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Chapter 1

A Long Way from Hyperestrogenism to Estrogen Deficiency As a Mediator of Cancer Risk in Obesity

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Abstract

Obesity is preferentially associated with female cancers, which correlation is consistent for endometrial, breast and ovarian malignancies. Increased risk for the cancers of female organ triad in obese women supports the presumption that high body weight may confer cancer risk through female hormonal mechanisms. In the 80s and 90s of the past century the carcinogenic capacity of female sexual steroid hormones had become a prevailing concept under the name of "estrogen hypothesis". Several authors presumed that high estrogen levels unopposed by progestin continuously stimulate estrogen receptors, which may be a mechanism of gynecologic and breast cancer initiation. As endometrial cancer cases exhibited even decreased total and bioavailable estradiol levels, it has been proposed that low progesterone, rather than increased estrogen level may be the crucial determinant of cancer risk. This presumption construed the concept of "unopposed normal estrogen level" attributed to defective progesterone synthesis. The next step on the route leading to the decoding of increased gynecologic and breast cancer risk in obese women was the revelation of "ovarian hyperandrogenism" based on the increased urinary androgen excretion of patients. Obesity associated hyperinsulinism promotes excessive luteinizing hormone (LH) and decreased follicle stimulating hormone (FSH) secretion in the hypophysis. These hormonal alterations induce a shift of ovarian and adrenal steroidgenesis to the predominance of androgen production at the expense of estrogen loss. In hyperandrogenic, anovulatory young women both insulin sensitizing Metformin and oral contraceptive treatment decrease the

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excessive insulin and androgen synthesis and at the same time help to achieve regular menstrual cycles and ovulation. These therapeutic possibilities justified that medical recovery of sexual hormone balance is strongly cancer preventive. Realistic evaluation of "estrogen loss" as cancer risk factor for the highly estrogen dependent female organs would promote both the primary prevention and causal therapy of malignancies at all sites.

Introduction

The incidence of obesity has been steadily increasing over the past few decades in the highly developed countries and US in particular [1, 2]. A number of comorbidities associated with obesity have been well-established such as type 2 diabetes and cardiovascular diseases [3]. Moreover, an epidemiological relationship between obesity and the prevalence of a variety of cancers has also been uncovered [1, 4]. High BMI is associated with increased risk of both common and less common malignancies. For some cancer types, these associations differ between sexes and populations of different ethnic origins [5]. Epidemiologic observations should forward the exploration of biological mechanisms that link obesity with cancer.

Obesity exhibits the strongest correlation with endometrial cancer risk from the malignancies of the female organ triad, especially in young premenopausal cases [6, 7]. Obesity and overweight have been associated with a 2-5-fold increase in endometrial cancer risk in both pre- and postmenopausal women [8]. Obesity related breast cancer risk is also conspicuously high, particularly in postmenopausal cases [9]. The association is increasing with ageing and strongest among elderly women. Nevertheless, in premenopausal women the obesity-related risk of mammary malignancies seems to be controversial [10]. Incidence of ovarian malignancies exhibits lower correlation with obesity. While excessive body weight defined by BMI conferred moderate ovarian cancer risk, central adiposity characterized by high waist to hip ratio was associated with significantly increased risk for ovarian cancer [11, 12, 13].

High risk for endometrial, breast and ovarian cancers in obese women supported the presumption that high body weight associated cancer risk may be mediated through female hormonal mechanisms. Excessive adipose tissue was erroneously supposed to be responsible for hyperestrogenism in postmenopausal women, which was regarded as a pivotal player in the initiation and progression of these specific female tumors [1, 7, 9, 11, 14].

Recent studies revealed that not only the female organ triad but all tissues need a balanced equilibrium of male to female sexual steroid levels for the health and preservation of their morphologic integrity and functional activity [15, 16]. The primacy of correlations between hormonal defects and cancer risk in the female organ triad may be attributed to the specifically high estrogen demand [17].

Increasing numbers of clinical observations support that exogenous hormone treatment, such as oral contraceptives or in vitro fertilization assisted childbirth may dramatically decrease the cancer incidence in obese, anovulatory young women having high risk for female cancers, [18-20]. Moreover, in postmenopausal obese cases, hormone replacement therapy (HRT) use equivocally reduces the risk of endometrial, breast and ovarian cancer as compared with women who never used HRT [7, 21, 22]. Morbidity studies on both

premenopausal and postmenopausal women as well as the results of animal experiments justified that low estrogen exposure instead of excessive estrogen production may be strongly pathogenic and carcinogenic [23].

Synchronous occurrence of malignancies in the female organ triad was already a conspicuous epidemiologic finding in the past century, especially in young premenopausal cases suggesting common risk factors and a possible hormonal etiology of these tumors [24, 25]. It has been established with certainty that young women with a single primary cancer of the breast or genital organs have an increased risk of developing a second primary cancer elsewhere in the female organ triad [24].

The most popular explanation for the development of these multiple primary tumors is that the high density of estrogen receptors in case of excessive hormonal stimulation may be responsible for the increased risk of malignancies in the predisposed tissues [26, 27]. Nevertheless, these organs have crucial role in reproductive capacity requiring high estradiol levels for ovulation, endometrial proliferation and fetoplacental development. Predisposition of the mammary gland for breastfeeding needs also high hormone level associated with pregnancy.

In obese young women, the most consistent risk for synchronous female tumors is the defective reproductive capacity; such as anovulatory infertility and nulliparity [6, 26, 28-30] suggesting rather defective estrogen synthesis instead of hyperestrogenism. Moreover, high parity and long term use of exogenous hormone treatment, such as oral contraceptives are regarded as primary female cancer reducing factors [27, 31], supporting the advantageous, protective effect of good female hormonal equilibrium.

The purpose of the present study is the comprehensive analysis of correlations among obesity, male to female sex hormone levels and cancer risk in women, affecting preferentially the breast, endometrium and ovary. Realistic evaluation of cancer risk factors for the highly estrogen dependent female organs would promote both the primary prevention and causal therapy of malignancies at all sites.

Obesity Related Cancer Risk for Women

In patients with increased BMI, the risk of developing overall cancer shows contradictory sex differences. Literary data support the fact that obese men have a higher risk for malignancies as compared with women [32]. By contrast, in Northern Sweden, a population based cohort study showed that obese women had a 36% higher risk of cancer as opposed to women with a BMI in the normal range, whereas, there was no association of BMI with overall cancer risk in case of men [33].

The gender-specific excessive risk for obesity associated female cancer morbidity in Northern countries may be associated with the deficient light exposure in regions of high altitude. Light deficiency displays thorough interplay with hormonal cancer risk factors mediated by excessive melatonin synthesis, such as insulin resistance and deficiencies of estrogen, thyroxin and vitamin-D. Darkness associated hormonal imbalance seems to be a stronger cancer risk for women as compared with men, attributed to their higher estrogen demand [34].

Among individual cancer sites the *endometrium* was most strongly related to overweight and obesity in Northern Sweden [33]. In the group being in the top quartile for obesity, the endometrial cancer risk was 3.53 as compared with the lowest quartile. In Hawaii strong association was found between increased body sizes and the development of endometrial cancer after adjustment for energy intake [35]. Both current adiposity and adult weight gain were associated with substantial increases in the risk of endometrial cancer, with relations particularly evident among never users of menopausal hormone therapy [36].

Women who were highly obese in their teenage had a risk of 1.62 of developing endometrial carcinoma when compared to women who exhibited milder obesity as teenagers [37]. These results indicate that teenage obesity may predispose to endometrial carcinoma by means of prolonged sex hormone imbalance, excessive androgen production at the expense of estrogen loss [17]. In premenopausal women with polycystic ovarian syndrome (PCOS) the coexistence of anovulatory infertility and insulin resistance represents high risk for endometrial cancer both in obese and lean cases [38]. Among obese postmenopausal cases endometrial cancer risk is higher in never HRT user women as compared with HRT users [7]. These findings suggest that female steroid treatment may at least partially compensate the obesity associated hormonal and metabolic imbalance thus reducing the risk of cancer.

Breast cancer risk and adiposity exhibit close correlations and the majority of authors suspect that obesity is associated with enhanced mammary cancer risk through hormonal mechanisms [9, 10, 21].

In adolescent girls, obesity associated insulin resistance is related to abnormal ovarian sexual steroidgenesis, resulting in excessive androgen and defective estrogen production and greater frequency of irregular, anovulatory cycles [39]. In conclusion, obesity related hormonal alterations in adolescents and at young age might really be defining factors for infertility and nulliparity and associated cancer risk of breast and female genitalia [17].

Before menopause, breast cancer incidence is relatively low and adiposity is regarded as a moderately protective factor against this tumor presumably conferred by the obesity associated defective estrogen synthesis [40]. Nevertheless, in the vast majority of young obese cases with healthy estrogen predominance, a female-like, gluteofemoral adipose tissue deposition is characteristic [41]. In premenopausal women, male-like, central body fat accumulation (high waist-hip ratio) is a predictor of breast cancer risk, whereas a lower body type adiposity (low waist-hip ratio) may be protective [42]. Consequently, in young obese women their preserved estrogen level may confer protective effect against breast cancer instead of obesity [17].

In postmenopausal women, obesity has been identified as a high risk factor for breast cancer being attributed to the presumed excessive estrogen production of their adipose tissue mass [9, 43]. However, in obese postmenopausal cases, the regional distribution of fat deposition typically affects the visceral region in close correlation with their dysmetabolism and high breast cancer incidence [9]. By contrast, hormone replacement therapy has protective effect against breast cancer risk [44] as estrogen substitution may counteract the central obesity related insulin resistance [17].

BMI and *ovarian cancer* risk exhibits weak positive association even after multivariate adjustment (RR=1.26) [11]. By contrast, male-like central adiposity measured by waist-to-hip ratio is a key factor in ovarian cancer development [12, 13] suggesting the involvement of androgen accumulation in abundant adipose tissue [45].

The correlation between BMI at adolescence and at age 18 years and ovarian cancer risk tended to be stronger than that with BMI at baseline [46, 47], suggesting that obesity related hormonal imbalance during puberty or early adulthood is particularly relevant for ovarian cancer [11]. Among premenopausal cases, obesity, nulliparity, irregular menstrual cycles and diabetes were strongly associated with endometrial cancer risk and it was frequently associated with synchronous primary cancer of the ovary [6]. Among postmenopausal cases, the adverse effect of excessive body mass on ovarian cancer risk is most apparent among women who never used HRT [11]. Conversely, in HRT user obese cases, interaction between dysmetabolism and hormone treatment cancelled the cancer risk of adiposity.

A Long Way from Unopposed Hyperestrogenism to Estrogen Deficiency as Mediator of Cancer Risk in Obesity

The idea of correlation between female sexual steroids and breast cancer risk had emerged more than 100 years ago based on empirical findings. Breast cancer was demonstrated to exhibit good remission after ovariectomy in premenopausal women [48]. These results were interpreted as equivocal justification for the cancer provoking effect of ovarian female sexual steroids and the surgical removal of ovaries was regarded as adequate therapy against the presumed excessive estrogen synthesis.

In the early 60s of past century endogenous hyperestrogenism as a causative factor of breast cancer in obese women was still under debate [49]. Since then, clinical and epidemiological studies have increasingly pointed to an elevated cancer risk of high circulating estrogen level for breast and female genital tract. At the same time, overweight and obesity in women seemed also to be strong breast cancer risk factors [50]. These principles were arbitrarily linked and finally, increased cancer risk in obese women was attributed to the elevated circulatory estrogen level as a presumed mediator between adiposity and cancer development.

Nevertheless, the exact role of male and female sexual steroids in the correlations between obesity and cancer risk seems to be highly controversial up to the present.

The Development of Estrogen Hypothesis

Breast cancers became the most important subjects of cancer research as they are the most frequent female tumors of the Western world. In the early 70s of the 20th century, the evidence that elevated estrogen level increases the risk of human neoplasms was not reassuringly justified [51]. In case of obese women increased estrogen level was regarded as mediator of breast cancer development by certain authors [52, 53], although other publications could not support this correlation [54, 55].

In the 80s and 90s of the past century the carcinogenic capacity of female sex steroid hormones had become a prevailing concept under the name of "*estrogen hypothesis*". Endogenous estrogen was regarded as a strong risk for breast cancer even in cases of slightly elevated circulatory levels [56, 57, 58]. Exogenous estrogens administered either alone or in

combination with progestin were also found to be risk factors for breast cancer. The majority of controversial results regarding hormone replacement therapy (HRT) in postmenopausal women further supported the relative breast cancer risk in summarized population based epidemiological studies [59, 60].

Endometrial cancer is the most common invasive malignancy of the female genital tract, with both pre- and postmenopausal variants [61]. Among others, obesity, metabolic syndrome, type 2 diabetes, anovulatory infertility, nulliparity and exogenous hormone use; such as HRT were regarded as risks for endometrial malignancies [62, 63]. Hyperestrogenism was regarded as a causal factor for endometrial hyperplasia, which may be the predecessor of endometrial adenocarcinoma [64]. Epidemiologists have accepted exogenous estrogen administration as high risk for endometrial cancer [65, 66] and increased endometrial cancer risk was established with increasing estrogen doses [67].

A dualistic model of endometrial carcinogenesis was proposed with the establishment of two main types of tumors in correlation with circulatory estrogen supply [68]. The highly differentiated type I form of endometrial cancer may be associated with HRT use and is less aggressive, whereas the poorly differentiated type II form typically affects elderly, hormone deficient women.

An important parallelism may be observed between breast and endometrial cancers. Only the estrogen receptor positive, highly differentiated, slow growing forms have been assumed to be associated with HRT use [63, 69] suggesting that the higher the female hormone supply the milder and more differentiated the developing tumor. Moreover, certain literary data established that hormone treatment by oral contraceptives decreases the cancer risk of highly hormone dependent organs [67, 70].

Ovarian cancer represents about 30% of all malignancies of the female genital tract and the economically advanced countries of North America and Europe show the highest rates. The age adjusted incidence rates vary from <2/100 000 women in most of Southeast Asia and Africa to >15/100 000 cases in Northern and Eastern Europe [71].

The incidence of ovarian cancer shows a steady increase with age. Reduced risk of the disease is consistently associated with high parity and oral contraceptive use [72]. Energy rich diet and insulin resistance have also been related to ovarian cancer risk [73]. In the USA an increased risk of ovarian cancer mortality was associated with postmenopausal estrogen use based on a large prospective study [74]. A collaborative reanalysis of European studies found a relative risk of ovarian cancer related to use of HRT [75]. In a cohort study a strong relationship was established between duration of estrogen therapy and risk of ovarian cancer [76].

In conclusion, the carcinogenic capacity of circulating estrogens became a prevailing concept at the turn of the millennium, particularly in association with the malignancies of highly hormone dependent female organs [77].

Sexual Hormone Levels and Cancer Risk in Obese Premenopausal Women

Polycystic ovarian syndrome (PCOS) is the most common endocrinopathy of women in the reproductive age with an increased prevalence of metabolic syndrome [78]. This entity seems to be a pathological model of the hormonal and metabolic alterations of postmenopausal status in premenopausal women. It is usually manifested by symptoms like

long and/or irregular menstrual cycles, anovulation, infertility, hirsutism, acne and obesity and indicates a conspicuously increased risk for cancers at highly estrogen dependent sites [79, 80].

Several authors presumed that *high estrogen levels unopposed by progestin* continuously stimulate estrogen receptors (ERs) in premenopausal women with PCOS, which may be a mechanism of gynecologic and breast cancer initiation [38]. Additional support of the carcinogenic effect of unopposed high estrogen levels comes from many studies reporting on the association of increased total and bioavailable estrogens and decreased sex hormone binding globulin (SHGB) levels with risk of endometrial cancer [7]. Combining the cases and controls from three prospective cohorts in New York, Northern Sweden and Milan, there was a six fold increase in endometrial cancer risk in the top quintile of bioavailable estradiol as compared with the bottom quintile [81].

Nevertheless, conspicuous geographic differences in altitude may have a great role in the finding of misleading correlations between bioavailable estrogen level and cancer morbidity. Poor light exposure in Northern countries may provoke deleterious hormonal alterations, including defective estrogen synthesis [34]. Consequently, it is hard to gain correct results by combining the data of cancer cases and tumor free controls deriving from New York, Northern Sweden and Milan.

A large case-control study showed even decreased total and bioavailable estradiol levels in premenopausal patients with endometrial cancers [82], seeming to contradict the high estrogen level hypothesis. It has been proposed that in premenopausal women low progesterone, rather than increased estrogen level may be the crucial determinant of endometrial cancer risk [83] construing the concept of *unopposed normal estrogen level* attributed to defective progesterone synthesis. Nevertheless, no studies have been conducted to examine the endometrial cancer risk in relation to measurements of endogenous progesterone. Such studies would be rather difficult because of the wide variation in progesterone levels during the menstrual cycle [7].

The unopposed normal estrogen level as cancer risk was apparently supported by the fact that neither endometrial mitotic activity nor cancer risk increase additionally at estradiol levels above a limit of 50 pg/ml. This limit was established in the early follicular phase of the menstrual cycle [83]. The stopping of endometrial mitotic activity in the early follicular phase may defend the endometrium from excessive proliferation though ovulation requires further hormone rise.

The self-limited proliferative activity of the endometrium even in case of rising estrogen supply suggests that obesity may not mediate increased endometrial cancer risk by either total or bioavailable estrogen production in premenopausal women [7]. Moreover, obesity in young women is typically associated with menstrual disorders and chronic anovulatory infertility [84], suggesting that they have rather low estrogen level instead of hyperestrogenism. This assumption seems to be consistent with the detected inverse relationship between BMI and serum estradiol levels found in premenopausal cases, particularly in the follicular phase of the cycle [85].

The next step on the route leading to the decoding of increased gynecologic and breast cancer risk in obese women was the revelation of *ovarian hyperandrogenism*. It was published in the early 1970s that in women with hormone dependent breast cancer increased urinary androgen excretion and endometrial hyperplasia are concomitant findings [86]. The menstrual cycle disorders, anovulatory infertility, hirsutism and acne also suggested excessive

androgen synthesis instead of dangerous hyperestrogenism. Similarly, women at increased risk of developing endometrial cancer exhibited elevated plasma levels of both androstenedione [85, 87] and testosterone [88].

In premenopausal women, PCOS is associated with insulin resistance and chronic elevated fasting and non-fasting plasma insulin levels [89]. Hyperinsulinism promotes excessive luteinizing hormone (LH) and decreased follicle stimulating hormone (FSH) secretion in the hypophysis. These hormonal alterations induce a shift of ovarian and adrenal steroidgenesis to the predominance of androgen production at the expense of estrogen loss [90]. Women with PCOS have strongly increased prevalence of endometrial cancer, particularly in young infertile cases below the age of 40 [89]. In cases with PCOS, excessive ovarian androgen production may play central role in the development of gynecologic malignancies [91].

The androgen-excess theory appeared to completely contradict the earlier accepted central role of estrogens in the carcinogenic process of the breast and endometrium. Histologic examination of the removed ovaries of premenopausal breast cancer cases with high androgen excretion exhibited strong interstitial theca cell hyperplasia justifying the increased ovarian androgen synthesis [92]. Breast cancer cases with supernormal urinary testosterone excretion have nearly twice as high tumor remission rate after therapeutic ovariectomy as do those with normal testosterone excretion [93]. The transitory remission of mammary cancer by medical or surgical ovariectomy could be explained by the definite cessation of excessive ovarian androgen production.

Nevertheless, the medical treatment of hyperinsulinism may improve the FSH synthesis of hypophysis resulting in a return to predominant estrogen production in the ovarian theca cells [94]. In young anovulatory women, insulin sensitizing Metformin treatment decreased the excessive insulin and androgen synthesis and at the same time helped to achieve regular menstrual cycles and ovulation. Moreover, an artificial hormonal cycle created by oral contraceptives or treatment with an estrogen derivative improves both the hormonal alterations and metabolic disorders and is preventive against cancer risk in young infertile women [19, 95]. These recently introduced therapeutic possibilities justify that in anovulatory young women medical recovery of sexual hormone balance is strongly cancer preventive [17].

Correlations between Obesity and Estrogen Loss after Menopause

For women aged 55-65 years, weight gain is one of their major health risks [96]. Many studies have focused on the question of whether midlife weight gain is simply an age related alteration or may be attributed to the hormonal changes that occur in relation to menopause [97, 98]. Effects of the loss of ovarian hormone production on body weight and body composition are thoroughly studied in both animal models and human populations.

In experimental mice, loss of ovarian function promoted a diet-independent increase in adipose tissue mass and associated dysmetabolic pathologies. Oophorectomized mice exhibit decreased energy expenditure without concomitant change in energy intake, resulting in hypertrophy and inflammation of adipose tissue as well as development of fatty liver [99]. By contrast, estradiol supplementation in oophorectomized mice supplied protection from hepatic steatosis, insulin resistance and adipose tissue hypertrophy [100].

Preferential accumulation of central fat is a special consequence of estrogen deficiency that was supported by studies on aromatase gene knock-out (ArKO) mice, being incapable of synthesizing endogenous estrogens [101]. Estradiol replacement in female ArKO mice reduced the volume of adipocytes without changes in their fatty acid synthesis. This observation suggests that the lower lipid uptake from the circulation may be the main mechanism by which estradiol decreases fat accumulation.

The prevalence of abdominal obesity is almost double that of general obesity and shows an increasing trend as women age. In the US, 65.5% of women aged 40-59 years and 73.8% of women over the age of 60 exhibited central adiposity in 2008 [2]. Studies on the correlation between menopause and changes in body composition in Chinese women suggest that menopause has an independent effect on the increase in both fat mass and abdominal adiposity [102].

Results of studies on both experimental animals and postmenopausal women justified that loss of ovarian function promotes a diet-independent increase in adipose tissue deposition particularly in the metabolically dangerous abdominal location [96]. Increasing body weight during the menopausal transition aggravates the menopausal symptoms as well. Obesity proved to be an independent risk factor for severe menopausal symptoms [103] suggesting that excessive fat mass disturbs the hormonal and metabolic adaptation to the menopausal transition.

Good hormonal equilibrium in premenopausal cases may be associated with later age at natural menopause. A later menopause has been associated with non-smoking, regular moderate alcohol consumption and strenuous exercise, which all are advantageous for estrogen synthesis. By contrast, as smoking and type-2 diabetes have a decreasing effect on estrogen production they may predict an earlier menopause [104].

Bilateral oophorectomy is applied as a supposed risk reduction strategy in BRCA mutation carrier women, although data on its long term effects are not available. The joint effect of obesity and early oophorectomy on mortality was significantly greater than expected. Obese women who had an oophorectomy at less than 40 years were more than twice more likely to die than their age matched non obese controls, attributed particularly to CVD [105]. Obesity associated defective estrogen synthesis and a further sudden estrogen loss caused by early artificial menopause may explain this increased mortality.

Correlations between postmenopausal obesity and hormone replacement therapy and their impact on cancer risk seem to be a highly controversial area. The prevailing concept is the hyperestrogenism of obese women after menopause as excessive endogenous estrogen is presumably synthesized in their abundant adipose tissue by means of aromatization of androgens [22]. In concordance with the estrogen hypothesis, in obese postmenopausal women a highly positive association between adiposity and female organ cancers is expected to be more evident in HRT users, attributed to their extra hormone supply [11]. By contrast, the relation between adiposity and female cancers is equivocally weaker among obese HRT users as compared with obese never users.

This puzzling, beneficial interaction between HRT and adiposity has been shown for all female cancers. HRT in obese postmenopausal women equivocally reduced the incidence of endometrial [7], breast [21] and ovarian malignancies [22]. As a forced explanation, the estrogen hypothesis was justified by an assumption that the high endogenous estrogen level of older obese women may not be markedly increased by HRT use. Nevertheless, if HRT could not modify the presumably high endogenous estrogen level in obese women, cancer risk

would be the same in HRT users and non-users. Conversely, a real approach is that estrogen use means a counteraction against female cancers in obese, hormone deficient postmenopausal women by its antiobesity, antidiabetogenic and anti-inflammatory capacities [17].

Changing Concepts Concerning Associations of Hormone Replacement Therapy and Women's Health

From the early 70s clinical and epidemiological studies increasingly pointed to elevated breast, endometrial and ovarian cancer risk of hormone replacement therapy (HRT) for postmenopausal women [77]. Principal results from the Women's Health Initiative (WHI) randomized controlled trial in 2002 established that overall health risks, particularly that of breast cancer exceeded benefits from use of combined estrogen plus progestin therapy among postmenopausal US women [106]. This publication led to a sharp decline in postmenopausal HRT use and many women unnecessarily refused hormone treatment.

Use of HRT exhibited highly controversial associations with female cancer risk in the past decades [15, 16, 107, 108]. Estrogen deficiency as cancer risk factor emerged among elderly female cases, based on the age and gender related risk of oral cancer [109, 110]. Nevertheless, the carcinogenic capacity of estrogen therapy remained the prevailing concept but recently, the opinions of scientists have been partially changed.

A breakthrough in breast cancer research came in 2010 in San Antonio when Canadian scientists reported on the re-evaluation of earlier results of the original WHI Hormone Replacement Therapy Trial. After proper selection of patients and controls according to their risk factors, HRT use proved to be not only safe but strongly protective against breast cancer as well as many other aspects of women's health [111].

In 2011, the results of great HRT studies on homogenously selected hysterectomized cases and controls yielded a strikingly unexpected breast cancer protective effect of one-armed estrogen treatment [112, 113]. As the health risk of women after hysterectomy may be near uniformly high because of the abrupt, shocking hormone deprivation, these methodologically strong studies resulted in correct conclusions [17, 108].

Since then an increasing number of evidences from clinical trials suggest that unopposed estrogen treatment does not increase the risk of breast cancer, even it may reduce it [111, 113-117]. Recently, the effect of estrogen avoidance on mortality rates was studied among hysterectomised women aged 50 to 59 years [118]. Over a 10-year span, starting in 2002, a minimum of 18 601 and as many as 91 610 postmenopausal women died prematurely because of the avoidance of estrogen therapy (ET). ET in hysterectomised postmenopausal women was associated with a decisive reduction in all-cause mortality. The authors established that changing concepts about the effects of ET seem to be a matter of considerable urgency.

The Global Consensus Statement on Menopausal Hormone Therapy means a milestone in core recommendations regarding HRT [119]. Representatives of major regional menopause societies cautiously but progressively established that in women with premature ovarian insufficiency, systemic HRT is recommended at least until the average age of natural menopause. Moreover, standard-dose estrogen-alone HRT use was regarded as an advantageous measure to decrease coronary heart disease and all-cause mortality in postmenopausal women.

Correlations between Estrogen Signaling and Lifestyle Factors Affecting Body Weight

The dramatic increase in occurrence of overweight and obesity over the past several decades is attributed in part to changes in dietary and lifestyle habits, such as rapidly changing diets, increased availability of high-energy foods, and reduced physical activity of people in both developed and developing countries [120, 121].

As estrogens have beneficial effects on energy metabolism and glucose homeostasis, sufficient estrogen exposure and intact signal transduction of estrogen receptors (ERs) have great role in defensive processes against obesity and insulin resistance [23, 122]. Body mass and insulin sensitivity are highly defined by food intake and physical activity, both of which are in close correlation with estrogenic regulation. These associations explain the impact of defective estrogen signaling on the increased risk of obesity, type 2 diabetes, cardiovascular disease and malignancy in both infertile young and postmenopausal women [108].

In the central nervous system hypothalamic nuclei are the key regulators of food intake and energy expenditure by means of their estrogen receptors [123]. In animal experiments ERα activation results in decrease in food intake [124], whereas silencing of ERα and predominance of ERβ leads to hyperphagia, obesity, decreased glucose tolerance and reduced energy expenditure [125]. The central effects of ERs seem to have a balanced interplay regarding the maintenance of ideal body mass with continuous adaptation to the changing intra and extracellular stimuli [122].

Emerging evidences suggest that diets rich in phytoestrogens (isoflavones and lignans), namely soy protein and flaxseed, may have beneficial effects on many aspects of diabetes and obesity [126]. These findings suggest that long-term substitution of animal protein by vegetable protein in a low-energy diet may provide additional benefit for weight reduction in obese subjects. Several nutritional intervention studies in animals and humans indicate that consumption of soy protein reduces body weight and fat mass in addition to lowering plasma cholesterol and triglyceride levels [127].

In animal models of obesity, soy protein ingestion limits or reduces body fat accumulation and improves insulin resistance. *In ovariectomized monkeys, both dietary soy protein and estrogen replacement therapy improved cardiovascular risk factors and decreased aortic cholesterol ester content* [128].

In obese people, dietary soy protein also reduces body weight and body fat mass in addition to reducing plasma lipid levels and improving insulin sensitivity [127]. Phytoestrogens, such as isoflavones and lignans may also exert beneficial effects on tissue lipid content through their antioxidant actions [126].

Soy in diet seems to be beneficial and preventive against breast cancer if consumed early in life before puberty or during adolescence based on the results of immigrant and epidemiological studies [129]. Prepubertal estradiol and genistein exposures may reduce later breast cancer risk even in BRCA gene mutation carrier cases by inducing a persistent, effective upregulation of the tumor suppressor gene [130]. Phytoestrogen containing diet is highly protective as regards breast cancer in adult women as well, based on epidemiological observations [131]. Soybean extract with phytoestrogen component also proved useful as therapeutic agent for solid cancers, such as mammary malignancies [132].

Skeletal muscle mass is responsible for 75% of the insulin-mediated glucose uptake in the body and consequently, physical activity is in direct correlation with insulin sensitivity [133]. The majority of literary data support the fact that strong physical exercise has beneficial effect on insulin sensitivity in normal as well as insulin resistant populations [134]. When energy intake exceeds energy expenditure over a prolonged period of time, the result is a positive energy balance, which leads to the development of obesity.

Adequate levels of regular physical activity appear to be important for prevention of weight gain and treatment of obesity. Physical activity also appears to have an independent, advantageous effect on health, suggesting that adequate levels of physical exercise may also counteract the negative influence of excessive body weight on health outcomes [135]. The health advantage of regular physical activity is equivocal and exercise plays pivotal role in the prevention of breast cancer in both obese and lean women [136, 137].

Sufficient estrogen exposure provides advantageous improvement of cellular glucose uptake via regulation of insulin receptor signaling and by the promotion of expression and intracellular translocation of glucose transporters [138, 139]. During estrogen loss in both perimenopausal and postmenopausal periods, muscle strength exhibits a striking decline that can be reversed by hormone replacement therapy (HRT), suggesting that estrogens are important players in muscle physiology [140, 141].

Nevertheless, there are controversial literary data concerning the correlations between health improving physical exercise and estrogen level in women. The traditional concept supports a role of estrogens in the development and growth of breast cancer. Lowered estrogen exposure associated with physical activity was erroneously presumed to reduce breast cancer recurrence and new diagnoses in high-risk women [142]. Further studies supplied evidences for an inverse association between physical activity and breast cancer risk, which was stronger against mammary carcinogenesis in postmenopausal than in premenopausal cases [143]. This valuable observation suggests that physical activity rather increases estrogen levels, which exhibits stronger anticancer defense for estrogen deficient older women as compared with young cases. Recently, physical activity seems to have become a potential intervention for treating women with reduced estrogen function [144]. Weight loss alone did not improve glucose utilization and insulin sensitivity in postmenopausal women; however, when weight loss was coupled with exercise training, it resulted in a significant improvement in both outcomes [145]. Healthy diet alone was not found effective at reducing circulating inflammatory markers in obese postmenopausal women; but when coupled with exercise training, there was a significant reduction in these same cytokines [146]. Recent data have shown that physical activity improves not only the metabolic dysfunctions but also the survival rates of postmenopausal women with breast cancer [147]. These data suggest that exercise training is an advantageous intervention that is critical to women clinically experiencing reductions in estrogen function.

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