# Etiology of breast cancer (C50) in Central and South America

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Breast cancer is a complex, heterogeneous, and multifactorial disease. Although some genetic factors have a strong and well-defined impact, such as mutations in the *breast cancer 1* (*BRCA1*) and *BRCA2* genes, most of the women who develop the disease do not present a clearly identifiable risk profile [1, 2]. Only 5–10% of all breast cancers are considered to be due to mutations in inherited high penetrance genes [3]. The risk of breast cancer has been consistently associated with age, a family or personal history of breast cancer, reproductive and hormonal factors (i.e., early menarche, late age at first pregnancy, small number of pregnancies, short or no periods of breastfeeding, and a later menopause), hormone replacement therapy (HRT), obesity (for postmenopausal breast cancer only), alcohol consumption, physical inactivity, exposure to ionizing radiation, and genetic predisposition [4–6]. This section briefly describes these factors and especially focuses on those that are modifiable and could guide efforts for prevention in the Central and South American region.

## Reproductive factors and hormones

### *Age at menarche and menopause*

Age at menarche and age at menopause can be used to calculate the reproductive years of a woman. During this time, the ovary produces steroid hormones that affect the development and function of the breast [7]. Early age at menarche and late age at menopause have been consistently associated with an increased risk of breast cancer development [7]. The Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC) recently conducted a meta-analysis of 117 studies (35 cohort and 56 case–control) that included 118 964 women with breast cancer and showed that the risk of breast cancer increased by 5% (95% confidence interval [CI], 4.4–5.7%) for each year younger at menarche and by 2.9% (95% CI, 2.5–3.2%) for each year older at menopause [7]. The CGHFBC also showed that the risk of breast cancer was 43% (95% CI, 33–52%) higher in premenopausal women (aged 45–54 years) than in postmenopausal women of the same age [7].

Long-term exposure to high concentrations of endogenous estrogens increases the risk of breast cancer in pre- and postmenopausal women, the related mechanisms of which have been suggested to be involved in the risk factors associated with estrogen receptor/progesterone receptor (ER/PR)-positive tumours, while the etiology of ER/PR-negative tumours could be non-hormonal [8, 9]. Ma et al. [10] found that late age at menarche reduced the risk of ER/PR-positive tumours by 28% and that of ER/PR-negative tumours by 16% compared with a younger age at menarche (< 12 or < 13 years) (summary rate ratio [RR], 0.72; 95% CI, 0.64–0.80 for ER/PR-positive tumours; summary RR, 0.84; 95% CI, 0.75–0.94 for ER/PR-negative tumours). A pooled analysis of 14 795 breast cancer cases (10 900 ER-positive and 3895 ER-negative) and 17 399 controls revealed that women who were younger at menarche (< 12 years) were at a higher risk of ER-positive tumours than those who were older at menarche (> 15 years) (pooled odds ratio [OR], 1.16; 95% CI, 1.07–1.25), but the association with ER-negative tumours was less clear (pooled OR, 1.11; (95% CI, 0.99–1.03) [11]. In a subanalysis by tumour characteristics, the CGHFBC found that the risk of breast cancer varied by age and menopausal status [7].

Early menarche has also been suggested to be related to a higher risk for luminal cancers. However, a pooled analysis by Phipps et al. [12] found that early menarche (< 13 years) was not associated with luminal cancers (OR, 1.0; 95% CI, 0.9–1.2) but early menarche was associated with an increased risk of tumours that overexpressed human epidermal growth factor receptor 2 compared with late menarche (> 13 years) (OR, 2.7; 95% CI, 1.4–5.5).

### *Nulliparity and later age at first pregnancy*

Delayed childbirth due in part to increases in both socioeconomic development and more effective contraception has been postulated to increase the burden of breast cancer [13, 14]. Nulliparity and delayed childbearing have been associated with an increased risk of ER-positive but not ER-negative tumours. In a meta-analysis of eight studies, Ma et al. [10] found that older age at first pregnancy (≥ 30 years) increased the risk of ER/PR-positive tumours by 27% (95% CI, 7–50%) compared with pregnancy at a younger age and that each birth reduced the risk of ER/PR-positive tumours by 11% (95% CI, 6–16%), but did not find associations between parity or age at first birth and ER/PR-negative tumours.

The age of the mother at births and birth spacing seem to change the magnitude and the timing of the increased risk associated with breast cancer, suggesting that the associations between reproductive history and the risk of breast cancer are complex. Furthermore, changes in childbearing patterns (fewer children and later age at births) over the past decades could probably affect the burden of breast cancer incidence in the future [15, 16]. In the Central and South American region, fertility rates (number of births per woman) have been declining since the 1960s and this decline has coincided with an increased burden of breast cancer [17, 18]. This is particularly noticeable in Argentina, Brazil, and Uruguay where the incidence of breast cancer is among the highest and the fertility rates are the lowest in the region (average ~2 children per woman, similar to the fertility rate in the USA), whereas in Ecuador, Guatemala, Nicaragua, and Peru, the mortality rates are among the lowest and fertility rates are among the highest (~3–4 children per woman) in the region [19].

### *Breastfeeding*

The effect of breastfeeding on the risk of breast cancer has been a subject of debate [20]. However, a growing body of evidence indicates that breastfeeding reduces the risk of developing breast carcinoma [8, 21]. In a recent meta-analysis of 27 studies that included 13 907 women with breast cancer, Zhou et al. [21] found that women who had ever breastfed had a 39% lower risk of breast cancer than those who had never breastfed (pooled RR, 0.613; 95% CI, 0.442–0.850) and that the longest duration of breastfeeding was associated with a 53% lower risk of breast cancer compared with the shortest breastfeeding categories (RR, 0.471; 95% CI, 0.368–0.602). In a pooled analysis of two population-based studies, Phipps et al. [12] found that, compared with women who had never breastfed, those who had breastfed for 6 months or longer had a 20% (95% CI, 0–40%) reduced risk of luminal cancers and a 50% (95% CI, 10–70%) reduced risk of triple-negative cancers (ER/PR/human epidermal growth factor receptor 2-negative).

In a hospital-based case–control study conducted in Mexico City, Mexico, Romieu et al. [22] found that the risk of breast cancer was 61% lower in parous women who reported ever having breastfed than in parous women who had never breastfed after adjusting for age (OR, 0.39; 95% CI, 0.25–0.62), and the effect was stronger for postmenopausal than for premenopausal women (OR, 0.29 for postmenopausal women; OR, 0.48 for premenopausal women). They also reported a dose–response relationship showing stronger protective effects with longer durations of lactation (*P* for trend < 0.001). Women who reported breastfeeding four children or more had a 61% lower risk of breast cancer than those who had never breastfed (adjusted OR, 0.39; 95% CI, 0.21–0.70); the protective effect was also observed for those who had breastfed one to two and three to four children (OR, 0.57 for 1–2 children; 0.52 for 3–4 children).

## Exogenous hormones

In the evaluation of pharmaceuticals as human carcinogens, the International Agency for Research on Cancer (IARC) concluded that there was sufficient evidence for the causative effect of combined estrogen–progestogen contraceptives (OC) and combined estrogen–progestogen menopausal therapy on breast cancer [23]. The evidence suggests that the risk of breast cancer increases with increasing duration of OC use among current users, but whether all current formulations and treatment regimens have similar carcinogenic effects has yet to be elucidated [24]. Furthermore, OC use has been associated with an increased radiological breast density [24]. The CGHFBC showed that current OC users had a 24% (95% CI, 15–33%) higher risk of breast cancer than never-users and the risk remained even 1–4 years or 5–9 years after cessation of use (RR, 1.16; 95% CI, 1.08–1.23 for 1–4 years; RR, 1.07; 95% CI, 1.02–1.13 for 5–9 years) [25].

Epidemiological evidence has consistently suggested that OC use is associated with an increased risk of breast cancer among carriers of *BRCA1* or *BRCA2* mutations [24, 26, 27], which may explain the risk of breast cancer among young women (aged < 35 years) who began using OC at a young age and were current or recent users (as cited in [24]). In a meta-analysis of eight studies in carriers of *BRCA1* and *BRCA2* mutations, Moorman et al. [28] showed that OC users had a 21% increased risk of breast cancer than non-users (summary OR, 1.21; 95% CI, 0.93–1.58). Another meta-analysis showed that *BRCA1*/*BRCA2* carriers who stopped using OC 10 years before the diagnosis had a 46% lower risk of breast cancer then never-users (RR, 1.46; 95% CI, 1.07–2.07) [26]. In a recent meta-analysis of three cohort studies, Friebel et al. [27] found that the risk of breast cancer in *BRCA1* carriers was

59% higher among ever-users of OC compared with never-users (hazard rate ratio [HR], 1.59; 95% CI, 1.32–1.92) and that in *BRCA2* carriers was 85% higher among ever-users of OC compared with never-users (HR, 1.85; 95% CI, 1.30–2.64 in 2 cohort studies) [27]. The differences in these meta-analyses were due to the way in which the studies were stratified to evaluate the associations.

Exposure to estrogen-only menopausal therapy has been linked to an increased risk of breast cancer, although IARC concluded that there was limited evidence for its causative effect [24]. Some studies suggested that longer-term use estrogen therapy increases the risk of breast cancer (as cited in [24]).The Women's Health Initiative Randomized Trial showed that the use of combined HRT for more than 2 years may increase mammographic density and thus reduce the sensitivity of mammography to provide an early diagnosis [29]. Lee et al. [30] evaluated the menopausal use of estrogen–progesteron therapy on the risk of breast cancer by histological subtype and found that it increased the risk by 7.6% per year of use. In a recent meta-analysis, Reeves et al. [31] showed that current use of HRT increases the risk of in-situ and invasive ductal breast cancers compared with never use (RR, 1.51; 95% CI, 1.39–1.63 for in-situ cancer; RR, 1.67; 95% CI, 1.62–1.73 for invasive ductile cancer).

## Personal history of breast cancer

A personal history of in-situ or invasive breast cancer increases the risk of developing a contralateral invasive cancer. In the USA, the incidence of contralateral breast cancer steadily declined from 1985 to 2006 by 3% (95% CI, –3.5% to −2.7%] per annum, which was mainly due to greater declines in contralateral breast cancer rates after an ER-positive primary breast cancer than after an ER-negative cancer (estimated annual percentage change, −3.18%; 95% CI, –4.2% to −2.2% for ER-positive; estimated annual percentage change, –1.68%; 95% CI, 0.0% to −3.4% for ER-negative). The declines were more evident for contralateral breast tumours diagnosed 1–4 years after a diagnosis of ER-positive primary breast cancer (estimated annual percentage change, −3.71%; 95% CI, –4.9% to −2.5% per year). Such declines are thought to be due to the widespread use of adjuvant hormone therapies [32]. Women with a history of atypical lobular or atypical ductal hyperplasia had a 4.4 (95% CI, 3.1–6.3) times higher risk of developing breast cancer than the general population and the association was nearly doubled in those with a family history of breast cancer (RR, 8.9; 95% CI, 4.8–17) [33].

## Family history of breast cancer and genetic susceptibility

Some genome-wide association studies conducted in Asia, Europe, and North America have shown that susceptibility genes and genomic sequences account for less than one third of all inherited breast cancers (as cited in [34]). The *BRCA1* and *BRCA2* tumour suppressor genes account for 5% of all breast cancers and 85% of all hereditary breast and ovarian epithelial cancers. Women with Cowden or Li-Fraumeni syndromes have an increased risk of developing breast cancer with a lifetime risk of 50% and 1%, respectively (as cited in [34]).

Women with any relative, a first-degree relative, a mother or a sister with breast cancer have about twice the risk of developing breast cancer. The risk is noticeably higher among women who have a mother and a sister with breast cancer (RR, 3.6; 95% CI, 2.5–5.0) and among younger women (RR, 2.5–3.3 for women < 50 years of age who have relatives with breast cancer diagnosed before the age of 50 years) [35].

The most frequent hereditary syndrome is hereditary breast and ovarian cancer (through a *BRCA1* or *BRCA2* gene mutation), with a 50–80% risk of breast cancer throughout the course of a lifetime. *BRCA1*-related cancers are frequently triple negative, while *BRCA2*-related cancers are often hormone-dependent but highly proliferative [36, 37]. Both gene mutations are associated with carcinomas appearing at an earlier age and also an increased risk of developing ovarian cancer (lifetime risk, 10–50%), especially with *BRCA1* mutations [38]. However, considerable inter-individual variability has been found among *BRCA1* and *BRCA2* carriers in terms of age at and site of cancer diagnosis which maybe a result of modifying factors (i.e., breastfeeding, oral contraceptive use, tubal ligation, alcohol consumption, exposure to X-rays or mammography, use of tamoxifen (and other selective estrogen receptor modulators), obesity, and physical activity) that influence cancer penetrance in carriers. A similar variability has also been described between families carrying the same *BRCA1*/*BRCA2* mutation genes [27].

In a population-based study conducted in the USA among white and black women aged 35–64 years, the overall prevalence of *BRCA1* and *BRCA2* carriers was 4.6% (2.4% and 2.3%, respectively) in the cases and 0.4% (0.04% and 0.4%, respectively) in the controls. Among the cases, the prevalence of *BRCA1* was higher in those of Jewish ancestry than in those of non-Jewish ancestry (10.2% vs 2.4%) and in whites than in blacks (2.9% vs 1.4%), whereas the prevalence of *BRCA2* was slightly higher in non-Jewish than in Jewish women (2.3% vs 1.1%) and in blacks than in whites (2.6% vs 2.1%) [38]. Some mutations are particularly frequent in specific populations through a 'founder effect', for example, in Ashkenazi Jewish ethnics, whose carrier frequency is higher [39, 40].

In the Central and South American region, genetic screening for *BRCA* mutations in patients with a family history of breast cancer is uncommon, probably because of the high costs and limitations of infrastructures [41]. However, a few studies were conducted in Central and South American women with a family history of breast cancer which revealed considerable variation in the frequency of *BRCA1*/*BRCA2* point mutations in the patients tested: 28% in Argentina [42], 2.3–13% in Brazil [43], 15.9% in Chile [43], 25% in Colombia [44], 4.5% in Costa Rica [45], 28% in Mexico [46], 5% in Peru [47], and 6.9–10.3% in Venezuela [46]. The reported prevalence of *BRCA1* and *BRCA2* mutations in Hispanic women with a personal or family history of the disease residing in the USA was 25% [48].

## Breast density

Breast density (radio dense fibroglandular tissue in the breast) has been suggested for use as a predictor of breast cancer risk [49]. A meta-analysis of the percentage density measured using pre-diagnostic mammograms in the general population revealed that women with a breast density of 5–24%, 25–49%, 50–74%, and 75% or more had a 1.79 (95% CI, 1.48–2.16), 2.11 (95% CI, 1.70–2.63), 2.92 (95% CI, 2.49–3.42), and 4.64 (95% CI, 3.64–5.91) times higher risk of developing breast cancer than women with a breast density of less than 5% [49]. High breast density (dense tissue in ≥ 75% of the breast) has been strongly associated with an increased risk of breast cancer (4–6 times higher than women with little to no breast density) [50, 51]. Younger women (aged 40–49 years) with an extremely dense or heterogeneously dense breast on mammographic examination had approximately twice the risk of having breast cancer than those with fibroglandular densities (RR, 2.04; 95% CI, 1.84–2.26 for extremely dense; RR, 2.33; 95% CI, 2.04–2.66 for heterogeneously dense) (as cited in [4]). Breast density is associated with age, gynaecological and obstetric history, HRT, body mass index (BMI), and genetic determinants. In addition to an increase in risk, high breast density reduces mammographic sensitivity at screening [52].

## Ionizing radiation

IARC has classified radiation (X-radiation or gamma-radiation) as a causative agent for female breast cancer [53]. The evidence was mainly found in survivors from atomic bomb outbursts and those exposed to radiation for medical purposes or in utero (offspring of pregnant medical patients and of atomic bomb survivors) [53]. In a review of 17 studies, Clemons et al. [54] found that women exposed to radiation for the treatment of Hodgkin lymphoma (usually between puberty and the age of 30 years) had 5.2 times the risk of developing breast cancer with an average latency period of approximately 14 years (range, 5–15.1 years). Women exposed to X-ray fluoroscopy for the treatment of tuberculosis (1 Gy per treatment with average of 88 treatments) have been shown to have a 61% increased risk of developing breast cancer approximately 10 years after exposure, with younger women having a higher risk than older women (as cited in [55]).

## Alcohol consumption and tobacco smoking

IARC has classified the consumption of alcoholic beverages as a carcinogenic agent for the female breast [56] and a dose–response relationship has been found between alcohol consumption and the risk of breast cancer [57]. The CGHFBC reported that women who consumed 35–44 g or 45 g or more of alcohol per day had a 32% (95% CI, 19–45%) or 46% (95% CI, 33–61%) higher risk of developing breast cancer than non-drinkers and the risk increased by 7.1% (95% CI, 5.5–8.7%) for each additional drink (10 g) of alcohol per day regardless of smoking status. For each additional drink of alcohol per day, the risk of breast cancer increased by 6.3% in premenopausal women and by 8.1% in postmenopausal women [8].

IARC considered tobacco smoking to be an agent with limited evidence of causing breast cancer because the number of women included in the available epidemiological studies was too small to draw conclusions [56]. However, in a recent meta-analysis of 15 cohort studies that included nearly 100 000 women, Gaudet et al. [58] showed that current smokers had a 12% (95% CI, 8–16%) higher risk of developing breast cancer than never-smokers and that former smokers had a 9% (95% CI, 4–15%) higher risk than never-smokers, although evidence of heterogeneity between studies was observed. In another meta-analysis of 10 studies on the association with smoking status at the time of diagnosis among 5892 women with invasive breast cancer (1987–2008), Berube et al. [59] found that breast cancer-specific mortality was 10% (95% CI, 1–20%) higher in smokers than in never-smokers (in 6 studies) and increased with increasing intensity and duration of smoking (*P* for trend < 0.005). These results suggested that tobacco smoking should be avoided due to its serious adverse effects on health.

## Increased body weight

Obesity and increased BMI have been consistently associated with an increased risk of breast carcinoma although the relationship differs according to pre-and postmenopausal status and ER/PR tumour status [8;60;61]. The World Cancer Research Fund/American Institute for Cancer Research (WCRF) panel evaluated the evidence of body fatness and the risk of cancer and concluded that there is convincing evidence indicating that greater body fatness causes postmenopausal breast cancer [57].

In a meta-analysis of 31 studies (9 cohort and 22 case–control), Suzuki et al. [61] found that each 5-kg/$m^2$ increase in BMI was associated with a 33% (95% CI, 20–48%) increase in ER-positive and PR-positive tumours (in 8 studies) but was protective against the incidence of ER/PR-positive tumours in premenopausal women (RR, 0.90; 95% CI, 0.82–0.99 in 4 studies). However, no associations were observed between increased BMI and ER/PR-negative tumours or ER-positive/PR-negative tumours in either pre- or postmenopausal women. In a meta-analysis of 31 prospective studies, Renehan et al. [62] found that a 5-kg/$m^2$ increase in BMI increased the risk of postmenopausal breast cancer by 12% (95% CI, 8–16%). Of the postmenopausal breast cancer cases occurring worldwide in 2012, 10% were estimated to be attributable to high BMI (≥ 25 kg/$m^2$) with noticeable variations by region (4–6% in SubSaharan Africa and Asia, and 10–15% in Europe, Latin America and the Caribbean, the Middle East and North Africa, North America, and Oceania) [63].

## Diet

Evidence for the influence of nutritional factors on the risk of breast cancer is heterogeneous, controversial, and inconclusive [57, 64–67]. The WCRF panel evaluated the available evidence on the consumption of several dietary products, such as meat, egg, or dairy foods, cereals, dietary fibre, vegetables and fruit, legumes, soya and soya products, and vitamins (i.e., A, B6, B12, folate, and riboflavin), and found limited non-conclusive evidence on their possible association with the risk of breast cancer [57], but concluded that red meat was a ‘possible cause’ of breast cancer. Although the WCRF found weak positive associations with fats and oils and an increased risk of postmenopausal breast cancer (RR, 1.06; 95% CI, 0.99–1.14 per 20 g per day in 5 cohorts with moderate heterogeneity; OR, 1.11; 95% CI, 1.06–1.16 in 7 case–control studies with no evidence of heterogeneity), the panel concluded that there was “limited evidence suggesting that [the] consumption of total fat is a cause of postmenopausal breast cancer” [57]. The impact of diet as a sole and isolated factor is difficult to determine because of the concurrence of other confounding factors.

In Uruguay, De Stefani et al. [68] evaluated the association between four dietary patterns and the risk of breast cancer and found an inverse association with having a diet pattern ‘typical of industrialized countries’ (high intake of red meat, processed meat, and total eggs) or a drinker diet pattern (consumption of beer, wine, hard liquor, and processed meat) were positively associated with the risk of breast cancer (OR, 1.81; 95% CI, 1.32–2.50 vs low intake for ‘industrialized’; OR, 1.40; 95% CI, 1.05–1.87 vs low intake for drinker), whereas having a ‘traditional’ diet pattern (high intake of cooked vegetables, all tubers, and legumes) was protective against breast cancer (OR, 0.53; 95% CI, 0.36–0.71 vs low intake). Having a ‘prudent’ diet pattern (high intake of white meat, dairy foods, raw vegetables, and total fruit) was not associated with the risk of breast cancer.

In a systematic review of 27 studies conducted in Central and South America (Argentina, Brazil, Chile, Colombia, Mexico, and Uruguay),Torres-Sanchez et al. [69] described the protective effects found in some studies for the consumption of fruit and vegetables, fish, fibre, vitamin B12, folate, phytoestrogens, and lycopene against breast cancer as well as the causative effects of high caloric diets, meat consumption (red and processed), cooking process (fried, roasted, and barbequed), saturated fats, and some dairy products on breast cancer. However, because of the lack of methodological rigor in some studies, the authors called for more research on dietary components and breast cancer in the region before any conclusions could be drawn [69]. In a review of meat consumption and exposure to their heterocyclic amines and cancer risk in the South American region, Matos and Brandani [70] highlighted the challenges of comparing results across the region due to the wide definitions of meat (may include poultry) and differences in cooking methods (i.e., grilled, barbequed, roasted, and stewed) and also called for further research regarding the potential association between meat consumption and cancer risk.

## Physical activity

The WCRF panel concluded that physical activity (all forms, recreational, or occupational) ‘probably protects’ against postmenopausal breast cancer but the evidence is limited for pre-menopausal breast cancer. The proposed mechanisms by which physical activity may be beneficial against breast cancer are related to effects on body fatness, endogenous steroid hormone metabolism, and the immune system (strengthening) [57]. In a recent meta-analysis of 31 prospective studies, Wu et al. [71] found that physical activity was protective against breast cancer (RR, 0.88; 95% CI, 0.85–0.91), with similar effects by type of activity (RR, 0.87; 95% CI, 0.83–0.91 for non-occupational activity (including recreational activity and household activity) in 27 studies; RR, 0.90; 95% CI, 0.83–0.97 for occupational activity in 7 studies). However, the inverse association between physical activity and the risk of breast cancer was stronger for women with a BMI of less than 25 kg/m$^2$ (RR, 0.72; 95% CI, 0.65–0.81), for premenopausal women (RR, 0.77; 95% CI, 0.72–0.84), and for ER/PR-negative tumours (RR, 0.80; 95% CI, 0.73–0.87).

A dose–response relationship between increased physical activity and the lower risk of breast cancer has been described. In a meta-analysis of five case–control studies, the WCRF showed a 10% reduction in the risk of breast cancer per 7-metabolic equivalent (MET) hours per week of recreational physical activity (OR, 0.90; 95% CI, 0.88–0.93). Wu et al. [71] also found a 2% reduction in the risk of breast cancer for every 25-MET hours per week increment in non-occupational physical activity, 3% for every 10-MET hours per week increment in recreational activity (i.e., 4 h per week of walking 2 miles per hour or 1 h per week of running 6 miles per hour), and 5% for every 2-h per week increment in moderate/vigorous recreational activity. In an age-matched case–control conducted study of 1074 Mexican women, Angeles-Llerenas et a [72] showed that women who participated in moderate-to-intense physical activity had a lower risk of having breast cancer compared with controls; for every 3 h per week of moderate-to-intense physical activity, the risk of breast cancer was 4% in premenopausal (OR, 0.96; 95% CI, 0.92–0.99) and 10% in postmenopausal women (OR, 0.90; 95% CI, 0.86–0.93).

In a meta-analysis of 75 studies, Lee et al. [73] found that physical inactivity (insufficient physical activity to meet current recommendations) increased the risk of breast cancer by 33% (95% CI, 26–42%). In a case–control study in low-income women in Brazil that included 106 incident cases of breast cancer and 181 hospital controls, women who had a sedentary lifestyle had a 2.39 (95% CI, 1.43–3.99) times higher risk of developing malignant breast diseases than controls; the strength and direction of the association remained the same after further adjustment for hormone-related factors, a family history of breast cancer, and the percentage of body fat [74].

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