

The Etiology of Breast Cancer

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ABSTRACT

The etiology of breast cancer is attributed to a complex interaction between various modifiable and non-modifiable factors. This etiology is determined by genetics, environmental, nutritional, hormonal, and heritable elements that contribute to the development of this disease. Risk factors include prior history of breast cancer, positive family history, obesity, tall stature, smoking, alcohol consumption, early menarche, late menopause, sedentary lifestyle, nulliparity and hormone replacement therapy. Factors associated with decreased risk of breast cancer include multiparity, history of breastfeeding, physical activity, weight loss, and prophylactic surgical and medical

interventions. In the United States, approximately one in eight women will be diagnosed with breast cancer in her lifetime. This disease is more common in white, post-menopausal females. Risk increases with older age with about 80% of breast cancer patients being older than 50 years. Analyzing the etiology of breast cancer allows for the development of improved screening and treatment interventions. In this chapter, the etiology of breast cancer along with the risk factors associated with this disease are discussed.

Keywords: breast cancer risk factors; ethnicity and breast cancer; etiology of breast cancer; family history of breast cancer; genetics of breast cancer

Running Title: Breast Cancer Etiology

INTRODUCTION

In the United States, there is a 12.3% average life risk that a woman will be diagnosed with breast cancer in her lifetime (1). This makes this disease the second most common cancer for women in the United States following skin cancer. The etiology of breast cancer is a complex interplay between multiple risk factors including prior history of breast cancer, positive family history, obesity, tall stature, smoking, alcohol consumption, early menarche, late menopause, sedentary lifestyle, nulliparity and hormone replacement therapy. Factors associated with decreased risk of breast cancer include multiparity, history of breastfeeding, physical activity, and weight loss. The influence of factors such as obesity and fertility on the etiology of breast cancer is displayed by the continued increase of breast cancer incidence rates of about 0.5% annually which has been attributed to a national increase in body weight and a decrease in fertility (1). Breast cancer is much more likely to occur in females than males, and it is also highly associated with advancing age and race with White females having the highest overall rates of breast cancer followed by Black, Asian, and Hispanic females respectively. Women with a first-degree relative who have had breast cancer are twice to three times more likely to develop breast cancer in their lifetime (2). The goal of this chapter is to explore the etiology of breast cancer to help provide a better understanding of the risk factors of this disease to potentially aid further research into the prevention and management of this disease.

FACTORS AFFECTING BREAST CANCER RISK

As noted, there are multiple interactive factors that impact breast cancer occurrences and in the subsequent sections the main features of these will be discussed.

Gender

Annually about 280,000 women and 3,000 men are diagnosed with breast cancer in the United States. Women are therefore about 100 times more likely to develop breast cancer compared to men (3). The more pronounced prevalence of breast cancer in women is mainly due to higher estrogen and progesterone stimulation. In post-menopausal women, the amount of circulating estrogens and androgens has been shown to be positively correlated with the risk of breast cancer (4). In men, the increase in estrogen to androgen ratio that is either due to estrogen excess or androgen deficiency is positively correlated with the risk of breast cancer (5). Also, both pre-menopausal and post-menopausal women experience more alternations of sex hormone levels in their lifetime compared to men resulting in higher breast cancer risk (6).

Age

Most cases of breast cancer are diagnosed in women older than 50 years, and the breast cancer risk continues to increase with advancing age (7-9). The Surveillance, Epidemiology, and End Results (SEER) database showed that the probability of a woman developing breast cancer is 2.4% in ages 50 to 59, 3.5% in ages 60 to 69, and 7.0% in ages 70 and older (10). The increased breast cancer incidence with advancing age parallels the age dependence of many common cancers that is partly due to age-related increase in carcinogenesis and the accumulation of cellular modifications throughout time (11). There is also a relationship between age of diagnosis and outcome prognosis. Women diagnosed with breast cancer at an age lower than 50 have lower survival rates than those diagnosed at ages between 50 and 70 (9). The lower survival rate in younger patients is most likely due to the greater occurrence of highly aggressive triple negative breast cancer in patients 40 years old or younger.

Heritable factors and cancer genetics

Personal history of breast cancer is associated with increased, but still low, risk of developing breast cancer in the contralateral breast. The average risk of breast cancer survivors developing

breast cancer on the opposite breast is estimated to increase by 0.5% each year following their initial cancer diagnosis (12). This increased risk could be largely attributed to increasing age since it is only slightly larger than the age-related increase in breast cancer in patients without prior history of breast cancer.

A first-degree family history of breast cancer increases the risk of breast cancer significantly. Studies show that the risk of breast cancer is doubled in a woman with a first-degree relative with prior breast cancer history. First-degree relatives for women are mother, sister, and daughter while a second-degree relative are grandmother, aunts, and nieces. A woman who has two first-degree relatives who have had breast cancer has triple the risk of a woman with no family history of breast cancer (13). According to a large cohort study of over 5,000,000 women, those who had a second-degree relative with breast cancer, but no first-degree relative with this history, had a 20% increased risk when the relative had carcinoma in situ and 30% when the cancer was invasive (14). The significant association between positive family history and increased breast cancer risk is linked to having gene abnormalities. Most women who test positive for a gene associated with hereditary breast cancer have a pathogenic variant in either breast cancer susceptibility gene 1 (BRCA1) or breast cancer susceptibility gene 2 (BRCA2). According to a large prospective study, the cumulative cancer risk is 72% (95% CI 65 to 79 percent) in BRCA1 mutation carriers and 69% (95% CI 61 to 77 percent) in BRCA2 mutation carriers (15). Breast cancer incidence was also shown to increase in early adulthood until average age of 35 years for BRCA1 carriers and until average age of 45 years for BRCA2 carriers. The overall risk of breast cancer is about 3% higher in carriers of BRCA1 mutations compared to women with BRCA2 mutations (16-18).

Geography, ethnicity and race

Breast cancer incidence differs around the world. Incidence rates of breast cancer are higher in North America, North and West Europe, Australia, and New Zealand. However, the mortality rate of breast cancer is similar around the world (19). In the United States, breast cancer risk differs among different race groups with the highest overall incidence of breast cancer is found in White women (131.8 per 100,000) followed by Black women (124.7 in 100,000) (20). The risk is decreased among Asian/Pacific Islander, Hispanic, American Indian/Alaskan Native women. It is important to note that although white women have the highest overall risk, black women have the

highest risk of early onset breast cancer under the age of 45 years old (21) Black women also have higher breast cancer mortality rate and are more likely to present with advanced disease (22).

Obesity

Obesity is associated with an overall increased risk of breast cancer. The link between increased Body Mass Index (BMI) and breast cancer is found primarily in post-menopausal women that form estrogen positive breast cancer (6, 23). However, the relationship between obesity and risk of breast cancer differs based on menopausal status. According to data obtained from several studies, a higher BMI of ≥ 30 kg/m² has been shown to be associated with post-menopausal breast cancer risk (24-27). According to a meta-analysis of several studies, the relative risk of breast cancer among obese post-menopausal women is 1.1 per 5 BMI units (95% CI 1.1-1.2) (28). The higher estrogen levels among obese women have been attributed to this association. This reasoning is further strengthened by the fact that a higher bodily fat percentage among women with a normal BMI is also associated with a higher breast cancer risk (29). However, in premenopausal women, a higher BMI is reported to be associated with a reduced breast cancer risk (30). The cause of this inverse relationship is not yet known.

Stature

Tall stature has also been associated with increased risk of breast cancer (3, 31). According to data from seven prospective cohort studies that included more than 337,000 women, increased height is an independent risk factor for breast cancer. The relative risk of breast cancer for women 1.75 meter (about 69 inches) or taller compared with women shorter than 1.60 meter (about 63 inches) were 1.22 for all women with a relative risk of 1.42 for premenopausal women and 1.28 for postmenopausal women (32). There is no definitive conclusion on the reason of the association between height and breast cancer. However, there are proposed explanations of nutritional, genetic and environmental factors during early childhood that play an effect on growth hormone release having direct impact on future breast cancer development (32).

Physical activity and nutrition

Several studies have shown that there is an association between increased physical activity and lower risk of breast cancer (33-35). As an example, a large-scale meta-analysis of more than

230,000 breast cancer cases and millions of controls has shown that the risk of breast cancer is lower among women who exercise regularly compared with those who are least active (33). Physical activity is protective against the development of breast cancer in all women including those with and without a family history of this disease (6). Both physical activity and dietary patterns are also linked with BMI which, as earlier discussed, if elevated to the level of obesity is strongly associated with the risk of developing breast cancer in post-menopausal women. Exercise has been linked to reduced estrogen and insulin levels which could also play an important factor in reducing breast cancer risk (36).

With regards to nutrition, a 20-year-long prospective study of post-menopausal women showed that a low-fat diet is associated with higher breast cancer survival rates (37). Overall, the consumption of red meats, processed foods, soy products, and fatty foods is linked to increased risk of breast cancer while increased consumption of fruits, vegetables, and fiber is linked to decreased risk (38). However, there are still several inconsistent findings with regards to the association and degree of impact these factors have on breast cancer development because different studies have yielded differing outcomes (38-40). Further research in the form of randomized trials and data gathering is needed to make a definite conclusion.

Alcohol consumption and smoking

A meta-analysis of more than 100 studies reported a positive association between breast cancer and low alcohol consumption (< 3-4 drinks/week), and high consumption (> 20 drinks/week), compared to no alcohol consumption (41). According to a large prospective study looking into the relationship between alcohol and breast cancer, there was a small increase in risk of breast cancer with 3 to 6 drinks/week compared with abstainers, with a relative risk of 1.15 (95% CI 1.06 -1.24) (42). Lifetime alcohol intake was reported to be linearly correlated with breast cancer risk and risk was most strongly associated with very early and very late adult life drinking habits (43). The link between alcohol consumption and breast cancer risk may be related to alcohol's effect on estrogen metabolism causing an increase in blood estrogen levels. A cross-sectional study of the relationship between breast cancer risk and hormone concentration among post-menopausal women found that estrogen levels, that correlate with increased breast cancer risk, are increased in

women who drink alcohol than in those who do not while dehydroepiandrosterone sulphate (DHEAS) and sex hormone-binding globulin (SHBG) levels were decreased (44).

Smoking has been shown by many studies to be associated with increased breast cancer risk. According to one meta-analysis of several prospective studies, the risk of breast cancer was higher among women with history of smoking with a relative risk of 1.10 (95% CI 1.02-1.14) (45). In one prospective study of more than 100,000 women, smoking was associated with a 5% increase in the risk of breast cancer particularly in women who started smoking as an adolescent (46).

Menarche and menopause

Younger age at menarche and later age of menopause increases breast cancer risk (47). These investigators reported that relative risk for breast cancer, attributable to late onset menopause, increased by a factor of 1.029 (95% CI 1.025 - 1.032) for each added year of menopause onset. Breast cancer risk attributable to early menarche is increased by a factor of 1.050 (95% CI 1.044 – 1.057) for every year younger at menarche (47). The younger the woman at menarche, the higher the risk of her developing breast cancer in the future. The effects of early menarche and late menopause on breast cancer has been attributed to greater lifetime exposure to endogenous estrogen. However, several studies have shown a more significant increase of breast cancer risk in women with early menarche compared to older age of menopause (47, 48). This suggests that the cause of this correlation is not entirely due to the duration a woman is exposed to high estrogen levels in her lifetime. Further research regarding the difference in breast cancer risk between early menarche and late menopause is needed to investigate the cause behind these findings.

Reproductive history and breastfeeding

Multiple studies have shown that both multiparity and breastfeeding have a protective effect against breast cancer. Breast feeding for at least six months has been shown to have the most effect in decreasing breast cancer risk. Data obtained from 47 epidemiological studies in 30 countries found that on average, women with breast cancer had less births and less or shorter breastfeeding history. The relative risk of breast cancer decreased by 4.3% (95% CI 2.9-5.8) for every one year of breastfeeding in addition to a decrease of 7.0% (95% CI 5.0-9.0) for each birth (49). There are

also findings that this reduction in breast cancer was most significant in receptor negative breast cancers thus reducing aggressive disease subtypes (50).

Endogenous estrogen and hormonal therapy

Higher levels of estrogen in premenopausal and post-menopausal women have been associated with increased risk of breast cancer. A systemic review that analyzed data from several epidemiologic studies found that in six prospective studies, serum estradiol concentration of 329 women who developed breast cancer later in their life had higher estradiol blood concentrations compared to women who did not subsequently develop breast cancer (51). The reported estradiol concentration was 15% greater in those who developed breast cancer (CI 95% 6% - 24%).

Post-menopausal women without a history of a total hysterectomy who underwent combined estrogen and progesterone replacement therapy have been shown to have increased risk of breast cancer (52). Multiple observational studies have reported an increased risk of breast cancer with use of menopausal hormone therapy, including unopposed estrogen therapy and combined estrogen-progestin therapy, for a prolonged duration (49, 53). The use of combined estrogen-progestin therapy for a short period of time, which was defined as four years or less, did not significantly increase breast cancer risk (54). However, both short-term and long-term use combined therapy has been linked to increased difficulty of breast cancer mammographic detection. The short-term use of unopposed estrogen therapy had similar outcomes to combined estrogen-progestin therapy neither of which caused increased risk (53). However, there was increased risk with long-term use of more than 10 years.

CONCLUSION

Breast cancer is caused by a complex interplay of multiple factors including age, genetics, environment, and reproductive history and probably yet unknown factors. The risk of breast cancer increases with older age and is most common in post-menopausal women. Genetics and heritable factors play an important role in the development of breast cancer. A first-degree family history of breast cancer significantly increases breast cancer risk. Potentially modifiable factors including obesity, alcohol consumption, smoking, physical inactivity, and replacement hormonal therapy have all been associated with increased breast cancer risk. Women's reproductive history also

affects risk with nulliparity associated with increased rates compared to multiparity. Breast cancer is the leading cancer affecting women in the United States and globally. Being aware of its etiology aids understanding its pathophysiology and helps bring into focus important preventative measures that can be taken to reduce risk. Screening measures, treatment modalities, and patient counseling and education can all be enhanced by understanding the etiology of breast cancer.

CONFLICT OF INTEREST

The author declares no potential conflicts of interest with respect to research, authorship and/or publication of this article.

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REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin.* 2021;71(1):7-33.
<https://doi.org/10.3322/caac.21654>
2. Alkabban FM, Ferguson T. Breast Cancer. *StatPearls.* Treasure Island (FL)2022.
3. Abdelwahab Yousef AJ. Male Breast Cancer: Epidemiology and Risk Factors. *Semin Oncol.* 2017;44(4):267-72.
<https://doi.org/10.1053/j.seminoncol.2017.11.002>
4. Key TJ, Appleby PN, Reeves GK, Travis RC, Alberg AJ, Barricarteet A, et al. Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. *Lancet Oncol.* 2013;14(10):1009-19.
[https://doi.org/10.1016/S1470-2045\(13\)70301-2](https://doi.org/10.1016/S1470-2045(13)70301-2)
5. Zeinomar N, Bandera EV, Qin B. Toward Understanding the Etiology of Male Breast Cancer: An Ongoing Research Challenge. *JNCI Cancer Spectr.* 2021;5(5).
<https://doi.org/10.1093/jncics/pkab079>
6. Lukasiwicz S, Czeczulewski M, Forma A, Baj J, Sitarz R, Stanislawek A. Breast Cancer- Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies- An Updated Review. *Cancers (Basel).* 2021;13(17).
<https://doi.org/10.3390/cancers13174287>

7. Benz CC. Impact of aging on the biology of breast cancer. *Crit Rev Oncol Hematol*. 2008;66(1):65-74.
<https://doi.org/10.1016/j.critrevonc.2007.09.001>
8. Feng Y, Spezia M, Huang S, Yuan C, Zeng Z, Zhang L, et al. Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. *Genes Dis*. 2018;5(2):77-106.
<https://doi.org/10.1016/j.gendis.2018.05.001>
9. McGuire A, Brown JA, Malone C, McLaughlin R, Kerin MJ. Effects of age on the detection and management of breast cancer. *Cancers (Basel)*. 2015;7(2):908-29.
<https://doi.org/10.3390/cancers7020815>
10. Merrill RM, Sloan A. Risk-adjusted female breast cancer incidence rates in the United States. *Cancer Epidemiol*. 2012;36(2):137-40.
<https://doi.org/10.1016/j.canep.2011.08.004>
11. White MC, Holman DM, Boehm JE, Peipins LA, Grossman M, Henley SJ. Age and cancer risk: a potentially modifiable relationship. *Am J Prev Med*. 2014;46(3 Suppl 1):S7-15.
<https://doi.org/10.1016/j.amepre.2013.10.029>
12. Davies KR, Cantor SB, Brewster AM. Better contralateral breast cancer risk estimation and alternative options to contralateral prophylactic mastectomy. *Int J Womens Health*. 2015;7:181-7.
<https://doi.org/10.2147/IJWH.S52380>
13. Collaborative Group on Hormonal Factors in Breast C. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. *Lancet*. 2001;358(9291):1389-99.
[https://doi.org/10.1016/S0140-6736\(01\)06524-2](https://doi.org/10.1016/S0140-6736(01)06524-2)
14. Mukama T, Fallah M, Brenner H, Xu X, Sundquist K, Sundquist J, et al. Risk of invasive breast cancer in relatives of patients with breast carcinoma in situ: a prospective cohort study. *BMC Med*. 2020;18(1):295.
<https://doi.org/10.1186/s12916-020-01772-x>
15. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA*. 2017;317(23):2402-16.
<https://doi.org/10.1001/jama.2017.7112>
16. Meijers-Heijboer EJ, Verhoog LC, Brekelmans CT, Seynaeve C, Tilanus-Linthorst MM, Wagner A, et al. Presymptomatic DNA testing and prophylactic surgery in families with a BRCA1 or BRCA2 mutation. *Lancet*. 2000;355(9220):2015-20.
[https://doi.org/10.1016/S0140-6736\(00\)02347-3](https://doi.org/10.1016/S0140-6736(00)02347-3)
17. Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. *Am J Hum Genet*. 1998;62(3):676-89.
<https://doi.org/10.1086/301749>

18. van der Kolk DM, de Bock GH, Leegte BK, Schaapveld M, Mourits MJ, de Vries J, et al. Penetrance of breast cancer, ovarian cancer and contralateral breast cancer in BRCA1 and BRCA2 families: high cancer incidence at older age. *Breast Cancer Res Treat.* 2010;124(3):643-51. <https://doi.org/10.1007/s10549-010-0805-3>
19. Baade P. Geographical Variation in Breast Cancer Outcomes. *Int J Environ Res Public Health.* 2017;14(5). <https://doi.org/10.3390/ijerph14050523>
20. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin.* 2022;72(1):7-33. <https://doi.org/10.3322/caac.21708>
21. Yedjou CG, Sims JN, Miele L, Noubissi F, Lowe L, Fonseca DD, et al. Health and Racial Disparity in Breast Cancer. *Adv Exp Med Biol.* 2019;1152:31-49. https://doi.org/10.1007/978-3-030-20301-6_3
22. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA.* 2006;295(21):2492-502. <https://doi.org/10.1001/jama.295.21.2492>
23. Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. *JAMA.* 2006;296(2):193-201. <https://doi.org/10.1001/jama.296.2.193>
24. Lahmann PH, Hoffmann K, Allen N, van Gils CH, Khaw KT, Tehard B, et al. Body size and breast cancer risk: findings from the European Prospective Investigation into Cancer And Nutrition (EPIC). *Int J Cancer.* 2004;111(5):762-71. <https://doi.org/10.1002/ijc.20315>
25. Fallone F, Deudon R, Muller C, Vaysse C. [Breast cancer, obesity and adipose tissue: a high-risk combination]. *Med Sci (Paris).* 2018;34(12):1079-86. <https://doi.org/10.1051/medsci/2018298>
26. Morimoto LM, White E, Chen Z, Chlebowski RT, Hays J, Kuller L, et al. Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). *Cancer Causes Control.* 2002;13(8):741-51. <https://doi.org/10.1023/A:1020239211145>
27. Lee K, Kruper L, Dieli-Conwright CM, Mortimer JE. The Impact of Obesity on Breast Cancer Diagnosis and Treatment. *Curr Oncol Rep.* 2019;21(5):41. <https://doi.org/10.1007/s11912-019-0787-1>
28. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K, et al. Body Fatness and Cancer--Viewpoint of the IARC Working Group. *N Engl J Med.* 2016;375(8):794-8. <https://doi.org/10.1056/NEJMs1606602>
29. Neuhauser ML, Aragaki AK, Prentice RL, Manson JE, Chlebowski R, Carty CL, et al. Overweight, Obesity, and Postmenopausal Invasive Breast Cancer Risk: A Secondary Analysis of

the Women's Health Initiative Randomized Clinical Trials. *JAMA Oncol.* 2015;1(5):611-21.
<https://doi.org/10.1001/jamaoncol.2015.1546>

30. Nelson HD, Zakher B, Cantor A, Fu R, Griffin J, O'Meara ES, et al. Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis. *Ann Intern Med.* 2012;156(9):635-48.
<https://doi.org/10.7326/0003-4819-156-9-201205010-00006>

31. Green J, Cairns BJ, Casabonne D, Wright FL, Reeves G, Beral V, et al. Height and cancer incidence in the Million Women Study: prospective cohort, and meta-analysis of prospective studies of height and total cancer risk. *Lancet Oncol.* 2011;12(8):785-94.
[https://doi.org/10.1016/S1470-2045\(11\)70154-1](https://doi.org/10.1016/S1470-2045(11)70154-1)

32. van den Brandt PA, Spiegelman D, Yaun SS, Adami HO, Beeson L, Folsom AR, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. *Am J Epidemiol.* 2000;152(6):514-27.
<https://doi.org/10.1093/aje/152.6.514>

33. Pizot C, Boniol M, Mullie P, Koechlin A, Boniol M, Boyle P, et al. Physical activity, hormone replacement therapy and breast cancer risk: A meta-analysis of prospective studies. *Eur J Cancer.* 2016;52:138-54.
<https://doi.org/10.1016/j.ejca.2015.10.063>

34. McTiernan A, Kooperberg C, White E, Wilcox S, Coates R, Adams-Campbell LL, et al. Recreational physical activity and the risk of breast cancer in postmenopausal women: the Women's Health Initiative Cohort Study. *JAMA.* 2003;290(10):1331-6.
<https://doi.org/10.1001/jama.290.10.1331>

35. Boraka O, Klintman M, Rosendahl AH. Physical Activity and Long-Term Risk of Breast Cancer, Associations with Time in Life and Body Composition in the Prospective Malmo Diet and Cancer Study. *Cancers (Basel).* 2022;14(8).
<https://doi.org/10.3390/cancers14081960>

36. Irwin ML, Varma K, Alvarez-Reeves M, Cadmus L, Wiley A, Chung GG, et al. Randomized controlled trial of aerobic exercise on insulin and insulin-like growth factors in breast cancer survivors: the Yale Exercise and Survivorship study. *Cancer Epidemiol Biomarkers Prev.* 2009;18(1):306-13.
<https://doi.org/10.1158/1055-9965.EPI-08-0531>

37. Prentice RL, Caan B, Chlebowski RT, Patterson R, Kuller LH, Ockene JK, et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA.* 2006;295(6):629-42.
<https://doi.org/10.1001/jama.295.6.629>

38. Jung S, Spiegelman D, Baglietto L, Bernstein L, Boggs DA, van den Brandt PA, et al. Fruit and vegetable intake and risk of breast cancer by hormone receptor status. *J Natl Cancer Inst.* 2013;105(3):219-36.
<https://doi.org/10.1093/jnci/djs635>

39. Du M, Liu SH, Mitchell C, Fung TT. Associations between Diet Quality Scores and Risk of Postmenopausal Estrogen Receptor-Negative Breast Cancer: A Systematic Review. *J Nutr.*

2018;148(1):100-8.
<https://doi.org/10.1093/jn/nxx015>

40. van den Brandt PA, Schulpen M. Mediterranean diet adherence and risk of postmenopausal breast cancer: results of a cohort study and meta-analysis. *Int J Cancer*. 2017;140(10):2220-31.
<https://doi.org/10.1002/ijc.30654>

41. Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, et al. Light alcohol drinking and cancer: a meta-analysis. *Ann Oncol*. 2013;24(2):301-8.
<https://doi.org/10.1093/annonc/mds337>

42. Chen WY, Rosner B, Hankinson SE, Colditz GA, Willett WC. Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. *JAMA*. 2011;306(17):1884-90.
<https://doi.org/10.1001/jama.2011.1590>

43. Zhang SM, Lee IM, Manson JE, Cook NR, Willett WC, Buring JE. Alcohol consumption and breast cancer risk in the Women's Health Study. *Am J Epidemiol*. 2007;165(6):667-76.
<https://doi.org/10.1093/aje/kwk054>

44. Key TJ, Appleby PN, Reeves GK, Roddam AW, Helzlsouer KJ, Alberg AJ, et al. Circulating sex hormones and breast cancer risk factors in postmenopausal women: reanalysis of 13 studies. *Br J Cancer*. 2011;105(5):709-22.
<https://doi.org/10.1038/bjc.2011.254>

45. Gram IT, Park SY, Kolonel LN, Maskarinec G, Wilkens LR, Henderson BE, et al. Smoking and Risk of Breast Cancer in a Racially/Ethnically Diverse Population of Mainly Women Who Do Not Drink Alcohol: The MEC Study. *Am J Epidemiol*. 2015;182(11):917-25.
<https://doi.org/10.1093/aje/kwv092>

46. Jones ME, Schoemaker MJ, Wright LB, Ashworth A, Swerdlow AJ. Smoking and risk of breast cancer in the Generations Study cohort. *Breast Cancer Res*. 2017;19(1):118.
<https://doi.org/10.1186/s13058-017-0908-4>

47. Collaborative Group on Hormonal Factors in Breast C. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. *Lancet Oncol*. 2012;13(11):1141-51.
[https://doi.org/10.1016/S1470-2045\(12\)70425-4](https://doi.org/10.1016/S1470-2045(12)70425-4)

48. Ritte R, Lukanova A, Tjonneland A, Olsen A, Overvad K, Mesrine S, et al. Height, age at menarche and risk of hormone receptor-positive and -negative breast cancer: a cohort study. *Int J Cancer*. 2013;132(11):2619-29.
<https://doi.org/10.1002/ijc.27913>

49. Collaborative Group on Hormonal Factors in Breast C. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet*. 2002;360(9328):187-95.
[https://doi.org/10.1016/S0140-6736\(02\)09454-0](https://doi.org/10.1016/S0140-6736(02)09454-0)

50. Fortner RT, Sisti J, Chai B, Collins LC, Rosner B, Hankinson SE, et al. Parity, breastfeeding, and breast cancer risk by hormone receptor status and molecular phenotype: results from the Nurses' Health Studies. *Breast Cancer Res.* 2019;21(1):40.
<https://doi.org/10.1186/s13058-019-1119-y>

51. Thomas HV, Reeves GK, Key TJ. Endogenous estrogen and postmenopausal breast cancer: a quantitative review. *Cancer Causes Control.* 1997;8(6):922-8.
<https://doi.org/10.1023/A:1018476631561>

52. Pompei LM, Fernandes CE. Hormone Therapy, Breast Cancer Risk and the Collaborative Group on Hormonal Factors in Breast Cancer Article. *Rev Bras Ginecol Obstet.* 2020;42(5):233-4.
<https://doi.org/10.1055/s-0040-1712941>

53. Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA.* 2013;310(13):1353-68.
<https://doi.org/10.1001/jama.2013.278040>

54. McTiernan A, Chlebowski RT, Martin C, Peck JD, Aragaki A, Pisano ED, et al. Conjugated equine estrogen influence on mammographic density in postmenopausal women in a substudy of the women's health initiative randomized trial. *J Clin Oncol.* 2009;27(36):6135-43.
<https://doi.org/10.1200/JCO.2008.21.7166>