Cancer Causes and Control **11**: 121–127, 2000.

Hypothesis: Iodine, selenium and the development of breast cancer

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Received 12 October 1998; accepted in revised form 28 August 1999

Key words: breast neoplasms, iodine, selenium, thyroid diseases.

Abstract

Background: In this paper we examine some of the evidence linking iodine and selenium to breast cancer development. Seaweed is a popular dietary component in Japan and a rich source of both of these essential elements. We hypothesize that this dietary preference may be associated with the low incidence of benign and malignant breast disease in Japanese women. In animal and human studies, iodine administration has been shown to cause regression of both iodine-deficient goiter and benign pathological breast tissue. Iodine, in addition to its incorporation into thyroid hormones, is organified into anti-proliferative iodolipids in the thyroid; such compounds may also play a role in the proliferative control of extrathyroidal tissues. Selenium acts synergistically with iodine. All three mono-deiodinase enzymes are selenium-dependent and are involved in thyroid hormone regulation. In this way selenium status may affect both thyroid hormone homeostasis and iodine availability.
Conclusion: Although there is suggestive evidence for a preventive role for iodine and selenium in breast cancer, rigorous retrospective and prospective studies are needed to confirm this hypothesis.

Introduction

During this century, medical science has made considerable advances in the management of breast cancer, including the fields of cancer biology, detection and treatment. With such an increase in the understanding of the disease one would expect to see a dramatic reduction in mortality. The fact that this has not been observed [1] should alert us that some aspect(s) in the understanding of this disease may have been overlooked. In 1956, Loeser [2] suggested that ''cancer formation starts and goes on when a carcinogenic substance hits continuously thyroid-deficient tissues''. Since then, various authors [3–5] have questioned whether *iodine* intake could have a significant influence on the development of malignant disease, particularly breast cancer.

Iodine and selenium intake in the UK, USA and Japan

In countries with a moderate iodine intake, such as the UK and the USA, the average intake level in adults (estimated from total diet studies) is approximately 166 [6] and 209 [7] μg/day, respectively. Measurement of the urinary iodine concentration (UIC) is an alternative method of estimating daily iodine intake. Japan has a comparatively high iodine intake with an average UIC of 3400 μg/L (approximately 5280 μg/day) as determined in a recent study of 4138 men and women in Sapporo, Japan [8]. Seaweed consumption is a key source of iodine in Japan and is widely used in sushi, soups, salads, and in powdered form, as a condiment. *Porphyra* (nori), *Undaria* (wakame), and *Laminaria* (kombu) are some of the most popular varieties, with an iodine content that may range from 80 to 2500 μg/g [9]. Other seafoods are, to a lesser degree, another important source of iodine in Japan. Selenium intake is similar in the USA and Japan (approximately 100–150 μg/day) [7, 10], but much higher than in the UK (less than 100 μg/day) [10, 11]. Important selenium sources include seafood, meat and meat products, whole grains and cereals [7, 10].

Iodine and benign breast disease

High-grade fibrocystic disease (*i.e.*, ductal or lobular hyperplasia, but especially atypical hyperplasia) is generally believed to be a precursor to ductal carcinoma *in situ* (DCIS) and subsequent invasive/metastatic carcinoma. Other symptoms of benign breast disease, including cyclical mastalgia [12] and apocrine cysts [13], have also been associated with an increased breast cancer risk. In the USA it has been estimated that 50–90% of women experience fibrocystic disease during their lifetime [14, 15]; a rate so high that some have suggested that this condition should no longer be classified as a disease [14, 15]. However, downgrading the disease status simply due to prevalence estimations is questionable when this condition, in populations at low risk for breast cancer, is so much less common [16]. Gravelle *et al.* [17] found that healthy British women had significantly less low-risk (low-density) and a greater proportion of high-risk (high-density) breast parenchymal patterns than Japanese women. Furthermore, immigration studies suggest that these breast parenchymal patterns may be influenced by nongenetic factors. For example, Sasamo *et al.* [18] found that the prevalence of breast epithelial hyperplasia was similar between Japanese women (18.4%) and Japanese issei Hawaiians (immigrant generation) (14.5%), but significantly lower than nisei Hawaiians (second generation) (51.4%).

In estradiol-treated rats, iodine deficiency has been shown to lead to pathological changes similar to those seen in benign breast disease – cystic changes, periductal fibrosis and lobular hyperplasia [19, 20]. Conversely, dietary iodine reintroduction has been shown to reverse these pathological changes [20]. Thus, iodine deficiency appears to enhance mammary-tissue sensitivity to estrogen. In humans, several studies have shown that iodine-containing desiccated thyroid [21] or thyroxine (T4) [22, 23] were effective in reducing mastalgia as well as other symptoms of benign breast disease [21, 22]. Iodine supplementation has also been examined in women with this disease. One of the first studies, by Vishnyakova and Muravieva [24], reported a beneficial effect in 71.7% of patients. More recently a large clinical trial was conducted which found that iodine supplementation significantly reduced the prevalence of breast cysts, fibrous tissue plaques and breast pain [25] – thus demonstrating that this precursor disease may be treatable through dietary modifications. Further clinical studies are now being conducted to confirm these observations.

Iodine and breast cancer

In the developed world, Japan has one of the lowest age-adjusted breast cancer mortality rates, 6.6 per 100,000 [26]. In the UK and the US, by comparison, these rates are 27.7 and 22.0, respectively [26]. Unfortunately, the breast cancer mortality rate in Japan has been increasing and it has been suggested that "westernization" of the diet may be responsible for this trend [27]. Evidence for a dietary link is further supported by the rise in breast cancer incidence seen in Japanese immigrants to the US, and their successive generations, whose rates gradually increase to that of white women in the US [28]. We suspect that a high iodine status may be a key protective factor against the development of breast cancer in Japanese women. Epidemiological studies investigating this potential association are lacking. One correlational study in Spain found a significant positive association between regions where iodine intake was low and breast cancer mortality rates [29]; however, more rigorous epidemiological studies are needed.

As with prevention, a role for iodine in the treatment of breast cancer awaits further study. Traditional eastern Asian medicine has long used iodine-rich seaweeds as a cancer treatment to "soften" tumors and "reduce" nodulation [30, 31]. Recent work with animal systems seems to support an antitumor effect for iodine. In dimethylbenz[*a*]anthracene-induced mammary carcinoma in rats, iodine supplementation has been shown to have a suppressive effect on the development of this disease [32]. This suppressive activity was enhanced when iodine treatment was combined with progesterone (medroxy-progesterone acetate) [33]. The suppressed tumors were found to have a significantly higher mean iodine content than nonsuppressed tumors, with uptake apparently enhanced by progesterone [33]. The enhancement of iodine uptake by progesterone has been observed in other hormone-dependent tissues including the uterus and oviduct [34]. We are presently initiating an analogous study in patients with metastatic breast cancer, in which subjects will take iodine supplements in combination with conventional progestin treatment [9].

Reproductive factors and breast cancer risk

During the follicular phase of the menstrual cycle, breast epithelium is largely composed of small lobules and a few terminal duct structures with intralobular stromal condensation; in the luteal phase, however, the ductal epithelium, lobules and terminal duct structures increase in size [35]. It has been shown that resting human breast

tissue can absorb iodine and secrete iodinated proteins from the terminal ductules and intralobular ducts [36]. However, dysplastic and malignant breast tissue has been shown to have an enhanced ability to take up iodine [37]. Similarly, in patients with iodine-deficient goiter, the thyroid shows enhanced iodine uptake, indicating that in both tissues insufficient iodine may be an underlying cause of pathological growth.

During pregnancy and lactation, hormonal stimulation of the mammary gland leads to glandular differentiation with dramatically enhanced iodine absorption and organification [38]. It is interesting to note that this iodine absorption occurs in the same ductal epithelium [19, 20] where the majority of breast cancers arise [39]. The preferential uptake of free iodine in breast tissue may also explain the reduction in nodularity and tissue density that is often observed following pregnancy and lactation [40]. Thus, a link may exist between enhanced breast iodine uptake during pregnancy/lactation and the subsequent reduction of breast cancer risk. A number of studies have also shown that early parity and lactation are associated with a reduction in breast cancer risk [41]. It has been suggested that these reproductive periods may be protective against breast cancer because of the lobular differentiation that occurs during these stages [39]. We suggest that increased iodine uptake 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 postmenopausal women [42–44]. In contrast, studies conducted in North America and Europe have generally shown breastfeeding to be protective only in premenopausal women [45, 46], or not at all [47, 48]. The reproductive characteristics more common in these western countries (*i.e.*, later age at first birth, shorter duration of breastfeeding and less frequent daily breastfeeding) [44, 49] and/or a lower level of iodine intake may be responsible for these differences.

Thyroid and breast cancer

Although a number of tissues have iodine-concentrating capabilities (*i.e.*, salivary glands, stomach, cervix, *etc.*), only in the thyroid and breast is iodine organified for storage [50]. In the thyroid this occurs *via* thyroperoxidase oxidation of iodide (I^-), which subsequently binds to tyrosyl residues [51]. In an analogous manner, lactoperoxidase organifies iodine in the breast – a process particularly active during pregnancy and lactation [38, 51]. In subjects with iodine-deficient goiter, iodine administration has been shown to be effective in reducing thyroid size [52]. Similarly, iodine treatment of patients with benign breast disease has been shown to cause a significant bilateral reduction in breast size, in addition to causing a remission of disease symptoms [25]. This evidence suggests that iodine plays an important role in the maintenance of both normal thyroid and breast physiology. A similar mechanism for this observation may be operative in both tissues. For example, in recent years a second pathway for iodine organification has been described, and involves iodine incorporation into lipid molecules. These iodolipids have been isolated from thyroid tissue and have been shown to be key regulators of thyroid cell proliferation and metabolism [53]. Iodide peroxidases (*i.e.*, thyro/lactoperoxidase) catalyze the iodination of lipids [54]. One such compound derived from arachidonic acid, 6-iodo-5-hydroxy-eicosatrienoic acid (δ-iodolactone), was found to be a potent inhibitor of human thyroid follicular cell proliferation *in vitro* [55] and to induce goiter regression in rats *in vivo* [56]. These or similar compounds may also play a role in the proliferative control of breast tissue.

Another possible link has been made by examining the relationship between thyroid dysfunction and breast cancer [57–60] – although controversy exists over this association [61]. In a study in Ireland, Smyth [62] found a significantly greater mean thyroid volume in patients with breast cancer compared to controls. A previous study by Smyth *et al.* [63] showed that as many as 30% of the population had iodine excretion values corresponding to less than half the minimum daily requirement. In addition, combined selenium and iodine deficiency in rats has been shown to cause an increase in thyroid size over that caused by iodine deficiency alone [64] and also may be a factor in these human subjects. Thus, iodine deficiency, in combination with other dietary factors, may be associated with the spectrum of thyroid dysfunction patterns often observed in patients with breast cancer.

Selenium and thyroid hormone homeostasis

Sediment concentrations of selenium throughout the world vary widely and are deficient in many soils [65]. Selenium deficiency in humans has been shown to affect the metabolism of thyroid hormones [66]. This is due to the fact that all three thyroid hormone deiodinases (IDs) are selenoenzymes [67]. ID-I catalyzes the conversion of T4 to the more active triiodothyronine (T3), providing the majority of plasma T3. ID-II is responsible for intracellular T4 to T3 conversion and may supply a significant level of T3 to peripheral tissues [67]. The other selenoenzyme, ID-III, is involved in T3 and T4 inactivation. In each

case, free iodine is released upon conversion of these hormones.

Selenium also plays a crucial role in the maintenance of normal thyroid physiology. For example, *iodine* supplementation alone, in a selenium- and iodine-deficient animal model, was shown to cause irreversible thyroid gland fibrosis [68, 69]. The selenoenzyme glutathione peroxidase was implicated as a necessary component for thyroidal protection during iodine supplementation [67]. In contrast, *selenium* supplementation alone, in human subjects with combined selenium and iodine deficiency, has been shown to cause an aggravation of iodine deficiency and hypothyroidism [70–72]. These studies demonstrate the complex interplay between these two essential elements.

Animal studies have shown selenium to be protective at both the initiation and post-initiation stages of mammary tumor development [73, 74]. With respect to human breast cancer, selenium status has been estimated using a variety of biological samples. Early correlation studies, which estimated regional selenium levels from forage crops [75], dietary intakes and whole blood [76], suggested that a high selenium status may protect against breast cancer. This work has been followed by a number of case–control and prospective cohort studies; a summary of those studies reporting odds ratios (OR) or relative risks (RR) is presented in Table 1. Selenium may afford protection against breast cancer in regions where selenium intake is deficient. Thus, especially in countries where intake of these trace elements may be low, it is important to consider the status of both elements simultaneously when investigating their role in disease.

Future prospects

Life expectancy in the human population is gradually increasing as a result of medical advances, public health programs and dietary changes. As a result of these changes there has been an increase in the prevalence of age-associated diseases such as cancer, autoimmune and other degenerative conditions. As age-associated diseases have a gradual onset and progress slowly over time, a relationship to nutrient deficiency may be obscured. Unfortunately, medical research has focused primarily on treatment strategies, when such diseases may be more responsive to a preventive approach.

Due to the lack of epidemiological research examining a role for iodine in breast cancer, case–control and cohort studies should be considered. The measurement of thyroid hormones may not be the ideal method for determining iodine status as deficient iodine intake may lead to hyper- or hypothyroidism [90, 91], and conversely, excessive iodine intake may also be associated with either hyper- or hypothyroidism [92, 93]. Direct measures of iodine content in foods in dietary studies may be contaminated by iodophor agents that are

Table 1. Selenium status and breast cancer risk

Study location	Cases	Selenium biomarker	Comparison groups highest *vs* lowest	OR or RR (95% CI) highest *vs* lowest[a]	Year (ref.)
Case–control					
Boston, MA	38	Erythrocytes	Tertiles	2.0 (0.8–5.0)	1987 [77]
The Netherlands	92	Erythrocytes	Quartiles	1.1 (0.5–2.5)	1990 [78]
	92	Plasma		0.5 (0.2–1.1)	
	124	Toenails		0.9 (0.5–1.7)	
Denmark	36	Serum	Tertiles	1.0 (0.3–2.9)	1991 [79]
Sweden	441	Plasma	Tertiles	0.4 (0.2–0.9)	1993 [80]
Tianjin, China	244	Whole blood	Quartiles	0.1 (0.0–0.4)	1994 [81]
Europe[b]	326	Toenails	Tertiles	1.0 (0.6–1.5)	1996 [82]
Prospective cohort					
The Netherlands	61	Toenails	Quartiles	1.1 (0.5–2.9)	1987 [83]
Washington state	20	Plasma/serum	Tertiles	3.4 ($P = 0.09$)	1988 [84]
USA	434	Toenails	Quintiles	1.1 (0.7–1.7)	1990 [85]
Finland	90	Serum	Quintiles[c]	0.5 ($P > 0.05$)	1990 [86]
Guernsey, England	46	Plasma	Quartiles	1.3 (0.5–3.4)	1991 [87]
The Netherlands	270	Toenails	Quintiles	0.8 (0.6–1.3)	1994 [88]
Columbia, MO	105	Serum	Quartiles	0.9 (0.4–1.8)	1998 [89]

[a] Odds ratios and relative risks presented are for age-matched subjects or with adjustment for age, and adjustment for other risk factors.
[b] Germany, The Netherlands, Northern Ireland, Spain and Switzerland.
[c] Four higher quintiles *vs* lowest.

poorly absorbed, such as the commonly used food colorants erythrosine and rose bengal [94]; furthermore, studies that estimate iodine intake through dietary questionnaires may not reflect the regional variations of important sources for this element [95]. Urinary iodine levels can be highly variable, reflecting only short-term iodine intake, and particularly in smaller studies would not be a useful measure of iodine status. Whole blood, plasma or serum specimens may be equally useful measures of iodine status; however, whole blood samples (which also account for cellular iodine) may best reflect long-term iodine status, as has been shown for selenium [96]. In case–control studies involving surgery, where blood or urine samples are used as indictors of iodine status, one must be careful of specimen contamination by iodine-containing surgical disinfectants (*i.e.*, povidone-iodine) – samples would ideally be collected in case subjects before such exposure. Prospective cohort studies could avoid this artifact; however, they can be considerably more expensive and would require many years of follow-up. Retrospective cohort or nested case–control studies using blood or urine samples that have been stored over a period of years may be more practical. Although selenium has received considerably more attention as it relates to cancer, studies simultaneously examining iodine and selenium status in patients with breast cancer have not been conducted and would be of considerable interest.

In this paper we have focused on deficient iodine and selenium intake as risk factors for breast cancer; however, these elements have also been implicated in the development of other hormone-dependent diseases, such as ovarian [5, 97], uterine [5, 97, 98] and prostatic carcinoma [99, 100]. In view of the complementary nature of these two nutrients, a re-evaluation of optimal iodine and selenium intake may be required. In-depth studies, examining a combined role for these elements in the prevention and treatment of cancer and other degenerative diseases, would be a step in the right direction.

Acknowledgements

We thank DM Derry and RP Finegan for their valuable comments during the preparation of this manuscript.

References

1. Bailar JC, Gornik HL (1997) Cancer undefeated. *N Engl J Med* **336**: 1569–1571.
2. Loeser AA (1956) Hormones and breast cancer. *Lancet* **ii**: 961–962.
3. Eskin BA (1970) Iodine metabolism and breast cancer. *Trans NY Acad Sci* **32**: 911–947.
4. Mittra I, Hayward JL (1974) Hypothalamic–pituitary–thyroid axis in breast cancer. *Lancet* **ii**: 885–888.
5. Stadel BV (1976) Dietary iodine and risk of breast, endometrial, and ovarian cancer. *Lancet* **i**: 890–891.
6. Lee SM, Lewis J, Buss DH (1994) Iodine in British foods and diets. *Br J Nutr* **72**: 435–446.
7. Pennington JAT, Schoen SA (1996) Total Diet Study: estimated dietary intakes of nutritional elements, 1982–1991. *Int J Vitam Nutr Res* **66**: 350–362.
8. Konno N, Yuri K, Miura K, Kumagai M, Murakami S (1993) Clinical evaluation of the iodide/creatinine ratio of casual urine samples as an index of daily iodide excretion in a population study. *Endocr J* **40**: 163–169.
9. Cann SA, van Netten C, van Netten JP (1998) Implementation of a study combining progestin treatment with iodine and selenium supplements in advanced breast cancer [Abstract # C-57] AACR/JCA Fourth Joint Conference.
10. Hirai K, Noda K, Danbara H (1996) Selenium intake based on representative diets in Japan, 1957 to 1989. *Nutr Res* **16**: 1471–1477.
11. Rayman MP (1997) Dietary selenium: time to act. *Br Med J* **314**: 387–388.
12. Plu-Bureau G, Thalabard JC, Sitruk-Ware R, Asselain B, Mauvais-Jarvis P (1992) Cyclical mastalgia as a marker of breast cancer susceptibility: results of a case–control study among French women. *Br J Cancer* **65**: 945–949.
13. Bruzzi P, Dogliotti L, Naldoni C, *et al*. (1997) Cohort study of association of risk of breast cancer with cyst type in women with gross cystic disease of the breast. *Br Med J* **314**: 925–928.
14. Love SM, Gelman RS, Silen W (1982) Fibrocystic "disease" of the breast – a nondisease? *N Engl J Med* **307**: 1010–1014.
15. Devitt JE (1986) Abandoning fibrocystic disease of the breast: timely end of an era. *Can Med Assoc J* **134**: 217–218.
16. Wang DY, Fentimen IS (1985) Epidemiology and endocrinology of benign breast disease. *Breast Cancer Res Treat* **6**: 5–36.
17. Gravelle IH, Bulbrook RD, Wang DY, *et al*. (1991) A comparison of mammographic parenchymal patterns in premenopausal Japanese and British women. *Breast Cancer Res Treat* **18** (suppl.): 93–95.
18. Sasano N, Tateno H, Stemmermann GN (1978) Volume and hyperplastic lesions of breasts of Japanese women in Hawaii and Japan. *Prev Med* **7**: 196–204.
19. Strum JM (1979) Effect of iodide-deficiency on rat mammary gland. *Virchows Arch [B]* **30**: 209–220.
20. Eskin BA, Grotkowski CE, Connolly CP, Ghent WR (1995) Different tissue responses for iodine and iodide in rat thyroid and mammary glands. *Biol Trace Elem Res* **49**: 9–19.
21. Daro AF, Collin HA, Samos FH (1964) The effect of thyroid on cystic mastitis. *J Int Coll Surg* **41**: 58–59.
22. Estes NC (1981) Mastodynia due to fibrocystic disease of the breast controlled with thyroid hormone. *Am J Surg* **142**: 764–766.
23. Peters F, Pickardt CR, Breckwoldt M (1985) Thyroid hormones in benign breast disease. Normalization of exaggerated prolactin responsiveness to thyrotropin-releasing hormone. *Cancer* **56**: 1082–1085.
24. Vishnyakova VV, Muravieva NI (1966) On the treatment of dyshormonal hyperplasia of mammary glands. *Vestn Akad Med Nauk SSSR* **21**: 19–22.
25. Ghent WR, Eskin BA, Low DA, Hill LP (1993) Iodine replacement in fibrocystic disease of the breast. *Can J Surg* **36**: 453–460.

26. Parker SL, Tong T, Bolden S, Wingo PA (1997) Cancer statistics, 1997. *CA Cancer J Clin* **47**: 5–27.
27. Tominaga S, Kuroishi T (1997) An ecological study on diet/nutrition and cancer in Japan. *Int J Cancer* **10** (suppl.): 2–6.
28. Ziegler RG, Hoover RN, Pike MC, *et al.* (1993) Migration patterns and breast cancer risk in Asian–American women. *J Natl Cancer Inst* **85**: 1819–1827.
29. Serra Majem LL, Tresserras R, Canela J, Salleras L (1988) Dietary iodine deficiency and breast cancer mortality: an ecological study. *Int J Epidemiol* **17**: 686–687.
30. Kun J (1989) *Prevention and Treatment of Cancer in Traditional Chinese Medicine*. Quarry Bay, Hong Kong: Commercial Press, pp. 211–212.
31. Zhang D-Z (1989) *The Treatment of Cancer by Integrated Chinese–Western Medicine*. Boulder, CO: Blue Poppy Press, pp. 21–43.
32. Kato N, Funahashi H, Ando K, Takagi H (1994) Suppressive effect of iodine preparations on proliferation of DMBA-induced breast cancer in rat. *J Jpn Soc Cancer Ther* **29**: 582–588.
33. Funahashi H, Imai T, Tanaka Y, *et al.* (1996) Suppressive effect of iodine on DMBA-induced breast tumour growth in the rat. *J Surg Oncol* **61**: 209–213.
34. Brown-Grant K, Rogers AW (1972) The sites of iodide concentration in the oviduct and the uterus of the rat. *J Endocrinol* **53**: 355–362.
35. Markopoulos C, Berger U, Wilson P, Gazet J-C, Coombes RC (1988) Oestrogen receptor content of normal breast cells and breast carcinomas throughout the menstrual cycle. *Br Med J* **296**: 1349–1351.
36. Strum JM, Phelps PC, McAtee MM (1983) Resting human female breast tissue produces iodinated proteins. *J Ultrastruct Res* **84**: 130–139.
37. Eskin BA, Parker JA, Bassett JG, George DL (1974) Human breast uptake of radioactive iodine. *Obstet Gynecol* **44**: 398–402.
38. Shah NM, Eskin BA, Krouse TB, Sparks CE (1986) Iodoprotein formation by rat mammary glands during pregnancy and early postpartum period. *Proc Soc Exp Biol Med* **181**: 443–449.
39. Russo J, Russo IH (1997) Role of differentiation in the pathogenesis and prevention of breast cancer. *Endo-Rel Cancer* **4**: 7–21.
40. Haagensen CD (1971) *Diseases of the Breast*. Philadelphia, PA: WB Saunders, pp. 62.
41. Kelsey JL, Gammon MD, John EM (1993) Reproductive factors and breast cancer. *Epidemiol Rev* **15**: 36–47.
42. Yoo KY, Tajima K, Kuroishi T, *et al.* (1992) Independent protective effect of lactation against breast cancer: a case–control study. *Am J Epidemiol* **135**: 726–733.
43. Ross RK, Yu MC (1994) Breast-feeding and breast cancer. *N Engl J Med* **330**: 1683.
44. Yang P-S, Yang T-L, Liu C-L, Wu C-W, Shen C-Y (1997) A case–control study of breast cancer in Taiwan – a low-incidence area. *Br J Cancer* **75**: 752–756.
45. Newcomb PA, Storer BE, Longnecker MP, *et al.* (1994) Lactation and a reduced risk of premenopausal breast cancer. *N Engl J Med* **330**: 81–87.
46. Katsouyanni K, Lipworth L, Trichopoulou A, Samoli E, Struver S, Trichopoulous D (1996) A case–control study of lactation and cancer of the breast. *Br J Cancer* **73**: 814–818.
47. Thomas DB, Noonan EA (1993) Breast cancer and prolonged lactation. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Int J Epidemiol* **22**: 619–626.
48. Michels KB, Willett WC, Rosner BA, *et al.* (1996) Prospective assessment of breastfeeding and breast cancer incidence among 89 887 women. *Lancet* **347**: 431–436.
49. London SJ (1994) Breast-feeding and breast cancer. *N Engl J Med* **330**: 1682.
50. Brown-Grant K (1961) Extrathyroidal iodide concentrating mechanisms. *Physiol Rev* **41**: 189–213.
51. Taurog A (1996) Hormone synthesis: thyroid iodine metabolism. In: Braverman LE, Utiger RD, eds. *The Thyroid: A Fundamental and Clinical Text*, 7th edn. Philadelphia, PA: Lippincott-Raven, pp. 47–81.
52. Hintze G, Kobberling J (1992) Treatment of iodine deficient goiter with iodine, levothyroxine or a combination of both. *Thyroidology* **4**: 37–40.
53. Dugrillon A (1996) Iodolactones and iodoaldehydes – mediators of iodine in thyroid autoregulation. *Exp Clin Endocrinol Diabetes* **104** (suppl.): 41–45.
54. Boeynaems JM, Watson JT, Oates JA, Hubbard WC (1981) Iodination of docosahexaenoic acid by lactoperoxidase and thyroid gland *in vitro*: formation of an iodolactone. *Lipids* **16**: 323–327.
55. Dugrillon A, Uedelhoven WM, Pisarev MA, Bechter G, Gartner R (1994) Identification of delta-iodolactone in iodide treated human goiter and its inhibitory effect on proliferation of human thyroid follicles. *Horm Metab Res* **26**: 465–469.
56. Pisarev MA, Krawiec L, Juvenal GJ, *et al.* (1994) Studies on the goiter inhibiting action of iodolactones. *Eur J Pharmacol* **258**: 33–37.
57. Takatani O, Okumoto T, Kosano H, Nishida M, Hiraide H, Tamakuma S (1989) Relationship between the levels of serum thyroid hormones or estrogen status and the risk of breast cancer genesis in Japanese women. *Cancer Res* **49**: 3109–3112.
58. Giani C, Fierabracci P, Bonacci R (1996) Relationship between breast cancer and thyroid disease: relevance of autoimmune thyroid disorders in breast malignancy. *J Clin Endocrinol Metab* **81**: 990–994.
59. Yokoe T, Iino Y, Takei H, *et al.* (1996) Relationship between thyroid-pituitary function and response to therapy in patients with recurrent breast cancer. *Anticancer Res* **16**: 2069–2072.
60. Strain JJ, Bokje E, van't Veer P, *et al.* (1997) Thyroid hormones and selenium status in breast cancer. *Nutr Cancer* **27**: 48–52.
61. Goldman MB (1990) Thyroid diseases and breast cancer. *Epidemiol Rev* **12**: 16–28.
62. Smyth PPA (1993) Thyroid disease and breast cancer. *J Endocrinol Invest* **16**: 396–401.
63. Smyth PPA, Hertherton AM, O'Carroll D, Smith DF, O'Halloran MJ, O'Donovan DK (1988) Iodine intake in Ireland – an update. *Ir J Med Sci* **157**: 377–379.
64. Beckett GJ, Nicol F, Rae PWH, Beech S, Guo Y, Arthur VR (1993) Effects of combined iodine and selenium deficiency on thyroid metabolism in rats. *Am J Clin Nutr* **57** (suppl.): 240–243.
65. Diplock AT (1993) Indexes of selenium status in human populations. *Am J Clin Nutr* **57** (suppl.): 256–258.
66. Olivieri O, Girelli D, Azzini M, *et al.* (1995) Low selenium status in the elderly influences thyroid hormones. *Clin Sci* **89**: 637–642.
67. Salvatore D, Bartha T, Harney JW, Larsen PR (1996) Molecular biological and biochemical characterization of the human type 2 selenodeiodinase. *Endocrinology* **137**: 3308–3315.
68. Contempre B, Dumont JE, Denef J-F, Many M-C (1995) Effects of selenium deficiency on thyroid necrosis, fibrosis and proliferation: a possible role in myxoedematous cretinism. *Eur J Endocrinol* **133**: 99–109.
69. Hotz CS, Fitzpatrick DW, Trick KD, L'Abbe MR (1997) Dietary iodine and selenium interact to affect thyroid hormone metabolism in rats. *J Nutr* **127**: 1214–1218.

70. Contempre B, Dumont JE, Ngo B, *et al*. (1991) Effect of selenium supplementation in hypothyroid subjects of an iodine and selenium deficient area: the possible danger of indiscriminate supplementation of iodine-deficient subjects with selenium. *J Clin Endocrinol Metab* **73**: 213–215.
71. Contempre B, Duale NL, Dumont JE, *et al*. (1992) Effect of selenium supplementation on thyroid hormone metabolism in an iodine and selenium deficient population. *Clin Endocrinol* **36**: 579–583.
72. Hofbauer LC, Spitzweg C, Magerstadt RA, Heufelder AE (1997) Selenium-induced thyroid dysfunction. *Postgrad Med J* **73**: 103–104.
73. Vernie LN (1984) Selenium in carcinogenesis. *Biochim Biophys Acta* **738**: 203–217.
74. El-Bayoumy K (1994) Evaluation of chemopreventative agents against breast cancer and proposed strategies for future clinical intervention trials. *Carcinogenesis* **15**: 2395–2420.
75. Shamberger RJ, Tytko SA, Willis CE (1976) Antioxidants and cancer. Part IV. Selenium and age-adjusted human cancer mortality. *Arch Environ Health* **31**: 231–235.
76. Schrauzer GN, White DA, Schneider CJ (1977) Cancer mortality correlation studies – III: statistical associations with dietary selenium intakes. *Bioinorg Chem* **7**: 23–34.
77. Meyer F, Verreault R (1987) Erythrocyte selenium and breast cancer risk. *Am J Epidemiol* **125**: 917–919.
78. van't Veer P, van der Wielen PJ, Kok FJ, Hermus RJJ, Sturmans F (1990) Selenium in diet, blood, and toenails in relation to breast cancer: a case–control study. *Am J Epidemiol* **131**: 987–994.
79. Overvad K, Gron P, Langhoff O, Tarp U, Foldspang A, Thorling EB (1991) Selenium in human mammary carcinogenesis: a case–referent study. *Eur J Cancer Prev* **1**: 27–30.
80. Hardell L, Danell M, Angqvist C-A, *et al*. (1993) Levels of selenium in plasma and glutathione peroxidase in erythrocytes and the risk of breast cancer. *Biol Trace Elem Res* **36**: 99–108.
81. Qi X-Y, Zhang A-Y, Wu G-L, Pang W-Z (1994) The association between breast cancer and diet and other factors. *Asia Pac J Public Health* **7**: 98–104.
82. van't Veer P, Strain JJ, Fernandez-Crehuet J, *et al*. (1996) Tissue antioxidants and postmenopausal breast cancer: the European Community Multicentre Study on Antioxidants, Myocardial Infarction, and Cancer of the Breast (EURAMIC). *Cancer Epidemiol Biomarkers Prev* **5**: 441–447.
83. van Noord PAH, Collette HJA, Maas MJ, de Waard F (1987) Selenium levels in nails of premenopausal breast cancer patients assessed prediagnostically in a cohort-nested case–referent study among women screened in the DOM project. *Int J Epidemiol* **16**: 318–322.
84. Coates RJ, Weiss NS, Daling JR, Morris JS, Labbe RF (1988) Serum levels of selenium and retinol and the subsequent risk of cancer. *Am J Epidemiol* **128**: 515–523.
85. Hunter DJ, Morris JS, Stampfer MJ, Colditz GA, Speizer FE, Willett WC (1990) A prospective study of selenium status and breast cancer risk. *JAMA* **264**: 1128–1131.
86. Knekt P, Aromaa A, Alfthan G, *et al*. (1990) Serum selenium and subsequent risk of cancer among Finnish men and women. *J Natl Cancer Inst* **82**: 864–868.
87. Overvad K, Wang DY, Olsen J, *et al*. (1991) Selenium in human mammary carcinogenesis: a case–cohort study. *Eur J Cancer* **27**: 900–902.
88. van den Brandt PA, Goldbohm RA, van't Veer P, *et al*. (1994) Toenail selenium levels and the risk of breast cancer. *Am J Epidemiol* **140**: 20–26.
89. Dorgan JF, Sowell A, Swanson CA, *et al*. (1998) Relationships of serum carotenoids, retinol, α-tocopherol, and selenium with breast cancer risk: results from a prospective study in Columbia, Missouri (United States). *Cancer Causes Control* **9**: 89–97.
90. Hintze G, Burghardt U, Baumert J, Windeler J, Kobberling J (1991) Prevalence of thyroid dysfunction in elderly subjects from the general population in an iodine deficiency area. *Aging* **3**: 325–331.
91. Weaver DK, Nishiyama RH, Batsakis JG (1976) Iodine induced thyroid disease. *Ann Clin Lab Sci* **6**: 545–550.
92. Ishizuki Y, Yamauchi K, Miura Y (1989) Transient thyrotoxicosis induced by Japanese kombu. *Nippon Naibunpi Gakkai Zasshi* **65**: 91–98.
93. Konno N, Makita H, Yuri K, Iizuka N, Kawasaki K (1994) Association between dietary iodine intake and prevalence of subclinical hypothyroidism in the coastal regions of Japan. *J Clin Endocrinol Metab* **78**: 393–397.
94. Katamine S, Mamiya Y, Sekimoto K, *et al*. (1987) Differences in bioavailability of iodine among iodine-rich foods and food colors. *Nutr Rep Int* **35**: 289–297.
95. Valeix P, Zarebska M, Preziosi P, Galan P, Pelletier B, Hercberg S (1999) Iodine deficiency in France. *Lancet* **353**: 1766–1767.
96. Longnecker MP, Stram DO, Taylor PR, *et al*. (1996) Use of selenium concentration in whole blood, serum, toenails, or urine as a surrogate measure of selenium intake. *Epidemiology* **7**: 384–390.
97. Sundstrom H, Ylikorkala O, Kappila A (1986) Serum selenium and thromboxane in patients with gynaecological cancer. *Carcinogenesis* **7**: 1051–1052.
98. Goodman MT, Wilkens LR, Hankin JH, Li-Ching L, Wu AH, Kolonel LN (1997) Association of soy and fiber consumption with the rise of endometrial cancer. *Am J Epidemiol* **146**: 294–306.
99. Key TJA, Silcocks PB, Davey GK, Appleby PN, Bishop DT (1997) A case–control study of diet and prostate cancer. *Br J Cancer* **76**: 678–687.
100. Clark LC, Dalkin B, Krongrad A, *et al*. (1998) Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. *Br J Urol* **81**: 730–734.