Chapter 3

Sexual Dimorphism in Obesity Related Cancer Risk

*Zsuzsanna Suba**

National Institute of Oncology, Surgical and Molecular Tumor Pathology Center,
Budapest, Hungary

Abstract

In the past decades disadvantageous changes in lifestyle caused a steady increase in average body weight, especially in the economically developed countries. Excessive adipose tissue deposition, particularly in visceral location may be regarded as a metabolically active endocrine organ inducing dysmetabolism and associated hormonal imbalances. Gender related similarities and differences in overall and site specific obesity related cancer incidence may provide revelation of associations among fatness, sexual hormone imbalance and cancer initiation. Male to female ratio of adiposity related cancer incidence may be highly influenced by the types of included malignancies, the age distribution of cases and controls and the ratio of examined pre- and postmenopausal women. Obesity and overweight cause deleterious metabolic and hormonal alterations in both male and female patients. In women, obesity associated excessive androgen and defective estrogen synthesis seem to be strong cancer risk factors in both pre- and postmenopausal cases, especially for the female organs. These organs exhibit active cell proliferation, which requires strict hormonal survaillance against mitotic failures and cancer initiation. In men, obesity associated insulin resistance and hyperinsulinemia are high risks for cancer at several sites. At the same time, obesity related diminished estrogen exposure exhibits no conspicuous additive carcinogenic effect on the male organs as their physiologic function requires much lower serum estrogen concentrations as compared with female organs.

Recognition of dangerous alterations in the male to female sexual steroid levels in obesity may open new possibilities for the prevention and treatment of obesity by the compensatory restoration of metabolic and hormonal equilibrium.

* Corresponding author: Prof. Dr. Zsuzsanna Suba. National Institute of Oncology, Surgical and Molecular Tumor Pathology Centre, Address: 1122 Ráth György str. 7-9, Budapest, Hungary. E-mail: subazdr@gmail.com.

Introduction

Obesity is an excessive deposition of adipose tissue caused by a complex interaction between genetic, metabolic, hormonal, behavioral and environmental factors. The deleterious effects of obesity are diverse, ranging from an increased risk of life threatening diseases, such as; type-2 diabetes, cardiovascular lesions and malignancies to several non-fatal diseases with an adverse impact on life quality [1, 2].

Obesity has become a crucial public health problem in many parts of the world. In the past decades disadvantageous changes in lifestyle caused a steady increase in average body weight, especially in the economically developed countries [3]. Obesity and overweight may also be associated with malnutrition attributed to the excessive fat and carbohydrate intake in the developing countries and those undergoing economic and political transitions.

Since the early 1980s fairly increased prevalence of obesity has been observed in the United States [1] and by the year 2000 nearly two-thirds of adults were overweight or obese [4]. Incidence of obesity is also enhanced in other parts of the world including the Caribbean region, South America and Southeast Asia [5, 6]. Trends in obesity from 1999 to 2008 and the prevalence of obesity and overweight for the years 2007-2008 were examined in the United States [7]. Over the 10-year period, prevalence of obesity showed no significant changes among women, whereas for men, there was a significant linearly increasing trend. In 2007-2008, the prevalence of obesity was shockingly high, 32.2% among adult men, and even higher, 35.5% among adult women.

Obesity is a multifaceted disorder and emerging research delineates the specific role of excessive visceral adiposity as opposed to predominantly subcutaneous fat deposition in morbidity and mortality of obese people [8]. Within each category of body mass index (BMI) there can be substantial individual variation in total and visceral adiposity, and in several related metabolic variables [1].

Excessive adipose tissue, particularly in visceral location is a metabolically active endocrine organ inducing insulin resistance with associated dysmetabolism and hormonal imbalances [1]. The self-generating insulin resistance and the coexistence of hormonal disturbances mediate the development of obesity-associated serious illnesses, such as type-2 diabetes, cardiovascular disease and malignancy [8, 9]. The incidence of type-2 diabetes during the examined time periods fairly increased too, mirroring a presumed co-morbidity of the obesity epidemic [10].

High prevalence of obesity plays pivotal role in both cardiovascular disease and cancer related mortality. Researchers speculate that cancer may share a similar mechanism and risk factor interaction with that of cardiovascular disease [11]. Correlations among body mass index (BMI), diabetes, hypertension and short term mortality were examined in a population based observational study in 2000-2006, in a representative, contemporary United States sample [12]. Severe obesity (but not overweight) was associated with increased premature mortality, an association primarily accounted for by coexisting diabetes and hypertension.

 In the United States, overweight and obesity were associated with 90 000 deaths from cancer per year and 280,000-325,000 deaths from all causes per year before 2000. [13, 14]. In the European Union, annual deaths from all causes attributed to overweight and obesity have been estimated at 279,000-304,000 [15]. Some studies estimate that the impact of overweight

and obesity in terms of both mortality and health-care costs equals or exceeds that associated with tobacco use [16].

Excessive androgen and defective estrogen synthesis may also be regarded as concomitant features of adiposity [6]. Obesity and overweight cause deleterious metabolic alterations in both male and female patients [1]. In women, obesity associated dysmetabolism and sexual hormone imbalances seem to be strong cancer risk factors in both pre- and postmenopausal cases, especially for the female organs with high estrogen demand [17]. In men, obesity associated insulin resistance, such as metabolic syndrome and type 2 diabetes are high risks for cancers at several sites [8]. At the same time, obesity associated diminished estrogen exposure has no conspicuous additive carcinogenic effect on the male organs as their physiologic function requires much lower estrogen concentration than female organs. Considering these correlations, disturbances in endogenous hormonal mechanisms might be important crossroads linking obesity and cancer risk [17, 18].

There have been global initiatives to reduce the rapidly increasing prevalence of obesity. Nevertheless, the prerequisite of a successful anti-obesity fight would be the revelation of exact mechanisms by which obesity develops and induces the high morbidity and mortality of life threatening diseases. Gender differences in overall and site specific obesity related cancer incidence may provide revelation of associations among fatness, sexual hormone imbalance and cancer initiation.

Hormonal and Metabolic Disorders As Links between Obesity and Cancer Risk in Males and Females

Healthy hormonal mechanisms and their signaling pathways have well identified roles in the promotion, maintenance and control of ideal body mass and the fat distribution characteristic to both males and females [19]. Consequently, hormonal disorders may be in strong correlation with pathologic changes in body weight. Obesity may be linked to endocrine diseases, including common ones such as type 2 diabetes, hypothyroidism and polycystic ovarian syndrome as well as rare ones such as Cushing's syndrome [20]. Similarly, certain hormonal disorders, such as hyperinsulinism, deficient estrogen signaling, hypothyroidism and vitamin D deficiency are considered as causal factors in excessive body weight gain [21].

Defective synthesis of estrogens and alterations in their receptor systems or signaling pathways in obese cases might be strong risk factors for cancer development [18, 22, 23, 24]. Moreover, excessive insulin production, hypothyroidism and vitamin D deficiency are also characteristic alterations in obese cases and these hormonal disorders are in close correlation with cancer risk [23, 25, 26]

Male to female sexual hormone equilibrium has a pivotal role in the maintenance of somatic health, body weight and reproductive capacity in both men and women [18, 27]. Obesity related anomalies in the balance of sexual steroids have different effects on body mass and fatty tissue distribution in male and female cases [6]. Female type subcutaneous, gluteofemoral adipose tissue deposition is frequent in young premenopausal women and may

be associated with healthy insulin sensitivity and regular, ovulatory cycles [17]. By contrast, male-like central obesity is associated with insulin resistance in men and women [8].

Disturbances in endogenous hormonal balance in obese patients mean crucial links between excessive body weight and risk for cancer. Moreover, deficient estrogen signaling in obese patients may explain the health disparity of obese women as compared with men highly affecting the sex dependent differences in obesity-related cancer morbidity and mortality [17].

Correlations among Obesity Associated Insulin Resistance, Hyperinsuinism and Cancer Risk

In obesity associated metabolic syndrome or type 2 diabetes, the primary disorder of cellular glucose uptake is at least partially counteracted by a reactive hyperinsulinemia [28]. In the compensated phase of insulin resistance excessive insulin synthesis may help to maintain the normal glucose level. Later on, with the self generated deepening of insulin resistance, the serum glucose level will increase in spite of the overproduction of insulin.

At the same time, insulin itself is a growth factor and excessive insulin secretion results in overproduction of further insulin-like growth factors. This overwhelming growth factor activity denotes a risk for uncontrolled, increased cell proliferation rate and possibility for mitotic failures as well as cancer initiation [29, 30]. Results of clinical and epidemiologic studies indicate that increased serum levels of both insulin and insulin-like growth factors may mediate cancer risk at several sites [31, 32].

Insulin excess may attribute to a wide range of endocrine disorders. Hyperinsulinism suppresses FSH and favors LH synthesis in the hypophysis, resulting in a shift in the direction of excessive androgen synthesis at the expense of defective estrogen production in both ovaries and adrenal glands [33]. As regards breast cancer cases, the cessation of ovarian hyperandrogenism by bilateral oophorectomy may provide a rationale explanation for transitory tumor regression [17].

In obese patients, insulin resistance and hyperinsulinism also decrease androgen to estrogen transformation by a strong inhibition of aromatase activity in the endocrine organs and peripheral tissues [34]. Decreased estrogen synthesis and defective estrogen receptor signaling induce further deterioration of cellular glucose uptake generating a vicious circle [22].

Does Excessive or Defective Estrogen Signaling Mediate Strong Cancer Risk in Obese Patients?

Role of estrogen levels in obesity associated cancer risk, particularly in female cancers, seems to be highly controversial posing a great challenge for clinicians and scientists.

Cancers of the highly estrogen dependent female organs are in the forefront of scientific interest since these are regarded as malignancies induced by hormones. Correlation between estrogen action and breast cancer growth has been acknowledged for more than 100 years, given that transitory remission of advanced breast cancer was experienced after performing bilateral oophorectomy in premenopausal cases [35]. Since that time,

evidence has accumulated that seemingly support the hypothesis that both endogenous and exogenous estrogens are thoroughly related to both the initiation and promotion of breast cancer [36, 37, 38, 39]. Strong relationship between the high level of female sexual steroids and breast cancer risk was erroneously justified by the excessive, or about 100-150-fold greater incidence of breast cancer in women compared to men [40].

By contrast, estrogen deficiency as cancer risk factor emerged first in a Hungarian study conducted in 2007 on oral cancer cases [41]. Although for a long time oral cancer was regarded a tumor associated with smoking and drinking, conspicuous accumulation of oral malignancies among non smoker non drinker elderly women suggested the carcinogenic impact of estrogen loss in these patients. Critical reevaluation of the contradictory results of hormone replacement therapy yielded a complete conversion; estrogen deficiency may confer cancer initiation even in the female breast [27].

Concepts regarding linkage between obesity associated malignancies and circulating estrogen levels are highly controversial [42]. In obese postmenopausal women, the mistakenly presumed excessive endogenous estrogen production of their adipose tissue mass is regarded as strong cancer risk for the highly hormone dependent female breast. On the other hand, obesity associated defective estrogen synthesis was established in premenopausal cases [43], which was erroneously supposed to be a cancer protective effect. Nevertheless, the conspicuously low risk for female cancers in obese young women and the steeply enhanced incidences of these malignancies with ageing justify the increasing trend of cancer development in women after menopause in association with low hormone exposure [17].

In young obese women, hormone measurements indicated adiposity to show inverse correlation with serum estrogen levels [43]. In concordance with those hormonal defects, obese young women frequently exhibit irregular anovulatory cycles, infertility and nulliparity as compared with normal weight cases [44, 45]. At the same time, fertility disorders and nulliparity are in close correlation with breast cancer risk in premenopausal women [46]. Nevertheless, obesity associated cancer risk among premenopausal women is much lower than in postmenopausal cases as even their partially preserved estrogen level may counteract the carcinogenic impact of obesity associated dysmetabolism [17].

In older obese women, hypothetical, deleterious hyperestrogenism after the cessation of ovarian estrogen synthesis seemed to be a puzzling paradigm. Epidemiologic studies justified that in obese women, the incidence of endometrial, breast and ovarian cancers increase with ageing, especially after menopause, in spite of the termination of ovarian hormone production [47, 48, 49].

Possibility of estrogen induced carcinogenesis in obese postmenopausal women was apparently supported by the justification of extraovarian estrogen synthesis at several sites, such as in the mesenchymal cells of adipose tissue [50]. Moreover, in the tumor free, fatty breast tissue of older, postmenopausal women, 8-10 fold higher estrogen concentration was found as compared with their low serum estrogen level [51]. This abundantly estrogen rich milieu seemed to be a reassuring justification of cancer initiation by hyperestrogenism in hormone deficient elderly women [52].

In obese postmenopausal women, exogenous estrogens in the form of postmenopausal hormone therapy equivocally reduce the risk of colorectal cancer [53]. As a speculative explanation, oral intake of exogenous estrogens could have inverse effects than endogenous estrogens on the risk of colon cancer.

A positive correlation was found between estrogen synthesis and estrogen receptor (ER) positivity of breast tumors [54], suggesting that the higher the differentiation of cancers the stronger the capacity for estrogen production. Considering the crucial role of ER positivity of tumors in the survival of patients [55], estrogen as the ligand of ERs and effective estrogen signaling seem to provide anticancer capacity [24].

Aromatase in human breast carcinoma is regarded as a key regulator of intratumoral sex steroid concentrations [56, 57, 58]. Tumor aromatase expression was a good prognostic factor in young breast cancer patients after breast-conserving surgical treatment [59]. This finding suggests that estrogen production in tumors may advantageously influence the tumor free survival [24, 60].

Further observation leaded to deduction concerning estrogen induced tumor progression in obese women. In breast cancer cases, much higher aromatase activities and estrogen levels were measured in the adipose tissue adjacent to the tumor as compared with distant regions [51]. Considering the concept of the anticancer capacity of estrogen, hormone synthesis by stromal cells and adipocytes adjacent to the invasive front of cancer may be regarded as a defensive host reaction against tumor spread [60].

Extraovarian estrogen synthesis from precursor steroids by aromatase enzyme activity is a physiologic protective process in many cell and tissue types including the vascular endothelium, bone, brain, breast and endometrium [51, 56, 61, 62]. Estrogen deficient elderly cases are highly endangered by cardiovascular diseases, osteoporosis and ischemic injuries of the central nervous system. Extragonadal estrogen synthesis in the highly estrogen dependent tissues, such as in the breast and endometrium provide important defensive biologic mechanisms so as to preserve their integrity rather than to increase the possibility of cancer initiation [27, 63].

In conclusion, high estrogen level in obese women does not seem to be a real mediator of cancer initiation. Clinical and epidemiologic studies support that obesity deteriorates both ovarian and peripheral estrogen synthesis resulting in deepening insulin resistance, hyperinsulinism and their comorbidities [22].

Controversial Results on Obesity Related Overall Cancer Incidence in Men and Women

High body weight, expressed as increased body-mass index (BMI), is associated with the risk of some common and less common cancers [64, 65, 66, 67]. Great studies have demonstrated gender differences in obesity associated overall cancer risk, revealing sometimes quite inverse data. Male to female ratio of adiposity related cancer incidence may be highly influenced by the types of included malignancies, the age distribution of cases and controls and the ratio of examined pre- and postmenopausal women [17, 18, 27]. Moreover, the geographic location of performed studies and the skin color of included patients also have defining role in the hormonally influenced sex prevalence of obesity related cancer risk [23].

Differences in the Gender Related Overall Cancer Risk of Obesity Defined by Geographic Regions

Contradictory correlations between obesity and gender related overall cancer morbidity may at least partially be explained by the *geographic differences* in the location of studies [66, 67]. Geographic differences in overall cancer risk suggest that the more northern the location of a country the higher the cancer incidence among the inhabitants, especially in women [23, 26]. Northern regions, such as Denmark, Iceland, Norway and Sweden, are conspicuously highly represented among European countries leading the rank of female overall cancer morbidity and mortality [68]. By contrast, countries with highest male cancer incidence and mortality do not exhibit accumulation in special geographic location. The excessive female risk for overall cancer morbidity and mortality in Northern countries suggests that women are especially vulnerable to certain environmental factors, such as light deficiency in Northern regions owing to their special hormonal features [69].

In Canada, a population based case-control study was conducted on 21,022 incident cases of 19 types of malignancies and on 5,039 controls aged 20-76 years, to examine the association between obesity and the risks of various cancers [66]. This study found that compared with people with normal weight (≤ 25 kg/m^2) obese men and women (≥ 30 kg/m^2) had an increased risk of overall cancer (OR: 1.34). In Canada, excessive body mass accounted for 7.7% of all malignancies; 9.7% among men and 5.9% among women. The study provided further evidence that obesity increases the risk of different malignancies; such as lymphoid tumors and many types of cancers. The much higher prevalence of obesity associated malignancies among men as compared with women may be at least partially attributed to the wide age range of the included cases (20-76 yrs) with the accumulation of young women who have stronger endogenous defense mechanisms. The Canadian study stressed a close correlation between postmenopausal status and increased obesity associated cancer risk in women regarding breast tumor cases in particular.

A population based cohort study in Northern Sweden provided evidence of a highly increased obesity related cancer risk in women, whereas men were not markedly affected. [67]. Effects of body mass index (BMI) on overall cancer risk and on the risk of several common cancer types were analyzed. Women with BMI ≥ 27.1 had a 29% higher risk of developing any malignancy as compared with women within normal weight range. In northern Sweden, up to 7% of all cancers were attributable to overweight and obesity in women. The highly estrogen dependent endometrium and ovary as well as the colon proved to be the individual cancer sites being most strongly related to obesity in women. These organs are characterized by their high cell proliferation rate requiring thorough estrogen surveillance by healthy female cycle, and even the slight or moderate defect in their estrogen signaling may provoke cancer initiation. In men, there was no significant association of BMI with overall cancer risk; however, obese men had a higher risk of developing kidney and colon cancer.

In Sweden, a further prospective study on obesity and cancer risk found a 33% excess incidence of cancer among obese patients, 25% in men and 37% in women. Conspicuously high risk elevations were observed for cancers of the larynx (SIR=2.1) and the endometrium (SIR=2.9) [65].

In northern regions, the higher incidence of obesity associated malignancies among women than men substantiates a harmful partnership in cancer initiation between obesity, darkness associated defective estrogen signaling and dysmetabolism.

Race Related Disparities in Obesity Associated Cancer Risk in Men and Women

Obesity associated cancer incidence may strongly be influenced by the coexistence of race related cancer risk factors. Dark skin associated cancer risk may be in direct or indirect correlation with deficient light exposure and hormonal alterations [69].

Results of studies on dark skinned immigrants in northern countries justified that they have excessive cancer risk as compared with the natives of their adoptive country. It was found in Sweden, that there is an excessive pharyngeal cancer risk of brown skinned immigrants, particularly in women. Moreover, the risk of cancer in black skinned immigrants was even greater, being disproportionately higher in black women [70]. Disparity of breast cancer risk among African-American women is a well known finding as compared with whites [71]. These patients may also be regarded as dark skinned immigrants in a northern country. Moreover, the 5-year relative survival rate is lower in African Americans than in whites for every stage of diagnosis for most cancer sites [72]. Central fat deposition and diabetes is more frequent among African American women as compared with Caucasian cases [73]. Central obesity associated dysmetabolism and hormonal imbalance may be in close correlation with the high risk and poor prognosis of breast cancer in dark skinned women [74, 75, 76]. Light exposure is a very important player in the healthy life of human beings and mammalians [77]. Diurnal changes of the illumination of daylight and nocturnal darkness evolve periodically different pineal melatonin hormone synthesis. Melatonin levels are low at daylight, during the period of physical and biologic activity in humans and the majority of mammalians, which requires higher speed of metabolic processes and increased insulin sensitivity. Higher melatonin production in the resting period during nighttime darkness suppresses thyroxin and estrogen synthesis and reduces insulin sensitivity [78]. Moreover, sunshine during daytime is an important source of vitamin-D synthesis in the skin and either the diminished exposure of sunshine or the excessive pigmentation of dark skinned people results in vitamin D deficiency [79, 80]. Disturbances in diurnal hormonal fluctuations associated with light deficiency may be in close correlation with an increased cancer risk, especially for hormonally challenged obese cases. Deficient light exposure and dark skin associated hormonal disorders strongly deteriorate the conversion of androgens to estrogen. High estrogen demand of female organs may be an important player in darkness associated cancer risk.

Gender Related Differences in the Obesity Associated Risk for Individual Cancer Sites

The main hormonal difference between men and women is the inverse sexual steroid hormone ratio, namely, estrogen predominance in women and androgen predominance in

men. Although for a long time estrogens were regarded as principally the hormones of female physiology, nowadays their physiological serum concentration in men seems to be similarly crucial in the regulation of cellular metabolism, growth and proliferation [81].

Healthy, cycling levels of estrogen in young, premenopausal women stand for a higher level of the surveillance of all cellular functions, and female organs and structures seem to be more resistant to endogenous or environmental injuries as compared with men at the same age [17]. By contrast, with ageing and after menopause in particular, a moderately or strongly estrogen deficient milieu results in a higher cancer risk for female organs as compared with aging men, which may be attributed to their higher estrogen demand [27].

Excess body weight, expressed as increased body-mass index (BMI) or circumference measurements are associated with the risk of several common adult cancers. Systematic review and meta-analysis of literary data help to assess the strength of associations between obesity and the different sites of cancer and to investigate differences in these correlations between male and female groups [64].

The association between overweight/obesity and *thyroid cancer risk* was confirmed [82]. The relationship between excess body weight or body mass index (BMI) and risk of thyroid cancer was examined by meta-analysis. Obesity was linked with increased thyroid cancer risk in males and females, the strength of the association increased with increasing BMI. The combined RR of thyroid cancer was 1.18 for overweight and obesity. Conversely, obesity was associated with differentiated thyroid cancer risk in women, while did not show associations with thyroid cancer risk in men [83].

Increased prevalence of obesity related *salivary gland tumors* suggests that obesity and the associated metabolic and hormonal alterations have important role in their development [84]. Close correlations between obesity, insulin resistance and risk for salivary gland tumors proved to be stronger among women as compared with men. Among women with malignant salivary gland tumors, the postmenopausal status was predominant and a high prevalence of insulin resistance and obesity were characteristic concomitants.

Quantitative assessment was performed on the associations between excessive body weight and the risk of *primary liver cancer* by an updated meta-analysis of prospective observational studies [85]. Obese males had a higher risk of primary liver cancer than obese females did (P=0.027). A stronger cancer risk of excessive body weight was observed for patients with HCV infection or cirrhosis compared with the general population.

An increased risk of *pancreatic cancer* was observed among obese men and women [86]. Risk of pancreatic cancer was independently increased among men and women who reported a tendency for central weight gain compared with men and women reporting a tendency for peripheral weight gain.

The risk for *kidney cancer* is 1.5-2.5-fold higher in overweight and obese persons than in normal weight cases. In several studies, the risk is higher in women than in men with increasing BMI [13, 87]. Obesity associated chronic hyperinsulinemia and type-2 diabetes may also contribute to the high prevalence of kidney cancer risk [88].

Increasing abdominal diameter was associated with an increased risk of *esophageal adenocarcinoma,* independent of BMI. Cancer risk was not mediated through gastro esophageal reflux-type symptoms. Abdominal obesity is more common among males; these findings suggest that increased obesity may disproportionately increase the risk of esophageal adenocarcinoma in males [89].

Colorectal cancer risk is increased in obese men and women [1]. There are certain controversial results suggesting gender related differences in colorectal cancer risk. In the majority of studies obese men were observed somewhat more likely to develop colorectal cancer than obese women [1]. As a speculative reason central adiposity and associated dysmetabolism emerged as it has higher prevalence in men than in women. By contrast, according to a further study high waist circumference was associated with slightly higher increase in colorectal cancer incidence in women (RR:1.75) as compared with men (RR:1.68) [90].

High incidence rate of obesity associated colorectal cancer risk in both men and women may partially be explained by the high proliferative activity of colorectal epithelial lining in both genders compensating the continuous intra-luminal shedding of epithelial cells. High rate of colorectal cell proliferation requires strong hormonal surveillance, and obesity related dysmetabolism and sexual hormone imbalance may induce failures in mitotic activity and cancer initiation.

The inconsistent epidemiologic results may be associated with differences in the age distribution of obese colon cancer cases included. Central obesity is prevalent in aged, hormonally challenged women, consequently; the older the examined group of obese cases with colon cancer the higher the ratio of female cases in relation to males.

Paradigm of Extreme Differences in Breast Cancer Incidence between Obese Men and Women

Breast cancer in men is an extremely rare disease, accounting for less than 1% of all breast cancer cases [91]. By contrast, in women, mammary cancers are the most frequently diagnosed malignant tumor and the leading cause of cancer death globally [92]. In the United States, mammary cancer is the most common malignancy in female patients and the second most common cause of cancer death among women [93].

Results of studies on the risk of breast cancer in males suggest that the causal factors may be quite similar to those of female breast malignancies [40, 91]. Obesity increases the incidence of male breast cancer cases, presumably through similar hormonal mechanisms as in case of females [94]. Aging, dietary factors, dysmetabolism, low physical activity, BRCA gene mutation, smoking and excessive alcohol consumption all deserve attention [91, 95].

In the Male Breast Cancer Pooling Project, including a consortium of 11 case-control and 10 cohort investigations involving 2405 cases, anthropometric and hormonal risk factors for male breast cancer were investigated [96]. The risk was statistically significantly associated with high body weight (highest/lowest tertile: OR = 1.36) with evidence that recent rather than earlier BMI was the strongest predictor. Diabetes also emerged as an independent risk factor for male breast cancer (OR = 1.19). There were also suggestive relations of male breast cancer risk with cryptorchidism (OR = 2.18) and orchitis (OR = 1.43), which disorders highly alter the male fertility. Moreover, men who never have had children, also exhibited increased breast cancer risk (OR = 1.29). This finding suggests parallelism with the high breast cancer risk of nulliparous women [46].

As estrogens are regarded as crucial fuels for breast cancer growth till now, certain investigations suggest that defective estrogen exposure and anovulatory infertility in

premenopausal women provide strong defense against breast cancer initiation [97]. This concept apparently justifies that men are highly protected from the risk of breast cancer by their physiologically lower estrogen level. Moreover, hyperestrogenism is mistakenly supposed as a breast cancer risk even in men [95] attributed to the analogy of erroneous findings in women.

Excessive endogenous estrogen level may be associated with gene anomalies causing defective estrogen signaling. Among patients with BRCA gene mutation and increased cancer risk, decreased ligand activated estrogen signaling was observed [98]. Reactively high estrogen level may occur in BRCA mutation carrier breast cancer cases but it may not be in causal correlation with cancer initiation. BRCA1 mutation is associated with high breast cancer risk and moderate increase in estrogen synthesis, while BRCA2 mutation cases exhibit lower breast cancer risk and higher increase in estrogen level [99]. Estrogen overproduction in these BRCA mutation carrier cases rather serves as counteraction so as to break through the dangerous defect of estrogen signaling.

Pregnancy and the administration of pregnancy analogue estrogen dose in animal experiments stabilize the DNA for a long time, may kill mutagenic cells and promote the differentiation of tumor cells occurring by chance [100, 101, 102]. Moreover, pregnancy mimicking estrogen dose proved to be protective from breast cancer in highly endangered nulliparous women [103].

Analysis of uniform embryonic mammary development and the dichotomy of pubertal breast tissue growth in male and female cases may at least partially reveal the extreme gender related differences in breast cancer risk. In the serum of pregnant women and in fetoplacental units, estrone, estriol and estradiol levels increase exponentially and reach about 60-300-fold levels during pregnancy as compared with the follicular phase levels of menstrual cycle [104]. This abundance of estrogens ensures the surveillance of safe, explosion-like cell proliferation in embryonic structures [24, 60]. Male and female sexual differentiation is genetically defined; however diverse inner and outer sexual organs and similarly rudimentary breasts of male and female embryos develop under the control of the same estrogen rich environment.

Sexual maturity during puberty means a milestone in the breast development of girls. Genetically programmed extreme cell proliferation and differentiation of mammary cells begin under the surveillance of the increased concentration of female sexual hormones. Failures in the hormonal and metabolic equilibrium in adolescent girls are crucial risk factors for the defective development of both regular, ovulatory menstrual cycles and female breast tissue maturation [17]. By contrast, in adolescent boys with high male to female sexual steroid ratio, the rudimentary breast tissue remains at rest.

Obesity in adolescent girls may strongly disturb the insulin sensitivity and estrogen signaling of highly proliferating tissues, the breasts in particular. Obesity associated insulin resistance, hyperinsulinism, excessive androgen and defective estrogen synthesis in this crucial period of rapid breast development may cause severe disturbances in cell proliferation, and induce mitotic failures and cancer initiation [17, 24]. In obese adolescent boys, insulin resistance and hormonal alterations are also dangerous. Although their male to female sex hormone ratio develops inversely as compared with females, a proper estrogen level also is essential for the surveillance of all cellular functions. Nevertheless, the resting male breast exhibits a very low rate of cell proliferation and does not require strong hormonal surveillance presenting minimal risk for tumor initiation.

In premenopausal women, the proper estrogen supply of mammary tissue cells remains crucial as the female breast undergoes continuously cycling proliferative activity parallel with the menstrual cycles. Close correlations between physiologic estrogen surveillance and the safety of cell proliferation may explain why actively proliferating female breast is much more vulnerable in obesity associated sexual hormone imbalance as compared with the resting male breast. Consequently, all exogenous and endogenous factors, which deteriorate estrogen synthesis or estrogen receptor signaling, increase the risk of cancer, particularly in highly proliferating female breast [22, 23, 24].

Conclusion

Obesity and the associated metabolic and hormonal imbalances may provoke severe, life threatening diseases in pre- and postmenopausal women, as well as in men. Results of animal experiments and human studies suggest that estrogens have advantageous impact against obesity associated dysmetabolism and hyperandrogenism, which have essential role in the development of obesity related co-morbidities; such as malignancies.

Differences in the cancer risks of obese men and women justify that obesity related hormonal alterations, such as sexual steroid imbalance may diversely mediate cancer risk in male and female cases. Recognition of the dangerous alterations in the male to female sexual steroid levels in obesity open new possibilities for the prevention and treatment of obesity and associated cancer risk.

References

[1]   Calle EE, Kaaks R. Overweight, obesity *Nat Rev Cancer*. 4: 579-91, 2004.
[2]   Davis SR, Castelo-Branco C, Chedraui P *et al*; Writing Group of the International Menopause Society for World Menopause Day 2012. Understanding weight gain *Climacteric*. 15: 419-29, 2012.
[3]   Bianchini F, Kaaks R, Vainio H. Overweight, obesity *Lancet Oncol.* 3: 565-74, 2002.
[4]   Flegal KM, Carroll MD, Ogden CL *et al*. Prevalence and trends in obesity *JAMA*. 288: 1723-7, 2002.
[5]   Seidell J, Rissanen A. Etiology and Pathophysiology. In: Bray G, Bouchard C Eds. Handbook of Obesity. New York: Marcel Dekker, 2004; pp. 93-107.
[6]   Björntorp P. Obesity. *Lancet*. 350: 423-6, 1997.
[7]   Flegal KM, Carroll MD, Ogden CL, *et al*. Prevalence and trends in obesity among US adults, 1999-2008. *JAMA*. 303: 235-41, 2010.
[8]   Donohoe CL, Doyle SL, Reynolds JV. Visceral adiposity *Diabetol Metab Syndr*. 3:12, 2011.
[9]   Suba Z, Ujpál M. Correlations of insulin *Magy Onkol*. 50:127-35 2006. [Hungarian].
[10]   Mokdad AH, Ford ES, Bowman BA, *et al*. Prevalence of obesity *JAMA*. 289: 76-9, 2003.
[11]   Jee SH, Kim HJ, Lee J. Obesity, insulin *Yonsei Med J*. 46: 449-55, 2005.

[12]   Jerant A, Franks P. Body mass index, diabetes, hypertension, and short-term mortality: a population-based observational study, 2000-2006. *J Am Board Fam Med*. 25: 422-31, 2012.

[13]   Calle EE, Rodriguez C, Walker-Thurmond K, *et al*. Overweight, obesity *N Engl J Med*. 348: 1625-38, 2003.

[14]   Allison DB, Fontaine KR, Manson JE, *et al*. Annual deaths *JAMA*. 282(16): 1530-8, 1999.

[15]   Banegas JR, López-García E, Gutiérrez-Fisac JL, *et al*. A simple estimate of mortality *Eur J Clin Nutr*. 57: 201-8, 2003.

[16]   Mokdad AH, Marks JS, Stroup DF, *et al*. Actual causes of death in the United *JAMA* 291: 1238-45, 2004.

[17]   Suba Z. Circulatory estrogen *Recent Pat Anticancer Drug Discov*. 8: 154-67, 2013.

[18]   Suba Z. Interplay between insulin *Pathol Oncol Res*. 18: 123-33, 2012.

[19]   Pallottini V, Bulzomi P, Galluzzo P, *et al*. Estrogen regulation of adipose *Infect Disord Drug Targets*. 8: 52-60, 2008.

[20]   Weaver J. Classical Endocrine Diseases Causing Obesity. Korbonits M (ed): Obesity and Metabolism. Front Horm Res. Basel, Karger, 2008, vol 36, pp. 212-228.

[21]   Kokkoris P, Pi-Sunyer FX. Obesity and endocrine disease. *Endocrinol Metab Clin North Am.* 32: 895-914, 2003.

[22]   Suba Z. Low estrogen exposure and/or defective estrogen signaling induces disturbances in glucose uptake and energy expenditure. *J Diabet Metab*. 272 4172/2155-6156.1000272.

[23]   Suba Z. Light deficiency confers breast cancer risk by endocrine disorders. *Recent Pat Anticancer Drug Discov*. 7: 337-44, 2012.

[24]   Suba Z. Triple-negative breast cancer risk in women is defined by the defect of estrogen signaling: preventive and therapeutic implications. *Onco Targets Ther*. 7: 147–164, 2014.

[25]   Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Rohan TE, Manson JE*, et al*. Insulin, insulin-like growth factor and risk of breast cancer in postmenopausal women. *J Natl Cancer Inst*. 101: 48-60, 2009.

[26]   Grant WB, Juzeninene A, Moan JE. Review article: Health benefit of increased serum 25 (OH)D levels from oral intake and ultraviolet-B irradiance in the Nordic countries. *Scand J Public Health*. 39:70-78, 2011.

[27]   Suba Z. Common soil of smoking-associated and hormone-related cancers: estrogen deficiency. *Oncol Rev.* 4:73-87, 2010.

[28]   Reaven GM. Role of insulin resistance in human disease (syndrome X): an expanded definition. *Annu Rev*. 44: 121-131, 1993.

[29]   Pollak MN, Schernhammer ES, Hankinson SE. Insulin-like growth factors and neoplasia. *Nat Rev Cancer.* 4:505-18, 2004.

[30]   Arcidiacono B, Iiritano S, Nocera A, Possidente K, Nevolo MT, Ventura V, Foti D, Chiefari E, Brunetti A. Insulin resistance and cancer risk: an overview of the pathogenetic mechanisms. *Exp Diabetes Res.* 2012;2012:789174. doi: 10.1155/2012/789174.

[31]   Gupta K, Krishnaswamy G, Karnad A, Peiris A: Insulin: A novel factor in carcinogenesis. *Am J Med Sci*. 323:140-145, 2002.

[32]   Yu H, Rohan Th: Role of insulin-like growth factor family in cancer development and progression. *J Natl Cancer Inst*. 92:1472-1489, 2000.

[33]   Nestler JE. Obesity, insulin *Int J Obes Relat Metab Disord*. 24 Suppl 2: S71-3, 2000.

[34]   Stamataki KE, Spina J, Rangou DB, Chlouverakis CS, Piaditis GP. Ovarian function in women with non-insulin dependent diabetes mellitus. *Clin Endocrinol (Oxf)*. 45: 615-21, 1996.

[35]   Beatson TG: On the treatment of inoperable cases of carcinoma of the mamma. Suggestions for a new treatment with illustrative cases. *Lancet*. 2:104-107, 1896.

[36]   International Agency for Research on Cancer: Monographs on the evaluation of carcinogenic risks to humans: hormonal contraception and postmenopausal hormone therapy. IARC, Lyon, France, vol. 72, 1999.

[37]   Feigelson HS, Henderson BE: Estrogens and breast cancer. *Carcinogenesis*. 17:2279-2284, 1996.

[38]   Toniolo PG, Levitz M, Zeleniuch-Jacquotte A, Banerjee S, Koenig KL, Shore RE et al. A prospective study of endogenous estrogens and breast cancer in post-menopausal women. *J. Natl. Cancer Inst.* 86:1076-1082, 1995.

[39]   Colditz GA, Hankinson SE, Hunter DJ, Willett EC, Manson JE, Stampfer MJ et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N. Engl. J. Med.* 332:1589-1593, 1995.

[40]   Thomas DB. Breast cancer in men. *Epidemiol Rev*. 15: 220-31, 1993.

[41]   Suba Z. Gender-related hormonal risk *Pathol Oncol Res*. 13:195-202, 2007

[42]   Rose DP, Vona-Davis L. Interaction between menopausal status and obesity in affecting breast cancer risk. *Maturitas*. 66: 33-8, 2010.

[43]   Potischman N, Swanson CA, Siiteri P, Hoover RN. Reversal of relation between body mass and endogenous estrogen concentrations with menopausal status. *J Natl Cancer Inst.* 88: 756-8, 1996.

[44]   Baer HJ, Colditz GA, Willett WC, Dorgan JF. Adiposity and sex *Cancer Epidemiol Biomarkers Prev*. 16: 1880-8, 2007.

[45]   Stoll BA. Teenage obesity *Int J Obes Relat Metab Disord.* 22: 1035-40, 1998.

[46]   Opdahl S, Alsaker MD, Janszky I, Romundstad PR, Vatten LJ. Joint effect of nulliparity and other breast cancer risk factors. *Br J Cancer*. 105: 731-6, 2011.

[47]   Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones *Cancer Epidemiol Biomarkers Prev*. 11: 1531-43, 2002.

[48]   La Vecchia C, Negri E, Franceschi S, Talamini R, Bruzzi P, Palli D, *et al*. Body mass index and postmenopausal breast cancer: an age specific analysis. *Br J Cancer*. 75: 441-4, 1997.

[49]   Leitzmann MF, Koebnick C, Danforth KN, Brinton LA, Moore SC, Hollenbeck AR, Schatzkin A, Lacey JV Jr. Body mass *Cancer*. 2009; 115: 812-22, 2009.

[50]   Simpson ER. Sources of estrogen and their importance. *J Steroid Biochem Mol Biol.* 86:225-30, 2003.

[51]   Miller WR, O'Neill J. The importance of local synthesis of estrogen within the breast. *Steroids*. 50:537-48, 1987.

[52]   Liehr JG. Is estradiol a genotoxic and mutagenic carcinogen? *Endocrine Rev.* 21:40-54, 2000.

[53] Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 288:321–333, 2002.

[54] Mason RC, Burns DA, Miller WR, Hawkins RA, Forrest AP. Tumour steroid hormone synthesis and estrogen receptor status in breast cancer patients. *Breast Cancer Res Treat.* 1:263-6, 1981.

[55] Hartley MC, McKinley BP, Rogers EA, Kalbaugh CA, Messich HS, Blackhurst DW, Lokey JS, Trocha SD. Differential expression of prognostic factors and effect on survival *Am Surg*. 72: 1189-94, 2006.

[56] Santen R. J., Martel J., Hoagland M., Naftolin F., Roa L., Harada N., Hafer L., Zaino R., Santner S. J.: Stromal spindle cells contain aromatase in human breast-tumors. *J. Clin. Endocrin. Metab.* 79:627-632, 1994.

[57] Suzuki T., Miki Y., Akahira J. I., Moriya T., Ohuchi N., Sasano H.: Review: Aromatase in human breast carcinoma as a key regulator of intratumoral sex steroid concentrations. *Endocrine J*. 55:455-463, 2008.

[58] Sasano H., Miki Y., Nagasaki S., Suzuki T.: In situ estrogen production and its regulation in human breast carcinoma: From endocrinology to intracrinology. *Pathology International*. 59:777-789, 2009.

[59] Bollet MA, Savignoni A, De Koning L, Tran-Perennou C, Barbaroux C et al. Tumor aromatase expression as a prognostic factor for local control in young breast cancer patients after breast-conserving treatment. *Breast Cancer Research.* 11:R54, 2009.

[60] Suba Zs. Failures and controversies of the antiestrogen treatment of breast cancer. In: Suba Z. Ed. Estrogen prevention for breast cancer. Chapter 6. Pp. 105-125. Nova Science Publishers Inc. New York, 2013.

[61] Simpson E, Rubin G, Clyne C, Robertson K, O'Donnell L, Davis S, Jones M. Local estrogen biosynthesis in males and females. *Endocr Relat Cancer*. 6:131-7, 1999.

[62] McCullough LD, Blizzard K, Simpson ER, Öz OK, Hurn PD. Aromatase cytochrome P450 and extragonadal estrogen play a role in ischemic neuroprotection. *J. Neurosci*. 23:8701-8705, 2003.

[63] Suba Zs. Discovery of estrogen deficiency as common cancer risk factor for highly and moderately estrogen dependent organs. In: Ed. Suba Zs. Estrogen prevention for breast cancer. Nova Science Publishers Inc. New York. 2013, pp. 1-22.

[64] Renehan AG, Tyson M, Egger M, *et al*. Body-mass *Lancet.* 371: 569-78, 2008.

[65] Wolk A, Gridley G, Svensson M, Nyrén O, McLaughlin JK, Fraumeni JF, Adam HO. A prospective study of obesity and cancer risk (Sweden). *Cancer Causes Control.* 12(1):13-21, 2001.

[66] Pan SY, Johnson KC, Ugnat AM, Wen SW, Mao Y; Canadian Cancer Registries Epidemiology Research Group. Association of obesity and cancer risk in Canada. *Am J Epidemiol.* 159:259-68, 2004.

[67] Lukanova A, Björ O, Kaaks R, *et al*. Body mass *Int J Cancer*. 118(2): 458-66, 2006.

[68] Otto Sz. Cancer epidemiology in Hungary and the Béla Johan National Program for the Decade of Health. *Pathol Oncol Res.* 9: 126-130, 2003.

[69] Suba Z. Newly recognized player in breast cancer risk: light deficiency. In: Suba Z. Ed. Estrogen prevention for breast cancer. New York: Nova Science Publishers Inc. 2013; pp. 77-92.

[70]   Mousavi SM, Sundquist J, Hemminki K. Nasopharyngeal and hypopharyngeal carcinoma risk among immigrants in Sweden. *Int J Cancer*. 127:2888-92, 2010.

[71]   Jones LA, Chilton JA. Impact of breast cancer on African American women: Priority areas for research in the next decade. *Am J Public Health*. 92: 539–542, 2002.

[72]   DeSantis C, Naishadham D, Jemal A. Cancer statistics for African Americans, 2013. *CA: A Cancer Journal for Clinician*. 63(3): 151–166, 2013.

[73]   Pi-Sunyer FX. Obesity and diabetes in blacks. Diabetes Care 1990; 13(11): suppl. 4, 1144-49.

[74]   Rose DP, Haffner SM, Baillargeon J. Adiposity, the metabolic syndrome, and breast cancer in African-American and white American women. Endocr. Rev. 2007; 28:763-77.

[75]   Conroy SM, Maskarinec G, Wilkens LR, White KK, Henderson BE, Kolonel LN. Obesity and breast cancer survival in ethnically diverse postmenopausal women: the Multiethnic Cohort Study. *Breast Cancer Res. Treat.* 2011; 129:565-74.

[76]   Sarkissyan M, Wu Y, Vadgama JV. Obesity is associated with breast cancer in African-American women but not Hispanic women in South Los Angeles. *Cancer.* 117:3814-23, 2011.

[77]   Mead MN. Benefits of Sunlight: A bright spot for human health. *Environ Health Perspect.* 116: A160–A167, 2008.

[78]   Vriend J, Bertalanffy FD, Ralcewicz TA. The effects of melatonin and hypothyroidism on estradiol and gonadotropin levels in female Syrian hamsters. *Biology of Reproduction.* 36:719-728, 1987.

[79]   Giovannucci E. The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). *Cancer Causes Control*. 16(2): 83-95, 2005.

[80]   Grant WB, Peiris AN. Possible role of serum 25-hydroxyvitamin D in black-white health disparities in the United States. *J Am Med Dir Assoc*. 11:617-28, 2010.

[81]   Faustini-Fustini M, Rochira V, Carani C. Oestrogen deficiency in men: where are we today? *European J Endocrinol.* 140: 111–129, 1999.

[82]   Zhao ZG, Guo XG, Ba CX, Wang W, Yang YY, Wang J, Cao HY. Overweight, obesity and thyroid cancer risk: a meta-analysis of cohort studies. *J Int Med Res.* 40:2041-50, 2012.

[83]   Pearce EN, Han JM, Kim TY, Jeon MJ, Yim JH et al. Obesity is a risk factor for thyroid cancer in a large, ultrasonographically screened population. *Clin Thyroidol.* 25:107–108, 2013.

[84]   Suba Zs, Barabás J, Szabó Gy, Takács D, Ujpál M: Increased prevalence of diabetes and obesity in patients with salivary gland tumors. *Diabetes Care*. 28:228, 2005.

[85]   Chen Y, Wang X, Wang J, Yan Z, Luo. Excess body weight and the risk of primary liver cancer: an updated meta-analysis of prospective studies. *Eur J Cancer.* 48(14):2137-45, 2012.

[86]   Patel AV, Carmen Rodriguez C, Bernstein L, Chao A et al. Obesity, recreational physical activity, and risk of pancreatic cancer in a large U.S. Cohort. *Cancer Epidemiol Biomarkers Prev.* 14; 459, 2005.

[87]   Chow WH, McLaughlin JK, Mandel JS, *et al* . Obesity and risk *Cancer Epidemiol Biomarkers Prev.* 5: 17-21, 1996.

[88]   Lindblad P, Chow WH, Chan J, *et al*. The role of diabetes *Diabetologia.* 42(1): 107-12, 1999.

[89] Corley DA, Kubo A, Zhao W. Abdominal obesity and the risk of esophageal and gastric cardia carcinomas. *Cancer Epidemiol Biomarkers Prev*. 17: 352–358, 2008.

[90] Wang Y, Jacobs EJ, Patel AV, *et al*. A prospective study of waist circumference and body mass index in relation to colorectal cancer incidence. *Cancer Causes Control*. 19: 783-92, 2008.

[91] Weiss JR, Moysich KB, Swede H. Epidemiology of male breast cancer. *Cancer Epidemiol Biomarkers Prev. 14:* 20-26, 2005.

[92] Siegel R, Naishadham D, Jemal A. Cancer statistics

[93] American Cancer Society. Cancer Facts & Figures. 2013. http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-036845.

[94] Hsing AW, McLaughlin JK, Cocco P, Co Chien HT, Fraumeni JF Jr. Risk factors for male breast cancer (United States). *Cancer Causes Control*. 9(3): 269-75, 1998.

[95] Ruddy KJ, Winer EP. Male breast cancer: risk factors, biology, diagnosis, treatment, and survivorship. *Ann Oncol*. 24(6): 1434-43, 2013.

[96] Brinton LA, Cook MB, McCormack V, Johnson KC, Olsson H, Casagrande JT, Cooke R et al. Anthropometric and hormonal risk factors for male breast cancer: male breast cancer pooling project results. *J Natl Cancer Inst*. 106(3):djt465, 2014.

[97] Terry KL, Willett WC, Rich-Edwards JW, Michels KB. A prospective study of infertility due to ovulatory disorders, ovulation induction, and incidence of breast cancer. *Arch Intern Med*. 166(22): 2484-9, 2006.

[98] Zheng L, Annab LA, Afshari CA, Lee WH, Boyer TG. BRCA1 mediates ligand *Proc Natl Acad Sci USA*. 98: 9587-92, 2001.

[99] Kim J, Oktay K. Baseline E(2) levels are higher in BRCA2 mutation carriers: a potential target for prevention? *Cancer Causes Control*. 24: 421-6, 2013.

[100] Rajkumar L, Kittrell FS, Guzman RC, Brown PH, Nandi S, Medina D. Hormone-induced protection *Breast Cancer Res*. 9:R12, 2007.

[101] Hong J, Holcomb VB, Kushiro K, Núñez NP. Estrogen inhibits the effects of obesity *Int J Oncol*. 39: 1443-53, 2011.

[102] Nkhata KJ, Ray A, Dogan S, Grande JP, Cleary MP. Mammary tumor *Breast Cancer Res Treat*. 114: 71-83, 2009.

[103] Tsubura A, Uehara N, Matsuoka Y, Yoshizawa K, Yuri T. Estrogen and progesterone treatment mimicking pregnancy for protection from breast cancer. *In Vivo*. 22(2): 191-201, 2008.

[104] Lindberg BS, Johansson ED, Nilsson BA: Plasma levels of nonconjugated oestrone, oestradiol-17beta and oestriol during uncomplicated pregnancy. *Acta Obstet Gynecol Scand Suppl*. 32:21-36, 1974.