“Iodine, Evolution and Gastric Carcinogenesis“

Sebastiano Venturi and * Mattia Venturi

Servizio di Igiene, Pennabilli (PU) and * Department of Oral Science, University of Bologna, Italy

partially reported at

the 2nd Esophageal & Cardiac Cancer Summit

第二届食管/贲门癌国际会议

October 18-20, 2007 Beijing, China
In population of Montefeltro, a mountainous and iodine-deficient region, in central Italy, in 1970’, we have reported a significant high rates of:

1. iodine-deficient endemic goiter,
2. cretinism and mental deficit
3. gastric cancer mortality
4. immune-deficiencies
5. oral and dental pathologies
We reported these findings in a book (in 1985) and in different medical journals.

The diseases of my patients were my true motivation for study iodine-metabolism and for try to research a possible correlation among them.


IODINE

Iodine is an essential component of the thyroid hormones. Moreover, some observations have suggested possible additional roles for iodine:

Iodine may have beneficial roles in mammary dysplasia and fibrocystic breast disease (Eskin, 1977; Ghent et al., 1993).

... and inadequate iodine nutrition impairs immune response and may increase incidence of gastric cancer (Venturi, 1993).
World map of prevalence of iodine-deficient goiter (1920), before iodine-prophylaxis (lp). **Shaded areas** show territories of **iodine-deficient endemic goitre** before lp. and **blue areas** show chains of mountains: \( n \) shows the % of gastric cancer mortality from all cancers (1977), and \( (n) \) shows the % of G.C. mortality in nations where a satisfactory **iodine intake** was been reached. 
Note that **some coastal regions** of **Japan** and **China** have **iodine-excess endemic goitre**. (from WHO, 1960).
According to current W.H.O. statistics more than 3 billion people in the world live now in iodine-deficient countries (in red and yellow).
For a better understanding the relation between Iodine-deficiency and Carcinogenesis, we studied the role of

Iodine

in

Evolution
The sea is rich in iodine, about 60 micrograms per liter, since most of the iodine was removed and washed away from the soil accumulated due to rains and the glacial ages.
Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis.

*The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit*

**CONTEXT:** Antioxidant supplements are used for prevention of several diseases. **OBJECTIVE:** To assess the effect of antioxidant supplements on mortality in randomized primary and secondary prevention trials.

**DATA SOURCES AND TRIAL SELECTION:** We searched electronic databases and bibliographies published by October 2005. All randomized trials involving adults comparing beta carotene, vitamin A, vitamin C (ascorbic acid), vitamin E, and selenium either singly or combined vs placebo or vs no intervention were included in our analysis.

**DATA EXTRACTION:** We included 68 randomized trials with 232,606 participants (385 publications).

**DATA SYNTHESIS:** When all low- and high-bias risk trials of antioxidant supplements were pooled together there was no significant effect on mortality (RR, 1.02; 95% CI, 0.98-1.06). Multivariate meta-regression analyses showed that low-bias risk trials (RR, 1.16; 95% CI, 1.05-1.29) and selenium (RR, 0.998; 95% CI, 0.997-0.9995) were significantly associated with mortality. In 47 low-bias trials with 180,938 participants, the antioxidant supplements significantly increased mortality (RR, 1.05; 95% CI, 1.02-1.08). In low-bias risk trials, after exclusion of selenium trials, beta carotene (RR, 1.07; 95% CI, 1.02-1.11), vitamin A (RR, 1.16; 95% CI, 1.10-1.24), and vitamin E (RR, 1.04; 95% CI, 1.01-1.07), singly or combined, significantly increased mortality. Vitamin C and selenium had no significant effect on mortality.

**CONCLUSIONS:** Treatment with beta carotene, vitamin A, and vitamin E may increase mortality. The potential roles of vitamin C and selenium on mortality need further study.
When about 500 million years ago plants and animals began to transfer from the sea to rivers and land, environmental iodine-deficiency was a challenge to the evolution of terrestrial life.

New endogenous antioxidants appeared in plants as ascorbic acid, polyfenols, carotenoids, flavonoids, etc.

A few of these appeared recently, about 200-50 million years ago in fruits and flowers of angiosperm plants.

In the wide range of antioxidants, we hypothesise an “evolutionary hierarchy”, where the most ancient antioxidants (as Iodide, Selenium, etc.) might be more essential than the modern ones in the developing stages of animal and human organisms.
2 I- → I2 + 2 e- (electrons) = -0.54 Volt

2 I- + Peroxidase + H2O2 + 2 Tyrosine →

2 Iodo-Tyrosine + H2O + 2 e- (antioxidants)

and

2 e- + H2O2 + 2 H+ (of physiological water-solution) → 2 H2O

Iodide acts as a primitive electron-donor, through peroxidase, and has an ancestral antioxidant function in all iodide-concentrating cells from primitive marine algae to more recent terrestrial vertebrates. (From Venturi, 1985)
2 I- + Peroxidase + H₂O₂ + Tyrosine, Histidine, Lipids, Carbons →
Iodo-Compounds + H₂O + 2 e- (antioxidants)

Iodo-Tyrosine
Iodo-Histidine,
Iodo-Lipids,
Iodo-Carbons

Proposed antioxidant biochemical mechanism of iodides, probably one of the most ancient mechanisms of defence from poisonous reactive oxygen species (Venturi, 1985)
Pedersèn believes that all algae have the ability to produce halo-carbons, as a result of the development of photosynthesis and oxygen production, some 3 billion years ago”.

“ This implies that production of halo-carbons by algae is due to an adaptation to sun-light, in order to reduce the amount of poisonous reactive oxygen species, such as hydrogen peroxide, superoxide radicals and hydroxyl radicals”.

( Pedersèn et al.,1996)
In kelp, inorganic iodide functions as an antioxidant.

Iodide neutralizes hydrogen peroxide in a two-step process, converting it first to hypoiodous acid and then water, thereby preventing it from becoming a hydroxyl radical.

Other investigators have shown that iodide is a specific scavenger of hydroxyl radicals, and that it, like vitamin C, increases the antioxidant status of human serum.

Iodine defends brain cells in rats from lipid peroxidation, attaching to the double bonds of polyunsaturated fatty acids in cellular membranes, rendering them less susceptible to free radicals.
**Algae** contain the highest amount of iodine (1-3 % of dry weight) and were the first living cells to produce oxygen in the atmosphere. **About 80% of the Earth's oxygen** is now produced by marine planktonic algae.

Brown algae accumulate iodine more than 30,000-70,000 times the concentration of this element in seawater.

**Algal phytoplankton is the basis of marine food-chain and acts as a biological accumulator of iodides, selenium (and n-3 fatty acids).**

Therefore, we suggested that **algal cells required a protective antioxidant action**, in which **iodides**, seem to have had this specific role.
Fig. 2. — Radioautogramme d'une partie du thalle de Laminaria flexicaulis, obtenu après immersion de 24 heures dans l'eau de mer additionnée d'iodures marqués (0,18 meq I$^{131}$ à l'état d'I$^{131}$Na sans entraîneur dans 2 litres d'eau de mer pour 20 g d'algue, 14 h de lavage après la fin de l'expérience, exposition 1 heure).
Living organisms were confined to the sea-water for more than 3 billion years. When about 500 million years ago plants and animals began to transfer from the sea to estuaries, rivers and land, environmental deficiency of antioxidant minerals (and iodine) was a challenge to the evolution of terrestrial life.
Evolution of iodine from non-hormonal to hormonal functions was made in **3 steps:**

1) Formation of the thyroidal-follicle as reservoir of iodine.

2) Utilization of the thyroxine as an iodide transporter.

3) The new hormonal action was made possible **by the formation** of **T3-receptors** (proteins and genes) in the cells of vertebrates.

**Firstly, about 500 Mya,** in marine chordates, the primitive T3-Rs with a **metamorphosing action** appeared.

**Then, about 250-200 Mya,** in the birds and mammalians, others more recent T3-Rs with **metabolic and thermogenetic actions** were formed.
T₃-R genes are c-erbA oncogenes, which have been implicated as tumor suppressor genes of non-thyroidal cancers and are altered in some human gastric and mammary cancers.

( Wang et al., 2002; Li et al. 2002).
T-3 is the active form of the thyroid hormone. Cells take up T4 and remove one of its iodine atoms, converting it to T3, which attaches to T3-receptors on the DNA of the genes and in T3-receptors of mitochondria.
Mitochondria play a central role in execution of apoptosis.
Mitochondria constitute the greatest source of reactive oxidants. The electron transport system consumes approximately 85—90% of the oxygen utilized by a cell, and, in the process,
Ware and Wishner and Cash et al. found that thyroxine and iodine-compounds have an important lipid-antioxidant activity and also protect from mitochondrial damages.

Ware CM, Wishner LA. (1968). The lipid-antioxidant properties of iodine-compounds (Thyroxine). *Lipids, 3 (2) :182-3.
Mitochondria constitute the greatest source of reactive oxidants. The electron transport system consumes approximately 85—90% of the oxygen utilized by a cell, and, in the process, generate pro-oxidants. The mitochondria also contain heavy metal ions such as iron and copper, a situation that favors formation of reactive oxygen species (ROS). The most damaging of ROS produced by mitochondria is the nonspecifically oxidizing hydroxyl radical which can cause oxidative damage to mitochondrial lipids, proteins, and DNA.

Mitochondria are pivotal in the causation and cure of cancer. The transformation of a normal cell to a malignant cell, the reversal of that process, and the destruction of transformed malignant cells are mitochondrial events, all mediated by changes in the form and function of mitochondria.
Thyroxine blocks mitochondrial swelling and lipid peroxidation caused by Fe^{++}. The hormone also blocks Cu^{++}-induced swelling.

A strong lipid antioxidant action is exhibited by thyroxine at a concentration of 1 \mu M. This concentration of the hormone is about one-tenth that necessary to produce appreciable mitochondrial swelling.
Mitochondria also play a central role in execution of apoptosis.

Mitochondrial proteins were observed to be predominantly iodinated in extra-tumoral tissue, but not in tumoral tissue mitochondria.

Treatment with iodine showed an increase in mitochondrial permeability of tumor and decrease in extra-tumoral tissue.

Iodine releases apoptogenic mitochondrial proteins and has a protective effect against tumor.

(Upadhyay et al. 2005)
Thyroid cells phylogenetically derived from primitive iodide-concentrating gastro-enteric cells which, during evolution, migrated and specialized in uptake and storage of iodine, also in order to adapt the organisms from iodine-rich sea to iodine-deficient land.
Marine fishes contain about 800 mg of iodine per kg, compared to about 20 mg of fresh-water fishes.
In amphibian metamorphosis iodides and thyroxine have an important role in the spectacular apoptosis on the cells of gills, tail and fins, and in transforming an aquatic animal (tadpole) into a “more developed” terrestrial animal (frog). (Venturi, 2000).
We reported that, on the contrary way to amphibian metamorphosis, in the mammals hypothyroidism might be considered like a sort of phylogenetical and metabolical regression to a former stage of reptilian life.

In fact, many disorders, similar to reptilian features, such as a dry, hair-less, scaly, cold skin and a general slowdown of metabolism, digestion, heart rate, nervous reflexes with lethargic cerebration, hyperuricemia, and hypothermia afflict hypothyroid humans.
About 350 M/y/a the “dry” terrestrial diet stimulated, firstly in amphibians and in reptiles, the formation of salivary glands, which maintain iodine-concentrating ability, and solubilize dry food.

Whole-body 131-Iodine scintiscans of reptile (lizard) showing high I-concentration in stomach (S) and in thyroid (T) and in salivary glands (SG).
(Modified from Levitus, 1971).
Percentage of radioactivity in serum, in salivary and gastric secretions and in thyroidal colloid, after intravenous injection of 131-I. Gastro-salivary clearance and secretions of iodides are a considerable part of “gastro-intestinal cycle of iodides”, which constitutes about 23% of iodides pool in the human body.
In October 7, 1999, the U.S.A. Committee of the House and Senate regarding "Marine Research" reported that:

"The Committee notes the low incidence of cancer in marine sharks, skates, and rays and encourages basic researches in these marine fishes, that have the potential to inhibit carcinogenesis in humans."
Various tumors that developed spontaneously. (a,b) thymic lymphoma. (c,d) Adenocarcinoma found in the right gill (e,f) Retinoblastoma in the right eye (g,h) A germ cell tumor found in the anterior upper part of the peritoneal cavity. Arrowheads indicate tumors.
When about 500-300 Mya some living plants and animals began to transfer from the sea to rivers and land,
in marine-fishes, plants and animals the terrestrial diet became deficient in many essential marine minerals, including iodine, selenium, etc.

Terrestrial plants, in replacement of marine antioxidants, optimized the production of other new endogenous antioxidants such as ascorbic acid, polyfenols, carotenoids, flavonoids, tocoferols etc., some of which became “essential vitamins” in the diet of terrestrial animals and humans (as vitamins C, A, E, etc.)

Chordates (the primitive vertebrates) began to use the “new” thyroidal follicles, as reservoir of antioxidant iodine.
In “Evolution of Dietary Antioxidant Defences” (2007) we have recently suggested that it is possible to differentiate 3 chronologic stages:

1) **The primitive antioxidants**, which are active in seawater from more than 3.5 billion years.

2) **The middle-aged antioxidants** (as ascorbic acid, and some carotenoids, flavonoids, tocoferols etc.), which are active, firstly, in estuary-waters from about 500 million years ago.

3) **The more recent antioxidants** (as some pigmented polyphenols, carotenoids, flavonoids, etc.), which appeared, firstly, in fruits and flowers of Angiosperm Plants from about 200 million years ago.
In “evolution of dietary antioxidants” we have recently suggested that it possible
differentiate 3 chronologic stages.
In terrestrial (and fresh-water) animals a new kind of diseases appeared:

mal-nutritional diseases,

as goiter, Keshan's disease, and probably cancer, atherosclerosis, etc.
Goiter (thyroid hyperplasia) in fresh-water salmon

When about 400 Mya some animals began to transfer from the sea to rivers and land, terrestrial diet became deficient in many marine trace-elements (as iodine, selenium, etc.)

In terrestrial iodine-deficient fresh-waters some salmonids suffer of thyroid hypertrophy or related metabolic disorders.
Thyroid Hyperplasia

*Thyroid follicles* in a gill filament.
In fact, Stone (in 1972) in his book "THE HEALING FACTOR: VITAMIN C" reported that

“primitive single-cell organisms, such as bacteria, which do not make and may not need ascorbic acid in their living environment…

The chicken egg is devoid of ascorbic acid, but it can be detected in the early stage of the growing embryo.

In plants, also, the seeds have no ascorbic acid, but as soon as the plant embryo start to develop, ascorbic acid is immediately formed”.

Thus all the available evidence points to the antiquity of the ascorbic acid-synthesizing systems in life on this planet.
Cultured freshwater salmons showing nutritionally induced spinal curvature (scoliosis and lordosis) by vitamin C deficiency.

If these fishes are housed in iodine-rich sea-water with algae and marine phytoplankton, symptoms of vitamin C deficiency improved, probably because of the presence of other antioxidants in sea-water.
The role of iodine in marine and fresh-water fishes is not well-understood, but it has been demonstrated that iodine-deficient fresh-water fishes suffer of higher incidence of infective, parasitic, and in particular of neoplastic, and atherosclerotic diseases than marine fishes.
Cancerous Lesions in South River Fish

Skin cancer. These catfish from the South River have the highest skin tumor rate and second highest liver tumor rate."
Various tumors that developed spontaneously.

(a,b) **thymic lymphoma**. (c,d) **Adenocarcinoma** found in the right gill (e,f) **Retinoblastoma** in the right eye (g,h) A **germ cell tumor** found in the anterior upper part of the peritoneal cavity.

**Arrowheads indicate tumors.**
Fig. 2. Distribution of $^{131}$I in the body of a pregnant mouse 1 hour after intravenous injection. High concentration in the gastric mucosa of the foetus.
Sequence of I-123 total-body scintiscans of a woman after intravenous injection of I-123 (half-life: 13 hours); (from left) respectively at 30 minutes, and at 6, 20 and 48 hours. It is evident the highest and rapid concentration of radio-iodide (in white) in gastric mucosa of the stomach, salivary glands and oral mucosa. In gastric mucosa of the stomach, 131-I (half-life: 8 days) persists in scintiscans for more than 72 hours. In the thyroid I-concentration is more progressive, as in a reservoir [from 1% (after 30 minutes) to 5.8 % (after 48 hours) of the total injected dose]. (Venturi, 2000)
Sequence of 123-I total-body scintiscans of a thyroidectomized woman after intravenous injection of I-123; (from left) respectively at 1, 6 and 24 hours. It is evident the highest and rapid concentration of radioiodide in oral mucosa and salivary glands and in gastric mucosa of the stomach and urinary I-excretion.

Distribution of radio-iodine through intact tooth-enamel into dentin, pulp, bone. It is evident high I-131 concentration in cementum, pulp, periodontal membrane, alveolar bone, and gingiva. (From Bartelstone, 1951)
Percentage of radioactivity in serum, in salivary and gastric secretions and in thyroidal colloid, after intravenous injection of 131-I. Gastro-salivary clearance and secretions of iodides are a considerable part of "gastro-intestinal cycle of iodides", which constitutes about 23% of iodides pool in the human body.
In 1961, Brown-Grant reported that:

“I would persuade workers in other branches of physiology, and non only thyroid-researchers, that iodide actions are of more general interest also in extra-thyroidal organs.”

In 2001, Marguerite Hays reported in “THYROID” that

“It is surprising that the precise total iodine-content of the human body remains uncertain, after many years of interest in iodine metabolism, and extra-thyroidal-iodine pool remains a matter of speculation and also the chemical nature non-thyroidal iodine is unknown.”
Sodium iodide symporter (NIS) is the proteic transmembrane transporter of iodide into the cells. Salivary glands and gastric NIS, are more primitive than the thyroidal ones, so have lower affinity for iodide, and does not respond to more phylogenetically recent TSH (Thyrotropin).
**NIS expression** in iodide-transporting probed with anti-NIS Ab showing basolateral plasma membrane immunoreactivity that exhibit active iodine-transport in:  

A. Thyroid;  
B. Gastric mucosa;  
C. Lactating Breast;  
D. Salivary Glands.  

(Wapnir, 2003)

Thyroxine and reverse T3 were found to be more effective in this antioxidant activity than vitamin E, glutathione and ascorbic acid.
Ware and Wishner and Cash et al. found that thyroxine and iodine-compounds have an important lipid-antioxidant activity and also protect from mitochondrial damages.

Ware CM, Wishner LA. (1968). The lipid-antioxidant properties of Iodine-compounds (Thyroxine). Lipids, 3 (2) :182-3.

Mitochondrial Swelling and Lipid Peroxidation Studies with Mixtures of Thyroxine and Micromolar Concentrations of Certain Metal Ions*

(Received for publication, December 1, 1965)

William D. Cash, Martin Gardy,‡ Harold E. Carlson,§ and Enobong A. Ekong¶

From the Department of Biochemistry, Cornell University Medical College, New York, New York 10021

- J. BIOL. CHEM. 1966, 241 :1745-50
Recently, Aceves et al. (2005) reported that the percentage of radio-labeled iodide in cellular homogenate of breast tissue is

40 % in lipid fraction,
50 % in protein fraction
8 % in nuclear fraction.

Aceves also reported that in mammary gland homogenates from virgin rats, the addition of iodine significantly decreases lipo-peroxidation.
500 million years ago, new endogenous antioxidants appeared in plants as ascorbic acid, polyphenols, carotenoids, flavonoids, etc.

A few of these appeared more recently, about 200-50 million years ago in fruits and flowers of angiosperm plants.

In the wide range of antioxidants, we hypothesise an

“evolutionary hierarchy”,

where the most ancient antioxidants might be more essential than the modern ones in the developing stages of animal and human organisms.

(Venturi, 2007)
Damaged reproduction: the most important consequence of iodine deficiency.


The worst of these are on reproductive function and include

more neonatal deaths, increased abortions, and defective progeny.
Iodine and Gastric Carcinogenesis


Self-reported goiter is associated with a significantly increased risk of gastric adenocarcinoma in a large population-based Chinese cohort.

Abnet CC, Qiao YL, Kamangar F, Dong ZW, Taylor P, Mark S; Fraumeni J Jr. Dawsey S

Iodine is concentrated by the gastric mucosa, where it may act as an antioxidant.

Therefore, iodine deficiency, and its sequelae goiter, may be associated with an increased risk of gastric cancer.

We found no association between H. pylori seropositivity and goiter.

These findings are consistent with the hypothesis that iodine-deficiency is associated with an increased risk of gastric cancer.
In Krakow, after iodine-prophylaxis a significant decline of incidence of stomach cancer was observed in men and women (2.3% and 4.0% per year respectively) in the years 1992-2004.

The improved iodine supply decreased the incidence of stomach cancer indicating a protective role against stomach cancer of iodine-prophylaxis in iodine deficient areas.
The thyroid gland is, embryogenetically and phylogenetically, derived from primitive stomach, in fact,

**Stomach and Thyroid share:**

1) Iodine-concentrating ability,

2) cell polarity and apical microvilli,

3) similar organ-specific antigens and associated autoimmune diseases,

4) secretion of similar mucinuous glycoproteins (thyroglobulin and mucin) and peptide hormones,

5) the digesting and reabsorbing ability and,

6) similar ability to form iodotyrosines by peroxidases.
The thyroid gland is, embryogenetically and phylogenetically, derived from primitive stomach.
Fig. 1. Distribution of $^{131}$I in the body of a pregnant mouse 1 min after intravenous injection. High concentration in the mucosa of the fundus of the stomach; no radioactivity as yet in the foetuses.
Fig. 2. Distribution of $^{131}$I in the body of a pregnant mouse 1 hour after intravenous injection. High concentration in the gastric mucosa of the foetus.
Reports from China have suggested that

* **tooth loss**
  may be associated with

* esophageal,
* gastric and
* oral **cancers.**


Distribution of radio-iodine-131 through intact tooth enamel and into dentin. It is evident high I-131 concentration in cementum, pulp, periodontal membrane, alveolar bone, and gingiva. (From Bartelstone, 1951)
It is evident high I-131 concentration in cementum, pulp, periodontal membrane, alveolar bone, and gingiva. (From Bartelstone, 1951).
Oral papilloma on the lips of terrestrial fresh-water salmon brown bullhead. Large papilloma on the right side and a smaller one on the left side of the lower jaw.
Inorganic iodine regulates the production of epidermal growth factor (EGF) in isolated thyroid cells, and controls DNA synthesis and cell proliferation (Tramontano et al., 1989). This action probably occurs in salivary glands and in gastric mucosa too.

EGF is a polypeptide found in many human tissues including submandibular gland, parotid gland.

Salivary EGF plays an important physiological role in the maintenance of oro-esophageal and gastric tissue integrity.

The biological effects of salivary EGF, and also esophageal derived EGF, include healing of ulcers, inhibition of gastric acid secretion, stimulation of DNA synthesis as well as mucosal protection from intraluminal injurious factors.
Fig. 3. Distribution of $^{131}$I in the abdomen of a pregnant mouse 24 hours after intravenous injection. Four foetuses with high concentration of $^{131}$I in the thyroid gland, the thymus and the gastric mucosa; the concentration is also high in the intestinal content and in the milk gland of the mother.


... an adequate iodine intake is necessary for normal immune response.
Mucosa from hamster’s stomach.  Autoradiographs showed selective concentration of iodide in the cells of surface epithelium and gastric pits of the fundus and pyloric part of the stomach (in lower part).

In upper part, the correspondent section stained with Haematoxylin and Eosin. Selective iodide-concentration was not observed in the fore-stomach gastric glands, duodenum, jejunum, ileum or colon.

(Modified, reproduced with permission from Logothetopoulos and Myant, 1956; Courtesy of J. Physiol.)
In the gastro-duodenal junction (ju) iodine-concentration interrupts suddenly.
Die Verteilung von Technetium-99m und Jod-131 in der Magenschleimhaut

Abb. Autoradiographische Darstellung der Verteilung von $^{131}$J in der Magenschleimhaut der Katze. (78 ×)

W. Meier-Ruge und R. Fridrich

Abb. Silberkorndarstellung über den Belegzellen der Magenschleimhaut des Menschen nach $^{99m}$Tc. (180 ×)

Abb. Prozentuale Anreicherung von $^{99m}$Tc und $^{131}$J in der Magenwand in Abhängigkeit von der Zeit. Die Werte sind auf 0,5 mCi i.v. applizierte Dosis pro Gramm Magenwand bezogen.
Daily dietary intake of iodine, according to Panel on Micronutrients, Food and Nutrition Board, Institute of Medicine, 2001.

*Note that an optimal iodine intake for breast of 6.0 mg is reported recently by Kessler in* 
*Breast J. 2004,10:328-36*
Iodide excess exerts oxidative stress in some target tissues of the thyroid hormones.
Joanta AE, Filip A, Clichici S, Andrei S, Daicoviciu D.

Iodide excess had pro-oxidant effects, leading to an increased lipid peroxides level in target tissues.
Acute toxic gastric mucosal damage induced by Lugol's iodine spray during chromoendoscopy.


Figure 1 (A, B) Oedematous and haemorrhagic mucosa with loss of superficial gastric mucosal layer in the greater curve. (C) Mucosal oedema, loss of superficial gastric epithelium, and sparse inflammatory infiltrate in the lamina propria.
World map of prevalence of iodine-deficient goitre (1920), before iodine-prophylaxis (Ip). **Oblique lines show areas of iodine-deficient endemic goitre** before Ip. and **blue areas** show chains of mountains: n shows the % of gastric cancer mortality from all cancers (1977), and (n) shows the % of GC mortality in nations where a satisfactory iodine intake was been reached. Some coastal regions of Japan and China have iodine-excess endemic goitre. (from WHO, 1960).
(Left) Italian map of provincial distribution of **GC mortality** (1975-1977, from Cislaghi).
(Right) Italian map of areas of high **endemic goitre** (1960-1993, from Costa).
Tuscany

G.C. mortality per 100,000 (1969-78) (M+F) crude rates

- Casentino: 117
- Val Tiberina: 94
- Prov. Arezzo: 79
- Prov. Pisa: 43

Mountain Sea
E. Romagna

G.C. mortality per 100,000 (1960-82) (M+F) crude rates

- Forli: mountain 137, plain 75
- Cesena: mountain 98, plain 70
- Rimini: sea 47
Group
Atrophic Gastritis
P<0.001

% of Atrophic Gastritis

percentage of goitre

A 16.2
B 51.6
C 82.5

100%
Figure 3. Map of stomach cancer mortality among men (left) and women (right) in Europe (1993–97) (relative scale)
Different national trends of gastric cancer mortality in relation to the beginning (arrows) of iodine prophylaxis (Ip.) and to the percentage of the population in which Ip. is used. Japan and most of Chile and Italy never used iodized salt.

In the USA iodized salt has been used since 1920-30 and is the most iodine-concentrated (100 mg of potassium iodide per kg). Canada, Australia and New Zealand show similar trends to the USA, since they have used similar iodized salt during the same period of time. (From Venturi et al. 1993)

Jagiellonian University, Collegium Medicum, Faculty of Medicine, Krakow, Poland.

Iodine prophylaxis: the protective factor against stomach cancer in iodine deficient areas.

Fig. 2 Goitre prevalence in schoolchildren aged 6–8 years in 1992–1993 and 2003
In Krakow (Poland), after iodine-prophylaxis a significant decline of incidence of stomach cancer was observed in men and women (2.3% and 4.0% per year respectively) in the years 1992-2004.
In Italy gastric cancer is more frequent in farmers than in fishermen, whose diet is richer in iodine.

Comparing the years 1980 to 1995, we found that Italians, whose gastric cancer mortality has decreased, have increased their yearly fish consumption (from 8.7 to 14.4 kg per person), and decreased their consumptions of fruit (from 86.6 to 84.9 kg per person) and vegetables (from 111.4 to 108.2 kg per person).
Gastric cancer mortality trend in Italy compared with the trends of the near endemic provinces of Cuneo and Aosta (M+F, crude rates). Only Aosta had carried out iodine-prophylaxis since 1930-35, but it was interrupted in 1975. After some years, its trend started to reverse and increase.

The same happened in Guatemala after 1976. (From Venturi et al. 1993).
Trends of goiter prevalence and of gastric cancer mortality in the population after reduction (in 1970) of iodine-prophylaxis in GUATEMALA

![Graph showing trends of goiter prevalence and gastric cancer mortality over time.](image-url)
Trend of Gastric Cancer Mortality per 100,000 in the city of Urbino (in blue) (M+F standardized rates), compared with Italian Gastric Cancer Mortality after iodine-prophylaxis started in 1984.
Iodine and Apoptosis
In amphibian metamorphosis iodides and thyroxine have an important role in the spectacular apoptosis on the cells of gills, tail and fins, and in adapting and transforming an aquatic animal (tadpole) into a “more developed” terrestrial animal (frog).
Non-radioactive Iodide Effectively Induces Apoptosis in Genetically Modified Lung Cancer Cells.

(by NIS and TPO-genes transported by an adeno-viral vector.)

Effect of Iodine on Tumor Growth in Mice

Genetically Modified Tumor Xenograft Controls

Genetically Modified Tumor Xenograft with Iodine

Fig. 2. Mammary tumors were not observed macroscopically in rats of the *mekabu* group (A) despite huge tumors in the control group (B).
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 Jan 10;7:5.

The sodium/iodide symporter (NIS) is a plasma membrane glycoprotein that mediates iodide (I-) transport in the thyroid, lactating breast, salivary glands, and stomach.

NIS expression is markedly decreased or absent in case of intestinalization or malignant transformation of the gastric mucosa, and also in esophageal precancerous lesions, such as Barrett’s mucosa esophagus.
Conclusion

It is possible that, in the wide range of the dietary antioxidants, there is an "evolutionary hierarchy", where the most ancient might be more essential than the modern ones.

The primitive antioxidant, trophic, apoptosis-inductor and anti-tumor activity of iodides might be an important new area for investigation.

References in:  http://web.tiscali.it/iodio/