

MINI-REVIEW

Overweight, Obesity, Oxidative Stress and the Risk of Breast Cancer

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Abstract

There is growing scientific evidence linking excess body weight to breast cancer risk. However, there is no common consensus on this relation due partly to methodologies used, populations studied and the cancer subtype. We report here a summary of the present state of knowledge on the role of overweight and obesity in pathogenesis of breast cancer and possible mechanisms through which excess body weight might influence the risk, focusing on the role of oxidative stress in breast cancer etiology. The findings demonstrate duality of excess body weight action in dependence on menopausal status: a statistically significant increased risk in postmenopausal overweight/obese women and non-significant preventive effect among premenopausal women. Due to several gaps in the literature on this topic, additional studies are needed. Future research should address factors influencing the excess body weight - breast cancer relationship, such as race/ethnicity, tumor subtype, receptor status, the most appropriate measure of adiposity, reproductive characteristics, and lifestyle components.

Keywords: Breast cancer - excess body weight - oxidative stress

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Introduction

Breast cancer (BC) is the most frequently diagnosed cancer in women worldwide. According to global cancer statistics, 1.38 million cancer cases (692,200 in developed and 691,300 in developing countries) accounting for 23% of all new cases of cancer worldwide, occurred in 2008 (Jemal et al., 2011). Also, 458,400 total BC deaths was estimated in this year. Incidence rate depends on the world region due to differences in race/ethnicity, reproductive and hormonal factors, physical inactivity and obesity. According to Moore's and Sobue's statement "The prevailing view is that the majority of cancers are due, very largely, to the environment, with only some 5-10% being primarily related to genetic abnormalities" (Moore and Sobue, 2009, p. 149). The prevalence of obesity is high and still increases. For example, using projection models it is suggested that in 2030 a number of obese adults will be higher by 65 million in comparison with 2010 (Wang et al., 2011). In 2008, 1.46 billion of overweighted (including 502 million obese) individuals was reported in analysis of epidemiological data from 199 countries (referred to Wang et al., 2011). As reviewed by Withrow and Alter (2011), the economic costs due to obesity are estimated to be 0.7-2.8% of the total health-care costs depending on a country. According to the World Cancer Research Found and the American Institute Cancer Research statement, there is convincing and consistent evidence that body fatness is positively correlated with the incidence of BC (WCRF/

AICR, 2007). However, the biological mechanisms by which body fatness becomes a risk for cancer development are not fully known. The hypothesized pathways include increased concentrations of endogenous hormones and inflammation (Renehan et al., 2008). An increased concentration of oxidants, in particular reactive oxygen species (ROS) and reactive nitrogen species (RNS) exceeding the antioxidant defense system capacity (so-called oxidative stress) leads to chronic inflammation (Durackova, 2010; Liou and Storz, 2010; Reuter et al., 2010; Nourazarian, et al., 2014). There is rapidly growing evidence that chronic inflammation is a factor leading to tumor development and progression. Furthermore, high concentrations of ROS have been measured in a majority of cancer cells (Liou and Storz, 2010; Valluru et al., 2014).

There is a lack of universal consensus on the relationship between obesity and BC risk. The strong positive correlation of postmenopausal obesity with BC risk was reported in previous and recent papers (e.g. Carmichael and Bates, 2004; Lahmann et al., 2004; Phipps et al., 2012; Xu et al., 2012). However, a few studies demonstrated a lack of this association (e.g. Cecchini et al., 2012; Ogundiran et al., 2012). Some authors suggested that BC risk is more associated with abdominal adiposity than with a BMI value (Harvie et al., 2003).

This article summarizes the most important conclusions available from the recent research, whether excess of body weight is associated with the risk of BC, and includes the actual state of knowledge on role of reactive oxygen

Overweight, Obesity and BC risk.

Obesity is a serious worldwide problem that affects of hundreds of millions of people; over 500 million adults were obese and 958 million overweight in 2008 (Chan et al., 2014). Body mass index (BMI) is used to recognize and determine obesity. According to Wang et al. (2011) categorization, BMI<25kg/m² presents not overweight, BMI=25-29.9kg/m² - overweight, and BMI≥30kg/m² corresponds with obesity. Carmichael and Bates (2004) describes BMI<20kg/m² to underweight, BMI=20-24.9 - to desirable weight, BMI=25-29.9 to overweight, BMI=30-39.9 - to obesity, and BMI≥40kg/m² - to morbidly obesity. Several factors contribute to obesity, like genetic, lifestyle (e.g. physical inactivity, unhealthy diet), metabolic, environmental, socioeconomic, and psychological (Dobbins et al., 2013). Matusitz and McCormick (2012) have analyzed the impact of Internet on children and adults obesity in the United States. They suggest that the obesity epidemic in the USA is positive correlated with Internet use, and that "sedentaris" may cause physical inactivity, what, in turn, increases obesity. Obesity increases the risk of several chronic diseases including cancer (Calle and Kaaks, 2004; Renehan et al., 2008). Epidemiological studies have shown that obesity causes about 20% of all deaths from cancer in women and 14% deaths in men (de Pergola and Silvestris, 2013). Wang et al. (2011) suggest that prevalence of obesity among adults are expected to increase by about 11 million in the UK and 65 million in the USA by 2030 and that additional cases of cancer (492000-669000) will present due to obesity. Further, they have estimated the costs of increasing obesity by \$ 48-66 billion/year in the USA and £ 1.9-2 billion/year in the UK linked with an increase of obesity - related diseases.

Several comprehensive reviews and meta-analyses have been performed examining this relationship or its lack, based on both cohort and case-control studies. For example, Bergström et al (2001) analyzed studies published between 1966 and 1997. The analysis of 9 studies of premenopausal BC risk demonstrated a relative risk (RR) of 0.98 per unit of increase in BMI (95% CI: 0.97-0.99). The authors identified 7 cohort studies reporting a statistically significant increase of BC risk in postmenopausal women with obesity and 6 studies where the relationship was no statistically significant. Further, they noted that 7 case-control studies exhibited a positive association and four studies showed no linkage. Given these data basing on 13 studies, the authors showed a 12% increase in BC risk in overweight women (25≤BMI<30kg/m²) and a 25% increase in the risk among obese women (BMI≥30kg/m²), compared to those of normal weight. In turn, Weir et al. (2007) conducted analysis of three systematic reviews and 14 research findings. They found that the risk of postmenopausal BC was higher in overweight women (OR=1.2) and in obese women (OR=1.25) compared to women of normal BMI. They also suggested that obesity rather than body fat distribution (central obesity) is responsible for an increase of a risk

for BC risk. Renehan et al. (2008) compiled the available evidence from 141 studies with the same topic and found that each 5kg/m² increase in BMI could increase the risk of BC in postmenopausal women, independently on the geographic region: of the North American (OR=1.15, 95% CI 1.08-1.25), European and Australian (OR=1.09, 95% CI 1.04-1.14) and Asia Pacific (OR=1.31, 95% CI 1.15-1.48). In meta-analysis of 15 cohort (2,104,203 subjects) and 35 case-control studies involving 71,216 subjects, Cheraghi et al. (2012) reported an inverse nonsignificant association between BMI and BC risk among premenopausal women in both, case-control (OR=0.93, 95% CI 0.86-1.02) and cohort (RR=0.97, 95% CI 0.82-1.16) studies. In contrast, the positive significant association was observed among postmenopausal women in case-control and cohort studies (OR=1.15, 95% CI 1.07-1.24; RR=1.16, 95% CI 1.08-1.25, respectively). Amadou et al. (2013) compiled the available evidence from 19 case-control and 11 cohort studies. The researchers analyzed the relationship between overweight, obesity and BC risk of premenopausal women according to ethnicity. They found that each 5kg/m² increase in BMI was significantly negatively associated with the risk (RR=0.95, 95% CI 0.94-0.97). However, when the authors stratified by ethnicity, the negative association appeared significant only among Africans and Caucasians. In contrast, the association was significantly positive in Asian women. In addition, the researchers found that each 0.1 unit increase in waist-to-hip ratio (a marker of the central fat) increases premenopausal BC (RR=1.08, 95% CI 1.01-1.16), being the largest among Asian women. In conclusion, they state that ethnicity and distribution of fat should be considered during the research of relationship between BMI and postmenopausal BC risk.

Evidence of a positive association between obesity and postmenopausal BC risk was confirmed in subsequent meta-analysis of 18 studies published from 1985 to 2011 by Dobbins et al. (2013). The authors found that obese women (BMI>30kg/m²) had a significant a 25% higher risk compared to women of normal weight (BMI 18.5-24.99kg/m²), (RR=1.25, 95% CI 1.07-1.46). The significant positive relationship between obesity and BC risk was also reported in the next recent review and meta-analysis of case-control studies, published from 2008 through 2011, for premenopausal women with triple-negative BC (the BC characterized by deficient expression of molecular markers such as estrogen receptor (ER), progesterone (PR), and the human epidermal growth factor-receptor 2) due to 10-20% of all BC subjects (Pierobon and Frankenfeld, 2013). An analysis included 3,845 patients with triple-negative BC. The authors found a 1.43-fold increased risk among premenopausal women with BMI≥30kg/m² compared to women of normal weight (OR=1.43, 95% CI 1.23-1.65) and non-significant association in postmenopausal women (OR=0.99, 95% CI 0.79-1.24). The next recent meta-analysis estimated the relationship in Chinese women (Zhang et al., 2013). The group found that overweight or obese individuals had increased risk compared to women of normal weight (OR=1.07, 95% CI 1.03-1.11). Magnitude of the risk was seen to be highly elevated after the adjustment for menopausal status, reaching a value of 56% (OR=1.56,

95% CI 1.29-1.84). In lately published meta-analysis of 82 follow-up studies, Chan et al. (2014) analyzed BMI and survival in women with BC. They found increased risk of mortality by a 7% in overweight women and by a 41% in obese women compared to of normal weight women (RR=1.07, 95% CI 1.02-1.12; RR=1.41, 95% CI 1.29-1.53 respectively). The summary risk due to obesity was calculated to be lower in postmenopausal women than in premenopausal women (RR=1.34, 95% CI 1.18-1.53 and RR=1.75, 95% CI 1.26-2.41, respectively). The authors also observed a higher risk of mortality in overweight women.

The results of the above presented meta-analyses revealed an important role of overweight/obesity in the risk of BC. In addition, these findings show that the relationship between BMI and BC should be assessed considering menopausal status. Generally, the conclusions of all meta-analyses are that obese women have a higher BC risk compared to those overweight. This suggestion is confirmed by previous case-control study carried by Senhadji and El Kébir (2010) on 484 BC cases. The authors reported that obesity (BMI \geq 30kg/m²) could increase the risk 2.66 times (OR=2.66, 95% CI 1.09-6.48), whereas overweight - 2.46 times (OR=2.46, 95% CI 1.74-3.48). Also, a previous study by Shahar et al. (2010) observed that abdominal obesity strongly increased BC risk (OR=3.3, 95% CI 1.8-6.2) among the Malaysian women. Similar and closely related results were obtained in the recent large case-control study (1,130 cases, 1,142 controls) conducted among Thai women. These authors reported a significant increased BC risk in women with BMI \geq 25kg/m², finding OR=1.33, 95% CI 1.07-1.65 in the total group and OR=1.67, 95% CI 1.24-2.25 among postmenopausal individuals (Sangrajrang et al., 2013), thus the study provides support for the notion that overweight is a risk for BC. In order to understand the evidence supporting the role of overweight/obesity in BC, it is necessary to briefly review the biochemical mechanisms responsible for this effect.

To date, these mechanisms are not yet completely understood: however three hormonal systems are hypothesized to explain this association, such as insulin and insulin-like growth factors (IGFs), especially IGF binding protein-1 factor (IGF-1); sex hormones; and adipokines (Travis and Key, 2003; Kaaks et al., 2005; Renehan et al., 2008; Mazur-Roszak et al., 2010; Vecchia et al., 2011; Alegre et al., 2013; De Pergola and Silvestris, 2013; Minatoya et al., 2013; Simpson and Brown, 2013a, 2013b; Barp et al., 2014). General and central obesity is positive correlated with insulin resistance followed by elevated its concentration in serum. At the insulin resistance state, in order to compensate the excess of free glucose the pancreas generates elevated concentration of insulin. Moreover, the increased level of glucose contributes to the tumor development, due to an usage of glucose by the tumor cells to proliferate (Vecchia et al., 2011). Further, chronic high level of insulin influences directly and indirectly the carcinogenesis through decreasing of binding proteins of IGF-1 and IGF-2 synthesis, resulting in an increased concentration of free or bioavailable IGF-1. Insulin and IGF-1 control cellular

proliferation, differentiation and apoptosis (Gunter et al., 2009). Although, the literature data on the role of insulin in BC development are cumulated they remain inconclusive. There is a suggestion that the inconsistencies in association between BC and insulin may be dependent, e.g. on menopausal status and usage of hormone therapy. Although a lack of consistency between premenopausal and postmenopausal BC and role of insulin or C-peptide (a marker of insulin secretion) was also observed (Lynch et al., 2011). IGF-1 participates in neovascularization and metastasis, inhibits the p53 tumor suppressor gene, prevents apoptosis, thus induces tumor formation and spread (Gunter et al., 2009; De Pergola and Silvestris, 2013; Minatoya et al., 2013). Further, it has been reported that insulin decreases production of adiponectin - the peptide that is inversely correlated with BMI. Adiponectin is a collagen-like peptide synthesized in adipose tissue that influences on several metabolic processes, such as oxidation of lipids, glucose uptake, weight loss and insulin sensitivity (Minatoya et al., 2013). Up till now, a linkage of adiponectin with BC risk is inconclusive as opposite effects of adiponectin were also observed.

The second way through obesity influences BC risk is due to increase in circulating of several sex steroids, including estrone, total estradiol and testosterone, and also to lowering of concentration of sex hormone binding globulin (SHBG) (Travis and Key, 2003; Kaaks et al., 2005). Numerous studies have demonstrated that the main hypothesis regarding the obesity - BC association in postmenopausal women is due to excessive stimulation of estrogen production in the adipose tissue by the aromatization of androstendione to estrone, followed by formation of estradiol. In obese women the aromatase activity is increased. Aromatase expression is regulated by inflammatory mediators such as prostaglandin E₂ (PGH₂), interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) (Simpson and Brown, 2013b). Estradiol was reported to stimulate endometrial and mammary cells proliferation by transcriptional activity and activation of intracellular signaling pathways, IGF-1 synthesis, and to inhibit apoptosis (Lynch et al., 2011). Evidence is emerging that during oxidative metabolism of estrone and estradiol ROS are generated, capable of modifying DNA, RNA, and proteins. Detailed discussion of steroidal estrogens metabolism to carcinogenic products was reviewed previously by Kruk and Aboul-Enein (2006).

In premenopausal women plasma estrogens originate mainly from the ovaries, their concentration is regulated, and obese women have decreased level of estrogens in plasma (Amadou et al., 2013). According to Key et al. (2004) suggestion, obesity does not increase BC risk among premenopausal women because obesity is frequently a reason of anovular menstrual cycles what involves decreases in estrogen level. Consistent with this hypothesis, earlier study that analyzed individual data from 8 prospective studies of postmenopausal women (624 cases and 1669 controls) reported that the increase in BC risk caused by a increased BMI results mainly from an increase of estrogens, particularly of estradiol (Endogenous Hormones and Breast Cancer Collaborative Group (2003). Earlier, Key et al. (2004) reported increased

risk of BC in postmenopausal women having the highest estrone and total estradiol level compared to those with the lowest level (OR=2.19, 95% CI 1.48-3.22; OR=2.00, 95% CI 1.47-2.71, respectively), based on 9 prospective studies. Also, the recent retrospective study by Kaviani et al. (2013) reported that women suffering from obesity had a higher stage of BC during diagnosis, and it was strongly correlated with the higher expression of estrogen and progesterone receptor, metastasis, higher lymph node rate, and a larger tumor size. The sex hormones hypothesis that steroidal hormones are positive correlated with postmenopausal BC is commonly accepted. In this point, it is worthy to note that the previous meta-analysis of the studies carried out from 1970 to 2007 by Suzuki et al. (2009) on the BMI - BC association, considering estrogen and progesterone status presented a decrease in the BC risk of estrogen positive (ER+) and progesterone positive O₂ (PR+) tumors among premenopausal women (RR=0.80, 95% CI 0.70-0.92) and a lack of the relationships for ER-PR-, ER+PR-, ER-PR+ tumors. In addition, the literature data have shown that the ER+ tumors respond favorably to treatment, in contrast to ER- tumors (Teras et al., 2011; Toriola and Colditz, 2013).

The third hypothesis to explain the relationship between obesity and BC involves adipokines (adiponectin, leptin, interleukins and resistin) produced by adipocytes and adipose tissue. In the normal cell adiponectin is considered as anti-inflammatory and antiproliferative agent for tumor cell growth that increases the catabolism of fatty acids, insulin sensitivity, and inhibits TNF- α . Unfortunately, in obese women the hormone fat cells can disturb the adiponectin secretion. The next adipokines, leptin participates in immunity, differentiation and proliferation of certain types of cells. Leptin stimulates DNA synthesis and cell growth, enhances expression of heat-shock protein 90, known to be responsible for increased formation of human epidermal growth factor receptor 2. The hormone also increases activation of estrogens and acts negatively on apoptosis (Jardé et al., 2011).

In obese postmenopausal women the release of proinflammatory cytokines, like interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) is increased what, beyond the above considered mechanisms as the major in BC etiology, can be responsible for inflammation by stimulation of macrophages. Interleukins and the TNF- α factor can affect the growth and differentiation of lymphocytes, stimulation of immune cell proliferation, and differentiation. Thus, obesity may lead to ROS generation followed by a decrease of an antioxidant potential of tissue (Crujeiras et al., 2013). Further, this process can lead to oxidative stress and alteration of immune response (Lee and Pratley, 2005; Renehan et al., 2008; Reuter et al., 2010; Nourazarian et al., 2014). Simpson and Brown maintain that "obesity is now recognized to be a chronic low-grade inflammatory condition in which deregulated metabolism play an integral role" (Simpson and Brown, 2013a, p.751). The role of oxidative stress present under chronic inflammation conditions in carcinogenesis is discussed in greater detail in the remainder section of this report.

Role of Free Radicals in BC Development

Carcinogenesis is multistep process that transforms the single cell in a stable state to malignant cell. The process requires of action of an agent capable to cause genetic alteration, cummulation of multiple molecular and cellular events, and may be characterized at least be three main stages: initiation, promotion, and progression (Sander et al., 2004; Micozzi, 2006; Moore and Sobue, 2009; Klaunig et al., 2010; Valluru et al., 2014). Numerous studies have demonstrated that ROS and RNS are involved in all stages of carcinogenesis (Hussain et al., 2003; Pala and Gurkan, 2008; Manda et al., 2009; Reuter et al., 2010; Liou and Storz, 2010; Nourazarian et al., 2014; Valluru et al., 2014). The term ROS obeys free molecules having an unpaired electron (free radicals), such as superoxide anion radical (O₂[•]), hydroxyl radical (HO[•]), peroxy radical (ROO[•]), and non-radical reactive species, like hydrogen peroxide (H₂O₂), lipid peroxides, and oxygen molecules that are in an electronically excited state, i.e. singlet oxygen (¹O₂). The major type of RNS include free radicals nitric oxide (NO[•]), nitric dioxide (NO₂[•]), and non-radical peroxy nitrite being the (O₂[•]) and product of O₂[•] the and NO[•] reaction (Halliwell and Gutteridge, 1999; Valko et al., 2004, 2007). During the initiation stage DNA in a normal cell undergoes mutation, thus a permanent change occurs in the genetic materials. The process leads to alterations of the cell genotype and an initiated cell is produced. ROS/RNS can participate directly in the initiation stage by reaction with DNA or indirect activating pro-carcinogens (e.g. polycyclic aromatic hydrocarbons) (Sander et al., 2004). The promotion stage is the process of an increased production of initiated cells, i.e. cells containing altered genotype. This etap of promotion is partly reversible. During this process promotors of carcinogenesis can oxidize membranes and stimulate and alter genetic expression. In the second irreversible etap-propagation, ROS participate in the cell proliferation and differentiation exerted by tumor promotors. Some promotors also can stimulate ROS production, followed by hydroperoxides formation, and/or elimination of uninitiated cells and toxicity. The progression stage involves expansion of initiated cells and their conversion to malignancy. In this stage several biochemical processes occur leading to the accelerated cell proliferation, of lack of the immune surveillance, tissue invasion and metastasis (Cooke et al., 2003). The initiation stage and increased production of initiated cells are reversible due to DNA repair and cell death (apoptosis), whereas the progression stage is irreversible process. For more information the reader is referred to a few excellent reviews within the area (Sander et al., 2004; Klaunig et al., 2010; Liou and Storz, 2010; Reuter et al., 2010; Nourazarian et al., 2014; Valluru et al., 2014).

Recent epidemiological and laboratory studies have demonstrated that oxidative stress plays an important role in all stages of the carcinogenesis (Ishikawa et al., 2008; Kumar et al., 2008; Pala and Gürkan, 2008; Manda et al., 2009; Klaunig et al., 2010; Reuter et al., 2010; Yeon et al., 2011; Kruk and Duchnik, 2014; Valluru et al., 2014). The oxidative stress results from an imbalance between

generation of ROS and RNS and products their oxidation, like semiquinones and their elimination by antioxidant systems (enzymes: superoxide dismutases; catalase; the glutathione system - glutathione, glutathione peroxidase, glutathione reductase, transferase; chelators of Fe and Cu ions-ferritin, lactoferritin and ceruloplasmin, thioredoxin system, and non-enzymatic antioxidants, such as vitamins E and C, zinc, selenium, carotenoids, plant polyphenols, compounds containing sulphur atom (Cadenas, 1997; Halliwell and Gutteridge, 1999; Valko et al., 2007; Durackova, 2010; Sarma et al. 2010). Under oxidative stress conditions the balance between the rates of oxidants generation and scavenging capacity of cells or tissues is disturbed. Disruption of the redox balance (homeostasis) has been implicated in several pathological conditions involving chronic diseases, such as neurological disorders, diabetes, cancer and other diseases (Valko et al., 2007; Liou and Storz, 2010; Nourazarian et al., 2014; Valluru et al., 2014). It is important to note that ROS/RNS are important mediators in signaling pathways that control maintain of cellular homeostasis. However, the species generated in excess are known to induce cell dysfunction, death or malignant transformation (Manda et al., 2009). With regard to the toxic activity, it is worth to add that ROS are used in chemical fight against pathogens and inflammatory responses. Moreover, recent studies also reported the link between phagocyte - generated ROS and cancer development (Klaunig et al., 2010).

The exogenous sources of the ROS generation include exposure to: environmental persistent chemicals, ultraviolet radiation, electromagnetic field, X-rays, γ -rays, physical inactivity and vigorous physical activity (Rundle, 2005; Kruk and Aboul-Enein, 2007; Little et al., 2008; Sachdev and Davies, 2008; Masaki, 2010; Kruk, 2011; Derbré et al., 2014). ROS/RNS are generated at mitochondrial electron transport chain, by peroxisomes and during the inflammatory cell activation (endogenous sources). Endogenous cellular production of these reactive species in mitochondria regulates hypoxia, activation of transcription factors called the hypoxia inducible factors (HIFs), that are modulators of a broad range of cellular functions, such as proliferation of a cell and angiogenesis (Brown and Bicknell, 2001). These two processes play a key function in tumor development and progression (Klaunig et al., 2010; Reuter et al., 2010). Indeed, elevated level of HIF-1 transcription factor has been reported in several cancers including breast (Rankin and Giaccia, 2008). Moreover, ROS play an important role in cell signaling due to activation of transcription factors such as AP-1 and NF- κ B, and to apoptosis (Valluru et al., 2014) which are also relevant to certain cancers. The beneficial or toxic role of ROS depends not only on their concentration but also on efficacy of cellular antioxidant defence system and repair mechanisms (Valko et al., 2001, 2004, 2007). All above listed oxygen species are oxidants relative to H₂O. Among ROS the most biological active species are hydroxyl radical and singlet oxygen. These species have short half-life time and react with the first encountered biomolecule (reviewed by Kruk, 1998). Under oxidative stress conditions, ROS may cause damages of: DNA, protein, lipids, sugars, leading to modification of proteins,

sugar changes, chromosome instability, genetic alteration, modulation of a cell growth and eventually results in cancer (Moore and Sobue, 2009; Klaunig et al., 2010; Liou and Storz, 2010). The most important biomolecule undergoing of the ROS attack is DNA. Numerous studies have shown that the ROS attack on DNA results in single or double-strand breakage, modifications of base and deoxyribose, and DNA cross-linking. All these damages may lead to cell death, DNA mutation, replication errors and genomic instability (Cooke et al., 2003; Valko et al., 2004; Klaunig et al., 2010; Reuter et al., 2010; Valluru et al., 2014). The hypothesis that the ROS/RNS species play an important role in carcinogenesis comes both from *in vitro* studies and evaluation of biomarkers on ill and healthy subjects (Hussain et al., 2003; Dalle-Donne et al., 2006; Pala and Gürkan, 2008). The most representative biomarkers of oxidative stress associated with cancer include: malondialdehyde (MDA), reduced/oxidized glutathione (GSH/GSSG) ratio, 3-nitro-tyrosine, 8-hydroxy-2'-deoxyguanosine (8-OH-dG) (Dalle-Donne et al., 2006; Manda et al., 2009). The prevailing scientific view that RNS may be damaging species to cells under a high concentration at site of damage is well recognized *in vitro*. There is scientific evidence that NO[•] at a high concentration is responsible for BC development (Valluru et al., 2014) acting as an initiator and a promoter. However the specific role of the radical is difficult to be identified (Hussain et al., 2003; Valluru et al., 2014). The NO radical plays a few dual roles, e.g. that can cause DNA damage and protect from toxicity, inhibit and stimulate cell proliferation. In addition, NO[•] can be pro-apoptotic and anti-apoptotic, depending on the conditions (its concentration, presence of metal ions, cell type and presence of other radicals). The NO radical forms peroxynitrite (ONOO⁻), the compound responsible for cyclooxygenase gene activation. The radical and its derivatives present at a high concentration can cause alternation in DNA. In addition, NO₂ and its derivatives can cause mutations in cancer related genes, thus induce clonal expansion of mutated cells and promote angiogenesis. For example, exposure of p53 on a high concentration of NO[•] results in p53 accumulation and post-translational modifications, following by selective clonal expansion of p53 mutant cells. Moreover, an increase in the expression of vascular endothelial growth factor was observed. These findings confirm that NO[•] stimulates angiogenesis and tumor progression. Another noteworthy finding is an increased expression of nitric oxide synthase (iNOS) in mammalian cells with p53-mutant cells (Hussain et al., 2003). The iNOS gene is an important molecule participating in tumour progression mediated by inflammation, able generate NO[•] at micromolar concentrations. Excessive and uncontrolled synthesis of NO[•] contributes to several cancers including breast cancers (Reveneau et al., 1999).

An interesting research by Thomsen et al. (1995) indicated that there is an association between increased iNOS expression and mutation in the p53 BC suppressor gene. Detailed discussion of the role of NO[•] in carcinogenesis may be found in excellent reviews of Hussain et al., 2003. In turn, ONOO⁻ is responsible for oxidative damage and nitration of DNA bases. Overall,

extensive studies to date have discussed the mechanisms by which ROS/RNS can mediate cancer. Considering the role oxidative stress in pathogenesis of BC Pala and Gürkan (2008) suggested that the disease is characterized by “pro-oxidants” shifting the thiol/disulphide redox state and impairing glucose tolerance the so-called “mitochondrial oxidative stress” conditions. This means that the intracellular thiol/disulfide state is shifted toward more oxidative condition, due to the persistent generation of large amounts of ROS or RNS (Droge, 2002). It is noteworthy, that oxidative damage of any cellular biomolecule, if not repaired can expand and induce damages in the whole cell. This leads to disturbance of the cellular metabolism and functionality.

In conclusion, consistent evidence from observational and laboratory studies strongly suggest a statistically significant positive relationship between obesity and BC in postmenopausal women, and non-significant preventive effect of overweight and obesity in premenopausal women. Several studies demonstrated also evidence of a dose-response effect of increasing BC risk with increasing BMI. The several basic biological mechanisms underlying the effect of overweight/obesity on BC development are hypothesized. They include insulin, IGFs especially IGF-1, sex hormones, and adipokines. Other hypothesized pathway leads by an increase of proinflammatory cytokines, like IL-1, IL-6 and TNF- α .

Although the role of obesity in chronic diseases is well documented and the Public Health Goals of the World Cancer Research Fund (WCRF) advocate that the healthy median adult BMI should be maintained between 21kg/m² and 23kg/m² (WCRF/AICR, 2007), there is no common consensus and clarity on the association between BMI and BC risk. This is due to limitations and potential biases linked with observational studies. Therefore, authors of reviews and meta-analysis studies advocate the need to be taken into account for future research the following factors: differences across race/ethnicity in body build and composition, tumor subtype, reproductive characteristics, the most appropriate measure of adiposity, receptor status, body weight changes throughout lifespan, and determinants of lifestyle. These factors should be considered as potential confounding variables in estimation the association between BMI and BC risk. The further studies can give answers for many basic questions, dealing with mechanisms of the body weight - BC risk relationship and improve its strength.

References

- Alegre MM, McKay HK, Robinson RA, O'Neill KL (2013). Mechanics behind breast cancer prevention - focus on obesity, exercise and dietary fat. *Asian Pac J Cancer Prev*, **14**, 2207-12.
- Amadou A, Ferrari P, Muwonge R, et al (2013). Overweight, obesity and risk of premenopausal breast cancer according to obesity: a systematic review and dose-response meta-analysis. *Obesity Reviews*, **14**, 665-78.
- Barp CG, de Almeida DJ, de Freitas GBL (2014). Breast cancer and postmenopausal obesity: the risk factors in this relationship. *Cancer Res J*, **2**, 9-14.
- Bergström A, Pisani P, Tenet V, Wolk A, Adami H-O (2001). Overweight as an avoidable cause of cancer in Europe. *Int J Cancer*, **91**, 421-30.
- Brown NS, Bicknell H (2001). Hypoxia and oxidative stress in breast cancer. Oxidative stress: its effects on the growth, metastatic potential and response to therapy of breast cancer. *Breast Cancer Res*, **3**, 323-7.
- Cadenas E (1997). Basic mechanisms of antioxidant activity. *Biofactors*, **6**, 391-7.
- Calle EE, Kaaks R (2004). Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nature Reviews Cancer*, **4**, 579-91.
- Carmichael AR, Bates T (2004). Obesity and breast cancer: a review of the literature. *Breast*, **13**, 85-92.
- Cecchini RS, Costantino JP, Cauley JA, et al (2012). Body mass index and the risk for developing invasive breast cancer among high-risk women in nsabp p-1 and star breast cancer prevention trials. *Cancer Prev Res*, **5**, 583-92.
- Chan DSM, Viera AR, Aune D, et al (2014). Body mass index and survival in women with breast cancer - systematic literature review and meta-analysis of 82 follow-up studies. *Ann Oncol*, **25**, 1901-14.
- Cheraghi Z, Poorolajal J, Hashem T, Esmailnasab N, Irani AD (2012). Effect of body mass index on breast cancer during premenopausal and postmenopausal periods: a meta-analysis. *Plos One*, **7**, 2811-22.
- Cooke MS, Evans MD, Dizdaroglu M, Lunec J (2003). Oxidative DNA damage: mechanisms, mutation, and disease. *FASEB J*, **17**, 1195-214.
- Crujeiras AB, Biaz-Lageras A, Carreira MC, Amil M, Casanueva FF (2013). Oxidative stress associated to dysfunctional adipose tissue: a potential link between obesity, type 2 diabetes mellitus and breast cancer. *Free Radic Res*, **47**, 243-56.
- Dalle-Donne I, Rossi R, Colombo R, Giustarini D, Milzani A (2006). Biomarkers of oxidative damage in human disease. *Clin Chem*, **52**, 601-23.
- De Pergola G, Silvestris F (2013). Obesity as a major risk factor for cancer. *J Obes*, **2013**, 291546.
- Derbré F, Gratas-Delamarche A, Gómez-Cabrera MC, Viña J (2014). Inactivity-induced oxidative stress: A central role in age-related sarcopenia? *Eur J Sport Sci*, **14**, 98-108.
- Dobbins M, Decorby K, Choi BCK (2013). The association between obesity and cancer risk: a meta-analysis of observational studies from 1985 to 2011. *ISRN Preventive Medicine*, 2013, article ID 680536.
- Droge W (2002). Free radicals in the physiological control of cell function. *Physiol Rev*, **82**, 47-95.
- Durackowa Z (2010). Some current insights into oxidative stress. *Physiol Rev*, **59**, 459-69.
- Endogenous Hormones and Breast Cancer Collaborative Group (2003). Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J Natl Cancer Institute*, **95**, 1218-26.
- Gunter MJ, Hoover DR, Yu H, et al (2009). Insulin, insulin-like growth factor-I, and risk of breast cancer in post-menopausal women. *J Natl Cancer Inst*, **1001**, 48-60.
- Halliwell B, Gutteridge IMC (1999). *Free Radicals in Biology and Medicine*. New York: Oxford University Press.
- Harvie M, Hooper L, Howell AH (2003). Central obesity and breast cancer risk: a systematic review. *Obesity Rev*, **4**, 157-73.
- Hussain SP, Hofseth LJ, Harris CC (2003). Radical causes of cancer. *Nature Reviews Cancer*, **3**, 276-85.
- Ishikawa K, Takenaga K, Akimoto M, et al (2008). ROS - generating mitochondrial DNA mutations can regulate tumor cell metastasis. *Science*, **320**, 661-4.
- Jardé T, Perrier S, Vasson M, Caldefie-Chézet F (2011).

- Molecular mechanisms of leptin and adiponectin in breast cancer. *Eur J Cancer*, **47**, 33-43.
- Jemal A, Bray F, Center MM, et al (2011). Global cancer statistic. *CA Cancer J Clin*, **61**, 69-90.
- Kaaks R, Berrino F, Key T, et al (2005). Serum sex steroids in premenopausal women and breast cancer risk within the European prospective investigation into cancer and nutrition (EPIC). *J Natl Cancer Institute*, **97**, 755-65.
- Kaviani A, Neishaboury MR, Mohammadzadeh N, et al (2013). Effects of obesity on presentation of breast cancer, lymph node metastasis and patient survival: a retrospective review. *Asian Pac J Cancer Prev*, **14**, 2225-9.
- Key TJ, Schatzkin A, Willett W et al (2004). Diet, nutrition and the prevention of cancer. *Public Health Nutrition*, **7**, 187-200.
- Klaunig JE, Kamendulis LM, Hocevar BA (2010). Oxidative stress and oxidative damage in carcinogenesis. *Toxicologic Pathology*, **38**, 96-109.
- Kruk I (1998). Environmental Toxicology and Chemistry of Oxygen Species. Hutzinger O, Kruk I (eds). Springer-Verlag Berlin Heidelberg.
- Kruk J (2011). Physical exercise and oxidative stress. *Med Sport*, **15**, 30-40.
- Kruk J, Aboul-Enein HY (2006). Environmental exposure, physical activity and other behavioral risk factors in breast cancer. *Current Cancer Therapy Reviews*, **2**, 3-21.
- Kruk J, Aboul-Enein HY (2007). Physical activity and cancer prevention: updating the evidence. The role of oxidative stress in carcinogenesis. *Curr Cancer Therapy Rev*, **3**, 81-95.
- Kruk J, Duchnik E (2014). Oxidative stress and skin disease: Possible role of physical activity. *Asian Pac J Cancer Prev*, **15**, 561-8.
- Kumar B, Koul S, Khandrika L, Meacham RB, Koul HK (2008). Oxidative stress is inherent in prostate cancer and is required for aggressive phenotype. *Cancer Res*, **68**, 1777-85.
- Lahmann PH, Hoffmann K, Allen N, et al (2004). Body size and breast cancer risk: Findings from the European prospective investigation into cancer and nutrition (epic). *Int J Cancer Res*, **186**, 13-42.
- Lee YH, Pratley RE (2005). The evolving role of inflammation in obesity and the metabolic syndrome. *Curr Diab Rep*, **5**, 70-5.
- Liou GY, Storz P (2010). Reactive oxygen species in cancer. *Free Radic Res*, **44**, 479-96.
- Little MP, Heidenreich WF, Moolgavkar SH, Schollnberger H, Thomas DC (2008). Systems biological and mechanistic modeling of radiation - induced cancer. *Radiat Environ Biophys*, **47**, 39-47.
- Lynch BM, Neilson HK, Friedenreich CM (2011). Physical activity and breast cancer prevention. In: Courneya KS, Friedenreich CM (eds). *Physical Activity and cancer. Recent Results Cancer Res*, **186**, Springer-Verlag Berlin Heidelberg.
- Manda G, Nechifor MT, Neagu T-M (2009). Reactive oxygen species, cancer and anti-cancer therapies. *Curr Chem Biol*, **3**, 342-66.
- Masaki H (2010). Role of antioxidants in the skin: anti-aging effects. *J Dermatol Sci*, **58**, 85-90.
- Matusitz, McCormick (2012). Sedentaryism: the effect of Internet use on human obesity in the United States. *Soc Work Public Health*, **27**, 250-69.
- Mazur-Roszak M, Litwiniuk M, Grodecka-Gazdecka S (2010). Obesity and breast cancer. *Contemporary Oncol*, **14**, 270-5.
- Micozzi MS (2006). Cancer as a cellular phenomenon. In: Micozzi MC (ed) *Complementary and Integrative Medicine in Cancer Care and Prevention*. Springer Publish Company, p.28.
- Minatoya M, Kutomi G, Asakura S, et al (2013). Equol, adiponectin, insulin levels and risk of breast cancer. *Asian Pac J Cancer Prev*, **14**, 2191-9.
- Moore MA, Sobue T (2009). Strategies for cancer control on an organ-site basis. *Asian Pac J Cancer Prev*, **10**, 149-64.
- Nourazarian AR, Kangari P, Salmaninejad A (2014). Roles of oxidative stress in the development and progression of breast cancer. *Asian Pac J Cancer Prev*, **15**, 4745-51.
- Ogundiran TO, Huo DZ, Adenipekun A, et al (2012). Body fat distribution and breast cancer risk: finding from the Nigerian breast cancer study. *Cancer Cases Control*, **23**, 565-74.
- Pala FS, Gürkan H (2008). The role of free radicals in ethiopathogenesis of diseases. *Advances in Molecular Biology*, **1**, 1-9.
- Phipps AI, Buist DSM, Malone KE, et al (2012). Breast density, body mass index and risk of tumor-marker-defined subtypes of breast cancer. *Ann Epidemiol*, **22**, 340-8.
- Pierobon M, Frankenfeld CL (2013). Obesity as a risk factor for triple-negative breast cancers: a systematic review and meta-analysis. *Breast Cancer Res Treat*, **137**, 307-14.
- Rankin EB, Giaccia AJ (2008). The role of hypoxia - inducible factors in tumorigenesis. *Cell Death Differ*, **15**, 678-85.
- Renahan AG, Tyson M, Egger M, Heller RF, Zwahlen M (2008). Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*, **371**, 569-78.
- Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB (2010). Oxidative stress, inflammation, and cancer. How are they linked? *Free Radic Biol Med*, **49**, 1603-16.
- Reveneau S, Arnould L, Jolimoy G, et al (1999). Nitric oxide synthase in human breast cancer is associated with tumor grade, proliferation rate, and expression of progesterone receptor. *Lab Invest*, **79**, 1215-25.
- Rundle A (2005). Molecular epidemiology of physical activity and cancer. *Cancer Epidem Biomark Prev*, **14**, 227-36.
- Sachdev S, Davies KJA (2008). Production, detection, and adaptive responses to free radicals in exercise. *Free Rad Biol Med*, **44**, 215-23.
- Sander CS, Chang H, Hamm F, Elsner P, Thiele JJ (2004). Role of oxidative stress and antioxidant network in cutaneous carcinogenesis. *Int J Dermatol*, **43**, 326-35.
- Sangrajrang S, Chaiwerawattana A, Ploysawang P, et al (2013). Obesity, diet and physical inactivity and risk of breast cancer in Thai women. *Asian Pac J Cancer Prev*, **14**, 7023-7.
- Sarma AD, Mallick AR, Ghosh AK (2010). Free radicals and their role in different clinical conditions: an overview. *IJPSR*, **1**, 185-92.
- Senhadji R, El Kébir FZ (2010). Hormonal status, obesity, age and risk of breast cancer: results of a case-control study on a western population of Algeria. *J Afr Cancer*, **2**, 72-6.
- Shahar S, Salleh RM, Ghazali AP, et al (2010). Roles of adiposity, lifetime physical activity and serum adiponectin in occurrence of breast cancer among Malaysian women in Klang Valley. *Asian Pac J Cancer Prev*, **11**, 61-6.
- Simpson ER, Brown KA (2013a). Minireview: obesity and breast cancer: a tale of inflammation and dysregulated metabolism. *J Mol Endocrinol*, **27**, 715-25.
- Simpson ER, Brown KA (2013b). Obesity and breast cancer: role of inflammation and aromatase. *J Mol Endocrinol*, **51**, 751-9.
- Suzuki R, Orsini N, Saji S, Key TJ, Wolk A (2009). Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status - a metastasis. *Int J Cancer*, **124**, 698-712.
- Teras L, Goodman M, Patel AV, et al (2011). Weight loss and postmenopausal breast cancer in a prospective cohort of overweight and obese US women. *Cancer Causes Control*, **22**, 573-9.
- Thomsen LL, Miles DW, Happerfield L, et al (1995). Nitric oxide synthase activity in human breast cancer. *Br J Cancer*,

- Toriola AT, Colditz GA (2013). Trends in breast cancer incidence and mortality in the United States: implication for prevention. *Breast Cancer Res Treat*, **138**, 665-73.
- Travis RC, Key TJ (2003). Oestrogen exposure and breast cancer risk. *Breast Cancer Res*, **5**, 239-47.
- Valko M, Izakovic M, Mazur M, Rhodes CJ, Telser J (2004). Role of oxygen radicals in DNA damage and cancer incidence. *Mol Cell Biochem*, **266**, 37-56.
- Valko M, Leibfritz D, Moncola J, et al (2007). Free radicals and antioxidant in normal physiological function and human disease. *Int J Biochem Cell Biol*, **39**, 44-84.
- Valko M, Morris H, Mazur M, Raptap P, Bitom RF (2001). Oxygen free radical generating mechanisms in the colon. Do the semiquinones or vitamin K play a role in the etiology of colon cancer? *Biochim Biophys Acta*, **1521**, 161-6.
- Valluru L, Dasari S, Wudayagiri R (2014). Role of free radicals and antioxidants in gynecological cancers: current status and future prospects. *Oxid Antioxid Med Sci*, **3**, 15-26.
- Vecchia C, Giordano SH, Hortobagyi GN, Chabner B (2011). Overweight, obesity, diabetes, and risk of breast cancer: interlocking pieces of the puzzle. *Oncologist*, **16**, 726-9.
- Wang YC, McPherson K, Marsh T, Gortmaker SL, Brown M (2011). Health and economic burden of the projected obesity trends in the USA and the UK. *Lancet*, **378**, 815-25.
- Weir R, Day P, Ali W (2007). Risk factors for breast cancer in women. New Zealand Health Technology Assessment. *NZHTA Report*, **10**, 1-361.
- Withrow D, Alter DA (2011). The economic burden of obesity worldwide: a systematic review of the direct costs of obesity. *Obes Rev*, **12**, 131-41.
- World Cancer Research Fund (2007). Nutrition, physical activity, and the prevention of cancer: a global perspective. American Institute for Cancer Research, Washington, DC, USA, 2nd edition.
- Xu YL, Sun Q, Shan GL, et al (2012). A case-control study on risk factors of breast cancer in China. *Arch Med Science*, **8**, 303-9.
- Yeon JY, Suh YJ, Kim SW, et al. (2011). Evaluation of dietary factors in relation to the biomarkers of oxidative stress and inflammation in breast cancer risk. *Nutrition*, **27**, 912-8.
- Zhang Q, Qian Y, Jin ZY, et al (2013). A meta-analysis on overweight, obesity and the risk of breast cancer in Chinese female population. *Zhonghua Yu Fang Yi Xue Za Zhi*, **47**, 358-62.