

Research on the Breast Cancer Risk Factors and Possible Therapy

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Abstract. This article introduces the benefits of public health that can be developed related policies through research to prevent or control pandemic or diseases. Cancer is now a major concern of public health worldwide. Research has been conducted to identify and solve the major problems for some types of cancer. This article gives some detailed information for one type of cancer, breast cancer. The third part of the article includes risk factors for breast cancer, which the unhealthy lifestyle is one of the possible risk factors includes alcohol intake, being overweight, that the likelihood of breast cancer development might grow. Also, the third part has the information that describe some of the genes that are commonly found in the breast cancer and some of could improve the breast cancer cells growth. For the fourth part, some possible and newly treatments will be mentioned. Through the assessment of risk factors, more people can be motivated to improve their lifestyles to decrease their risk, or to undergo genetic checking to identify whether have the high risk to diagnosis the breast cancer, which help people to know their risk and treat breast cancer earlier. The hormone therapy is one of the treatments which includes SERM that compete with estrogen and SERD directly block estrogen to bind to control the development of breast cancer cells. Hormonal therapy could contribute to controlling breast cancer recurrence, but people who use tamoxifen may develop resistance. In this way some targeted needs to be combined with hormone therapy.

Keywords: Breast cancer; Risk factors; Gene; Therapy.

1. Introduction

Nowadays, public health is a very important field. Each person may face different health problems, which means that the degree of impact on each person will be different [1]. Some people may have more serious health conditions that may affect their daily life such as pain from illness or fatigue that often affects their activities and may also have psychological problems [1]. Developments in the public health field may better promote or influence the health of people around the world by trying to find solutions to some public health problems, such as a new study, a policy update, etc. [2]. As a result, some of the policies proposed in the field of public health can better prevent or predict a stream of diseases. Researchers can put the data set into different models to predict the prevalence of some diseases, diabetes, hypertension, cancer, etc. For example, through the diabetes data analysis of many factors that may become diabetes risk factor variables, these risk factors will play a role in professional advice to reduce the risk of disease [3]. At the same time, prevention policies can also be developed to reduce the incidence of disease based on risk factors, such as to decrease the certain cancer, for example, reducing the rate of developing cervical cancer the promotion of get human papilloma virus vaccine is needed, tobacco control and timely CT of the lungs to lower the risk of lung cancer or detect lung cancer as soon as possible, and x-ray examination can also help to detect early breast tumors [4]. Relevant interventions are critical in disease control and treatment [4].

Public health faces some major problems, including the health care system, the crisis of mental illness, cancer, diabetes, climate change, and environmental pollution [5]. The major factor in fatalities is cancer, as one of the major problems, which possible reasons include medical limitations that prevent diagnosis at an early stage of cancer or ineffective treatment methods [5]. There are many types of cancer. Among the malignancy's cancer in the United States, the breast cancer be the most prevalent for women that is diagnosed in approximately 30% of women newly each year [6]. Breast cancer is categorized into different types based on different cells [7]. Most breast cancers are carcinoma, which means that they originate in the epithelial cells of the body organ [7]. When carcinoma occurs, it



becomes adenocarcinoma, which means that the cancer cells are in the breast glands, such as milk ducts, near the organ of the breast [7]. Also, breast cancer is divided into in situ and invasive [7]. In situ means that it has not yet spread to the rest of the breast, and invasive means that the cancer cells from the milk duct have already started to metastasize or have already metastasized to the rest of the breast [7].

2. Epidemiology

Breast tumors are classified as benign and malignant, and usually breast tumors are considered benign [8]. Benign breast tumors are relatively unlikely to metastasize [8]. Through the lymphatic system, including lymph nodes, malignant breast cancers metastasis is considerably more prone to occur than the cancer cells move to the other tissues or organs [8]. The primary cause of mortality in women is breast malignant tumor. 99% is the 5-year survival rate for the non-metastasis tumor, while metastasis breast tumor has 30% [9]. Earlier getting a clear and accurate diagnosis, higher the cure rate as well as lower the mortality rate [10]. Further research on the associated risk factors would also be of great help in the diagnosis and treating breast cancer.

Most people who diagnosed with breast cancer are women over the age of 50 [11], with very few women diagnosed under the 45 years old [6]. Starting menstruation earlier or stopping menstruation later may raise the breast cancer risk [11]. Hormone use, timing of pregnancy, and alcohol consumption are the possible factors in daily life that boost breast cancer risk [11]. Also, there are some treatments for breast cancer such as surgical excision, radiotherapy, hormonal, etc., and the cure rate of breast cancer is relatively high in terms of 5-year survival from non-metastatic breast cancer.

This article will mention the breast cancer related risk factors, treatments for breast cancer and the advantages and disadvantages of some of these treatments, and possible prevention methods such as being aware of risk factors. This article will help to diagnose breast cancer at an earlier stage, and to treat it in a more appropriate way to increase the cure rate.

2.1. Risk Factors

Risk factors are factors that directly or indirectly make getting disease more likely. However, the risk factors do not necessarily mean that will lead to the development of a disease. Research has identified several risk factors that may be associated with breast cancer, some of which can be avoided through changes in lifestyle habits such as alcohol intake. However, there are some risk factors that may be difficult to change, such as the inheritance of breast cancer-related gene mutations.

3. Detailed risk factors

3.1. Lifestyle

Certain unhealthy lifestyles may make having breast cancer more likely. Alcohol can damage some organs in the body [12]. Drinking alcohol raises the chance of developing breast cancer and make the tumor bigger. [13]. This is due to the possibility that alcohol may affect the body's levels of hormones like estrogen or hormones linked to breast cancer. [13]. The hormone imbalance increases the risk of breast cancer [13]. Data show that women who have three drinks every week, there will be a 15% higher chance of breast cancer developing than those who abstain from alcohol [13].

Being overweight is also a risk factor. First, being overweight also increases the weight of the breasts. The increase in breast size is accompanied by a corresponding increase in fat tissue. Therefore, when diagnosing breast cancer, the increased adipose tissue may have an impact on the determination of mammogram [14]. Second, the adipose tissue can be the storage place for estrogen. A woman stops menstruating, the ovaries no longer produce estrogen. The adipose tissue become main source of estrogen in the body, so a hormonal imbalance that increase the risk to have breast cancer [15]. The timing of being overweight is also an important aspect. If a woman becomes obese as an adult, the

adipose tissue will have more time to store more estrogen increasing the breast cancer possibility, whereas gaining weight before menopause will not raise the risk too much [15]. If more exercise is added in daily life, the weight will be reduced thus the breast cancer risk will be reduced.

3.2. Hormones

There are several reasons that can cause hormonal changes in the body to reduce or increase the risk to have breast cancer. First, pregnancy, when a woman becomes pregnant, she releases estrogen as well as progesterone [16]. The breasts may be in an immature state until the age of 30, and all these hormones help the normal and regular growth of the breasts, thus reducing the breast cancer risk [17]. Therefore, the breast cancer developing chance increases accordingly if woman does not get pregnant before the age of 30 or if woman never gets pregnant [17]. Pregnancy also reduces the total number of menstrual cycles, which means that the total amount of estrogen released is reduced [17]. This will lead to more balanced hormone levels after menopause.

Secondly, breastfeeding after having a baby is not only good for the baby but also reduces the having breast cancer likelihood in women both before and after menopause. The delay in menstruation during breastfeeding due to hormonal changes in the body, which reduces a woman exposure to estrogen [18]. In addition, some breast tissue is shed during breastfeeding which may contain DNA-damaged cells [18].

Thirdly, some of the medications used for contraception are worked by controlling hormone levels in the body. Artificial hormones such as estrogen and progesterone are introduced into the body through pills or injections. These two hormones are known to stop the production of eggs, but also increase a woman exposure to estrogen [19]. Additionally, studies have revealed that women who use injectable or cyclical contraceptives have a higher probability of having breast cancer than those who do not use birth control pills. [15].

3.3. Gene

Genetic factors are also one of the possible causes of having breast cancer or make the tumor progress. There are some gene mutations that may be hereditary and others that are principal for cancer cells growth. Some gene mutations are highly associated with the developing breast cancer, the BRCA1 and BRCA2 are the genes that important for breast cancer development.

3.3.1. BRCA1 and BRCA2.

The BRCA1 gene plays a key role in repair, checkpoint control, and transcriptional control, while researchers found that BRCA2 gene plays a more important role in repair than BRCA1. It has been shown that C-terminal binding protein CtBP is one of the factors that may affect the transcription of BRCA1, and when CtBP binds to the BRCA1 promoter, it will inhibit the transcription of BRCA1 [21]. However, when estrogen is increased, CtBP is destabilized and separated from the BRCA1 promoter, allowing BRCA1 to be transcribed and controlling genomic homeostasis. The main function of BRCA2 is to repair homologous genes by preferentially binding to ssDNA and promoting the invasion of RAD51 into the DNA strand [21]. The functions of BRCA1 and BRCA2 are very important, for example, when hormonal changes occur in the body, these two genes can be controlled responding accordingly to transcription and inhibit abnormal proliferation. Therefore, a mutation in these two genes may increase the risk of hyperplasia and thus increase having breast cancer chance.

3.3.2. ATM.

ATM is Ataxia-telangiectasia mutated. Breast cancer risk is linked to ataxia-telangiectasia mutation. ATM acts on DNA double-strand breaks and regulates the phosphorylation of proteins controlled by DNA checkpoints [21]. If a faulty DNA is not stopped at the checkpoint in time and continues to mitigate, it can increase the number of abnormal cells and cause problems [21].

3.3.3. CHEK2.

CHEK2 is an intermediate penetrance gene, which means this gene carries a trait that is at the intermediate level of expression for the allele. The main role of CHEK2 is to encode an enzyme that regulates proteins that carry out checkpoint control which also includes BRCA1 [21]. If BRCA1 and BRCA2 gene do not undergo abnormalities, testing for CHEK2 alternations may result in a two-fold increase in the chance to breast cancer development. [21]. However, mutations in CHEK2 will not be superimposed the occurrence of breast cancer if mutations in BRCA1 are screened for.

3.3.4. PTEN.

PTEN is a tumor suppressor gene for control cell proliferation, and mutations or locus changes in the PTEN gene have been found in several types of malignant cancer tumors. PTEN also work in breast cancer cells controlling. Moreover, PTEN gene mutations or site-specific alterations are relatively common in breast cancers [22]. PTEN mutations cause patients to develop Cowden Syndrome, a syndrome that raise the likelihood of both benign and malignant tumors. This syndrome is not only associated with a raise the possibility of breast cancer but also with abnormal growth of the ovaries and uterus [15].

3.4. Other Factors

While the previously mentioned lifestyle or hormonal modifications can be lower the possibility of having breast cancer, there are other risk factors as well. The first one is age, most of the patients diagnosed with breast cancer are over 60 years old, which may be due to the accumulation of some genetic mutations or other reasons [20]. Secondly, the presence of some benign problems in the breast may make the having breast cancer possibility higher, but the increased level of having breast cancer probability can vary from problem to problem [20]. Non-proliferative lesions such as simple cysts, benign lobular tumors, and fat necrosis do not raise breast cancer risk too much [20]. However, atypical hyperplastic lesions, which make the breast tissue look abnormal increase probability of breast cancer significantly more than other types of lesions [20]. Atypical ductal hyperplasia and atypical lobular hyperplasia are two examples of atypical hyperplastic lesions [20].

4. Possible Therapy

4.1. Surgery

The breast tumor is removed through a mastectomy. The most common mastectomy is cut all breasts, but it is also possible to remove only the tumor and preserve the normal cells and tissue surrounding the breast tumor [23]. But the recurrence rate of breast cancer is about the same for total and conserving mastectomy [23]. And one of the problems with a conserving mastectomy is small calcifications of the surrounding tissue. Such calcification may also be malignant [23]. Another surgery is the removal of axillary lymph nodes, which may also help prevent cancer cells from spreading through the lymphatic system [23]. However, it is not mandatory to cut the lymph nodes surround breasts, and it is possible to control metastasis and recurrence with radiation therapy or hormone therapy [23].

4.2. Radiotherapy

High-energy radiation can be used to reduce and suppress breast cancer cells, so it is important for patients who have had surgery especially if they have not had a total mastectomy or an axillary lymph node resection to decrease chance of having breast cancer recurrence to some extent [23]. Radiation therapy is also not necessary for low-risk breast cancer subtypes because it is relatively effective for high-risk breast cancer subtypes. Radiation therapy can also be combined with hormonal therapy and targeted therapy [23]. Radiation therapy is critical for triple negative breast cancer at this stage of research because there is currently no suitable chemotherapy or targeted therapy [23]. But one of the

obvious drawbacks of radiation therapy is radiation to other parts of the body, so pay attention to protection [23].

4.3. Hormone Therapy

Hormonal therapy is a treatment that works by controlling receptors in the body. Signaling pathways, a crucial role for cancer cells growth, and estrogen and progesterone receptor signaling pathways have been found to have an essential function in the breast cancer emergence, and most breast cancers are hormone receptor positive [24]. As a result, targeted therapies for hormones are gradually emerging. Hormone therapies often work by preventing the receptor from receiving the hormone, the tissue from producing the hormone or preventing the conversion of androgens, and common drugs are tamoxifen, aromatase inhibitors, etc. [24].

4.3.1. SERM.

Selective estrogen receptor modulators (SERMs) are one of the treatments that changing the hormone binding level. The mechanism of this method to control the breast cancer occurrence is reducing the binding of estrogen to the estrogen receptor. Burguin et al. mentioned that tamoxifen is the most widely used SERM, which is effective in controlling the recurrence of breast cancer within 5 years [23]. However, according to data, about 40% of breast cancer patients develop resistance to this hormonal therapy [23]. One explanation for patient resistance to hormone therapy is due to demethylation of CpG islands, an epigenetic modification, which may inhibit estrogen receptor (ER) transcription. Still another explanation is the lack of expression of coregulators of ER [23].

4.3.2. SERD.

Burguin et al. also proposed SERD which is another type of hormone therapy; SERMs reduce the amount of estrogen binding to the ER by counteracting it, but SERDs control estrogen binding by completely shutting down the pathway of ER [23]. The main drug is Fulvestrant, which binds more tightly to the ER and degrades it [23]. Burguin et al. also mention that for breast cancer with ER-positive and at advanced or metastatic stages, Fulvestrant in conjunction with CDK4/6 inhibition is the first choice of treatment. Again, patients can become resistant to Fulvestrant. One of the mechanisms is the up-regulation of PI3K. Due to the up-regulation of PI3K and the fact that PI3K belongs to a different signaling pathway than ER and transmits signals by binding to epidermal growth factor [23].

4.4. Targeted Therapy

4.4.1. CDK4/6 Inhibitors.

Regarding the SERM hormone therapy mentioned earlier, in the article by Tong et al. that there is a need for further research on the resistance of patients to tamoxifen. Tong et al. state that CDK4/6 inhibitors could work in patients who are resistant to tamoxifen [24]. cell cycle, which means that CDK4 still allows cancer cells to expand when patients are resistant to hormones. Therefore, inhibition of CDK4/6 is also critical. The G1 phase of the cell cycle slows down when hormone therapy and CDK4/6 inhibitors are combined with each other [24]. The treatment of hormone therapy and CDK4/6 in conjunction with first- and second-line therapy is described in more detail in article of Burguin et al. Firstly, the drugs for first-line treatment, Palbociclib was the first approved CDK4/6 inhibitor [23]. In Tong et al. state that Ribociclib is in a phase III study, but Burguin et al. mention the outcomes of a clinical investigation showed the use of Letrozole and Ribociclib together increased time progression free survival which means cancer cells to stop spreading. But resistance needs to be obtained in further follow up [23]. Burguin et al. also mention that that Palbociclib and fulvestrant together can be used for phase II treatment of advanced or metastatic breast cancer [23].

4.4.2. PI3K Inhibitors.

There is also a corresponding more effective combination of SERD hormone therapy and targeted therapy to achieve more favorable results. Tong et al. also mentioned the inhibition of PI3K in their

article [24]. In article for Burguin et al., PI3K is abnormally activated due to different mechanisms, so PI3K inhibition is also a therapeutic approach in advanced breast cancer [23]. Buparlisib has a relatively significant improvement in PIK3CA mutation, but the toxicity is relatively high [24]. The combination of Fulvestrant and Buparlisib has been shown to improve the time of progression free survival, but adverse effects such as hyperglycemia and respiratory distress have been reported [23]. Pictilisib has been shown in clinical trials that do not have effect on breast cancer patients with PI3K mutations. Also, when Pictilisib add with Fulvestrant, the result shows that did not increase the time to cessation of cancer cell growth [23].

5. Conclusion

The second greatest cause of cancer-related fatalities among women is breast cancer, so trying to avoid the factors that raise the breast cancer chance and providing the right treatment in a timely manner can be an effective way to minimize breast cancer mortality. This article mentions, firstly, include alcohol intake that is associated with organ damage throughout the body, excessive obesity makes fat the main source of hormones for menopausal women and some unhealth lifestyles will increase the breast cancer risk. Secondly, some hormonal changing aspect in the female body like pregnancy and breastfeeding that delay menstruation and reduce the female menstrual cycle. These factors could reduce the amount of estrogen to which the woman is exposed during lifetime. However, pregnancy may increase the risk if not before the age of 30 when the breasts are still immature. Some genes may be mutated in both inherited and non-inherited ways, which could enhance cancer cells growth or breast tumor get bigger. The most frequent mutations in breast cancer are BRCA1 and BRCA2. There are more genetic mutations that have been linked to an elevated breast cancer risk. Hereditary PTEN gene mutations are one of them, which can cause Cowden syndrome that increase the probability of hyperplasia not only in the breast but also in the uterus and other organs. Finally, some relevant and updated treatment methods are compared, including SERM and SERD hormone therapy, and by inhibiting CDK4/6 and PI3K to improve the stop time of breast cancer tumor development.

References

- [1] Healthtalk. org. Living with multiple health problems. Retrieved 29 June 2023, from <https://healthtalk.org/multimorbidities/the-personal-impact-of-multiple-health-problems>.
- [2] Murphy A. (2020). Why Study Public Health? Healthcare studies.
- [3] Ranapurwala S I, et al. (2019). Public health application of predictive modeling: an example from farm vehicle crashes. *Injury Epidemiology*, 6 (31).
- [4] Ryerson A B, Massetti G M. (2017). CDC's Public Health Surveillance of Cancer. *Preventing Chronic Disease: Public Health Research, Practice and Policy*, 14.
- [5] Lomte T S. (2023). What are the top 10 public health challenges in 2023? News Medical.
- [6] American Cancer Society. Key Statistics for Breast Cancer. Retrieved 29 June 2023, from <https://www.cancer.org/cancer/types/breast-cancer/about/how-common-is-breast-cancer.html>
- [7] American Cancer Society. Types of Breast Cancer. Retrieved 18 July 2023, from <https://www.cancer.org/cancer/types/breast-cancer/about/types-of-breast-cancer.html>.
- [8] American Cancer Society. What is Breast Cancer? Retrieved 29 June 2023, from <https://www.cancer.org/cancer/types/breast-cancer/about/what-is-breast-cancer.html>.
- [9] American Cancer Society. Survival Rates for Breast Cancer. Retrieved 29 June 2023, from <https://www.cancer.org/cancer/types/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-survival-rates.html>.
- [10] Wei M, et al. (2020). A Benign and Malignant Breast Tumor Classification Method via Efficiently Combining Texture and Morphological Features on Ultrasound Images. *Computational and mathematical methods in medicine*.
- [11] Breast Cancer Research Foundation. What are the major risk factors for breast cancer? Retrieved 18 July 2023, from <https://www.bcrf.org/blog/risk-factors-for-breast-cancer/>.
- [12] World Health Organization. Alcohol is one of the biggest risk factors for breast cancer. Retrieved 30 July 2023, from <https://www.who.int/europe/news/item/20-10-2021-alcohol-is-one-of-the-biggest-risk-factors-for-breast-cancer>.

- [13] Breast Cancer Organization. Drinking Alcohol. Retrieved 30 July 2023, from <https://www.breastcancer.org/risk/risk-factors/drinking-alcohol>.
- [14] Centers for Disease Control and Prevention. What Are the Risk Factors for Breast Cancer? Retrieved 30 July 2023, from https://www.cdc.gov/cancer/breast/basic_info/risk_factors.htm.
- [15] American Cancer Society. Lifestyle-related Breast Cancer Risk Factor. Retrieved 30 July 2023, from <https://www.cancer.org/cancer/types/breast-cancer/risk-and-prevention/lifestyle-related-breast-cancer-risk-factors.html>.
- [16] Cuffari B. (2022). The Role of Estrogen in Pregnancy. *The Role of Estrogen in Pregnancy*.
- [17] Breast Cancer Organization. Breast Cancer Protection from Childbirth Starts Later Than Thought. Retrieved 30 July 2023, from <https://www.breastcancer.org/research-news/bc-protection-from-childbirth-starts-later>.
- [18] Cordeiro B. (2014). Breastfeeding lowers your breast cancer risk. Retrieved 30 July 2023, from <https://www.mdanderson.org/publications/focused-on-health/breastfeeding-breast-cancer-prevention>.
- [19] National Library of Medicine. Birth control – slow-release methods. Retrieved 30 July 2023, <https://medlineplus.gov/ency/article/007555.htm>.
- [20] American Cancer Society. Breast Cancer Risk Factors You Cannot Change. Retrieved 30 July 2023, from <https://www.cancer.org/cancer/types/breast-cancer/risk-and-prevention/breast-cancer-risk-factors-you-cannot-change.html>.
- [21] Shuen A Y, Foulkes W D. (2011). Inherited Mutations in Breast Cancer Genes – Risk and Response. *Journal of Mammary Gland Biology and Neoplasia*. 16, 3-15. <https://doi.org/10.1007/s10911-011-9213-5>.
- [22] Depowski P, Rosenthal S I, Ross J S. (2001). Loss of Expression of the PTEN Gene Protein Products is Associated with Poor Outcome in Breast Cancer. *Modern Pathology*. 14 (7), 672 - 676. <https://doi.org/10.1038/modpathol.3880371>.
- [23] Tong, C. et al. (2018). Recent Advances in the Treatment of Breast Cancer. *Frontiers in Oncology*. 8. <https://doi.org/10.3389/fonc.2018.00227>.
- [24] Burguin A, et al. (2021). Breast Cancer Treatments: Updates and New Challenges. *Journal of Personalized Medicine*. 11 (8), 808. <https://doi.org/10.3390/jpm11080808>.