

NEW CONCEPTS OF BREAST CANCER AETIOLOGY

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Introduction

Breast cancer is a cancer of the glandular breast tissue, which is a progressive disease. Globally it is the fifth most common cause of cancer deaths. In 2005, breast cancer caused 502,000 deaths throughout the world, accounting for 7% of cancer deaths and 1% of all deaths. Among women worldwide, breast cancer is the most common cause of cancer death (1).

Today breast cancer, like other forms of cancer, is considered to be the final outcome of multiple environmental and hereditary factors. These range from failure of immune surveillance, abnormal growth factors signaling the interactions between stromal cells and epithelial cells to inherited defects in DNA repair genes, such as BRCA1, BRCA2, and p53. However, the primary risk factors that have been identified are sex, age, childbearing, hormones, a high-fat diet, alcohol intake, obesity, and environmental factors such as tobacco use and radiation.

Yet, no aetiology is known for 95% of breast cancer cases, while approximately 5% of new breast cancers are attributed to hereditary syndromes (2). In particular carriers of the breast cancer susceptibility genes, BRCA1 and BRCA2, are at a 30-40% increased risk for breast and ovarian cancer, depending on portion of the protein the mutation occurs (3).

Currently it is necessary that all breast cancers are tested for expression of the oestrogen receptor, progesterone receptor, and Human Epidermal Growth Factor receptor (HER2) proteins (4). The receptor profile of a given tumour helps predict its prognosis and helps the oncologist to choose the most appropriate treatment.

Aetiological factors of breast cancer

Effects of certain drugs on breast cancer

Inflammation contributes to the development of many diseases, including arthritis, atherosclerosis, and also its role in cancer has also been identified. But drugs with anti-inflammatory properties have not been proven to affect breast cancer. A study has revealed that aspirin appears to have no effect on the risk of getting breast cancer, which contradicts the results of earlier studies that suggested aspirin might help reduce that risk. Based on what we know now, taking aspirin is not an effective strategy to reduce the risk of breast cancer. Taking NSAIDs regularly for other medical reasons does not increase the breast cancer risk either (5, 6).

High blood pressure medications are given to millions of women around the world. With many women on high blood pressure medicine it makes sense to ask whether that medicine affects breast

cancer risk. Researchers found no difference in breast cancer risk between women who took antihypertensive drugs and women who did not (7). But women with higher than normal diastolic blood pressure, who were not taking medicine to control it, were found to have a higher risk of breast cancer (8).

Statins lower LDL cholesterol in people whose cholesterol levels are high. In laboratory studies, statins have been shown to halt the growth, survival and migration of certain cancer cells. Though it is believed that statins on their own were associated with a reduction in breast cancer, recent study reviewed here found that statins had no effect at all on the risk of several cancers, including breast cancer (9, 10). The target enzyme for cholesterol-lowering statins, HMG-CoA Reductase is associated with improved prognosis among ER-positive breast cancer patients, whereas ER negative patients seem to have a better outcome when HMG-CoAR is absent (11).

Digoxin treatment has shown to increase the risk of invasive breast cancer among post-menopausal women (12).

Drugs used to treat female infertility do not appear to be associated with an increased risk of breast cancer (13,14). The researchers found that clomiphene and four synthetic hormones used to boost fertility did not significantly affect the risk of breast cancer (15, 16).

Tamoxifen has shown to reduce the incidence of oestrogen receptor positive breast cancer by approximately 50% in high risk women (17, 18). Similar results are seen for raloxifene which has a more favourable side-effect profile (19). Side effects appear to be fewer with the aromatase inhibitors, with no excess gynaecological (induced endometrial cancer) or thromboembolic events but an increase in fracture risk and joint symptoms does occur (20, 21).

Hormone use and breast cancer

Hormonal factors are implicated in tumour progression and it is possible that factors influencing breast cancer induction could affect prognosis.

Younger ages at menarche were significantly associated with higher grade tumours and increased risk of lymph node metastases (22).

Based on research, most healthcare professionals generally believed that using modern birth control pills (oral contraceptives) did not increase breast cancer risk, but researchers did find a slight increase in breast cancer risk in women who took birth control pills. However, the absolute risk, even for women mostly at risk, parous women and who used oral contraceptives for at least 4 years before their first full term pregnancy, was very small (23).

Post-menopausal hormone therapy has been a controversial issue with regard to breast cancer in the past. Previous studies suggest that only women who used the hormones for at least 5 years have an increase in breast cancer risk, but none have evaluated how shorter durations of use impact risk of lobular breast cancer. New research shows that women using combination HRT (hormone replacement therapy) for three or more years roughly triple their risk of 2 types of breast cancer: invasive lobular carcinoma and mixed ductal-lobular carcinoma. Therefore the current trend is for women considering hormone use should still try and use hormones for the shortest time possible and should use the lowest dose possible (24).

A number of reports in the early 2000s showed a higher risk of hormone-receptor-positive breast cancer in post-menopausal women who took combined HRT for an extended period of time. Since year 2000, use of HRT by post-menopausal women has decreased dramatically. A couple of years later, scientists noticed that cases of new breast cancers were also declining and rates of hormone-receptor-positive breast cancer also dropped. Decreased HRT use linked to decreased risk makes it very likely that HRT really affects breast cancer risk (25, 26),

Taking oestrogen only HRT for fewer than five years was not associated with an increased risk of breast cancer. When oestrogen only HRT was used for more than five years, breast cancer risk increased

slightly (27). Also researchers have found that current, but not past use, compared to non usage of menopausal hormone therapy before diagnosis was shown to be associated with favourable tumour characteristics and survival (28).

Mental illnesses and breast cancer

A study reviewed here found that people diagnosed with schizophrenia were 3 times more likely to develop colon cancer and about 50% more likely to develop breast cancer compared to people without schizophrenia. The higher rate of some common cancers in people with schizophrenia emphasizes the need for proactive monitoring of their physical health (29).

Environmental factors affecting breast cancer

One's personal risk of breast cancer is the result of many factors. Some of these factors such as the genes and the family history are things one cannot control. Others, such as what one eats, maintaining a healthy weight, and minimizing the exposure to chemicals in the environment, are things one can control.

Working in the clothing or textile industry, radiation exposure (a potential risk for women who work in hospital X-ray departments) and a family history of breast cancer, increase the risk of breast cancer. Eating a diet that is high in fiber and low in salt and working in an administrative position seems to reduce breast cancer risk.

High levels of sun exposure lowered the risk of breast cancer in the fair-skinned women by 47% compared to fair-skinned women who got less sun exposure. Exposure to high levels of sunlight didn't have the same benefit for women with darker skin. Vitamin D appears to be the link between sunlight and reduced risk, which is produced by the body with exposure to sunlight. Getting 10 minutes of sun rays on your face and hands each day gives you the benefits of sunlight without the risks (30).

Pre-natal environment affects breast cancer risk in adulthood

Researchers have shown that large birth size significantly increases subsequent risk for breast cancer in adulthood, independent of established risk factors. In addition, birth length and head circumference were also positively associated with breast cancer risk, leading the researchers to suggest that the pre-natal environment may influence breast cancer risk later in life.

Analysis of women with data from birth records showed that a 0.5 kg increase in birth weight was associated with an estimated 7% increase in the risk for breast cancer.

Some speculate that the foetal hormonal environment associated with large birth size may alter programming of the breast, making it more susceptible to cancer initiation by endogenous hormone levels and other carcinogens later in life (31).

Lack of sleep linked with breast cancer

Women who get 6 hours of sleep or less a night face an increased risk for developing breast cancer compared with their peers who sleep more. A previous study reported that women with low levels of the sleep hormone, melatonin, have an increased risk for breast cancer.

Melatonin may have an inhibitory effect on gonadal function, including the synthesis and secretion of sex hormones, by promoting the release of gonadotropin-releasing hormone; it also exerts an antiproliferative effect on breast cancer cell lines (32).

Link between obesity and cancer

Keeping slim turned out to be one of the most important things a woman can do to lower the risk of cancer. Because the hormones that can influence breast cells and the development of breast cancer are made in fat tissue, excess body fat can increase a woman's chance of developing breast cancer after menopause (33).

Overweight women have increased risk of getting breast cancer after menopause and being overweight can increase the risk of breast cancer coming back in women who have had the disease. This may be because fat cells make extra oestrogen and other hormones, which might stimulate breast cell growth. Excess weight can also make it harder to detect breast cancer early, when it's most treatable. Gaining weight after menopause seems to increase breast cancer risk in post-menopausal women. The good news is that weight loss was associated with a decreased risk of breast cancer (34).

Exercise and breast cancer

The studies reviewed here add to the growing amount of information on the role exercise can play in staying healthy. When it comes to exercise, more seems to be better. A study reviewed here reinforces the findings from a very similar study reviewed on Feb 21, 2007: regular strenuous exercise can lower your risk of breast cancer (35). Exercise may reduce cancer risk through changes in metabolism and the immune system, and by reducing weight gain (36). All needed for a significant reduction in breast cancer risk is,

- A substantial weekly commitment (5 or more hours per week).

- A strenuous routine (lap swimming, aerobics, running, kickboxing, etc.).

- A regular routine that is done for years.

Researchers have found that even females with abnormal BRCA1 and BRCA2 genes benefit from exercise. So if they know that they have one of these abnormal genes, losing weight in their twenties, they may be able to lower the risk of developing breast cancer at a younger age (37).

Habits

The fluid in the breasts of women who smoke contains many of the same cancer causing substances found in tobacco smoke. This fact led scientists to suspect that smoking could increase breast cancer risk. Researchers have looked carefully at the link between breast cancer and smoking in young women. They found that smoking

before childbearing years appears to increase the risk of breast cancer later in life. Women who had smoked for 10 pack-years before having their first child were 78% more likely to develop breast cancer than those who never smoked. There wasn't a link between breast cancer risk and smoking later in life. These results were inconsistent with the biologic data indicating that the female breast is sensitive to tobacco carcinogens before first childbirth (38). But researchers found that women who smoke are not more likely to have advanced breast cancer than women who do not smoke.

Drinking alcoholic beverages can increase breast cancer risk. How much alcohol is too much? The study found that alcohol consumption is associated with a linear increase in breast cancer incidence in women over the range of consumption reported by most women. Among women who consume alcohol regularly, reducing alcohol consumption is a potential means to reduce breast cancer risk (39). If you are interested in doing all you can to lower your risk of breast cancer or breast cancer recurrence, limiting your alcohol consumption makes sense. If you do enjoy alcoholic beverages and plan to continue using them, try to have fewer than 5 alcoholic drinks a week (40).

Researchers have found a link between coffee consumption, cytochrome P450 1A2 (CYP1A2) genotype, and breast volume, which could have implications for breast cancer development.

They show that coffee has a protective effect on breast cancer risk restricted to women with the CYP1A2*1F C-allele. Previous studies have reported that coffee may reduce the risk of breast cancer in women with the CYP1A2*1F C-allele but not in those with the CYP1A2*1F A/A genotype. As breast volume is associated with breast cancer risk in lean women, our finding is compatible with earlier reports of a protective effect of coffee on breast cancer risk restricted to women with the CYP1A2*1F C-allele(41). One study suggest that coffee consumption reduces the risk of breast cancer in lean women, whereas coffee might have the opposite effect in relatively obese women (41).

Hair relaxers not seen linked to breast cancer

Because African American women use chemical hair relaxers to straighten their hair more regularly than white women and because African American women are more likely to develop breast cancer before age 45 than white women, researchers wanted to know whether breast cancer was diagnosed more often in women who used hair relaxers. There was no evidence that the major ingredients in hair relaxers, such as lye and calcium hydroxide, promote cancer (42).

Prevention

To keep your risk of breast cancer or breast cancer recurrence as low as it can be, try to make choices that help control these factors:

- Figure out your ideal body weight and work hard to get there.
- Get 3 to 4 hours of moderate exercise per week.
- Eat a low-fat diet with 5-9 servings of fruits and vegetables a day.
- Avoid red and processed meats, simple carbohydrates and salt.
- Don't smoke, if you do smoke, quit.
- Avoid alcohol (if people must drink, they should limit their intake to 2 units per day for a man or one for a woman). Limit alcohol to less than 5 drinks a week.
- If you have a baby, breast-feed for at least the first 6 months.
- If possible, avoid hormone replacement therapy.

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