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Mastopathy, breast cancer and iodolactone

Review

Summary

An enlargement of the thyroid gland is often found in patients with breast cancer and fibrocystic disease. Experimental analysis in animals shows that iodine deficiency causes proliferations and dysplasia in the mammary gland similar to human fibrocystic disease. Elemental iodine supplementation can stop and partially lead to an involution of the mammary proliferations and dysplasia. Probably iodolactones are involved in the process of involution, similar to thyroid gland. The basis for iodolactone production in the mammary gland is given. Like the thyroid gland, the mammary gland can concentrate iodide by expressing the sodium / iodide symporter, the cell membrane transport protein. The sodium / iodide symporter is not only expressed during lactation but also in fibrocystic disease and in the majority of breast cancers. Iodolactones are synthesized with the mammary enzyme lactoperoxidase, an enzyme that is used for the pharmacological synthesis of iodolactones. Iodolactones can inhibit the EGF-receptor, thereby playing an important role in the pathophysiology of breast cancer and fibrocystic disease. Using the sodium / iodide symporter there are new options for the therapy of metastatic breast cancer.

Full text article: https://www.thieme-connect.de/ejournals/html/10.1055/s-2004-834453

Beitrag in Volltext: https://www.thieme-connect.de/ejournals/html/10.1055/s-2004-820575

Proliferative mastopathy and breast cancer are frequently associated with an enlarged thyroid gland. It was possible to confirm in animal experiments that iodine deficiency can induce breast proliferations with dysplasia which are comparable to grade III mastopathy. To a certain degree the replacement of elemental iodine can stop breast dysplasia and proliferations and cause them to regress. As in the thyroid gland, the formation of iodolactones appears to play a role in the involution of tissue altered by mastopathy. The necessary conditions for iodolactone formation are found in the breast.

Like the thyroid gland, the breast can express the sodium / iodide symporter (NIS) – the iodine transport protein located on the cell membrane – and actively take up iodine. The NIS is not only expressed during lactation, but also in proliferative mastopathy and in the majority of breast cancers. The synthesis of iodolactones occurs enzymatically via lactoperoxidase, a breast enzyme which is used in the production of iodolactones. Iodolactones specifically inhibit the EGF receptor (epidermal growth factor) which plays an important role in the pathophysiology of proliferative mastopathy and breast cancer. By using the NIS, new treatment options become available for metastatic breast cancer.

Epidemiology of Breast Cancer

The worldwide incidence of breast cancer varies by up to a factor of 5. While it is the most frequent female cancer in Europe and the USA, Asian countries like Japan have a notably low rate of breast cancer. In Germany it is the most frequent cancer and the most frequent cancer-related cause of death in women [33].

The etiology of breast cancer still remains unexplained. From migration studies it is known that Japanese emigrants realize an increase of about 80% in their incidence of breast cancer after having resided in the USA for 10 years. The daughters born in the USA to Asian immigrants basically grow up with the risk of breast cancer prevalent in the USA. A Scandinavian study performed on 44788 monozygotic and dizygotic twins determined that genetic causes only play a subordinate role in breast cancer. The majority of cancers which occurred in this study were most likely attributable to exogenic factors such as the environment, lifestyle, and nutrition. Even a genetic predisposition such as a germ-line mutation on genes BRCA 1 (chromosome 17q) and BRCA 2 (chromosome 13q) is not associated with an increased incidence of breast cancer and resulting mortality [27, 28].

In short: **Mainly exogenic factors are involved in the etiology of breast cancer.**

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submitted: 23.06.2003 accepted: 7.11.2003
Bibliography
DOI: 10.1055/s-2004-834453

Risk Factors for Breast Cancer

Depending on the menopausal status, there are only a few confirmed risk factors for breast cancer. The following factors are controversial: early menarche and late menopause, low parity, late first pregnancy, nursing habits, hypercaloric fatty diet, regular consumption of alcohol, and tobacco abuse, as well as declining participation in athletic activities. While late menopause is confirmed as a risk factor in epidemiological studies, the findings associated with the other risk factors are contradictory. Proliferative mastopathy with atypical cells (grade III) is associated with a 4 to 5 fold increased risk of developing cancer [31].

In short: **Grade III mastopathy is associated with 4 to 5 fold increased risk of developing breast cancer.**

Breast Cancer and Nutrition

The incidence of breast cancer is inversely correlated with the quantity of fish and fish oil consumed, so that epidemiologically, a high consumption of fish and fish oil exerts a strong protective effect. The fat from fish and fish oil contains a high proportion of polyunsaturated omega-3 fatty acids. These fatty acids are important building blocks of the cell membrane [23].

On a worldwide basis, Japan has the highest per capita consumption of saltwater fish and up to 25% of daily Japanese nutrition consists of economical marine algae. This traditional source of nutrition, common in that country, appears to be associated with a low incidence of breast cancer. With decreasing consumption of saltwater fish and fish oil, the incidence of breast cancer in Japan is also increasing [22].

In short: **Epidemiologically, a high consumption of fish, fish oil, and marine algae correlates with a low incidence of breast cancer.**

A daily diet rich in fish and marine algae has significant quantities of polyunsaturated fatty acids and iodine. Based on the excretion of iodine in the urine, iodine consumption in Japan was determined to be up to 20 mg/day. This quantity exceeds the recommended iodine consumption in western countries by a factor of 1,000.

Marine algae exhibits an antineoplastic effect both in vitro and in vivo. In animal experiments it was possible to achieve a strong tumor-suppressive effect with a suspension of marine algae in receptor-positive DMBA (7,12- dimethylbenz(a)anthracene)-induced breast cancer. The tumor growth in the experimental animals was proportionally correlated to the concentration of marine algae suspension in the animal feed. The serum thyroxine values in the experimental animals were unchanged while the serum iodine concentration was clearly elevated. A marine algae suspension was able to increase the rate of apoptosis in a cell culture of breast cancer cells. Compared to the cytostatic agent, 5-fluorouracil, the marine algae suspension exhibited a stronger antineoplastic effect. Healthy breast tissue was not affected. The breast cancer cells which were most strongly suppressed had the highest concentration of intracellular iodine [14, 16].

In short: **Marine algae exhibits an antineoplastic effect both in vitro and in vivo.**

Breast Cancer and Goiter

In many epidemiological studies from the 1980s, it was determined that in regions of the USA with endemic goiter and pronounced iodine deficiency the incidence of breast cancer was elevated [1].

Female breast cancer patients overproportionally exhibit morphological changes of the thyroid gland and abnormal thyroid parameters. A study of 207 female patients with breast cancer revealed that 85% of them had a histologically confirmed lesion of the thyroid gland. Of these 59% exhibited thyroid gland atrophy. This older study from the 1960s is consistent with more recent findings from which it follows that an overproportional number of individuals suffering from breast cancer are simultaneously affected with autoimmune thyroiditis, which is the most frequent cause of an atrophic thyroid gland. In Japan autoimmune thyroiditis is associated with a 4-fold increased risk of developing breast cancer [20]. The latest studies show that women with breast cancer much more frequently suffer from a sonographically enlarged thyroid gland. Already in existing cases of proliferative mastopathy significantly more frequent enlargements of the thyroid gland are found [36].

In short: **Proliferative mastopathy and breast cancer are significantly more frequently associated with a sonographically enlarged thyroid gland.**

In female breast cancer patients the thyroid parameters TSH and fT4 show significantly more frequent changes which are typically found in iodine deficiency. As was shown in a Hawaiian study, a negative correlation exists between the level of serum fT4, an iodine-dependent thyroid parameter, and the risk of developing breast cancer [1, 20, 36].

Taken together these epidemiological and clinical findings indicate that iodine deficiency may be a possible pathophysiological basis of breast cancer. Epidemiologically, the incidence of breast cancer correlates with the alimentary intake of iodine. Countries in which high quantities of iodine are consumed have an incidence of breast cancer which is 5 times lower than that of countries with a low consumption of iodine. It has been possible to confirm in animal experiments that an adequate quantity of iodine must be consumed for proper breast development to occur. Breast dysplasia which develops in the breasts of experimental animals who are not given an adequate supply of iodine is characteristic and comparable to grade III mastopathy in humans. It has been possible to confirm that the histological changes are caused by an iodine deficiency and are not the consequence of a concomitant case of hypothyroidism. Providing an optimal iodine supply can reverse such breast dysplasia. Elemental iodine has proven to be the best for this in animal experiments. Even DMBA-induced, receptor-positive breast cancer can be suppressed with iodine in an animal experiment. The breast cancer cells which are most strongly suppressed have the highest intracellular iodine concentration [2, 11–13, 15, 39].

In short: **Iodine deficiency appears to play a role in the pathophysiology of breast cancer.**

In the literature on the pathophysiology of breast cancer, stages of life with relative estrogen dominance and corpus luteum insufficiency play an important role. Endocrinologically, estrogens cause an iodine deficiency if supplementation is inadequate due to elevated TBG (thyroxine-binding globulin) and the turnover of T4. Even autoimmune thyroiditis, which in Japan is associated with a 4-fold increased risk of developing breast cancer, can cause an iodine deficiency, because some of the female patients have blocking autoimmune antibodies against the sodium / iodide symporter.

Iodine Storage in the Breast

It has been observed a number of times in whole-body scintigrams that iodine is taken up in both the lactating and the non-lactating breast. The histological examination of iodine-storing breast tissue outside of pregnancy revealed that it is proliferating tissue which has been changed by mastopathy. The more extensive the mastopathic changes of the breast tissue, the more iodine it is able to take up [10, 21].

Elemental iodine was administered in a clinical study in cases of mastopathy with concomitant symptoms which had been confirmed by mammography, and the information obtained was collected over a period of 14 years. A clinical improvement of the symptoms was observed in 70% of the cases. Up to 98% of the patients subjectively reported being asymptomatic for some time, whereby 72% of the cases exhibited an objective improvement. During therapy, 65% of the female patients noticed a reduction in breast size. In 6% of the cases no improvement of the symptoms was seen. In these patients histology confirmed an advanced fibrotic transformation of the breast. The examination was repeated as a prospective, double-blind study. The results were confirmed. After six months of oral substitution with elemental iodine at a dose of 0.07–0.09 mg / kg body weight / day, 65% of the patients experienced an improvement ($p < 0.001$). Side effects associated with the thyroid gland did not occur [19].

In short: **Elemental iodine can be used in the treatment of proliferative mastopathy.**

Iodine Deficiency and Goiter

To better understand the proliferative processes in the breast which are induced by iodine deficiency, it is necessary to understand the pathophysiology of endemic goiter.

In iodine deficiency the thyrocytes produce growth factors which are secreted into the surroundings. These growth factors stimulate the thyrocytes in an autocrine manner and the surrounding connective tissue in a paracrine manner. The most important intrathyroidal growth factors are IGF-1 (insulin-like growth factor I), EGF (epidermal growth factor), bFGF (basic fibroblast growth factor) and TGF-β (transforming growth factor). These growth factors are not specific to the thyroid gland, but are identical with the growth factors which are formed in other epithelial organs [18].

Growth Factors

In the pathophysiology of breast cancer and proliferative mastopathy these growth factors also play an important role. Perimenopausal women with a high IGF-1 serum level and a low IGF-1 binding protein have an increased risk of developing breast cancer. Iodine can inhibit the production of IGF-1 in a dose-dependent manner [5, 18].

The risk is clinically increased with the concentration of EGF in the breast cyst fluid. The EGF receptor concentration of breast cancer is inversely related to the degree of differentiation. The higher the receptor concentration, the less differentiated is the cancer. In animal experiments and in the MCF-10A breast cancer cell line, the activation of the protooncogenes c-Ha-ras and c-erbB2 can increase the concentration of EGF and TGF-α several fold. A high concentration of TGF-α is found in DMBA-induced receptor-positive breast cancer [3, 32].

EGF and TGF-α consist of a single polypeptide chain. They are structurally similar and bind to the same receptor. Physiologically, they are mainly active in the regeneration of damaged epithelial cells such as in subacute thyroiditis and gastric ulcers. In combination with estrogens they induce the proliferation of the uterine smooth muscle cells during pregnancy [24].

EGF and TGF-α are extremely potent growth factors of the breast. Their physiological significance for the breast consists of promoting development and differentiation. The formation of the ductal lobular unit depends on their action, whereby EGF preferentially participates in the development of the ductal structures while TGF-α promotes lobular differentiation. If breast epithelial cells are stimulated in vitro with EGF and TGF-α, the mitosis rate in the cell culture increases very significantly. To stimulate DNA synthesis EGF requires additional growth factors such as insulin or IGF-1. TSH, which is elevated in iodine deficiency, increases the binding of EGF to its receptor [24, 32, 37].

EGF stimulates TGF-α formation in the breast, possibly because its effect depends on TGF-α. An overexpression of TGF-α can cause breast hyperplasia and adenocarcinomas in animal experiments. EGF and TGF-α have a dedifferentiative effect on the fully developed breast [37].

In short: **EGF and TGF-α participate in physiological growth and differentiation processes of the breast. On the fully developed breast they have a dedifferentiative effect.**

The EGF or TGF-α cell membrane receptor is a transmembranous glycoprotein. It consists of a binding-specific extracellular component, a short transmembranous component and an intracellular cytoplasmatic component which activates tyrosine kinase. Four different EGF receptors are distinguished. The prototype of the EGF receptor is HER 1 (Human epidermal growth factor receptor). In addition there are HER 2 which, because of its

homology with the oncogenes neu or c-erb-B2, is also called neu/erbB2, and HER 3 and HER 4, which are also designated erbB3 and erbB4. Approximately 30% of breast cancers express HER 1 and approximately 70% of breast cancers express HER 1 and HER 2. The loss of estrogen sensitivity of the tumor and a worsening of the prognosis is associated with this.

Arachidonic Acid Metabolism

The activation of the EGF receptor and, thereby, of tyrosine kinase leads to signal transduction of inositol-3-phosphate via activated phospholipase C, and to activation of protein kinase C. This process initiates cell proliferation and dedifferentiation. The phospholipases activated by the EGF receptor promote the hydrolysis of arachidonic acid and other polyunsaturated fatty acids from the cell membrane phospholipids. (**Figure 1**) The intracellular equilibrium between the free and cell membrane-bound portion of arachidonic acid is displaced towards the free portion. Both arachidonic acid itself and the metabolites of the enzymes cyclooxygenase and lipoxygenase, such as PGE2 and 12-HETE (12-hydroxyeicosatetraenoic acid) exert a dedifferentiative effect on breast tissue. Furthermore, they promote metastasis. PGE2, as a product of cyclooxygenase, stimulates the gene expression of aromatase in the fatty tissue of the breast, whereby intramammary estrogen production increases. In addition it promotes the formation of cAMP. An increased expression of the isoenzyme cyclooxygenase 2 is clinically associated with a poor prognosis [4].

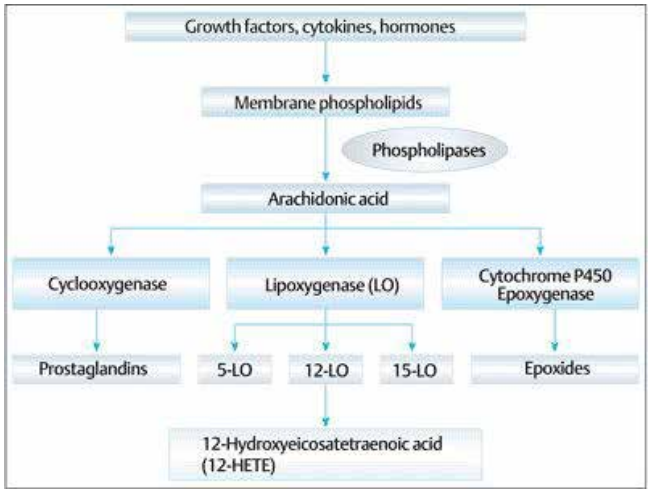

Fig. **1** Arachidonic acid metabolism [30].

The metabolites of lipoxygenase stimulate protein kinase C and the oncogenes c-fos and ras, in addition to other substances. Additionally, they possess a mitogenic and chemotactic effect. Both PGE2 and 12-HETE have been detected at high concentrations in strongly metastasizing breast cancer [29, 30].

In a cell culture with breast epithelial cells it is possible to achieve a dose-dependent increase of lipoxygenase-dependent metabolites by addition of EGF. These metabolites promote hematogenous metastasis and inhibit apoptosis.

Likewise, it is possible to produce mitosis-promoting substances from linoleic acid and its metabolites which are also hydrolyzed from the cell membrane through the enzymatic action of lipoxygenase. The metabolites of linoleic acid potentiate the effect of EGF. In contrast to normal breast cells the intracellular content of lipoxygenase in breast cancer cells is elevated and the activity is increased [29, 30].

In short: **The metabolites of arachidonic acid metabolism exert an effect which results in the dedifferentiation of breast epithelial cells. They promote the metastasis of breast cancer.**

Iodolactone Formation

The antiproliferative effect of iodine was first confirmed in goiter. In the thyroid gland not only tyrosyl residues of thyroglobulin are iodinated, but also polyunsaturated fatty acids which originate from the cell membrane. The synthesized iodolipids, also called iodolactones, consist of polyunsaturated fatty acids such as arachidonic acid, eicosapentaenoic acid and docosahexaenoic acid which exhibit saturation characteristics upon iodination. The delta-iodolactone of arachidonic acid specifically inhibits the EGF receptor, whereby the metabolism of arachidonic acid induced by EGF and TGF-α is inhibited. This in turn suppresses goiter formation. In the case of an already existing goiter delta-iodolactone can induce involution. Neither arachidonic acid by itself nor other iodolactones have this antiproliferative effect. The delta-iodolactone of eicosapentaenoic acid already exerts an antiproliferative effect in the nanomolar range [6–9, 17, 18, 33, 34].

The synthesis of delta-iodolactone from arachidonic acid, iodine, and H2O2 is catalyzed with the assistance of peroxidases. Thereby, iodolactone formation is not limited only to the thyroid gland, but can be completed in all organs which contain peroxidases. In the breast, lactoperoxidase can catalyze the formation of iodolactone. This enzyme is used in the laboratory to produce iodolactone [41].

In short: **Iodolactones specifically inhibit the EGF receptor.**

Thyroidal and Extrathyroidal Sodium/Iodide Symporter

A notable uptake of iodine into the cell requires the membrane-bound transport protein, the sodium/iodide symporter (NIS). Since its cloning, NIS has been detected in many organs, including the breast. The hormonal regulation of the NIS varies. In the thyroid gland the NIS is synthesized by cAMP-dependent TSH stimulation. In the breast the synthesis of the NIS is subject to prolactin and oxytocin in a dosedependent manner. The NIS can concentrate iodine up to a concentration gradient of 25 : 1 within the cell. For this reason, the iodine concentration in breast milk is approximately 50 times higher than in the serum [26].

By means of the NIS, the breast – like the thyroid gland – is able to take up iodine to organify it via lactoperoxidase and insert it

into the tyrosyl residues of casein. This also appears to be the reason why after pregnancy and lactation (i.e., in a time period with increased uptake of iodine and organification) the symptoms of a mastopathic breast improve. The extrathyroidal peroxidases namely, lactoperoxidase, myeloperoxidase and eosinophilic peroxidase also play a role in the organification of other organs with a presumably similar antiproliferative function [41].

The uptake of iodine in the breast via the NIS is independent of lactation. Active iodine storage has been confirmed in mastitis, proliferative mastopathy, and in breast cancer. For instance, iodine storage is characteristic of receptor-positive breast cancer cells. In a smaller study it was possible to confirm the presence of the NIS both on the cell membrane and within the cell in 87% of the invasive breast cancers and in 83% of the ductal cancers in situ. Histologically normal breast tissue from reduction plasties does not contain the NIS [40].

The NIS can be used for diagnostic and therapeutic purposes. In the diagnosis of thyroid gland cancers the NIS can be used to detect both postoperative tumor remnants and distant metastases. Radioiodine therapy also uses the NIS as a radioiodide transporter [38].

In short: **By means of the NIS, the breast is able to take up and concentrate iodine.**

Induction of the NIS in Cancer Tissue

The formation of the NIS can be medicinally induced with retinoids, vitamin A derivatives. 13-cis-retinoic acid is used to induce the NIS in differentiated thyroid gland cancer. In receptor-positive breast cancer all-trans-retinoic acid is used for NIS induction [25, 35].

In short: **Retinoids are used to induce the NIS.**

Conclusion

A source of nutrition which emphasizes seafood and, thereby, provides a source of polyunsaturated fatty acids and iodine is a dietary basis for iodolactone formation. This could be the reason for the low incidence of breast cancer in Japan. Iodolactones can be synthesized in the laboratory. Their therapeutic use in goiter has been tested successfully. A possible application in proliferative mastopathy and breast cancer is conceivable based on the associated pathophysiology.

Conflicts of Interest: None declared

References

1 *Adamopoulos D, Vassilaros S, Kapolla N, Papadiamatis J, Georgiakodis F, Michalakis A.* Thyroid disease in patients with benign and malignant mastopathy. Cancer. 1986; 57 125–128
2 *Aquino T I, Eskin B A.* Rat breast structure in altered iodine metabolism. Arch Path. 1972; 94 280–285
3 *Boccardo F, Marenghi C, Ghione G, Pepe A, Rubagotti A.* Intracystic epidermal growth factor level is predictive of breast cancer risk in women with gross cystic disease of the breast. Int J Cancer. 2001; 95 260–265
4 *Denkert C, Winzer K J, Müller B M.* et al . Elevated Expression of Cyclooxygenase-2 Is a Negative Prognostic Factor for Disease Free Survival and Overall Survival in Patients with Breast Carcinoma. Cancer. 2003; 97 2978–2987
5 *Druckmann R, Rohr U D.* IGF-1 in gynaecology and obstetrics: update 2002. Maturitas. 2002; 41 (Suppl 1) 65–83
6 *Dugrillon A, Bechtner G, Uedelhoven W M, Weber P C, 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
7 *Dugrillon A, Gärtner R.* δ-Iodolactones decrease epidermal growth factor-induced proliferation and inositol-1, 4, 5-trisphosphate generation in porcine thyroid follicles – a possible mechanism of growth inhibition by iodide. Eur J Endocrinol. 1995; 132 735–743
8 *Dugrillon A, Gärtner R.* The role of Iodine and Thyroid Cell Growth. Thyroidology. 1992; 4 31–36
9 *Dugrillon A, Uedelhoven W M, Pisarev M A, Bechtner G, Gartner R.* Identification of delta-iodolactone in iodide treated human goiter and its inhibitory effect on proliferation of human thyroid follicles. Horm Metab Res. 1994; 26 465–469
10 *Eskin B A, Parker F J, Bassett J G, George D L.* Human breast uptake of radioactive iodine. Obstet Gynecol. 1974; 44 398–402
11 *Eskin B A, Grotkowski C E, Connolly C P, Ghent W R.* Different tissue responses for iodine and iodide in rat thyroid and mammary glands. Biol Trace Elem Res. 1995; 49 9–19
12 *Eskin B A, Shuman R, Krouse T, Merion J.* Rat mammary gland atypia produced by iodine blockade with perchlorate. Cancer Research. 1975; 35 2332–2339
13 *Eskin B A.* Iodine metabolism and breast cancer. Trans Ny Acad Sci. 1970; 32 911–947
14 *Funahashi H, Imai T, Mase T.* et al . Seaweed prevents Breast cancer?. Jpn J Cancer Res. 2001; 92 483–487
15 *Funahashi H, Imai T, Tanaka Y.* et al . Suppressive effect of iodine on DMBA-induced breast tumor growth in the rat. J Surgil Oncol. 1996; 61 209–213
16 *Funahashi H, Imai T, Tanaka Y.* et al . Wakeame seaweed supresses the proliferation of 7, 12-Dimethylbenz(a)-anthracene-induced mammary tumors in rats. Jpn J Cancer Res. 1999; 90 922–927
17 *Gärtner R, Dugrillon A, Bechtner G.* Evidence that iodolactones are the mediators of growth inhibition by iodine on the thyroid. Acta Med Austriaca. 1996; 23 47–51
18 *Gärtner R, Dugrillon A.* Vom Jodmangel zur Struma. Internist. 1998; 39 566–573
19 *Ghent W R, Eskin B A, Low D A, Hill L P.* Iodine replacement in fibrocystic disease of the breast. Can J Surg. 1993; 36 453–460
20 *Giani C, Fierabracci P, Bonacci R.* et al . Relationship between breast cancer and thyroid disease: Relevance of autoimmune thyroid disorders in breast malignancy. Clin Endocrinol Metab. 1996; 81 990–994
21 *Hammami M M, Bakheet S.* Radioiodine breast uptake in non-breast-feeding women: clinical and scintigraphic characteristics. J Nucl Med. 1996; 37 26–31
22 *Hill P, Wynder E L.* Comparision of mammary adipose fatty acid composition in Japanese and American breast cancer patients. Eur J Cancer Clin Oncol. 1987; 23 407–410
23 *Kaizer L, Boyd N F, Kriukov V, Tritchler D.* Fish consumption and breast cancer: An ecological study. Nutr Cancer. 1989; 12 61–68
24 *Klijn J GM, Berns P MJJ, Schmitz P IM, Foekens J A.* The clinical significance of epidermal growth factor receptor (EGF-R) in human breast cancer: A Review on 5232 patients. Endocr Rev. 1992; 13 3–17
25 *Kogai T, Schultz J J, Johnson L S, Huang M, Brent G A.* Retinoic acid induces sodium-iodide symporter gene expression and radioiodide uptake in the MCF-7 breast cancer cell line. Proc Natl Acad Sci USA. 2000; 97 8519–8524
26 *Köhrle J.* Der Natrium-Iodid-Symporter NIS: Funktion, Regulation und klinische Relevanz. Z Ärztl Fortbild Qual Sich. 1999; 93 (Suppl 1) 17–22

27 *Koifam S, Koifam R J.* Breast cancer among Ashkenazi Jewish women in Sao Paulo and Porto Alegre, Brazil. Breast Cancer Res. 2001; 3 270–275
28 *Lichtenstein P, Holm V N, Verkasalo P K.* et al . Enviromental and heritable factors in the Causation of cancer. N Engl J Med. 2000; 343 78–85
29 *Natarajan R, Esworthy R, Bai W, Gu J L, Wilczynski S, Nadler J.* Increased 12-lipoxygenase expression in breast cancer tissues and cells: Regulation by epidermal growth factor. J Clin Endocrinol Metab. 1997; 82 1790–1798
30 *Natarjan R, Nadler J.* Role of lipoxygenases in breast cancer. Front Biosci. 1998; 3 E81–88
31 *Nienhaus A, Hensel N, Roscher G.* et al . Hormonelle, medizinische und lebensstilbedingte Faktoren und Brustkrebs. Geburtsh Frauenheilk. 2002; 62 242–249
32 *Normanno N, Ciardiello F.* EGF-related peptides in the pathophysiology of the mammary gland. J Mammary Gland Biol Neoplasia. 1997; 2 143–151
33 *Pisani P, Parkin D M, Ferley J.* Estimates of the worldwide mortality from eighteen major cancers in 1985. Implications for prevention and projections of future burden. Int J Cancer. 1993; 55 891–903
34 *Pisarev M A, Krawiec L, Juvenal G J.* et al . Studies on the goiter inhibiting action of iodolactones. Eur J Pharmacol. 1994; 158 33–37
35 *Simon D, Koehrle J, Reiners C h.* et al . Redifferentiation therapy with retinoids: Therapeutic option for advanced follicular and papillary thyroid carcinoma. World J Surg. 1998; 22 569–574
36 *Smyth P PA, Smith D F, McDermott E WM, Murray M J, Geraghty J G, O'Higgins N J.* A direct relationship between thyroid enlargement and breast cancer. J Clin Endocrinol Metab. 1996; 81 937–941
37 *Spitzer E, Zschiesche W, Binas B, Grosse R, Erdmann B.* EGF and TGF alpha modulate structural and functional differentiation of the mammary gland from pregnant mice in vitro: Possible role of the arachidonic acid pathway. J Cell Biochem. 1995; 57 495–508
38 *Spitzweg C, Harrington K J, Pinke L A, Vile R G, Morris J C.* The sodium iodide symporter and its potential role in cancer therapy. J Clin Endocrinol Metab. 2001; 86 3327–3335
39 *Strum J M.* Effect of iodine-deficiency on rat mammary gland. Virchows Arch B Cell Pathol Incl Mol Pathol. 1979; 30 209–220
40 *Tazebay U H, Wapnir I L, Levy O.* et al . The mammary gland iodide transporter is expressed during lactation and in breast cancer. Nat Med. 2000; 6 871–878
41 *Turk J, Henderson W R, Klebanoff S J, Hubbard W C.* Iodination of arachidonic acid mediated by eosinophil peroxidase, myeloperoxidase and lactoperoxidase. Biochim Biophys Acta. 1983; 751 189–200