The role of obesity, physical activity and dietary factors on the risk for breast cancer: Mexican experience

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Abstract
We provide an overview of the role of adiposity, physical activity and diet in the risk for breast cancer in Mexican women. Lack of physical activity, diets high in carbohydrates and in glycemic load and low intake of folate and vitamin B12 have been shown to increase the risk of breast cancer in Mexican women, in particular postmenopausal breast cancer. Other dietary factors that may begin to play a more relevant role in breast cancer incidence in Mexico are alcohol intake and vitamin D status. Recommendations to maintain a healthy weight, practice moderate physical activity, decrease intake of rapidly absorbed carbohydrates and increase consumption of fruits and vegetables could have an important impact on the epidemic of breast cancer in Mexico.

Keywords: breast cancer; adiposity; physical activity; carbohydrate; fats; alcohol; folic acid; Mexico

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Resumen
Se proporciona una revisión general del papel de la adiposidad, la actividad física y la dieta sobre el riesgo de cáncer de mama en mujeres mexicanas. La falta de actividad física, una dieta alta en hidratos de carbono y en carga glicémica y la baja ingesta de ácido fólico y vitamina B12 se han relacionado con un aumento en el riesgo de cáncer de mama en mujeres mexicanas, sobre todo en mujeres posmenopáusicas. Otros factores dietéticos que han tenido un papel más relevante en la incidencia de cáncer de mama en México son la ingesta de alcohol y las concentraciones de vitamina D. Las recomendaciones sobre cómo mantener un peso saludable, realizar actividad física moderada, disminuir la ingesta de hidratos de carbono de absorción rápida e incrementar el consumo de frutas y verduras podrían tener un impacto importante en la disminución de la epidemia de cáncer de mama en México.

Palabras clave: cáncer de mama, adiposidad, actividad física, carbohidratos, grasas, alcohol, ácido fólico; México

The incidence of breast cancer (BC) in Mexico is still relatively low as compared to Western countries but is increasing steadily. Breast cancer recently became the first cause of cancer mortality in Mexican women doubling between 1980 and 1990 from 6.4 to 13.1 per 100 000 women among women 25 years and older and reaching 16.4 per 100 000 women in 2007.[1] This increase in mortality, while treatment has improved, reflects an increase in incidence linked in part to changes in women's lifestyles. Later age at first pregnancy, decreasing duration of lactation, fewer pregnancies, increasing hormone use for contraception and menopausal therapy,

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less active lifestyles and substitution of traditional dietary habits have probably contributed to this upward trend.[2] Understanding the importance of these factors in the risk for BC is important because life style and dietary factors are potentially modifiable. The current review is a short summary of the available evidence relating adiposity, physical activity and dietary factors to BC focusing on factors that have been evaluated in Mexican women and on emerging factors that may prove to be of relevance in the future.

Adiposity

Overweight and obesity increase the risk of all-cause mortality and cancer mortality even among non-smokers.[3] The relation between excess body weight and BC is complex: as compared to women who are not overweight, premenopausal overweight women are at a lower risk while postmenopausal overweight women are at a higher risk of BC. Pooled data from seven cohort studies comprising 703 premenopausal women with BC observed a relative risk 0.58 (95% CI: 0.34-1.00) for women with a body mass index[1] greater or equal to 33 kg/m^2 as compared to those with less than 21 kg/m^2.[2,4] In this same analysis, the relative risk of postmenopausal BC for the same comparison was 1.27 (95%CI: 1.03-1.55). These results are consistent with an analysis on 176 886 women from nine European countries from the EPIC[5] and a recent analysis on twins observed that the inverse association in premenopausal women and the positive association in postmenopausal women may be even stronger after adjusting for genetic factors and early life environment.[6] Several potential mechanisms may explain the differences observed between premenopausal and postmenopausal women. Among premenopausal women, the inverse association between BMI and BC was more clearly observed for ER^+ tumors, suggesting that this association is likely due to sex steroid hormones.[7] Premenopausal women may experience anovulation and may have a lower exposure to ovarian hormones due to anovulatory infertility.[8]

Among postmenopausal obese women, a large pooled analysis observed an almost twofold increase in the geometric mean of estradiol as compared to normal weight women, probably because of increased aromatization of adrenal androgens in adipose tissue.[9] This same analysis reported that adjustment for estradiol level attenuated almost completely the linear association between BMI and BC risk.

Adult weight gain appears to be even a stronger determinant of BC than recent weight. For premenopausal women an increase of more than 25 kg was associated to a relative risk of 0.74 (95%CI: 0.54-1.03) and for postmenopausal women the relative risk was 1.41 (95%CI: 1.12-1.78).[10] Among postmenopausal women, the association appears to be even stronger among women who never used hormone replacement therapy as compared to those who did suggesting that menopausal hormone therapy may have a residual effect on breast tissue and that the adiposity-mediated estrogenic effect may be dampened.

In recent years Mexico has experienced a dramatic rise in the prevalence of overweight and obesity. The prevalence rose from 33.4% in 1988 to 59.6% in 2000 to 71.9% in 2006 in adults. The increase is also dramatic among children, the prevalence increased by 33% in girls between 5 and 11 years of age between 1999 and 2006.[11,12] There is no data on the association of adiposity and BC incidence in Mexico. However, given the magnitude of the obesity epidemic, the relevance of adiposity for postmenopausal BC and the susceptibility of the Mexican population to insulin resistance and metabolic syndrome[13] we can expect adiposity to be an important driving factor in the increasing incidence of BC in Mexico.

Physical activity

Physical activity can affect hormonal levels[14,15] and increase levels of sex hormone-binding globulin (SHBG), thereby reducing bioavailable estrogens.[16] Increased physical activity also reduces insulin resistance and hyperinsulinemia,[17] hypothesized to be related to BC.[18] Many epidemiologic studies have evaluated the association between physical activity and BC. A recent study identified 19 cohort studies and 29 case-control studies amiable for analysis.[19] After taking into account the quality of the studies, there is evidence of a least 20% lower risk of postmenopausal BC when comparing high to low leisure time activity. In contrast, results for premenopausal BC are inconclusive. More recently the EPIC study evaluated household physical activity, which is seldom measured, and observed a lower risk of BC in premenopausal [RR=0.71 (95%CI: 0.55-0.90), highest versus the lowest quartile] and postmenopausal women [RR=0.81 (95%CI: 0.70-0.93), highest versus the lowest quartile]. In the Iowa Women's Health Study, a strong inverse association for ER^+/PR^- BC was found and this association was not attenuated after adjustment for BMI.[20] The suggestion that physical activity may affect BC risk through a hormone dependent pathway is supported by the inverse association observed between physical activity and several sex-hormones in the Women's Health Initiative.[21]

In a recent large case-control study in Mexico moderate physical activity (yoga, light biking, light walking)

was inversely associated to BC risk. In postmenopausal women, there was a 9% reduction in the odds of BC for every hour per week increase of moderate physical activity. Among premenopausal women no association was observed [OR=0.99 (95% 0.94-1.05)].[22] Regular recreational physical activity is uncommon in Mexican women. Only 16% of women exercise regularly and the national daily average of recreational physical activity for women is 5 minutes per day.[23] Regular physical activity has clear cardiovascular benefits and may influence BC risk. The ongoing demographic transition from rural to urban areas is likely to result in lower overall physical activity in Mexico. Strategies to increase regular physical activity among Mexican women should be explored and further research on the impact of the lack of physical activity in this population is needed.

Dietary factors

Few dietary factors have been consistently associated with BC risk. This apparent lack of association may be real, or may be due to measurement error exceeding the variation in the diet studied, and to a low heterogeneity of intake in the populations under study. While some dietary factors like fat and alcohol have been extensively investigated, other dietary factors potentially detrimental such as rapidly absorbed carbohydrates or potentially beneficial, such as vitamin D and folate have not been sufficiently explored.

Carbohydrates

Chronically 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.[24] Experimental studies have found strong proliferative and antiapoptotic effects of IGF-1 in breast tissue.[25] 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.[26]

There is no strong epidemiological evidence to support the role of carbohydrate intake or carbohydrate quality, as measured by overall glycemic index and glycemic load on overall BC risk.[27-44] In the Nurses' Health Study, the largest study conducted to date, the relative risk of BC comparing extreme categories of carbohydrate intake was 0.97 (95%CI 0.87-1.08), glycemic index was 1.08 (95%CI 0.97-1.19) and glycemic load was 0.99 (95%CI 0.89-1.10).[37] 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 intake[32] suggesting that carbohydrates intake may be of relevance for BC in the presence of underlying insulin resistance. This study also found a direct association between carbohydrate intake and glycemic load and estrogen receptor–negative BC.

In a population-based case-control study in Mexico carbohydrate intake was directly associated with BC risk.[30] 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% confidence interval (95% CI): 1.63-3.04]. This association was present in premenopausal and postmenopausal women. Results were further confirmed when the dietary glycemic load and glycemic index were evaluated. The odds ratio for all women comparing the highest to the lowest quartile of dietary glycemic load was 1.62 (95% CI 1.13–2.32). However, overall glycemic index was not significantly associated with BC risks. Carbohydrates account for 64% of caloric intake in the Mexican population.[45] 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.

Fat

The role of dietary fat as a risk factor for BC is controversial. Animal feeding studies have shown for several decades that high-fat diets induce mammary carcinogenesis.[46] Experimental and epidemiologic data have been unable to clearly define the biological pathways that would lead to carcinogenesis.[47,48] Epidemiological studies have yielded conflicting results. Initial evidence from ecologic and case-control studies suggested a direct association between fat intake and BC risk.[49,50] However, most subsequent prospective cohort studies have not lent strong support to this hypothesis. A pooled analysis of eight prospective cohorts that included 351 821 women and 7 329 cases reported no clear evidence of an association between total fat intake and pre and

postmenopausal BC but the risk ratio for saturated fat intake was 1.09 (95%CI 1.00-1.19).[51] The controversy persists. A recent analysis in the Nurses' Health Study evaluated this hypothesis with a 20 year follow-up using six repeated measures of dietary intake and found a null association.[52] In contrast, a well-conducted large cohort with close to 200 000 participants found evidence of a direct association.[53] Furthermore, 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.[54] 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.

Total fat intake appears to have a relatively modest association with BC risk if at all. In the absence of strong evidence of the underlying biologic pathways that lead to carcinogenesis, fat restriction as a strategy to reduce BC risk is not warranted. In Mexico two case-control studies[30,55] did not observed an association for saturated fat yet a inverse association was observed for polyunsaturated fat among postmenopausal women when comparing extreme quartiles of intake [OR= 0.37 (95% CI 0.20-0.66) [30] and OR= 0.10 (95% CI 0.02-0.39).[55] Nevertheless, more research is needed to assess the association of fat intake during childhood and adolescence as well as different types of fat.

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).[56,57] The association is present in both premenopausal and postmenopausal women, does not vary by type of alcoholic beverage, [56,57] does not seem to depend on drinking frequency[56,58] and is mostly restricted to estrogen positive breast tumors.[59] The relevant timing of exposure seems to be recent alcohol intake: alcohol intake during adolescence[60,61] and after adjustment for current alcohol consumption, intake in the 20s, 30s and 40s age periods is not associated to subsequent BC.[56] 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.[62,63] Controlled feeding trials have shown that moderate alcohol intake increases circulating estrogen levels in both pre and postmenopausal women.[64,65] Alcohol intake in Mexican women is still relatively low, less than 5% of middle age women report weekly consumption of alcohol.[12] 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.[66] Most prospective studies do not provide evidence of an association between folate intake and BC risk[67,68] and results from the Nurses' Health Study are only suggestive of an inverse association with circulating folate levels.[69] High intake of folate as well as circulating levels may be associated with lower risk of BC among moderate to high alcohol-drinkers.[69,70] Ethanol may produce a physiologic deficiency that affects one-carbon metabolism by reducing folate absorption in the gastrointestinal tract or by inhibiting enzymatic activity.[66] 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.[71-75] 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).[75] Folate may play a dual role in human cancer etiology by confering 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].[76] 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 a 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.[75-78]

Dietary folate comes primarily from grean leafy vegetables, citrus fruits and legumes.[79] Vegetable and fruit intake in Mexican women is low (97% of Mexican women consume < 400 g/day) and in 1999 median

folate intake among Mexican women was 221 μg/day, which is close to half of the US RDA.[45,80] Mexicans have the highest reported prevalence of homozygous TT genotype for the 677C→T transition in the methylenetetrahydrofolate reductase (MTHFR) gene (32%).[81] Among individuals with this variant, low folate intake has been associated to a higher risk of BC as compared to other genotypes.[71] It is likely that both low dietary folate intake and a genetic susceptibility in the Mexican population may partially contribute to the increase in the incidence of BC in Mexican women as observed for gastric cancer (GC). A significant increase in GC risk was found among carriers of the 677TT genotype compared with those with the 677CC genotype [odds ratio (OR) 1.62, 95% confidence interval (CI) 1.00-2.59].[82] Vitamin deficiencies are potentially modifiable risk factors which can be addressed by supplementation and fortification of food. Folate deficiency is associated to other health outcomes and research to evaluate alternatives to address this problem should be conducted. However caution is required given results from trial that suggest that folate possesses dual modulatory effects on the development and progression of cancer depending on the timing and dose of folate intervention.[83]

Vitamin D

Vitamin D has recently emerged as potentially an 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 (D_3) from animal sources and ergocalciferol (D_2) from plant sources. The main source of vitamin D_3 in humans is epidermally-generated through the exposure to UV light.[84] Vitamins D_2 and D_3 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].[85] 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.[86]

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 Study[87] and 0.65 (95%CI: 0.42-1.00) in the Women's Health Study.[88] A pooled analysis found a strong linear inverse association between serum 25(OH)D and BC risk;[89] 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 men in the US race, latitude of residence, physical activity, body mass index, dietary intake and season explained 28% of the variability.[90] Among Mexican women, intake of vitamin D is well bellow the Recommended Dietary Allowance of 5μg/day[45] and the finding that Mexican-Americans have a significantly lower level of circulating vitamin D as compared to US whites[91] is supported by the observation that individuals with pigmented skin may have deficient vitamin D levels even when sun exposure is abundant.[92]

There is no information on circulating levels of vitamin D in Mexico. High exposure to UV light due to Mexico's latitude may result in a vitamin D-replete population with little variability. However, a setting with low dietary intake and no fortification, skin pigmentation, high prevalence of obesity and low physical activity circulating levels of vitamin D may be suboptimal. Vitamin D may therefore potentially contribute to BC incidence in Mexico.

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.[93] 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.[94] However to date there is no clear data on the role of fiber on the risk of BC.[95] In Mexico, case-control studies suggest a protective effect of fiber intake on BC risk.[30,55] Tea has been hypothesized to be associated with a reduced risk of BC through the anticarcinogenic effect of polyphenolic flavonoids.[96] 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).[96] However, results for black tea have been consistently null and a prospective analysis of total polyphenol intake did not yield significant findings.[97-99] 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.[100] However, results for coffee intake and BC on most large prospective cohorts are essentially null.[101,102] 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.[103] 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.[104,105] A recent meta analysis reported a pooled relative risk comparing high and low soy intake of 0.86 (95%CI: 0.75-0.99).[106] In Mexico, case-control studies observed a protective effect of phytoestrogen intake on BC risk.[107,108] High dietary intake of lignans (lariciresinol and pinoresinol) was associated with a significant reduction for premenopausal BC (high v. low tertile: OR = 0.32, 95 % CI 0.10, 0.99 and OR=0.19, 95% CI 0.06-0.62).[108]

Conclusion

Lifestyle and dietary habits in Mexican population have dramatically changed in the last 20 years as reflected by an increased prevalence of obesity in both urban and rural populations. Based on the 2006 National Nutrition Survey (ENSANUT 2006)[109] 35% of women over age 20 are overweight (BMI 25 to 29) and 31.7% are obese (BMI>=30). This represents a 41% and a 160% increase in the prevalence of overweight and obesity in just a decade.[110] Moreover, Mexicans appear to have a genetic susceptibility to insulin resistance and altered carbohydrate and lipid metabolism.[111-113] Carbohydrates are the major source of calories in the Mexican population with a mean daily carbohydrate intake of 357 g/day, equivalent to 64% of total caloric intake.[45] Low intakes of vegetables and fruits (97% of Mexican women consume < 400 g/day) and animal products and increasing consumption of processed foods may account for the high prevalence of micronutrient deficiencies observed in Mexican women such as folate, vitamin B12[7] and n-3 PUFA. Thirty five percent of Mexican women had deficient serum levels of folate and 17% had low levels of vitamin B12 in serum.

Obesity, lack of physical activity, high intake of carbohydrate, high glycemic load, low fiber intake, low intake of folate and vitamin B12 have been shown to increase the risk of BC in Mexican women, in particular postmenopausal BC. Other nutrients such as omega3 fatty acid, phytoestrogen of low intake in the Mexican population and vitamin D could also play an important role in the risk for BC.

Recommendations to loose weight, practice moderate physical activity and decrease intake of fast absorbed carbohydrate could have an important impact on the epidemic of BC. In addition, increased intake of folate and vitamin B12 in subjects with deficiency could also have a protective effect. To improve our knowledge on these and other factors, we recently implemented a large cohort study of Mexican teachers (EsMaestra) whom we plan to follow biannually over 10 years or more. The prospective assessment of lifestyle and diet will provide the adequate setting to evaluate causal factors of BC risk in Mexican women.

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