and retention of iodine has the potential to create a local deficiency of iodine and associated mastopathies for the mother. It also has the potential to affect transfer of this essential nutrient to the developing fetus and nursing baby.

It has been observed that the mammary gland has the ability to amplify iodine accumulation during lactation in direct competition with the thyroid.[12,17,20] "A large body of data has demonstrated that the mammary gland during pregnancy and lactation is highly effective in capturing iodide, even more efficiently than the thyroid gland."[12] In the case of the thyroid gland, a mechanism for this amplification of iodide/iodine uptake and accumulation has been identified. With induced hypothyroidism, an increase in the number and function of iodide pumps in the thyroid gland, but not in other tissues, has been demonstrated.[21] A preferential increase in iodide pump numbers and function[20] in the thyroid gland facilitates a greater uptake of iodide for increased thyroid hormone production at the expense of other organs and tissues, such as the nonlactating mammary gland, in situations of iodide/iodine insufficiency.

This review examines the potential ability of F to interfere with the critically balanced competition between the mammary gland and thyroid gland for the often scarce but essential nutrient iodine. The available research suggests that F may have a disruptive effect on iodine amplification mechanisms in times of increased need as during lactation. Such disruption may further amplify or reverse the balance of iodine uptake between thyroid and mammary glands, with potentially disastrous consequences for the thyroid gland or the mammary gland and the suckling infant.

PROPOSED PATHWAYS OF F INTERFERENCE

F has a well-demonstrated ability to disrupt the normal activity of many enzymes[22a] required for the metabolism of iodine and delivery of iodine to the breast. F may contribute to mastopathies through the following five pathways:

Pathway 1: F in combination with aluminum (AlF_x) mimics normal phosphates[23] that are an integral part of G-proteins, which regulate the thyroid stimulating hormone (TSH) and deiodinase activity.[1,23-26]

Pathway 2: F interferes with enzymes involved in iodide "pumps"[20] that transport iodide from the blood into the cell against a concentration gradient.[5,20,27,41]

Pathway 3: F interferes with cellular energy production needed for thyroid hormone transport into cells where deiodination occurs to release iodide ions.[22,30]

Pathway 4: F interferes with intracellular conversion of thyroxine (T4) to other thyroid hormones (e.g., triiodothyronine or T3) and subsequent release of free iodide ions by the disruption of deiodinase enzymes (D1, D2, and D3).[23,30]

Pathway 5: F interferes with antioxidant systems.[4,5,12,16,35-9]

PATHWAY 1: THYROID HORMONE PRODUCTION—F AS A TSH MIMIC

Thyroid hormone production is partially regulated by a negative feedback loop. The hypothalamus, a small area of the deep brain, releases thyrotropin releasing hormone (TRH) that acts as a signal to another part of the brain, the pituitary, which secretes the thyroid stimulating hormone (TSH) as well as the hormone prolactin. The blood levels of thyroid hormones are sensed by specialized cells in the pituitary, modifying TSH levels, thereby providing the negative feedback regulation required to either increase or decrease thyroid hormone output.

F in combination with aluminum (AlF_x) is hypothesized to be a TSH mimic, sending false signals to TSH receptive cells through activation of associated receptor-G-protein complex.[23] Over-activation of the TSH receptor by F may lead to desensitization of TSH receptors.[25] Any de-activation of TSH receptors could cause the thyroid gland to decrease thyroid hormone production. These effects can cause the thyroid hormone feedback loop to reach a new equilibrium, resulting in elevated TSH levels. F also interferes with pathways that are not directly a part of this TSH feedback loop, as discussed below.

PATHWAY 2: F INTERFERES WITH IODIDE PUMPS

Iodide uptake across cell membranes and accumulation in cells involves active transport systems present in approximately twenty-three distinct tissues (identified so far), including the thyroid and mammary glands.[2] Iodide uptake is facilitated by the combined actions of a sodium pump (Na,K-ATPase) and an iodide pump (sodium-iodide symporter or NaIS). The sodium pump creates a sodium concentration gradient by exporting sodium from the cell. The iodide pump utilizes the sodium gradient to import iodide into the cell where iodide can accumulate.[21] (See Figure.)

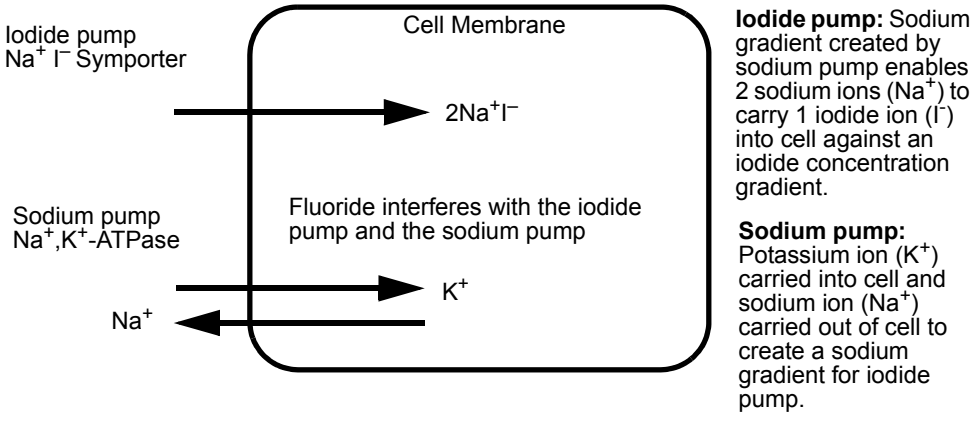

Figure. The iodide/sodium pump.

ATPase is an enzyme that F is known to inhibit.[31,32] F in combination with aluminum as AlF_x[23] also inhibits ATPase function. Blocking the transfer of iodide

via direct interference with these pumps by F would lead to localized iodine deficiency in the breast and to alteration of thyroid hormone production in the thyroid gland.[5,12]

It has been suggested, though not confirmed, that F interferes with iodide transport, causing damage to iodide pump binding sites.[5] It has also been suggested, but not confirmed, that F may displace iodide and accumulate in the thyroid gland.[1a,2]

Thyroid hormone levels, prolactin, iodine supplementation and TSH all influence the number of pumps.[5,16,33] TSH may also position these pumps in the cell membrane where they are functional; "In the absence of TSH, NaIS was redistributed from the plasma membrane to intracellular compartments, and thereby lost its ability to transport iodide across the plasma membrane."[20] F may disrupt pump generation and placement through its TSH mimicking effect described in pathway 1 above. Additionally, TSH levels may be further influenced by F distortion of the feedback loop of pituitary-TSH signaling also described above in pathway 1.

The multi-linked relationship between the TSH-thyroid hormone feedback control loop and cellular iodide transport provides a multiplicity of points for F interference. If F disrupts any one of these points while amplification of thyroid hormone production is in effect (due to iodide deficiency), then F effects are potentially enhanced due to the sensitivity of feedback loops to disruption of their feedback signals. This interpretation is consistent with the National Research Council 2006 review that discusses how the vulnerability to F increases as iodide deficiency increases.[1c] F may affect individual pathways or F may interfere with the amplification mechanism(s). The combined interactions permit an amplification of F effects, potentially destabilizing the negative feedback thyroid hormone regulation mechanism. This situation can be exacerbated by additional pathways of F interference described below.

PATHWAY 3: F INTERFERES WITH THYROID HORMONE TRANSPORT

As described in many papers,[22a] F interferes with enzymes involved with cellular energy production. According to Henneman,[29] an energy-dependent, active transport of thyroid hormones over the plasma membrane, into cells, occurs in studied situations. Any interruption of cellular energy production by F has the potential to interfere with this active transport of thyroid hormones and resultant iodide delivery into the mammary gland, thyroid, and other tissues requiring iodine.

Metabolism of fats, carbohydrates, and proteins is disturbed by F.[22c] F interferes with oxidative metabolism via the electron transport system, glycolysis, and the tricarboxylic acid cycle. This decreases the pool of intracellular adenosine triphosphate (ATP).[22c] F also binds to magnesium ions and ferric iron, leading to inhibition of magnesium-dependent and iron-dependent enzymes.[22c,22d] By interfering with a large number of enzyme systems involved in energy production,

F has the potential to interfere with active thyroid hormone transport across cell membranes.

PATHWAY 4: F INTERFERES WITH DEIODINASE ENZYMES

There is evidence F interferes with deiodinase enzymes that are required to metabolize organified iodides such as thyroxine (T4) into its various derivative forms.[1,34] Deiodinases are differentially expressed and regulated by the physiological need in an organ or tissue.[3,19,24]

The mammary gland expresses two different deiodinase enzymes (D1 and D2), which locally convert thyroxine (T4) into other biologically active thyroid hormones such as triiodothyronine (T3) and diiodothyronine (T2),[34] thereby releasing free iodine into cells.[12] The higher levels of iodine needed during puberty, pregnancy, and lactation[16] are mediated by D1, and lower but continuous amounts of iodine evident in virgin or non-lactating, postpartum conditions are catalyzed by D2.[12]

F has been shown to interfere with hormone signals that regulate deiodinase function (e.g., prolactin, thyroid—see pathway 2 above).[12,23,33] A recent paper discusses how G-protein coupled receptors regulate deiodinase function.[26] F-aluminum complexes are well known to influence G-proteins.[23] F has also been shown to influence the balance between reverse T3 (rT3) and T3[30] that can result in localized decreases in the production of T3 required for activation of genes in DNA.[34]

PATHWAY 5: FLUORIDE INTERFERES WITH ANTIOXIDANT SYSTEMS

A delicate balance exists between oxidants and antioxidants in biological systems. Tilting the balance in favour of oxidants results in oxidative stress on cells, tissues, and glands. Iodine and its carbon-bonded products (e.g., thyroid hormones and iodolactones) are important antioxidants.[35] F is capable of disrupting the antioxidant actions of iodine and other important antioxidants.[36] Any disruption of the iodine antioxidant system by F[36] may disturb both architecture and function of the mammary and thyroid glands.[35]

Living organisms must protect themselves against oxidants such as reactive oxygen species (ROS) produced during cellular respiration and other cellular activities. Protection against ROS is accomplished by the use of both enzymatic and non-enzymatic antioxidants. Examples of enzymatic antioxidants include superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). Non-enzymatic antioxidants include selenium, vitamins A, E, C, and iodine.[36]

Iodine, iodinated amino acids (e.g. thyroid hormones) and iodinated fats (iodolactones) have significant antioxidant capacity.[12,16,17,35,39] Iodine may exert an antioxidative effect by competing with the reaction of free radical ROS with membrane lipids, thus preventing lipoperoxidation.[4,12,16,35] Iodine may also prevent free radicals from interfering with DNA transcription.[35] Thyroid hormones may exert an antioxidative effect by also influencing lipoperoxidation and regulating mitochondrial oxidative metabolism.[5,16,33,35] Additionally,

iodolactones, iodine, and thyroid hormones may have an antioxidative effect as demonstrated by their ability to influence TSH.[4,35]

Without adequate iodine, increased levels of TSH create an imbalance between oxidants and antioxidants. TSH increases the production of hydrogen peroxide (H_2O_2), an important ROS in the body used in the oxidation of iodide.[35] Iodine and other antioxidants, like GPx, reduce H_2O_2 to a more benign form so that it does not cause cell damage.[35] F further disturbs this balance by decreasing the availability of GPx, as described in reports published in this journal.[22e,36] When an imbalance in the oxidant-antioxidant system occurs, the potential for tissue damage increases. Specifically, mastopathies of the breast are associated with disturbances of the antioxidant system.[4,35]

Iodine and F also influence this antioxidant system indirectly. As described in pathways 1 to 4 above, iodine deficiency, exacerbated or caused by F interference, may interfere with thyroid hormone production or metabolism. Abnormal thyroid function (hyperthyroid or hypothyroid) seems to play an important role in the regulation of oxidative stress.[40a] Restoration of euthyroid status restores the antioxidant capacity of organisms.[40b] In this way, the combined action of iodine deficiency and F interference with thyroid hormone transport and function may indirectly cause an imbalance in the antioxidant system.

Various studies on oxidative stress in cell systems *(in vitro),* fluorotic humans, and fluoride-intoxicated animals indicate that ROS and lipid peroxidation (MDA - malondealdehyde formation) can be directly induced by F in a time- and dose-dependent manner. Two reviews in this journal[36,37] discuss the concept of hormesis whereby different physiological effects may occur at low F concentration levels compared to high or very high F concentration levels.[38] For example, data are available supporting the view that F at relatively low concentrations stimulates lipid peroxidation, but at high concentrations F may act as an inhibitor of lipid peroxidation.[36] Studies by Shivarajashankara demonstrated the presence of elevated levels of the lipid peroxidation by-product MDA, along with decreased activities of the protective antioxidants GPx and SOD in fluorotic children.[39] Understanding the tissue specificity and dose and time specificity together with the myriad of co-factors involved in these complex biological feedback systems will enable clarification of these so-called paradoxical (or hormesis) effects.

Both direct and indirect influences of iodine deficiency and the presence of fluoride may lead to imbalances in the antioxidant system. Such oxidative stress may be involved in the alteration of both architecture and function of tissues and organs such as the mammary gland and the thyroid gland,[35] which may lead to carcinogenesis.[4,5,12,16,35-9]

CELLULAR CHANGES IN BREAST MASTOPATHIES INDUCED BY IODINE DEFICIENCY

The ability of F to interfere with mechanisms that facilitate the uptake and metabolism of iodine as described in this review, may induce tissue-specific iodine deficiency and disturb the oxidant systems critical to homeostasis. Such perturbations may lead to mastopathies of the breast and increase the need for

iodine. No survey data are available on the daily required dose of dietary iodine to withstand inhibition by F. Three human trials using iodine prophylaxis have shown that sustained iodine supplementation well in excess (3–6 mg/day) of the RDA (0.15 to 0.3 mg/day) was required to alleviate or eliminate fibrocystic breast disease and cyclical mastalgia.[6-8] The Appendix below describes several case studies of successful nutritional intervention (elimination of F and use of I_2/I^- and vitamin supplementation) to treat breast mastopathies.

Several important observations have been made about cellular changes in breast tumors. These pathologic tissues have: a) lower iodine concentrations in the cancer cells compared to normal tissue or suppressed cancer cells;[9,14c,19,28] b) fewer functional iodide "pumps" (NaIS, Pendrin);[41] c) a loss of deiodination ability.[12,16,35] Here various pathways have been reviewed by which F may contribute to all three of these pathologies. As one group has stated: "Chronic I_2 treatment is not accompanied by any harmful secondary effect on the health of the animals (body weight, thyroid economy, reproductive cycle). Thus, we propose that I_2 treatment must be considered a candidate to be used in clinical trials as an adjuvant of breast cancer therapy."[16] As emphasized here, elimination of F sources that potentially impair iodine and thyroid transport and utilization also appears to be an important component of such breast cancer therapy.

SUMMARY AND CONCLUSIONS

From over one hundred years of research,[9,13] iodine has been found to be essential for normal architecture and function of the breast. During the last fifty years, the ubiquitous and expanding presence of F in our expanding modern industrial economy makes it likely that, via several pathways, F impairs the uptake and metabolism of iodine required by the breast. This review has discussed how F may decrease deiodinase function and may interfere with iodide/sodium pumps that are required for tissue-specific delivery of iodine. Continuing research also demonstrates that F may interfere with the antioxidant systems implicated in carcinogenesis. F also suppresses prolactin and interferes with important regulatory feedback loops in thyroid hormone production. The U.S. National Research Council 2006 review, *Fluoride in Drinking Water*, drew attention to the high prevalence of thyroid dysfunction in our society today and how the ability of F to disturb thyroid function increases with iodine deficiency.[1]

In the case of the mammary gland, iodine concentrating mechanisms ensure an adequate supply of this essential nutrient for mother and her newborn child. For the lactating mother, the mammary gland competes efficiently with the maternal thyroid to concentrate iodide. For the nonlactating woman, the thyroid gland seems to compete efficiently with the mammary gland for iodide. The available evidence suggests that F may interfere with iodine uptake amplification mechanisms, resulting in commensurately amplified inhibition for iodine uptake. The implications of F interference are potentially disastrous for tissues like the mammary gland that critically rely on amplified iodine uptake during lactation.

The combination of iodine/iodide deficiency and ubiquitous and uncontrolled doses of F potentially affects the health and function of iodine sensitive tissues such as the mammary glands and thyroid gland. A better understanding the pathways by which F interferes with iodine and thyroid uptake and metabolism may significantly help avoid breast mastopathies such as fibrocystic breast disease and breast cancer. It may also enable understanding the potential of F to affect the transfer of the essential nutrient iodine to the developing fetus during critical windows of fetal development and later to the suckling child.

Based on our current knowledge about the interaction of iodine metabolism and breast health, this review hypothesizes that F has the potential to interfere with iodide transport and function. Clearly more research is needed to resolve the many issues raised here. The potential treatment effects of both increased iodide and decreased F, singly and in combination, on the thyroid, breast and other iodide concentrating tissues need to be addressed and assessed. Although the available evidence suggests that F interferes with deiodinase function, the cellular mechanisms still require elucidation.

Does F interfere via G-protein cascades that are known to influence deiodination?

Does F interfere directly with these deiodinating enzymes or are there other cellular mechanisms involved?

A biologically-based dose-response model is being developed for dietary iodide and the hypothalamic-pituitary-thyroid axis to evaluate and predict dose-dependent alterations of the axis and ultimately to interpret dose-response characteristics of this axis to thyroid toxicants.[42] Such "*in silico*" analyses for fluoride would also be useful.

Finally, how sensitive is the thyroid amplification control system during iodine/iodide deficiency to disruption from any one of these pathways by F?

APPENDIX: CASE STUDIES

Case Study 1:[43a] Female, age 45, suffered from fibrocystic breast disease for over 15 years. She was contemplating mastectomy due to unbearable pain. Dr David Brownstein determined that she was severely iodine deficient. The iodine challenge test showed 27% excretion compared to normal levels defined as 90% or more. She was advised to eliminate fluoride sources as much as possible. After one month of treatment with an iodine/iodide combination she reported a dramatic improvement in her condition; cysts disappeared, pain disappeared, and the breast tissue became soft.

Case Study 2:[43a] Female, age 39, suffered from fibrocystic breast disease for over 5 years. Symptoms worsened around her menses. Dr. Brownstein determined that she was iodine deficient (iodine test showed a 50% excretion). After 2 weeks of supplementing with an iodine/iodide combination, her breast condition rapidly improved. She also reported improved energy and mood. This patient was also advised to eliminate fluoride sources as much as possible.

Case Study 3: Clinical work by the doctors in the Iodide Project consistently demonstrates that inorganic iodide/iodine supplementation causes excretion of the halides fluoride and bromide. Average measurement of urinary excretion of fluoride in 8 patients had a baseline rate of 1.07 mg F/24 hr.[43b] Fluoride excretion rate increased to 1.95 mg F/24 hr after 30 days of iodine supplementation.[43b] Prior to iodine supplementation, urine fluoride levels measured by chromatography in 24 normal subjects had a mean ±SD of 0.95±0.072 mg/24 hr.[44] Fluoride excretion rate increased to a mean ±SD of 1.8±0.13/24 hr after iodine supplementation.[44] These examples seem to demonstrate how the body adapts to the iodine supplementation by eliminating fluoride and increasing uptake of the essential nutrient iodine.

Case Study 4:[28] To assess sodium iodide symporter (NaIS) function in a minimally invasive manner, the ratio of saliva iodide/serum iodide is employed. A ratio near unity indicates a severe defect/damage of the symporter function while an increase in the ratio following nutritional intervention would reflect an improvement in the symporter function. After treatment, a female patient with breast cancer demonstrated a 3-fold increase in the saliva/serum iodide ratio (from 22 to 61).

Note: Inorganic iodide/iodine was used in the above case studies, not the organic iodide drug called amiodarone. The authors who are cited manufacture and sell iodine/iodide products and therefore can be seen as having a potential conflict of interest.

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