

Diet and breast cancer

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Abstract

Both diet and nutrition have been studied in relationship with breast cancer risk, as the great variation among different countries in breast cancer incidence could possibly be explained through the inflammatory and immune response, as well as antioxidant intake, among others. To date, no clear association with diet beyond overweight and weight gain has been found, except for alcohol consumption. Nonetheless, the small number of studies done in middle to low income countries where variability of food intake is wider, is beginning to show interesting results.

Key words: breast neoplasms; diet; risk; epidemiology; energy intake

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Resumen

Tanto la dieta como la nutrición han sido estudiadas en relación con el riesgo de cáncer de mama, dada la gran variación de incidencia de cáncer entre países, y la posibilidad de explicarla a través de la respuesta inflamatoria o inmune, así como ingesta de antioxidantes, entre otros. Hasta la fecha, ninguna asociación clara con la dieta ha sido encontrada, excepto para el consumo de alcohol, más allá del sobrepeso y del incremento de peso. Sin embargo, los estudios que se están realizando en países de mediano a bajo nivel de ingresos, con mayor variabilidad de ingesta de alimentos, comienzan a mostrar resultados interesantes.

Palabras clave: neoplasia de mama; dieta; riesgo; epidemiología; ingestión de energía

Breast cancer is the most common cancer in women of high-income countries: however, over the past 20 to 30 years, data support a trend of increasing incidence and mortality from breast cancer in lower income countries.¹ Multiple risk factors have been identified for breast cancer and can be divided into those that cannot be modified and those that are potentially modifiable. Diet is part of the modifiable risk factors together with adiposity, physical activity, smoking, alcohol consumption, and use of hormonal replacement therapy.²

A role for diet in cancer etiology has been suggested in part because of the large international variation in cancer rates and may be ascribed to the antioxidant

properties of selected nutrients, their influence on inflammatory and immune response, on the progression of cells through the cell cycle and DNA repair, DNA mutations, DNA adducts, metabolic detoxification, the stimulation of growth factors and the potential antiestrogen influence of some nutrients³ (Figure 1).

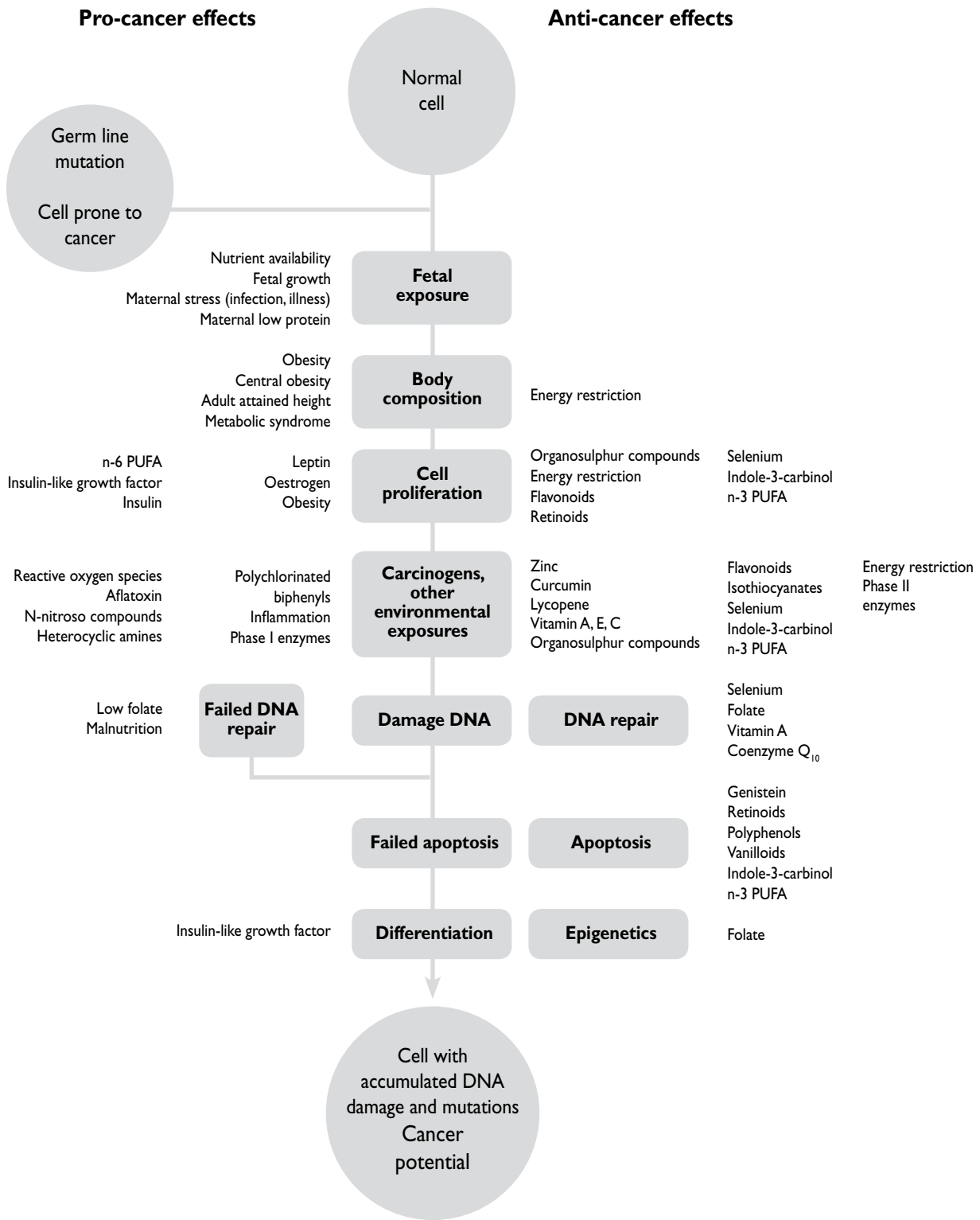
Some foods and nutrients have also been suggested to increase the risk for breast cancer through an increase in circulating levels of endogenous estrogen, insulin like growth factor 1 or other growth factors. Energy balance, the interplay of caloric intake, physical activity and metabolic rate, is another important factor impacting breast cancer risk through mechanisms not entirely understood.⁴

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FIGURE 1. THE INFLUENCES OF FOOD, NUTRITION, OBESITY, AND PHYSICAL ACTIVITY ON THE CANCER PROCESS

Study design

Both case-control and cohort studies have been used to evaluate the association between diet and breast cancer, while few randomized trials have been conducted because it is difficult to randomize large numbers of women to specific diet and maintain long term compliance. The long latency of breast cancer makes evaluation of diet during early life, a period when environmental exposure may play a strong role, a further methodological challenge.²

Dietary assessment

The use of a questionnaire to assess diet in the past is limited by participant's memory, in particular with a self administered questionnaire. In addition dietary intake reported by subjects most likely represents current diet or diet a few years in the past. The measurement error resulting from inaccurate reporting would tend to underestimate the association between dietary factors and breast cancer. Dietary questionnaires usually provide adequate ranking of individuals for dietary intake but cannot provide accurate quantitative intake. In case-control studies, recall of diet might be differential between cases and controls and lead to bias in the estimation.

Biomarkers of intake

The use of biomarkers that reflect dietary intake has potential advantages compared with the assessment of dietary intake through self reports, as reporting errors and limitations of food composition tables are avoided. However, levels of biomarkers can be affected by several factors other than diet, such as smoking or metabolic factors. In addition, levels of biomarkers reflecting intake

in an accurate manner are only for a limited number of foods and nutrients. Finally, depending on the biomarkers it can reflect longer or shorter exposure (e.g. the fatty composition of adipose tissue reflects long-term intake, whereas the fatty acid profile of serum or plasma phospholipids reflect medium term intake).⁴

Links between diet and risk of breast cancer have been extensively investigated but many topics remain controversial. This apparent lack of association may be real, or may be due to measurement error exceeding variation in the diet studied, and to a low heterogeneity of intake in the populations under study.

Diet and breast cancer

The large body of literature on nutrition and breast cancer has been recently reviewed and summarized.^{2,4-6} An international panel of the World Cancer Research Fund and the American Institute for Cancer Research concluded that there is convincing evidence that alcohol intake raises the risk of breast cancer at all ages, while body fatness increase the risk of breast cancer after menopause.⁷ Taller height is related to elevated risk of breast cancer, possibly because it is a marker for genetic, environmental, hormonal and nutritional factors affecting growth, and body fatness is probably related to a decreased risk of premenopausal breast cancer. The panel found limited evidence and drew no firm conclusions on the role of individual's foods and nutrients on overall breast cancer risk (Table I).

Carbohydrates, glycemic index and glycemic load

Carbohydrates and carbohydrate quality could influence breast cancer risk by affecting insulin resistance and plasma levels of insulin and glucose.⁴ Chronically

Table I
FOOD, NUTRITION, PHYSICAL ACTIVITY AND BREAST CANCER

	Premenopause		Postmenopause	
	Decreases risk	Increases risk	Decreases risk	Increases risk
Convincing	Lactation	Alcoholic drinks	Lactation	Alcoholic drinks Body fatness Adult attained height
Probable	Body fatness	Adult attained height Greater birth weight	Physical activity	Abdominal fatness Adult weight gain
Limited-suggestive	Physical activity		Total fat	

Source: World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington, DC: AICR, 2007. Reprinted with permission

raised insulin levels may increase carcinogenesis in breast tissue by directly stimulating insulin receptors or through a reduction in plasma and tissue levels of IGF binding proteins 1 and 2, which may in turn increase the availability of IGF-1.⁸ Experimental studies have found strong proliferative and antiapoptotic effects of IGF-1 in breast tissue.⁹ Elevated carbohydrate intake, and in particular rapidly-absorbed carbohydrates, may affect BC risk by maintaining a constant insulin demand through rapid increases in blood glucose. Nevertheless, these insulin-mediated mechanisms have not been fully supported by observational studies where circulating IGF-1 levels have not been associated to postmenopausal cancer and seem to be only marginally relevant for premenopausal cancer.¹⁰ To date the 12 prospective cohort studies have not shown consistent associations between total carbohydrate, glycemic index, glycemic load and breast cancer.² Nevertheless, there is a suggestion that carbohydrates may play a role when lifestyle factors, menopausal status and hormone receptor status are considered. In a recent large prospective study in France, overall glycemic index was associated with BC risk among overweight women (RR= 1.35 (95% CI: 1.00, 1.82)] when comparing extreme quartiles of intake¹¹ suggesting that carbohydrates intake may be of relevance for BC in the presence of underlying insulin resistance. Data from Mexico support the association between carbohydrate intake and glycemic load with breast cancer among pre- and postmenopausal women.¹² Compared with women in the lowest quartile of total carbohydrate intake, the odds ratio of BC for women in the highest quartile was 2.22 (95% CI: 1.63-3.04). Carbohydrates account for 64% of caloric intake in the Mexican population.¹³ This large variability in intake is not observed in western populations and may account for the apparent discrepancy between observations made in Mexico and elsewhere. It is also likely that high intake of refined carbohydrates could have stronger associations with risk of BC in populations genetically susceptible to insulin resistance, such as in Mexico, particularly when combined with low levels of physical activity and obesity.

Dietary fat

Potential mechanisms of fat intake of breast cancer include an influence on sex hormone levels or higher energy density affecting other risk factors such as weight gain or age at menarche.² While animal feeding studies have shown for several decades that high-fat diets induce mammary carcinogenesis,¹⁴ experimental

and epidemiologic data have been unable to clearly define the biological pathways that would lead to carcinogenesis.^{15,16} Evidence from large cohort studies has been unresponsive. Two meta analyses and clinical trials have not supported a strong association with total fat. A pooled analysis of eight prospective cohorts and a recent analysis of the Nurses' Health study over a 20 years follow up found a null association.^{17,18} In the large Women's Health Initiative (WHI) randomized trial low-fat diet was related to a 9% lower risk of BC in the intervention group.¹⁹ However, results of this trial are difficult to interpret because actual fat intake between the intervention and the control group was small. The difference in BC incidence between groups could be explained by the observed reduction of weight and an increase in fruit and vegetable intake in the intervention group.

Considering specific type of fats, results are also inconclusive. Long chain polyunsaturated fatty acids (LCPUFA) might increase breast cancer risk and than high levels of antioxidants might oppose the apoptotic effect of n-3 LCPUFA.²⁰ Data using the lipidome approach (integrated view over the complex lipid interaction or lipid profile based on adipose tissue samples) suggest that elevated monounsaturated and low n-6/n-3 fatty acids ratio is associated with decreased breast cancer risks.²¹

Recently interest has been raised on the impact of trans-fatty acids on cancer. Trans-fatty acids are unsaturated fatty acids with at least a double bond in the trans-configuration. Humans do not synthesize trans-fatty acids; the main source is therefore dietary intake of industrialized products containing partially hydrogenated oils such as margarine, rolls, etc.²² Little data is available on the role of trans fatty acids on BC. However in a large cohort of French women (E3N cohort study), an increased risk of BC was observed with increasing levels of the trans-monounsaturated fatty acids (palmitoleic and elaidic acid) (OR 1.75, 95% CI: 1.08-2.83) suggesting the role of industrially processed food on the risk of BC.²²

Red meat and processed food

Red meat consumption could affect the risk of breast cancer because of the highly bioavailable iron content, growth-promoting hormones used in animal production, carcinogenic heterocyclic amines formed during cooking and its specific fatty acids contents. Pooled analyses of case-control and cohort studies have yielded conflicting results.² However, recent reports suggest a positive association between the consumption of red meat and processed meat and the risk of breast cancer

according to specific receptor status [estrogen receptors (ER) and progesterone receptors (PR)]²³ and potential susceptibility to carcinogenic amines due to polymorphisms in N-acetyl transferase.²⁴

Fruits and vegetables

The antioxidant and fiber content of fruits and vegetables has been hypothesized to protect from BC. A pooled analysis from eight prospective studies found no significant association for neither vegetable nor fruits with breast cancer²⁵ and results from a large prospective European study confirm those results.²⁶ No reduction on recurrence or mortality was observed in the Women's Health Eating and Living (WHEL) trial randomized to a very high intake of fruits and vegetables and fiber and low fat.²⁷ When considering antioxidant intake, there is no consistent association between any antioxidant and BC incidence;⁴ However, three studies have suggested a protective effect of vitamin E. In a Danish study, vitamin E intake has been related to a lower risk of BC among postmenopausal women²⁸ and two reports suggest a protective effect of high serum vitamin E on breast cancer risk.^{29,30}

Alcohol

Alcohol is the dietary factor for which the association with BC is most consistent and biological mechanisms are more clearly defined. Prospective studies involving several thousand BC cases report that increasing alcohol consumption is associated with a moderate linear increase in the risk of BC ranging from 3 to 9% for one additional drink per day (10 g).^{31,32} The association is present in both premenopausal and postmenopausal women, does not vary by type of alcoholic beverage,^{31,32} does not seem to depend on drinking frequency,^{31,33} and is mostly restricted to estrogen positive breast tumors.³⁴ The relevant timing of exposure seems to be recent alcohol intake: alcohol intake during adolescence^{35,36} and after adjustment for current alcohol consumption, intake in the 20s, 30s and 40s age periods is not associated to subsequent BC.³¹ The best supported mechanism underlying this association is related circulating estrogen levels. Experimental studies have shown that addition of alcohol to BC cells results in estrogen-mediated signaling and proliferation.^{37,38} Controlled feeding trials have shown that moderate alcohol intake increases circulating estrogen levels in both pre- and postmenopausal women.^{39,40} Alcohol intake in Mexican women is still relatively low, less than 5% of middle aged women report weekly consumption of alcohol.⁴¹

However, 10% of adolescent girls aged 16 to 19 report alcohol consumption at least once a week. Elevated alcohol intake in younger women may result in alcohol intake patterns later in life that may increase BC risk.

Folate

Folate participates in DNA metabolism in the synthesis of purines and thymidilate and is a methyl donor for DNA methylation reactions. Low levels of folate may result in a disruption of DNA repair and replication processes and in abnormal methylation and gene expression.⁴² Most prospective studies do not provide evidence of an association between folate intake and BC risk^{43,44} and results from the Nurses' Health Study are only suggestive of an inverse association with circulating folate levels.⁴⁵ High intake of folate as well as circulating levels may be associated with lower risk of BC among moderate to high alcohol-drinkers.^{45,46} Ethanol may produce a physiologic deficiency that affects one-carbon metabolism by reducing folate absorption in the gastrointestinal tract or by inhibiting enzymatic activity.⁴² It is possible that the benefit of folate may only be observable in individuals with low folate status. This is supported by observations in populations where folate fortification is not present and vitamin supplementation is infrequent.⁴⁷⁻⁵¹ In a population-based case-control study in Mexico, where folate intake is low, the odds ratio for the highest quartile of folate intake compared to the lowest was 0.62 (95% CI: 0.45-0.90).⁵¹ Folate may play a dual role in human cancer etiology by conferring protection in early carcinogenesis and promoting cancer growth later in the carcinogenic process. In a screening trial in the United States after widespread folate fortification a significant increase in BC risk with increasing folate intake was observed [RR=1.32 (95%CI: 1.04-1.68) comparing the highest to the lowest level of intake].⁵² In this population total folate intake was several times higher than what was observed in other studies and the increased risk was mostly related to folic acid supplementation. Furthermore, there is a suggestion that vitamin B12, a co-enzyme in folate metabolism, may be associated to lower risk of BC and that low vitamin B12 intake may reduce the apparent protection in the risk for BC conferred by folate.⁵¹⁻⁵⁴

Vitamin D

Vitamin D has recently emerged as a potentially important determinant of BC; however, information is still scant. Vitamin D is a fat-soluble vitamin and a hormone present in food in two forms: cholecalciferol

(D₃) from animal sources and ergocalciferol (D₂) from plant sources. The main source of vitamin D₃ in humans is epidermally-generated through the exposure to UV light.⁵⁵ Vitamins D₂ and D₃ are metabolized to 25-hydroxyvitamin D [25-(OH) D] in the liver and then transformed in the kidneys into the biologically active and closely regulated 1,25-dihydroxyvitamin D [1,25-(OH)₂ D].⁵⁶ Experimental studies have shown that 1,25-(OH)₂ D can inhibit cellular proliferation, induce differentiation and apoptosis, inhibit angiogenesis in normal and cancer cells and modulate gene expression.⁵⁷

Results from epidemiologic studies suggest an inverse association between vitamin D intake and BC, particularly among premenopausal women. The risk ratio for premenopausal BC comparing extreme categories of intake was 0.72 (95%CI: 0.55-0.94) in the Nurses' Health Study⁵⁸ and 0.65 (95%CI: 0.42-1.00) in the Women's Health Study.⁵⁹ A pooled analysis found a strong linear inverse association between serum 25(OH)D and BC risk;⁶⁰ while results for 1,25-(OH)₂ D were less clear.

Vitamin D status appears to be affected by factors associated to intake, UV light exposure and factors that may affect its metabolism. Among Mexican women, intake of vitamin D is well below the Recommended Dietary Allowance of 5µg/day¹³ and the finding that Mexican-Americans have a significantly lower level of circulating vitamin D as compared to US whites⁶¹ is supported by the observation that individuals with pigmented skin may have deficient vitamin D levels even when sun exposure is abundant.⁶²

Dietary fiber and other foods and nutrients

Fiber could play a role on the risk of BC by decreasing the intestinal reabsorption of estrogen and therefore lowering its circulating levels.⁶³ Fiber intake has also been related to an increase in serum levels of insulin growth factor binding protein-3 (IGFBP-3), the main protein carrier for IGF-1.⁶⁴ However to date there is no clear data on the role of fiber on the risk of BC.⁶⁵ In Mexico, case-control studies suggest a protective effect of fiber intake on BC risk.^{12,66} Tea has been hypothesized to be associated with a reduced risk of BC through the anticarcinogenic effect of polyphenolic flavonoids.⁶⁷ A meta-analysis found an inverse association between green tea and BC, the summary odds ratio for the highest versus the lowest exposure level was 0.78 (95%CI: 0.61-0.98).⁶⁷ However, results for black tea have been consistently null and a prospective analysis of total polyphenol intake did not yield significant findings.⁶⁸⁻
⁷⁰ Interest in coffee as a potential determinant of BC

originated from observation that women who reduced consumption of coffee experienced a regression of fibrocystic disease of the breast, a known risk factor for BC.⁷¹ However, results for coffee intake and BC on most large prospective cohorts are essentially null.^{72,73} In Sweden, the largest per capita consumer of coffee, women who consumed four or more cups of coffee a day had a relative risk of 0.94 (95% CI: 0.75-1.28) as compared to women who had one cup a week or less.⁷⁴ Phytoestrogens have been evaluated as nutrients that may potentially reduce BC risk. Isoflavonoids, coumestrol and lignans are mainly found in soybeans, cereals and grains and these nutrients have been hypothesized to act as weak estrogen agonist or antagonists.^{75,76} A recent meta analysis reported a pooled relative risk comparing high and low soy intake of 0.86 (95%CI: 0.75-0.99).⁷⁷ In Mexico case-control studies observed a protective effect of phytoestrogen intake on BC risk.^{78,79}

Early-life diet and breast cancer

Exposure in early life may be particularly important in predicting later risk of breast cancer. The mammary gland is most susceptible to environmental exposure before the accelerated cell differentiation during puberty and first pregnancy. Animal studies suggest that mammary tissue is especially sensitive to carcinogenic exposures that occur after menarche and before first pregnancy.⁸⁰ Nutrition in early life can affect height and age at menarche, established risks factors for BC. Data from case-control studies suggest decreased risk for cancer with diets high in fat from dairy foods, milk, vitamin D and increased risk with high consumption of meat with visible fat.² Data from the NHSII suggest a protective effect of vegetable consumption and vitamin E and an increased risk with the consumption of foods with high glycemic index during adolescence with BC.⁸¹ Data in Asian population suggest that high intake of soy and phytoestrogen in adolescence is related to lower risk of BC.⁸²⁻⁸⁴

Dietary pattern and breast cancer

Assessment of dietary patterns reported in population studies is an approach to analyzing intake of foods in the context of the whole diet and may be of particular interest to public health, providing a basis to make recommendations on eating practices to prevent disease, such as healthy food choices. A recent meta-analysis of studies on dietary pattern and breast cancer suggest a decreased risk of breast cancer in the highest compared to the lowest categories of prudent/healthy pattern and

an increased risk in the highest category of a drinker pattern.⁸⁵ Data from Singapore suggest that a diet rich in vegetable (cruciferous) fruit and tofu items had a protective effect on breast cancer among postmenopausal women.⁸⁶ Data from a large cohort study conducted in French women support the protective effect of a healthy/Mediterranean pattern (essentially vegetables, fruits, seafood, olive oil and sunflower oil) on breast cancer among postmenopausal women particularly on ER+ and PR+ tumors.⁸⁷

Conclusion

Among the prospective epidemiological studies conducted on diet and breast cancer to date there is no clear association with diet except for alcohol consumption in addition to overweight and weight gain. Most of the studies have been conducted in Western countries with some limitations in variability of diet exposure. Few studies are available from middle to low income countries where variability in food intake is wider and food supplementation less prevalent. Data from Mexico suggest that high intake of carbohydrate and high glycemic load is related to an increase of breast cancer and that high intake of folate and phytoestrogens are related to lower risk. Although these results need to be confirmed in other populations, they suggest that baseline nutritional status and genetic susceptibility might interact with food intake in relation with BC.

Several factors need to be considered in the interpretation of the current literature:

1. Variation in diet in the study population conditions the power of a study to detect a true association. While some studies have combined several populations with different diet, the variability might not be sufficient to evaluate small effect of diet. Taking advantage of international variation and population in epidemiological transition as observed in low to middle income countries would increase our ability to evaluate the role of diet and changing diet on cancer risk.
2. Dietary assessment was mostly based on questionnaires and self reports. Although in many studies these questionnaires had been validated, there is potential for measurement error leading to an underestimation of any causal association between diet and breast cancer. Development of methods for a better evaluation of dietary intake is needed using biomarkers and metabolic profiles.
3. Timing of dietary assessment and follow up time. Experimental data suggest that adolescence might be a period of more susceptibility to environmental factors. Most of the cohort studies have focused on adult intake assessed at baseline among women 40 and older, exploring mostly the relation of diet in postmenopausal women. There is not sufficient information on the relation of diet during early years and the association with premenopausal breast cancer. In addition, in some cases follow up may not be sufficient to fully capture the effect of diet.
4. Stratification of breast cancer by specific characteristic should be considered, in particular receptor status (ER, PR, HER). It is likely that diet may act differently on different types of cancer and this need to be further explored. However, given the lost of power in stratified analyses, only studies with large numbers of cases or pooling of studies will allow such analyses.
5. Food toxins might be ingested with regular diet and could counteract some beneficial effect of foods. Studying intake of organic foods or, vegetarian regimes need to be further explored.
6. Foods and nutrients have interactive effects and this is difficult to capture in epidemiological studies. Having metabolic profiles of individuals through a metabolomic approach could provide a more integrated evaluation about the impact of diet on breast cancer.
7. Gene-diet interaction is particularly important in the field of diet and breast cancer because most existing evidence has not revealed strong association with risk. Large genome wide association studies are on their way and will provide further insight on potential gene-diet interaction.
8. Diet may also interact with genetic predisposition via epigenetic mechanisms. Epigenetic refers to the study of processes that alter gene activity without changing the DNA sequences.⁸⁸ Dietary intake of methyl donors (such as folate, vitamin B12, choline and betaine) during pregnancy influence methylation in mouse models.⁸⁹ In addition, emerging evidences suggest that exposures during adulthood can influence methylation⁹⁰ and epigenetic malfunction appear to play an important role in cancer development.⁹¹ Further investigations are needed in order to unravel the role of diet on the DNA hypermethylome in breast cancer cells.

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