NUTRITIONAL EPIDEMIOLOGY - DIETARY PATTERNS AND THE ROLE OF HORMONES IN BREAST CANCER

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Abstract
Breast cancer (BC) is the leading global cause of cancer-related death in women worldwide. There is growing evidence for a role of hormones and dietary patterns in BC pathophysiology. The aim of the present review was to evaluate the impact of dietary factors in BC risk.

Bibliographical searches were performed in available studies and reports using the following terms: “breast cancer epidemiology”, “nutrition and breast cancer”, “dietary factors and breast cancer”, “steroid hormones and risk of breast cancer” and “hormone intake and breast cancer”.

Body fatness directly affects levels of many circulating hormones, such as insulin, insulin-like growth factors, and estrogens, creating an environment that encourages carcinogenesis and discourages apoptosis. But, there is considerable speculation around a biologically plausible interaction of hormone levels in meat, poultry and eggs, as well as of soya and soya products with breast cancer development, due to their high phytoestrogen content.

There is increasing evidence that some dietary patterns which leads to increased body fatness, play an important role in the development of BC. Despite the large randomized clinical and epidemiological studies have been reported, clear conclusions are difficult to design due to the number of variable factors.

Key words: Breast cancer, Dietary factors, Steroid hormones, Estrogen.

1. Introduction
Cancer of the breast is the most common cancer in women worldwide. Around 1.15 million cases were recorded in 2002, 1.38 million cases in 2008, and 1.68 million cases in 2012, accounting for around 23 percent of all cancers in women (11 percent overall) [1]. Observed rates of this cancer increases with industrialization and urbanization, and also with facilities for early detection. It remains much more common in high-income countries, but now is rapidly increasing in middle- and low-income countries (LMI), including Africa, much of Asia, and Latin America. Breast cancer is fatal in under half of all cases and is the leading cause of death from cancer in women (fifth overall), accounting for 14 percent of all cancer deaths worldwide [1].

Breast cancer is hormone related, and the factors that modify the risk of this cancer when diagnosed pre-menopaually and when diagnosed (much more commonly) post-menopaually are not the same [2]. These data are showing the importance of early life events, including food and nutrition, as well as factors that affect hormone status, in modification of the risk of breast cancer [3]. Overall risk doubles each decade until the menopause, when the increase slows down or remains stable. However, breast cancer is more common after the menopause. Studies of women who migrate from areas of low risk to areas of high risk show that rates of breast cancer in migrants assume the rate in the host country within one or two generations. This shows that environmental factors are important in the progression of the disease [4].

2. Breast cancer pathogenesis, dietary patterns and the risk

2.1 Pathogenesis
Breast tissue, as well as hormones and hormone-receptor status, varies at different stages of life. It is therefore possible that individual risk factors will have different effects at different life stages. Early menarche, late menopause, not bearing children, and late (over 30) first pregnancy all increase breast cancer risk. The age when breasts develop, and menopause, are both
influenced by nutrition, with over-nutrition leading to early puberty and late menopause; under-nutrition delays puberty and advances menopause [4].

Hormones play an important role in breast cancer progression because they modulate the structure and growth of epithelial tumor cells. Different cancers vary in hormone sensitivity [5]. Many breast cancers also produce hormones, such as growth factors, that act locally, and these can both stimulate and inhibit the tumor’s growth [6, and 7]. Between 4 and 9 percent of breast cancer cases are hereditary, and are usually caused by inherited mutations in either the Breast Cancer-1 (BRCA-1) or Breast Cancer-2 (BRCA-2) gene. In addition, growth factor receptor genes, as well as some oncogenes, are overexpressed in many breast cancers [8].

2.2 Dietary patterns and the risk of breast cancer

The large body of literature on nutrition and breast cancer has been recently reviewed and summarised by an international panel gathered by the World Cancer Research Fund (WCRF) [9]. In reviewing the literature, it is important to consider a number of issues related to study design, model systems and interpretation of studies. These issues, along with scarce information on the interaction of the epigenome with the response to nutrients, lead to difficulty in understanding the impact of nutrients on breast cancer risk.

Another important issue is the level of nutrients compared in studies pertaining to breast cancer risk. If this level is in the severely deficient range it might have multiple effects on the organism and breast cancer development might be a secondary consequence of the deficiency.

The effects of diets may also vary based on race, menopausal status, tumour characterisation (oestrogen receptor (ER)-positive (ER +) or ER-negative (ER−) and weight or body mass index (BMI), and these factors are not always considered in the analysis or the interpretation of the results. Finally, it is difficult to maintain compliance to dietary regimens for long periods of time. Therefore it will be critical to identify biomarkers for very early signs of breast cancer development that can be utilised to rapidly determine the impact of environmental factors on breast cancer risk and the success of actions proposed to reduce breast cancer incidence.

In contrast to the increased risk of breast cancer with obesity in postmenopausal women are reports that increased weight may protect premenopausal women from breast cancer. For example, the higher the BMI at 18 years of age, the lower the risk in premenopausal women in the overweight to obese category (BMI ≥ 25 kg/m²) compared with a low BMI (< 20kg/m²) (OR 0·76; 95% CI 0·63, 0·90) [10]. Thus, obesity makes an impact on the risk of breast cancer positively and negatively, depending on the menopausal status (or age).

Observational population studies suggest that breast cancer risk is increased in postmenopausal women with high BMI, waist circumference and waist:hip ratio. However, higher BMI may confer protection against breast cancer in premenopausal women. The distribution of the adiposity (central v. overall) may also influence the risk in addition to menopausal status and race. Finally, evidence supports that there may be a relationship between maternal BMI and offspring, but further evidence is required to clarify these relationships [11].

Dietary patterns such as macronutrient intake including alcohol, high-fat diet and carbohydrates, insulin sensitivity as well as micronutrients influence the development and maintenance of an obese status. Thus, the bearing of obesity on breast cancer risk may be due to the obese state and/or the dietary effect on obesity. There are multiple potential mechanisms that may mediate breast cancer risk associated with obesity and determining which mechanism is predominant will be a challenge.

An important aspect to investigate is the potential epigenetic component of the risk brought by obesity, such as the role of Insulin growth factor-2 (IGF-2), suggested by the impact of maternal exposures on the risk for the offspring to develop breast cancer [12, and 13].

2.2.2 Soya intake

Epidemiological studies suggest that higher soya isoflavone intakes are associated with lower breast cancer risk, though not all are supportive [14, and 15]. For example, in Asian populations where soya consumption is high, the incidence of breast cancer was found to be lower than in other cultures with low soya intake levels [16, and 17].

The active component proposed to mediate the effect on breast cancer is genistein, a metabolic product of soya, which is structurally very similar to oestriadiol and activates α- and β-ER [18]. Soya and genistein promote tumorigenesis in postmenopausal rodent models, suggesting a link between oestrogen pathways and the effect of soya. An added level of potential variability for the effect of soya is shown by the fact that chemoprevention by genistein in carcinogen-induced mammary cancer in rats is dependent on the diet matrix [18].
In regards to epigenetics, there is much to learn from soya and related compounds. As for other nutrients, the modulation of gene expression, notably that controlled by oestrogen, occurring upon exposure to soya suggests that epigenetics-mediated effects might be involved in alterations in breast cancer risk.

2.2.3 Alcohol
The only dietary factor identified by the WCRF analysis for which there was convincing evidence for its association with increased breast cancer risk beside obesity in postmenopausal women is alcohol intake (9). The mechanism underlying the relationship between alcohol consumption and breast cancer risk has not been clearly defined [19]. However, the action of alcohol consumption on breast cancer risk might be linked to the induction of endogenous oestrogen levels. For example, consumption of approximately one to two alcoholic drinks per day increases oestrogen levels in premenopausal and postmenopausal women [20]. Moreover, a metabolite of alcohol, acetaldehyde, has genotoxic action that may contribute to the development of cancer [21].

2.2.4 Fat intake
A correlation between high-fat diets and risk of cancer has been noted for more than two decades [22]. In a combined analysis of twelve case-control studies, there was a positive association between breast cancer risk and saturated fat intake [23]. In contrast, the results of a meta-analysis of eight prospective trials did not support a strong association between breast cancer incidence and total fat [24]. Specific types of fat, provided with the diet and normally stored in cell membranes, are metabolised very differently in cells, serving not only as an energy substrate that can alter membrane susceptibility to lipid oxidation, but also produce biologically active signals. For example, arachidonic acid and EPA are precursors for eicosanoids, which are potent intracellular signals.

More specifically, n-3 fatty acids can inhibit inflammatory mediators that are proposed to promote cancer progression. Different types of lipids may differentially affect breast cancer risk, and the mechanisms involved are likely to also differ depending on the type of lipid [25]. Unfortunately, in whole organisms it is difficult to separate the effect of a high-fat diet from obesity. Therefore, studies performed in appropriate cell model systems are necessary to tease out a possible link between specific fatty acids and epigenetic mechanisms.

2.2.5 Carbohydrate intake
Carbohydrates and carbohydrate quality could influence breast cancer risk potentially by affecting insulin resistance and plasma levels of insulin and glucose [26]. The mechanisms underlying the relationship between carbohydrate intake, and particularly glycaemic index, and breast cancer risk is proposed to be through greater insulin action. Chronically raised insulin levels may increase carcinogenesis in breast tissue by directly stimulating insulin receptors. Insulin can also reduce plasma and tissue levels of IGF-binding proteins 1 and 2, which may in turn increase the availability of IGF-1, and experimental studies have revealed strong proliferative and anti-apoptotic effects of IGF-1 in breast tissue [27].

2.2.6 Folates
Most prospective studies do not provide evidence of an association between folate intake and breast cancer risk [28], but there is also evidence to support that folate supplementation may increase the risk for breast cancer [29]. Interestingly, a benefit from folate intake is observable in individuals with low folate status, suggesting a protective effect against breast cancer only in non-supplemented vitamin B users [30]. Protective effects have also been observed in populations with low folate status, in which vitamin supplementation is infrequent [31]. Furthermore, vitamin B_{12}, a coenzyme in folate metabolism, might be associated with a lower risk of breast cancer and low vitamin B_{12} intake may reduce the potential protection conferred by folate against breast cancer development [32].

Folate studies are further complicated by the fact that, as for other dietary components, additional factors may have an impact on the relationship between folate intake and breast cancer risk. For example, an inverse association between breast cancer development and circulating folate levels among alcohol drinkers has been noted [33]. Ethanol may induce a physiological deficiency that affects the one-carbon metabolism involved in the epigenetic control of gene transcription by reducing folate absorption from the gastrointestinal tract or by inhibiting enzymic activity.

The impact of folate may also be related to the tumour type, since the incidence of Estrogen negative (ER-) and Human Epidermal Growth Factor Receptor-2 (HER2)-positive breast cancers is increased in women in the highest tertile of plasma folate compared with the lowest [34].

2.2.7 Carotenoids
The putative effect of carotenoids may be modified by age or menopausal status since an inverse association with breast cancer risk was noted in premenopausal women rather than in postmenopausal women. Furthermore, the potential impact of carotenoids may be greater when associated with other lifestyle factors. This is exemplified by the link between carotenoids and the reduced risk of invasive breast cancer in premenopausal, but not postmenopausal, smokers [35].
2.2.8 Vitamin D

Vitamin D is one of the most studied micronutrients as a cancer-preventive agent, but the controversy regarding its potential use in prevention is not yet settled. A main reason is that, like for folate, the efficacy of vitamin D may depend on individual baseline level, dose and supplementation period [36]. Epidemiological studies have shown an inverse association between vitamin D intake or serum 25OHD and breast cancer development, in both premenopausal women [37] and postmenopausal women [38].

2.2.9 Fruits, vegetables and animal proteins

In the case control study of Bao and ShuWe [39] 3443 breast cancer patients have been evaluated. The goal of this study were the associations between dietary intakes and breast cancer and investigation whether the dietary associations varied by hormone receptor status using data from the Shanghai Breast Cancer Study (SBCS). This large case-control study showed that fruit, vegetable, milk, and egg consumption were each inversely associated with risk of breast cancer, while meat consumption was positively related to risk. In general, the associations of dietary factors with breast cancer did not vary by estrogen or progesterone receptor status or by menopausal status.

Similar results were reported in the case-control study of Chandran and Zirpoli [40] involving a large sample of Afro-American and Caucasian women. In this study, a positive association between intake of processed and unprocessed red meat, poultry and breast cancer risk was limited to Caucasian women. This is particular investigation of these foods and breast cancer risk in a study of both Afro-American and Caucasian women with evaluation by menopause as well as ER status. Consumption of processed meat in the highest quartile appeared to be more strongly associated with postmenopausal breast cancer while unprocessed red meat and poultry were strongly associated with premenopausal breast cancer in Caucasian women, but odds ratios across menopausal status were significantly different only for poultry intake. Similarly, poultry consumption appeared particularly harmful for ER negative tumors among Caucasian women.

Red meat intake in both processed and unprocessed forms increased breast cancer risk in Caucasian women regardless of hormone receptor status, albeit not all risk estimates reached statistical significance. Among Afro-American women, there was no strong evidence relating red meat and poultry intake to breast cancer risk except for a significant positive linear trend between consuming processed meat and ER positive tumors.

3. Conclusions

- It is evident from the studies reported in the present review that there is a divergence in the results from population studies compared with more controlled conditions. There are several reasons for this lack of consensus beside the possibility of confounding factors and the many differences in the experimental design and endpoints. We need to resolve the discrepancies to launch a global effort to fight the rise of breast cancer incidence which includes diverse populations. Indeed, few studies are available from LMI countries where variability in food intake is large and nutritional supplementation less prevalent.

- In addition, stratification of breast cancer by specific characteristic has to be further considered, particularly breast cancer grades, receptor status (ER, PR, HER2 (human epidermal growth factor receptor-2)) and other molecular classification, as specific diets and nutrients interact with these factors to promote or protect from a defined type of breast cancer.

- Finally, it seems that dietary factors are particularly important in determining premenopausal breast cancer risk. Efforts ought to be placed on developing studies in countries where breast cancer incidence is high in younger women.

4. References


