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REVIEW ARTICLE

A REVIEW OF BREAST CANCER RISK FACTORS

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Abstract

Breast cancer is a commonly diagnosed neoplastic ailment in females particularly near menopause. This ailment signifies a substantial health problem as it has influenced a large number of women. Several risk factors are associated with breast cancer that cannot be altered, but certain can be modified. The existence of risk factors of breast carcinoma does not mean that cancer is unavoidable; numerous females having risk factors not ever developed the disease. The risk factors aid in identifying the females who may get help at maximum from screening or other precautionary measures. It is noteworthy that breast carcinoma can also ensue in females with no recognizable risk factors. The augmented occurrence of breast cancer worldwide revealed by several epidemiological investigations indicates the need of aiming multidirectional investigations so as to ascertain risk factors linked with the incidence of this disease.

Keywords: Breast cancer, cancer, incidence, occurrence, risk factors.

INTRODUCTION

Breast carcinoma incidence has been amplified than before universally[1]. Its existence has been rising in Asia and it is also recognized as the most widespread malignancy in Asian women[2]. Breast carcinoma in Pakistan is on top in Asia after Israel and it is also 2.5 times greater than that in various neighboring states[3]. In Pakistan, this cancer is among the topmost 20 reasons of deceases[4]. Breast carcinoma risk factors have been investigated and acknowledged in numerous researches[5,6]. It is probable that females surviving to 85 years of age would have a 1 in 9 lifetime chance of attaining this cancer but the amount of risk is inconsistent through the populace since some persons would not ever develop breast carcinoma while others would be at augmented risk[7]. Breast cancer is often diagnosed in females around menopause thereby reducing their capability to function normally in daily life. Researches done since over the years revealed that 20-30% of new cases of breast cancer might be related to the manifestation of different risk factors that actively start or modify the course of breast cells neoplastic transformation e.g. age above 40 years, family history in first-degree members, early menarche and late childbirth (after the age of 35 years), etc[8]. Even though various factors augmenting the risk of breast cancer incidence have been recognized, yet no risk factor is found in 75-80% of females[8].

RISK FACTORS

If the risk factors of breast carcinoma are present in an individual, it does not ascertain that cancer is unavoidable; numerous females with risk factors not ever attained breast cancer. However, the risk factors aid in identifying the females who can get help from screenings or further preventive processes. It is should also be remembered that breast carcinoma can also develop in females having no identifiable risk elements[9].

Types of Risk Factors

Various risk factors linked with breast cancer cannot be changed, but certain can be modified.

1. Non-modifiable risk factors are intrinsic; all of them institute independent factors and do not go through simple alteration in a person's life[10]. The ACS[11] includes non-modifiable risk factors for breast cancer e.g. gender, progressing age, genetic features, race, ethnicity, family history, dense breast tissue, certain benign breast conditions, previous chest radiations tobacco smoke, and exposure to diethylstilbestrol[4].
2. Modifiable risk factors are extrinsic factors; they may modify neoplastic course to a certain level. If

modifiable factors are identified then they may be helpful in developing prevention schemes thereby reducing breast cancer occurrence[10]. Lifestyle-related risk factors take account of the birth control, number of children given birth to, breastfeeding, hormone therapy, overweight or obesity, alcohol use and physical activity.

3. Controversial risk factors have uncertain, debatable or unconfirmed effect on the risk of attaining breast carcinoma i.e. diet and vitamin intake, induced abortions, chemicals in the environment, etc[11, 14].

Different risk factors of breast cancer are discussed as follows:

Standard risk factors

1. Gender

Breast cancer is very common in females and is 100 times as compared to the males[9].

2. Age

It is the primary, strongest risk factor and is proportional to risk[4] i.e its relationship with breast carcinoma is stated to be slighter in youngsters but then it surges as the age is more than 40 years[12]. Also, if the females of < 65 years of age are related with females having 65 years of age or more, the relative risk of breast carcinoma linked with increasing age is reported to be 5.8[7].

3. Education and Socio-Economic Status

These are considered as important aspects concerning the occurrence of breast cancer. Due to poorer education level and low SES, there are patients' deferments to seek medical support from the healthcare centers[13]. Those females who are educated and have a relatively higher SES, get more into contact and avail healthcare services and hence are recognized to be linked with breast cancer[14, 15]. This leads to reduction in mortality rates of breast cancer due to timely identification of the ailment and prompt commencement of its management[16]. It has also been reported that the females of higher socio-economic status with early menarche, late menopause and those who conceived in 30 years of age are at a greater risk of developing breast cancer[17]; also, women with more than 40 years of age with higher social class have greater risk[18]. As revealed in various investigations, this association is linked with the point that females in developed nations have on average lesser children, and also partial and infrequent period of breastfeeding[19]. Those women who have increasing age with middle class family background, greater body mass index and an increased ratio of incomplete pregnancies are at considerably greater risk of developing breast cancer[4].

4. Race/ethnicity

It is a very significant intrinsic element that raises the risk of breast cancer occurrence[10]. The degree of breast cancer is lesser in black females i.e.113 per 100,000; American Indians/Alaska inhabitants i.e. 92 per 100,000; Hispanic females i.e. 90 per 100,000; and it is lowermost in Asian Americans/Pacific Islanders i.e. 82 per 100,000[9]. Ban *et al.*,[20] examined the data incorporated in database of SEER (Surveillance, Epidemiology, and End Results) in his study, and found breast cancer occurrence in Caucasian females to be approximately 127.4 in 100 000 persons.

5. Weight

Body mass index has been linked to an augmented risk of breast carcinoma chiefly in postmenopausal femlaes[21,22] while a higher body mass index (BMI) is related to a diminished premenopausal breast cancer risk, though the process behind this relationship is unclear. Those women who are more active than others are at 15-20% decreased risk[23]. To study the association between BMI and breast cancer, 570,000 Norwegian females (aged 30 to 69 years) were enrolled and studied. The follow up was taken for 6 to 18 years regarding occurrence and consequences of breast cancer[24]. BMI was not observed as a risk factor for pre-menopausal breast cancer but in case of postmenopausal females, the relative risk of occurrence of breast cancer in the highest versus the lowest BMI quintile was 1.1 (in females from 55 to 59 years of age), 1.18 (in females from 60 to 64 years of age) and 1.22 (in females aged 65 to 69 years). Furthermore, a number of researches propose that greater BMI is linked with greater insulin and insulin-like growth factors levels that are related to enhanced breast cancer risk[25-27]. This is of exceptional significance in pre- and postmenopausal females since body fat accumulation in such ages is generally abdominal, and abdominal obesity is intensely linked with hyper-insulinemia which is a breast cancer risk factor[28].

6. Increased exposure of estrogen

a. Benign breast disease- Women may develop abnormal breast abnormalities due to proliferative lesions i.e. excessive progression of the glandular breast tissue or may have growths in fibrous tissue, ductal amplification, or non-proliferative lesions i.e. cyst formations. Females with a history of proliferative breast lesions have an enhanced risk for breast cancer, principally if there is atypical hyperplasia[9].

b. Breast density- Breast density is established as a strong and an independent risk factor of breast cancer[29]. Women whose mammograms show less dense breast have nearly 5 times lesser breast cancer risk. Estrogen-progestin treatment is linked with a rise in % mammographic density (% PMD) i.e. the proportion of the total breast area covered by dense tissue. Histo-pathological examination have revealed that widespread PMD is related to a larger number of cells and total nuclear area (inclusive of epithelial and non-epithelial cells) and an elevated quantity of collagen and glandular structures[30] leading to widespread percent mammographic density.

c. High bone density- Bone has estrogen receptors and is sensitive to levels of circulating estrogen. So, BMD (bone mineral density) is taken as a surrogate marker to circulating estrogen levels. Different studies instituted that females with a greater BMD have an enhanced breast cancer risk[9].

7. Other hormonal elements

a. Androgens- High testosterone levels in females are related to a greater breast cancer risk; some investigations proposed an enhanced risk for hormone receptor-positive ailment specially[9].

b. Insulin- High levels of insulin and growth factors related to the insulin pathway may affect breast cancer risk[9].

c. Menopausal hormonal therapy — If combined oral estrogen-progestin (specifically conjugated equine estrogens – CEE and medroxy progesterone acetate – MPA) [31] is used on long term basis i.e. for 5 years or more in females from 50 to 79 years of age then it escalates a female's risk of breast cancer and also stroke, heart disease and clots in legs. The risk of breast carcinoma on use of only estrogen for a short time does not appear to be increased[9].

8. Endogenous hormones

The presence of high levels of endogenous estrogen is a distinctive risk factor leading to a greater breast carcinoma incidence[10]. Post-menopausal females who have greater levels of testosterone and oestrogen are 2-3 times more at risk as compared to those having lower levels[32]. This was also confirmed by prospective studies that there is a substantial relationship amid higher concentrations of sex hormones (total estradiol, estrone sulfate, free estradiol, estrone, dehydroepian-drosterone, and rostenedione, dehydro epiandrosterone sulfate and testosterone) in postmenopausal females and greater risk of breast cancer[33]. Also, levels of circulating estrogens and androgens have been noticed in large cohorts of participants to play a significant part in the occurrence of breast cancer in premenopausal females[34,35]. A reduced risk of breast carcinoma was reported due to enhanced insulin levels in females who did not take hormone replacement therapy; likewise, insulin-like growth factor 1 is linked with risk of breast cancer positively[36].

9. Oral contraceptive pills

Oral contraception (OC) as breast cancer risk is controversial[10]; there is an insignificant rise in the risk of breast carcinoma owing to the usage of oral contraceptives[37]. The risk is greater for attaining breast cancer when HRT (combination of estrogens and progesterone) is used by females for ≥15 years[38] as compared to those who take oral contraceptives[39]. Hormone replacement therapy, whether estrogen or estrogen plus progestin, is found to be related to an increased risk of breast cancer[40,41]. By the use of hormonal oral contraceptives, risk of breast cancer was observed to be increased by 24% than in those females who have never used them[42]; the biggest incidence increase being seen during the use of contraception. On the contrary, a reanalysis of various investigations revealed almost no link between oral contraception and breast cancer risk[43]. The inconsistencies among analyses might be linked with formulation changes of oral contraceptives; besides, various formulations of oral contraceptives might be related to various breast cancer risks. It has been instituted that the risk of breast carcinoma falls considerably 10 years subsequent to discontinuation of hormonal treatment; it is independent of the length of their use[44]. The non-triphasic levonorgestrel preparations were not related to augmenting breast cancer risk[45].

10. Reproductive factors

Reproductive factors are also considered as risk for breast carcinoma.

a. Age at time of menarche and at menopause

In the mid 19th century, the average age of menarche in developed states was from 16-17 years to 12-13 years which was constantly linked with high breast cancer risk[46]. A woman undergoing menopause at age of 55 years would have 30% greater breast cancer risk than the one who gets it at age of 45 years[47]. Hence, both younger menarche age and mature menopausal age enhance breast cancer risk. This is probable in a woman's lifespan owing to the extended general estrogen exposure[9]. It was observed by by Brinton *et al*. that females having menarche before 12 years of age had relative risk of 1.3 in lieu of invasive breast malignancy than those after 15 years of age[48,27]. The females not experiencing menopause up to 55 years of age or later, presented a relative risk =1.22 than those who had it at less than 45 years of age[48]. Based on these findings, Vogel proposed that breast malignancy risk from such gynecologic variables is a function of number of ovulatory menstrual cycles that a female experiences through her lifespan[49].

b. Pregnancy and breastfeeding- Nulliparous females are more at risk to attain breast cancer than those who have given birth many times; the younger a female is at her first full-term pregnancy, the lesser her breast cancer risk[9]. This association is mostly concerned with postmenopausal females with hormone dependent (ER positive) breast cancer[42]. It has also been established that as compared to nulliparous females, the women having children have 30% reduced risk; with each full-term pregnancy, the risk falls overall by 7%[50]. Breastfeeding has been noted to be a protective factor against attaining breast[9] cancer- the lengthier the period, the more will be the safety. It is considered as an uncertain protective factor due to indecisive results but it is considered as a modifiable risk factor[51]. It was also established by the Brinton studies that breast cancer risk augmented for nulliparous female or if the first live birth at or after 30 years of age; relative risk for nulliparous female was 1.67 in comparison with one having first live birth at less than 20 years of age and the risk for the female was 2.23 with live birth at or after 30 years of age[52,53]. Moreover, not any protective outcome due to early gravidity was observed if it was not conceded to full term[52,53].

11. Personal history of breast malignancy

Previous history of malignancy in single breast leads to an augmented risk of cancer in the other[9]. There is a significantly greater risk for developing invasive breast cancer in those persons having a former account of invasive carcinoma, carcinoma in situ, or atypical breast hyperplasia. Most doctors have a preference to cope such cases with conservative therapy and close observation, while a small number of females at elevated risk may go for prophylactic mastectomy[54-57].

a. Family history- is an intrinsic factor that increases breast cancer risk about double, chiefly in first-degree affected family member i.e. mother or sister.

The risk further surges if two or more relatives are affected and also if the cancer is diagnosed below age of 50 years[58]. In general, < 10 % of all breast cancers are linked with inherited genetic mutations in one of two genes known as BRCA1 and BRCA2[9] (breast cancer susceptibility 1 and 2) accomplishing the functioning of tumor suppressor genes in cells[10]. These

two genes are established to be related to an inherited susceptibility to ovarian and breast cancers[60].

12. Lifestyle characteristics

Various modifiable risk factors linked with greater risk of breast cancer include:

a. Physical inactivity- is related to an enhanced breast cancer risk; physical exercise seems to be protective factor in both premenopausal and postmenopausal females though there is no direct confirmation[9]. More active females were reported to be at 15-20% reduced risk[61]. Further studies have demonstrated that regular physical activity (3-5 times a week) reduced 20-40% breast cancer risk, supported immunological system, improved health overall and also the quality of life[61].

b. Smoking- particularly in premenopausal females, both passive and active tobacco smoking have been related to an enhanced breast cancer risk. This risk is connected with early start, extended period, and/or greater pack-years of smoking[9]. An in vitro study revealed that cigarette smoke initiated neoplastic changes in breast epithelial cells[63]. There is miscellany in structure and biological activity of PAHs, therefore, all PAHs cannot lead to same grade of cancer. The metabolites of PAH can be more toxic than the parent compounds[64] rather only a mild positive and substantial link between second hand (passive) smoking and breast carcinoma risk was recognized[68,69].

13. Diet

a. Alcohol- Alcohol ingestion as little as 3 drinks a week has been related with a significant risk of breast cancer. The risk seems to rise with more alcohol ingestion and is additive with the usage of menopausal hormone treatment[9]. Several mechanisms have been suggested that might enhance breast cancer risk due to alcohol ingestion. These mechanisms range from stimulating the carcinogens' metabolism such as acetaldehyde to declining DNA repair efficacy or decreasing consumption of protective nutrients[49]. More than 6% breast cancers have been found to be alcohol-linked in UK. Breast cancer risk may rise by drinking even a minor quantity of alcohol since it influences the metabolism of estrogen in liver[9].

b. Dietary habits- Studies have revealed conflicting results regarding the link amid dietary patterns and risk of breast cancer[4]. There have been varying patterns of relation as risk for breast cancer due to use of dairy products. Cheese and milk are established to be linked with breast malignancy due to existence of insulin growth factor I and pesticides.

c. Intake of Dietary fat- An association has been seen in some researches between greater ingestion of dietary fat and breast cancer, even though the effect seems to be small on the whole[9]. There is convincing confirmation that high fat diet leads to obesity which is associated with breast cancer[11]. This may be an element stimulating the neoplastic transformation mechanism in breast cells. This association leads to an augmented risk of breast cancer incidence deprived of over expression of estrogen, progesterone or HER2 receptors, mainly observed in postmenopausal women in the period[42].

c. Red meat consumption- there may be an enhanced risk of hormone-positive breast cancer in premenopausal females if they consume more than 5 servings of red meat per week[9].

14. Environmental factors

Miscellaneous factors - There are certain compounds that are frail estrogens, very lipophilic, and having capability of persisting in body for ages i.e. organochlorines like dioxins, polychlorinated biphenyls and organochlorine pesticides like dichlorodiphenyl-trichloroethane (DDT). However, their relation with breast cancer has not been significantly established[9].

CONCLUSIONS

Breast cancer has been established as a common malignancy among females globally. Major risk factors of breast cancer take account of age, family history, socio-economic status, BMI, age at menarche and menopause, use of hormonal therapy, alcohol use, smoking, etc. Positive full-term gravidities and lactation have found to be protective elements. In general, a healthy diet and lifestyle may diminish the risk of attaining this disease. The risk factors may foretell the probabilities of developing this disease to a certain level. Knowledge and research is required in different geographical zones from time to time about the susceptibility elements in the inhabitants in order to prevent or treat and decrease its occurrence since all the established risk factors of breast cancer are not applicable in every area of the world due to miscellany of various elements.

AUTHOR'S CONTRIBUTION

Anjum F: designed the study. **Razvi N:** acquired the data. **Maqbool A:** analyzed the data and interpreted the results. **Jahan N:** drafted the article. All authors revised the article and approved the final version.

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CONFLICT OF INTEREST

No conflict of interest associated with this work.

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