

Insights in Breast Cancer: A Review

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Abstract

Breast cancer is the most common cancer affecting women in India, with increasing incidence and mortality rates in recent years. This review addresses the specific challenges associated with breast cancer in the Indian setting, including its epidemiology, risk factors, and disparities in healthcare. In India, the disease tends to be diagnosed at a younger age and at more advanced stages compared to Western populations, primarily due to factors such as limited awareness, cultural stigma, and restricted access to healthcare services. Delays in diagnosis, socioeconomic challenges, and the absence of widespread screening programs further complicate the issue. Although recent public health initiatives, including awareness campaigns and the establishment of screening and treatment facilities, have shown progress, significant gaps remain in early detection, individualized treatment, and survivorship care. This review underscores the need for targeted strategies, improved healthcare infrastructure, and equitable access to diagnostic and therapeutic resources to reduce the impact of breast cancer in India and enhance patient outcomes.

Key words: Breast cancer, challenges, India, prospects, treatment

INTRODUCTION

Breast cancer is the most common cancer diagnosed in women and the second most common cause of death from cancer among women worldwide.^[1] The breasts are paired glands of variable size and density that lie superficial to the pectoralis major muscle. They contain milk-producing cells arranged in lobules, multiple lobules are aggregated into lobes with interspersed fat. Milk and other secretions are produced in acini and extruded through lactiferous ducts that exit at the nipple. Breasts are anchored to the underlying muscular fascia by Cooper ligaments, which support the breast.^[2]

Breast cancer most commonly arises in the ductal epithelium (i.e., ductal carcinoma) but can also develop in the breast lobules (i.e., lobular carcinoma). Several risk factors for breast cancer have been well described. In Western countries, screening programs have succeeded in identifying most breast cancers through screening rather than due to symptoms. However, in much of the developing world, a breast mass or abnormal nipple discharge is often the presenting symptom.^[3] Breast cancer is diagnosed through physical examination, breast imaging, and tissue biopsy. Treatment options include surgery, chemotherapy, radiation, hormonal therapy, and, more recently,

immunotherapy. Factors such as histology, stage, tumor markers, and genetic abnormalities guide individualized treatment decisions [Figure 1].

Epidemiology

Breast cancer is the most common invasive cancer in women in most countries, accounting for 30% of cancer cases in women.^[4] In 2022, an estimated 2.3 million women were diagnosed with breast cancer, and 670,000 died of the disease.^[4] The incidence of breast cancer is rising by around 3%/year, as populations in many countries are getting older.^[5]

Rates of breast cancer vary across the world, but generally correlate with wealth.^[5] Around 1 in 12 women are diagnosed with breast cancer in wealthier countries, compared to 1 in 27 in lower income countries.^[4] Most of that difference is due to differences in menstrual and reproductive histories women in wealthier countries tend to begin menstruating earlier and have children later, both factors that increase risk of developing

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breast cancer.^[6] People in lower income countries tend to have less access to breast cancer screening and treatments, and so breast cancer death rates tend to be higher.^[5] 1 in 71 women die of breast cancer in wealthy countries, while 1 in 48 die of the disease in lower income countries.^[4]

Breast cancer predominantly affects women <1% of those with breast cancer are men.^[6] Women can develop breast cancer as early as adolescence, but risk increases with age, and 75% of cases are in women over 50 years old.^[6] The risk over a woman's lifetime is approximately 1.5% at the age of 40 years, 3% at the age of 50 years, and more than 4% risk at the age of 70 years.

Etiology

Age

The age-adjusted incidence of breast cancer continues to increase with the advancing age of the female population.

Gender

Most breast cancers occur in women.

Personal history

A history of cancer in one breast increases the likelihood of a second primary cancer in the contra lateral breast.

Histologic

Histologic abnormalities diagnosed by breast biopsy constitute an essential category of breast cancer risk factors. These abnormalities include lobular carcinoma *in situ* and proliferative changes with atypia.

Family history and genetic mutations

First-degree relatives of patients with breast cancer have a 2-fold to 3-fold excess risk for the development of the disease. Genetic factors cause 5% to 10% of all breast cancer cases but may account for 25% of cases in women younger than 30 years. *BRCA1* and *BRCA2* are the most important genes responsible for increased breast cancer susceptibility.

Reproductive

Reproductive milestones that increase a woman's lifetime estrogen exposure are thought to increase breast cancer risk. These include the onset of menarche before age 12, first live childbirth after age 30 years, nulliparity, and menopause after the age of 55.

Exogenous hormone use

Therapeutic or supplemental estrogen and progesterone are taken for various conditions, with the most common scenarios being contraception in premenopausal women and hormone replacement therapy in postmenopausal women.

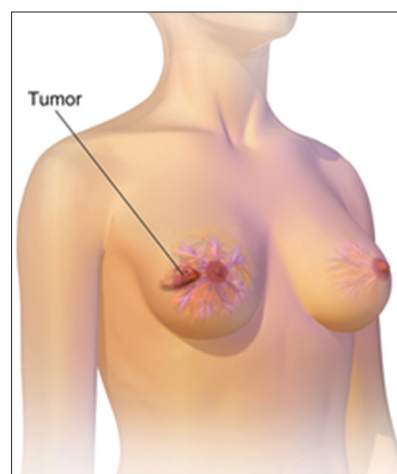


Figure 1: Breast cancer

Other

Radiation, environmental exposures, obesity, and excessive alcohol consumption are some other factors that are associated with an increased risk of breast cancer.

SIGNS AND SYMPTOMS

General breast cancer symptoms

Most people with breast cancer have no symptoms at the time of diagnosis (detected through screening). A new lump in the breast is the most common. Most breast lumps are not cancerous, but cancerous lumps are more likely to be:

- Painless
- Hard
- Irregular in shape
- Swelling or pain in the breast
- Dimpling, thickening, redness, or dryness of the breast skin
- Pain or inversion of the nipple
- Unusual discharge from the breasts
- Swelling of lymph nodes under the arms or along the collarbone

Less common forms of breast cancer inflammatory breast cancer (up to 5% of cases): Cancer cells block lymph vessels in one breast, causing significant swelling and redness over 3–6 months.

Paget's Disease of the breast (up to 3% of cases): Causes red, scaly, eczema-like irritation on the nipple and areola.

Advanced breast cancer (Metastasis)

Tumors can spread beyond the breast to:
Bone: Swelling, progressive bone pain, bone weakening leading to fractures.

Liver: Abdominal pain, nausea, vomiting, skin rash, itchy skin, jaundice (yellowing of the skin).

Lungs: Chest pain, shortness of breath, regular cough.

Brain: Persistent headache, seizures, nausea, vomiting, speech/vision/memory/behavior disruptions.

PATHOPHYSIOLOGY

Breast cancer begins when cells in the breast tissue start to grow uncontrollably, usually in the ducts or lobules, due to genetic mutations and disruptions in normal cell functions.

Key mechanisms involved

1. Genetic changes: Mutations in certain genes, such as BRCA1, BRCA2, and TP53, can increase the risk of breast cancer. These mutations either activate oncogenes, which promote cell growth, or deactivate tumor suppressor genes, which normally keep cell division in check. This imbalance leads to uncontrolled cell growth.
2. Hormonal influence: Hormones such as estrogen and progesterone can fuel the growth of certain breast cancers. Cancers that have receptors for these hormones, called ER-positive or PR-positive cancers, rely on them to grow. Treatments often aim to block these hormones to slow down the cancer.
3. HER2 overexpression: Around 15–20% of breast cancers have too much of a protein called HER2, which makes them grow faster and more aggressively. Targeted therapies like trastuzumab are used to block this protein and slow down the disease.
4. Tumor environment and blood supply: The area around the tumor, known as the tumor microenvironment, helps

cancer grow and spread. New blood vessels form to supply the tumor with nutrients and oxygen, a process called angiogenesis, driven by factors like VEGF.

5. DNA repair problems: Breast cancer cells often have trouble repairing DNA damage, especially in cancers with BRCA mutations. This inability to repair DNA correctly leads to more genetic changes and cancer progression.
6. Spread and invasion: Cancer cells can undergo a process called epithelial–mesenchymal transition, which gives them the ability to move and invade other tissues. This is how breast cancer spreads (metastasizes) to other parts of the body, such as the bones, liver, or lungs [Figure 2].

Breast cancer can start as a non-invasive form, such as ductal carcinoma *in situ*, where the cancer cells are confined within the ducts. If it progresses to invasive cancer, the cells break through the ducts or lobules and can spread to nearby tissues and eventually to other parts of the body through the lymphatic system or bloodstream. The behavior and spread of the cancer depend on its subtype (e.g., luminal, HER2-positive, or triple-negative), which also influences treatment options and outcomes. Understanding these mechanisms helps in developing targeted therapies and improving treatment strategies for breast cancer, making ongoing research in this field crucial.

Clinical characteristics

- A new lump or thickening in or near the breast or in the armpit
- A change in the size or shape of the breast
- A dimple or puckering in the skin of the breast. It may look like the skin of an orange

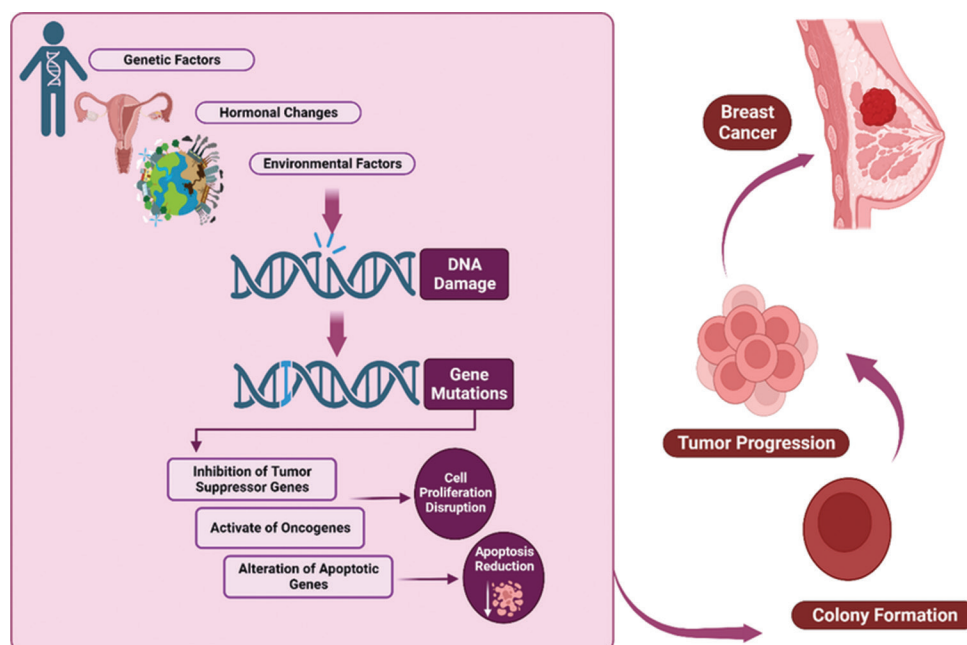


Figure 2: Pathophysiology of breast cancer

- A nipple turned inward into the breast
- Nipple discharge other than breast milk. The discharge might happen suddenly, be bloody, or happen in only one breast
- Scaly, red or swollen skin in the nipple area or the breast & Pain in any area of the breast.

Diagnosis

Those who have a suspected tumor from a mammogram or physical exam first undergo additional imaging typically a second “diagnostic” mammogram and ultrasound to confirm its presence and location. A biopsy is then taken of the suspected tumor. Breast biopsy is typically done by core needle biopsy, with a hollow needle used to collect tissue from the area of interest.^[7] Suspected tumors that appear to be filled with fluid are often instead sampled by fine-needle aspiration.^[8] Around 10–20% of breast biopsies are positive for cancer.^[9] Most biopsied breast masses are instead caused by fibrocystic breast changes a term that encompasses benign pockets of fluid, cell growth, or fibrous tissue.^[9]

Prognosis

Breast cancer prognosis varies widely depending on how far the tumor has spread at the time of diagnosis. Overall, 91% of women diagnosed with breast cancer survive at least 5 years from diagnosis. Those whose tumor(s) are completely confined to the breast (nearly two thirds of cases) have the best prognoses – over 99% survive at least 5 years.^[10] Those whose tumors have metastasized to distant sites have relatively poor prognoses – 31% survive at least 5 years from the time of diagnosis. Triple-negative breast cancer (up to 15% of cases) and inflammatory breast cancer (up to 5% of cases) are particularly aggressive and have relatively poor prognoses.^[11] Those with triple-negative breast cancer have an overall 5-year survival rate of 77%–91% for those whose tumors are confined to the breast; 12% for those with metastases.^[11] Those with inflammatory breast cancer are diagnosed after the cancer has already spread to the skin of the breast. They have an overall 5-year survival rate of 39%; 19% for those with metastases.^[12] The relatively rare tumors with tubular, mucinous, or medullary growth tend to have better prognoses.^[13] In addition to the factors that influence cancer staging, a person’s age can also impact prognosis. Breast cancer before age 35 is rare, and is more likely to be associated with genetic predisposition to aggressive cancer. Conversely, breast cancer in those aged over 75 is associated with poorer prognosis.

Complications

- Older age.
- History of breast cancer or benign (non-cancer) breast disease
- Inherited risk of breast cancer, including having *BRCA1* and *BRCA2* gene changes

- Dense breast tissue.
- A reproductive history that leads to more exposure to the estrogen hormone, including
- Menstruating at an early age
- Being at an older age when you first gave birth or never having given birth
- Starting menopause at a later age
- Taking hormone therapy for symptoms of menopause
- Radiation therapy to the breast or chest
- Obesity
- Drinking alcohol.

Management

Medications

Selective estrogen receptor modulators (SERMs) reduce the risk of breast cancer but increase the risk of thromboembolism and endometrial cancer. There is no overall change in the risk of death.^[14] They are thus not recommended for the prevention of breast cancer in women at average risk but it is recommended they be offered for those at high risk and over the age of 35.^[15] The benefit of breast cancer reduction continues for at least 5 years after stopping a course of treatment with these medications.^[16] Aromatase inhibitors (such as exemestane and anastrozole) may be more effective than SERMs (such as tamoxifen) at reducing breast cancer risk and they are not associated with an increased risk of endometrial cancer and thromboembolism.

Preventive surgery

Removal of the breasts before breast cancer develops (called preventive mastectomy) reduces the risk of developing breast cancer by more than 95%.^[17] In women genetically predisposed to developing breast cancer, preventive mastectomy reduces their risk of dying from breast cancer. For those at normal risk, preventive mastectomy does not reduce their chance of dying, and so is generally not recommended.^[17] Removing the second breast in a person who has breast cancer (contralateral risk-reducing mastectomy or CRRM) may reduce the risk of cancer in the second breast, but it is not clear whether removing the second breast improves the chance of survival.^[18] An increasing number of women who test positive faulty *BRCA1* or *BRCA2* genes choose to have risk-reducing surgery. The average waiting time for undergoing the procedure is 2 years, which is much longer than recommended.^[19]

Supportive care

Breasts after double mastectomy followed by nipple-sparing reconstruction with implants

Many breast cancer therapies have side effects that can be alleviated with appropriate supportive care. Chemotherapy causes hair loss, nausea, and vomiting in nearly everyone who receives it. Antiemetic drugs can alleviate nausea and vomiting; cooling the scalp with a cold cap during

chemotherapy treatments may reduce hair loss.^[20] Many complain of cognitive issues during chemotherapy treatment. These usually resolve within a few months of the end of chemotherapy treatment.^[20] Those on endocrine therapy often experience hot flashes, muscle and joint pain, and vaginal dryness/discomfort that can lead to issues having sex. Around half of women have their hot flashes alleviated by taking antidepressants pain can be treated with physical therapy and non-steroidal anti-inflammatory drugs counseling and use of personal lubricants can improve sexual issues.^[21]

In women with non-metastatic breast cancer, psychological interventions such as cognitive behavioral therapy can have positive effects on outcomes such as cognitive impairment, anxiety, depression and mood disturbance, and can also improve the quality of life.^[22] Physical activity interventions, yoga and meditation may also have beneficial effects on health-related quality of life, cognitive impairment, anxiety, fitness, and physical activity in women with breast cancer following adjuvant therapy.

Lifestyle

Women can reduce their risk of breast cancer by maintaining a healthy weight, reducing alcohol use, increasing physical activity, and breastfeeding.^[23] These modifications might prevent 38% of breast cancers in the US, 42% in the UK, 28% in Brazil, and 20% in China. The benefits with moderate exercise such as brisk walking are seen at all age groups including postmenopausal women.^[23] High levels of physical activity reduce the risk of breast cancer by about 14%.^[24] Strategies that encourage regular physical activity and reduce obesity could also have other benefits, such as reduced risks of cardiovascular disease and diabetes.^[25] A study that included data from 130,957 women of the European ancestry found “strong evidence that greater levels of physical activity and less sedentary time are likely to reduce breast cancer risk, with results generally consistent across breast cancer subtypes.”^[26]

The American Cancer Society and the American Society of Clinical Oncology advised in 2016 that people should eat a diet high in vegetables, fruits, whole grains, and legumes.^[27] Eating foods rich in soluble fiber contributes to reducing breast cancer risk.^[28] High intake of citrus fruit has been associated with a 10% reduction in the risk of breast cancer.^[29] Marine omega-3 polyunsaturated fatty acids appear to reduce the risk. High consumption of soy-based foods may reduce risk.^[30]

CONCLUSION

Breast cancer remains a significant global health concern, impacting millions of individuals each year. This review has underscored the multifaceted nature of breast cancer, highlighting various risk factors and diagnostic approaches crucial in understanding and managing this disease.

Moreover, advancements in diagnostic techniques have significantly improved early detection and treatment outcomes. Mammography, alongside emerging technologies such as magnetic resonance imaging and molecular testing, plays a pivotal role in identifying breast cancer at its early stages, enabling prompt intervention and potentially improving patient prognoses. Moving forward, continued research into identifying additional risk factors, enhancing screening methods, and developing targeted therapies remains imperative. Furthermore, promoting awareness, advocating for increased screening accessibility, and fostering global collaboration among medical professionals and researchers is crucial in the ongoing fight against breast cancer. A comprehensive approach that integrates research, education, early detection, and accessible healthcare services is essential in combating breast cancer and reducing its impact on individuals and societies worldwide.

REFERENCES

1. Watkins EJ. Overview of breast cancer. *JAAPA* 2019;32:13-7.
2. Alex A, Bhandary E, McGuire KP. Anatomy and physiology of the breast during pregnancy and lactation. *Adv Exp Med Biol* 2020;1252:3-7.
3. Kashyap D, Pal D, Sharma R, Garg VK, Goel N, Koundal D, *et al.* Global increase in breast cancer incidence: Risk factors and preventive measures. *Biomed Res Int* 2022;2022:9605439.
4. Breast Cancer. World Health Organization; 2024. Available from: <https://www.who.int/initiatives/global-breast-cancer-initiative> [Last accessed on 2024 Mar 29].
5. Wuerstlein R, Kates R, Gluz O, Grischke EM, Schem C, Thill M, *et al.* Strong impact of mammaprint and blueprint on treatment decisions in luminal early breast cancer: Results of the WSG-PRIME study. *Breast Cancer Res Treat.* 2019;175:389-99. doi: 10.1007/s10549-018-05075-x
6. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, *et al.* Cancer statistics, 2008. *CA Cancer J Clin.* 2008;58:71-96.
7. National Breast Cancer Foundation. Breast Biopsy. Frisco: National Breast Cancer Foundation; 2024.
8. Caswell-Jin JL, Plevritis SK, Tian L, Cadham CJ, Xu C, Stout NK, *et al.* Change in survival in metastatic breast cancer with treatment advances: Meta-analysis and systematic review. *JNCI Cancer Spectr.* 2018;2:pk062.
9. Stolpner I, Heil J, Feißt M, Karsten MM, Weber WP, Blohmer JU, *et al.* Clinical validation of the BREAST-Q breast-conserving therapy module. *Ann Surg Oncol.* 2019 Sep;26(9):2759-67. doi: 10.1245/s10434-019-07456-y. PMID: 31115853
10. Cancer Stat Facts: Female Breast Cancer. National Cancer Institute; 2024 Available from: <https://seer.cancer.gov/statfacts/html/breast.html> [Last accessed on 2024 Jun 20].
11. Triple-Negative Breast Cancer. American Cancer Society;

2023. Available from: <https://www.cancer.org/cancer/types/breast-cancer/about/types-of-breast-cancer/triple-negative.html> [Last accessed on 2024 Jun 20].
12. Inflammatory Breast Cancer. American Cancer Society; 2023. Available from: <https://www.cancer.org/cancer/types/breast-cancer/about/types-of-breast-cancer/inflammatory-breast-cancer.html> [Last accessed on 2024 Jun 20].
 13. 1997 update of recommendations for the use of tumor markers in breast and colorectal cancer. Adopted on November 7, 1997 by the American Society of Clinical Oncology. *J Clin Oncol*. 1998;16:793-95.
 14. Nelson HD, Smith ME, Griffin JC, Fu R. Use of medications to reduce risk for primary breast cancer: A systematic review for the U.S. Preventive services task force. *Ann Intern Med* 2013;158:604-14.
 15. Owens DK, Davidson KW, Krist AH, Barry MJ, Cabana M, Caughey AB, *et al*. Medication use to reduce risk of breast cancer: US preventive services task force recommendation statement. *JAMA* 2019;322:857-67.
 16. Cuzick J, Sestak I, Bonanni B, Costantino JP, Cummings S, DeCensi A, *et al*. Selective oestrogen receptor modulators in prevention of breast cancer: An updated meta-analysis of individual participant data. *Lancet* 2013;381:1827-34.
 17. Mocellin S, Goodwin A, Pasquali S. Risk-reducing medications for primary breast cancer: A network meta-analysis. *Cochrane Database Syst Rev* 2019;4:CD012191.
 18. Carbine NE, Lostumbo L, Wallace J, Ko H. Risk-reducing mastectomy for the prevention of primary breast cancer. *Cochrane Database Syst Rev* 2018;4:CD002748.
 19. Earlier Decisions on Breast and Ovarian Surgery Reduce Cancer in Women at High Risk. NIHR Evidence (Plain English summary). National Institute for Health and Care Research; 2021. Available from: <https://pubmed.ncbi.nlm.nih.gov/35168943/> [Last accessed on 2022 Dec 21].
 20. Marcinkute R, Woodward ER, Gandhi A, Howell S, Crosbie EJ, Wissely J, *et al*. Uptake and efficacy of bilateral risk reducing surgery in unaffected female BRCA1 and BRCA2 carriers. *J Med Genet* 2022;59:133-40.
 21. Jassim GA, Doherty S, Whitford DL, Khashan AS. Psychological interventions for women with non-metastatic breast cancer. *Cochrane Database Syst Rev* 2023;15:CD008729.
 22. Lange M, Joly F, Vardy J, Ahles T, Dubois M, Tron L, *et al*. Cancer-related cognitive impairment: An update on state of the art, detection, and management strategies in cancer survivors. *Ann Oncol* 2019;30:1925-40.
 23. Janelsins MC, Kesler SR, Ahles TA, Morrow GR. Prevalence, mechanisms, and management of cancer-related cognitive impairment. *Int Rev Psychiatry* 2014;26:102-13.
 24. Lifestyle-related Breast Cancer Risk Factors; 2020. Available from: <https://www.cancer.org> [Last accessed on 2018 Apr 18].
 25. Eliassen AH, Hankinson SE, Rosner B, Holmes MD, Willett WC. Physical activity and risk of breast cancer among postmenopausal women. *Arch Intern Med* 2010;170:1758-64.
 26. Kyu HH, Bachman VF, Alexander LT, Mumford JE, Afshin A, Estep K, *et al*. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: Systematic review and dose-response meta-analysis for the global burden of disease study 2013. *BMJ* 2016;354:i3857.
 27. Hayes J, Richardson A, Frampton C. Population attributable risks for modifiable lifestyle factors and breast cancer in New Zealand women. *Intern Med J* 2013;43:1198-204.
 28. New Study Finds 'Strong Evidence' that Exercise Cuts Breast Cancer Risk. Available from: <https://www.aol.com/study-finds-strong-evidence-exercise-223000791.html> [Last accessed on 2022 Sep 07].
 29. Runowicz CD, Leach CR, Henry NL, Henry KS, Mackey HT, Cowens-Alvarado RL, *et al*. American cancer society/American society of clinical oncology breast cancer survivorship care guideline. *CA Cancer J Clin* 2016;66:43-73.
 30. Farvid MS, Spence ND, Holmes MD, Barnett JB. Fiber consumption and breast cancer incidence: A systematic review and meta-analysis of prospective studies. *Cancer* 2020;126:3061-75.

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