Diet and risk of breast cancer

Diet may play a role in both promoting and inhibiting human breast cancer development. In this review, nutritional risk factors such as consumption of dietary fat, meat, fiber, and alcohol, and intake of phytoestrogen, vitamin D, iron, and folate associated with breast cancer are reviewed. These nutritional factors have a variety of associations with breast cancer risk. Type of fat consumed has different effects on risk of breast cancer: consumption of meat is associated with heterocyclic amine (HCA) exposure; different types of plant fiber have various effects on breast cancer risk; alcohol consumption may increase the risk of breast cancer by producing acetaldehyde and reactive oxygen species (ROS); intake of phytoestrogen may reduce risk of breast cancer through genomic and non-genomic action; vitamin D can reduce the risk of breast cancer by inhibiting the process of cancer invasion and metastasis; intake of dietary iron may lead to oxidative stress, DNA damage, and lipid peroxidation; and lower intake of folate may be linked to a higher risk of breast cancer.

Key words: diet, nutrition, mechanism, breast cancer.

Manas Kotepui

Medical Technology Program, School of Allied Health Sciences and Public Health, Walailak University, Thailand

Introduction

Breast cancer is the most common cancer among women worldwide and the incidence has continued to rise over time [1]. Nutrition influences cancer etiology in about 35% of cancer cases [2]. Preventive dietary advice often includes reducing intake of alcohol, red meat, and fat and increasing intake of fiber and vitamin D as well as phytoestrogens from various food sources. The mechanisms of dietary risk factors are not entirely understood. This review aims to describe potential nutritional risk factors of dietary components associated with breast cancer as well as the proposed mechanism of each risk factor.

Dietary fat and breast cancer

Epidemiological studies

Epidemiological studies have reported conflicting results regarding the association of dietary fat with breast cancer risk. Diets high in polyunsaturated fat have been reported to increase the occurrence of mammary tumors in animal models [3]. One case-control study indicated a weak association [4], and prospective cohort studies and a meta-analysis have also shown weak [5, 6] or no association [7–10]. Other studies have explored the association of consumption of different types of fat on breast cancer risk. A large cohort study ($n = 49\ 261$) reported no association between intake of total fat, monounsaturated fatty acids, polyunsaturated fatty acids (PUFA), or saturated fatty acids (SFA) and risk of breast cancer [10]. A prospective investigation of fat consumption in a larger population ($n = 319\ 826$) indicated a weak positive association between intake of SFA and breast cancer risk [11]. These findings suggest that different types of fat may have different effects on breast cancer risk. A recent study reported that intake of myristoleic, erucic acids, palmitic, margaric, linoleic acid, and stearic acids is associated with an increased risk of breast cancer while intake of trans-fatty acids and PUFA was not associated with risk of breast cancer [12]. Fat from different types of food may have different effects on risk of breast cancer. For example, intake of alpha-linolenic acid (ALA) from fruit and vegetable oils is inversely associated with risk of breast cancer. Conversely, intake of ALA from nut mixes and processed foods is positively related to risk of breast cancer [12]. PUFA from fish such as eicosapentaenoic (EPA) and docosahexaenoic acids (DHA) have been shown to be inversely associated with risk of breast cancer [13]. One study suggested that relative amounts of n-6 PUFA such as linoleic acid to marine-derived n-3 PUFA such as ALA, EPA, and DHA may be more important to breast cancer risk than individual dietary amounts of these fatty acids. Low intake of marine-derived n-3 PUFA and high intake of n-6 PUFA have been reported to increase risk of breast cancer [14].

Mechanism

There are several mechanisms proposed to explain the association of fat intake with breast cancer risk. High fat intake leads to accumulation of adipose tissue, which is an important site for the conversion of androstene-

dione to estrone. Arachidonic acid, a metabolite of PUFA, activates P450 aromatase that then increases conversion of androstenedione to estrone. PUFA can reduce the binding of estrogens to serum binding proteins, including both sex-hormone binding globulin (SHBG) and albumin, thereby increasing the circulating levels of the biologically potent estrogens which may activate breast cell growth [15]. EPA and DHA have been found to inhibit the production of arachidonic acid-derived eicosanoids in tumors [16]. Lipid peroxidation of fat can induce apoptosis [17, 18]. n-3 PUFA can bind and activate peroxisome proliferator-activated receptor gamma, leading to activation of the proteoglycan syndecan-1 in human breast cancer cells, promoting apoptosis leading to cell growth inhibition [19]. Linoleic acid can generate 13-hydroxylinoleic acid (13-HODE), which enhances the growth stimulating signal of peptide growth factors such as epidermal growth factor (EGF) and insulin, which can in turn promote the growth of cancer cells [18].

Meat consumption and breast cancer
Epidemiological studies

Several studies have investigated the association between intake of meat cooked at high temperatures and HCA exposure and risk of breast cancer [20–27]. Some reported no association [22, 23] while others reported positive associations [20, 21, 24–26]. One study found that women who had a consistent intake of well-done meat had a 4.6-fold (95% CI: 1.4–15.7) elevated risk of breast cancer [21]. In a large prospective cohort of the Black Women's Health Study (n = 52 062), no association was observed between total meat intake and risk of breast cancer [23]. In a larger cohort study (n = 61 433), no association between intake of total red meat, fresh red meat, or processed meat and risk of breast cancer was observed when high total red meat intake (98 g/d) was compared to low total red meat intake (< 46 g/d) [24]. Among women who eat red meat, a higher risk of breast cancer was observed in those who were postmenopausal than those who were premenopausal [26]. A possible explanation for the inconsistency between meat intake and breast cancer risk is that these associations differ according to type of meat consumed, cooking method, and degree of doneness [27]. The amount of meat-derived mutagens, such as heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs), is related to methods of cooking as well as cooking temperatures and duration. These mutagens have been shown to induce mammary gland tumors in animal models [28–30].

Mechanism

The mechanism proposed to explain the association between meat consumption and risk of breast cancer is the metabolic activation of HCAs involving the cytochrome P450-mediated N-hydroxylation in liver and transportation of HCA metabolites to the breast, where high *N*-acetyl transferase activity makes HCAs most reactive. These highly reactive metabolites then bind to DNA where DNA adducts are generated. These DNA adducts can induce genetic mutations which result in mammary gland carcinogenesis [31]. Several studies have also suggested that intake of well-done meat and risk of breast cancer may be associated with genetic polymorphisms such as those of *NAT1*, *NAT2*, *GSTM1*, *GSTT1*, and *SULT1A1* genes which encode enzymes for HCA activation or detoxification [25, 32–35].

Dietary fiber and breast cancer
Epidemiological studies

The protective effect of dietary fiber on breast cancer risk is currently inconclusive. Several prospective cohort studies have examined the association between dietary fiber intake and risk of breast cancer and found inconclusive results [36–38], with mostly weak or no association. Recently, several studies have observed a significant inverse association between dietary fiber intake and risk of breast cancer [39–44]. A meta-analysis of large prospective cohort studies (n = 16 848) showed that high dietary fiber intake is a protective factor for breast cancer (RR = = 0.89; 95% CI: 0.83–0.96) compared with low intake; every 10-g/d incremental increase in dietary fiber intake was associated with a 7% reduction in risk of breast cancer [42]. Dietary fiber from different sources of food has been shown to have different protective effects. One study reported that increasing intake of berries and peaches by 1–2 servings/week is a protective factor compared with no consumption of the same foods [43]. As another example, high dietary intake of plant lignans and enterolignans, but not lariciresinol, is associated with reduced risk of breast cancer [44].

Mechanism

More than one mechanism explaining the role of fiber in lowering risk of breast cancer has been proposed [45, 46]. A high fiber diet can increase the excretion of estrogens and decrease plasma estradiol concentrations and high fecal fiber can inhibit absorption of estrogens in the gut, thereby reducing the total body pool of estrogen. Another proposed mechanism is the binding of unconjugated estrogens to fiber in the gut, thereby decreasing estrogen reabsorption [45]. Disturbance of the enterohepatic circulation of cholesterol, a precursor of estrogens, may also reduce the risk of breast cancer [46].

Alcohol consumption and breast cancer
Epidemiological studies

Epidemiological studies have consistently found that alcohol consumption can increase the risk of breast cancer. Among women who consume alcohol regularly, an increase in alcohol consumption may potentially increase breast cancer risk [47–49]. In addition, alcohol consumption over the recommended amount is associated with a linear increase in incidence of breast cancer [50]. Risk depends upon the amount of alcohol consumed; relative risk of breast cancer has been shown to increase by 7.1% (95% CI: 5.5–8.7%; p < 0.00001) for each additional 10 g per day intake of alcohol [51]. Inconsistencies in some studies of the association between alcohol consumption and risk

of breast cancer are thought to be due to the low magnitude of association, low consumption patterns, and under reporting of alcohol consumption [52].

Mechanism

Several mechanisms explaining the association of alcohol consumption and risk of breast cancer have been proposed. Alcohol may affect breast cancer risk by increasing levels of intracellular estrogens which act through the estrogen receptors (ER) to promote breast tumor growth [53]. Among premenopausal women, moderate intake of alcohol can decrease menstrual cycle variability and increase frequency of long menstrual cycles, thereby increasing exposure to endogenous estrogens [49]. The metabolism of alcohol can produce acetaldehyde and other reactive oxygen species (ROS) which are known to induce DNA modifications, by generating protein adducts, chromosomal aberrations, and DNA point mutations [53–56]. Alcohol can also inhibit absorption of folate and therefore interfere with the DNA repair mechanism [48].

Phytoestrogens and breast cancer

Epidemiological studies

Phytoestrogens are plant substances which are categorized into three classes according to their structure: isoflavones, coumestans, and lignans. Most researchers are interested in isoflavones, present mostly in soybean and soy products, because their structures are similar to mammalian estrogens [57]. A meta-analysis of observational studies reported that intake of isoflavones may be associated with reduced risk of breast cancer [58, 59]. Reduced risk of breast cancer was found especially in postmenopausal women and Asian populations but not in Western populations, which may be due to the low intake of isoflavones in Western countries [58–60]. The risk of breast cancer significantly decreased in women with high intake of flavonols and flavones while no significant association of flavan-3-ols, flavanones, anthocyanins, or total flavonoids intake and risk of breast cancer was observed [61].

Mechanism

Phytoestrogens can act as estrogen agonists and antagonists known as selective estrogen receptor modulators (SERMs) [62]. SERMs are non-steroidal chemicals with a similar structure to estrogen and an affinity toward ER [63] depending on the tissue, ER, and concentration of circulating endogenous estrogens [64]. Phytoestrogen activity can act though both genomic and non-genomic mechanisms [65]. By genomic action, it can pass through cell membranes to interact with enzymes and receptors [66]. Isoflavones can competitively bind to ER, blocking estrogens from binding to their receptor [57]. The opposite mechanism, binding to ER, induces estrogen-responsive gene products which can stimulate ER-positive breast cancer cell growth. By non-genomic action, phytoestrogen can induce differentiation of cancer cells, inhibit tyrosine kinase and activities of DNA topoisomerase, and suppress angiogenesis [67]. Moreover, isoflavones and flavonoids are the most potent inhibitors of aromatase, the enzyme that converts androgens to estrogens [68].

Vitamin D and breast cancer

Epidemiological studies

It has been hypothesized that vitamin D can reduce the risk of breast cancer. Several studies have examined the effects of vitamin D on mammary carcinogenesis in cell lines and animal models and found a protective role of vitamin D in breast cancer development [69–71]. A high concentration of plasma 25(OH)D is associated with a significantly reduced risk of premenopausal breast cancer [72]. Reduction in risk of breast cancer depends on the amount of vitamin D. A serum 25-hydroxyvitamin D (25(OH)D) level of 50 ng/ml was associated with 50% lower incidence of breast cancer, compared to a baseline of < 10 ng/ml [73]. Every 1 ng/ml increment of plasma 25(OH)D level can decrease breast cancer risk by 16% [74]. Some studies have not supported the role of vitamin D in the development of breast cancer [75, 76]. In a large prospective cohort ($n = 319\ 985$), no association between intake of dietary vitamin D and risk of breast cancer was observed [77]. The relationship of vitamin D with risk of breast cancer may be subtype-specific, with evidence of stronger effects of vitamin D for more aggressive breast cancer, especially in African women [78]. Many epidemiological studies have reported positive associations between gene polymorphisms and risk of breast cancer; these include vitamin D related genes such as *Fok1* [79] and *Bsm1* [80], and vitamin D-binding protein genes such as *rs4588* and *rs7041* [81], as well as the *CYP24A1* gene [78].

Mechanism

The mechanism associated with reduction in risk of breast cancer related to vitamin D intake is the growth arrest and apoptosis such as 1,25(OH)2D and cell-cycle arrest caused by increasing the expression of cyclin-dependent kinase inhibitors such as p21 and p27 [82, 83]. 1,25(OH)2D can also induce morphological changes associated with apoptosis in breast cancer cells [84]. Vitamin D can inhibit the invasion and metastasis of cancer cell 1,25(OH)2D and has potent anti-angiogenic properties that can inhibit tumor cell invasion [70], decrease the activity of matrix metalloproteinases (MMPs), and increase the expression of plasminogen activator inhibitors and MMP inhibitor 1 [71]. Vitamin D can act as an anti-inflammatory such that 1,25(OH)2D can down-regulate the expression of cyclo-oxygenase-2 (COX-2), which plays a role in prostaglandin synthesis in human breast cancer [85]. Vitamin D can also inhibit the estrogen pathway such that 1,25(OH)2D can reduce the expression of the aromatase gene, a gene encoding an enzyme that converts androgens to estrogens [85].

Dietary iron and breast cancer

Epidemiological studies

Some postmenopausal women appear to have high circulating iron concentrations because of high intake of meat, fortification of foods with iron, and the wide use of

iron-containing dietary supplements [86, 87]. High levels of dietary iron have been linked epidemiologically to increased development of tumors in humans [88, 89] and animal models [90, 91]. Studies have suggested that a low iron diet may lead to slow growth of tumors [92, 93].

Mechanism

High intake of dietary iron may lead to oxidative stress, DNA damage, and lipid peroxidation, which can increase the risk of breast cancer since iron has pro-oxidant properties [94–96]. Recently, a pathway that mediates iron efflux in breast cancer growth and metastasis was discovered [97]. This pathway is mediated by ferroportin and hepcidin. Ferroportin is an iron efflux pump and hepcidin is a peptide hormone that binds to ferroportin and triggers its degradation, leading to decreased export of cellular iron [98].

Dietary folate and breast cancer

Epidemiological studies

Results from previous studies on the association between intake of folate and risk of breast cancer have been inconsistent [32, 99–104]. One study found that folate intake was related to a decreased risk of breast cancer among premenopausal women [99], whereas other studies found an inverse association restricted to postmenopausal women [32, 102, 103, 105–107], especially those who drank alcohol regularly [108]. A more recent study revealed no overall association between intake of folate and risk of breast cancer, but a higher intake of folate was marginally associated with a lower risk for ER- breast cancer patients [104]. A large prospective cohort study (n = 70 656) found that intake of folate was associated with a higher risk of breast cancer [106] and that women who consumed ≥ 1,272 dietary folate equivalents (DFE)/day of total folate have a 22% decreased risk of breast cancer compared with women who consumed ≤ 345 DFE/day [107].

Mechanism

Several studies have suggested that lower intake of folate may increase the risk of breast cancer by promoting the progression of pre-neoplastic lesions, expanding the breast stem cell population, or preventing terminal differentiation in ductal cells [109]. This promoting effect of folate on breast cancer development may be of particular importance among individuals who are predisposed to developing cancer, including women with high mammographic density, benign breast disease, a strong family history of breast cancer, or a BRCA1 or BRCA2 mutation. A family history of breast cancer is one of the strongest risk factors for breast cancer [110, 111]. The lifetime risk depends on the number of relatives affected with breast cancer and their ages of diagnosis [110, 112]. The lifetime risks of breast cancer in these women are between 20 and 40% and are significantly higher than risk levels in the general population [113].

In conclusion, the role of several dietary factors in breast cancer causation is not conclusively resolved. The evidence to date from epidemiologic studies suggests that diet may be associated with both increases and reductions of breast cancer risk, which may be related to the amount and type of foods consumed. Higher intake of foods containing n-3 PUFA, vitamin D, phytoestrogen, fiber, and folate, together with lower intake of saturated fat, n-6 PUFA, grilled meat, and alcohol, may be beneficial. However, additional investigations of the relationship between diet and breast cancer risk with well-designed epidemiological and laboratory studies should be conducted. Continued follow-up of patients with breast cancer to collect information on dietary intake and relevant biomarkers can be used to further investigate the potential benefits and risks related to diet as well as their mechanism of action in promoting breast cancer development.

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Address for correspondence

Manas Kotepui
Medical Technology Program
School of Allied Health Sciences and Public Health
Walailak University
Nakhon Si Thammarat, 80161, Thailand
tel. 66860390260
fax 6675672106
e-mail: manas.ko@wu.ac.th