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REVIEW ARTICLE

Dietary influence on breast cancer

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Summary

Certain lifestyle and environmental factors play an important role on breast cancer (BC) risk, but data on the influence of nutritional factors are still conflicting. Migrational data have pointed to nutrition as one of the more relevant external factors involved. So far, the only well established nutrition-related risk factors for BC are obesity and alcohol consumption. The evidence that body fatness is a cause of postmenopausal breast cancer is convincing as is the evidence that alcoholic drinks are a cause of BC in all ages. On the other hand, body fatness probably protects against BC diagnosed premenopause. It is more likely that the BC risk is related to life-long dietary habits. The general preventive recommendation often includes a reduction of alcohol, red meat and total dietary fat, and increase in vegetable and fruit consumption. The purpose of this work was to summarize and present current opinions on the influence of diet and nutrition on BC etiology and to suggest possible preventive measures.

Key words: alcohol consumption, breast neoplasm, diet, obesity

Introduction

BC is the second most common malignancy in the world, and the most common cancer among women [1]. Its incidence has been shown to be rising in developing countries, but it is highest in the highly industrialized areas of the world with a tendency for further increase. BC is also the major cause of death from cancer among women globally, responsible for about 410,000 deaths in 2002 [2]. International variations between incidence, environmental or lifestyle differences point to a multifactorial cause of this disease [3]. Hormones play a key role in BC etiology, most likely through stimulation of cell proliferation, and thus increased probability that a mutation will lead to cancer [1,4]. Different cancers vary in hormone sensitivity. Many BC also produce hormones, such as growth factors, that act locally, and these can both stimulate and inhibit the tumor's growth [5]. Although the principal risk factors for BC are hormone-related, several observational studies suggested strong environmental influence on etiology and course of the disease. It is also generally accepted that some features of a diet could represent independent risk factors for BC.

Adoption of a western lifestyle in terms of diet, which is characterized with high energy and saturated fatty acids (SFA) intake, and alcohol consumption, further increases the incidence of this disease [6]. Several studies have examined the association between BC and individual foods and nutrients such as fats, alcohol, fruits and vegetables, dietary fibers, dairy products, meat, fish, tea, coffee and vitamins [7]. Defining the major dietary patterns which are highly associated with BC may be of a great interest because, once identified, they could be successfully corrected. This task may not be easy as it seems because diet high in fat is usually associated with high intake of meat, dairy products, protein and sugar, thus making it hard to distinguish which specific dietary component is causally related with BC.

The purpose of this work was to summarize and present current opinions on the influence of diet and nutrition as a risk factor for BC. Dietary risk factors once identified as undesirable, could lead to appropriate preventive measures. Attitudes towards this specific matter are conflicting, ranging from those advocating protective effect of high intake of fibers, fruits, vegetables and anti-oxidants, to those stating that diet plays

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Table 1. Risk factors for breast cancer (from [54])

Risk factor	*Relative risk*	*High risk group*
Age	>10	Elderly
Reproductive risk factors		
Age at menarche	3	Menarche before age 11
Age at menopause	2	Menopause after age 54
Age at first pregnancy	3	Nulliparous or first child in early 40s
Lifestyle factors		
Diet	1.5	High intake of saturated fat
Body weight (postmenopausal)	2	Body mass index > 35
Alcohol	1.3	Excessive intake
Hormonal status		
Oral contraceptives	1.24	Current use
Hormone replacement therapy	1.35	Use for > 10 years
Radiation	3	Abnormal exposure after age 10
Family history	≥ 2	Breast cancer in first degree relative when young

a restricted role in BC etiology or may even worsen or induce BC (alcohol and SFA consumption). The main purpose of this review was to consider the evidence that nutritional factors may affect BC risk through hormonal mechanisms.

Dietary risk factors for breast cancer development

Recognized non-modifiable risk factors for development of BC include age, familial, menstrual and reproductive factors (Table 1). Several factors are referred to as modifiable. These factors are alcohol intake, dietary intake, physical activity and body weight [8]. Links between diet in adults and risk of BC have been extensively investigated, but many topics remain controversial. As it is difficult to randomize large numbers of women to specific diets and maintain good long-term compliance, we necessarily rely on evidence from large, well-conducted cohort and case-control studies to draw inferences about causal relationships [9]. The first authors to mention possible nutritional influence in BC development were Doll and Peto in 1981 [10]. According to them, 35% of cancer cases are somehow connected with incorrect nutrition. Unfortunately, this association was shown to be due to confusion with other factors. In everyday clinical practice one may be given preventive dietary advice to reduce alcohol intake and limit red meat and animal fat consumption, increase the intake of vegetables and fruits, and maintain certain level of physical activity [11]. It is clear that this kind of advice is general with no real evidence if this recommendation is in fact effective.

A positive correlation between accelerated juvenile growth and the chance for BC development later in life had been established [12]. This is most likely due to earlier menarche, a well recognized BC risk factor. The age when breasts develop, and menopause, are both influenced by nutrition, with over-nutrition leading to early puberty and late menopause while under-nutrition delays puberty and provokes menopause [5]. Abundance of food promotes juvenile growth through increasing the levels of bioactive circulating estrogens. These findings can be used to propagate preventive programs to reduce juvenile obesity with the purpose of preventing hyperestrogenicity later on. Several other studies also suggested that weight at certain life points is more important than just current weight [13].

The global influence of certain kinds of food on BC development has been investigated by the American Institute for Cancer Research [5]. According to this research, the levels of evidence have been categorized as convincing, probable, possible and insufficient. Increased SFA and protein intake has been designated as a probable risk-elevating factor (Table 2).

Table 2. Nutrition and breast cancer (from [5])

Level of evidence	*Risk-reducing*	*Risk-elevating*
Convincing		Rapid juvenile growth and elevated height in adulthood
Probable	Vegetable and fruit	Elevated postmenopausal body mass index, weight gain in adulthood, alcohol consumption
Possible	Physical exercise, non starch polysaccharides, fibre, carotenoids	Total fat intake, saturated fatty acids, animal fat and meat
Insufficient	Vitamin C, isoflavones and lignans, fish	Animal protein

Studies in the UK and USA have shown that women's perceptions of the population risk of BC and their personal vulnerability are inconsistent with medical perspectives [14-16]. It has been suggested that women are aware of BC in general, although their knowledge of risk factors and risk perception is misinterpreted. A recent study reported that 66% of females overestimated their risk of developing BC, 88% underestimated the age at which it was most likely to develop it and 56% underestimated 5-year survival [17].

Fat intake and body mass index as risk factors for breast cancer

Increased consumption of SFA has been accused for the global epidemic proportions of BC and regional variations in BC incidence [5]. However, 10 prospective studies in developed countries have failed to show a clear association between a woman's daily total fat intake and BC risk [18,19]. Further investigations have been conducted to clarify the influence of separate fractions of fatty acids. Some reports have suggested a protective effect of monounsaturated fatty acids and possibly a deleterious effect from trans fatty acids [20], while others reported a greater risk for saturated and monounsaturated fats than for polyunsaturated fats [21]. A non significant decrease in BC risk was observed in the Women's Health Initiative (WHI) trial (RR = 0.91; 95% CI=0.83-1.02 comparing low to high-fat groups) [22].

BC is clearly less prevalent in the Mediterranean as compared to northern Europe. Several case control studies analyzing eating behavior of BC patients concluded that a high intake of olive oil is associated with the lower incidence of BC [23,24] It is believed that the main constituent of olive oil, oleic acid - ω9 mono unsaturated fatty acid, has a protective effect on BC development. On the other hand, ω6 unsaturated linoleic fatty acid has been suspected to increase BC risk, especially if not balanced by sufficient amounts of ω3 unsaturated fatty acids [25]. Considering the results of more than 70 studies on this topic, any effect of dietary fat during midlife on risk of BC is likely to be small if it exists at all [9]. A general recommendation is often issued to reduce total fat intake to 30% of daily energy consumption.

There is extensive evidence linking body weight, weight change over time and various alternative measurements of body size to BC risk [8]. Obesity is associated with an increased risk of BC in postmenopausal women – in particular, the effect of large weight gain after the age of 18 – with risk increasing by 2% per unit of the body mass index (BMI) [26]. Moreover, studies indicate a non-significant or decreased risk in women with a high BMI who are under the age of 50 and/or premenopausal. In a meta-analysis of prospective cohort data among postmenopausal women a higher BMI was associated with an increased risk for BC (for BMI of 28 vs. 21 kg/m^2, RR = 1.26, 95% CI=1.09-1.46) [27]. Among premenopausal women, BC risk decreases with increase in body weight (in general among overweight and obese premenopausal women, average RR = 0.6-0.7) [8]. Most studies find that higher weight or BMI during teenage and young adulthood (18-20 years) is associated with a 10-30% decrease in BC risk for both pre- and postmenopausal women [8].

The effect of BMI on BC risk is probably due to the effects of BMI on endogenous oestradiol levels. Women with a high BMI and more adipose tissue have more aromatase, which catalyses the conversion of androstenedione to oestrone, which can then be converted to oestradiol [1]. In turn, oestradiol is a key promoting factor for the development of the estrogen receptor-positive tumors.

Fruits and vegetables

Consumption of large amounts of plant-derived food is usually associated with smaller incidence of certain types of cancer, in particular cancers of the digestive tract. A comprehensive review of the literature found that a diet high in vegetables and fruit probably decreases BC risk [6,28,29]. Unfortunately, conclusions in favor of protective effect of this type of food were based on case observational studies. Pierce et al. in their multi-institutional randomized controlled trial with 3,088 women, concluded that among survivors of early-stage BC, adoption of a diet that was high in vegetables and fruit and low in fat did not reduce additional BC events or mortality during a 7.3 year follow-up period [30]. Smith-Warner et al., in their study with 7,000 cases, evaluated the possible association between high intake of fruits and vegetables and the risk for BC [31]. They suggested that fruit and vegetable consumption during adulthood does not have an important effect on BC risk.

In Mediterranean countries it has been observed that BC rates are usually relatively low compared with most other western countries. "Mediterranean diet" is characterized by a high intake of vegetables and fruits in parallel with high intake of olive oil. Several studies have indicated that these specific properties of the "Mediterranean diet" could play an important role in BC prevention [32].

Meat

Several hypotheses exist to explain how consumption of red meat could induce carcinogenesis: high bioavailability of its iron content, growth-promoting hormones used in animal production, carcinogenic heterocyclic amines formed in cooking, and its specific fatty acid content may all contribute. On the other hand, processed red meat products (bacon, sausage and ham) may contain carcinogenic N-nitroso compounds [33]. Epidemiological studies on meat intake and the association with BC yielded inconsistent results, with a positive association observed in a meta-analysis and in some prospective studies but not in a pooled analysis of 8 prospective studies [34,35] (Table 3). The findings from the latest study from Larsson et al. do not support the hypothesis that high intake of red or processed meats increases the risk of BC [36]. A meta-analysis of 22 case–control and 9 cohort studies based on the results published in 2003 showed a significantly increased risk of overall BC when comparing the highest and lowest levels of total meat intake in both case–control (summary RR = 1.13, 95% CI=1.01–1.25) and cohort studies (summary RR = 1.32, 95% CI=1.12–1.56) [37]. Meanwhile, there are several case-control studies indicating that a high exposure to heterocyclic amines through broiled or deep fried meat can contribute to an elevated BC risk in certain subpopulations due to polymorphic xenobiotic metabolism (Table 4) [12]. Until further elucidation of these nutritional aspects it might be wise to limit the intake of broiled and deep fried meat products.

Fish is generally considered as a desirable source of food. Many valuable nutrients are delivered by fish. Yet, fish can be heavily contaminated with persistent organic residues and heavy metals. The exact relation between fish consumption and BC has not been clarified. Seven prospective cohort studies have been dealing with this issue with a partial success [38,39]. Five of these studies (4 conducted in the USA and 1 in Japan) were unable to find any positive correlation between the amount of fish consumed and BC risk. Two Norwegian studies detected a trend towards reduced risk when fish was consumed at least 5 times monthly. New studies which would focus on individual fatty acids and omega acids are expected to clarify the relation to the BC risk.

Table 3. Meta-analysis of 9 prospective studies on meat and breast cancer; pooled data from 351,041 women included, 7,379 of whom were diagnosed with invasive breast cancer (from [35])

Pooled data for	*Relative risk*	*95% CI*
Total meat	1.08	0.98-1.19
Red meat	0.94	0.87-1.02
White meat	1.02	0.91-1.13

Table 4. Enzymes and enzyme families in which polymorphism has been correlated with breast cancer (from [12])

N-acetyl-transferase
Glutathione-S-transferase
Cytochrome P450
Alcohol-dehydrogenase
Aldehyde-dehydrogenase

Alcohol

Alcohol consumption consistently predicts higher BC rates in epidemiologic and animal studies [6]. Ethanol as a chemical itself is not a carcinogen. It has profound metabolic effect by which it interferes with the metabolism of other, potentially cancer-promoting agents [12].

A recent collaborative reanalysis of individual data from nearly 60,000 women with BC in 53 epidemiological studies reported that the relative risk for BC increased by 7% for each additional 10 g of alcohol per day, i.e. 7% for each alcoholic drink consumed on a daily basis [40]. The association between alcohol intake and BC risk has not been shown to be due to confusion with other factors, and it is likely to be due to a causal effect. There is a linear correlation between alcohol intake and the risk of BC: intake of around 30 g of alcohol per day is associated with about a 20% increase in BC risk [1]. Willett et al., in a cohort study, estimated the relative risk at 1.6 (95% CI=1.3-2.0) when comparing ≥ 15 g of alcohol per day against none [41]. The most recent study conducted by Allen and colleagues concluded that for every additional drink regularly consumed per day, the increase in incidence of BC up to the age of 75 years per 1,000 women in developed countries is estimated to be about 11 [42].

However, an interaction between folate and alcohol intake suggests that an adequate folate intake (most commonly achieved by taking multivitamin preparations) seems to reduce or eliminate the excess risk due to alcohol consumption [9]. Alcohol may be an important contributor to total caloric intake or act to stimulate prolactin secretion to enhance BC risk.

Phytoestrogens

Certain types of food are rich in potent hormone-like activity substances. Since BC is a hormone-dependent entity, the question of pathogenetic relevance of

such substances has been raised. Phytoestrogens are intermediate plant products that exert estrogen-like activities [12]. There are two types of phytoestrogens: isoflavones found in soy products and lignans found in many cereals, seeds, berries, tea and some vegetables. When digested, the metabolites of these compounds can mimic or modulate the actions of endogenous oestrogens, usually by binding to oestrogen receptors and thus potentially reducing the effect of more potent endogenous oestrogens [1,43]. Lignans are converted to the active metabolite enterolactone by the intestinal flora. Isoflavonoids (daidzein and genistein) are also intestinally converted to their active metabolite equol [44].

Adlercreutz et al. concluded that sustained soy intake throughout life, like in Japan or other Asian countries, may have beneficial effect on BC risk [12,45-47]. As opposed to this statement, the authors did not see any convincing evidence to suggest that soy or isoflavone consumption during adult life is protective against BC for women living in western countries [45,46]. High soya protein intake would be about 3 g/day (about 9% of total protein) as compared to 2% or less in western populations, and this may be one of the lower risk of BC among Asians [44]. There is some suggestion that a high intake of isoflavone-rich foods during adolescence may reduce BC risk later on in life, which supports the hypothesis that exposure to phytoestrogens at critical periods of development might be an important determinant of BC risk [1].

Dietary fibers

Dietary fibers have been shown to alter the metabolism of endogenous oestrogens, interrupting the enterohepatic circulation and increasing the excretion of oestrogens in the feces [1]. This was the base premise on which several studies have been conducted with, again, conflicting results. Several case-control studies have suggested a protective effect of high intakes of dietary fibers on BC risk, while several prospective studies have generally not supported this finding [48,49]. Despite these conclusions, one may suggest regular use of dietary fibers (cereals, pasta and vegetables) because of their known effect on regulating bowel movements and diminishing hunger, altogether leading to maintaining a desirable BMI.

Antioxidant vitamins

Free radicals can cause lipid peroxidation in cell membrane and damage its function, and antioxidant vitamins have been found to be effective scavengers of these radicals [18]. This effect may be considered as protective against carcinogenesis in general. Beta-carotene (provitamin A), retinol (vitamin A), alpha tocopherol (vitamin E) and ascorbic acid (vitamin C) are considered as antioxidant vitamins. Numerous epidemiological studies have investigated their protective effect against BC [50,51]. In general, the results of case-control and prospective studies are unconvincing in the case of beta-carotene, vitamin E and vitamin C. Based on the Canadian study, the likely protective effect of dietary fibers (RR=0.68, 95% CI: 0.46-1.00) persisted after adjustment for total vitamin A, beta-carotene, vitamin C and vitamin E [52]. It has been postulated that the anticarcinogenic effect of antioxidant vitamins is heavily influenced by the interactions with polyunsaturated fatty acids (PUFA). It is possible that antioxidant vitamins protect against BC only in the presence of high PUFA intake. On the other hand, it is possible that the protective effect of these vitamins may be lost or even reversed by the presence of certain types of PUFA [18].

Physical activity

Changes in both caloric intake and energy expenditure are critical for weight loss and maintenance of weight loss, and it is well documented that physical activity is important to promoting weight control and maintain weight loss [8]. The American Cancer Society guidelines for cancer survivors also addressed the benefits of weight control through physical activity [53,54]. Ballard-Barbash et al. in their work, reviewed some 50 studies and came up with the conclusion that the risk of developing BC is 20% lower among the most active women than among the least active, regardless of menopausal status [8]. Evidence suggests that 4-7 hours per week of moderate to vigorous intensity training is required for adequate risk control. Like diet, physical activity is difficult to measure in epidemiological studies, and more data from carefully conducted prospective studies are needed to define this probable effect.

Conclusion

Certain lifestyle and environmental factors play an important role in BC risk, but the influence of nutritional factors remains yet to be determined. The lack of an overall association between dietary patterns and BC risk may be due to several reasons. We consume the food as a whole, not the constituents, so the sum of several food items may result in pro- and anti-carcino-

genic factors canceling each other's effects. The second reason is the so-called "saturation effect". Most of the studies were conducted in western developed countries where the populations are homogeneously high consumers of fat- at least 30% of total caloric intake. Thus, the range of variability would be too narrow to show differences in effects.

The evidence that body fatness is a cause of postmenopausal BC is convincing as is the evidence that alcoholic drinks are a cause of BC in all ages. On the other hand, body fatness probably protects against BC diagnosed pre-menopause. Current dietary advice should be to avoid obesity, restrain from alcohol intake, to maintain a varied diet and to maintain a desirable level of physical activity.

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