Medical Hypotheses 7: 601-613, 1981

THE CONSUMPTION OF SEAWEED AS A PROTECTIVE FACTOR IN THE ETIOLOGY OF BREAST CANCER

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ABSTRACT

A review of the biological properties of seaweed is presented and the role of seaweed as a breast cancer anti-carcinogen is suggested. Proposed mechanisms of action are: reduction of plasma cholesterol, binding of biliary steriods, inhibition of carcinogenic fecal flora, binding of pollutants, stimulation of the immune system, and the protective effects of beta-sitosterols. In an experiment using sarcoma-180 in mice, seaweed extract appeared to have an antitumor effect. Thus it is suggested that breast cancer may be prevented and that this dietary habit among the Japanese could be an important factor in understanding the lower breast cancer rates reported in Japan.

breast cancer epidemiology prevention diet

seaweed

> "also, it has been commonly claimed to be important in eliminating or reducing any carcinogenic substances in human food, but it is rarely considered that anti-carcinogenic substances may also be present in our diet. The presence or absence of these factors or the counterbalance of the opponents may be involved in the geographical incidence of certain tumors."
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> C. P. Li, A. Goldin, and J. L. Hartwell. "Antineoplastic Substances From the Sea:A Review" Cancer Chemotherapy Reports Vol 4 (3) Part 2. July 1974.

INTRODUCTION

Studies of the role of nutrition in cancer etiology have focused on excesses in fat intake (1) specific food additives (2), naturally occurring carcinogens (3) as well as trace element deficiencies (4). The role of protective dietary factors which may act as anti-carcinogens has been less investigated, although beta-sitosterols (5) and butylated hydroxytolene (BHT) (6) have been shown to protect rats against chemically induced tumors.

To date, no food per se has been studied which may serve to protect a population from one or more kinds of cancer. It is the purpose of this paper to examine two populations, Japanese and American, to see what effects a food eaten almost exclusively in Japan might have on the Japanese breast cancer rates. Breast cancer rates in Japan are only one sixth as high as in the United States (1). Migrant studies of Japanese show that breast cancer mortality increase in the progeny of Japanese migrants to the United States. It is therefore unlikely that racial differences are the important variable. Dietary changes, in particular increases in dietary fat, are most often implicated. Although suggestive, this association does not appear sufficient. Women in Finland, where dietary fat intake is high, have an intermediate breast cancer mortality rate (1). It is thus necessary to expand the hypothesis to include other foods that may act as anticarcinogens and in understanding the profoundly lower breast cancer rates in Japan, to look at food that is eaten in Japan which is not eaten in the United States. Seaweed is a logical choice, since it is a food commonly eaten by all people in Japan and rarely eaten by people in the United States. Reports of the frequency with which Japanese eat seaweed range from 4.9 grams per person (7) to 25% of the Japanese diet (8). Since it is consumed in soups, salads, as parts of entrees and as a vegetable, the exact amount eaten may be difficult to determine. It is rarely eaten in an identifiable form in the United States, where its most common uses are as stabilizers in dairy products, canned meat, frozen fruits and beer (8).

One way seaweed, or any breast cancer anti-carcinogen, might logically be expected to act would involve fat metabolism. As cholesterol is the precurser for the peripheral conversion of sex hormones, an alteration in fat metabolism could also affect hormone levels. Another possible mechanism for an anti-carcinogen would be to block the absorption of an ingested carcinogen, either by binding with it or by inhibiting its absorption. A third possible mechanism would be to increase the body's defenses against cancer by supplying important trace minerals or by stimulating the immune

system. These possible modes of action will be considered in examining the known properties of seaweed and its proposed role as an anti-carcinogen.

Seaweed and Low Thyroid Theory

The role of seaweed in breast cancer treatment was indirectly implicated at the inception of the low thyroid-breast cancer hypothesis. In a Letter to the Editor, published in 1956 in Lancet, A. A. Loeser proposed that thyroid medication could enhance the effect of natural thyroid hormone which he felt was the key anti-carcinogen in breast cancer patients. The alternative he was trying to displace was oophorectomy, which he felt worked only by increasing the thyroid hormone production. As an incidental background piece of information, he mentioned that ancient Egyptians had given seaweed to breast cancer patients (Ebers Papyrus), and suggested that it was the iodine content of the seaweed which was responsible for stimulating the thyroid (9). This hypothesis concerning the role of the thyroid in the etiology of breast cancer has generated many studies over the last twenty-five years, although none have been able to establish a causal link between thyroid dysfunction and subsequent breast cancer. It has been observed that women with breast cancer who also have thyroid dysfunction have a poorer prognosis for both five and ten year survival (10). The most convincing data arguing against this theory is that as a result of iodized salt, endemic goiter rates have declined in the United States whereas breast cancer mortality rates have not. It is therefore intriguing to consider the alternative explanation, that it was the seaweed rather than the iodine content which lent efficacy to the Egyptian treatment.

Seaweed and Breast Cancer in Japan

When areas of low breast cancer rates within Japan are compared to the areas of seaweed production, there are some areas of similarity. In Sago prefecture, the area of lowest breast cancer rates, Porphyra is harvested (11, 12). Hokkaido has the next lowest breast cancer rates and is the prefecture where 65-80% of the two most common brown seaweeds, Laminaria and Undaria pinnatifida, are harvested. There are areas of high Porphyra production which do not have low breast cancer rates, so these correlations are only suggestive of an association between seaweed production and low breast cancer rates. Since other factors besides the presence or absence of seaweed clearly must be important in breast cancer etiology, it unlikely that there would be a perfect inverse correlation between a protective factor and low breast cancer rates. The magnitude of cancer producing stimuli would also need to be considered. The existing data

are supportive of the idea that seaweed consumption might be a protective factor.

An important question is whether Japanese in Japan eat enough seaweed to make a real difference, and whether there is variation in the consumption of seaweed. Katsura and Nakamichi (13), in a study of the iodine intake of Japanese, found the daily intake varied between 200 μg to 20 mg. The average intake was 500-1000 μg. According to their data, the individual variations were due to differences in seaweed consumption. A study of 3,609 households from three districts in Japan provides further evidence of the popularity of seaweed. The reported daily range for amounts consumed per person varied between 0 to 5 grams per person to 65 to 70 grams per person. The average daily per capita consumption was 7.3 grams (with a standard deviation of 11 grams) (14).

In a study of dietary changes adopted by migrant Japanese living in Hawaii, Nomura and his colleagues (15) reported that among spouses of breast cancer patients, fewer ate seaweed than spouses of non-breast cancer patients. The differences were 12% and 20%, both of which are very different from the estimated 100% consumption of seaweed among Japanese living in Japan. It thus appears that seaweed is an important part of the Japanese diet, and that it is consumed less frequently by migrant Japanese.

Seaweed and Cholesterol Metabolism

The dietary factor most often associated with breast cancer is the amount and quality of fat intake (1) The Japanese in Japan eat less fat than do Americans in America. There appears to be a linear correlation between dietary fat and breast cancer mortality (7, 16) This relationship appears to be true both in international comparisons and within Japan. Comparison of the United States and Japanese breast cancer mortality rates show a 3:1 difference in mortality for premenopausal women and a 9:1 difference for postmenopausal women (1). The most striking difference occurs among postmenopausal women. Diet almost certainly does not change with menopause. The metabolism of a woman's dietary intake does change, in particular with regard to cholesterol and conversion of cholesterol to androgens and estrogens. It is therefore likely that an alteration in the availability of cholesterol for peripheral conversion to hormones might have a profound effect on the tumor promoting aspects of hormones in hormone dependent breast cancer. Aminoglutethimide and adrenalectomy have both been used in postmenopausal metastatic breast cancer patients to alter the peripheral conversion of cholesterol into hormones,

thereby slowing the progression of the cancer (17). Thus, if seaweed were a likely candidate for prophylaxis, it would be logical if it had an effect on cholesterol levels and possibly on metabolism of dietary fats.

Experiments on the effects of edible seaweeds on cholesterol metabolism have been carried out by Abe and Kaneda (18), and Kimura and Kuramoto (19). Both studies showed a hypocholesteremic effect of seaweed, and both found that Porphyra (purple laver or asakusan nori) was superior. In the Abe and Kaneda study, five rats were fed for twenty-eight days with diets containing five percent seaweed. The total plasma cholesterol for the rats fed Porphyra was reduced by 40% and free cholesterol was reduced by more than 80%.

A possible mechanism of action for seaweeds in the reduction of plasma cholesterol is related to its properties as fiber. In 1955, Schwimmer and Schwimmer (20) reported, "In more recent times, the U.S. Dispensatory recommended agar as a laxative, eaten in small pieces like cereal with sugar and cream, or else in chocolate-coated form. Its value as a laxative is due to its colloidal property of absorbing and holding water without being digested. This attribute makes it desirable as intestinal bulk or roughage...Mulinos (21) tested the sodium and calcium salts of alginic acid in 60 humans with colonic constipation. He found them effective, and thought that, even though the alginates swelled minimally in water or gastric juice, they increased their original bulk 25 to 65 times in the alkalinity of intestinal secretions." In a more recent study of the comparative value of different fiber in reducing cholesterol, Story and Kritchevsky (22) reported, "The capacity for various types of fiber to bind bile acids or bile salts is quite variable, and a high capacity seems to correspond with a hypocholesteremic effect." Although seaweed was not among the fibers tested, by inference, it seems likely that seaweed may work by binding bile acids. As an anti-carcinogen, fiber may work to dilute the effects of carcinogens in the alimentary canal. If Mulinos' estimation of the swelling capacity of alginic acid in intestinal secretions is accurate, then seaweed would be an excellent diluter and hence protector against carcinogens present in the gut.

Seaweed and Sterol Content

A second aspect of seaweeds which may be important in lowering cholesterol depends on the type of sterols contained in the seaweed. Porphyra, the commonly eaten red seaweed, contains 12% beta-sitosterols, 28% desmosterols and

60% cholesterol (23). Using a 0.2% beta-sitosterol supplemented diet, rats fed a colon carcinogen, N-methyl-N-nitrosourea had significantly lower incidence of colon cancer than the control group ($p<0.05$ by chi square test) (5). The lipid content of red algae is typically 0.3-3.8% of dry weight (24). It is therefore possible that the amount of beta-sitosterol could be of physiologic importance in protecting against colon cancer. There are no data available on its effect when fed to rats challenged with a mammary carcinogen.

Seaweed and Antioxygenic Activity

There is an indirect source of evidence for the role of Porphyra in protecting against breast cancer. Kaneda and Ando (25) analyzed the component lipids of Porphyra and tested for antioxygenic activity. They found that whole lipids and phospholipids had similar antioxygenic activities as butylated hydroxytolene (BHT). When BHT was fed as a dietary supplement to rats who were challenged with dimethylbenzanthracene, a mammary carcinogen, King and her colleagues found a lower tumor incidence and rate of tumor growth (significant for the high polyunsaturated diet plus BHT, $p<0.0049$, and high saturated fat diet compared to high saturated diet plus BHT, $p<0.002$) (6).

Seaweed and Intestinal Flora

Another aspect of high fat intake as a promoter of tumors is the interaction between fat and intestinal flora. In 1971, Hill (26), proposed that, "The intestinal flora is able to produce carcinogens in the colon from biliary steroids." Bokkenheuser (27), in 1978, reported, "Steroids in bile, therefore undergo further metabolism. Present evidence suggests that both the intestinal flora and the gut itself participate in posthepatic metabolism of sterols, bile acids and steroid hormones." When germ-free rats were fed dimethylbenzanthracene, significantly fewer ($p<0.05$) mammary tumors were seen than in the conventionally fed rats (28). This suggests that intestinal flora may be involved in enhancing a mammary carcinogen.

When fecal flora in Japanese diet consuming versus Western diet consuming populations were compared, Finegold and Sutter found significant differences in kinds and numbers of aerobic organisms in the fecal flora as a result of dietary manipulations. The importance of seaweed to fecal flora may be the reported antibiotic activity reported by Mautner (30). They found that, "Ether extracts of the marine red algae Rhodomela larix inhibit the growth of several species of gram-positive and gram- negative

pathogens in vitro...Among the organisms inhibited are Micrococus pyogenes var. aureus, (S. aureus), Bacillus megtherium, Mycobacterium phlei, Myco tuberculosis (607 and H37Rv), and Myco. avium. Less sensitive are Bacillus subtilis, Proteus vulgaris, Escherichia coli, Aerobacter aerogens, Klebsiella pneumoniae, Salmonella gallinarum, Candida albicans, Saccharomyces patorianus, Trichophyton mentaogrophytes, and Trichophyton rubrum." Pratt (31) and Vacca and Walsh (32) also reported antibiotic activity from extracts of brown, green and red algae. These investigators proposed that the antibiotic activity was related to the brominated phenalic compounds and not to their iodine content.

When a seaweed supplement of Ascophyllum nodosum, a brown seaweed shown to have antibiotic properties (32) was fed to one of each of seven pairs of monozygotic twin cows over seven years, several differences were noted (33) During 19 of the 23 lactation periods, the seaweed supplemented cows yielded significantly more milk than did the control cows ($p<0.01$), producing an overall 6.8% increase in the total amount of milk produced over the seven years. In addition, the incidence of mastitis in the treatment animals was one compared to nine cases among the controls. Since mastitis in cows is most often associated with unhygienic conditions, the mild antibiotic properties of seaweed may be responsible for this difference.

Seaweed and Binding of Toxic Materials

Another property reported for seaweed is its ability to bind metal and radioactive pollutants. Tanaka and his colleagues presented data on this aspect of alginic acid, finding that, "Metal compounds, because of their wide distribution and extensive use, represent an important sector of our increasing pollution problems. Our investigation has shown that alginate can bind radioactive strontium, one of the most hazardous pollutants, effectively in the gastrointestinal tract, thus preventing its absorption into the body, and it has been shown to bind other metal pollutants such as barium, cadmium, and zinc. The principle of this method lies in the in vivo ion exchange reactions between acidic polysaccharides and the metal ion in question, resulting in the formation of insoluble salts of the macromolecules, which are unabsorbable and are thus excreted (34)." Alginic acid is found only in the brown seaweeds. Although there is no direct evidence to support pollution as an etiological factor in breast cancer, urbanization, and its attendant pollution is a risk factor (35).

Seaweed and Trace Elements

Newberne and his colleagues (4, 36) have reported that rats deficient in trace minerals of zinc and copper are more susceptible to cancer producing agents. Yamamoto and Ishibashi, in a study of the trace elements found in seaweeds, document the presence of these minerals in seaweeds (37). It is possible that seaweed is an important source of these minerals, rendering the people who eat seaweeds at less risk of carcinogens. Shamberger reported, "statistically significant differences in age-specific cancer death rates in states with high, medium and low selenium levels (38)." Many of the seaweeds, notably Porphyra contain possibly physiologically significant levels of selenium (39).

Seaweed Toxicity

In studies of two kinds of seaweeds, carrageenan, a red algae, and two of the brown seaweed kelps, insights into the variety of tumor promoting and tumor inhibiting properties of seaweeds have been suggested. Carrageenan, made from Chrondus crispus and Gigartina stellata, has been implicated as a colorectal tumor enhancer in rats (40, 41). It is thought that carrageenan is selectively cytotoxic for macrophages, thereby enhancing and possibly causing malignant tumors (42). Porphyra, also a red seaweed, is in a different order of Rhodophyta (43) and has never been tested for oncogenic activity. In addition, while carrageenan is a food additive widely used in the United States (8), it accounts for only 0.7% of the seaweed harvested in Japan (11). Since colorectal cancers are uncommon in Japan, it is unlikely that other seaweeds have such tumor enhancing roles in humans.

Seaweed and Antitumor Documentation

To date, only Sargassum and Laminaria have been tested for antitumor effect (44, 45). In describing the experiment, Yamamoto and his colleagues reported that, "An almost purified antitumor polysaccharide fraction (SFPP) was obtained by fractional precipitation with ethanol from hot-water extract of Sargassum fulvellum. The fraction showed remarkable tumor-inhibiting effect against sarcoma-180 implanted subcutaneously in mice. The results of chemical and physical analyses suggested that the active substance may be either a sulphated peptidoglycuronoglycan or a sulphated glycuronoglycan." They concluded that the response was probably host-mediated immunity stimulated by the seaweed extract.

CONCLUSIONS

Seaweed may be important in preventing breast cancer. Proposed mechanisms of action are: reduction of plasma cholesterol, binding of biliary steroids, antioxygenic activity of the phospholipids, inhibition of carcinogenic fecal flora, binding of pollutants and addition of important trace minerals to the diet. In an experiment of sarcoma-180 in mice, Sargassum extract was reported to have an antitumor effect. Thus it is suggested that by eating seaweed, breast cancer may be prevented, and that this dietary habit among the Japanese is an important factor in understanding their lower breast cancer rates.

Future Goals

The importance of seaweed to breast cancer is described. It is likely that if such an inhibiting effect can be demonstrated for breast cancer, seaweed might also be protective against colon and prostate cancer, both of which appear to have the same world wide distribution and possibly the same etiology as breast cancer (1). The ultimate goal of research into protective agents against carcinogenesis is to isolate the active component and, if there is no accompanying toxicity, to introduce it as an additive in commonly consumed American foods. Precedents for this approach include iodized salt, which reduced the incidence of goiter in the United States.

ACKNOWLEDGEMENTS

I would like to thank F. Mosteller, H. Hiatt, D. Hornig, R. Raffauf, E. Frei, L. Nadler, C. Reinisch, F. Bang, B. McPeek, J. Hedley-Whyte, M. Ettling, R. Gelman, R. Bast, D. Kufe, F. Li, G. Weiss, and M. Minden for advice, critical discussions and encouragement. This work was carried out while a fellow in the Interdisciplinary Programs in Health and supported by a grant from the Rockefeller Foundation.

FOOTNOTES

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