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Iodine and Cancer [4]

A summary of the evidence to date

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Abstract

Iodine is an essential element in human physiology. Its role in thyroid function is well known and heavily weighted in the literature. Its putative role as an anticarcinogenic agent is just beginning to be widely appreciated. The molecular effects of iodine as well as ongoing epidemiological evidence points to its probable role in prevention of cancers through its antioxidant, antiinflammatory, prodifferentiating, and proapoptotic effects. This is particularly evident with stomach and breast cancers but may be relevant for many other cancers that have yet to be substantially studied.

Introduction

The first report of geographical regions with high rates of goiter having higher rates of cancer mortality was published in 1924.[1,2] Ongoing epidemiological data has corroborated the association between goitrogenous regions and cancer incidence/mortality, particularly that of stomach cancer.[3,4] Epidemiological evidence also suggests that thyroid disorders, particularly goiter, may be associated with breast cancer incidence and/or mortality.[5–8] Other cancers associated with goitrogenic state include prostate cancer, endometrial, ovarian, colorectal, and thyroid cancer. It is not clear whether these associations are due to an underlying hypothyroid state, the presence of occult autoimmune processes, or iodine deficiency itself.[9] Ultimately, the etiology of all cancers is multifactorial, with benefit assumed in the reduction of modifiable risk factors. There is substantial evidence that iodine deficiency is a modifiable risk factor in cancers of the stomach and breast and possibly many other organs. This review will outline evidence on iodine as an independent influence in cancer development and/or progression.

Total iodine content of the body is estimated at 25 mg to 50 mg, with 50%–70% of that found in extrathyroidal tissues.[10] Systemic absorption of iodine takes place in the small intestine, where it is absorbed and transported into the bloodstream primarily as iodide (I-). Ultimately, excretion is via the kidneys with a minor amounts excreted in feces.

To enter cells, iodide (I-) must be cotransported with 2 molecules of sodium to overcome the electrochemical gradient. This sodium/iodide symporter (NIS) is well characterized on the basement membrane of thyroid follicular cells, where it allows for requisite iodide uptake. The means of iodide transport into enterocytes has only recently been attributed to the same symporter, NIS, that is expressed in the thyroid.[11] NIS found in enterocytes is controlled via a negative feedback system, such that high iodine intake reduces NIS production.[12]

Several extrathyroidal tissues also concentrate iodine via NIS found on their basement membranes. Most notably, the stomach mucosa, salivary glands, and the lactating mammary gland all have NIS that is identical to that found in the thyroid. Other tissues with high concentrations of iodine include the choroid plexus, ciliary body of the eye, lacrimal gland, thymus, skin, placenta, ovary, uterus, prostate, and pancreas.[13] The role of concentrating iodine in lactating mammary tissue is clearly to provide necessary iodine to the developing child. The role of iodine in most other tissues is believed to include antioxidant, antiinflammatory, antiproliferative, antibacterial, proapoptotic, and prodifferentiating effects.[14]

> Ultimately, the etiology of all cancers is multifactorial with benefit assumed in the reduction of modifiable risk factors. There is substantial evidence that iodine deficiency is a modifiable risk factor in cancers of the stomach and breast.

It is estimated that the gastrosalivary pool of iodine accounts for 23% of all iodine in the body.[15] As mentioned, iodide is taken up from the bloodstream primarily via NIS found on enterocytes. Once plasma iodide reaches the mouth and stomach, it is taken up via NIS found on the basement membrane and is secreted out the apical surface to form a concentrated amount in and on the mucosa. This sets up the gastrointestinal recirculation of iodide (I-) that acts to conserve the overall iodine pool of the body.[16] Local effects appear to contribute to the proper health and integrity of the mouth and stomach.[17]

While NIS allows for a high concentration of intracellular iodine in specific tissues mentioned above, iodine is believed to be in every tissue of the body.[18] As early as 1961, the ubiquitous distribution of radiolabelled iodide was noted on full body imaging.[19] Emerging research is showing that other receptors (such as pendrin and apical NIS) may be important in the uptake of iodine into various tissues.[20] In addition, iodine is liberated intracellularly when thyroxine (T4) is converted to triiodothyronine (T3), a process requiring the selenium dependent enzyme deiodinase.

Iodine has been proposed as a primitive antioxidant, with algae having an effective and perhaps necessary evolutionary role in squelching free radicals from the atmosphere.[21] In humans, iodide has been shown to favorably affect serum antioxidant status.[22] Iodide may be acting directly as an electron donor, squelching free radicals such as hydroxyl radicals. It may also be acting indirectly through iodination of amino acids (ie, tyrosine and histidine) or fatty acids (arachadonic acid), rendering them less likely to be oxidized themselves.[23] In an experiment to determine antioxidant capacity (ferrous reducing/antioxidant power assay, FRAP), molecular iodine (I2) was 10 times more potent than ascorbic acid and 50 times more potent than potassium iodide (KI).[24] It also appears to act with thiol redox systems, such as glutathione and thioredoxin, to maintain an optimal redox balance in cells.

Iodine also has well known antiinflammatory effects.[25] For example, povidone-iodine has been shown to have antiinflammatory effects on wounds.[26] Antiinflammatory effects from iodine may be derived from actions on nitric oxide or cyclooxygenase-2.[27] This antiinflammatory effect has been credited with lessening the risk of peritoneal spread of cancerous cells during abdominal surgeries.[28,29]

In concert with its antioxidant and antiinflammatory actions, iodine affects several molecular pathways that are part of differentiation and apoptosis in cells. As mentioned above, molecular species generated intracellularly through iodination of fatty acids may be significant contributors of iodine's molecular effects. One such product is 6-iodolactone (6-IL), formed from iodine (I2) covalently bonds with arachadonic acid.[30] 6-IL, as well as molecular iodine (I2), significantly influence the expression of peroxisome proliferator-activated receptor type gamma (PPAR-

gamma).[31] PPAR-gamma is implicated in cancerous growth and development through its influences on proliferation, differentiation, apoptosis, and metabolic processes.[32] One preliminary clinical study of 22 women with breast cancer given 5 mg/day of molecular iodine (I2) found that PPAR expression was increased, along with the expected favorable effects on the cancerous tissue including increased apoptosis, decreased proliferation, and a decrease in estrogen's cellular effects.[33]

In the medical literature, the generalization of the term iodine can create confusion. The term *iodine* represents essentially any form of the molecule, including molecular iodine (I2), iodide salts (NaI or KI), iodate (NaIO), and/or lipids or proteins containing iodine (iodo) moieties such as iodotyrosine or iodolactones. The most well studied form is iodide salts, such as sodium iodide (NaI) and potassium iodide (KI), which are frequently used in supplementation of iodine to entire populations. Throughout this review the term *iodine* will be used as a general term, and specific forms given as a parenthetical descriptor whenever possible [eg, iodide (I-)].

Review of the Evidence

Breast cancer

Iodine's role in maintaining the health of breast tissue is suggested by its therapeutic effects on benign breast conditions. In a publication reviewing three clinical trials of varied designs, molecular iodine (I2) reduced fibrocystic signs/symptoms while iodide (I-) was less effective and affected thyroidal function more readily.[34] In one of the trials included in that review, the dose of molecular iodine was 0.07 mg to 0.09 mg/kg body weight per day. Converting this to something more clinically useful, this is approximately 3.2 mg to 4.0 mg/100 lb body weight per day of molecular iodine (I2).

In another study of 111 women with cyclic mastalgia, women took either 6 mg/day, 3 mg/day, or 1.5 mg/day of a combination iodide/iodate (I-/IO3-), or a placebo.[35] Sodium iodate (NaIO3) was used with the prediction of dissolution in the stomach to molecular iodine (I2). In that study, more than 50% of the women taking 6 mg/day had a reduction in mastalgia symptoms at 6 months.

In keeping with iodine's effects in benign breast conditions, *in vitro* and *in vivo* studies suggest that the therapeutic form of iodine in breast cancer is molecular iodine (I2). While NIS has been considered a necessary means for iodide uptake, human breast cancer cells (MCF-7) have been found to use facilitated diffusion of I2 as well.[36] This may explain why levels of iodine are higher in cancerous breast tissue than surrounding normal tissue.[37] As mentioned, I2 is capable of inducing apoptosis in human breast cancer cells through mitochondrial mediated pathways. In a rodent model of mammary carcinogenesis molecular iodine—but not iodide—was able to prevent promotion of disease.[38]

There are several lines of evidence to support the role of molecular iodine (I2) as preventive of carcinogenic processes. In a chemical carcinogenesis model of mammary tumors, using Sprague-Dawley rats given methyl-nitrosurea, iodine (I2) was given as a 0.05% of water source and the rats were allowed unrestricted access. The incidence of mammary tumors was 37.5% lower in the treated rats vs controls. Further, there was an increase in proapoptotic caspase 2 and PPAR gamma expression. They also demonstrated that the vasculature of tumors in the rats given iodine (I2) as well as vascular endothelial growth factor expression was significantly less in the tumors developed by those consuming iodine. In rats that developed tumors, there was no difference in tumor number or volume.[39]

Iodine may also be affecting the binding of estrogen receptors to the steroid-binding element. Using breast cancer cells (MCF-7 cells), Stoddard and colleagues demonstrated that Lugol's solution (5%

iodine/10% iodide) affected 43 genes involved cell cycle growth, proliferation, and differentiation.[40] Many of the 43 genes are those upregulated by estrogens, implying that the Lugol's solution interfered with this action and had a net "antiestrogenic" effect on gene expression. This is in keeping with a rodent study using DMBA-induced mammary cancers that found a supplement of 0.1% of a combination I2/KI (0.05%/0.05%) lessened estrogen induced DNA adduct formation and increasing PPAR-gamma expression.[41]

Gastric cancer

The link between gastric cancers and areas of endemic goiter dates back to 1924,[42] and ongoing data continue to corroborate this association. In a case control study of people with gastric cancer, the prevalence of goiter was more than twice that of matched controls (49.1% vs 20%).[43] In another case control study in Iran, urinary iodine excretion was assessed in 100 patients with gastric cancer. They found that "mean urinary iodine levels were lower in the patients with stomach cancer, 61.9 µg/g creatinine, compared to 101.7 µg/g creatinine in the control group (P<0.0001). More of the cancer patients (49.0%) had severe iodine deficiency (< 25 µg/g creatinine) than people in the control group (19.1%) (P<0.0001)."[44] In a Turkish study using direct tissue measurements, "iodine levels were lower in gastric cancer tissue (17.8±3.4 ng I/mg protein) compared with surrounding normal tissue (41.7±8.0 ng I/mg protein) (P<.001)."[45] In other studies, gastric cancers as well as later stages of Barrett's esophagus were shown to have limited or absent NIS.[46,47] Lastly, the addition of iodine-containing salt in Poland in the 1990s to 2000s has been postulated to be responsible for the decreased incidence of stomach cancer there.[48]

Its actions as an antioxidant, antiinflammatory, and prodifferentiation agent are thought to be essential to the health of cells lining the stomach.[49,50] Systemically, iodine is recognized as an integral nutrient for proper immune function by the Institute of Medicine and as well as the United Nations Nutritional Policy Board.[51,52] Correlations between immune deficiency, goiter, and gastric cancer have been documented in regions of Italy.[53] Another hypothesis of how iodine deficiency may contribute to gastric cancer comes from its local effects. In one experiment, iodine was able to inhibit carcinogenic processes involving *Helicobacter pylori*.[54]

Prostate cancer

Countries such as Japan, with high iodine intake, have much lower rates of prostate cancer compared to the United States. (22.7/10,000 vs 83.8/100,000 per year, respectively).[55] While there may be other dietary and genetic influences involved, the Japanese diet is remarkably high in iodine content, with estimated intake 25 times that of the US (5,280 µg/d vs 209 µg/d).[56,57] While intakes in the United States are relatively low, US men with the highest intake may derive some benefit, as suggested in the First National Health and Nutrition Examination Survey (NHANES I). In NHANES I, stratification of iodine excretion into tertiles showed that there was a 29% lower risk of prostate cancer in those with the highest levels vs those with the lowest [HR: 0.71 (0.51–0.9)].[58]

There is ample evidence that iodine is taken up readily by the prostate and affects overall health of the organ. In animals 0.05% molecular iodine (I2) supplementation lessened symptoms of benign prostatic hyperplasia.[59] In men with BPH, 5 mg daily of Lugol's solution improved urine flow and reduced PSA values over an 8 month period.[60] In one study, NIS was found in 52% of prostate adenocarcinomas and was associated with greater aggressiveness of tumors (stage > or = or =pT2a, or Gleason > or = 8).[61] In another study, normal and prostate cancer cell lines were exposed to iodide, molecular iodine, and 6 iodolactone (6-IL). Unlike the normal cells, which

depended on NIS for uptake, both cancer cell lines took up I- independent of NIS. Further, one prostate cancer cell line (LNCaP) was most susceptible to molecular iodine (I2). An extension of this same study showed that iodine inhibited the growth of xenografts of prostate cancer (DU 145) in nude mice.[62] While NIS is found in some prostate cancers, independent uptake of molecular iodine (I2) is likely present through a facilitated diffusion process as well.[63]

Other cancers

Molecular iodine (I2) and 6-iodolactone (6-IL) were systematically tested on many different human cell lines, including neuroblastoma, 4 mammary cancer lines, normal mammary cells, lung, 2 glioblastoma cell lines, melanoma, 2 pancreatic cell lines, and colon carcinoma cells.[64] After a 2-day culture with molecular iodine (I2), all cell lines were inhibited except for colon cancer. Neuroblastoma cells underwent the most complete inhibition, with MCF-7 breast cancer cells the second most sensitive. They found similar inhibitory effects were found with 6-IL. It appeared the mechanism of action included the inhibition of endothelial growth factor in this experiment. However prior experimentation by the same group found that the inhibition is most likely due to changes in the mitochondrial membrane potential, resulting in apoptosis. An effect that was completed thwarted with the addition of N-acetyl-cysteine.[65]

How and whether 6-IL affects colon cancer cells is still not known. In a separate experiment, 6-IL was able to inhibit growth and induce apoptosis in colon cancer cell line (HT-29).[66] Going forward, research should clarify which cancers are most affected by I2 and/or 6-IL.

Discussion

Historically, iodine's essential role in thyroid hormone formation and function has overshadowed its independent physiological effects. However, it is clear that iodine acts intracellularly as an antioxidant, prodifferentiating, antiinflammatory, and proapoptotic agent that is necessary for proper health and cellular renewal.

Intracellular iodinases, more specifically called iodothyronine selenodeiodinases, are essential contributors to the pool of free iodine within cells.[67] All deiodinases liberate 1 iodine (I-) from T4. Type 2 deiodinase (DOI2) is found throughout various tissues and converts T4 into T3, resulting in the requisite loss of iodine (I-) into the cytoplasm. Type 3 deiodinase (DOI3), also found throughout various tissues, deiodinates T4 but results in inactive metabolites reverse T3 (rT4) or 3,3′-diiodothyronine (T2). Type 1 deiodinase (DOI1) is only found in thyroid, liver, and kidney organs and can either result in active or inactive metabolites.[68] Within each cell, the deiodinases act in concert to maintain a specific level of active T3 that is independent of circulating levels of thyroid hormone. For example, in a hypothyroid state, DOI2 will be upregulated to increase the intracellular production of T3 as compensation.

Normally, the various deiodinases are balanced to provide the intracellular environment with the proper amounts of T3 and/or iodine.[69] However, they can also be manipulated within cancerous cells by the oncogenic processes. For example DOI3 is essential for the proliferation and survival of basal cell carcinoma.[70] While speculative, it is possible that reverse T3 production serves as a means of allowing a cell to increase its intracellular pool of iodine without increasing its pool of active T3.

The established consequences of iodine deficiency in population-based studies and the implications of iodine deficiency in the etiology of cancer certainly justify repletion of iodine in all populations through diet and/or supplementation. According to the National Institutes of Health (NIH), adults should consume a minimum of 150 mcg/day of iodine, pregnant women 220 mcg/day, and

breastfeeding women 290 mcg/day.[71] The safe upper limit of consumption according to the NIH is 1,100 mcg/day for adults, with lesser amounts for teens and children. However, the NIH concedes that higher doses may be necessary for some, explaining "These [upper safe limit] levels do not apply to people who are taking iodine for medical reasons under the care of a doctor."

When assessing the physiological effects of ingested iodo-compounds, the form that is consumed is highly relevant. Most pertinent to the nutritional supplementation of iodine compounds is the finding that iodide salts (ie, KI, NaI) affect the thyroid while molecular iodine (I2) has less influence. This is the Wolff-Checkoff effect, which is essentially the shutdown of thyroid hormone synthesis in the presence of large amounts of ioidide (I-). This effect is due to impaired transport of the iodide (I-) molecule, which is the only means for the thyroid to obtain the necessary iodine for thyroid hormone synthesis. While this effect is generally thought to be transient until the thyroid gland reequilibrates to the available iodide, there are also published studies showing a permanent impairment of thyroid function.[72–75] Those most likely to have adverse effects were more likely to be elderly, have severe iodine deficiency, and/or have a larger increase in iodine consumption.

While the NIH recommends 1,100 mcg/day as the safe upper limit, doses up to 4.0 mg/100 lb body weight of I2 appears to be both safe and therapeutic for benign breast diseases. The most effective anticarcinogenic form of iodine appears to be molecular iodine and intracellular 6-iodolactone. Doses exceeding 4.0 mg/100 lb of body weight have not been clinically documented as safe. In fact, there is documentation that doses 9 mg and higher may induce transient hypothyroidism as well as minor side effects such as respiratory tract infection, headache, sinusitis, nausea, acne, diarrhea, rash, or abdominal pain.[76] These side effects abated with the discontinuance of iodine, but it is important to realize that high-dose iodine is not without risk of side effects.

Many of the iodine supplements on the market provide iodide (I-), usually potassium iodide, either alone or in combination with molecular iodine (I2). While this is safe for physiological repletion of iodine (doses less than 1,100 mcg/day), the salts carry greater risk of interfering with thyroid function at higher doses. The ideal supplement would contain molecular iodine with very little iodide. The difficulty is that iodine (I2) is rendered much more soluble with iodide (I-) and water (ie, Lugol's solution). Given that whole food sources are generally safe, perhaps the best means of iodine repletion for prevention of thyroid disorders as well as reduction in cancer risk is though moderate consumption of whole foods such as seaweed and fish.[77–79] This brings with it one difficulty—dosing. Seafoods vary dramatically in their iodo-compound type and concentration. Seaweed alone varies from 16 mcg to 2,984 mcg iodine/g depending on the type of seaweed and where it is sourced.[80]

One last cautionary note, even with molecular iodine (I2), is that patients with antithyroid antibodies can have an exacerbation of symptoms with use.[81,82] All patients should undergo testing for autoantibodies before beginning any supplementation of iodine. In the benign breast disease studies referred to above, there were no such adverse reactions because women with autoimmune disease were excluded from the study designs.

Conclusion

Human data, including epidemiological and histological evidence along with animal and *in vitro* models, all corroborate the hypothesis that iodine compounds are essential in the health and proper differentiation of tissues. Iodine deficiency may be a hidden risk factor for cancer development and/or progression. The evidence is strongest for stomach cancer, but emerging data indicate that it may also be a risk factor in breast, prostate, and perhaps many other cancer types. There is little risk to adding whole sea vegetables to the diet. For those patients wanting to use high dose iodine

therapeutically, it is best done under the guidance of a practitioner who can monitor for any untoward effects.

About the Author

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References

1. Stocks P. Cancer and goitre. *Biometrika.* 1924;16:364-401.

2. McClendon J. The statistical relation between goiter and cancer. *Am J Cancer.* 1939;35:554-8.

3. Venturi S, Venturi A, Cimini D, Arduini C, Venturi M, Guidi A. A new hypothesis: iodine and gastric cancer. *Eur J Cancer Prev.* 1993;2(1):17-23.

4. Abnet CC, Fan JH, Kamangar F, et al. Self-reported goiter is associated with a significantly increased risk of gastric noncardia adenocarcinoma in a large population-based Chinese cohort. *Int J Cancer.* 2006;119(6):1508-10.

5. Eskin BA. Iodine metabolism and breast cancer. *Trans N Y Acad Sci.* 1970;32(8):911-47.

6. Kalache A, Vessey MP, McPherson K. Thyroid disease and breast cancer: findings in a large case-control study. *Br J Surg.* 1982;69:434-5.

7. Smyth PP, Smith DF, McDermott EW, Murray MJ, Geraghty JG, O'Higgins NJ. A direct relationship between thyroid enlargement and breast cancer. *J Clin Endocrinol Metab.* 1996;81:937-41.

8. Vassilopoulou-Sellin R, Palmer L, Taylor S, Cooksley CS. Incidence of breast carcinoma in women with thyroid carcinoma. *Cancer.* 1999;85:696-705.

9. Smyth P. The thyroid, iodine and breast cancer. *Breast Cancer Res.* 2003;5(5):235-8.

10. Venturi S, Venturi M. Iodine in evolution of salivary glands and in oral health. *Nutr Health.* 2009;20(2):119-34.

11. Nicola JP, Basquin C, Portulano C, Reyna-Neyra A, Paroder M, Carrasco N. The Na+/I symporter mediates active iodide uptake in the intestine. *Am J Physiol Cell Physiol.* 2009;296(4):C654-62.

12. Nicola JP, Reyna-Neyra A, Carrasco N, Masini-Repiso AM. Dietary iodide controls its own absorption through post-transcriptional regulation of the intestinal Na+/I symporter. *J Physiol.* 2012;590(Pt 23):6013-26.

13. Riesco-Eizaguirre G, Santisteban P. A perspective view of sodium iodide symporter research and its clinical implications. *Eur J Endocrinol.* 2006;155:495-512.

14. Aceves C, Anguiano B, Delgado G. The extrathyronine actions of iodine as antioxidant, apoptotic, and differentiation factor in various tissues. *Thyroid.* 2013;23:938-46.

15. Hays MT, Solomon DH. Influence of the gastrointestinal iodide cycle on the early distribution of radioactive iodide in man. *J Clin Invest.* 1965;44:117.

16. Venturi S, Venturi M. Iodide, thyroid and stomach carcinogenesis: evolutionary story of a primitive antioxidant? *Eur J Endocrinol.* 1999;140:371-2.

17. Venturi S, Venturi M. Iodine in evolution of salivary glands and in oral health. *Nutr Health* 2009;20(2):119-34..

18. Venturi S, Donati FM, Venturi A, Venturi M, Grossi L, Guidi A. Role of iodine in evolution and carcinogenesis of thyroid, breast and stomach. *Adv Clin Pathol.* 2000;4(1):11-7.

19. Brown-Grant K. Extrathyroidal iodide concentrating mechanisms. *Physiol Rev.* 1961;41:189-213.

20. Elio Torremante P, Rosner H. Antiproliferative effects of molecular iodine in cancers. *Curr Chem Biol.* 2011;5:168-76.

21. Venturi S, Venturi M. Iodide, thyroid and stomach carcinogenesis: evolutionary story of a primitive antioxidant? *Eur J Endocrinol.* 1999;140(4):371-2.

22. Winkler R, Griebenow S, Wonisch W. Effect of iodide on total antioxidant status of human serum. *Cell Biochem Funct.* 2000;18:143-6.

23. Smyth PP. Role of iodine in antioxidant defence in thyroid and breast disease. *Biofactors.* 2003;19:121-30.

24. Aceves C, Anguiano B, Delgado G. The extrathyronine actions of iodine as antioxidant, apoptotic, and differentiation factor in various tissues. *Thyroid.* 2013;23:938-46.

25. Beukelman C, van den Berg AJ, Hoekstra MJ, Uhl R, Reimer K, Mueller S. Anti-inflammatory properties of a liposomal hydrogel with povidone-iodine (Repithel) for wound healing in vitro. *Burns.* 2008;34:845-55.

26. Moore K, Thomas A, Harding K. Iodine released from the wound dressing Iodosorb modulates the secretion of cytokines by human macrophages responding to bacterial lipopolysaccharide. *Int J Biochem Cell Biol.* 1997;29:163-71.

27. Nyska, A., Lomnitski L, Maronpot R, et al. Effects of iodine on inducible nitric oxide synthase and cyclooxygenase-2 expression in sulfur mustard-induced skin injury in guinea pigs. *Arch*

Toxicol. 2001;74(12):768-74.

28. Wu JS, Pfister SM, Ruiz MB, Connett JM, Fleshman JW. Local treatment of abdominal wound reduces tumor implantation. *J Surg Oncol.* 1998;69:9-14.

29. Neuhaus SJ, Watson DI, Ellis T, Rofe AM, Jamieson GG. Influence of cytotoxic agents on intraperitoneal tumor implantation after laparoscopy. *Dis Colon Rectum.* 1999;42:10-5.

30. Arroyo-Helguera O, Rojas E, Delgado G, Aceves C. Signaling pathways involved in the antiproliferative effect of molecular iodine in normal and tumoral breast cells: evidence that 6-iodolactone mediates apoptotic effects. *Endocr Relat Cancer*. 2008;15(4):1003-11. .

31. Nuñez-Anita RE, Arroyo-Helguera O, Cajero-Juárez M, López-Bojorquez L, Aceves C. A complex between 6-iodolactone and the peroxisome proliferator-activated receptor type gamma may mediate the antineoplasic effect of iodine in mammary cancer. *Prostaglandins Other Lipid Mediat.* 2009;89(1-2):34-42.

32. Nunez-Anita RE, Cajero-Juarez M, Aceves C. Peroxisome proliferator-activated receptors: role of isoform gamma in the antineoplastic effect of iodine in mammary cancer. *Curr Cancer Drug Targets.* 2011;11(7):775-86..

33. Vega-Riveroll L, et al. Impaired nuclear translocation of estrogen receptor alfa could be associated with the antineoplastic effect of iodine in premenopausal breast cancer. Paper presented at: 33rd Annual San Antonio Breast Cancer Symposium. December 8-12, 2010; San Antonio, Texas. Abstract 14.

34. Patrick L. Iodine: deficiency and therapeutic considerations. *Alt Med Rev.* 2008;13:116-27.

35. Kessler JH. The effect of supraphysiologic levels of iodine on patients with cyclic mastalgia. *Breast J.* 2004*;*10:328-36.

36. Arroyo-Helguera O, Anguiano B, Delgado G, Aceves C. Uptake and antiproliferative effect of molecular iodine in the MCF-7 breast cancer cell line. *Endocr Relat Cancer.* 2006;13(4):1147-58.

37. Eskin BA, Parker JA, Bassett JG, George DL. Human breast uptake of radioactive iodine. *Obstet Gynecol.* 1974;44(3):398-402.

38. Garcia-Solis P, Alfaro Y, Anguiano B, et al. Inhibition of N-methyl-N-nitrosourea-induced mammary carcinogenesis by molecular iodine (I2) but not by iodide (I-) treatment: Evidence that I2 prevents cancer promotion. *Mol Cell Endocrinol.* 2005;236(1-2):49-57.

39. Kato N. Suppressive effect of iodine preparations on proliferation of DMBA-induced breast cancer in rat. *J Japan Soc Cancer Ther.* 1994;29:582.

40. Stoddard FR 2nd, Brooks AD, Eskin BA, Johannes GJ. Iodine alters gene expression in the MCF7 breast cancer cell line: evidence for an anti-estrogen effect of iodine. *Int J Med Sci.* 2008;5(4):189-96.

41. Soriano O, Delgado G, Anguiano B, et al. Antineoplastic effect of iodine and iodide in dimethylbenz [a] anthracene-induced mammary tumors: association between lactoperoxidase and estrogen-adduct production. *Endocr Relat Cancer.* 2011 Jul 25;18(4):529-39.

42. Stocks P. Cancer and goitre. *Biometrika.* 1924*;*16:364-401.

43. Kandemir E, Yonem A, Narin Y. Gastric carcinoma and thyroid status. *J Int Med Res.* 2005;33:222-7.

44. Behrouzian R, Aghdami N. Urinary iodine/creatinine ratio in patients with stomach cancer in Urmia, Islamic Republic of Iran. *East Mediterr Health J.* 2004;10:921-4.

45. Gulaboglu M, Yildiz L, Celebi F, Gul M, Peker K. Comparison of iodine contents in gastric cancer and surrounding normal tissues. *Clin Chem Lab Med.* 2005;43:581-4.

46. Altorjay A, Dohán O, Szilágyi A, Paroder M, Wapnir IL, Carrasco N. Expression of the Na+/I- symporter (NIS) is markedly decreased or absent in gastric cancer and intestinal metaplastic mucosa of Barrett esophagus. *BMC Cancer.* 2007;7:5.

47. Farnedi A, Eusebi LH, Poli F, Foschini MP. Immunohistochemical expression of the human sodium/iodide symporter distinguishes malignant from benign gastric lesions. *Int J Surg Pathol*. 2009;17:327-34.

48. Golkowski F, Szybiński Z, Rachtan J, et al. Iodine prophylaxis—the protective factor against stomach cancer in iodine deficient areas. *Eur J Nutr.* 2007*;*46(5):251-6.

49. Venturi S, Grossi L, Marra G, Venturi A, Venturi M. Iodine, *Helicobacter pylori*, stomach cancer and evolution. *Eur EPI-Marker.* 2003;7:1-7.

50. Valverde RC, Orozco A, Carlos Solis SJ, Robles-Osorio L. Iodothyronine deiodinases: emerging clinical crossroads. In: Ulloa-Aguirre A, Conn PM, eds. *Cellular Endocrinology in Health and Disease*. Boston: Academic Press; 2014:365-77.

51. Panel on Micronutrients, Food and Nutrition Board, Institute of Medicine. *2001 Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc.* Washington, DC; National Academy Press; 2001.

52. Lotfi M, Mason JB. The prevention and control of iodine deficiency disorders: nutrition policy discussion paper No. 3. Geneva: United Nations; 1988.

53. Marani L, Venturi S. Iodine and delayed immunity. *Minerva Med.*1986;77(19):805-9.

54. Ma F, Zhao W, Kudo M, Aoki K, Misumi J. Inhibition of vacuolation toxin activity of *Helicobacter pylori* by iodine, nitrite and potentiation by sodium chloride, sterigmatocystin and fluoride. *Toxicol In Vitro.* 2002;16(5):531.

55. Ferlay J, et al. Cancer incidence and mortality worldwide. IARC Cancer-Base no. 10. Lyon, France: International Agency for Research on Cancer; 2010. http://globocan.iarc.fr. Accessed April 7, 2014.

56. Sonoda T, Nagata Y, Mori M, et al. A case-control study of diet and prostate cancer in Japan: possible protective effect of traditional Japanese diet. *Cancer Sci. 2004;*95:238-42.

57. Key TJ, Silcocks PB, Davey GK, Appleby PN, Bishop DT. A case-control study of diet and prostate cancer. *Br J Cancer.* 1997;76(5):678-87.

58. Hoption Cann SA, Qiu Z, van Netten C. A prospective study of iodine status, thyroid function, and prostate cancer risk: follow-up of the First National Health and Nutrition Examination Survey. *Nutr Cancer.* 2007;58:28-34.

59. Aceves C, Anguiano B. Is iodine an antioxidant and antiproliferative agent for the mammary and prostate glands? In: Preedy VR, Burrow GN, Watson RR, eds. *Comprehensive Handbook of Iodine: Nutritional, Endocrine and Pathological Aspects.* Academic Press, San Diego: Academic Press; 2009: 249-58.

60. Anguiano B, et al. Therapeutic effect of iodine on human benign prostatic hyperplasia. Paper presented at: 14th International Thyroid Congress. September 11-16, 2010. Paris, France. Abstract ITC2010-2585.

61. Navarra M, Micali S, Lepore SM, et al. Expression of the sodium/iodide symporter in human prostate adenocarcinoma. *Urology.* 2010;75:773-8.

62. Aranda N, Sosa S, Delgado G, Aceves C, Anguiano B. Uptake and antitumoral effects of iodine and 6-iodolactone in differentiated and undifferentiated human prostate cancer cell lines. *Prostate.* 2013;73:31-41.

63. Olvera-Caltzontzin P, Delgado G, Aceves C, Anguiano B. Iodine uptake and prostate cancer in the TRAMP mouse model. *Mol Med.* 2013;19:409.

64. Elio Torremante P, Rosner H. Antiproliferative effects of molecular iodine in cancers. *Curr Chem Biol.* 2011;5:168-76.

65. Rosner H, Torremante P, Muller W, Gartner R. Antiproliferative/cytotoxic activity of molecular iodine and iodolactones in various human carcinoma cell lines. No interfering with EGF-signaling, but evidence for apoptosis. *Exp Clin Endocrinol Diabetes.* 2010;118(7):410-9.

66. Thomasz L, Oglio R, Rossich L, et al. 6 Iodo-δ-lactone: A derivative of arachidonic acid with antitumor effects in HT-29 colon cancer cells. *Prostaglandins Leukot Essent Fatty Acids*. 2013;88(4):273-80.

67. Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. *Endocr Rev*. 2002;3:38-9.

68. Dentice M, Marsili A, Zavacki A, Larsen PR, Salvatore D. The deiodinases and the control of intracellular thyroid hormone signaling during cellular differentiation. *Biochim Biophys Acta.* 2013 Jul;1830(7):3937-45.

69. Valverde RC, Orozco A, Carlos Solis SJ, Robles-Osorio L. Iodothyronine deiodinases. In: Aguirre A, Conn PM, eds. *Emerging Clinical Crossroads.* Boston: Academic Press; 2014: 365-77.

70. Luongo C, Ambrosio R, Salzano S, Dlugosz AA, Missero C, Dentice M. The sonic hedgehog-induced type 3 deiodinase facilitates tumorigenesis of Basal cell carcinoma by reducing gli2-inactivation. *Endocrinology*. 2014;155(6):2077-88.

71. National Institutes of Health. Office of Dietary Supplements. Iodine: Fact sheet for consumers. http://ods.od.nih.gov/factsheets/Iodine-QuickFacts/. Accessed May 14, 2014.

72. Galofre JC, Fernandez-Calvet L, Rios M, et al. Increased incidene of thyrotoxicosis after iodine supplementation in an iodine sufficient area. *J Endocrinol Invest.* 1994;17:23-7.

73. Todd CH, Allain T, Gomo ZAR, et al. Increase in thyrotoxicosis associated with iodine supplements in Zimbabwe. *Lancet.* 1995;346:1653-4.

74. Krohn K, Fuhrer D, Bayer Y, et al. Molecular pathogenesis of euthyroid and toxic multinodular goiter. *Endocr Rev. 2005;*26:504-24.

75. Stanbury JB, Ermans AE, Bourdoux P, et al. Iodineinduced hyperthyroidism: occurrence and epidemiology. *Thyroid.* 1998;8:83-100.

76. Kessler J. Are there side effects when using supraphysiological levels of iodine in treatment regimens? In: Preedy VR, Burrow GN, Watson RR, eds. *Comprehensive Handbook of Iodine: Nutritional, Endocrine and Pathological Aspects*. San Diego: Academic Press; 2009: 801-10.

77. Ulbricht C, et al. Seaweed, kelp, bladderwrack (*Fucus vesiculosus*): an evidence-based systematic review by the Natural Standard Research Collaboration. *Altern Complement Ther.* 2013;19:217-30.

78. Noda K, Ohno N, Tanaka K, et al . A water-soluble antitumor glycoprotein from *Chlorella vulgaris. Planta Med.* 1996;62(5):423-6.

79. Mathew B, Sankaranarayanan R, Nair PP, et al . Evaluation of chemoprevention of oral cancer with Spirulina fusiformis. *Nutr Cancer.* 1995;24(2):197-202.

80. National Institutes of Health: Office of Dietary Supplments. Iodine: Fact sheet for health professionals. Table 2 http://ods.od.nih.gov/factsheets/Iodine-HealthProfessional/#h3. Accessed May 27, 2014.

81.Teng W, Shan Z, Teng X, et al. Effect of iodine intake on thyroid diseases in China. *N Engl J Med.* 2006;354:2783-93.

82. Teng X,Shan Z, Chen Y, et al. More than adequate iodine intake may increase subclinical hypothyroidism and autoimmune thyroiditis: a cross-sectional study based on two Chinese communities with different iodine intake levels. *Eur J Endocrinol.* 2011;164:943-50.