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Topic 3.6

Toxicity vs. beneficial effects of phytoestrogens*

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Abstract: Phytoestrogens are nonsteroidal plant-derived compounds possessing estrogenic activity. These include two major classes: isoflavonoids and lignans. Phytoestrogens have have received recently great attention because of their beneficial effects, which include the prevention of cancer, atherosclerosis, and bone density loss. However, they have estrogenic activity and may affect as endocrine disruptors. In this review, we pay attention to both the toxic and beneficial effects of phytoestrogens.

Epidemiological data support that isoflavonoids help prevent cancer of breast, prostate, stomach, and lung. However, there have been some reports about a positive association between some phytoestrogens (e.g., campesterol and stigmasterol) and prostate cancer risk. Animal experiments and in vitro experiments have shown that the biological effects of phytoestrogens may be organ-specific, inhibiting cancer development in some sites, yet showing no effect or an enhancing effect on tumorigenesis at other sites. Also, their effects may be dependent on the timing and duration of exposure. For example, several studies in rodents have established that the favorable effect of an isoflavone-rich diet on breast cancer risk may be significant only if consumption occurs before puberty or during adolescence. On the other hand, prenatal exposure of genistein was reported to have a carcinogenic effect on the uterus of rodents. Phytoestrogen, especially soy products, has been used as hormone-replacement therapy, reducing such symptoms as hot flashes, vaginal dryness, and mood changes while protecting women from osteoporosis and heart disease. However, the animal data suggest that the timing of exposure to such compounds is crucial, with neonatal exposure having the most pronounced effects. Given the exposure of neonates to phytoestrogens, this should be a cause for concern.

INTRODUCTION

Phytoestrogens are nonsteroidal plant-derived compounds that may mimic or interact with estrogen hormones in mammals. Phytoestrogens include two main groups: isoflavones and lignans. For isoflavones, the main dietary sources for humans are soybeans and other legumes. Mammalian lignans are products of intestinal microbial breakdown of plant lignans found in whole grains, fibers, and flax seeds, and many fruits and oil.

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Epidemiological studies suggest that the consumption of a phytoestrogen-rich diet may have beneficial effects on health. As phytoestrogens can have both agonist and antagonist action on estrogenic activity, it has also been proposed that dietary phytoestrogens could play a role in the prevention of certain cancers (breast, uterus, and prostate) in humans. Phytoestrogens were also found to modulate other estrogen-related disorders when consumed in ordinary diet, namely cardiovascular diseases, menopausal symptoms, and post-menopausal osteoporosis. On the other hand, consumption of relatively high levels of some phytoestrogens may pose some health risk. Reproductive problems have been documented in laboratory animals, farm animals, and wild animals that consumed very high amounts of phytoestrogen-rich plants. In this review, we pay attention to the beneficial effects and toxicity of phytoestrogens.

BENEFICIAL EFFECTS

Phytoestrogens and cancer

Diets rich in phytoestrogens (plant estrogens, particularly soy and unrefined grain products) may be associated with low risk of some hormone-dependent cancers.

Breast cancer

Reduced risk of breast cancer in premenopausal women was found to correlate significantly with high soy intake in Singapore [1,2]. Another experiment showed that soy intake during adolescence conferred a strong significant protective effect on breast cancer [3]. In addition, most recent reports revealed that high soy intake in childhood in Asian-Americans is associated with reduced breast cancer risk, which may be further reduced by intake as an adult. These benefits do not extend to Westerners, however, who don't traditionally eat these products [4].

Numerous in vitro studies on breast cancer cells in culture have shown that phytoestrogens stimulate tumor growth when administered at low concentrations but inhibit tumor growth at high concentrations. Genistein, an isoflavone found in soy products, was found to exert antiproliferative effects when administered at concentrations above 10 micromolars (μM) to both positive estrogen receptor (ER+) and negative estrogen receptor (ER–) human breast cancer cells in vitro [5,6]. But it exerted marked hyperproliferative effects when administered at concentrations below 100 nM due to its estrogen agonistic actions [6]. At higher concentrations, the chemoprotective effects of genistein are mediated by multiple mechanisms independent of ERs, such as inhibition of tyrosine kinase activity of growth factor receptors and oncogene products [5].

Genistien markedly inhibited dimethylbenazanthracene- (DMBA-) and methyl-nitrosourea- (MNU-) induced rat mammary carcinogenesis during the neonatal or prepubertal and perinatal periods [7–11]. Several studies in rodents established that the favorable effects of isoflavone-rich diet on breast cancer may be significant only if administration occurred before puberty or during adolescence [8–10]. These results demonstrate that the timing of exposure to the isoflavones is important for breast cancer chemoprevention [12]. These important experimental studies have now gained support from a recent human study in which high soy intake during adolescence was found to reduce the risk of breast cancer later in life [3,4].

Soy isoflavones may reduce breast cancer risk by affecting endogenous sex hormone concentrations and the menstrual cycle [13]. There is evidence from early studies in vitro and in vivo that suggests that phytoestrogens stimulate the production of sex hormone binding globulin (SHBG) in the liver cells [13,14]. An increase in SHBG, leading to lower free-sex-hormone concentrations and a longer menstrual cycle, which would lower breast cancer risk, was seen in some, but not all, studies [13,15,16].

Endometrial cancer

A case-control study in Hawaii [17] showed that high consumption of soy products and other legumes was associated with a decreased risk of endometrial cancer (p for trend = 0.01; odds ratio = 0.46).

However, animal experiments do not support the epidemiological data (see toxicity of phytoestrogen, endometrial cancer).

Prostate cancer

Epidemiological data of phytoestrogens and prostate cancer strongly support the cancer protective effects of isoflavones found in soy products [18].

In experimental animal studies, many of the studies with dietary administration of soy, pure isoflavones, or rye bran reduced the incidence of prostatic carcinomas [19–22].

Prostate tissues have both estrogen receptor ERα and ERβ [23]. ERβ binds phytoestrogens and may inhibit ERα-mediated estrogen action through heterodimerization [13]. It could be postulated that the mechanisms of genistein could help prevent prostate cancer by regulating steroid-receptor pathways [24]. It inhibits the expression of epidermal growth factor and the erbB2 receptors in rat dorsolateral prostate, and could, therefore, block the growth factor-mediated stimulation of cell proliferation [25].

Colon cancer

A number of epidemiological studies, primarily of Asian origin, have examined the relationship between soy intake and the risk of colorectal cancer; however, these studies provide little support for a protective effect of soy [26]. In animal experiments, rye bran, flax seed, and purified lignans seemed to protect against colon carcinogenesis [27,28]. However, some studies provided little support for a protective effect of soy, rich in phytoestrogens [29,30].

Other cancers

Recently, a prospective study has reported that soy intake may reduce the mortality rate of stomach cancer [31]. Another case control study of the relationship between soy products and cancer, conducted in the Far East, reported that increased soy consumption is also protective in lung and stomach cancers [32].

Phytoestrogens as hormone replacement therapy

Selective estrogen receptor modulators (SERMs) have been developed to restore the benefits of traditional hormone therapy while avoiding undesired side effects. Phytoestrogens may be added to the list of SERMs, given their agonist/antagonist properties in estrogen-sensitive tissue [33]. The ideal SERMs would treat postmenopausal symptoms, such as hot flashes, vaginal dryness, and mood changes, while protecting women from osteoporosis and heart disease. More women have looked to phytoestrogen, such as the isoflavones found in the soy plant, to tailor their menopausal therapy in a "natural" way.

The most widely studied phytoestrogens are genistein and coumestrol, which both exerted typical estrogen-like actions in female and male experimental animals [34–36]. Animal studies suggest that soy protein and/or isoflavones may prevent cardiovascular disease by multiple mechanisms [37,38] and inhibit ovariectomy-induced bone loss in rats [39]. The protective effect could be related to reduction in androgen production, either via central nervous system-gonadal axis, or through inhibition of 5-reductase and, consequently, a decrease in the synthesis of dihydrotestosterone, which is the most active androgen in the prostate [40,41].

Reports concerning broad tissue distribution of ERβ [42,43] that show that phytoestrogens usually bind with ERβ [44] indicate that it may be possible to develop new natural substances from phytoestrogens for treatment and prevention of menopausal symptoms, including osteroporosis, and cardiovascular disease.

Toxicity of phytoestrogens

Endometrial cancer

Newbold et al. (2001) showed that uterine adenocarcinoma was induced in mice that were treated neonatally with diethylstilbestrol (DES) or genistein [45]. In this experiment, newborn female CD-1 mice were treated on days 1 through 5 with DES at the dose of 0.001 mg/kg/day subcutaneously (s.c.) or with genistein at the dose of 50 mg/kg/day, s.c. At 18 month of age, incidence of uterine adenocarcinoma was 31 % for DES-treated mice, 35 % for genistein-treated mice, and 0 % for control mice. Such a close correlation of activities indicates that the critical events in the carcinogenic effect of these two chemicals on the mouse uterus resulted from ER-mediated interactions in the neonates [46].

Prostate cancer

Although most of the epidemiological studies of phytoestrogens and prostate cancer indicated the protective effects of isoflavones on prostate cancer, an epidemiological study indicates an increase of prostate cancer risk due to some phytoestrogens (campesterol and stigmasterol) [47].

Colon cancer

In a report promoting the potential of genistein in colon tumor model [48], Rao et al. investigated the effects of genistein on azoxymethane- (AOM-) induced colon carcinogenesis in male F344 rats, and revealed that administration of genistein (250 ppm in diet) significantly increased noninvasive and total adenocarcinoma multiplicity in the colon, as compared to the control diet [48]. The results of this investigation emphasize that the biological effects of genistein may be organ-specific, inhibiting cancer development in some sites yet showing no effect or an enhancing effect on tumorigenesis at other sites, such as the colon [48].

Other cancers

Some recent reports revealed strong in vitro genotoxicity, as well as in vivo carcinogenic potential of soy isoflavones in p53 knock-out mice [49]. In a recent experiment in our lab, genistein enhanced lung carcinogenesis in rat medium-term multi-organ carcinogenesis bioassay at dietary doses of 25 and 250 ppm [50].

PROBLEMS OF PHYTOESTROGENS AS A SOURCE OF HORMONE REPLACEMENT THERAPY

Although phytoestrogens are thought to contribute to the prevention of hormone-dependent cancers, compounds with estrogenic activity also have the capability of causing endocrine disruption, particularly when exposure occurs prior to puberty [51]. Phytoestrogens are also capable of altering the toxicological behaviors of other endocrine active compounds, and the interactions of these compounds may involve complexities that are difficult to predict based on their in vitro steroid receptor reactivities. The primary concern of phytoestrogens as dietary supplements stems from the reports that estrogens are associated with perinatal toxicity to the reproductive tract. During the fetal and early period, when reproductive organs are developing, changes in the hormonal milieu can induce dramatic structural and functional alterations in the reproductive tract of both male and females [52]. You et al. investigated the potential of the phytoestrogen genistein to influence the reproductive developmental toxicity of the endocrine active pesticide, methoxychlor [53]. The estrogenic responses to genistein and methoxychlor administered together were apparently accumulative of the effects associated with each compound alone. Soy-based formula for human infant nutrition is widely used, with approximately 25 % of formula-fed infants in the United States consuming soy-based formula [54]. Infants consuming soy formula are exposed to high levels of genistein and daidzein. On average, infants fed soy-based formula consume isoflavones an order of magnitude greater than adults eating high-soy diets. Total plasma levels of isoflavones and genistein in soy-fed infants are 10-fold greater than levels in Japanese adults whose diets have traditionally induced soy, and 200-fold greater than plasma levels in infants fed cow's

milk formula or human breast milk. Total plasma isoflavone levels in soy-fed infants are up to 22 000 times greater than 17β-estradiol levels [55]. However, estrogenicity of genistein is only one 1000th to one 10 000th that of 17β-estradiol [56]. Yellayi et al. [57] recently have examined thymic and immune effects of genistein in mice, and reported the possibility that serum genistein concentrations found in soy-fed infants may be capable of producing thymic and immune abnormalities, as suggested by previous reports of immune impairments in soy-fed human infants [58,59]. For the phytoestrogen genistein, it has been shown that injections of neonatal female rats with high doses of genistein (500 or 1000 μg/day on days 1 through 10 after birth) decreased basal luteinizing hormone (LH) levels and pituitary responsiveness to gonadotrophin-releasing hormone (GnRH) and increased the volume of the sexually dimorphic nucleus of the hypothalamus [60]. On the other hands, lower doses of genistein (10 to 100 μg) had opposite effects on LH secretion and increased pituitary response to GnRH. More recent developmental toxicology studies have demonstrated that dietary exposure to physiological concentrations of genistein yields little or no toxicity [61]. Most recent studies revealed that supraphysiological concentrations of daizein administered via the diet did not cause significant toxicity to the female reproductive tract or provide a protective effect against chemically induced breast cancer [62]. Recently, Burton and Well reported on the effect of phytoestrogens on the female genital tract [63]. This review discussed the evidence from both animal studies and humans of an effect of these ubiquitous compounds on the development of the human female genital tract, in addition to prolonging the menstrual cycle, alleviating symptoms of menopause, and protecting against the development of endometrial carcinoma.

CONCLUSION

In conclusion, the animal data suggest that the timing of exposure to such compounds is crucial, with neonatal exposure having the most pronounced effects. Given the exposure of neonates to phytoestrogens, this should be a cause for concern. It has been assumed that exposure to these compounds is always good, but inappropriate or excessive exposure may be detrimental [64]. Many natural compounds, especially natural hormones, can be potent and can have both good and bad health affects, because, like any other hormone, too much or too little can alter hormone-dependent cellular and tissue functions. These substances should be used in moderation to avoid any unintentional health consequences. At present, because there is too little information to make any firm conclusions on the impact of phytoestrogens on human health, we need more information on well-designed animal studies.

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