OBESITY: A CAUSATIVE RISK FACTOR OF BREAST CANCER

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Background. Obesity, a global health burden and one of the most deleterious diseases have substantially increased prevalence attributable to changing lifestyle of modern times. Persuasive evidence indicates obesity as an independent prognostic factor for developing malignancy in the form of breast cancer particularly in post-menopausal women.

Objective. This review aims to focus in comprehensive manner on the biochemical, hormonal and immunological pathways governing the obesity linked breast cancer so that potential treatments may be improvised consequently to provide a cure to this menace, threatening the lives of many.

Methods. Literature review of published materials that provide examination of recent or current literature on problem of obesity.

Results. Increased body fatness, mainly visceral adiposity may account for predisposing an obese individual to the risk of encountering cancer although the mechanisms for such cancers may vary depending upon the organ affected. Metabolic and biochemical alterations influencing obesity related carcinogenesis, consisting of heightened oxidative stress and bodily inflammation levels with the concomitant rise in pro-inflammatory cytokines are discussed. Pertinent references about elevated levels of serum insulin, insulin-like growth factor, sex steroids and the imbalance in adipokines (adiponectin and leptin) are included as well.

Conclusions. Persuasive evidence indicates obesity as an independent prognostic factor for developing malignancy in the form of breast cancer particularly in post-menopausal women. Generation of novel and effective therapeutic interventions for combating the ailment along with positive lifestyle modifications may be improvised consequently to provide a cure to this menace, threatening the lives of many.

KEY WORDS: obesity; breast cancer; lipotoxicity; adiponectins.

Introduction

Obesity is a major health problem of this century, characterized by excess accumulation of fat due to positive energy balance, resulting from energy intake that exceeds the energy expenditure [1]. A 15-20% of body fat for men and 25% of body fat for women are generally accepted as ‘normal’, but these are not essentially the optimal values, as a 10% to 20% of excess body fat over the usual values is generally considered to be “obesity” [2].

According to the World Health Organization (WHO) criteria, a BMI greater than or equal to 25 kg/m² is overweight, while obesity is defined as having a BMI equal to or higher than 30 kg/m².

Obesity has been recognized, as a major risk factor for many cancers and, following tobacco use, may be the greatest modifiable cancer risk factor [3, 4, 5]. The incidences of overweight and obesity is dramatically rising in most parts of the world, and is generally higher in women than in men [6]. Convincing data associate being overweight to the risk for various types of cancer as well as other chronic ailments, including cardiovascular disease, stroke and diabetes that are accountable to a large percentage of premature mortality [7, 8]. The International Agency for Research on Cancer reviewed the literature on the involvement between excess body weight and cancer risk. They evaluated the available data as sufficient for a plausible connection with cancers of colon, female breast (postmenopausal), endometrium, kidney (renal cell), and oesophagus (adenocarcinoma). Preliminary information also exists to indicate a relationship with ancillary cancer [9, 10]. Specifically, obesity is related with a twofold increase in the risk of developing breast cancer in case of postmenopausal women while among premenopausal women it is associated with a reduced incidence [11]. Numerous
interacting hormonal and metabolic pathways seem to underlie the link between being overweight and cancer, with insulin-resistance harbouiring a major role. Since evidence is swelling that surplus body weight can also unfavourably influence cancer prognosis, obesity is a prime target for cancer management programs. This review explores the epidemiological and biological evidences concerning the linkage between excess body weight/obesity and particularly cancer in the breast in females, available from several accessible and thorough systematic literature surveys, along with a brief insight into the probable therapeutic interventions in vogue.

**Obesity Related Health Disorder**

Now a day’s obesity and overweight are considered as main causative factors for several chronic diseases, most notably hypertension, type 2 diabetes, dyslipidaemia and coronary heart diseases, osteoarthritis and muscular-kkeletal disorders, fatty liver, gall stones, psychologiscal disorders and psychosocial problems [12, 13]. Direct relationship of obesity with mortality has also been documented [14]. Among its many health consequences, obesity is increasingly recognized as a risk factor for numerous malignancies, and the obesity-cancer link has recently received much attention [15,16]. Sufficient evidences exist to link obesity with increased risk of colon cancer, postmenopausal breast cancer, endometrial cancer, renal cell cancer and adenocarcinoma of the oesophagus [17].

**Obesity and Cancer**

World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) concluded that obesity is an established risk factor for several cancers [18]. According to the reports of the last 25 years, obesity was found as a reason of approximately 14% of cancer deaths in men and up to 20% of deaths due to cancer in women [19]. Over this time-period, the commonness of overweight and obesity has gone up from 15% in 1980 to 35% in 2005 [20]. Recent investigations count on the fact that the total health onus of overweight and obesity may surpass that for cigarette smoking [20]. A major review of weight, physical activity, and cancer incidence by the International Agency for Research on Cancer (IARC) concluded in 2002, that obesity was the aetiology of 11% of colon cancer cases, 9% of postmenopausal breast cancer cases, 39% of endometrial cancer incidences, 25% of kidney cancer cases, and 37% of oesophageal cancer incidences [17]. Additionally, data from the American Cancer Society indicated, that overweight and obesity are connected to mortality from liver cancer, pancreatic cancer, non-Hodgkin’s lymphoma, and myeloma [19].

**Obesity and Cancer – General Mechanism**

The cause effect relationship of obesity and cancer are not well known. However, it is well established that it acts through obesity-related hormones, growth factors, multiple signalling pathways of calorie restriction and modulation of energy balance and inflammatory processes. These factors affect the promotion and progression of the cancer cells [21, 22, 23, 24, 25, 26].

**Obesity and Breast Cancer**

Obesity has been marked as a noteworthy risk factor for breast cancer and the association varies depending upon the menopausal status in females. Breast cancer, as evident from the recent estimates is the most frequent type of cancer in women (28.9% of all female incident cancers) of European population and is the second most common cancer overall [27, 28]. Obesity is found to consistently rise in postmenopausal women by 30%-50% [29, 30, 31, 32]. Breast cancer incidence varies considerably between developed and developing countries which may be attributed to nutritional factors and lifestyle behaviours due to different socioeconomic conditions and variation in ethnicity [33]. Literature clearly indicated the intimate association between obesity and breast cancer that might provide insight in exploring and identifying the various mechanisms involved in this process. Obesity linked breast cancer is multifactorial and involves a network of hormonal and metabolic pathways. Hence understanding the molecular and cellular mechanisms of the obesity-cancer link is imperative for developing potential therapeutics.

**Mechanisms Underlying Obesity Related Breast Cancer in Females**

**Bio-energetic homeostasis and cancer**

Metabolic parameters associated with body fatness might influence the bioenergetic balance of the cells and favour the expansion of cells with high anaerobic glycolytic capacity which is a characteristic feature regarding the bioenergetics adaptation of the cancer cells. This effect is termed as “Warburg effect” described by intense lipogenesis and glycolysis and low mitochondrial oxidative phosphorylation capacity even in the presence of adequate oxygen [34, 35]. High blood glucose
levels and hyperinsulinaemia, which is frequent in obese individuals, are thought to pose a selective advantage for the growth of such cells [36]. Increased risk of breast cancer attributed to higher energy intake has been reported in some research studies [37]. Adenosine 5′-monophosphate activated protein kinase (AMPK) is a master sensor of cellular energy status that plays a key role in the regulation of whole-body energy homeostasis [38]. Recently, studies were conducted to examine targets such as AMP activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), fatty acid synthase, deacetylase SIRT1 (sirtuin1) and epigenetic modulators as in nutrient sensing pathways coupled to insulin signalling have been hypothesized to participate in carcinogenesis [19].

**Insulin, IGFs, IGFBPs and Insulin resistance – the interplay**

Insulin resistance is a metabolic state characterized by a reduced response capacity to insulin by the muscle and liver cells [10]. Insulin resistance has been correlated to a subsequent compensatory excess production of pancreatic insulin leading to hyperinsulinaemia. Chronic hyperinsulinaemia in turn is related to carcinogenesis and linked to breast cancer [39, 40]. This can be explained in the light of the postulates of insulin-IGF hypothesis, which states that chronic hyperinsulinaemia decreases the production of Insulin like growth factor binding proteins (IGFBP1 and IGFBP2) that results in the subsequent rise of plasma levels of free IGF-1 with concomitant alterations in the cellular environment. Both insulin and IGF-1 are anabolic molecules that are capable of tumorigenesis by inhibiting apoptosis, stimulating cell proliferation and motility and being pro-angiogenic [41, 42, 43, 44]. High concentrations of circulating total IGF-1, a major determinant of free IGF-1 concentrations have been associated to an increased risk of premenopausal breast cancer [45]. However, the insulin-IGF hypothesis has two shortcomings. First, levels of total IGF-1 increases linearly with increased BMI but only up to a certain extent around 27 kg/m² and thereafter it reduces with further increase in weight [44]. Secondly, in overweight and/or obese individuals, who purposely lose weight (a presumed cancer-protective action), the total IGF-1 concentration tends to escalate the insulin-signalling pathway. This is very much relevant in case of cancer progression because both extracellular signal regulated kinase (ERK) and phosphatidyl inositol-3 kinase (PI3K) pathways are triggered by activation of the insulin receptor (IR). Contrarily, over expression of the IR is evident in breast cancer patients [10, 46, 47, 48, 49]. Insulin and IGF-1 signal by mean of the Akt/PI3K/mTOR cascade for promotion of cell growth and proliferation, thereby inhibiting cell survival [50, 51]. This Akt/PI3K/mTOR cascade has emerged as a target of the obesity and cancer linkage and is activated by both insulin and IGF-1 that are detected frequently at higher concentrations in the serum of the overweight and obese individuals, culminating [52, 53, 54].

**Alterations in sex hormones**

Steroid hormones including oestrogen, progesterone, androgens and adrenal steroids are related with energy homeostasis and obesity related progression of different types of male and female cancers [55]. Obesity increases the risk of developing breast cancer after menopause and it has been indicated that up to 50% of postmenopausal breast cancers are linked to obesity [37]. Predisposing risk factors familiar in developing breast cancers are related to oestrogen e.g., early menarche, late menopause and hormone replacement therapy (HRT) [56, 57, 58, 59]. Obesity and age has been ascertained as factors that may negatively influence the survival of patients with breast cancer [60,61]. Increased adiposity may influence sterol synthesis and metabolism of oestrogens. Obesity has been associated with increasing levels of oestrogen because of accelerated peripheral aromatization of adrenal androgens in adipose tissue among postmenopausal women, that can promote cell proliferation, have anti-apoptotic and pro-angiogenic effects [62,63]. In postmenopausal women, plasma levels of free oestradiol and testosterone are positively associated to breast cancer occurrence [64]. Studies revealed that the relationship between obesity and breast cancer risk in postmenopausal women might be justified by heightened levels of oestrogens, particularly bioavailable oestradiol [65, 66]. Further, in case of postmenopausal women the link between body mass index (BMI) and risk of breast cancer has been strongly evident among women, who do not use hormone replacement therapy (HRT), compared to women, who have undergone HRT [67]. Some studies showed an inverse relationship between BMI and pre menopausal breast cancer and this may be supported by the fact that for pre menopausal women obesity is linked with a higher frequency of anovulatory cycles and with reduced levels
of circulating sex steroids [67]. Another dimension to the association between BMI and breast cancer is mammographic density, the latter being negatively correlated with BMI. For adjustment of mammographic density, estimates for BMI, cancer risk rise [68].

**Lipotoxicity**

Cancer cells exhibit accentuated de novo lipogenesis by means of elevated fatty acid synthase (FASN), an enzyme responsible for synthesizing endogenous fatty acids, that may be modified and packaged into structural lipids required for cell division [69]. Both obesity and cancer cell-derived lipolytic enzymes produce free fatty acids for the tumour to supply structural as well as oncogenic lipid signalling molecules such as platelet activating factor (PAF), sphingosine 1-phosphate (S1P), lysophosphatidic acid (LPA) and prostaglandins [70]. Elevated FASN enzyme, mRNA, and enzymatic activity have been documented in human breast cancer cell lines and the rise in FASN is thought to be essential for evoking the malignant effects of proliferation and survival although this alone is not the reason for malignancy [71]. Thus elevated basal lipolysis followed by increased plasma levels of free fatty acids (FFAs) leads to enhanced intracellular accumulation which can impair non-adipose cells in their normal role as well as insulin signalling and the phenomenon is known as “lipotoxicity” [72].

**Obesity induced immunosuppression**

Obesity induces chronic, low-grade inflammation leading to increased levels of local and systemic proinflammatory cytokines including prostaglandin E2 (PG E2), tumour necrosis factor-alpha (TNF-α), interleukin (IL-2, IL-8, IL-10), C-reactive protein (CRP) and monocyte chemoattractant protein (MCP-1). In this context activation of NF-κB complex may be cited as a possible mechanism by which inflammation may stimulate cancer progression [24,25]. Thus, the proinflammatory state evident in the metabolic cells of adipocyte and the recruitment of immune cells along with the consequent release of inflammatory cytokines (TNF-α, IL-6, adiponectin etc.) is the outcome of obesity.

**Tumour necrosis factor–α or TNF-α**

A pro-inflammatory cytokine by nature TNF-α exerts several effects in adipose tissue encompassing lipid metabolism and insulin signalling in which the circulating levels are elevated with obesity and levels off with weight loss. A rise in TNF-α stimulates the secretion of other pro-inflammatory cytokines like IL-6 while decreasing the levels of anti-inflammatory cytokines like adiponectin [73]. Research findings indicated that TNF-α promoted adipocytes apoptosis and induced insulin resistance by means of inhibiting the insulin receptor substrate 1 signalling pathway [74,75].

**Interleukin–6 or IL–6**

Macrophage is the preliminary source of circulating IL-6 that plays a pivotal role in the whole-body energy homeostasis, as well as inflammation. The fact that IL-6 has the potential to suppress the activity of lipoprotein lipase has been deduced from both in vitro and in vivo studies. Expression of IL-6 receptor is evident in certain brain regions and hypothalamus being one of them is responsible for controlling appetite and energy intake [76].

**Adiponectin**

Contrary to the reduced levels of adiponectin as seen in cases of animal models of obesity and insulin resistance, weight loss has been found to elevate the adiponectin levels. Regulation of lipid and glucose metabolism, increased sensitivity towards insulin, body weight and food intake regulation and protection against chronic inflammation are some of the vital roles of adiponectin [77].

**Intracellular pathways of inflammation**

Overfeeding has been hypothesized to be the starting signal of inflammation in obesity and the pathway has its inception in the metabolic cells like the adipocyte, hepatocyte or myocyte. Acute evocation of inflammatory responses due to consumption of nutrients has been suggested from studies in mice and humans [78,79]. Adipose tissue and liver in obese men and women, when compared to lean controls, exhibit hyperactivation of three kinases, namely: the c-jun N-terminal kinase (JNK), the inhibitor of K kinase (IKK) and the protein kinase R (PKR) capable of inducing inflammatory cytokines’ expression [80,81]. The inflammasome and the Toll-like receptors (TLRs) of the innate immune system are activated as well in those same metabolic tissues [82, 83, 84]. Inflammatory signals or nutrients may trigger off the TLRs pathways and downstream JNK, IKK and PKR. These kinases control downstream transcriptional programs by means of the transcription factors activator protein-1 (AP-1), NF-κB and interferon regulatory factor (IRF) inducing upregulation of inflammatory mediator gene expression. The rise in cytokines aggravates receptor activation through a positive feedback loop of inflammation and the inhibitory signalling of metabolic pathways [85].
Dysregulation in adipokines

The adipose tissue, known primarily as an energy storage organ, by virtue of recent studies has also been established as an endocrine organ, producing and secreting polypeptide hormones, adipokines, among which leptin and adiponectin are most common and involved in cancer development [86]. Adipokines (leptin, adiponectin and hepatocyte growth factor (HGF) are recognized for their participation in the mechanisms by which obesity and related metabolic disorders affect breast cancer risk [87]. The physiological and pathological communications of leptin and adiponectin are mostly antagonistic, as are their biological consequences on breast cancer cells [88].

Leptin, a hormone essentially exclusive to adipose tissue acts centrally in the hypothalamus for regulation of body weight and peripheral energy expenditure [87, 89]. Circulating leptin levels are strongly correlated to the body fat content and are prominent in obese subjects to normal individuals [90, 91, 92]. Thus leptin, a potential mediator of obesity-related cancer influences cancer progression by activating PI3K, MAPK and STAT3 pathways, while the stimulatory effects of leptin on breast cancer growth were noted to occur primarily via oestrogen receptor activation [21, 26, 88, 93, 94]. Further, evidences through extensive research suggest that adiponectin, the most abundant adipokine, affect the proliferation and insulin sensitivity of various types of cells [95]. Unlike leptin, adiponectin is inversely related with adiposity, hyperinsulinaemia and inflammation [22]. Moreover, adiponectin may incur anticancer effects by diminishing insulin/insulin like growth factor (IGF-1) and mTOR signalling via activation of 5' AMP-activated protein kinase (AMPK) and providing anti-inflammatory action by the inhibition of nuclear factor kappa-light chain enhancer of activated B cells (NF-κB) [22]. Current findings indicate that the low serum adiponectin levels are significantly associated with an increased risk for breast cancer and that tumours arising in women with the low serum adiponectin levels have greater likelihood of expressing a biologically aggressive phenotype [95]. Another adipokine, hepatocyte growth factor (HGF) or 'scatter factor' may exert a positive influence on tumorigenesis as a consequence of its anti-angiogenic properties but is mainly known for its ability to promote cell invasion [88]. Numerous investigations revealed that the serum concentration of HGF are often elevated in patients with breast cancer and particularly so in those suffering from the advanced disease stage [96, 97, 98].

Conclusions

The striking association between obesity and incidence of breast cancer has been established through several investigations and experiments until date. The various metabolic and endocrine mechanisms that account for the pathogenesis of obesity linked breast cancer have been discussed here to further probe into the nodal points of control in these cascades that may be beneficial to the researchers for generation of novel and effective therapeutic interventions for combating the ailment along with positive lifestyle modifications. Currently hormonal therapy with selective estrogen receptor modulators (SERMs) (such as tamoxifen and raloxifene) as well as aromatase inhibitors (such as exemastane, anastrozole, and letrozole) has been approved as standard mode of treatment of women with estrogen receptor-positive breast cancer. This therapy alongside adjuvant therapy acts in curing of advanced disease form though issues relating to their side effects are also a major concern [99, 100]. The efficacy of another drug which acts as an insulin lowering agent named metformin, in reducing breast cancer recurrence is presently being studied extensively [101, 102, 103]. Simultaneously in the recent years Yoga based lifestyle interventions that is a form of physical activity facilitating in accomplishing recommended levels of physical fitness have gained much attention and are found to effectively thwart and hinder the progression of cardiovascular and metabolic syndromes like that of obesity [104, 105]. The method of action of such benefit may be credited to a reduction in weight and stress, networking at mind and body levels, thereby leading to a decline in inflammation, and causation and progression of the disease [106]. Thus, any further information about the drugs and other treatment modalities that can ameliorate the adverse effects of breast cancer by altering the markers of obesity may also be useful in this regard.

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ОЖИРІННЯ – ФАКТОР РИЗИКУ РАКУ МОЛОЧНОЇ ЗАЛОЗИ

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Вступ. Ожиріння – це глобальна проблема здоров’я, що набула значної поширеності зі зміною сучасного способу життя. Також це незалежний прогностичний фактор розвитку раку молочної залози, особливо у жінок в період постменопаузи.

Мета огляду – комплексний аналіз біохімічних, гормональних та імунологічних чинників, які пов’язують ожиріння з раком молочної залози, та пошук потенційних методів лікування.

Методи дослідження. Аналіз даних літератури для оцінки поточного стану проблеми.

Результати. Надмірна вага, та головним чином накопичення вісцерального жиру, пов’язані з підвищеним ризиком розвитку злоякісних захворювань, однак механізми їх розвитку значно варіюють залежно від ураженого органу. Обговорюються метаболічні та біохімічні показники, що впливають на канцерогенез, пов’язаний з ожирінням; включно з розвитком оксидативного стресу та ознак запального процесу з одночасним підвищенням рівня прозапальних цитокінів. А також такі фактори як підвищений рівень сироваткового інсуліну, інсуліноподібного фактора росту, статевих стероїдів та дисбалансу адипокінів (адипонектину і лептину).

Висновки. Переконливі докази вказують на ожиріння як незалежний прогностичний фактор розвитку раку молочных залоз, особливо у жінок після менопаузи. Розробка нових ефективних терапевтичних заходів для лікування раку та модифікація стилю життя можуть забезпечити позитивні зрушення.

КЛЮЧОВІ СЛОВА: ожиріння; рак молочної залози; ліпотоксичність; адипонектини.

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