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Review Article

Review on: relevance of breast cancer recurrence with body mass index or obesity

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ABSTRACT

Breast cancer is considered to be the second most life taking malignancy after lung cancer in the world. Some studies also show that changed lifestyle including alcohol and junk food is also increasing incidence or prevalence. Obesity is one of the side effects of the changed lifestyle so it can be a key to evaluate the relationship between obesity and breast cancer. Recurrence happens in about 40% of the breast cancer cases and is lethal too. Besides the treatments developed, breast cancer mortality still is increasing. Relationship of obesity and breast cancer is in such a way that obesity is not responsible for the causing of cancer but obesity can increase the risk of recurrence or improper treatment due to higher level of hormones which may directly or indirectly affect the pathways.

Keywords: Genetic predisposition, Atypical hyperplasia, Antiestrogens, Molecular marker, Procarcinogenic

INTRODUCTION

Breast cancer is a malignant tumor that causes highest morbidity and second highest mortality in females after lung cancer in the world. According to global statistics of Cancer, more than 2 million new cases of breast cancer were reported in 2018, with 11.6% new cancers accounted.[1]

According to the data of GLOOCAN 2020, Breast cancer is one of the most prevalent cancers and cause of enormous number of cancer-related deaths with an estimation of about 2.3 million new cases worldwide.[2] Approximately 88% more of these deaths due to breast cancer were prevalently reported in transitioning countries (The Caribbean, Melanesia, Micronesia/ Polynesia and Western Africa) in comparison to the transitioned ones (Australia/New Zealand, Northern America, Northern Europe and Western Europe).

In the last three decades, incidence of breast cancer has been increased. Breast cancer incidence has been doubled between 1990 and 2016 in 60 countries whereas deaths were doubled in 43 out of 102 countries.[3] According to the current projections, new cases diagnosed will reach at 2.7 million worldwide annually by 2030, and the number of deaths at 0.87 million.[4] Due to westernization of lifestyles in low- and medium-income countries, the incidence of breast cancer is expected to increase further (e.g., poor diet, lack of physical activity, low age at menarche, delayed pregnancies and reduced breastfeeding).[5,6]

The risk factors such as exposure to exogenous and endogenous estrogens (also include long term hormone replacement therapy), genetic predisposition, ionizing radiations, high breast density, low parity and a history of atypical hyperplasia are most important. Junk food intake obesity and alcohol consumption play role in rising of breast cancer incidence.[7,8]

In USA, the incidence of breast cancer is 1 in 8 women whereas in Asia it accounts 1 in 35 women. In Iran, 10 cases come in a population of 100,000 with 7000 new cases annually.[9] Its prevalence has been increasing in

Pakistan.[10-12] In the densely populated areas of South Asian developing countries, more incidence of breast cancer is found.[13-15]

At present, recurrence happens in around 40% of all breast cancer patients among which, almost all patients die.[16-18] In women, it is the most common cause of death due to cancer. Recurrence rate has been found to be highest during first 2-3 years and decreases afterwards but never reaches zero.[19,20]

Recurrence of breast cancer is proved to be more lethal but the causes are yet unknown. Some putative molecular markers are being investigated for their possible role in recurrence determination.[21]

MANAGEMENT OF BREAST CANCER

In modern medicine system, several medicines are present to treat breast cancer. Antiestrogens viz. raloxifene or tamoxifen are used to avoid breast cancer in people with high possibility of occurrence.[22] Higher probability of cancer development is also treated by surgery of both breasts as an additional preventative measure. Hormone therapy, chemotherapy, radiation therapy, surgery and targeted therapy are such strategies which have been implicated for the persons with breast tumor. Aim of managing individuals with distant metastasis is to enhance survival rate and life quality.[23] In one million new cases of breast cancer in the world, in Britain, one female gets breast cancer in twelve cases of cancer in age between 1-85 years. Out of all women cancers, breast cancer comprises 18% of the females.[15,24]

One of these treatments is natural which include herbal drugs that proved to contain anticancer properties.[25-29]

BREAST CANCER AND OBESITY ASSOCIATED RISKS

Relationship of obesity and cancer has been researched more for the past several years. Research is keep going but obesity is not considered to be a risk for the development of all type of cancers. But obese people are more prone to die of developed cancers.[30] It is also linked to greater risk of recurrence and mortality, data are less consistent though.[31-37] Obesity dependent poor outcomes may be seen strongly in breast, colorectal and prostate cancers. Current data suggest that it may be prognostic factor in other type of cancers also such as childhood leukemia.[38]

In several risk factors, risk of breast cancer due to obesity is found to be increased in postmenopausal not in premenopausal period.[39,40] In a study, obesity, overweight and mortality were examined for a period of 16 years, it was found that obese women with highest quintile of BMI had doubled risk of breast cancer when compared with women with lowest quintile of BMI.[41] Greater risk of lymph node metastasis, larger tumors and death were shown in obese breast cancer patients when compared with non obese ones.[41,42]

Breast cancer risk has been reported to increase with body weight only in postmenopausal women older than approximately 50 years. High BMI is often seen in postmenopausal women due to slower basal metabolism, hormonal alteration and reduced physical activity. They often have increased risk of some cancers.[43] In obese women, after menopause, level of estrogens increases in serum and peripheral site of hormone generation which cause hormone sensitive tumors. Adipose tissues contain aromatase which affect sex hormone level generated by peripheral site that sway breast carcinogenesis. Probability of reduction of efficiency of endocrine therapy due to obesity poses a possibility of increased efficiency in weight loss conditions.[44]

Primary tumors in obese post menopausal mice cause decreased vascularization which triggers hypoxia, neutrofil infilteration and EMT, which leads to expansion of TNBC/ Claudin-low tumors and increase in metastasis initiating cells.[45] This explains that obese patients have higher ratio of TNBC and higher metastasis incidence which challenge the notion of relevance between tumor cell extrinsic factors at secondary site and breast cancer patients. In obese women diagnosed with invasive breast cancer, there is also increased risk of recurrence due to BMI. Association between obesity and cancer becomes more strong if the analysis were obesity related or of second cancer or estrogen receptor related second breast cancer. Specifically obesity related cancer and estrogen receptor positive cancers examined first in this study.[46]

Obese patients found to have increased lymph node metastasis and larger tumors. But the tolerance of chemotherapy in obese patients was greater than non obese patients and they have less severe neutropenia.[47] In breast cancer patients, prognosis becomes poor due to obesity or high BMI which is also related to menopausal status. Diagnosis for disease free survival/overall survival is not being affected by obesity. It was found that breast cancer recurrence/ mortality and BMI are not associated with each other.[48,49] Survival of breast cancer patients found to be affected by obesity, overweight and decrease in PA. Inflammatory microenvironment, estrogen levels are reduced, antitumor immunity is increased with weight loss and exercising. Better outcomes ad reduction in breast cancer risk is also possible due to low BMI.[50] It was also observed that breast cancer is the reason of oxidative stress not obesity.[51]

In Arab women, obesity is common so they must be aware of healthier lifestyle due to the risk of breast cancer in pre and post menopausal women.[52]

It was concluded in a dose response meta analysis that 2% breast cancer risk increases with 5 kg/m^2 increase in BMI whereas in premenopausal women, higher BMI can probably be a protective factor in risk of breast cancer.[53]

In estrogen and progesterone receptor positive disease, risk of breast cancer increases post menopause due to obesity.[54] Some findings implicated for cancer survival and cancer preventions and found 7% increase in risk of cancer recurrence out of which 7.9% was attributable to BMI elevation which is similar to estimated 9.6% proportions of all cancers in women of US and attributable to elevated body weight.[55] It is also evident that obesity affects premenopausal breast cancer inversely.[56]

In obese patients, breast cancer can be progressive colorectal cancer survivors, obese patients shown to have higher risk of second cancer than the normal weight patients. Risk of second cancer in colorectal cancer survivors can be elevated due to obesity /overweight.[57]

A study based on 1049 patients with ongoing chemotherapy, it was concluded that obesity had no post diagnostic effect on survival or recurrence.[58] Pathogenesis of breast cancer is a long process which can be contributed additionally by obesity related dietary habits, dysregulation of metabolism or inflammatory pathways due to high levels of some factors such as adipokines, proinflammatory cytokines, estrogen and insulin related factors which also induce hypercholesterolemia and oxidative stress. Exact connection between obesity and breast cancer can be determined in the procarcinogenic effects could be neutralized.[59] In Taiwanese women, obesity is considered to be an influencial promoter of post menopausal breast cancers.[60] Obesity /overweight is associated with premenopausal breast cancer in Asian women.[61]

Development of breast cancer and post diagnostic outcomes. Secondary or tertiary prevention of breast cancer may be done with means of dietary interevent ions and be considered as adjunctive therapy component.[62] In general population of Brazilian women breast cancer prevalence was found high in obese patients. The patients were also having less frequent HER2 subtypes and luminal B and more infections post surgery mainly in HER2+, negative triple and HER2+ Hybrid than without obesity.[63]

Obesity is a risk factor for recurrent cancer, mortality rate in cancer and metastatic diseases. Only mortality in lung cancer and melanoma are reduced due to obesity (obesity paradox).[64] In Postmenopausal women, obesity is related to HER2-, ER+, Bcl-2+, PR+, Ki67low and p53-tumors.[65] In general postmenopausal female population of US, It was suggested that deaths due to breast cancer were 30-50% attributable to overweight/ obesity in reference to the lean or normal weight women.[66] It is though conflicting due to the emerging data, some show adverse effects due to obesity during administration of the ICIs at the standard dose whereas some suggest that there is no negative effect shown clinically of the high BMI.[67]

MOLECULAR LINKS OF OBESITY AND BREAST CANCER

Obesity is linked to postmenopausal breast cancer risk which is explained through molecular mechanisms. Every pathway of ligand or growth factor receptors is interconnected with each other and affect tumor formation or metastasis.[68] Evidences suggest that adipose tissues play role of endocrine sites of substances secretion which may be regulating immune responses, inflammations and cancer predisposition. Inflammation which is associated with obesity starts with macrophage infiltration into adipose tissues. Degenerated or necrotic adipocytes can be surrounded by macrophages and form crown like structures. These structures can be seen more in obese patients and their ratio seems to affect frequency of breast cancer recurrence and survival.[69]

Cancer specific mortality in obese women is more than non obese patients.[70] Adipokines, adiponectins, leptin and some other inflammatory cytokines are derived from adipose tissues which are recognized as metabolically active tissues. Increased levels of Leptins induce proliferation of breast tumor cells via various signal transduction pathways and alteration of checkpoints of cell cycle via cyclin D1 and CDK2 (cyclin-dependent kinase 2) upregulation.[71-73] In patients with obesity insulin resistance is found frequently which is in crosstalk with estrogen signaling pathaways.[74] Increased levels of insulin and insulin-like growth factors (IGFs) may also stimulate tumor proliferation, independent of sexual hormone pathways.[75,76]

High ORPS (obesity-related protein score) (PS5pre or PS4post) levels increase the risk of breast cancer and can predict breast cancer risk between obese and non obese women (Pre and post menopause).[77]

CONCLUSION

Breast cancer is considered to be the second most life taking cause after lung cancer in the world. Some studies also show that changed lifestyle including alcohol and junk food also contribute to the incidence/ prevalence. Obesity is one of the side effects of the changed lifestyle which can be a key to evaluate the relationship between obesity and breast cancer. Recurrence happens in about 40% of the breast cancer cases which could also be lethal. Besides the treatments developed, breast cancer mortality still is increasing. Relationship of obesity and breast cancer certainly leads to the conclusion that obesity is not largely responsible for the cause of cancer but obesity can increase the risk of recurrence or improper treatment due to higher level of hormones which may directly or indirectly affect the pathways.

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