MINI-REVIEW

Protective Effects of Asian Dietary Items on Cancers - Soy and Ginseng

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Abstract

Dietary factors are regarded as exerting major influences on cancer development in various organ sites and in Asia there is particular interest in the potential preventive effects of foodstuffs such as soy products and gingseng. The so-called phytoestrogens, like genistein and daidzein in soy, can bind to estrogen receptors and therefore interfere with the action of estrogen itself, a well-established risk factor for breast, ovarian and endometrial cancers. Although not all results are consistent, there is good evidence for protective influence of soy products against all three of these cancers. In addition, there have been many reports of preventive effects in the prostate. With ginseng, whether white or red, the included polyphenol compounds and saponins may play roles in many different organs, although preventive potential is perhaps best documented for gastric cancer. The traditional diets in Eastern Asia may need more emphasis in efforts to combat the growing problem of cancer in this region of the world

Key Words: Cancer development - dietary factors - soy products - gingseng

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Introduction

Cancer is called 'malignancy' or 'neoplasia' in medical terms, and is a class of diseases in which a group of cells display uncontrolled growth (disturbance of normal control mechanism for growth and proliferation of cells, that is, division beyond the normal limits), invasion (intrusion of adjacent normal tissues, and destruction of them through release of biological active materials), and sometimes metastasis (bring about lots of various clinical symptoms through spreading to other locations in the body via lymph or blood) (WCRF 2007). More than 10% of all deaths worldwide are caused by cancers (WHO July 2008), and control with currently available medicines is limited despite dramatic improvements. Cancers have been reported to be associated with various genetic factors, radiation, virus, chemicals, drugs, age, race, income or education level, smoking, and diet. It is known that about 80-90% of nearly all cancers may be associated with environmental factors, and about 35% of them may be due to the effects of dietary factors (Doll and Peto, 1981). Therefore, selection of food can influence whether prevention or promotion of cancer development results. Some specific foods in Asia have attracted particular attention with regard to neoplasia, two examples being 'soy foods' and 'ginseng'.

Soy foods and protective effect on cancers

Soy or soybean (soya or soya bean) is one of legumes with yellow (white) color, and is distinguished with peas, beans, and lentils in legumes. Most research pointing to positive effects on cancers are related to hormone-dependent cancers. In addition to examples of phytochemicals with functions as antioxidants (preventing cellular aging and injury, and exclude oxidative reaction in DNA, lipids, and cellular membrane as they combine with and eliminate free radicals), there are a number of compounds from plants with similar chemical structures to estrogen in human body and naturally occurring oestrogenic activity. These are called 'phytoestrogens', and soy phytoestrogens (isoflavones) comprise mainly genistein (60%) and daidzein (30%), with smaller quantities of glycitein (10%). Genistein and daidzein are able to bind to oestrogen receptors, albeit with a lower affinity than oestradiol (Eldridge and Kwolek, 1983). Isoflavones have been reported to have beneficial effects on prevention and treatment for dyslipidemia and osteoporosis as well as breast cancer, endometrial, prostate, colon, lung, and skin cancers.

The lower breast and prostate cancer mortality rates in Asian countries and the potential anti-oestrogenic effects of phytoestrogens have led to speculation that soy foods reduce risk of these particular types of hornone-dependent cancers (Jian, 2008). They also act as antioxidants to inhibit free radical damage, and have antiproliferative properties to inhibit tumour growth (The Cancer Council September, 2006). Estrogen, which is a female hormone in body, can promote breast or endometrial cancer, and isoflavones are, especially, known well to halt proliferation of breast or endometrial cancer cell as they combine with estrogen receptor and interrupt

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the activity of estrogen in body. They also lead to apoptosis (automatic death of cancer cell) or interrupt the nutrients absorption of cancer cells that lead to a reduction in cancer cell proliferation and angiogenesis by halting the action of enzymes relating to them (Zhou et al., 1999; Bylund et al., 2000; Castle and Thrasher, 2002; Zhou et al., 2002).

The exact mechanism of action by which soy consumption is associated with a lower risk of prostate cancer remains to be elucidated. Short intervention studies show that serum sex hormone-binding globulin concentrations increase in men consuming tofu (Habito et al., 2000; Habito and Ball 2001). In communities consuming traditional soy foods, estimates of average isoflavone intakes range between 11 and 54mg/day (Ho et al., 2000; Somekawa et al., 2001).This is equivalent to one or two servings of soy foods on a daily basis. Generally, it is thought that 30-50mg of isoflavones is enough to offer health benefits.The ability to produce equol or equol itself may be closely related to the low incidence of prostate cancer in the region (Akazu et al., 2002; 2004), Since higher consumption of soybeans and green tea are strongly related to the establishment of a capacity for equol production (Miyanaga et al., 2003), the change in dietary habits resulting in low incidence of equol production in the young generation is a major potential risk factor for prostate cancer, not only in Japan but also in Korea (Fujimoto et al., 2008).

Soy also includes 'saponins' (about 0.5% of soy) which is a kind of glycosides and is reported as antitumor ingredient. Recent publications describing anticancer activity of crude and purified soybean saponins have sparked a renewed interest in these compounds. In recent review, the epidemiological studies were summarized concerning the cancer protective effects of soy and the efforts to elucidate the constituents responsible for this effect (Kerwin, 2004). It is concluded that the soy saponins may represent promising leads both in terms of elucidating the soy constituents involved in the cancer protective effect of soy as well as in the discovery of anticancer agents with novel mechanisms of action. Some experimental studies were conducted to evaluate the effects and mechanisms of soybean saponins on cancer cells (Sung et al., 1995; Koratkar and Rao, 1997; Oh and Sung, 2001; Gaidi et al., 2002; Tin et al., 2007). Taken together, those study results suggest that soybean saponins have a significant growth-inhibitory effect on colon tumor cells in culture.

Foods containing soy include tofu (bean curd), soy milk, or soy flour, tempeh (a Indonesian food fermented from soy), etc., which are rich sources of phytoestrogens (The Cancer Council September, 2006). However, studies vary as to whether they report on the different types of soy products. Although fermentation of soy can reduce the amount of isoflavones present, the bioavailability of isoflavones is higher in fermented products (Cornwell, Cohick et al. 2004). Tofu contributes the largest amount of soy to most Asian diets (Wu, Ziegler et al. 1998). Whereas the majority of the isoflavone/phyto-oestrogen intake comes from non-soy foods, such as soy additives in baked goods, tuna or coffee in western diets (Horn-Ross et al., 2000).

Current studies are still lack to clarify protective effect on cancers of soy. While most of studies reported a protective effect of soy foods on cancers, some epidemiological or experimental studies also showed no association between soy foods and the risk of cancers. In 2004, the American Soybean Association petitioned the Food and Drug Authority in the USA for permission to use a health claim for the association between soy protein intake and lower risk of certain cancers, including breast cancer. However, the inconsistency of the evidence appears to have been the driving force in the withdrawal of this petition for a health claim (The Cancer Council September, 2006). The World Health Organization in the Diet, Nutrition and the Prevention of Chronic Diseases Report (2003), the Committee on Medical Aspects of Food and Nutrition Policy in the Nutritional Aspects of the Development of Cancer report (1998), and the World Cancer Research Fund in Food, Nutrition and the Prevention of Cancer (Glade 1999) concluded that there was insufficient evidence that soy foods or phytoestrogens reduce the risk of cancers.

Many epidemiological studies were conducted to test the effect of soy intake on various cancer risks. Among them, the association between soy intake and the breast cancer risk is most studied. A recent meta-analysis (12 case-control and 6 cohort studies) found that soy intake is associated with a modest reduction in breast cancer risk (odds ratio (OR)=0.86), and that the inverse association between soy exposure and breast cancer risk was slightly stronger in premenopausal women than in post menopausal women (Trock et al., 2006). In the same year, another meta-analysis was published including 21 epidemiological studies (Qin et al., 2006). This analysis added 9 more recent studies, especially published in Japanese and Chinese, and is consistent with the study by Trock et al with a stronger association. The difference in those results was caused by the observational items each analysis used. The former tried to convert the different measures of exposure into the amount of soy protein, and the latter focused on the multiple assumptions. Moreover, the analysis by Qin et al estimated the pooled relative risk with and without the addition of studies published in Japanese and Chinese. The result showed lower risk as adding those Asian studies. In 2008, Wu et al. published another meta-analysis focused on studies with relatively complete assessment of dietary soy exposure in the targeted populations (Wu et al., 2008). The analysis of 8 studies conducted in high-soy-consuming Asian countries showed a significant trend of decreasing risk with increasing soy food intake. Whereas soy intake was unrelated to breast cancer risk in studies conducted in Western populations in which the average intake of was low and exposure is mainly in the form of soy components added as fillers/extenders to typical Western foods. Comparing with this, a prospective study (the Japan Collaborative Cohort (JACC) Study, 1988 - 1990, 30,454 women aged 40-79 years) suggested that consumption of soy food has no protective effects against breast cancer (Nishio et al., 2007).

For endometrial cancer, there is some limited evidence to suggest that phyto-oestrogens have enough

oestrogenic activity to stimulate cell growth in the endometrium of post menopausal women, although the evidence overall is inadequate to draw conclusions on whether phyto-oestrogens taken by premenopausal or post menopausal women eventually would cause endometrial cancer (Sacks et al. 2006). Sakauchi et al. found that a high intake of soy bean curd (tofu) might have preventive effects against the risk of ovarian cancer in their analysis (The Japan Collaborative Cohort (JACC) Study, 1988-1990, 46,465 men and 64,327 women observed until the end of 2003) (Sakauchi et al., 2007). Soy foods may also be protective in the endometrium (Xu et al., 2004; 2007).

For prostate cancer, some trials (although not randomized) suggest that phytoestrogen supplements may benefit some patients with prostate cancer, by decreasing or stabilizing PSA values but the evidence is too limited to recommend supplementation (Hussain et al., 2003; Kumar et al., 2004). In 2005, Yan and Spitznagel published a meta-analysis to evaluate epidemiologic studies of soy and prostate cancer (Yan and Spitznagel, 2005). Results of the analysis including 8 epidemiological studies showed the consumption of soy food was related to an approximately 30% reduction in prostate cancer risk. Even the overall risk reduction was significant, only the 3 studies in the analysis showed statistically significant lower risk of prostate cancer. Those results are consistent with findings from a cross-national analysis of prostate cancer mortality in relation to nutritional factors using data from United Nations sources (Hebert et al., 1998). In this analysis, soy consumption was correlated with a significantly lower mortality rate from prostate cancer.

In the relation of soy to the stomach cancer, there is inconsistent evidence mostly from case control studies. Some case-control studies conducted to evaluate the effect of soy intake on stomach cancer found decreased risk for the highest intake groups when compared to the lowest (You et al., 1988; Hoshiyama and Sasaba, 1992; Ji et al., 1998; Gao et al., 1999; Takezaki et al., 2001; Hamada et al., 2002; Kim et al., 2002; Nan et al., 2005) which was statistically significant in five studies (You et al., 1988; Hoshiyama and Sasaba, 1992; Ji et al., 1998; Gao et al., 1999; Kim et al., 2002). An apparent dose-response relationship was seen in those studies.

There does not appear to be an association between soy consumption and colorectal cancer (Spector et al., 2003). Although most case-control and cohort studies show weak inverse associations between higher soy consumption and colorectal cancer, the results have not been statistically significant, with most of the confidence intervals crossing one (Spector et al., 2003). Another study (1992-2000, 13,894 men and 16,327 women) also exhibited a weak benefit of soy foods only among women in colorectal cancer risk (Oba et al., 2007).

The results from experimental studies have been also conflicting, with soy foods and phytoestrogens showing both risk enhancing and risk reducing effects. A better understanding of the factors that affect the bioavailability of ingested phytoestrogens, such as absorption rate, incorporation rate into the bloodstream, and metabolism of the intestinal bacterial environment, are required. In addition, the issue of when soy foods are eaten during the lifetime needs to be also resolved, with early life exposure to soy foods appearing to be of most benefit.

There were many reports related to antitumor effect of phytoestrogens with soy products. However, there is still a need for better quality, well-reported larger and longer duration studies with other nutritional factors. Studies need to be performed in populations with sufficient variation in intake of soy and phytoestrogens.

Caution is required in interpreting the results of epidemiologic studies relating to phytoestrogens due to potential exposure misclassification, confounding and lack of a dose response, whereas, safe and efficacious levels of phytoestrogens could not also have yet to be established for cancer prevention. The Cancer Council supports the consumption of soy foods in the diet rather than use of supplements such as soy protein isolates or isoflavone capsules for healthy men and women to prevent cancer. As the results of some experimental studies suggest adverse effects from phytoestrogens, high dose phytoestrogen supplementation is not recommended or justified, especially for women with existing breast cancer. There is evidence to support that women with existing breast cancer or past breast cancer should be cautious in consuming large quantities of soy foods or phytoestrogen supplements, and clinical trials to assess the efficacy and safety of soy foods and supplements for women with existing breast cancer are also needed (The Cancer Council September, 2006). It would be also useful in future studies to report associations for both soy foods and specific phytoestogens.

Ginseng and its Protective Effects Against Cancers

The scientific name of ginsengs is 'Panax ginseng', and 'Panax' means 'cure all diseases' in Greek. Ginseng is a deciduous perennial plant that belongs to the *Araliaceae* family. Currently, twelve species have been identified in the genus Panax. Among them, *Panax ginseng* C. A. Meyer (Araliaceae), cultivated in China, Korea, Japan, Russia, and the US, *P. quinquefolium* L (American ginseng), grown in southern Canada and the US and *P. notoginseng*, cultivated in Yunnan and Guangxi provinces in China, represent the three most extensively investigated species (Yun, 2001). In Asia, it has been widely believed that ginseng is a miraculous medicine or mysterious tonic, improves one's physical condition, and prolongs life with long-term administration (Yun, 2001).

Ginseng have been proven as an excellent food for preventive effect on various types of human cancers through many evidences.An animal study, the life in animals (with cancer) injected ginsengs was longer than animals (with cancer) injected anticancer medicine. There was also a report that treatment of cancer more decreased in patients with cancer has taken ginsengs than anticancer medicine.

Major antitumor ingredients in ginseng are polyphenol compounds and saponins. Polyphenol compounds prevent the formation of carcinogen-induced tumors as they halt cancer cell proliferation as well as eliminate free radicals and active oxygen. Saponins are rich in ginsengs

with 5% of them. Especially a group of compounds called ginsenosides which recent studies indicate that they might act in a similar way as steroid hormones attributes to the effect in combating cancer.

In a recent study in China, it has been found that ginsenosides can act as functional ligands to activate different steroid hormone receptors (Yue et al., 2007) Through such mechanisms, ginseng can exert its effects on the human body by acting in a similar way as the steroid hormones. The study results show that the anti-tumour effects of ginsenosides include its ability to induce cell death (such as apoptosis and necrosis), and having effects of anti-proliferation, anti-invasion and metastasis, and anti-angiogenesis.

Ginseng has been established as non-organ specific cancer preventive, having dose response relationship (Yun et al., 2001). In case-control studies, odds ratios (OR) of the cancer of lip, oral cavity and pharynx, larynx, lung, esophagus, stomach, liver, pancreas, ovary, and colorectum were also significantly reduced with ginseng (*Panax ginseng* C.A. Meyer) intake (Yun, 2003). Another findings strongly suggested that ginseng (*Panax ginseng* C.A. Meyer) cultivated in Korea is a non-organ specific cancer preventive against human cancers and also indicated that the anticarcinogenicity or human cancer preventive effect of ginseng (*Panax ginseng*) is due to ginsenoside Rg(3), Rg(5) and Rh(2), saponin components in red ginseng.

Although ginsengs may have protective effect on various cancers as above, they have been mainly associated with reduction of gastric cancer (60-70% reduction in gastric cancer risk) (Suh et al., 2002). Suh et al. look at the effects of red ginseng upon postoperative immunity and survival in patients with stage III gastric cancer.This study demonstrated a five-year disease free survival and overall survival rate that was significantly higher in patients taking the red ginseng powder during postoperative chemotherapy versus control (68.2% versus 33.3%, 76.4% versus 38.5%, respectively, $p < 0.05$). In a cohort study with 5 years follow-up also conducted in a ginseng cultivation area, the relative risks (RRs) of ginseng users were decreased in gastric cancer and lung cancer comparing with non-users (Yun and Choi, 1998). Further evaluation in Asian cohort studies may help to clarify ginseng's role in gastric carcinogenesis.

Antitumor effect of ginseng has difference according to its habitat, type of intake or processing, etc. In classification according to habitat, the most commonly used types of ginseng are American ginseng (*Panax qinquefolius*), and white and red ginseng, which are prepared from Chinese/ Korean ginseng (*Panax ginseng*) (Kamangar et al., 2007). *Panax ginseng* C.A. Meyer has been the most highly recognized medicinal herb in the Orient (Yun, 2003), and Korean ginseng includes the most saponins (34 types) comparing with American or Chinese ginseng (both, 14 types) (KSG, 2004).

According to the type of intake, undried ginseng (raw, non-processed type), dried ginseng, and red ginseng (steamed and dried with undried ginseng) are classified. Undried ginseng has a problem for short preservation period because it includes a high moisture content (75%). The preservation period of dried ginseng (14% moisture) is about 2 years, and that of red ginseng is about 10 years because some enzymes are inactivated, and quality is improved (increase of some ingredients and formation of new pharmacological ingredient). Red ginseng also includes most saponins (30 types) comparing with dried ginseng (22 types), therefore, red ginseng is the most excellent ginseng product. As to the same type of the ginseng (*Panax ginseng* C.A. Meyer), the ORs for cancer were reduced in user of fresh ginseng extract intakers, white ginseng extract, white ginseng powder, and red ginseng (Yun, 2003). However, natural type may be more recommended than isolated, refined, made as a medicine or fortified type to other foods.

Adverse effects on over-intake of specific foods like ginseng having antitumor should be carefully considered, and objective toxicity test is still needed. More studies also need a larger sample size to fully evaluate the antitumor effect of ginseng and need to establish this mechanism of action as well as identify the active components associated with antitumor activity and immunomodulation with advanced cancers.

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