



Breast Cancer Prevention with a Plant-Based Diet



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Abstract

Diet may be an independent risk factor for breast cancer, along with alcohol, physical activity, BMI and smoking. Several epidemiological studies show a decreased risk of breast cancer for vegetarians and vegans. Studies show an increased risk in women exposed to heterocyclic amines (HCAs), polyaromatic hydrocarbons (PAHs) and persistent organic pollutants (POPs). POPs resist environmental degradation and accumulate in animal adipose tissue, while PAHs and HCAs are produced during cooking of meat. In addition to reducing their exposure to these carcinogenic compounds, those following a plant-based diet benefit from the increased consumption of phytochemicals and fiber found in plant foods. In particular, studies show that soy may reduce the risk of breast cancer and breast cancer recurrence, due to its isoflavone content. Dietary fiber also reduces the risk of breast cancer, most likely by affecting estrogen levels. Most breast cancer patients tend to be older. The plant-based diet can reduce the risk of common comorbidities in post-menopausal women such as type II diabetes, coronary artery disease, arthritis, hypertension and thyroid disease. The plant-based diet is safe and has no adverse reactions or contraindications. It presents a valuable additional therapeutic measure to chemotherapy, radiation and surgery which will continue as standard of care.

Keywords: Breast cancer; Carcinogens; Dietary fiber; Estrogen; Heterocyclic amines; Persistent organic pollutants; Plant-based diet; Polyaromatic hydrocarbons; Phytochemicals; vegan

Abbreviations: BMI: Body Mass Index; ER+: Estrogen Receptor Positive; HCAs: Heterocyclic Amines; HER2: Human epidermal growth factor receptor-2; PAHs: Polyaromatic Hydrocarbons; PCBs: Polychlorinated Biphenyls; POPs: Persistent Organic Pollutants; PR+: Progesterone Receptor Positive

Introduction

The World Cancer Research Fund (WCRF) and American Cancer Society (ACS) cancer prevention guidelines recommend maintaining a healthy weight, undertaking at least 150 minutes of moderate intensity exercise per week, limiting alcohol consumption, and eating a plant-based diet [1]. Recent expert reports estimate that successful lifestyle changes could prevent 25% to 30% of cases of breast cancer [1]. In a study of post-menopausal women, the lowest quintile level of a combination of selected modifiable risk factors (diet, alcohol, physical activity, BMI, and smoking), compared to those in the highest quintile level had 30%, 37%, and 30% lower risk for overall, ER+/PR+, and HER2+ breast cancers respectively [2]. This study observed inverse associations between the modifiable factors and risk of breast cancer, irrespective of nodal status, tumor grade, and stage of the disease. Most individual lifestyle factors were independently associated with the risk of breast cancer.

It appears that diet may be an independent risk factor for breast cancer. In addition, studies show that those who follow a

plant-based diet have lower rates of obesity, a risk factor for breast cancer independent of diet. For instance, in one study patients following a plant-based diet had an average BMI of only 23 [3]. In light of the fact that a plant-based diet helps reduce the risk and recurrence of both prostate cancer [4] and colon cancer [5] it is not surprising that it is efficacious for breast cancer as well.

Epidemiology

Several studies show a decreased risk of breast cancer for vegetarians and vegans:

In a study of Taiwanese vegetarian women, long term vegetarians had a 58% reduced risk of breast cancer, compared to women following an omnivorous diet. Looking at specific foods, frequent consumption of meat and animal fat increased the risk of breast cancer 2.2 times, and processed meat increased the risk 49%, while soy isoflavones decreased the risk [6].

In a study of women who follow a healthy lifestyle, those following a vegan diet showed a not-quite-significant 22%

reduced risk of breast cancer [7]. A study of lifelong South Asian vegetarians who migrated to Britain showed a not-quite-significant risk reduction of 23% for breast cancer [8]. A metastudy comparing the highest to the lowest category, red meat (unprocessed) consumption was associated with a 6% higher breast cancer risk and processed meat consumption was associated with a 9% higher breast cancer risk both before and after menopause, although results were not quite significant for premenopause [9].

Carcinogenic compounds

Research has shown the carcinogenicity of persistent organic pollutants (POPs), heterocyclic amines (HCAs), and polyaromatic hydrocarbons (PAHs). Meat and other animal products are the main sources of these compounds in the human diet.

Persistent Organic Pollutants

Persistent organic pollutants (POPs) are a group of synthetic organic chemicals used for industrial, agricultural or domestic purposes, that persist in the environment and progressively bioaccumulate and concentrate in the food chain due to their lipophilic properties [10,11]. They include dioxins, furans, polychlorinated biphenyls (PCBs), and organochlorine pesticides, chemicals mainly created by industrial activities either intentionally or as by-products [12]. The introduction of POPs into the environment from anthropogenic activities has resulted in their widespread dispersal and accumulation in soils and bodies of water, ecological food chains, and in humans where they are known to induce toxic effects. There is evidence of long range transport of these substances to regions where they have never been used or produced, resulting in exposure of most human populations to POPs through consumption of fat-containing food such as fish, dairy products, and meat, [13-15] with the highest POP concentrations being commonly found in fatty fish [12-18]. Due to their ubiquity in the environment and lipophilic properties, there is mounting concern over the potential risks of human exposure to POPs [13].

A primary consideration in the evaluation of chemicals is the potential for substances to be absorbed and retained in an organism's tissues at concentrations sufficient to pose health concerns. Substances that exhibit properties that enable biomagnification in the food chain are of particular concern due to the elevated long-term exposures these substances pose to higher trophic organisms, including humans [19]. POPs measured in breast adipose tissue are associated with higher breast cancer incidence [20]. Given the abundance of adipose tissue in the human breast, mammary epithelial cells' exposure to POPs sequestered in breast adipose tissue may promote carcinogenesis and progression of mammary cancers [21]. POPs measured in breast adipose tissue were associated with higher breast cancer incidence and were associated with worse breast cancer prognosis and mortality [20].

Heterocyclic Amines

HCAs are mutagenic and carcinogenic compounds formed in meat and fish prepared by high temperature cooking methods, such as frying, grilling and barbecuing. The precursors are amino acids, reducing sugars and creatine, found specifically in muscle meat [22]. Steck et al. [23] found an association between higher lifetime consumption of grilled meats and fish and increased incidence of post-menopausal breast cancer. Laboratory studies of HCAs in systems using cultured breast cancer cells demonstrated that these chemicals can mimic estrogen, and they also can have direct effects on cell division processes in ways that might enhance the development of tumors [24].

One of the HCAs, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), the most abundant HCA in the Western diet, has been found to be a mammary gland carcinogen in rats [22]. Studies demonstrate that PhIP is also a significant DNA-damaging agent in humans [25]. Studies of both milk and cells from the ducts of women's breast revealed the presence of DNA adducts in association with HCAs [26,27].

Polyaromatic Hydrocarbons

When meat and fish are cooked over an open flame or smoked, PAHs are formed [28]. If the grilled food is in direct contact with the flame, pyrolysis of the drippings from meat or fish generates PAHs that can be deposited on its surface. Even if not in direct contact, fat dripping onto the flame or hot coals generates these compounds that can then be carried back onto the surface of the food [29,30].

PAHs are lipophilic and stored in fat tissue [31] and have been associated with breast cancer incidence [23]. The breasts are particularly susceptible to aromatic carcinogenesis, and the implementation of biomarkers has provided promising insights regarding PAH-DNA adducts in breast cancer. The use of biomarkers measuring these adducts assesses the exposure to eliminate bias inherent in self reporting measures, in case-control studies investigating the link between PAHs and cancer [30]. PAH-DNA adducts are a biomarker of recent exposure and reflect DNA damage, a step-in carcinogenesis. Detectable PAH-DNA adducts, or their proxy, have been consistently linked to breast cancer in previous studies [32-34] with one exception [35].

In 1996, Li et al. assessed aromatic adducts in human tissue from breast cancer patients undergoing mastectomy versus breast tissue from non-cancer patients undergoing reduction mammoplasty. Aromatic DNA adducts, although detected in all samples, were significantly higher in the breast cancer patients versus the healthy controls. These results indicate that PAHs may play a role in the development of breast cancer [36]. The association between PAH-DNA adducts and breast cancer incidence may be elevated even more among overweight/obese women [31].

Chemoprotective effects of plant-foods

In addition to reducing the intake of harmful substances by not consuming animal products, those following a plant-based diet have the advantage of consuming large quantities of substances that help block the development of cancerous cells. These substances are called phytochemicals. Dietary fiber found in plant foods can also play a beneficial role. Phytochemicals, often referred to as phytonutrients, are natural bioactive components rich in foods such as vegetables, fruits, whole grain products, nuts and seeds, and legumes [37].

Cancerous tissue transformation, developing usually over years or even decades of life, is a highly complex process involving strong stressors damaging DNA, chronic inflammation, interaction between relevant molecular pathways, and cellular crosstalk within the neighboring tissues [38]. The flavonoids, carotenoids, phenolic acids, and organosulfur compounds affect a number of cancer-related pathways. Phytochemicals may positively affect processes of cell signaling, cell cycle regulation, oxidative stress response, and inflammation. They can modulate non-coding RNAs, upregulate tumor suppressive miRNAs, and downregulate oncogenic miRNAs that synergistically inhibits cancer cell growth and cancer stem cell self-renewal [38].

Soy

The phytochemicals in soy have been the most studied. Questions were initially raised with regard to the isoflavone phytoestrogens found in soy, expressing concern that soy consumption could lead to the potential for an increased risk of breast cancer. However, these fears were unfounded. There is good evidence that soy foods not only do not raise the risk of breast cancer, but actually can lower it, especially when consumed early in life. Soy may also lower the risk of recurrence of breast cancer in adults.

Phytoestrogens are naturally occurring polycyclic phenols found in certain plants, with high levels in soy. These are chemicals that may have very weak estrogenic effects when they are ingested and metabolized. One important group of phytoestrogens are isoflavones [39]. The absorption and metabolism of phytoestrogens demonstrate large interindividual variability, which may relate to differences in both human pharmacokinetics and metabolism by intestinal bacteria [39]. Compared to physiologic estrogens such as 17 β -estradiol, isoflavones have approximately 100 times weaker affinities [40]. A major difference between endogenous and dietary estrogens is that once made in the ovaries, the former reach responsive tissues in the unconjugated, i.e., biologically active, form whereas dietary estrogens are almost entirely conjugated, even in portal blood just after their absorption from the intestine [41].

In an extensive and authoritative review, Messina finds that "clinical trials consistently show that isoflavone intake does not adversely affect markers of breast cancer risk, including

mammographic density and cell proliferation. Furthermore, prospective epidemiologic studies involving over 11,000 women from the USA and China show that postdiagnosis soy intake statistically significantly reduces recurrence and improves survival." [42]. In one study, premenopausal women were fed soy isoflavones for approximately 100 days and urine samples were collected to quantify estrogen excretion levels [43]. This study demonstrated that soy isoflavone consumption may exert cancer-preventive effects by decreasing estrogen synthesis, presumably by altering aromatase enzyme activity, based upon previously published reports [43]. Research shows the consumption of soy does not increase the risk of breast cancer [44] and may significantly reduce the risk of recurrence. One study showed that generous amounts of soy lowered the risk of breast cancer [45]. Soy appears safe for breast cancer patients both premenopausal and post-menopausal.

Breast cancer is known to be less common in countries where soy consumption is common [44]. The difference in breast cancer incidence rates between Western and Eastern women are largely influenced by changes in lifestyle and diet rather than genetics [46]. Several reports indicate that the occurrence of breast cancer is considerably lower in Asian women compared with other populations because they incorporate high levels of isoflavones as part of their regular diet [47,48]. The amount of dietary isoflavonoids consumed is geographically dependent. For instance, the mean daily isoflavone intake of 30 to 50mg among older individuals in Japan [49], whereas in the United States and Europe, per capita intake is less than 3mg [50,51].

As vegetarians and vegans are typically frequent soy consumers, serum isoflavone levels may increase dramatically in these groups [6]. In one study it was found that the mean isoflavone level of vegetarians was 25.9mg. Therefore, in addition to finding that vegetarians had lower breast cancer risk, the results support a possible chemo preventive effect of isoflavones [6].

Several reports demonstrate that high soy consumption during childhood may reduce one's risk of developing breast cancer later in life and that the risk may be further reduced by soy intake as an adult [52-56].

In one study, substituting median intakes of dairy milk users with those of soymilk consumers was associated with 32% reduced risk of breast cancer. Similar-sized reductions of risk was found among pre- and post-menopausal cases [57]. In another study, high dietary intake of soy isoflavones was associated with lower risk of recurrence among post-menopausal patients with breast cancer positive for estrogen and progesterone receptors, and for those who were receiving anastrozole as endocrine therapy [58]. Soy does not appear to interfere with tamoxifen or anastrozole therapy [59]. Among women with breast cancer, soy food consumption was significantly associated with decreased 34% risk of death and a 33% recurrence for the highest quartile of soy consumption [60]. The reduced risk was evident among

women with either ER-positive or ER-negative breast cancer and was present in both users and non-users of tamoxifen.

In one study, soy isoflavones consumed at levels comparable to those in Asian populations may reduce the risk of cancer recurrence in women receiving tamoxifen therapy and moreover, appears not to interfere with tamoxifen efficacy [61]. The positions of the American Cancer Society [62] and the American Institute for Cancer Research [63] are that soy foods can be safely consumed by women with breast cancer. In addition, an evidence-based conclusion in response to a recent clinical inquiry published in the *Journal of Family Practice*, was that post-diagnosis soy intake improves the prognosis of breast cancer patients [64].

Dietary Fiber

Epidemiological studies have shown conflicting results for the relationship between intake of dietary fiber and breast cancer [65]. While there has been some inconsistency of results from studies of fiber and its association with breast cancer, a random-effects meta-analysis of prospective observational studies demonstrated that high total fiber consumption was associated with a reduced risk of breast cancer. This finding was consistent for soluble fiber as well as for women with premenopausal and postmenopausal breast cancer [65]. Dietary fiber reduces the risk of breast cancer, most likely by decreasing the level of estrogen in the blood circulation [66-73]. Results of the most recent meta-analysis published in 2012, which included 17 publications, supported this hypothesis [74]. An increase in consumption of dietary fiber enhances its protective effect, indicating a possible dose response relationship [75].

A study of vegetarian women found that they have an increased fecal output, which leads to increased fecal excretion of estrogen and a decreased plasma concentration of estrogen due to the much larger amount of fiber they consume [66]. Components of dietary fiber not only absorb and retain moisture, but more importantly, combine with harmful and carcinogenic substances in the gut and promote their discharge and decomposition [76].

It may be that fiber has a greater effect on breast cancer risk in the context of a vegetarian diet than in an omnivorous one. Further studies are needed.

Clinical considerations

Most breast cancer patients tend to be older. When treating these patients, comorbidities must be considered. The prevalence of comorbidities among women treated for breast cancer aged older than 66 is 32.2%, a statistic comparable to those without cancer at 31.8% [77]. The presence of comorbidities in patients with cancer has been negatively associated with patients' health outcomes. Poorer survival from cancer has been found overall in cancer survivors with comorbidities compared to those without [78,79]. In developed countries, 40% of breast cancer patients are older than 65 years of age at diagnosis,

of whom 16% additionally suffer from diabetes [80]. Older women are more likely to die of diseases other than breast cancer, and cardiovascular disease (CVD) is the most frequent cause [81,82]. In older, postmenopausal women, the risk of mortality attributable to CVD is higher in breast cancer survivors than in women without a history of breast cancer. This greater risk typically manifests itself 7 years after the diagnosis of breast cancer, which highlights the need to reduce the additional burden of CVD during this time frame with early recognition and treatment of CVD risk factors [83].

One study of breast cancer patients showed that the prevalence of hypercholesterolemia at 22%, arthritis at 44% hypertension at 44% and thyroid disease at 30% [84]. A plant-based diet can help prevent and treat these diseases and can be very efficacious [85-88]. For instance, in one study a plant-based diet was found to be twice as efficacious in treating type 2 diabetes as Metformin [89]. A plant-based diet can also lower cholesterol as much as lovastatin [90]. Angina can also be treated with a plant-based diet, with one study showing 74% of patients put on a plant-based diet had no pain after 12 weeks and an additional 9% had pain reduction. (91) A plant based can lower the risk of both Grave's disease and Hashimoto's thyroiditis [88] and treat arthritis [86,87]. In treating their comorbidities, while also reducing the risk of breast cancer recurrence, the plant-based diet thus provides a double benefit for the patient.

Patient compliance on plant-based diets has been good in almost all studies. The degree of compliance has often been very high. For instance, one study obtained a 99% compliance [92]. In a 22-week study 94% of subjects on a vegan diet were compliant [93]. In a somewhat longer study, 84% of the participants in each group completed all 24 weeks [94]. In studies of patients placed on plant-based diets for coronary artery disease, high compliance has been noted even over several years. For instance, one study of patients placed on a plant-based diet showed 89% compliance for 3.7 years [95]. Compliance may be enhanced when the rationale for the treatment, and that the treatment is backed by research, is explained to the patient [96]. The doctor should prescribe the treatment by writing it down on a prescription form or other stationery with the physician's name on it. This written prescription is not only valuable to the patient but can also be valuable in enlisting the support of family, friends and social contacts. It may take a few weeks for the treatment effects to become evident. Lab work and follow up visits should be scheduled accordingly.

Discussion

There are multiple risk factors for breast cancer. Some are not modifiable but other risk factors are modifiable, in particular those which are lifestyle related. A plant-based diet can help reduce the risk of breast cancer and its recurrence. While getting sufficient physical exercise and reducing consumption of alcohol

and cigarettes are well established, fewer patients are aware of the impact of their dietary choices. It is important for the physician to explain how their food choices impact their risk of breast cancer. Some plant foods seem to be especially valuable. Soy, especially when its consumption starts before puberty, can reduce the risk of breast cancer. Soy may also have some efficacy in preventing recurrence of breast cancer especially when consumed in generous amounts. Soy is now widely considered safe.

The plant-based diet has no adverse reactions and no contraindications. It can safely be used as an adjunct to pharmacotherapy. It presents a valuable additional therapeutic measure to chemotherapy, radiation and surgery which will continue as standard of care. It also helps provide some sense of locus of control that many oncology patients desire. Vegetarian and vegan diets are not so unusual as they once were. Patient awareness of these diets is much higher than they used to be, and thus prescribing a plant-based diet is likely to be met with higher patient acceptance than in the past.

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