Maria George *et al*. / *International Journal of Pharmacy & Therapeutics*, 7(3), 2016, 106-110.

e- ISSN 0976-0342
Print ISSN 2229-7456

International Journal of Pharmacy & Therapeutics

Journal homepage: www.ijptjournal.com

IJPT

OVERVIEW ON OBESITY AN ARISING RISK FACTOR FOR BREAST CANCER

Maria George[1], K. Krishna Kumar[1], Lincy George[1], K. Jayaprakash[1], L.Panayappan[2*]

[1]Department of Pharmacy Practice, St. James College of Pharmaceutical Sciences, Chalakudy, Kerala, India.
[2]St. James Hospital Trust Pharmaceutical Research Center (DSIR certified), Chalakudy, Kerala, India.

ABSTRACT

Obesity one of the chronic metabolic disorder, has become a major global health challenge, due to its high prevalence and provides a pathway for many of the chronic diseases including breast cancer. It is emerged as an epidemic in the developed and developing countries. Here we review the obesity its risk factors, complications and its pathogenic relation with breast cancer susceptibility and thus it provides multiple opportunities for its prevention and treatment. Poor food choices, sedentary lifestyle, physical inactivity, lack of sleep leads to obesity. So proper dieting and physical activity is needed for the weight loss and thus to improve patient compliance and there by quality of life. Recent reports showing that the obesity is a trigger factor for cancer, especially breast cancer. The main mechanisms that have been proposed as the potential producers of breast cancer in obesity are insulin, insulin like growth factor (IGF-1), sex hormones and adipokines. Along with diet and physical activity mechanisms like chronic inflammation, cross talk between normal and tumor cells, oxidative stress, migrating adipose stromal cells, obesity induced hypoxia, immunity problems are discussed. In this review article we stress on how obesity be a trigger factor for breast malignancies and also about the effect of dieting and physical activity in obesity.

Key Words:- Obesity, Adipokines, Breast Cancer, Physical Activity, Insulin Resistance.

INTRODUCTION

Obesity the silent killer is a global burden, which heightens the risk of several chronic diseases, including cancer, independent of sex, ages and socio economic groups. From various epidemiological studies it has been found that 20% of all malignancies are influenced by diet, body fat distribution and excessive weight. An increased BMI is associated with increased incidence of post - menopausal breast cancer. Recent researches showed that as BMI increases by 5 kg/m^2 then cancer mortality increases by 10%.Scientists have estimated that 7-15% of breast cancer seen in developed countries are due to obesity. Being a complex condition, the prevalence of obesity has doubled globally over the past few years. Urbanization and globalization results in dramatic change in the lifestyle and behavior of people which further leads to the emergence and progression of overweight and obesity. [1]Energy balance depends on food intake, storage and energy expenditure. If any alterations occurred in the energy balance which was regulated by hormones leads to cancer development. If overweight people are able to reduce their BMI by 1% equivalent to weight loss of 1 kg, leads to avoidance of many new malignancy cases (Karen B and Maria C, 2011).

Corresponding Author

L.Panayappan
Email:- stjamesdruginfo@gmail.com

Global Trends of Obesity and Breast Cancer Risk

Obesity prevalence rates have increased worldwide in the last three decades and Globally, India holds 3rd position and in India, Kerala stood 2nd position

in number of obese people. In India, morbid obesity in the 21st century has reached 5% of the country's population**.** India is just behind US and China in this global hazard list of top 10 countries with highest number of obese people (11 % of adolescents, and 20 % of all adults. Moreover, if recent trends continue, by 2030 up to 57.8% of the world's adult population could be either overweight or obese. Breast cancer is the 2nd leading cause of death in women exceeded only by lung cancer and is the commonest malignancy in women comprising 18% of all female cancers. About 3% death in women is due to breast cancer .Obesity is a controllable life style disorder, with regular exercise and healthy eating being the best ways to regulate body fat and to maintain a healthy body weight (K Mcpherson *et al.,* 2000; Cancer Prevention, 2015; NDA India, 2015)

Introduction of Breast Cancer Risk

As in menopause, the sex hormones level will came to decrease and thus leading to the production of these hormones from the fatty depositions .Age, the change in the location of fat deposits, the size and total amount of adipose tissue may explain the change in the shape of women after menopause, either gynecoid or visceral. During menopause, estrogen level diminishes, leading to fat migration from the hips, arms and thighs, and responsible for the higher susceptibility of post-menopausal women breast cancer. As years passes the number of obese patients are rising. As of 2010, the WHO estimated that at about 300-400 million adults were obese, while 1 billion were overweight. If nothing is done to reverse the epidemic, more than 1 billion adults are projected to be obese by 2030.There are several risk factors that are leading to breast cancer like age, geographical variations, hormone replacement therapy, oral contraceptives, family history, obesity…here we will look upon how obesity be a cause of breast cancer (Michael L, 2013).

Biological Mechanisms Linking Breast Cancer Susceptibility

Obesity had a great influence in the risk of breast cancer in postmenopausal obese women than normal weight women. There are several mechanisms that have been suggested to explain the causal link between the obesity and breast cancer risk, particularly the effects of metabolic syndrome and insulin resistance, peripheral estrogen aromatization in adipose tissue, effect of adipokines and so on. Obesity may also promote more rapid growth of cancer because of impaired cellular immunity. Several meta- analysis, systematic reviews, and large cohort studies have shown that obesity worsens breast cancer mortality.

DIET

The breast cancer is highly related to dietary intake. If excess caloric intake leads to altering the energy balance and will promote cancer cell proliferation .iIt is a main contributing factor for breast cancer. At the same time, limited long-term calorie intake has led to a decrease in cancer incidence and improves the quality of life. The low-fatty diets will decrease the risk and recurrence of breast cancer. According to the International Agency for Research on Cancer, there is sufficient scientific evidence that alcoholic beverages triggers breast cancer due to the increased estrogen levels. Consumption of high levels of monounsaturated fatty acids(MUFAS) also leads to post-menopausal breast cancer. Vitamin D is related to reduce risk of breast cancer and disease prognosis (Alcohol and cancer, 2012). In the Nurse's Health Study, a high dietary intake of calcium showed 33% lower risk of breast cancer, as calcium reduces cell proliferation and reduce the risk of benign proliferative epithelial disorders which are thought to be the precursors of breast cancer. Dietary fibers, fruits and vegetables may exert a protective effect in the development of several cancers through prevention of insulin-resistance, decrease in IGF-1 activity, decrease circulating hormones level and antioxidant, anti-proliferative activities, modulation of xenobiotic and hormonal metabolism and immunity (Paule L *et al.,* 2016).

Physical Activity

The women who exercise regularly equivalent of walking 3 to 5 hours per week after being diagnosed with breast cancer can improve their chances of surviving the disease, reduces the mortality and improve the quality of life. The physical activity decrease obesity by limiting fat content and promote body lean mass. The mechanisms for its beneficial effect is by decreasing the circulating levels of various hormones and growth factors, including decreased plasma levels of estrogens, insulin and IGF-1 .The level will increase with increased BMI and promote cancer development. Physical activity may also lower cancer risk by improving insulin sensitivity, stimulate immunity and by decreasing adipokine levels, oxidative stress and inflammatory markers (Paule L *et al.,* 2016).

Insulin Resistance

The hypothesis explaining the association between obesity and breast cancer is that of lower insulin sensitivity, as it leads to tumerigenesis by the abundant production of mitogenic insulin growth factor IGF1 critical to breast cancer. It also exerts proangiogenic

effects and induce tumor related lymphangiogenesis. Circulating C-peptide(cleavage product of pro insulin) levels and postmenopausal breast cancers are also correlated .Both insulin and IGF1 are believed to exert tumor enhancing effects by cell proliferation directly via binding to the insulin receptor(IR) and hybrid IR/ IGF-1receptor(IGF-1 R) on neo plastic cells. Due to increased tumour invasion, ligand-induced activation of the IGF-IR kinase results in the loss of epithelial integrity .IGF 1 mediates the metastasis and this mitogenic anti apoptopic environment caused by increased serum level of insulin and IGF 1 accelerates the genetic mutation and in metabolic syndrome, tissues are not able to absorb, store, and metabolize glucose efficiently. Therefore, to prevent elevated concentrations of glucose in the blood, the pancreas will secrete increasing amounts of insulin leads to hyperinsulinemia. Insulin signals through its receptors will activate tyrosine kinase signaling and a cascade of intracellular responses. Interestingly, type-2 DM in postmenopausal women is correlated with a slight increase in breast cancer risk. Reducing hyperinsulinemia and blocking IR/IGF-IR activation with a specific tyrosine kinase inhibitor ,decreases tumor burden (Hursting SD *et al.,* 2012; Darren LR *et al.,* 2010; Key TJ *et al.,* 200)

Sex Hormones

The postmenopausal risk of breast cancer increases in women with heightened levels of circulating sex steroids and low levels of sex hormone binding globulin. Endogenous sex hormones are active in tumor cell growth and directly mediate the effect of obesity on tumors of the breast. Mitogenic estrogens will, regulate the expression of insulin receptor substrate-1 (IRS-1) in the breast, and induce free radical-mediated DNA damage and genetic mutations in cells. Biological cause of the association between obesity and post menopausal breast cancer is the elevated circulating estrogens from peripheral aromatization of androgens in adipose tissue in obese postmenopausal women. It is also associated with metabolic syndrome results in circulating insulin and insulin like growth factor (IGF), and action is mediated by estrogen receptor pathway in breast cells. Together, IGF-I and estradiol increase the transcriptional activation of ER .Inhibition of MAPK(mitogen activated protein kinase) or PI 3-kinase pathways with specific inhibitor sabrogates the mitogenic effects of both IGF-I and estrogen in human breast cancer cells. SHBG ,an anti proliferative factor may bind to its specific site on MCF-7 breast cancer cells induces the second messenger cAMP and causes a complete inhibition of estradiol –induced MCF-7 cell proliferation, and the loss of which in obese women could contribute to tumerigenesis (Lorincz AM *et al.,* 2006)

ADIPOKINES

When the adipose tissue expands, adipocytes enlarges and produces chemotactic factors like monocyte chemoattractant protein (MCP 1). It will attract the macrophages .Along with adipose tissue dysfunction, production of adipokines, inflammatory cytokines and decreased production of adiponectin leads to the accumulation of fatty acids. Adipocytes produce certain hormones called adipokines that they stimulate or inhibit cell growth. Leptin is abundant in obese and promote cell proliferation whereas adiponectin the abundant adipokine have anti-proliferative effects. It also has direct and indirect effects on other tumor growth regulators, including mammalian target of rapamycin (mTOR) and AMP activated protein kinase. Adiponectin increases insulin sensitivity directly by stimulating tyrosine phosphorylation of insulin and also protects from insulin resistance by activating 5"AMP activated protein kinase (AMPK) (Rob CM *et al.,* 2013). In obesity, there is over secretion of deleterious proinflammatory molecules like interleukin-6 (IL-6), tumour necrosis factor- (TNF-), leptin, resistin, retinol binding protein-4, plasminogen activator inhibitor-1 (PAI-1), hepatic growth factor (HGF), and hyposecretion of beneficial adipokines such as adiponectin and visfatin. Human adipose tissue macrophages resemble human tumor-associated macrophages and play an important role in cancer cell survival by increasing the expression of FAS in cancer cells.The mitogenic, proinflammatory, anti-apoptotic, and proangiogenic factor leptin foster cancer development, as it upregulates oestrogen signaling and intensifies the expression of aromatase, oestrogen production . However, breast tumour cells proliferate after leptin stimulation. Blocking cancer-stromal cell communication may well be a strategy to target breast cancer therapy, and, interestingly, it has been shown that leptin drives tumor progression by a bidirectional crosstalk between breast cancer cells and cancer-associated fibroblasts. Breast cancer risk was much lower in postmenopausal women with elevated adiponectin level. Obesity is correlated to chronic inflammatory response, with abnormally high cytokine production and the activation of pro inflammatory signaling pathways. The chronic inflammatory state in obesity might be important in the initiation and promotion of cancer cells (Giovanni D *et al.,* 2013).

Cross Talk between Tumor Cells and Surrounding Adipocytes and Migrating Adipose Stromal Cells

Tumor metastasis results from the crosstalk between tumor cells and the "normal" cells which surround them. In breast cancer, mature adipocytes are

part of the breast cancer tissue and thus contribute to cancer progression and modify breast cancer cell behaviour. It has been proposed that evolving bidirectional crosstalk is functional between breast cancer cells and tumor-surrounding adipocytes, and that the tumor-modified adipocytes are actively involved in tumor progression (Giovanni D *et al.*, 2013).

Fig 1. Relationship between obesity and breast cancer

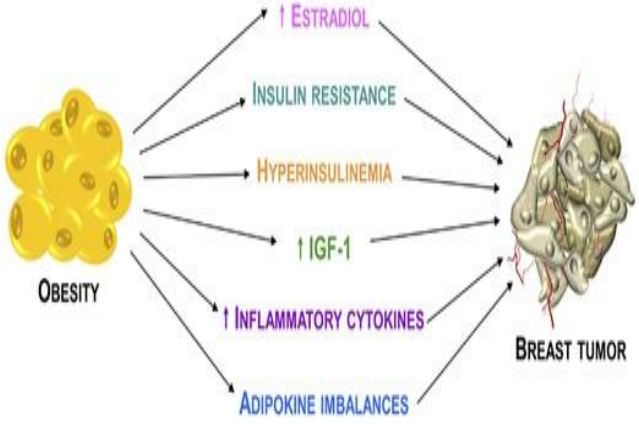


Fig 2. Relationship between obesity and breast cancer. Principal mechanisms through which the obesity condition may promote breast cancer development and progression.

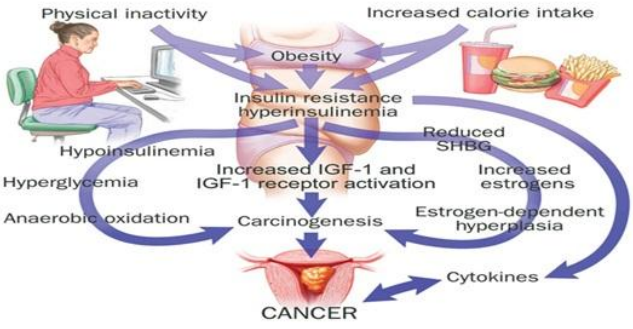
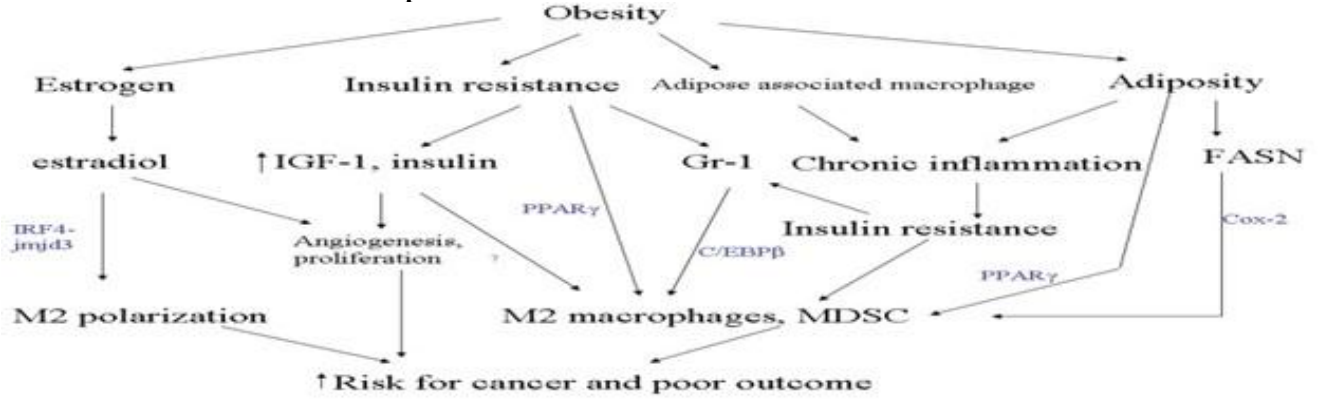


Fig 3. Crosstalk between components of obesity and MDSC and M2 induction. Different aspects of obesity, namely elevated estrogen, increased insulin resistance, increased inflammation secondary to recruited adipose tissue macrophages and adiposity employ a variety of mechanisms, all of which coalesce on M2 macrophage and MDSC induction to facilitate cancer development.



CONCLUSION

The prevalence of overweight and obesity is increasing at an alarming rate throughout the world. Life style factors are also a leading cause of cancer like high fatty food, rich carbohydrate foods, less intake of fruits, vegetables, fibers, lack of exercise, sedentary life style, as these all leads to obesity. There is a relation between abdominal obesity and cancer, it increases the cancer mortality risk up to 24%..Obesity results from over-nutrition, low physical activity, change of dietary habits, urbanization, or metabolic disturbance. The defining metabolic changes in obesity are decreased glucose tolerance, decreased sensitivity to insulin, hyperinsulinemia and reduced life expectancy. In adipose tissue, obesity is associated with increased aromatization of circulating androgens to estrogens and reduced levels of sex hormone binding globulin, thereby increasing estrogen level. Therefore, studies designed to measure both estrogen and progesterone levels in breast tissue and identify the determinants of these levels are needed To treat obesity, restricting food intake and engaging in physical fitness are necessary. Although exercise can help a patient reach a target weight, dietary restriction and control may be more effective for the treatment of obesity. In addition better screening, early detection, awareness on treatment options will be able to reduce the annual incidence of breast cancer.

ACKNOWLEDGEMENT

None

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

Body Weight and Cancer Risk Excess body weight: A major health issue in America ;. Cancer Prevention & Early Detection Facts & Figures. *American Cancer Society*, 2015, 1-10

Darren L, Caroline D, Andrew G. Biological Mechanisms Linking Obesity and Cancer Risk: New Perspectives. *Annual Review of Medicine Clinical and Experimental Pharmacology*, 61, 2010, 301-316.

Giovanni D and Franco S. Obesity as a Major Risk Factor for Cancer. Journal of Obesity Department of Biomedical Sciences and Human Oncology. *Section of Internal Medicine and Oncology*, 1, 2013, 1-11.

http://www.cancer.gov/about-cancer/causes-prevention/risk/obesity/obesity-fact-sheet.reviewed on Jan 3, 2012

Hursting SD, Digiovanni J, Dannenberg AJ, Azrad M, Leroith D. Obesity,Energy balance And Cancer. *New Oppurtunities For Prevention*, 5(11), 2012, 1260-72.

Karen B and Maria C. Obesity and Cancer Risk: Recent Review and Evidence. *Current Oncol Rep*, 13(1), 2011, 71–76.

Key TJ, Appleby PN, Reeves GK, Roddam A W. Insulin Like Growth Factor 1(Igf1),Igf Binding Protein 3(Igfbp3) And Breast Cancer Risk:Pooled Individual Data Analysis Of 17 Prospective Studies, Endogenous Hormones And Breast Cancer Collaborative Group. *The Lancet Oncology*, 11(6), 2010, 530-42.

Lorincz AM and Sukumar S. Molecular Links Between Obesity And Breast Cancer. *Endocrinology Journals.org*, 13, 2016, 279-292.

Mcpherson K, Steel CM, Dixon JM.ABC Of Breast Diseases Breast Cancer-Epidemiology,Risk Factors,Genetics. *British Medical Journal*, 321, 2000, 624-628.

Michael L. A Literature Review of Role Of Obesity In Adult Health With Reference To Africa. *African Journal Of Food, Agriculture , Nutrition and Development*, 13, 2013, 1-17.

Paule L, Vanessa C, Nathalie D, Fabrica H, Marina T, Mathilde T, Marie P. Alcoholic Beverages, Obesity, Physical Activity And Other Nutritive Factors And Cancer Risk;A Review Of Literature . *Critical Reviews In Oncology/Hematology*, 99, 2016, 308-323.

Rob CM, Van Kruijsdijk, Elsken van der Wall ,Frank LJ. Visseren. Obesity and Cancer: The Role of Dysfunctional Adipose Tissue. *American Journal of Cancer*, 3(1), 2013, 21–33.

www.ndaindia.com assessed on 9th April 2015.