INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com ISSN 2230 – 8407
Review Article

OBESITY RELATED TO DIFFERENT TYPES OF CANCER: A REVIEW

S. Asha Devi* and S. Babu
Division of Biomolecules and Genetics, School of Biosciences and Technology, VIT University, Vellore-632014, India

Article Received on: 14/03/12 Revised on: 20/04/12 Approved for publication: 10/05/12

*Email:devi_asha@reediffmail.com

ABSTRACT
Obesity is a complex disease caused by the interaction of myriad genetics, dietary, lifestyle and environmental factors which favours a chronic positive energy balance leading to increased body fat mass. There is an emerging evidence of strong association between obesity and different types of cancer. These include breast cancer, prostate cancer, pancreatic cancer, ovarian cancer, endometrial cancer, gastric cancer etc. The mechanisms linking both the diseases are not fully understood. We have therefore assembled the review evidence on obesity and different types of cancer. The review includes all the population based studies that assessed the association between overweight BMI 25-29.9 and obesity (BMI>=30), a cohort studies was conducted among post menopausal women to determine whether genetic polymorphisms in selected obesity related genes that may cause breast cancer. This review paper presents the existing knowledge about how obesity can enhance different types of cancer and focusing on therapeutic, molecular mechanisms for obesity and different types of cancer.
Keywords - Obesity, BMI, Estrogen, Glucose intolerance, Hyperinsulinemia, SHBG, mTOR.

INTRODUCTION

Obesity is defined as abnormal excessive fat deposition that causes risk to health. Body mass index (BMI) between 25-30kg/m square is considered as overweight and BMI with 30kg/m square is defined as obesity[1]. It is a multifactorial disease caused by the interaction of myriad genetics, dietary and an environmental factor which enhances positive energy causing increase fat body mass[2]. There is emerging evidence between the relation of obesity and cancer. The concept of relation between obesity and deregulated metabolism was first given by Otto Warburg. In 2002 International agency for research on cancer (IARC) scientist predicted the link between obesity and different types of cancer[3,2]. Recently American cancer society has performed studies based on BMI, height and weight. It has been seen that the relative risk for cancer death is estimated in men as 4% and 14% in women for BMI greater than 24.9 due to obesity[1]. Other epidemiological studies also suggests that the association of different biological agents such as adipokines, cytokines, mainly adipose tissue, sex steroids and hormones like estradiol, signalling molecules such as PTAB1 are associated with obesity and shows relative risk for different types of cancer [4,5].

Energy balance in obesity

The concept of energy balance involves equilibrium between caloric intake and energy utilization. Energy expenditure includes basal metabolism, physical activity and adaptive thermo genesis. Physical activity term includes all the involuntary movement, while basal metabolism includes all the complex biochemical process necessary to sustain life and adaptive thermeogenesis refers to energy released in the form of heat in response to environmental changes such as diet, chemicals or exposure to cold. (Fig 1) The fundamental cause of overweight or obesity is positive energy expenditure over a prolonged time leading to increased BMI including the deposition of subcutaneous and visceral fat. Obesity is a major cause for insulin resistance, leptin resistance and also leads to dysfunctional adipose tissue that leads to cancer[2]. Energy imbalance is related to obesity which is involved in different types of cancers. IARC and other epidemiological studies have suggested obesity shows risk factor for developing different types of cancers. These include breast cancer[6], pancreatic cancer[7,2], ovarian cancer[8], gastric cancer[9], prostate cancer[10] etc. Dysfunctional adipose tissue is also one of the reasons for causing cancer in obese people. Management of obesity is the best way to prevent cancer in humans[2].

Breast cancer

Breast cancer is the second most common cancer among postmenopausal women. Obesity constitutes 50% for breast cancer in postmenopausal women. Various studies have shown the interaction between the body size and the risk for breast cancer differs according to the menopausal status[6,2]. It has been shown that BMI and body weight is positively related to the breast cancer and also seen associated with hormonal changes and adiposity[6,11]. The androgenic steroids are converted to estrogens in presence of enzyme aromatse. This enzyme is largely expressed by premenopausal women in ovaries but after menopause it is produced in adipose tissue which is the principle site for estrogen production where aromatization occurs in both ovaries of menopause women and the adrenal glands secrete estrone. Estrogens have positive association with obesity[6,11,12]. Estradiol has higher affinity for estrogens receptor (ER) than estrone[6,1]. Normally it circulates as non protein bound fractions. Approximately 30-50% of estradiol tightly bound to SHBG (sex hormone binding globulin) which make it non-functional, so providing high amount of estrogen[13,14]. Both plasma estrone and estradiol are elevated and contributes for breast cancer in obese menopausal women. SHBG is inversely related with body weight and BMI. Ovulation and low levels of progesterone is also one of the responsible for developing breast cancer in obese women. Genes encodes obesity such as PPARG, LPL, and TNF alpha shows high polymorphism that leads to breast cancer. Since obese women have larger breast and tumour detection is difficult in these women, as tumour are more difficult to palpate in larger breast. Thus obesity is one of the major reason for developing breast cancer[4,11,12].

Pancreatic cancer (PC)

Pancreatic cancer (PC) is one of the dangerous malignant cancers with worst prognosis. The prevalence of PC is higher in American men than in women. It has been diagnosed 37000 people with PC and 34000 men have been died due to

this disease. In 2007, a meta-analysis of 21 prospective studies was conducted including 3,495,981 individuals and 8,062 PC cases which reveal positive association of obesity with pancreatic cancer[2]. Recently the women health initiative conducted a prospective cohort studies in 138,503 postmenopausal women[3]. The result obtained shows that women with highest quintile value of waist to hip ratio constitutes 70% for the relative risk of PC compared with women in the lowest quintile. This suggests that obesity, especially central adiposity, is positively associated with the increased risk of PC[2,7]. Obesity is related with insulin resistance, hyperinsulinemia, glucose tolerance and with subsequent development of type II diabetes[3,11]. Metabolic consequence of central obesity leads to insulin resistance which induces increases in secretion of insulin from pancreas[2,3]. Increased insulin production leads to hyperinsulinaemia which leads to insulin resistance. The development of insulin resistance is one of the major causes of obesity and is related to impaired glucose metabolism, chronic inflammation, oxidative stress, decreased adiponectin and PPAR gamma key regulators[3]. For adipogenesis altered regulation of cytokines, adipokines leads to insulin resistance in obese people, abnormal glucose metabolism even in absence of diabetes leads to PC. Several studies have demonstrated that levels of fasting plasma glucose, abnormal glucose metabolism and degree of insulin resistance are highly associated with PC. Adiponectin and leptin are the most abundantly expressed adipokines secreted by adipocytes. Adiponectin is negative regulator of diabetes, high level can cure type II diabetes and low level leads to insulin resistance and finally development of PC[2,3]. Chronic inflammation is also one of the major causes for pancreatic cancer. Obesity induced chronic inflammation leads to adipose tissue dysfunction that regulates local inflammatory response which include macrophage infiltration, insulin and leptin resistance, increased production of TNF-alpha, IL-6 and IL-1 which are linked to chronic inflammation. So by reducing weight all these biomarkers get decreases and thus reduce the risk for development of PC[4]. (Fig 2)

Endometrial cancer

There is emerging evidence that obesity is strongly related with endometrial cancer. The risk of developing endometrial cancer is 2 to 3 fold higher in obese woman than in normal weight woman[2]. It has been estimated 40% of endometrial cancer is caused due to increase in circulating estrogen. The factors which cause endometrial cancer include menopause, history of infertility, obesity, polycystic ovarian syndrome, colon cancer and western lifestyle[2,14].

Colorectal cancer

Colorectal cancer is the 3rd most common cancer in the world. Prevalence includes 10 fold higher in developed countries than in developing countries. Many cohort studies demonstrated a positive association between obesity and related risk for colorectal cancer development[2]. Different studies has also determined that waist circumference and waist/hip ratio are also strongly related to higher risk of colorectal cancer and large adenomas in men supported by European body weight and BMI associated with colon risk in men but not in women. Increased consumption of animal meat especially red meat is also one of the risk factors of colorectal cancer[15].

Esophageal cancer

Obesity is related with 3- fold increase in risk for adenocarcinoma of the esophagus. Quantitative analysis by 12 case-control studies and 2 cohort studies confirms the link between obesity and risk of esophageal cancer. High BMI is associated with gastro-esophageal reflux and frequent reflux is very strongly associated with esophageal adenocarcinoma. Thus, the increased in gastro-pharyngeal reflux itself is a major risk factor for esophageal cancer[2].

Prostate cancer

It is the commonly diagnosed cancer in men. More than 40 cohort studies including prospective and case control studies show the positive association between obesity and prostate cancer[2]. Waist to hip ratio also shows the major integration of obesity with prostate cancer. In addition to obesity and its related diseases, lines of evidence indicate that adiponectin may influence cancer pathogenesis. Adiponectin has been shown to inhibit cell proliferation and induce apoptosis in leukemia cells in vitro and to suppress tumor growth. However, direct effect of adiponectin on solid tumour cell growth has not been reported but clinical evidence indicates that plasma adiponectin levels are lower in patients with prostate cancer and negatively associated with the histological grade and disease stage. Recently it is reported that prostate cancer cells express mRNA of AdipoR1 and AdipoR2 cell surface receptors for adiponectin. These findings lead to a hypothesis: adiponectin inhibits prostate cancer cell growth[10]. To determine adiponectin receptor expression in prostate cancer, neuro endocrine expression was evaluated by western blot analysis with anti NSE antibody. The membranes are separated and re-hybridized with anti GAPDH antibody to normalize sample variation. Now MTT and LNCaPFGc cells were introduced in 96 well plates 24 h prior to serum starvation and then incubated in serum free medium with and without cytokines, DHT and MTT was added to a concentration of 0.5 mg/dl. After being incubated at 37ºC optical density was measured at 530 to 670 nm and on performing velocity sedimentation determines that adipokines can inhibit the growth of cancer cells. Therefore it serves as a biomarker for the treatment of prostate cancer[10].

Other types of cancers

Other types of cancer such as ovarian cancer, gastric cancer, stomach cancer etc shows the positive interaction of obesity with cancer. Obesity a risk factor of ovarian cancer remains in debate. Statistical analysis is done to detect the effects, mainly for histological subtypes of ovarian cancer. The statistical studies included all population-based studied which has association between overweight, body mass index [BMI], obesity and histological confirmed ovarian cancer[3,13]. Overweight/obesity in early adulthood was also associated with an increased risk of ovarian cancer. A positive relationship observed between obesity and gastric cancer[9]. However, its association is not well understood; therefore a systematic review and meta-analysis of published cohort studies were carried out to identify the relationship between excess body weight and gastric cancer. Recently studies were conducted on the basis of meta-analysis to determine the association of cervical cancer and obesity which shows a positive association. But still some evidence is needed[3,9].

Environmental and other factors

Lifestyle and other factors influence obesity may causes cancer. A tobacco smoke contains mutagens such as polycyclic aromatic hydrocarbons and nitrosamines; this mixture constitutes a complete carcinogen. So smoking is a risk factor for several types of cancers, mainly lung cancer and cancers of the upper aero digestive tract and also, to a certain extent, for esophagus, stomach, pancreas, liver, bladder, kidney and cervical cancers, as well as myeloid leukemia. Excess weight and obesity indirectly contribute to

cancer genesis through a progressive accumulation of environmental chemical carcinogens in the adipose tissue. Accumulation of lipophilic xenomolecule in adipose tissue leads to death of adipocytes through apoptosis or necrosis, leading to the release of toxic compounds into the plasma and also xenomolecules can favour obesity by stimulating adipose tissue lipolysis. Imbalance diet such as fast food, lack of physical activity leads to cancer. Alcohol causes depletion of detoxifying of CYPRE1 that leads to carcinogenesis[3]. PTP1B is a signal transduction which is highly expressed in obese individual. It shows negative regulation of oncogenic signaling through the dephosphorylation of PTKs such as IGF-I, EGF, PDGF. Over expression of PTP1B was found in epithelial carcinomas cells and the expression of PTP1B mRNA in carcinoma cells shows how obesity is related with cancer[15,16]. Dietary factors communicate the risk of type 2 diabetes which is actively involved in breast cancer, pancreatic cancer, endometrial cancer etc. A dietary fat changes the fat composition in membranes which impairs the insulin binding due to decrease in insulin binding receptors[13,17]. The environmental carcinogens such as organochlorine pesticides, polychlorinated biphenyls are lipophilic and get accumulated in adipose tissue, which causes cancer[18]. Adipokines impairs the endocrine and paracrine process of adipose tissue. Lipids gets deposited in drops, on exposure of fatty acids to cells it causes metabolic dysfunction[16]. Diet rich in fibers, fruits and vegetables can prevent type2 diabetes thus indirectly it can prevent cancer. AkT and mTOR a signalling molecule can prevent cancer by energy availability and growth factor supply which affects the cancer cells. mTOR is activated by AkT and inhibited by AMP kinase. mTOR makes translational control on new proteins which influences cancer, which leads to availability of growth factors and energy requirements. Therefore active mTOR inhibits cancer.

Increase in physical exercise can prevent obesity and cancer[19]. There is a complex association between obesity and different types of cancer. Many meta analysis and different cohort studies has shown the prevalence of obesity related to cancers. On activating mTOR energy balance and many growth factors is produced which can prevent cancer. It is clearly shown how adiponectin can inhibit prostate cancer. Many of the cancers such as ovarian cancer, gastric cancer and cervical cancer are not well understood. Insulin resistance and type2 diabetes is one of the main reasons for causing pancreatic and breast cancer. It has also been shown that breast cancer is mainly seen in obese menopause women. So all these condition shows the role of obesity in different types of cancer.

DISSCUSION

The enlargement of adipose tissue could highly contribute for the onset and development of cancer through deregulated metabolism and impaired secretion of proinflammatory cytokines, chemokines and adipokines. But more investigation is needed to understand its molecular mechanism which can provide therapeutic way to prevent cancer. Reducing Weight can decrease the incidence of mortality of cancers. The analysis of dietary factors, signaling molecules such as PTAB, mTOR molecule that affects some proteins and provide energy balance to reduce weight gain. So by consuming balance diet, physical exercise, lose weight can reduce cancer effect. The association between obesity and cancer is not well understood so studies should continue to analyse obesity and cancer. Thus cancer can be prevented in obese people by maintaining diet, such as consumption of fibre rich diet, fruits and vegetables, reducing fat rich diet such as red meat, fast food, high physical exercise and weight lose plan. These can reduce risk for cancer with obesity. More studies are needed to analyze the elevated risk factors for cancer with obesity.

REFERENCES

1. Anthony P. Estimating the number of U.S. incident cancer attributable to obesity and the impact on temporal trends in incidence rates for obesity-related cancers. Cancer detection and prevention 2008; 32: 190-199.
2. Pedro LPH, Pérez-Matute P, Fernández-Galilea M, Matilde B. Role of obesity associated dysfunctional adipose tissue in cancer. A molecular nutrition approach. Biochemica et Biophysica Acta 2011;1087: 664-678.
3. Irigaray P, NewBy JA, Clapp LH, Howard V, Montaginer L, Epstein S et al. Cancer: influence of life style –Related factors and environmental agents causing cancer, an overview. Biomedice and Pharmacotherapy 2007; 61: 640-658.
4. Lisa G, Meghan AM, Han-yao H, Kathy JH. Body mass polymorphism in obesity related genes and the risk of developing breast cancer among women with benign breast disease. Cancer detection and prevention 2007; 31: 95-107.
5. Nadia D, Michel LT. Involvement of the small protein tyrosine phosphatases TC-PTP and PTP1B in signal transduction and diseases from diabetes, obesity to cell cycles and cancer. Biochemica et Biophysica Acta 2005; 1754: 108-117.
6. David PR, Linda VD. Interaction between menopausal status and obesity in affecting breast cancer risk. Maturitas ; 66: 33-88.
7. Bin B, Zhiwei W, Yiwei LDK, Shadan A, Sanjeev B, Aamir A. The complexities of obesity and diabetes with the development of pancreatic cancer. Biochimica et Biophysica acta 2011; 1815:135-146.
8. Catherine MO, Adele CG, David CW, Shaharam SFK, Phenolype MW. Obesity and the risk of epithelial ovarian cancer, a systematic review and metaanalysis. European Journal of cancer 2007; 43: 690-709.
9. Ping Y, Yong Z, Bo C, Hong WW, Gui QJ, Hai-long B et al. Overweight, obesity and gastric cancer risk: Result from metaanalysis of cohort studies. European Journal of cancer 2009; 45: 2867-2873.
10. Jeffery DB, Ioshiaki M, Yoshiki I. Adiponectin as growth inhibitor in prostate cancer. Biochemical and biophysical research communications 2006; 340: 1158-1166.
11. Pichard C, Plu-Bureau.M, Neves EC, .Gompel A. Insulin resistance obesity and breast cancer risk. Maturitas 2008; 60: 19-30.
12. Amitabh R, Katai JN, Joseph PG, Margot PC. Diet induced obesity and mammary tumour development in relation to estrogen receptor. Cancer letters 2007; 253: 291-300.
13. Trond MM, Are HP, Serena T, Claes GT, Anne D. A metabolic syndrome after risk and reducing salphingo oophorectomy in women at higher risk for hereditary breast ovarian cancer. A controlled observational study. European Journal of cancer 2005;45:82-89.
14. Fiana L, Robert E, Judith B, Zoya Y, Barbara S, Anna L, Emanulla I. Endometrial hyperplasia, endometrial cancer and prevention gaps in existing research of modifiable risk factors. European journal of cancer 2008; 44: 1632-1644.
15.Thorling EB. Obesity, fat intake, Energy balance, Exercise and cancer risk A review, Nutritional research 1996; 16: 315-368.
16. Stoeckli R, Keller U. Nutritional fats and the risk of type 2 diabetes and cancer. Physiology and Behaviour.2004; 83:611-615.
17. Sorenson TIA, Virtue S, Vidal Puig A. Obesity as a clinical and public health problem; Is there a need for a new definition based on lipotoxicity effects? Biochemica et biophysica Acta 2010; 1801400-404
18. Renato P. Obesity, fat distribution and infertility. Maturitas 2006; 54: 363-371.
19. Stephen DH, Laura ML, Lisa HC, Nomeli PN, Perkins N. Reducing the Weight of cancer Mechanistic Targets for breaking the obesity – carcinogenesis link. Best practice and research clinical Endocrinology and metabolism 2008; 22: 654-669.

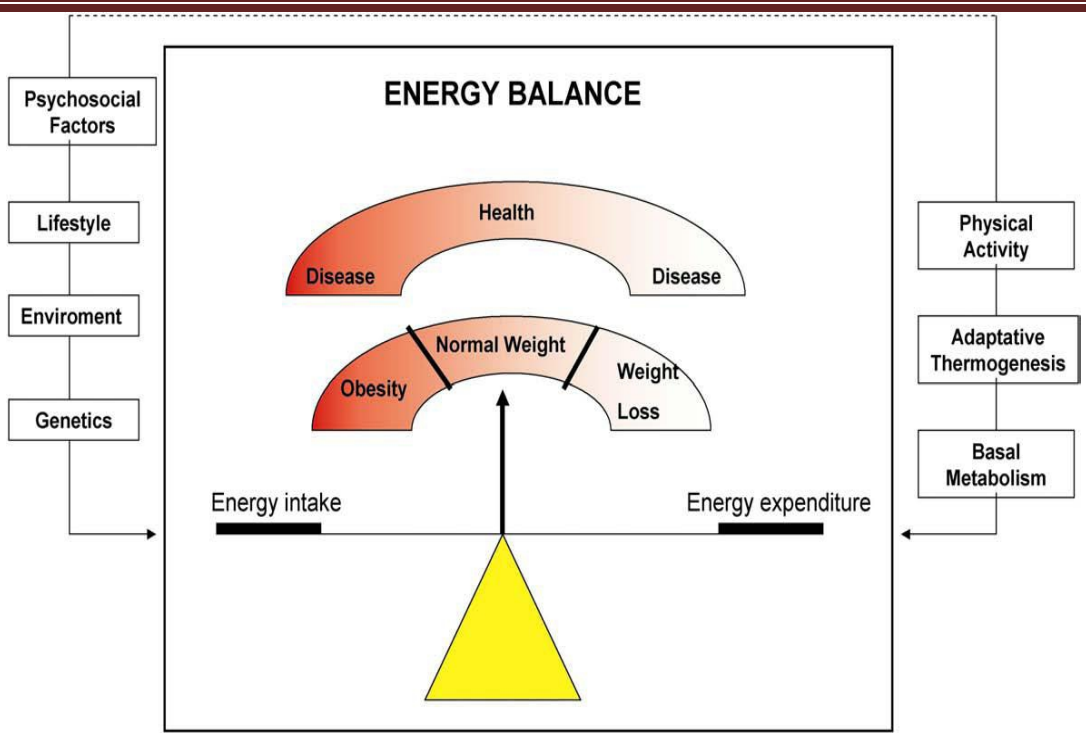

Figure 1: Energy balance

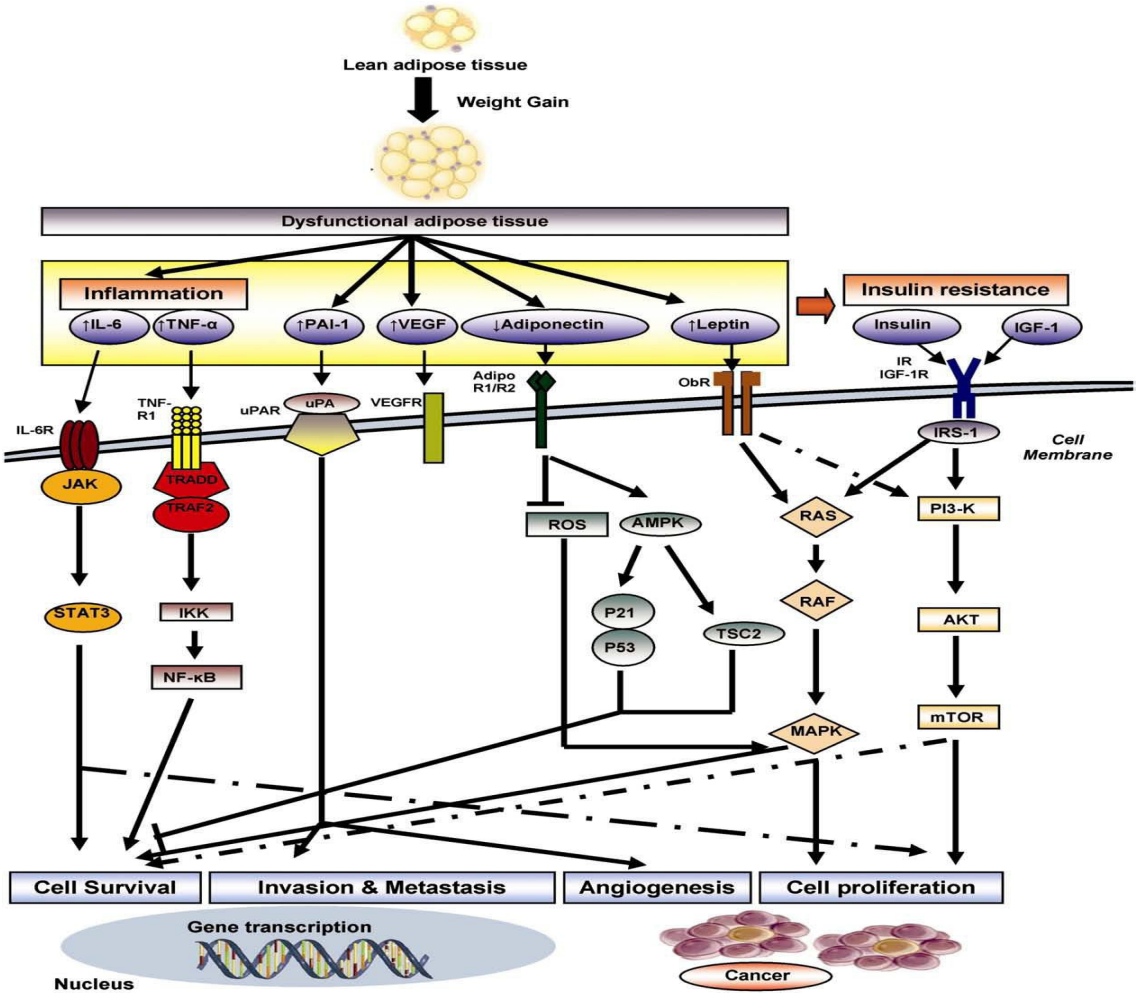

Figure 2: Dysfunction of adipose tissue