A Mini-Review on Breast Cancer-Risk factors, Treatment and Prevention.

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Micro abstract

In now a day's life, cancer deaths are increasing tremendously, especially breast cancer deaths in women increasing rapidly all over the world. Due to change in life style and several other factors breast cancer easily develops in women. The current review article describes the various risk factors associated with breast cancer and also describes the different modes of treatment, preventive factors.

Abstract

Cancer is a result of uncontrolled growth of abnormal cells in the body caused by genetic and environmental factors. Modern lifestyle changes, food choices, genetic vulnerability, family history, oestrogen exposure, age, late night working, hazardous chemical exposure, obesity in the post-menopausal phase, exposure to high doses of radiation are some of the main factors which increases the risk of breast cancer. It is the frequently diagnosed and leading cause of cancer deaths in women in worldwide. This article presents a systematic review of the Breast Cancer literature describing the risk factors, treatment methods and preventive steps of breast cancer. Breast cancer treatment and prevention are prominent issues in publichealth and medical practice. The current approach to this disease involves early detection and treatment. The available literature in this review aims to bring the awareness of healthcare professionals and clinical doctors to improve the quality of treatment and suggesting breast cancer patients to follow the preventive steps.

Key words

Breast cancer, ductal carcinoma in situ, lobular carcinomain situ, breast cancer treatment, Risk factors, Treatment and Prevention.

Introduction

Breast cancer is the most common cancer of adult females in all over the world (140 of 180 countries) [1], andafter lung cancer, it is thesecond leading cause of cancer death [2}. One in eight women in the UK, USA and one in twenty in Indiadevelop the disease in their lifetimes. Theage-standardized incidence rate (ASR) of breast cancer is 39.0 per 100,000, which is higher than that of cervical cancer (cervical cancer ASR=15.2 per 100,000)[3, 4, 38, 39]. In 2015, an estimated 60,290 in situ breast cancer cases and 2, 31,240 invasive breast cancer cases were diagnosed in United States. And approximately 40,290 women expected to die from breast cancer [93]. Between 2008-2012 the breast cancer incidence increased by 25%, while death rate due to breast cancer increased by 14% [36]. In US, it is estimated that there are 3.1 million breast cancer survivors presently [37]. It is estimated that 70% of breast cancers are hormone receptor positive, and genetic mutations like BRCA 1 and BRCA 2 genes leads to breast cancer development with 60-80% life time risk [40-42].It is more common in the Western countries than South America, Asia, and Africa.Several aetiological factors have been implicated in its pathogenesis.

The causative factors include age, genetics, family history, diet, alcohol, obesity, life style, physical inactivity, chemical exposure, previous benign disease, mammographic density and exposure to high dose of ionizing radiation. Each factor has its unique role in the pathogenesis of breast cancer and difficult to

predict that the single factor has higher risk of causing breast cancer. In most of the areas this cancer is seen in one fourth of all female cancers, which concludes that this cancer is most common in western countries and fast grown up cancer in Asian countries [2, 5, and 37].

Breast cancer is a tumour that starts from cells of the breast tissue, cells of the ducts and lobules where breast cancer mostly begins. Breast cancer are of two types benign and malignant, the former are not life-threatening, can usually remove by surgery, they do not invade adjacent tissue or do not spread to the other parts of the body. Malignant breast tumours are cancerous and can invade adjacent tissue or metastasize to other part of the body through lymphatic system. If breast cancer cells enter into the lymphatic system then there is a higher probability that the tumour enter into the blood stream and metastasizes to other part of the body [92].

Risk factors

Genetic risk factors: The mutations in BRCA1 and BRCA2 increase the risk of breast cancer and account for 5%-10% of all female breast cancers. [70, 71] the average risk for *BRCA1* and *BRCA2* mutation carriers is estimated to be between 57%-65% and 45%-55%, respectively [72-74].

Family history: Breast cancer risk is higher in closed bloodrelatives (mother, sister, daughter, father, brother, or son). Risk increases with increasing first degree relatives. [94]

Personal history of breast cancer: A woman with cancer in one breast has a higher chance of getting breast cancer in another breast.The risk is high at the age of 40, and decreases significantly with increasing age at diagnosis of primary breast cancer [77-79].

Race

Black women have higher chances of getting breast cancer before age 45. Generally white women have higher chances of getting breast cancer than African-American women, Asian women due to changes in their lifestyle. African-American women are more likely to die of breast cancer. [95-96]

Dense breast tissue: Dense breast tissue means there is more gland tissue and lessfatty tissue. Women with denser breast tissue have a higher risk of breast cancer [97].Breast glandular and connective tissue increases the risk of breast cancer, density may be reduced by pregnancy and menopause. Breast density is lower in heavy weight women due to higher production of fatty tissue [98]

Benignbreast problems: Benign breast disease is fibrocystic disease with changes in breast tissue, it has no clinical symptoms, and it can be removed by biopsy. Benign breast disease is classified in to non-proliferative including fibro adenoma, adenosis, cysts and fibrosis, proliferative without atypia and proliferative with atypia. Women with benign breast disease have higher risk of breast cancer. [99]

Lobular carcinoma in situ: In this condition, cells that look like cancer cells are inthe lobules andcannot spread to other parts of the body. There are no clinical symptoms observed and cannot be detected in mammography. Women with LCIS have higher risk of getting invasive breast cancer within 5- 10 years. [84, 85]

Menstrual periods: Epidemiological studies of breast cancer have shown that Women who have periods before the age of 12 and after the menopause age of 55 are slightly increased the risk (10% to 20%) of breast cancer.[80, 81-83]

Breast radiation early in life: Women exposed to ionizing radiation for medical purposes for diagnosis and some working women exposes to highly lethal radiation at work place which influence the risk of breast cancer. Women exposes to radiation before the age of 20 have higher chances of getting breast cancer. [100, 101]

Treatment with DES: Diethylstilboestrol (DES), a potent pharmaceutical estrogen used by millions of pregnant women between 1940 and the 1970s to prevent miscarriages. Studies eventually revealed that *in utero* DES exposure of both male and female offspring increased neoplastic lesions of the reproductive

tract and the incidence of benign reproductive problems. Women who were exposed *in utero* to DES had a significantly increased risk of breast cancer. Their mothers also experienced an increased risk of breast cancer [11, 12].Importantly; the highest risks were correlated with the highest cumulative doses of DES during pregnancy [13].

Not having children or having them later in life: Women who had first child at the age of 30, who do not had children up to 30 and 35 years have slightly higher risk of breast cancer. Being pregnant many times or pregnancy at young age also reduces the risk of breast cancer [93].

Birth control pills: women using birthcontrol pills or an injectable form of birth control called *depot-medroxyprogesteroneacetate* (DMPA or Depo-Provera®) have a slightly greater risk of breast cancer thanwomen who have never used them. The risk go back to the normal when women stops using birth control pills [93].

Hormone therapy after menopause: A pooled analysis in 1997 suggest that taking oestrogen alone after the menopause increase the risk of 14% of getting breast cancer. Women who had hormone replacement therapy up to 5 years had 35% of higher risk than non-users [102].
A women's risk increases within a year and goes up for each year if she continues the combination hormones.

Not breastfeeding:
Breast feeding for duration more than one year lowers the risk of getting breast cancer and protective of breast cancer. Breast feeding less than 10 months have a little high risk of breast cancer. [24]
Alcohol: The intake of alcohol is directly linked to the risk of getting breastcancer. Even one drink per a day can increase risk.
Alcohol (especially beer) consumed more than 10 g/day especially among postmenopausal women is a risk factor for developing invasive breast cancer.[43,44]
Being overweight or obese: Women with large weight before and after the menopause has a higher chances of getting breast cancer [75]. Risk is about 1.5 times higher in overweight women than in non-obese women [76]. Due to heavy weight, fat deposition increases in the body and the fat tissue is the largest source of oestrogen in post-menopausal women.

Tobacco smoke: Studies linking smoking to breast cancer have had mixed results, epidemiological studies have reported that smoking may increase the risk of breast cancer. The increased riskseems to be higher in certain groups, such as women who started smoking before they hadtheir first child and continues for longer durations. [86-89]

Diet rich in fats
Diets rich in fats increases the incidence of breast cancer, diets containing 35-40% of fat in calories have a higher chances of producing breast tumour. Diet containing higher amount of fats are the source of cholesterol which is a precursor for the synthesis of estrogen hormone, exposure of breast to higher amount of estrogen leads to the development of cancer. [1]

Hyper-insulinemia
It has been hypothesised that excessive levels of insulin in blood levels is associated with increased risk of breast cancer, because excessive levels of insulin in circulation would promote cell growth in breast tissues and increase circulating levels of oestrogens, testosterone and insulin-like growth factors.[23]

A metaanalysis including case–control studies and cohort studies says that breast cancer risk for women with diabetes mellitus was 20% higher than for women without diabetes mellitus (RR 1.20, 95% CI: 1.12-1.28). The summary estimates were similar for case–control and cohort studies. [24]

The association between hyperinsulinemia and breast cancer risk represents a public healthchallenge, due to the high and increasing prevalence of insulin resistance in most developed countries. However, it would also represent a modifiable risk factor that could be controlled by physical activity and weight control.

Obesity Lifestyle

Obesity elevates the risk of breast cancerin post-menopausal women. Breast cancer risk iscommonly seen among obese women who don't use hormonereplacement therapy, and for each 5 kg of weight gain, breast cancerrisk increases by 9%. These fats in adiposetissue are the main source of oestrogens, exposure of higher levels of estrogen increases the risk of breast cancer. [2]

Working women

A woman working at night has a 35% higher in risk of getting breast cancer than women who works in day shifts. The women who works at least 3 night shifts per week for more than two years has a higher risk of getting breast cancer than the women who works one to two night shifts per week.

Working at night and sleeping at day time reverse the body's circadian rhythm, which alters the melatonin level, artificial light at night supress the levels of melatonin, which further affects the hormone levels and leads to the development of breast cancer. Breast cancer patients have low levels of melatonin compared to women without disease. [19-22]

Human Epidermal Growth Factor

The human epidermal growth factor receptor 2 (ErbB2; formerly HER2) gene is part of a

Family of genes that plays roles in regulating cell growth. Amplificationof this gene occurs in a significant proportion of breast, ovarian, and gastric cancers, so that instead of having two gene copies of ErbB2, as would be the case in a normal cell, there are multiple copies, referred to as "ErbB2-positive." As a result, there is far more expression (activity) of the ErbB2 protein on the cell surface, resulting in tumour's that are faster growing, more aggressive and less sensitive to therapy. An estimated 20 to 25 percent of breast cancers make these extra copies of the ErbB2 gene.[6]

Treatment

Surgery

Surgery is the most preferred first line treatment for breast cancer people. The aim of surgery is to remove cancerous tissue in breast and to find out affected lymphatic vessels in armpit area.

Surgery is of two types:

Breast conserving surgery-where the affected cancer tissue is removed along with the little amount of surrounding tissue but healthy breast tissue is not removed.

A mastectomy– where the whole breast is removed, often including some or all lymph nodes in the armpit.

Increasingly, although long-term outcomes are very similar for patients who have BCS and mastectomy, patients eligible for BCS are electing mastectomy. Reasons include reluctance to undergo radiation therapy after BCS and fear of recurrence.68 Younger women (those under 40 years of age) and patients with larger and/or more aggressive tumours are also more likely to undergo mastectomy. [68, 69]

Axillary (armpit) surgery:
Brest cancer can invade to the adjacent lymphatic vessels in the armpit area. Lymphatic vessels found in armpit area and other areas of the body are part of the immune system. If lymph nodes and lymphatic vessels are affected with the cancer tissue, then surgery to remove the affected area and further follow the radiotherapy, which reduces the recurring of breast cancer back.
Techniques used to detect the cancer in armpit area:
Sentinel node biopsy- one lymph node is removed from armpit area
Axillary node sampling- more than four lymph nodes are removed from armpit area.

Chemotherapy
Chemotherapy is a treatment with one or more anticancer (cytotoxic) drugs to kill the cancer cells. It aims to stop the breast cancer spreading or coming back. It makes less chances of breast cancer to come back in future. Most women having chemotherapy are treated with combination of two different drugs – this is known as multi- drug chemotherapy or combination therapy. Chemotherapy is a systemic treatment, which means it circulates throughout the body. It affects healthy body cells as well as cancer cells – and this is what causes side effects. The dose of given drug is calculated in such a way that it should show higher impact on cancer cells and least impact on normal body cells. Research studies have shown that combination chemotherapy (using more than one drug) is generally more effective than treatment with just one drug.This is because the different drugs act in slightly different ways, so together they have potentially greater impact on cancer cells.

Doxorubicin (Adriamycin) is one of the anthracyclines, an antibiotic and class ofchemotherapy that is effective against several types of cancer including breast.
Their mechanisms of action are to inhibit and block DNA and RNA synthesis and create free oxygen radicals that damage the DNA and cell membranes. [45,46]

Radiotherapy
Radiotherapy- treatment with radiation- is given after surgery to remove cancer cells after surgery. Generally radiotherapy is given after surgery for early breast cancer. Radiotherapy is usually given externally with high energy x-rays.
Radiotherapy also affects healthy cells, but they are generally able to recover andrepair themselves. Damage to healthy cells can be reduced by giving small doses of radiotherapy regularly. [47]Breast conserving surgery (BCS) is almost always followed by radiation therapy because it has been shown to reduce the risk of breast cancer recurrence by about 50% and the relative risk of breast cancer death by about 20% in most patients [60]. Although there is a higher risk of local recurrence (cancer returning to the breast) with BCS than with mastectomy, clinical trials have confirmed that a woman who chooses BCS and radiation will have the long-term survival. [61-63]

Hormone therapy
Hormones are chemical messengers that are created in endocrine glands which controls the growth and activity of cells in the body. Oestrogen and progesterone are female sexual hormones which are essential for the development and functioning of female reproductive organs and they help to maintain healthy bones and heart. However, they can also encourage the growth of some breast cancers. About 2 to 3% of breast cancers are sensitive to hormones. Hormone therapies block the production of oestrogen and progesterone hormones and stop the hormones from signalling to the breast cancer cells. Hormone therapies are only effective in treating breast cancers that are hormone positive.
Hormone therapies for breast cancer should notbe confused with hormone replacement therapy (HRT), which is used to treat the symptoms of menopause. HRT **increases** the levels of hormones in the body, whereas hormone therapies **decrease** hormone levels.

Types of hormone therapy

Two types of hormone therapy that are commonly used are:

1) Tamoxifen-　　For the treatment of women with hormone positive breast cancer. It can be used in women both before and after the menopause

2) Aromatase inhibitors, ex:anastrazole (Arimidex),

Exemestane (Aromasin), and Letrozole (Femara) - An addition or alternate to tamxifen for post-menopausal women with hormone positive breast cancer.

Tamoxifen has been commonly used in the treatment of hormonepositive early breast cancer for many years. Tamoxifen works by preventing oestrogen from signalling to cancer cells. Most women who are giventamoxifen take it for five years. The usual dose is one 20mg tablet, taken once a day. Treatment of ER+ breast cancer with tamoxifen for at least 5 years has been shown to reduce the rate of recurrence by approximately 40%-50% throughout the first decade, and reduces breast cancer mortality by about one-third throughout the first 15 years.[64] More recently, studies have shown that extended use of tamoxifen (10 years versus 5 years) further reduces the risk of breast cancer recurrence and mortality, so clinical practice guidelines now recommend consideration of adjuvant tamoxifen therapy for 10 years.[65-67]

PREVENTION

Healthy Lifestyle Modifications

Alcohol:

Many studies have proven that alcohol consumption increases the risk of breast cancer in women by about 7%-10% for each 10g (roughly one drink) of alcohol consumed per day on average [53, 54-56].Women who have 2-3 alcoholic drinks per day have a 15% greater chance of getting breast cancer than those who do not drink.One of the mechanisms by which alcohol increases risk of breast cancer is by increasing estrogen and androgen levels [57].Alcohol use has been more strongly related with increased risk for ER+ than ER-breast cancers [58, 59].

Body Weight: Women with heavy body weight have higher body mass index (BMI >25 kg/m^2).After menopause they have greater risk of arriving breast cancer than women with normal weight. Being overweight increases one'schance of recurrence [90, 91]. So reduce the weight and maintain the BMI <21 kg/m^2, which lowers the risk of getting breast cancer.

Physical activity&Exercise: The women who get involve in regular physical activities or exercise have a 10%-25% lower risk of breast cancer compared to women who are inactive or non-exercise with stronger evidence for postmenopausal than premenopausal women [52, 48-50].An American Cancer Society study describes that the breast cancer risk was 15% lower among women who reported walking 7 -9 hours per week or exercising 4-7 hours per week compared to women who had not walked and exercised 3 or less than 3hours per week [49].The benefit may be due to the effects of physical activity on body mass, hormones, and energy balance [51].

Diet: *Brassica (Cruciferous) vegetables*

Diet including cruciferous vegetables has the higher chances of reducing breast cancer. Cruciferous vegetables are belongs to brassica family which contain indole-3-carbinol, which helps in reduction of cell proliferation, increases apoptosis. Breast cancer risk may be reduced by 20-40% with 1-2 servings of cruciferous vegetables daily. [14, 15, 16]

Green Tea

Green tea is a polyphenol and natural aromatase inhibitor. Green tea ingestion of 3 cups or more per day in two studies reduced the risk of breast cancer.[17,18]

Calcium and Vitamin-D

The role of calcium in carcinogenesis derives from its involvement in regulating cell proliferation, differentiation, and apoptosis (26-28). The concentration of calcium is inversely proportional to the cell proliferation and induces differentiation of mammary cells in experimental studies (25, 29, and 30). In rodent models, high intake of calcium has been shown to suppress high-fat diet-induced epithelial hyper proliferation of the mammary gland and mammary tumorigenesis induced by 7, 12-dimethylbenz (a) anthracene (25). Vitamin-D compounds induces the apoptosis in breast cancer cells [27]. 1, 25(OH) 2D, a biologically active form of vitamin-D, expresses its activity mainly by binding to specific receptors [31]. Experimental studies have shown that 1, 25(OH) 2D regulates the cell proliferation and induces apoptosis in normal and malignant breast cancer cells [32-35].

Clinical practice points

Clinically breast cancer has different modes of treatments. Surgery, chemotherapy and hormone therapies, radiation are commonly used therapies to treat the breast cancer. In chemotherapy, anthracyclins like doxorubicin and paclitaxel are generally used compounds. In hormone therapy, tamoxifen and arimidex are the two compounds frequently used to treat the hormonal positive breast cancers. The above treatments including with radiation treatment are generally preferred at stage iii and stage iv levels of breast cancer. The above study signifies that prevention is key to reduce the burden of breast cancer. Regular exercise and physical activities, low alcohol intake, consumption of fruits and cruciferous vegetables in died, maintaining BMI > 21 kg/m2, avoid late night shift works, awareness of work place exposure to hazardous chemicals are some of the clinical points which might reduce the risk of breast cancer.

CONCLUSION

Breast cancer is a fast growing cancer in women in the world, the life expectancy of breast cancer patients decreases due to lack of awareness, improper treatment and not following the preventive steps. Increased awareness among women and improvement in diagnostic procedure, earlier detection of breast cancer may increases the long-term survival of patients. From this review article it is concluded that risk of breast cancer is reduced by following some preventive steps like doing regular exercises or yoga, physical activity, include brassica (cruciferous) vegetables and fruits in diet which contains many anti-oxidants, avoid alcohol intake, take green tea regularly and avoid smoking because the long term smoking also affect the risk of breast cancer. More research on the connection between workplace exposures and the risk of breast cancer is urgently needed, obtaining detailed occupational histories and tracking and understanding the impact of shift work is difficult to find. Workplace and governmental agencies should protect workers from occupational exposures to hazardous chemicals that adversely affect quality of life, shortens the life span of workers.Maintain higher levels of Calcium and vitamin-D which regulates cell proliferation, inhibits the growth of malignant breast cancer cells. In addition to use of chemotherapeutic and hormone therapeutic drugs, changing life style modifications and following preventive steps will reduces the risk of breast cancer.

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