

Aetio-pathogenesis of breast cancer

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ABSTRACT

This is a literature review on the aetiology and pathogenesis of breast cancer, which is the most common cancer worldwide, and the second leading cause of cancer death, especially in Western countries. Several aetiological factors have been implicated in its pathogenesis, and include age, genetics, family history, diet, alcohol, obesity, lifestyle, physical inactivity, as well as endocrine factors. These factors act separately or together in the causation of breast cancer. More recently, triple negative breast cancer has been described in certain categories of patients and is associated with poorer prognosis and earlier recurrence compared with the conventional breast cancer. Therefore, adequate knowledge of these factors is important in identifying high risk groups and individuals, which will help in screening, early detection and follow-up. This will help to decrease the morbidity and mortality from this life-threatening disease.

Keywords: Aetiology, breast cancer, early detection, interaction, multifactorial, pathogenesis, prognosis, screening

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INTRODUCTION

Breast cancer is the most common cancer worldwide, and the second leading cause of cancer death.¹ One in nine women in the UK and USA will develop the disease in their lifetimes.¹ It is more common in the Western countries than in Africa, South America or Asia, and several aetiological factors have been implicated in its pathogenesis.² These causative factors include age, genetics, family history, diet, alcohol, obesity, lifestyle, physical inactivity, as well as endocrine factors (both endogenous and exogenous).³ Triple negative breast cancer (TNBC) has recently been identified in certain sub-groups of patients, and has a higher recurrence rate, faster growth and poorer prognosis.⁴ Other associated factors for breast cancer are mammographic density⁵ and previous benign disease.⁶ However, it is still not very clear which of the factors has any predominant role (s) over others, in the pathogenesis of breast cancer.

EPIDEMIOLOGY

Breast cancer is the most common cancer of adult females all over the world,⁷ and after lung cancer, it is the second

leading cause of cancer death.¹ As a result of its common occurrence in the Western countries, 1 in 12 women in England and Wales will develop the disease in their lifetime.² But this risk is believed by some other workers to be higher and could be as high as one in nine women in both the UK and USA.³ Overall, this cancer is seen in one quarter of all female cancers, which supports the fact that it is the most common cancer in women in the Western world.^{7,8}

AETIOLOGICAL FACTORS

Geography

The observed annual incidence of breast cancer globally is about one million cases, with more than half occurring in the Western world: 200,000 cases in the US and 320,000 cases in Europe.¹ Furthermore, it accounts for 3-5% of deaths in the Western world, 1-3% in the developing countries and believed to be rare in Japan. However, Dumitrescu and Cotarla more recently reported a death rate of 2.3% annually in the USA, and attributed the decrease to improved screening techniques as well as new and better treatment options.¹

Age

Russell *et al.* observed that breast cancer is very uncommon before the age of 20 years, but the incidence gradually increases with age, and by the age of 90 years, one-fifth of women are affected.² In addition to that, Dumitrescu and Cotarla reported that less than 10 new cases were recorded per 100,000 women aged below 25 years, and increased up to 100 times by the age of 45 years.¹ This indicates that the reproductive hormones produced by the ovaries and the adrenal glands are involved in the pathogenesis of breast

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cancer, since cancers that are not responsive to hormones will not show any appreciable change of incidence during the female reproductive period.⁶

Furthermore, it is also believed that the age at menarche and menopause contribute to the duration of exposure to the carcinogenic effects of the gonadal (sex) hormones.⁷ In support of this, Aguas *et al.* observed that the risk of breast cancer reduces 15-20% for each year that menarche is delayed, and that late menopause at 55 years or older is a risk factor.⁷ This is because early menarche and delayed menopause will increase the duration of oestrogen exposure during a woman's reproductive years, but there has to be collaboration with genetic and environmental factors for breast cancer to develop.⁷

Gender

Only less than 1% of patients with breast cancer are males.² However, the differences are thought to be hormonal since even the male breast cancer has been shown to express oestrogen, progesterone and androgen receptors (ARs) and men with Klinefelter's syndrome have been observed to have increased chance of developing breast cancer.⁹

Genetic factors

Breast cancer is more common in women with a family history compared with the general population. Russell *et al.* observed that only about 5% of breast cancers are related to a specific mutation.² Also, a meta-analysis of 52 separate epidemiological studies revealed that 12% of women with this disease have one affected family member and 1% of the patients have one or more relatives affected.¹ The study concluded that women with one or more first degree relatives affected with breast cancer have higher breast cancer risk than those who do not.¹

Diet and alcohol

These are thought to play a role in the aetiology of breast cancer, and there is a link between diets low in phyto-oestrogens and this disease, as well as high intake of alcohol.² According to Dumitrescu and Cotarla, the risk increases progressively in a dose-dependent manner to an alcohol intake of 60 g (2-5 drinks) per day, depending on the strength of the drink and for every 10 g increment (approximately 0.75-1 L drink) in daily alcohol consumption, the risk increases with 9%.¹

Furthermore, well-cooked meat and diets rich in fats are associated with increased incidence of breast cancer, and it has been observed that diets containing 35-40% of fat in calories like most Western diets have a mammary tumour-producing effect.⁷ This is because high fat diets are rich in cholesterol, which is a precursor in the synthesis of oestrogens and other steroid hormones, therefore exposing the breast to higher amounts of oestrogen, which can stimulate the development of cancer.⁷

It was also observed that dietary fibre ingestion inhibits the intestinal resorption of oestrogens and this protection is higher with a daily intake of 35-45 g of dietary fibre.⁷ This is probably why breast cancer is not as common in the developing countries as it is in the Western world, due perhaps to consumption of large amounts of dietary fibre in Africa, Asia and South America (even though diets do not just differ in fibre contents). Other dietary factors like soya beans and vitamins are also thought to reduce the incidence of this disease, but the precise mechanisms have not been explained.⁷

Obesity lifestyle and physical activity

Along with diet, exercise can interfere with plasma levels of hormones, which may influence breast cancer development.⁷ Aguas *et al.* observed that these two factors separately or in combination influence the body weight and obesity increases the risk of breast cancer in post-menopausal women.⁷ Dumitrescu and Cotarla supported this observation in their paper and noted that breast cancer risk is particularly evident among obese women who do not use hormone replacement therapy (HRT), and for each 5 kg of weight gain, breast cancer risk increases by 8%.¹ This is explained by the fact that fat in adipose tissue is an important source of oestrogens, which are synthesised from cholesterol.

ENDOCRINE FACTORS

Endogenous

This cancer is more commonly seen in infertile women and those who do not breast-feed their babies. First full-term pregnancy at an early age, especially if associated with late menarche and early menopause (which decrease the duration of oestrogen exposure of a woman) has been found to be protective.² Both early age (less than 20 versus 30 years) at first full-term pregnancy and higher parity decrease breast cancer risk to half of the risk of women who did not bear children. This is because the level of oestrogen is lower in pregnancy and in women who had many children.

Exogenous factors

A large meta-analysis demonstrated that long-term HRT is responsible for the cumulative excess of breast tumours over those expected in women aged between 50 and 70 years.¹ Aguas *et al.* also reported that HRT is associated with an increased risk of breast cancer (with a relative risk of 1.21-1.40), especially among current users of oestrogen plus progestin for 5 years and longer.⁷ However, HRT has many advantages, which include relief of vaginal dryness and itching, decreased tension headaches, mood swings and depression, decreased risk of osteoporosis and pathological fractures, as well as enhancement of the general well-being of the individual.¹⁰

Therefore, it is important to recognise and weigh these facts against the supposed role of HRT in breast cancer before condemning it, especially since the risk of breast cancer following HRT for many years is small, though not insignificant. The same is true for oral contraceptives as the report showed a modest increase in breast cancer risk associated with current and recent use, with a relative risk of 1.24 reported in a meta-analysis of 54 studies involving 150,000 women. The risk is believed to be greater for those who began contraception before 20 years of age.⁷ Dumitrescu and Cotarla also demonstrated a connection between breast cancer and oral contraceptive use independent of dose, age of first use, length of use, age of diagnosis or a family history of breast cancer.¹ The risk is attributed to the oestrogen content of the contraceptives, which contributes to the pathogenesis of breast cancer. Again, it is important to point out the obvious advantages of oral contraceptives in preventing unwanted and untimely pregnancies, as well as giving individuals' choice in planning their families.¹

Mammographic density

This is well documented risk factor for the development of breast cancer during and after the reproductive ages. Studies have demonstrated that women with >75% increased breast density on mammography have up to a 5-fold increased risk over those with <5% increased breast density.¹ This view is also supported by Aiello *et al.*, who conducted a cross-sectional study of 546 women diagnosed with invasive breast cancer to evaluate the association between breast density and tumour size.⁵ They found that women with a tumour size of >1 cm were more likely to have dense breasts compared with those with a tumour size <1 cm, and that lymph node status, lymphatic and/or vascular invasion were positively associated with breast density.⁵

Benign breast disease

A previous history of benign breast disease like fibrocystic disease (fibro-adenosis) and fibro-adenoma are known to increase the risk of breast cancer. Fibro-adenosis with severe dysplasia and epitheliosis is considered to be pre-malignant even though not all cases progress to cancer.⁶ However, close surveillance and screening of patients at risk is required to help in early detection and treatment of breast cancer.⁶

MOLECULAR GENETICS OF BREAST CANCER

Five to ten percent of all breast cancers arise from germ-line mutations in high-penetrance breast cancer susceptibility genes such as BRCA1, BRCA2, p53 and PTEN, and confer a high individual risk for developing hereditary breast cancer.¹ The BRCA1 gene is located on the long arm of chromosome 17, while BRCA2 is located on the long arm of

chromosome 13. Gene-positive patients have an 80% risk of developing breast cancer especially in the pre-menopausal age group.²

Aguas *et al.* observed that BRCA1 and BRCA2 predispose a woman to breast cancer in only 5–10% of the total number of breast cancers and believe that even though family history may reflect shared genes, it may also suggest shared environmental lifestyle exposures.⁸ They therefore advised that due to ethical and legal issues, as well as psychological consequences, genetic screening should only be carried out in the research settings, rather than in routine clinical practice.⁸ But we know that genetic screening is carried out selectively in affected families.

Furthermore, Russell *et al.* agreed on the presence of polymorphisms in breast cancer susceptibility genes with low penetrance, which have a greater contribution to breast cancer pathogenesis in combination with exogenous factors such as diet, alcohol and pollution, as well as endogenous factors such as oestrogens and progesterone exposures.² This accounts for majority of the sporadic (non-familial) breast cancers which form 90–95% of all breast cancers in women. The familial cancers usually occur in younger patients, are often multifocal or bilateral and have poorer prognosis, compared with the sporadic cases, which are mostly unilateral, occurring in older patients and have better outcomes.¹

The role of HER-2/NEU antigen

This is a growth factor protein, which is over-expressed in different types of human cancers, including breast, ovarian, lung, gastric and oral cancers.¹¹ In 1987, the HER-2/neu proto-oncogene was revealed to be amplified and over-expressed in 20–30% of invasive breast cancers, and also shown to be associated with poorer outcome and shortened survival.¹² In addition, HER-2/neu-positivity is thought to predict the likelihood of resistance or sensitivity to some conventional hormonal therapies like tamoxifen. Herceptin (trastuzumab), a recombinant humanised anti-HER-2/neu monoclonal antibody has been shown to improve outcomes for women with metastatic breast cancer, either alone or in combination with chemotherapy.¹³

Triple negative breast cancer (TNBC)

This is breast cancer, which is negative for oestrogen, progesterone and HER-2/neu receptors, and has been noticed to occur in certain categories of patients mostly from lower socio-economic groups or deprived communities.⁴ It makes up to 20% of all breast cancers and currently has no standard treatment.¹⁴ This type of breast cancer (TNBC) has also been associated with higher recurrence rates, faster growth and poorer prognosis, compared with other conventional breast cancers; and it is only sensitive to chemotherapy.¹⁵

In addition to that, TNBC is associated with inactivation of BRCA1 and over-expression of the epidermal growth

factor receptor (EGFR), which makes it sensitive to anti-EGFR therapies currently under trial.¹⁶ Novel molecular-targeted treatments are currently being developed, but still undergoing trials.¹⁷ However, a sub-group of patients have recently been described who have chemo-resistant TNBC, and therefore, other therapeutic manoeuvres such as targeting AR activation or cancer stem cells may be have to be considered in future.¹⁸

STEROID HORMONES AND THEIR RECEPTORS

Steroid hormones

These include oestrogens, progesterone and androgens, which belong to a group of structurally related hormones called sex hormones, that are secreted into the systemic circulation by the adrenal gland and gonads. They are manufactured from one common parent molecule, cholesterol via a reaction catalysed by several enzymes to produce a wide variety of hormones for different target tissues and organs.⁸ This process is well controlled and the release of these substances into the blood is followed by entry into the target cells by crossing the plasma membrane to exert their action through binding to high-affinity receptor proteins known as steroid hormone receptors.¹⁹

Oestrogens have significant effects on growth, differentiation and functioning of many tissues such as breast, uterus, cardiovascular system, brain and urogenital tract of both males and females.^{8,19} In line with this, Kato *et al.* noted that the development of reproductive organ tumours like breast and prostate cancer often depends on the action of the sex hormones (oestrogens, progesterone and androgens), which exhibit a large number of biological effects in both normal and abnormal cellular conditions.

It has also been observed that breast stromal cells can modulate the growth of normal and neoplastic breast epithelial cells and can secrete growth factors following stimulation by endogenous hormones. The adipose tissues contain aromatase enzyme, which produces oestradiol from circulating cholesterol. Because of the higher proportion of these fat cells in breasts of older women, the levels of oestradiol in breast tissues of post-menopausal women are much greater than their plasma levels.²⁰ This probably accounts for the rising incidence of breast cancer with ageing and supports the role of steroid hormones in the pathogenesis of breast cancer.

Steroid hormone receptors

These are structurally related intra-cellular proteins that bind to steroid hormones such as oestrogens and progesterone and relay their signals leading to downstream gene expression (signal transduction). Cancers dependent on steroid hormones include breast, prostate, testicular, ovarian and endometrial cancer, which result

from deregulation of hormone secretion, signalling and receptor action.⁶ The concept of steroid hormone playing an important role in carcinogenesis was first demonstrated by surgical removal of the ovaries, which was followed by reduced levels of circulating hormones and remarkable improvement in women with breast cancer.²¹

Oestrogen is now believed to mediate its various functions through two specific intra-cellular receptors, oestrogen receptor- α and - β (ER- α and ER- β), which are produced by different genes and function as ligand-activated transcription factors.⁸ These, along with ARs are the members of the nuclear hormone receptor superfamily, which form homo-dimers and bind specific DNA elements called hormone responsive elements (HRE) in the target gene promoters.²²

CONCLUSION

The aetiology of breast cancer is multi-factorial, and several factors have been implicated, which may act independently or in combination, especially in high risk individuals. It is important to understand the aetio-pathogenesis of this common disease, which is associated with high morbidity and mortality, especially if not detected early. Furthermore, TNBC poses special diagnostic, treatment and prognostic challenges, because of the absence of the commonly identified receptors, as well as associated poor survival in this group of patients. Therefore, the roles of early screening in high risk or susceptible individuals, as well as proper surveillance of treated cases in order to detect recurrence at the early stages have been advocated.

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