Radiol Oncol 1996; 30: 281-5.

Vegetarian diet and cancer

Dražigost Pokorn

Institute of Hygiene, Medical Faculty, University of Ljubljana, Slovenia

Several components in plant foods, namely protease inhibitors, izoflavones, inositol hexaphosphate, phytosterols and saponins, inhibit a variety of tumors in various tissues.
It is clear that population consuming high levels of fruit and vegetables have low overall cancer mortality rates for the major cancers, common in the western hemisfere. There are many theories offering explanations for the variations in cancer frequency in different population.
The evidence obtained is not yet sufficient for any specific dietary recomendation and further work is needed to establish the role of these natural compounds in human health and disease.

Key words: vegeterianism, vegetarian diet; neoplasms

Introduction

Epidemiologic studies have suggested that diet is an important environmental factor involved in the etiology of the most prevalent forms of cancer.[1] There is enough evidence from case -- control, correlation and cohort studies to show that high meat and fat consumption increase the risk of developing cancer, whereas consumption of diets high in cereals, fruits and vegetables reduces the risk.[2]

Over the last few years there has been an increasing body of literature suggesting that vegetarian diet may be protective against cancer.

Studies of diet and cancer are limited by the fact that cancer is a group of several different diseases developing over decades in a multistage process involving both initiation and promotional events.[3]

All epidemiological studies are dependent on variability in both risk factor and rates of disease as evidence for environmental influences on diseases. Especially important are variations among migrant groups and rapid changes over time, because changes within a few decades are unlikely to be caused by genetic mutations. For instance, rates of breast cancer, thought to be related to high fat diets, are lower in Japan than in the United States and increased among Japanese migrating to Hawaii. The rapidity with which cancer rates change is thought to reflect the time in life at which the risk factor is influential. Thus, the risk of colon cancer changes within a few decades of migration, while the risk of breast cancer does not increase until the second generation implying a dietary effect early in life.[4]

Even where diet can be measured prospectively in population with sufficient variation over time, cross – correlations among dietary variables have rendered indentification of specific dietary risk factors extremely difficult. Thus, ecological and migration studies relating fat to risk of breast cancer rates have been unable to separate effects of total fat from cholesterol, saturated fat and low fiber intake or from protective factors present in fruit and vegetables.[5,6]

Many epidemiological studies, including migrant studies, support the view that the Western diet is one of the main factors causing the high incidence of the so – called Western diseases, including the major hormone – depending cancer, colon cancer and coronary heart disease.[1,2,4-6]

Western diet, compared with the vegetarian or semivegetarian diet in developing and Asian Coun-

Correspondence to: Prof. Dražigost Pokorn, M.D., Ph. D., Institute of Hygiene, Medical Faculty, University of Ljubljana, 1000 Ljubljana, Slovenia

UDC: 613.261:616-006.6

tries, may alter hormone production, metabolism or action at the cellular level by some biochemical mechanisms. The compounds, which mainly occur in legumes, fruits, vegetables, whole – grain products and various seeds, have now been shown to influence not only sex hormone metabolism and biological activity but also intracellular enzymes, protein synthesis, growth factor action, malignant cell proliferation and angiogenesis supporting their role as cancer protective compounds.

It is clear that population, consuming high levels of fruits and vegetables, have low overall cancer mortality rates for the major cancers, common in the western hemisfere. There are many theories offering explanations for the variations in cancer frequency in different populations.[7]

Lee et al[8] compared 200 Singapore Chinese women with histologically confirmed breast cancers with 420 matched control subjects. In the premenopausal women, high intake of red meat was associated with increased risk for breast cancer. He concluded that decreased risk was associated with intake of soya products. It has been known that diets rich in legumes and fiber[8] decrease cancer risk relative to those diets which include animal products.[9]

Recently, the consumption of soy products has been associated with low rates of hormone dependent and hormon – independent cancers. Asians, who consume 20-50 times more soy per capita than Americans, have lower incidence and death rates from breast and prostate cancer.[8,10]

The current discussion will outline general issues in epidemiologic studies of diet and cancer relevant to vegetarian diet, summarizing the current epidemiologic literature relating cereals, fruits and vegetables intake and cancer risk.

Food constituents known to have anticarcinogenic activity.

Certain normal dietary components have the potential to affect carcinogenesis,[11] either by action as a carcinogen or tumor promoter or by modifying the action of such agents. Although deliberate addition of carcinogenic agents into the diet is legislatively forbidden, various agents, such as fats, and components produced during cooking, notably pyrolysis products, or storage, oxidized fats, have some carcinogenic or promoting potential. However, many more agents in the diet appear to inhibit carcinogenesis. Some of these reduce metabolic activation or enhance detoxification of carcinogens, other may protect against the attack of electrophilic carcinogens on DNA and still other seem to have an antitumor – promoting effect on cells. The role of chemoprevention appears to lie in reversal of the premalignant process rather than supression of malignant growth.[12]

Epidemiological evidence has related decreased cancer risk to increased consumption of phytoestrogen and lignans in a vegetarian diet.

The lignans and isoflavonoid phytoestrogens are normal constituents of human urine, plasma and feces and occur in large amounts in plasma, urine and feces, particularly in vegetarians, in subjects consuming large amount of whole – grain products, vegetables, berries, fruits, linseeds and sesame seeds[13]. The same findings can be applied to the Chinese and the Japanese, whose traditional diet contains similar food.[13] Plasma levels are higher in vegetarian women compared with omnivarous women, correlating negatively with rates of breast cancer risk.[14]

Plant food contains, in addition to the traditional macronutrients, a wide variety of microcomponents such as enzyme inhibitors, phytosterols, indoles, flavones and saponins. These micro components are known to be biologically active. Their role in the prevention of chronic diseases is currently being investigated. [4,7,15]

According to one hypothesis, the anticancer effect of soy products and other legumes is due to the presence of the isoflavone genistein in legumes. Isoflavones are weak estrogens and can function both as estrogen agonists and antagonists depending on the hormonal milieu and the target tissue and species under investigation. Genistein, one of the two primary isoflavones in soybeans, whole – grain products and various seeds, has attracted much attention from the research community, not only because of its potential antiestrogenic effect, but because it inhibits several key enzymes thought to be involved in carcinogenesis.[16,17]

The list of the tumors, responding to hormonal influence, is usualy limited to breast. endometrium, prostata, thyroid, pituitary and ovary, and to certain categories of leukemias and lymphomas.

The list should be considered temporary, because many specific growth factors (insulin, insulin – like growth factor, platelet – activating factor) have been shown to influence the growth and biological evolution of many normal and neoplastic cells and tumors.[17] Receptors for hormones (steroid hormone) and factors are found in many tumors but their precise role in modulating tumor growth is not yet fully and completely understood. Phytoestrogens

and, in particular isoflavones in soybean, possess binding capacity to many of these receptors and complete with the physiologic hormones and/or growth factors bind to them. By doing so isoflavones may, by virtue of this competitive celular binding, play a role in the modulation and evolution of neoplastic growth.[18] Lignans and isoflavonoides also seem to stimulate sex hormone binding globulin synthesis in the liver and in this way they may reduce the biological effects of sex hormones.[13,19]

They decrease the relative amount of free testosterone and free estradiol and reduce both the albumin – bound and the free fraction of the sex hormones. This reduces the metabolic clereance rate of the steroids and thereby lowers their biological activity. Subjects with breast cancer or those at high risk of breast cancer, omnivorous women living in Boston, excrete low amount of lignans and isoflavonoids.[20]

In Finland the lignan excretion is mainly associated with the intake of grain fiber or whole – grain products. Intake of fruits and berries in Finnish women also has a positive correlation with lignan excretion. Berries contain the seeds of the plant and these may be rich in lignan precursors.

In Japanese subjects lignan excretion shows the strongest correlation with the intake of whole soybeans.[13,20]

The significantly positive association between lignan excretion and intake of whole – grain products and total fiber is altered by the intake of various seeds with relatively low fiber but high content of lignan precursos. This occurs particularly in vegetarians.

Another factor, affecting the association between intake of whole – grain products and lignan excretion, is the fact that many subjects consume purified grain fiber directly or in the form of whole – meal bread which is a mixture of bran and white meal containing only small amount of meal from the aleurone layer of the grain where the lignan precursors occur. Also the preparation of tofu products seems to eliminate the lignan precursors from the beans.

Intake of fiber – rich food definitely affects the plasma levels of estrogen, increases phytoestrogen intake, but also reduces energy intake which may be an important risk – reducing factor.[13]

The well known therapeutic effect of estrogens in prostatic cancer suggests that phytoestrogens may inhibit prostatic cancer cell growth during the promotional phase of the disease or they may influence differentation as shown for genistein with leukemic cells and other cancer cells. Despite high fat intake, the prostatic cancer incidence in Finland is much lower than in USA but higher than in Japan.[21] The higher production of lignan in the gut, due to relatively high intake of whole – grain products, particularly rye bread, in the low – incidence rural areas in Finland, may perhaps explain this phenomenon.

Lignan excretion is also higher in Finish subjects living in areas with lower colon cancer risk.[21]

Epidemiological evidence obtained in Japan points to lower colon cancer incidence in areas with high tofu consumption.[22]

High concentrations of genistein in urine of vegetarians suggest that genistein may contribute to the preventive effect of plant – based diet on chronic diseases, including solid tumors, by inhibiting neovascularization (angiogenesis, angiogenesis diseases) and tumor cell proliferation.

Genistein reduces the incidence of tumors or other angiogenic diseases like rheumatoid arthritis, psoriasis, and diabetic retinopathy.[22]

Soy products that contain isoflavonoids and lignans may also play a role in the prevention of several types of cancer.

The concentration in plasma of these compounds may easily reach biologically active levels without toxic effect. By inhibiting the effect of growth factors and angiogenesis, genistein may be a general inhibitor of cancer growth. By modulating drug transport, genistein may prove to be a good addition to the established cancer therapy. The described biological effect may also be used as a preventive strategy for other western diseases not discused in this connection, such as cardiovascular diseases and osteoporosis, due to the estrogenic and antioksidative effect.

Saponins, which are present in plants, have been suggested as possible anticarcinogens. Legumes such as soybeans and chickpeas are a major source of saponins in the human diet.[23] They possess surface – active characteristics that are due to the amphiphilic nature of their chemical structure. The proposed mechanisms of anticarcinogenic properties of saponins include direct cytotoxicity, immune – modulatory effect, bile acid binding and normalization of carcinogen – induced cell proliferation[24].

The biological activity in *ginseng* is largely attributed to the triterpanoid saponins (ginsenoides), which constitute 2-4 % of ginseng's dry weight. Ginseng is widely used in Oriental medicine for treatment of cancer, diabetes and hepatic and car-

diovascular diseases. Growth inhibition and reverse transformation of B_{16} melanoma cells were observed with ginsenosides treatment.[25,26]

Phytic acid, inosital hexaphosphate is ubiquitous in the plant kingdom and is abundant in cereals and legumes. Because phytic acid is high in high – fiber diet, the epidemiologic observations showing high – fiber diet, are associated with a lower incidence certain kinds of cancer.

It reduces cell proliferation and increases differentiation of malignant cells often resulting in reversion to the normal pheno type.[27]

Studies report that consumption of soy protein diets inhibits the growth of various tumors in rats. The inhibitory effect has been attributed to the phytoestrogens or protein kinase inhibitor in soy protein products.

Recent studies indicate that additional factors in soy protein products may also contribute to the inhibition of tumorgenesis, namely the deficiency of the essential amino acid methionin. Metastatic growth of a primary rhabdomysarcoma lung tumor was inhibited by adopting a soy protein diet.[12]

Conclusion

In conclusion, it has been established that several components in plant foods, namely protease inhibitors, izoflavones, inositol hexaphosphate, phytosterols and saponins, inhibit a variety of tumor in various tissues in the animal model. Current studies also indicate that the lower amount of methionin in soy protein compared with casein may be important in selectively retarding the growth of tumors.

The evidence obtained is not yet sufficient for any specific dietary recomendation and further work is needed to establish the role of these natural compounds in human health and disease.

References

1. Armstrong AC, Doll R. Environmental factors and cancer incidence and mortality in different countries with special reference to dietary practices. *Int J Cancer* 1975; **15:** 617-31.
2. Kolonel LN, Hankin JH, Lee J, Chu SY, Nomura AMY, Ward Hinds M. Nutrient intakes in relation to cancer incidence in Hawaii. *Br J Nutr* 1981;**44:** 332-9.
3. Persky V, VanHorn L. Epidemiology of soy and cancer: Perspective and direction. *J Nutr* 1995; **125:** 709S-12S.
4. Messina MJ, Persky VP, Setchell KDR, Barnes S. Soy intake and cancer risk: a review of the in vitro and in vivo data. *Nutr Cancer* 1994; **21:** 113-31.
5. Correa P. Epidemiological correlations between diet and cancer frequency. *Cancer* 1981; **41:** 3685-90.
6. Doll R, Petro R. The causes of cancer: Quantitative estimates of avoidable risk of cancer in the United States today. *J Natl Cancer Inst* 1981; **66:** 1193-308.
7. Kennedy AR. The evidence for soybean products as cancer preventive agents. *J Nutr* 1995; **125:** 733S-743S.
8. Lee HP, Gourley L, Duffy SW, Esteve J, Lee J, Day NE. Dietary effects of breast cancer risk in Singapore. *Lancet* 1991; **337:** 1197-200.
9. Saio K. Dietary pattern and soybean processing in Japan today. *Trop Agric Res Serv* 1990; **17:** 153-61.
10. Severson RK, Nomura AMY, Grove JS, Stemmerman GN. A prospective study of demographic, diet and prostate cancer among men of Japanese ancestry in Hawaii. *Cancer Res* 1989; **49:** 1857-60.
11. Ashendel CL. Diet, signal transduction and carcinogenesis. *J Nutr* 1985; **125:** 686S-91S.
12. Alberts DS, Garcia DJ. An overview of clinical cancer chemoprevention studies with emphasis on positive phase III. studies. *J Nutr* 1995; **125:** 692S-7S.
13. Adlercreutz CHT, Hockerstedt KAV, Hamalainen EK, Markkanen MH, Wahala KT, Fotsis T. Soybean phytoestrogen intake and cancer risk. *J Nutr* 1995; **125:** 757S-70S.
14. Adlercreutz H. Western diet and Western diseases: Some hormonal and biochemical mechanisms and associatiens. *Scand J Clin Lab Invest* 1990; **50(suppl 20):** 3-23.
15. Liener IE. Possible adverse effect of soybean anticarcinogens. *J Nutr* 1995; **125:** 744S-50S.
16. Swanson CA, Mao BL, LiJY, Lubin JH, Yao SX, Wang JZ et al. Dietary determinants of lung – cancer risk: results from a case – control study in Yunnann province. *China Int J Cancer* 1992; **50:** 876-80.
17. Molteni A, Brizio-Molteni L, Persky V. Invitro hormonal effect of soybean isoflavones. *J Nutr* 1995; **125:** 751S-6S.
18. Martin OM, Horwitz KB, Ryan DS, Mc Guire WL. Phytoestrogen interaction with estrogen receptors in human breast cancer cells. *Endocrinology* 1978; **103:** 1860-67.
19. Adlercreutz H, Fotsis T, Bannwart C, Wähälä K, Mäkela T, Brunow G, Hace T. Determination of urinary lignans and phytoestrogen metabolites, potential antiestrogen and anticarcinogens, in urine of women on various habitual diets. *J Steroid Biochem* 1986; **25:** 791-7.
20. Adlercreutz H, Fotsis T, Heikkinen R, Dwyer JT, Woods M, Goldin BR, Gorbach SL. Excretion of the lignans, enterolacton andenterodiol and of equol in omnivorous and vegetarian women and in women with breast cancer. *Lancet* 1982; **2:** 1295-9.

21. Teppo L, Pukkala E, Hakama M, Hakulinen A, Herva A, Sexén E. Way of life and cancer incidence in Finland. *Scand J Social Med* 1980; (suppl 19): 1-84.

22. Barnes S. Effect of genistein on in vitro and in vivo models of cancer. *J Nutr* 1995; **125:** 777S-83S.

23. Rao AV, Sung MK. Saponins as anticarcinogens. *J Nutr* 1995; **125:** 717S-24S.

24. Cheek PR. Nutritional and physiological implications of saponins. *Nutr Rep Int* 1976; **13:** 315-24.

25. Ha TY, Lee JH. Effect of Panex ginseng on tumorgenesis in mice. *Net Immun Cell Growth Regul* (abstr) 1985; **4:** 281

26. Odasshima S, Ote T, Kohno H, Matsuda T, Kitagawa I, Abe H, Arichi S. Control of phenotypic expression of cultured B_{16} melanoma cells by plant glycosides. *Cancer Res* 1985; **45:** 2781-84.

27. Shamsudden AM. Inosital phosphates have novel anticancer function. *J Nutr* 1995; **125:** 725S-32S.