

BREAST CANCER RISK FACTORS AND PREVENTION**Boya Lu^{1*} and Elango Natarajan¹**¹Faculty of Engineering Technology and Built Environment, UCSI University, Kuala Lumpur, Malaysia

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ABSTRACT

Over the previous two decades, the global rate of young-onset breast cancer has gradually increased. In general, inherited genetic mutations are responsible for fewer than 10% of breast cancer cases. Environment, reproduction, lifestyle factors are more frequently associated with breast cancer and some of which are theoretically changeable. The risk factors and the prevention method for breast cancer are highlighted in this comprehensive study. This in depth illustrates the data regarding for possible risk factors for breast cancer among females, which includes fertility and hormonal factors, medical risk factors, genetic factors and breast related risk factors, and the relationship between genetic and non-genetic factors. In addition, prevention plays a critical part in struggle against the breast cancer. Therefore, summary the different degrees of breast cancer prevention can assist in the early diagnosis of tumors and prolong life.

Keywords: breast cancer, risk factors, genetic factors, prevention

INTRODUCTION

The most common malignant tumor among women in the world is breast cancer, accounting for 22.9% of all tumors of women. [1-3]. Females are more likely than males to suffer breast cancer, and they are 100 times more frequent than men [4]. It is difficult to cure this kind of metastatic disease because it can spread to distant organs [5-7]. Despite the fact that it is more common in North America, the data shows that the survival rate of breast cancer patients in the following five years is great than 80% because of prompt discovery [8]. In addition, the incidence rate is still increasing in the developing countries. Early identification of breast cancer can result in a favourable prognostic effect and a high survival percentage [9-10].

According to the molecular characteristics, breast cancer can be divided into five types, namely luminal A, luminal B, basal-like, HER2-enriched, and normal-like [11-12]. Different molecular subtypes are related to the different etiologies and risk factors, resulting the diverse onset age and prognosis effect. Many risk factors are linked to the occurrence of breast cancer and rising likelihood of incidence, including the age, genetic mutations, family history, hormonal factor, pregnant situation, unhealthy lifestyle, dietary choices [13-16].

As a result, the purpose of this review is to present the summary of current progress on the association between different risk factors and breast cancer. We will go through the impact of genetic factors on the hazard of breast cancer occurrence and recurrence in greater depth. Morbidity and reactivation of breast cancer are increased by a variety of hereditary and environmental variables, especially when they coexist. In order to achieve a better knowledge about the necessity of prevention for cancer patient, we will also highlight new studies on the influence of environmental and lifestyle prevention and the early detection.

Risk factors

Generally speaking, the hereditary genetic mutation is responsible for only small proportion of breast cancers. While factors such as environment, reproduction, and lifestyles are more commonly linked to more than 90% of breast cancer incidence.

Breast related factors. Breast density is an significant indicator for breast health, reflecting the amount of fibrous and glandular tissue compared to the fatty tissue in the breast, which can be observed through mammography [17-18]. However, the mammographic density has been verified with a higher chance of having the cancer, no matter it was identified by screening or other ways [19-21]. Although females who have dense breasts have a higher risk of breast cancer, it is unclear whether low breast density can reduce risk. For example, increasing age and weight

gain after menopause are associated with decreased breast density, while these are also connected to increased hazard of breast cancer [22]. More research will be needed in the relationship between breast density and risk. In addition, the incidence rate of breast cancer will increase if people have simple cysts and fibroadenomas, despite these are the benign breast lesions [23-25]. Previous research indicated that the risk ratio of patients with benign breast lesions was 1.41, higher than those without breast lesions [26].

Reproductive factors. Another risk factor for breast cancer is reproductive factors such as menarche, menopause, age at first pregnancy, and so on. Women who experience early menarche have a higher lifetime risk of acquiring breast cancer. Data from previous study suggested that delaying menarche by one year decreases the incidence of premenopausal breast cancer and postmenopausal breast cancer by 9% and 4%, respectively. As for each year of delay in menopause, the relative risk added by 1.029 times [27-28]. Besides, a strong relationship between age at first birth and the risk was identified in the previous studies [29]. The higher risk can be found in the females who give birth to the first kid at the older age. The data shows females who have their first child under 35 year old have a lower chance of breast cancer [30-32]. Generally speaking, breast cancer risk is inversely related to the number of children born. Breast cancer risk for women without children is twice that of women who have five children or more [33]. One of the another risk factor that go hand-in-hand with having a baby is breastfeeding. The length of breastfeeding is related to the incidence of breast cancer. Prolonging the breastfeeding time will reduce the level of estrogen and have a positive preventive effect on breast cancer [34-36]. A study from the institute pointed out that if the mother's breastfeeding period for each child is extended by 6 months, the risk of breast cancer can be reduced by 6% to 6.3% [37]. In addition, there is a hypothesis about the relationship between the abortion and breast cancer, that is abortion grows a woman's opportunity of suffering breast cancer. However, this has not been proven by the quality scientific data and this hypothesis is currently not in mainstream scientific opinion [38-39].

Lifestyles. Among the high-risk factors for breast cancer, dietary habits may also have an important effect on the pathogenesis of breast cancer. In terms of diet, numerous epidemiological researches have studied the relation between individual foods and breast cancer risk [40]. For example, a high intake of red meat and animal fats in the Western diet is connected with a growing risk of breast cancer. Obesity also brings risks, for Asians, the higher the BMI before diagnosis, the greater hazard of breast cancer. There was a 13% increase in specific mortality for every 5 kg increase in body weight after breast cancer diagnosis [41-42]. Women who take the physical activity regularly have a declined risk of breast cancer than women who do not exercise [43]. There is a 10-20% probability in the hazard of breast cancer between the two types of people. Additionally, physical activity is crucial in prevention and rehabilitation of breast cancer. Physical activity in diagnosed patients is connected with reduced breast cancer recurrence, mortality, improved patient fitness and reduced lymphedema and complications [44]. As for the smoking, young women who have ever smoked are 30% more likely than those who have never smoked to get breast cancer. An independent analysis of different types of breast cancer found that long-term heavy smoking was significantly connected with prevalence of estrogen receptor-positive breast cancer. Various carcinogens in tobacco, such as polycyclic aromatic hydrocarbons and aromatic amines, have been shown to promote the occurrence of breast cancer [45-46]. Drinking alcohol can elevate estrogen-related hormone levels in the blood and activate estrogen receptor pathways [47-48]. Premenopausal women will have a 1.74-fold increased chance of developing breast cancer if they drink heavily. A 53 epidemiological studies found consuming 35-44 grams of alcohol each day raises chances of developing breast cancer by 32%, the relative risk will get to 1.46 if the amount of alcohol consumed reaches 45g per day [49].

Family history and genetic factors. Breast cancer has obvious genetic factors. Previous data shows that a family history is linked to about a quarter of all instances [50]. Women who have multiple relatives in the paternal or maternal line with breast cancer, or have a family history of bilateral or early breast cancer, have a significantly higher chance of developing breast cancer than normal women [51-52]. The first-degree relatives with the breast cancer will be associated with a threefold increase in risk.

BRCA1, BRCA2, HER2, p53, PTEN are the significant genes in the formulation of breast cancer [53]. The most common cause of hereditary breast cancer is the BRCA1 or BRCA2 mutation, and they can be found on chromosomes 17q21 and 13q12, respectively [54]. The mutation of these two genes can cause the abnormal cell proliferation, finally leading to the cancer [55-56]. The BRCA1 have functions in the aspects of cell cycle checkpoint regulation, centrosome duplication and genetic stability [57]. Breast cancer caused by BRCA1 mutated is more prone to be triple negative and around 2% of breast cancer patients have a BRCA1 mutation. When the DNA double strand breaks, the BRCA2 protein play a role in recombination repair by interacting with RAD51 and DMC1 [58]. BRCA2-related breast cancers have the histological pattern of sporadic breast cancers, with ER and PR positivity and HER2 negativity [59]. HER2 is a key breast cancer oncogene. It is a kind of protein that promotes the growth of breast cancer cells. It links to a greater risk of recurrence and a higher fatality rate. The overexpression of HER2 accounts for around 20%-30% of breast cancers and the higher levels of HER2 can be found in the type of HER2-positive breast cancer [60-61]. After the mutation of another tumor suppressor gene p53, the tumor suppressor functions such as repairing damaged DNA and inducing apoptosis are lost, finally producing a tumor-promoting effect [62]. Generally, the mutation rate of p53 in breast cancer cases reaches 25% to 30% [63]. Among patients diagnosed with breast cancer before 30 years old, around 4% patients are thought to have inherited a p53 gene mutation. Phosphatase and tensin homolog deleted on chromosome ten (PTEN) is another crucial tumor suppressor gene by regulating proliferation, cell migration, invasion to achieve the suppressor function [64-65]. Women with a hereditary PTEN mutation have a higher lifetime risk, getting to 40-60% while the average risk is 12.5%.

Primary prevention

Primary prevention mainly targets for the unhealthy lifestyles that causes the high hazard of breast cancer, and good ways to strengthen the immune systems. Some of the efforts we can take to avoid breast cancer include keeping physically active, exercising consistently, eating the appropriate foods and limiting alcohol.

Obesity. The BMI determines if a person's weight is healthy relative to their height. A BMI of 18 to 25 is regarded healthy, over 25 is considered overweight, and over 30 is considered obese. High obesity (high BMI) is a risk point for breast cancer [66]. The relationship between overweight/obesity and risk varies depending on a number of factors, including menopausal status, life stage, and others [67]. For postmenopausal women, multiple analysis showed that high obesity is positively associated with the risk of hormone receptor-positive breast cancer (estrogen receptor positive/ER+ and progesterone receptor positive/PR+). Keeping a normal body weight lowers the hazard of developing breast cancer, with a possibility of improving prognosis, and decreasing the oncological treatment complications [68].

Physical activity. Proper exercise can reduce estrogen grades in the body and avoid breast cancer [68]. The study discovered that when comparing mental workers to manual employees, the former had a considerably greater risk of breast cancer than the latter. In comparison to women who do not exercise, epidemiological studies reveal that moderate- to vigorous-intensity exercise reduces the incidence of breast cancer by around 10% to 25%. For breast cancer prevention, it is advisable to exercise 5 times a week for 35 to 45 minutes each time. Because regular exercise can not only prevent obesity, but also reduce the content of estrogen and insulin in the human body, which can effectively prevent breast cancer [69].

Diet. A healthy, balanced diet that includes the proper variety of foods can reduce risk and aid in breast cancer prevention [70]. There should be adequate nutrition in the diet, and the food should be diversified, mainly plant-based food, which should account for more than two-thirds of each meal [71]. And each meal should be rich in fruits, vegetables, grains, and legumes, with less red meat and salt, and excludes processed meat. There are five representative foods that can effectively prevent breast cancer, namely soy food, seafood, whole grains, healthy fats, fungi. Phytoestrogens are abundant in soy meals, and regular eating of soy will significantly reduce the hazards. In the seafood, fish protein and vitamin D have a protective effect on the breast, and omega-3 fatty acids can kill the cancer cells and inhibit its growing. Another example is that olive oil contains squalene, which can suppress the aberrant development of mammary epithelial cells and is a good anti-cancer ingredient.

Alcohol. According to research, the more alcohol women consume, the higher their chance of developing breast cancer. Breast cancer risk rises by 8% after menopause, 9% before menopause, and 10% overall when 10g of ethanol is used daily [72]. Alcohol's impact on the development of breast cancer might be explained by the followings: effects on estrogen and estrogen receptor levels, and the production of alcohol metabolic by-products [73-74]. Alcohol should not be consumed by breast cancer sufferers. This is because alcohol raises estrogen levels in the blood, which might increase the chance of breast cancer recurrence.

Secondary prevention

Secondary prevention refers to women of suitable age receiving routine breast cancer screening according to the recommendations of screening guidelines in order to obtain early detection, diagnosis, and treatment [75]. This is because early breast cancer typically lacks conventional symptoms and indicators, making it difficult to detect. It is often found through physical examination or breast cancer screening. Self-examination, magnetic resonance imaging, mammography and ultrasonography are commonly used secondary preventative methods.

Breast self-examination. Breast self-examination is a low-cost, widely available approach that does not require much technical expertise and may be done at home [76]. This way enables women to find out the breast anatomy approximately. Specific detection methods include observing the appearance of the breast, observing whether there is any abnormal secretion from the nipple, the size, skin and the character of the breast are keeping normal or not. Alternatively, women can palpate the breast area in small increments to see if there is any lump. It is worth noting that using self-examination this method alone can not comprehensively prevent breast disease, although they still play a crucial role in detecting cancer early [77].

Mammogram. A mammogram is a diagnostic imaging scan that uses low-dose X-rays to check females' breasts. Mammograms can visualize tumors before they invade breast tissue, distant organs, or lymph nodes [78]. This screening can visualize tumors before they invade breast tissue, distant organs, or lymph nodes. This makes it possible to find breast cancers that are too small to touch through self-examination. Currently, it is the most effective method of detecting breast cancer [79]. Generally, mammogram screening is recommended to start at the age of 40, but for those at high risk, the starting screening age can be advanced to before the age of 40.

Ultrasonography. Ultrasonography is a non-invasive and safe way to examine patients' breasts without using ionizing radiation. Ultrasonography is suitable for every woman to take the screening, especially for women of childbearing age. Breast ultrasound has many advantages, the first one is that ultrasound examinations are non-radioactive and can be repeated as necessary. In addition, it is possible to distinguish cystic and solid masses and a preliminary diagnosis can be made for the differentiation of benign and malignant solid masses [80]. It is typically used to supplement other diagnostic tests and to do biopsies under ultrasound for pathological diagnosis.

MRI. MRI is an important tool for detecting breast cancer. To obtain breast images, MRI employs a changing magnetic field to monitor changes in the migration of protons in fat and water. The use of MRI to detect breast cancer is based on the fact that the tumor causes angiogenesis, or new blood vessels. This dynamic fast enhancement pattern helps differentiate benign lesions from breast cancer [81]. The value of MRI in the detection and diagnosis of breast cancer is increasingly important, due to the advantages of high sensitivity, specificity, and multi-planar imaging [82]. Non-invasive and safe MRI complements mammography primarily by increasing the detection of malignant lesions, and using MRI can effectively detect 90 percent of breast malignancies.

Tertiary prevention

The tertiary prevention is the clinical treatment after the diagnosis of the disease, namely prompt and successful treatment of breast cancer that has been clearly detected in order to minimize mortality and enhance survival rates. Topical treatment (including surgery, radiotherapy) and systemic therapy (including chemotherapy, endocrine therapy and targeted therapy) can be selected according to the stage of breast cancer.

Surgery. Breast cancer surgery is a critical element remedy to eliminate the cancer cells. For patients at extremely high risk of breast cancer, surgical operation could be chosen to reduce the hazard in the future [83]. Surgical treatment can independent or combined with other remedy, including hormone therapy, targeted therapy, surgical chemotherapy and radiotherapy. Surgical therapy is frequently applied in the multi-state treatment breast cancer, such as high risky breast cancer, non-invasive breast cancer, locally advanced breast cancer and recurrent breast cancer [84-85]. However, there is limited surgery are applied to cope with the breast cancer (metastatic breast cancer), especially for that has spread to left body component. The surgical operation of breast cancer contains vast types which includes mastectomy (eliminating the whole breast), mastectomy (elimination of part of the breast tissue), and elimination of adjacent lymph nodes. The surgical operation of breast cancer contributes the development of control rates locally and regionally while reducing recurrence rates

Radiotherapy. Breast cancer radiotherapy enjoys the capability of killing cancer cells via X-rays with high energy density and some special particles which can eliminate the cancer cells, e.g. protons. It should be noted that fast-growing cells, e.g. cancer cells, have better radiation therapy performance compared with other normal cells. The strategies of breast cancer radiotherapy can be divided into external radiation and the other is internal radiation (brachytherapy). External radiation is when a machine administers radiation to the breast from outside the body. Internal radiation is when doctors temporarily place a radiation convey facilities in the breast which is adjacent the tumor site after surgery to remove the tumor, temporarily placing the radiation source in the device during treatment. Almost all stages of breast cancer can be treated with radiotherapy. Radiation treatment is a proven method for lowering the risk of breast cancer recurrence following surgery, extending survival time and increasing cure rates [86-87]. In principle, all patients after breast conserving surgery (including intraductal carcinoma and invasive carcinoma) and high-risk patients after mastectomy all require postoperative radiation therapy. In addition, radiation treatment is also frequently applied to alleviate indications of cancer that has progressed to other parts of the body [88-89]. Depending on the patient's specific circumstances, the total course of treatment can be as short as one week or as long as 6-7 weeks, depending on the patient's specific circumstances.

Chemotherapy. Chemotherapy makes use of drugs to target and destroy breast cancer cells. The medications are generally administered as an intravenous infusion or as tablets. Chemotherapy for breast cancer patients can help them live longer and with a higher quality of life by reducing their symptoms, lowering their chance of recurrence. Breast cancer chemotherapy is frequently coupled with other therapies including surgery, radiation, or hormone therapy [90]. Chemotherapy is typically classified into two types, namely preoperative chemotherapy and chemotherapy after surgery for early breast cancer [91]. This method is occasionally used before surgery to decrease bigger tumors in early-stage breast cancer. This provides the doctor the best chance of totally removing the tumor, rather than the entire breast. Chemotherapy after surgery means that after surgery to remove a lump in the breast, chemotherapy may be recommended by doctors to destroy any unknown cancer cells and limit the likelihood of the disease returning. However, the main goal of chemotherapy for late stage of breast cancer is to improve quality of life and prolong life, instead of curing the disease. It should not be overlooked that breast cancer chemotherapy can also have side effects, some of which are mild and temporary, and there may be have long-term or permanent consequences in some circumstances [92].

Endocrine therapy. Breast cancer endocrine therapy is a significant therapeutic strategy that prevents the binding of estrogen in the body to cancer cells. Breast cancer cells differ from other tumors in that they rely on the hormone estradiol to grow [93]. 70% of breast cancer cells have estrogen receptors, and those who are positive for estrogen receptors need endocrine therapy. Generally, the purpose of endocrine therapy includes two aspects: namely lower estrogen levels to avoid estrogen stimulation of the tumor, and inhibition of estrogen synthesis [94]. The tumor cells will be killed as a result of cutting off the source of estrogen or limiting the supply of estrogen, achieving the goal of treating breast cancer. The recurrence rate and mortality of breast cancer can be considerably decreased after obtaining adequate endocrine therapy as an indication, and the 5-year survival rate is superior [95-96]. In clinical practice, there are three primary types of medications (methods) for endocrine

treatment, each with its unique set of benefits. The first is tamoxifen, which has been regarded as the "gold standard" for endocrine therapy in the past, and is responsible for the majority of endocrine therapy for breast cancer. Premenopausal and postmenopausal women with breast cancer benefit similarly from this drug [97]. The second category is the commonly used aromatase inhibitors. This drug is more effective than tamoxifen in postmenopausal women; however, it is ineffective in premenopausal women or must be used in conjunction with a third class of pharmaceuticals. The last category is ovarian castration drugs, it is also up to skilled doctors to make decisions based on the patient's unique circumstances.

Targeted therapy. Targeted therapy is to inhibit the targets through molecular targeted drugs, blocking the signal transduction of tumor cells or related cells, therefore inhibiting or killing tumor cells [98]. Targeted therapy for breast cancer is to target tumor cells, and to combine with drugs at specific sites, which can kill tumor cells to the greatest extent and cause little damage to normal cells. Targeted therapy, as a novel treatment option in addition to the classic treatment options of surgery, radiation, and chemotherapy, has shown to be one of the most effective solid tumor treatments because to its high specificity, exceptional curative impact, and low toxic and side effects [99-100]. However, finding the ideal targets that influence on tumor growth and proliferation with biological effects in clinical practice is difficult. At present, the targets or pathways targeted by breast cancer mainly include HER-2, VEGF, EGFR, TROP-2, LIV-1, etc. For HER-2 overexpression, it is the most commonly used and well-researched targeted treatment. Currently, drugs targeting HER2 are mainly divided into small molecule tyrosine kinase inhibitors (representative drugs are lapatinib), monoclonal antibodies (including trastuzumab and pertuzumab) and antibody conjugated drugs (Trastuzumab Emtansine) three types [101].

CONCLUSIONS

Breast cancer is becoming more common over the world and many factors will related to hazard of breast cancer. Breast condition, reproductive factors, and lifestyles have all been found to be connected with a growing hazard of breast cancer. Breast cancer risk has also been shown to be related to family history and hormone levels. Breast cancer, on the other hand, can be prevented in three ways: primary, secondary, and tertiary prevention. Primary prevention is a relatively basic preventive measure, mainly by adjusting the diet structure, reducing obesity and weight control, avoiding alcohol consumption and increasing physical activity. Secondary prevention mainly include breast self-examination, mammogram, ultrasonography and MRI. Tertiary prevention measures are mainly through surgery, radiotherapy, chemotherapy, endocrine therapy and targeted treatment of patients diagnosed with breast cancer. In general, endocrine treatment is a good option for patients with estrogen receptor-positive breast cancer. HER2-positive breast cancer patients can benefit from molecular targeted treatment. Targeted drugs is by blocking HER2 to treat breast cancer. While chemotherapy is the most common treatment for triple-negative breast cancer patients. With the introduction of screening and prevention, however, more women are being detected with breast cancer at the early stage. With advances in sequencing technology, a better knowledge of breast cancer molecular subtype heterogeneity, and the development of more effective therapies, breast cancer mortality will decrease in the future.

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