Nutrition in Breast Cancer Prevention

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Key Words

Breast cancer risk: dietary factors, fruit, vegetables, fiber, fat, alcohol, phytoestrogens

Summary

Nutrition has been widely studied as a leading environmental factor in the prevention of breast cancer (BC). Despite the challenges in relating consumption of specific nutrients to BC risk, particularly in the context of a total diet, many investigators have contributed valuable information. This article summarizes dietary factors and cancer risk associations and makes specific dietary recommendations to reduce risk of specific cancers. These include reducing alcohol and animal fat and increasing the intake of vegetables, fruit and fiber and, lately, phytoestrogens.

Schlüsselwörter

Brustkrebs-Risiko: Ernährung, Obst, Gemüse, Ballaststoffe, Fett, Alkohol, Phytoöstrogene

Zusammenfassung

Die Ernährung als wesentliche Ursache zur Prävention von Brustkrebs wurde vielfach untersucht. Neben Nahrungsergänzungsmitteln zur Verminderung des Brustkrebs-Risikos wurde von vielen Studiengruppen die Bedeutung der Ernährung untersucht. In diesem Artikel werden die alimentären Faktoren, die im Zusammenhang mit Brustkrebs von Bedeutung sind, dargestellt, und entsprechende Empfehlungen zur Reduktion bestimmter Krebserkrankungen gegeben. Zu den risikoreduzierenden Maßnahmen gehören die Reduktion des Alkoholkonsums und der tierischen Fette sowie die Erhöhung des Anteils von Gemüse, Obst und Ballaststoffen und letztlich auch die Einbeziehung von Phytoöstrogenen bei der Nahrungszusammenstellung.

Introduction

Aspects of nutrition and lifestyle may largely be responsible for the development of common cancers in Western countries, as indicated by the large differences in breast cancer (BC) rates between countries, the striking changes in these rates among migrating populations, and the rapid changes over time within countries [1]. The fact that incidence has been rising in parallel with economic development indicates that environmental factors might play a role in the causation of BC. Nutrition and 'lifestyle' may exert its carcinogenic effects indirectly by cell stimulations (alcohol, hormone replacement therapy), inhibition of DNA repair mechanisms (lack of vitamins), ef-

fecting estrogen metabolism (phytoestrogen), or to enhance growth of tumors (body mass index, BMI) [2]. Therefore preventive dietary advice often includes a reduction of alcohol and animal fat and an increased intake of vegetables, fruit and fiber from various sources. Lately, phytoestrogens have been added to these recommendations.

Fruit and Vegetables

The intake of vegetables and fruit has been thought to protect against breast cancer. Most of the evidence comes from case-control studies, but a recent pooled analysis of the relatively

few published cohort studies suggests no significantly reduced breast cancer risk is associated with vegetable and fruit consumption [3].

While there is no overall protective effect of a high fruit and vegetable consumption speculation remains over possible beneficial effects of certain subcategories, especially brassica vegetables like broccoli, cauliflower, and cabbage. These plants contain a range of secondary metabolic compounds, e.g. phenolics and isothiocyanates, some of which have shown chemoprotective effects against BC in animal and laboratory studies [4, 5]. Furthermore, indole-3-carbinol (13C) rich cabbage species might contribute to BC protection by diet. Under acidic conditions, 13C is converted to a series of oligomeric products thought to be responsible for the biological effects of dietary 13C. The major antiproliferative component is 2-(indol-3-ylmethyl)-3,3'-diindolylmethane (LTr-1). LTr-1 can inhibit the proliferation of both estrogen-dependent and -independent breast tumor cells [6]. Nevertheless, clear-cut recommendations for or against single nutrients or secondary plant metabolites are not yet possible, lacking sufficient data on individual bioavailability, safety and long-term outcome.

Dietary Fiber Intake

The term fiber encompasses a great variety of chemically diverse plant constituents which are non-digestible to humans. They are believed to protect from BC by binding enteral carcinogens and endogenous sex hormones on enterohepatic cycling and facilitating their enteral elimination [7]. Higher dietary fiber intake is associated with lower serum levels of androstenedione (−8% between the lowest and highest quartiles of intake, $P_{\text{trend}} = 0.06$), but not estrogens. Similarly, consumption of fruits (−12%, $P_{\text{trend}} = 0.03$), vegetables (−9%, $P_{\text{trend}} = 0.15$) and whole grain (−7%, $P_{\text{trend}} = 0.07$) showed inverse associations with androstenedione levels [8]. However, the only available prospective study investigating grain consumption in relation to BC risk in postmenopausal women (cumulative 29,119 years) could not find a significant difference between whole and refined grain intake and risk of incident postmenopausal BC in the US [9]. The beneficial aspect of a high fiber intake is the consumption of certain fibre-rich foods with hormonally active ingredients, e.g. phytoestrogen containing grain and soy products.

Phytoestrogens

The impact of soyfood intake on breast cancer risk has been investigated extensively. Much of this focus can be attributed to the soybean being a dietary source that is uniquely rich in isoflavones. The chemical structure of isoflavones is similar to that of estrogen, and they bind to both estrogen receptors (ER alpha and ER beta). Although they preferentially bind to and

activate ER beta, they exert estrogen-like effects by interacting with both receptor types under some experimental conditions. Isoflavones also possess nonhormonal properties that are associated with the inhibition of cancer cell growth. Thus, there are several possible mechanisms by which soy may reduce the risk of BC [10]. However, the role of isoflavones in BC has become controversial because, in contrast to the possible beneficial effects, some data from in vitro and animal studies suggest that isoflavones, especially genistein, the aglycone of the main soybean isoflavone genistin, may stimulate the growth of estrogen-sensitive tumors [11]. The pioneer of phytoestrogen research, Adlercreutz, concluded in a recent review that sustained soy intake throughout life, like in Japan or other Asian countries, may have beneficial effects on BC risk. He does not, however see 'any convincing evidence to suggest that soy or isoflavone consumption during adult life is protective against BC for women living in western countries'. Since negative (i.e. estrogen-like/proliferative) effects on the breast tissue cannot be excluded Adlercreutz advises against the use of concentrated phyto-estrogen (e.g. genistein) supplements [12].

Traditional western diets also have their beneficial ingredients that should be regular constituents in our meals. Lignans from traditionally made sourdough rye bread, linseed/flaxseed and berries are local sources of potentially cancerprotective phytoestrogens [13]. Lignans are plant compounds metabolized in the mammalian gut to produce the phytoestrogens enterolactone and enterodiol [14]. Because estrogens have been linked to breast cancer etiology, lignans could affect breast cancer risk through modulation of endogenous estrogen metabolism or competitive inhibition with estrogen receptors.

Premenopausal women in the highest quartile of dietary lignan intake had reduced breast cancer risk (OR = 0.66; 95% CI = 0.44–0.98). No association was observed between lignan intakes and postmenopausal breast cancer [15].

Mediterranean-Type Diet

Secondary prevention trials and observational prospective epidemiologic studies have demonstrated the efficacy of a Mediterranean-type dietary pattern to decrease risk of both cancer and cardiovascular diseases [16]. Olive oil is an integral ingredient of the 'Mediterranean diet' and accumulating evidence suggests that it may have a potential role in lowering the risk of several types of cancers. Recent findings further reveal that oleic acid (OA; 18:1n-9) exposure may suppresses HER2 at the transcriptional level by up-regulating the expression of the Ets protein PEA3 – a DNA-binding protein that specifically blocks HER2 promoter activity – in breast, ovarian and stomach cancer cell lines. This anti-HER2 property of OA offers a previously unrecognized molecular mechanism by which olive oil may regulate the malignant behavior of cancer cells [17].

The adoption of dietary patterns like in Mediterranean-type diets does not only consist of the use of olive oil but also emphasizing regular physical activity and eating fruit and vegetables, whole grain, legumes, nuts, seeds, and low-fat dairy products. This form of food pattern lowers the risk for breast cancer and cardiovascular disease [18].

Monounsaturated Fat

Dietary fat has received the most attention and also created the most uncertainty. Specific types of fat, particularly monounsaturated fat and the ratio of ω -3 to ω -6 fatty acids, demonstrate more potential to influence BC risk. Although cohort studies did not find a clear-cut interrelationship between BC risk and individual fatty acids, experimental and animal data indicate that oils rich in ω -6-unsaturated linoleic acid, e.g. sunflower and corn oil, can promote cancer. ω -6-Unsaturated linoleic acid has been suspected to increase BC risk especially if not balanced by sufficient amounts of ω -3-unsaturated fatty acids. It is concluded from these observations that not individual fatty acids but the ratio of the various fatty acid families modifies BC risk: A higher ω -3/ ω -6 ratio seems to be protective. ω -6-Unsaturated fatty acids are predominant in grain oils, e.g. corn- and sunflower oil, whereas ω -3-unsaturated fatty acids are richer in nut oils, canola and linseed (flax) oil in oily fish) [19]. However, the epidemiological studies that have examined the association between fish consumption and BC risk in humans are inconsistent. The European Prospective Investigation Into Cancer and Nutrition (EPIC) examined fish consumption and BC risk in 310,671 women aged between 25 and 70 yr. During follow-up, 4,776 invasive incident breast cancers were reported. No significant associations between intake of total fish and BC risk were observed, hazard ratio (HR) 1.01 (95% CI 0.99–1.02; $p = 0.28$ per 10 g fish/day) [20].

Energy Intake

Cross-cultural studies have long suggested that the high incidence of BC in developed Western countries may be linked to the high prevalence of obesity and to high total energy intake [21]. Heavier women (baseline BMI >31.1) had an elevated risk of postmenopausal breast cancer (relative risk (RR) = 2.52; 95% confidence interval (CI) = 1.62–3.93), compared to slimmer women (baseline BMI <22.6). The elevation in risk associated with increasing BMI appeared to be most pronounced among younger postmenopausal women. Change in BMI since age 18, maximum BMI, and weight were also associated with breast cancer. Recent studies show that hyperinsulinemia, increased concentration of insulin-like growth factor 1 and greater abdominal fat accumulation are markers of high risk for breast cancer. Increased serum concentrations of free

estradiol and free testosterone are similar risk markers and are frequent concomitants of hyperinsulinemia [22]. Body size is an important modifiable risk factor for breast cancer [23].

Although obesity has generally been found to be associated with increased risk for postmenopausal breast cancer, some questions remain concerning the role of body fat distribution, lifetime weight history, and effects within specific subgroups of women [24, 25].

Fat Intake

For many years high energy intake, most of all the consumption of animal fat and saturated fatty acids was accused of a causal relationship to BC. However, the results from 13 prospective cohort studies clearly speak against a general association between fat consumption and BC risk [26, 27]. A study from Cambridge points to an interesting result regarding breast cancer: no association was observed with saturated fat intake, but according to the food diary a daily total fat intake of 35 g doubles the risk of breast cancer compared to women with daily intake of 10 g or less. These data were confirmed by a recent meta-analysis on this subject (25,000 cases). An elevated BC risk was found for total fat and saturated fatty acids but only in a combined risk estimate derived from 45 case-control and cohort studies [28].

Alcohol Consumption

Women with a moderate intake of alcohol have higher concentrations of sex steroids in serum and a higher risk of developing breast cancer, compared to non-drinkers. In the European Prospective Investigation into Cancer and Nutrition (EPIC) the relationship between alcohol consumption and serum levels of sex steroids and sex-hormone binding globulin (SHBG) in 790 pre- and 1,291 post-menopausal women were investigated. Pre-menopausal and post-menopausal women who consumed more than 25 g/day of alcohol had higher dehydroepiandrosterone sulphate (DHEAS), testosterone (T) and free T (fT), higher androstenedione (Delta 4) and higher estrone (E₁) concentrations compared to women who were non-consumers. Estradiol (E₂), free E₂ (fE₂) and sex-hormone binding globulin (SHBG) concentrations showed no association with current alcohol intake. This study supports the hypothesis of an influence of alcohol intake on sex hormone concentrations in blood [29]. Alcohol intakes in excess of 30 g per day are generally considered to produce adverse effects [30]. This should be true especially in young women and adolescent girls, when the glandular breast tissue is considered particularly vulnerable.

Conclusion

The relevance of nutrition on the cancer process is evident. Dietary factors may contribute to approximately one third of

all cancers. Nevertheless, important issues remain to be solved and further studies are needed. Prospective epidemiologic studies have provided strong evidence supporting regular physical activity and minimal adult weight gain to lower risk of breast cancer [31]. A healthy lifestyle, consisting of 'healthy diet', physical activity and renunciation of stimulants, is recommended from childhood throughout life. Generally, hyperestrogenicity has been recognized as one of the prime

contributors to an elevated BC risk [32]. Therefore, all measures leading to a reduced level of bioactive circulating estrogens are likely to reduce the individual risk. This accumulative knowledge should be used by public health authorities to develop recommendations and activities to reduce overweight and obesity and to promote healthy dietary habits [33].

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