Journal of Mammary Gland Biology and Neoplasia, Vol. 10, No. 2, April 2005 (© 2005)
DOI: 10.1007/s10911-005-5401-5

Is Iodine A Gatekeeper of the Integrity of the Mammary Gland?

Carmen Aceves,[1,2] Brenda Anguiano,[1] and Guadalupe Delgado[1]

This paper reviews evidence showing iodine as an antioxidant and antiproliferative agent contributing to the integrity of normal mammary gland. Seaweed is an important dietary component in Asian communities and a rich source of iodine in several chemical forms. The high consumption of this element (25 times more than in Occident) has been associated with the low incidence of benign and cancer breast disease in Japanese women. In animal and human studies, molecular iodine (I_2) supplementation exerts a suppressive effect on the development and size of both benign and cancer neoplasias. This effect is accompanied by a significant reduction in cellular lipoperoxidation. Iodine, in addition to its incorporation into thyroid hormones, is bound into antiproliferative iodolipids in the thyroid called iodolactones, which may also play a role in the proliferative control of mammary gland. We propose that an I_2 supplement should be considered as an adjuvant in breast cancer therapy.

KEY WORDS: mammary gland; iodine; deiodinase; breast cancer; antioxidant; lipoperoxidation.

INTRODUCTION

Most of the investigations of iodine status in humans and animals have been focused on the role of iodine in thyroid function. Relatively little attention has been given to its extra thyroidal roles. Iodides are necessary for all living vegetable and animal cells, but only vertebrates possess a thyroid gland and its iodinated hormones. In humans the total amount of iodine in the body is about 30–50 mg; less than 30% is present in the thyroid gland and its hormones. About 60–80% of the total iodine is non-hormonal and is concentrated in extrathyroidal tissues, but its biological role is still unknown *(1)*. Recently some groups have postulated that iodide may have an ancestral antioxidant function in all iodide-concentrating cells, from primitive algae to more recent vertebrates *(1–3)*. In these cells iodide acts as an electron donor in the presence of H_2O_2 and peroxidase; the remaining iodine atoms readily iodinate tyrosine, histidine and certain specific lipids. In fact, iodine can attach to double bonds of some polyunsaturated fatty acids in cellular membranes, making them less reactive to free oxygen radicals *(4)*. Moreover, it has been demonstrated that iodine distribution in the organism depends on the chemical form of iodine ingested *(5)*, and that molecular iodide (I_2) is not reduced to iodine (I^-) in the blood before it is absorbed systemically from the gastrointestinal tract *(6)*. Indeed, in iodine deficiency conditions, I^- appears more efficient than I_2 in restoring the thyroid gland to normal from goitrous state, whereas I_2 is distinctly more effective in diminishing mammary dysplasia and atypia

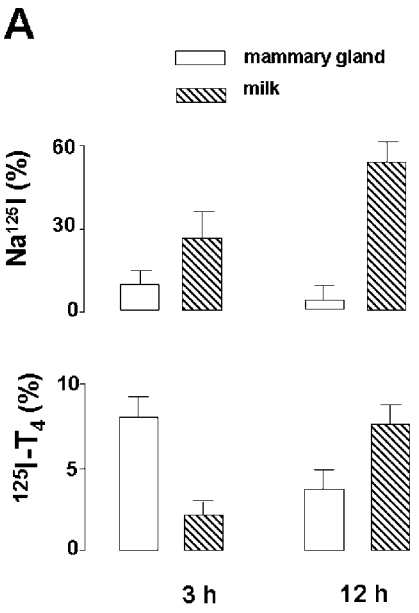
[1] Instituto de Neurobiología, Universidad Nacional Autónoma de México, Juriquilla, Juriquilla Qro. 76230, México.
[2] To whom correspondence should be addressed at Instituto de Neurobiología, Universidad Nacional Autónoma de México, Juriquilla, Km 15 Carretera Qro-SLP, Juriquilla, Querétaro, 76230, México; e-mail: caracev@servidor.unam.mx.

Abbreviations used: H_2O_2, hydrogen peroxide; I_2, molecular iodine; I^-, iodide; I^+, iodinium; I^0, iodine free radical; I*, oxidized iodine species; IO^-, hypoiodite; IO_3^-, iodate; KI, potassium iodide; LPO, lactoperoxidase; MNU, *N*-methyl-*N*-nitrosourea; NIS, sodium iodide symporter; O_2, single oxygen; O_2^-, superoxide anions; $^\bullet OH$, hydroxyl radicals; PEN, pendrin; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; T_3, triiodothyronine; T_4, thyroxine; TPO, thyroperoxidase.

secondary to iodine deficiency *(7,8)*. In this paper, we review the different reports related to non-thyroidal iodine functions described in normal and neoplastic mammary glands.

IODINE AND NORMAL MAMMARY GLAND

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 *(9,10)*. The physiological significance of this mammary I^- avidity has been explained as a vital evolutionary mechanism to provide the neonate with iodine to make his/her own thyroid hormones necessary to normal neural development *(10)*. Lactating mammary gland takes up iodide principally by the sodium/iodide symporter (NIS) and by a specific peroxidase called lactoperoxidase (LPO), by which I^- is oxidized and bound to the lactoprotein casein, which together with free iodine is secreted into milk *(11,12)*. Although it was reported that the mammary gland from sexually mature virgin animals does not express NIS, recent studies have demonstrated that during this period mammary gland expresses another I^- transporter called pendrin (PEN) and exhibits I^- capture *(13,14)*. Studies related to uptake and metabolism of I^- or other iodine components, such as I_2, during virgin or other physiological states relative to non-thyroidal functions are scarce; however, it has been demonstrated that iodine contributes to the maintenance of the normal integrity of the mammary gland. Eskin *et al. (7)* showed that an iodine deficiency alters the structure and function of mammary gland in virgin rats, and that I_2 is effective in diminishing ductal hyperplasia and perilobular fibrosis secondary to this iodine deficiency *(7)*. Similarly, I_2 treatment of patients with benign breast disease is accompanied by a significant bilateral reduction in breast size, in addition to causing a remission of disease symptoms, which is not observed when I^- or protein-bound iodide is administrated *(8)*. The importance of I_2 in the treatments for mammary gland dysfunctions has been corroborated in human and animal models. Seaweeds, such as *wakame*, *nori* or *mekabu* (used in sushi, soup, salads, and in powdered form as a condiment), are widely consumed in Asian countries and contain high quantities of iodine in several chemical forms, (i.e. I^-, I_2, IO_3^-), and protein-associated *(15,16)*. This element has been associated with the low incidence of benign and malignant breast disease in Japanese women (iodine average consumption in the Japanese population is 5,280 μg/day versus 166–209 μg/day in the UK and USA, respectively) *(2)*. It is possible that different chemical forms of iodine exhibit a differential function in the diverse organs. This notion is supported by recent data obtained in our laboratory. Mammary gland expresses two different deiodinase enzymes, which locally convert the prohormone T4 into the active thyroid hormone, T3. This conversion results in variable intracellular concentrations of free iodine: Higher levels during pubertal, pregnancy, and lactation mediated by deiodinase type 1, and lower but continuous amounts in virgin or postpartum conditions catalyzed by deiodinase type 2 *(17)*. Although the chemical form of the iodine that results from deiodination has not been determined, it possibly corresponds to a different and perhaps more reactive form than I^-. As shown in Fig. 1, the $Na^{125}I$ uptake exhibits a different compartmental profile than that of ^{125}I generated by local deiodination of ^{125}I-T4 in lactating mammary glands. $Na^{125}I$ is avidly taken up, and 12 h later 80% of radiolabeled agent (as free iodine or associated with the protein fraction) is present in the milk. In contrast, labeled ^{125}I from T4 remained in the mammary gland (only 10% was present in the milk 12 h later) as ^{125}I-T3 or ^{125}I-labeled components in lipids, proteins, and nuclear fractions. These data agree with recent findings *(18)*, in which we demonstrated that in mammary gland homogenates from virgin rats, the addition of I_2, but not potassium iodide (KI), significantly decreases lipoperoxidation measured by the thiobarbituric acid reaction and expressed as malondialdehyde (MDA). The lack of effect of I^- in decreasing lipoperoxidation may be explained by the absence of LPO in mammary glands from virgin rats, being only present during pregnancy and lactation *(19)*. LPO is a homologue protein of thyroperoxidase (TPO); both enzymes are able to oxidize I^- to link iodine to proteins or lipids. A specific iodination species generated from LPO activity has not yet been identified but several candidates exist, such as I^+ (iodinium), I^0 (iodine free radical), IO^- (hypoiodite), and I_2 *(3)*. Thus, we hypothesize that iodine generated by LPO activity is bound to an abundant and specific protein (e.g. thyroglobulin in the thyroid and casein in lactating mammary gland), whereas I_2 or other oxidized iodine component, obtained by deiodination or in the diet, binds primarily to lipids and/or other membrane or nuclear components. Thus, iodine generated continuously by deiodination acts primarily as an antioxidant,



B

cellular fraction	% radiolabeled
lipid	40
protein	50
nuclear	8

C

	% radiolabeled in cellular fraction		
^{125}I component	lipid	protein	nuclear
^{125}I-T_3	63	5	70
^{125}I-bound	35	80	20
^{125}I free	0	0	0

Fig. 1. Differential uptake and cellular compartmentalization of radiolabeled iodine. Primiprarous lactating animals (10 days pospartum/8 pups) received one i.p. injection of 100 μCi of $Na^{125}I$ or ^{125}I-T_4. After 3 or 12 h animals were anesthetized (Ketamine/Xylazine 30/6 mg/Kg BW). Milk was obtained by administration of oxytocin (30 mU; i.p.) 1 min before sacrifice (*panel A*). On mammary glands from 3 h post-^{125}I-T_4 injected animals, cellular fraction and ^{125}I components are analyzed. Lipid fraction was obtained by methanol/chloroform extraction (1:2); protein fraction by 10% trichloroacetic acid, and nuclear fraction by centrifugation 800 g, 10 min 4°C (*panel B*). The identity of the components was made by paper descending chromatography (solvent system, teramyl alcohol, 2N NH_4OH, hexane 5:6:1) (*panel C*). In $Na^{125}I$ injected animals 80% of the labeled components corresponded to ^{125}I free (not bound to cellular components or T3, data not shown).

whereas the iodine capture as iodide and the iodine-bound-casein generated by LPO during lactation contributes to the iodine pool in milk.

REPRODUCTIVE FACTORS AND BREAST CANCER RISK

Epidemiological studies indicate sexual reproductive history as the most important risk factor for breast cancer. A very interesting hypothesis by Wynne–Edwards *(20)* suggests that from an evolutionary perspective the modern increased risk in breast cancer is the result of recent cultural and reproductive changes in women's lives. These include: (a) an increased exposure to endogenous estrogen which is a weak carcinogen (via early menarche, low parity, abbreviated breast feeding, and pharmaceutical hormone manipulation) *(21)* and (b) an increased risk of breast cancer by altering the proportion our lives spent in developmental stages of breast tissue with an underlying high rate of mitotic cell division (cell breast tissue that has never undergone differentiation to produce milk divides 20 times more often than cells that have acquired the terminal phenotype) *(22)*. There are no studies relating the role of iodine and estrogen effects, but it has been observed that during pregnancy and lactation, hormonal stimulation of mammary gland leads to glandular differentiation that dramatically enhance both iodide absorption and local generation of free iodine by deiodination *(17,23)*. It is interesting to note that this generation occurs in the same lobuloalveolar epithelium where the majority of breast cancer arises *(17,19,24)*. A high iodine concentration in breast tissue may also explain the reduction in modularity and tissue density that are often observed following pregnancy and lactation *(25)*. Thus, a link may exist between enhanced breast iodine content during pregnancy/lactation and subsequent reduction in breast cancer risk. It has been suggested that these reproductive periods may be protective

against breast cancer given the lobuloalveolar differentiation present during these stages *(24)*. Cann *et al. (2)* have proposed that increased iodine content may also play a pivotal role in this differentiation process. For example, most studies in Asia have found lactation to be protective in preventing subsequent breast cancer development in both pre-and post-menopausal women *(26,27)*. In contrast, studies conducted in North America and Europe have generally shown breastfeeding to be protective only in pre-menopausal woman *(28)*, or not at all *(29)*. Thus, recent cultural and reproductive changes and/or the lower levels of iodine intake may be responsible for these differences.

IODINE IN NEOPLASTIC MAMMARY GLAND

In mammary cancer from humans or animals the cell oxidative status is disrupted *(30,31)*. It has also been postulated that reactive oxygen species (ROS) such as single oxygen (O_2), superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($^\bullet OH$) are intimately related in the etiology of cancer *(31,32)*. A substantial amount of H_2O_2 is produced by human tumor cells *(32)*. ROS have a wide range of cellular and molecular effects resulting in mutagenicity, cytotoxicity, and changes in gene expression. G–C base pairs in CpG dinucleotide sequences are a common site for point mutations in *p53* tumor suppressor gene closely related to breast cancer *(33)*. Cellular genes are usually converted into oncogenes, particularly *ras* family oncogenes in codons 12 and 13 *(34)*. It has been demonstrated that these G–C sites are the main targets of oxidative damage *(35)*. In this respect, we and others postulate that I_2 or other oxidized iodine species (I^*), either act in competition with ROS for different cellular components, or neutralize $^\bullet OH$ radicals by the formation of HOI, resulting in less cellular oxidative damage. Thus, assuming that iodine may exert this antioxidant effect, it is evident that carcinogenetic mechanisms may involve the turning off of genes related to the local generation of oxidized iodine components. Although in a wide variety of primary or immortalized mammary tumors, cells express NIS and PEN *(12,36)* and are capable of taking up I^-, effectively, the LPO necessary to oxidize it is not present *(37,38)*. Moreover, cancer progression in thyroid or mammary glands from animals and humans is generally accompanied by the loss of the deiodinative capacity, impaired by the local generation of oxidized iodines *(39–41)*.

The notion that oxidized iodine is the active chemical form with a tumor suppressive effect is strongly supported by data showing that anticarcinogenic effects of seaweeds or iodine supplements contain in both cases a portion of oxidized iodine. Previously, we mentioned that seaweeds contain iodine in several chemical forms although the exact proportion is not known *(15,16)*. Traditional eastern breast cancer medicine has long used iodine-rich seaweeds as a cancer treatment to "soften" tumors and "reduce" nodulation. Teas *et al. (42)* showed that the addition in the diet of 5% of *Laminaria angustata* significantly delays the occurrence of tumors in animals treated with the chemical carcinogen, 7,12-dimethylbenzanthracene (DMBA). Yamamoto *et al. (43)* found that only 2% of *Porphyra tenera*, *Lamaninaria religiosa* or *Laminaria japonica var ochotensis* is necessary to obtain the same protective effect. Funahashi *et al. (44)* reported that 1 and 5% of *wakame* seaweed in the diet reduce significantly the size of tumors generated by DMBA and showed that the consumption of algae is accompanied by increased levels of iodine in the serum with no changes in the thyroid hormone, thyroxine (T4).

In mammary carcinomas induced by DMBA in rats, Lugol's solution (mixture of I^- and I_2) supplementation exerts a suppressive effect on the development and size of the neoplasias *(45)*. This suppressive effect is enhanced when Lugol treatment is combined with progesterone (medroxy-progesterone acetate). The suppressed tumors were found to have a significantly higher mean iodine content than nonsupressed tumors, with uptake apparently enhanced by progesterone *(46)*. The enhancement of iodine uptake by progesterone has been observed in other hormone-dependent tissues, including the uterus and ovary *(47)*. Data generated in our laboratory have shown that chronic administration of I_2 exhibits a potent protective effect (70%) on mammary cancer induced by the carcinogen *N*-methyl-*N*-nitrosourea (MNU). This effect is exerted only by I_2 but not by KI or T4. The suppression by I_2 treatment is accompanied by the development of latent mammary cancers that do not progress to overt cancers, suggesting that the mechanism of action of I_2 is due to a decrease in carcinogenesis at the promotion level. Moreover, this protective effect of I_2 is accompanied by a significative reduction in lipoperoxidation, which is significantly higher in "normal" mammary glands from animals treated with MNU or in patent tumors *(18)*.

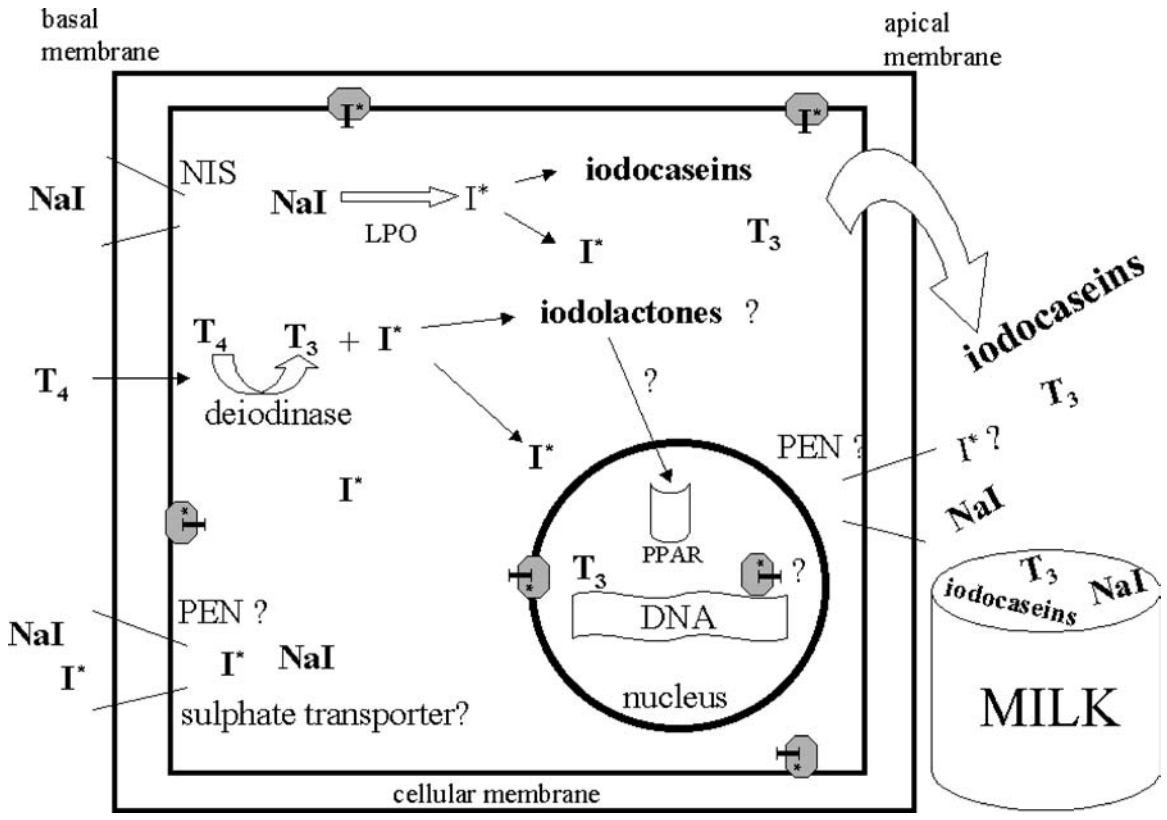


Fig. 2. Model of different ways of action of iodine in the mammary gland. In this model iodine is captured as: Iodide (NaI), thyroid hormone component (T4) or as oxidized iodine species (I^*). Iodide is transformed in I^* by the lactoperoxidase enzyme (LPO) and binds primarily to the protein casein (iodocasein) to be driven to the milk, or is maintained in the cell as I^*. The I^* obtained by direct capture, by LPO action or by deiodination is mainly bound to membrane components (gray hexagon) and acts as antioxidant or joins to iodolactones regulating the proliferative cycle through its union with peroxisome proliferator-activated receptor (PPAR). Finally iodine may participate as a T_3 component, in the turning off or on of genes through its union to nuclear thyroid receptors. Interrogation signal denotes non demonstrated event or component.

Another important effect of iodine on the thyroid is its ability to diminish the hypervascularity and hyperplasia characteristic of the diffuse goiter in Graves' disease. The molecular mechanism of this phenomenon widely used to facilitate surgical therapy of this disorder is uncertain, but it has been postulated that iodine might be oxidized to a more reactive form, bind to organic components and, as a consequence, interfere with metabolic or molecular processes necessary for the maintenance of hyperplasia *(48,49)*. Vitale *et al. (50)* showed that an excess of KI induces apoptosis in cultured thyroid cells, but if TPO activity is blocked with propylthiouracil, the apoptotic effect of KI is cancelled. Besides, Zhang *et al. (37)*, using lung cancer cells transfected with NIS or NIS/TPO, observed that only in NIS/TPO transfected cells does a KI excess induce apoptosis, indicating that I^- from KI needs to be oxidized to have a cytotoxic effect. The postulated mechanism of iodine's ability to induce apoptosis is the formation of specific iodinated lipids called iodolactones *(51)*. The iodolactones of arachidonic acid are capable of inhibiting *in vitro* thyroid cell proliferation and inducing apoptosis *(52–53)*. Our group recently reported that in the human breast cancer cell line MCF-7, I_2 and KI administration significantly decrease (50 and 25%, respectively) the cellular proliferative rate, and that in agreement with this effect, $^{125}I_2$ is internalized more rapidly and effectively than $Na^{125}I$, even in the absence of NIS *(54)*. The possibility that this I_2 antiproliferative effect in mammary cells is secondary to the generation of iodolactones is now being analyzed by our laboratory.

Iodolactone toxicity to thyroid or mammary gland cells at the molecular level has not yet been

fully documented, although the involvement of different apoptotic pathways has been hypothesized *(52)*. In this respect, we and others have found no differences in p53 expression due to *in vivo* or *in vitro* iodine treatments *(18,50)*; however, it is possible that I_2 or other oxidized iodine components (such as iodolactones) participate in antiproliferation or apoptotic mechanisms unrelated to p53. In this respect, we have postulated that the peroxisome proliferator-activated receptor (PPAR) may be an excellent candidate. PPARs, originally related only to the regulation of lipid metabolism, are widely expressed in almost every tissue, and form part of the nuclear receptor family that binds thyroid hormones, steroids, and vitamins *(55)*. Recently, PPARs have been implicated in mechanisms involved in cellular differentiation, proliferation and apoptosis *(56)*. Polyunsaturated fatty acids such as linoleic acid, eicosanoids, and arachidonic acid (one of the targets of oxidized iodine) have been identified as endogenous PPAR ligands *(57)*.

In conclusion and as summarized in Fig. 2, it is possible that iodine in vertebrates exhibits the following different ways of action:

1. As an antioxidant by exerting a competition with free radicals for membrane lipids, proteins, and DNA to help stabilize the cells. This antioxidant action can be exerted through oxidized iodine species (I^*) obtained by the diet or by local deiodination.
2. As inducers of antiproliferative and apoptotic mechanisms through the formation of iodolactones.
3. As a constitutive part of thyroid hormones.

As other authors and ourselves *(7,8,18,45,46)* have demonstrated, a chronic I_2 diet supplement is not accompanied by any harmful secondary effects on the health of women or animals (body weight, thyroid economy, reproductive cycle). Thus, we propose that I_2 supplementation should be considered for use in clinical trials of breast cancer therapies.

ACKNOWLEDGMENTS

The authors are grateful to Pablo Garcia-Solis and Omar Arroyo for their critical analysis and suggestions, and Marcela Sánchez-Alvarez for proofreading this manuscript. The work of our group was partially supported by grants: UNAM/DGAPA-PAPIIT IN224602 and CONACYT 44976-M.

REFERENCES

(1) Venturi S. Is there a role for iodine in breast disease? The Breast 2001;5:379–82.
(2) Cann SA, van Netten JP, van Netten C. Hypothesis: Iodine, selenium and the development of breast cancer. Cancer Causes Control 2000;11:121–127.
(3) Smyth PP. Role of iodine in antioxidant defence in thyroid and breast disease. Biofactors 2003;19:121–130.
(4) Cocchi M, Venturi S. Iodide, antioxidant function and omega-6 and omega-3 fatty acids: A new hypothesis of biochemical cooperation? Prog Nutr 2000;2:15–9.
(5) Thrall KD, Bull RJ. Differences in the distribution of iodine and iodide in the Sprague–Dawley rat. Fundam Appl Toxicol 1990;15:75–81.
(6) Thrall KD, Sauer RL, Bull RJ. Evidence for thyroxine formation following iodine administration in Sprague–Dawley rats. J Toxicol Environ Health 1992;37:443–449.
(7) Eskin BA, Grotkowski CE, Connolly CP, Ghent WR. Different tissue responses for iodine and iodide in rat thyroid and mammary glands. Biol Trace Elem Res 1995;49:9–18.
(8) Ghent WR, Eskin BA, Low DA, Hill LP. Iodine replacement in fibrocystic disease of the breast. Can J Surg 1993;36:453–460.
(9) Aceves C, Morales T, Pineda O, Rodón-Fonte C. Navarro L, Valverde-R C. T3 and iodine in milk. Mammary 5'deiodinase is neurally regulated. In: International symposium on hormones and bioactive substances in milk. Smolonice, Eslovak Republic; 1996; p 7.
(10) Topper YJ, Freeman CS. Multiple hormone interaction in the developmental biology of the mammary gland. Physiol Rev 1980;60:1049–1067.
(11) Memphan TB. Physiology of lactation. Philadelphia: Open University Press; 1987.
(12) Tazebay UH, Wapnir IL, Levy O, Dohan O, Zuckier LS, Zhao QH, et al. The mammary gland iodide transporter is expressed during lactation and in breast cancer. Nature Med 2000;6:871–878.
(13) Rillema JA, Williams CH, Moulden J, Golden KL. Effect of insulin on iodide uptake in mouse mammary gland explants. Exp Biol Med 2002;227:32–35.
(14) Rillema JA, Hill MA. Prolactin regulation of the pendrin-iodide transporter in the mammary gland. Am J Physiol Endocrinol Metab 2003;284:E25–E28.
(15) Kupper FC, Schweigert N, Ar Cali E, Legendre JM, Vilter H, Koareg B. Iodine uptake in laminariales involves extracellular, haloperoxidase-mediated oxidation of iodide. Planta 1998;207:163–171.
(16) Hou X, Chai C, Quian Q, Yan X, Fan X. Determination of chemical species of iodine in some seaweeds (I). Sci Total Environ 1997;204:215–221.
(17) Aceves C, Rodón C, Ramírez-C I, Wilson S, Pineda-C O, Lopez-B L, *et al.* Mammary 5′deiodinase (5′D) during the breeding cycle of the rat: Indirect evidence that 5′D type I is specific to the alveolar epithelium. Endocrine 1995;3:95–99.
(18) García-Solís P, Alfaro Y, Anguiano B, Delgado G, Guzmán RC, Nandi S, Díaz-Muñoz M, Vázquez-Martínez O, Aceves C. Inhibition of induced-MNU mammary carcinogenesis by

molecular iodine (I_2) but not by iodide (I^-) treatment. Evidence that I_2 prevents cancer promotion. Mol Cell Endocrinol, in press.

(19) Strum JM. Site of iodination in rat mammary gland. Anat Rec 1978;192:235–244.

(20) Wynne-Edwards KE. Breast cancer etiology and prevention from an evolutionary perspective. In: Review of lifestyle and environmental risk factors for breast cancer. The Canadian Breast Cancer Initiative (CBCI). Workshop on Primary Prevention of Breast Cancer. Vol. III, Québec City, Québec Canada; 2000. p. 1–31.

(21) Helzlsouer KJ, Couzi R. Hormones and breast cancer. Cancer 1995;76:2059–2063.

(22) Pihan GA, Doxsey SJ. The mitotic machinery as a source of genetic instability in cancer. Semin Cancer Biol 1999;9:289–302.

(23) Shah NM, Eskin BA, Krouse TB, Sparks CE Iodoprotein formation by rat mammary glands during pregnancy and early postpartum period. Proc Soc Exp 1986;181:443–449.

(24) Russo J, Russo IH, Role of differentiation in the pathogenesis and prevention of breast cancer. Endocr Rel Cancer 1997;4:7–21.

(25) Haagensen CD. Disease of the breast. Philadelphia, PA: WB Saunders; 1971. p. 62.

(26) Yoo KY, Tajima K, Kuroishi T, et al. Independent protective effect of lactation against breast cancer: A case-control study. Am J Epidemiol 1992;135:726–733.

(27) Yang PS, Yang TL, Liu CL, Wu CW, Shen CY. A case control study of breast cancer in Taiwan. A low incidence area. Br J Cancer 1997;75:752–756.

(28) Newcomb PA, Storer BE, Longnecker MP, et al. Lactation and reduced risk of premenopausal breast cancer. N Engl J Med 1994;330:81–87.

(29) Michels KB,Willett WC, Rosner BA, et al. Prospective assessment of breastfeeding and breast cancer incidence among 89,887 women. Lancet 1996;347:431–436.

(30) Ray G, Batra S, Shukla NK, Deo S, Raina V, Ashok S, Husain SA. Lipid peroxidation, free radical production and antioxidant status in breast cancer. Breast Cancer Res Treat 2000;59:163–170.

(31) Cook JA, Gius D, Wink DA, Krishna MC, Russo A, Mitchell JB. Oxidative stress, redox, and the tumor microenvironment. Semin Radiat Oncol 2004;14:259–266.

(32) Szatrowski TP, Nathan CF. Production or large amounts of hydrogen peroxide by human tumor cells. Cancer Res 1991;51:794–798.

(33) Lane DP. p53 and human cancer. Br Med Bull 1994;50:582–599.

(34) Bos J. The *ras* family and human carcinogenesis. Mutat Res 1988;195:255–271.

(35) Moraes EC, Keyse SM, Tyrell RM. Mutagenesis by hydrogen peroxide treatment in mammalian cells: A molecular analysis. Carcinogenesis 1990;11:283–293.

(36) Rilema JA, Hill MA. Pendrin transporter carries out iodide uptake into MCF-7 human mammary cancer Cells. Exp Biol Med 2003;228:1078–1081.

(37) Zhang L, Sharma S, Zhu LX, Kogai T, Hershman JM, Brent GA, et al. Nonradioactive iodide effectively induces apoptosis in genetically modified lung cancer cells. Cancer Res 2003;63:5065–5072.

(38) Schmutzler C, Brtko J, Biernert K, Köhrle J. Effects of retinoids and role of retinoic acid receptors in human thyroid carcinomas and cell lines derived therefrom. Exp Clin Endocrinol Diab 1996;10:393–406.

(39) Schreck R, Schieders F, Schmutzler C, Köhrle J. Retinoids stimulate type I iodothyronine 5′-deiodinase activity in human follicular thyroid carcinoma cell lines. J Clin Endocrinol Metab 1994;79:791–798.

(40) Aceves C, Gopainathrao G, Rajkumar L, Guzman RC, Yang J, Nandi S. Deiodinase type 1 (D1) in *N*-methyl-*N*-nitrosourea-induced rat mammary carcinomas. Differential expression in early and late arising tumors. 84th Annual Meeting. San Francisco CA: The Endocrine Society. 2002; pp. 731.

(41) García-Solis P, Aceves C. 5′Deiodinase in two breast cancer cell lines: Effect of triiodothyronine, isoproterenol and retinoids. Mol Cell Endocrinol 2003;201:25–32.

(42) Teas J, Harbison ML, Gelman RS. Dietary seaweed (Laminaria) and mammary carcinogenesis in rats. Cancer Res 1984;44:2758–2761.

(43) Yamamoto I, Maruyama H, Moriguchi M. The effect of dietary seaweeds on 7,12-dimethyl-benz[a]anthracene-induced mammary tumorigenesis in rats. Cancer Lett. 1987;35:109–118.

(44) Funahashi H, Imai T, Tanaka Y, Tsukamura K, Hayakawa Y, Kikumori T, et al. Wakame seaweed suppresses the proliferation of 7,12-dimethylbenz(a)-anthracene-induced mammary tumors in rats. Jpn J Cancer Res 1999;90:922–927.

(45) Kato N, Funahashi H, Ando K, Takagi H. Suppressive effect of iodine preparations on proliferation of DMBA-induced breast cancer in rat. J Jpn Soc Cancer Ther 1994;29:582–588.

(46) Funahashi H, Imai T, Tanaka Y, Tobinaga J, Wada M, Morita T, et al. Suppressive effect of iodine on DMBA-induced breast tumor growth in the rat. J Surg Oncol 1996;61:209–213.

(47) Brown-Grant K, Rogers AW. The sites of iodide concentration in the oviduct and the uterous of the rat. J Endocrinol 1972;53:355–362.

(48) Mutaku JF, Poma JF, Many MC, Denef JF, van Den Hove MF. Cell necrosis and apoptosis are differentially regulated during goiter development and iodine-induced involution. J Endocrinol 2002;172:375–386.

(49) Pisarev M, Gärtner R. Autoregulatory actions of iodine. In: Braverman E, Utiger R, editors. Werner and Ingbar's The Thyroid. A fundamental and clinical text. Philadelphia: Lippncott-Williams & Williams, 2000; p. 85–90.

(50) Vitale M, Di Matola T, D'Ascoli F, Salzano S, Bogazzi F, Fenzi G, et al. Iodide excess induces apoptosis in thyroid cells through a p53-independent mechanism involving oxidative stress. Endocrinology 2000;141:598–605.

(51) Boeynaems JM, Hubbard WC. Transformation of arachidonic acid into an iodolactone by the rat thyroid. J Biol Chem 1980;255:9001–9004.

(52) Dugrillon A, Bechtner G, Uedelhoven WM, Weber PC, Gartner R. Evidence that an iodolactone mediates the inhibitory effect of iodide on thyroid cell proliferation but not on adenosine 3′-5′-monophosphate formation. Endocrinology 1990;127:337–343.

(53) Langer R, Buzler C, Bechtner G, Gartner R. Influence of iodide and iodolactones on thyroid apoptosis. Exp Clin Endocrinol Diab 2003;111:325–329.

(54) Arroyo-Helguera O, Aceves C. Mecanismos de captura y actividad antiproliferativa del yodo molecular (I_2) en la línea celular de cáncer MCF-7. In: XXIV Congreso Nacional de la Sociedad Mexicana de Bioquímica, Zihuatanejo, Gro. México; 2004. pp. 345.

(55) Kliewer SA, Forman BM, Blumberg B, Ong ES, Borgmeyer U, Mangelsdorf DJ, Umesono K, Evans RM. Differential expression and activation of a family of murine peroxisome proliferator-activated receptors. Proc Natl Acad Sci USA 1994;91:7355–7359.

(56) Shen Q, Brown PH. Novel agents for the prevention of breast cancer: Targeting transcription factors and signal transduction pathways. J Mammary Gland Biol Neoplasia 2003;8:45–73.

(57) Kliewer SA, Sundseth SS, Jones SA, Brown PJ, Wisley GB, Koble CS, Devchand P, Wahli W, Wilson TM, Lenhard JM, Lehmann JM. Fatty acids and eicosanoids regulate gene expression through direct interaction with peroxisome proliferator-activated receptors α and γ. Proc Nat Acad Sci USA 1997;94:4318–4323.