

Review

# Insulin resistance, obesity and breast cancer risk

C. Pichard<sup>a</sup>, G. Plu-Bureau<sup>a</sup>, M. Neves-e Castro<sup>b</sup>, A. Gompel<sup>a,\*</sup>

<sup>a</sup> *Unité de Gynécologie endocrinienne, Hôtel-Dieu, APHP, Université Paris-5, 1 Place du Parvis Notre-Dame, Paris, France*

<sup>b</sup> *Clinica de Feminologia Holistica, Lisbonne, Portugal*

Received 1 November 2007; received in revised form 10 March 2008; accepted 17 March 2008

## Abstract

Breast cancer (BC) is one of the most important problems of public health. Among the avoidable risk factors during a woman's life, overweight and obesity are very important ones. Furthermore they are increasing worldwide. The risk of breast cancer is traditionally linked to obesity in postmenopausal women; conversely, it is neutral or even protective in premenopausal women. Since the initiator and promoter factors for BC act over a long time, it seems unlikely that the menopausal transition may have too big an impact on the role of obesity in the magnitude of the risk. We reviewed the literature in an attempt to understand this paradox, with particular attention to the body fat distribution and its impact on insulin resistance. The association of insulin resistance and obesity with BC risk are biologically plausible and consistent. Estradiol (E2) and IGFs act as mitogens in breast cancer cells. They act together and reciprocally. However the clinical and biological methods to assess the impact of insulin resistance are not always accurate. Furthermore insulin resistance is far from being a constant feature in obesity, particularly in premenopausal women; this complicates the analysis and explains the discrepancies in large prospective trials. The most consistent clinical feature to assess risk across epidemiological studies seems to be weight gain during lifetime. Loss of weight is associated with a lower risk for postmenopausal BC compared with weight maintenance. This observation should be an encouragement for women since loss of weight may be an effective strategy for breast cancer risk reduction.

© 2008 Elsevier Ireland Ltd. All rights reserved.

**Keywords:** BMI; Waist-to-hip ratio; Waist circumference; Estradiol; Testosterone; IGF-I; Adipocytokines

## Contents

1. Introduction .....	20
2. Obesity and breast cancer risk .....	20
3. Relationship between height, BMI and BC .....	22
4. Anovulation and menstrual cycle disturbances in obese women .....	22

**Abbreviations:** BMI, body mass index; HT, hormonal therapy; IR, insulin resistance; WHR, waist-to-hip ratio; WC, waist circumference; SHBG, sex hormone binding globulin; ERE, estrogen responsive element.

\* Corresponding author. Tel.: +33 142348099; fax: +33 143298766.

E-mail address: [anne.gompel@htd.aphp.fr](mailto:anne.gompel@htd.aphp.fr) (A. Gompel).

5.	Detection bias .....	22
6.	Heterogeneity of obesity in premenopausal women .....	22
7.	Biological data in premenopausal women .....	23
8.	Central obesity .....	23
9.	Breast cancer in women with type 2 diabetes .....	24
10.	Biological markers of insulin resistance and BC risk .....	24
11.	Adipocytokines as markers of insulin resistance and BC risk (Table 2) .....	25
12.	Insulin resistance, obesity and breast cancer risk: biological plausibility .....	26
12.1.	Insights from biology: IGF-I and breast cancer .....	26
12.2.	Insulin resistance and IGF-I during fetal life .....	26
12.3.	Insulin resistance and IGF-I during adult life .....	26
13.	Effects of HT on insulin resistance and IGF-I .....	27
13.1.	HT and insulin resistance .....	27
13.2.	HT and IGF-I plasma level .....	27
14.	The best body size predictor: weight gain along women life .....	27
15.	Conclusions .....	28
	Conflict of Interest .....	28
	References .....	28

## 1. Introduction

BC is the first prevalent cancer in women with an unacceptable high morbidity and mortality. The development of breast cancer may involve genetic predisposition and environmental exposure, such as a high energy western diet, weight gain (WG), lack of physical activity, alcohol consumption.

Thus, the most promising strategy to control cancer is a global commitment to prevent it; there is a compelling need to identify modifiable factors that are related to BC, like overweight and obesity. The progressive dramatic increase in obesity, both in western and in developing countries, might contribute to the recent increase in the incidence BC.

However, the classical assumption derived from epidemiological studies is that obesity is protective of BC, or even neutral, during the premenopause whereas it would be deleterious in the postmenopause. It is quite paradoxal that the same factor may have such opposite effects. Since the initiator and promoter factors for BC are acting over a long time it seems very unlikely that the menopausal transition may be in itself so important for the risk of obesity. Obesity may increase the risk through different mechanisms, such as the estrogen production through the aromatisation androgens in the adipose tissue and the insulin resistance, too. Insulin resistance, which usually increases with age, is a feature of postmenopausal estradiol

deficiency; estrogenic treatments may improve the postmenopausal insulin resistance. Insulin resistance is not always present in premenopausal obese women, what reflects the heterogeneity of obesity. The mechanism through which obesity might protect from BC is unclear.

## 2. Obesity and breast cancer risk

Recent epidemiologic studies have shown a positive relationship between BMI and BC with a significant relative risk (RR) ranging from 1.26 to 2.52 (Table 1). The effect of the increase in BMI on BC risk was especially observed in ER+PR+ tumors and in HT (hormonal therapy) non-users [1].

From these results it appears that the increase in BMI (or weight) is correlated to BC risk only in postmenopausal women. The relationship between the increased BC risk and obesity is explainable by an increase of estrogens; in obese women they are produced by the aromatisation of adrenal androgens in the peripheral and central fat mass. Alternatively, insulin resistance may counteract it, resulting in lower SHBG levels and thus more available free steroids.

However, much less studies have looked at the risk of BC in premenopausal women; they found either no effect or an inverse relationship between BMI and BC risk (Table 1), but three previous studies (1991–1998)

Table 1  
BMI and breast cancer risk in pre- and postmenopausal women

		N cases	Age (years)	RR BMI K postmenop	RR BMI premenop	Anthopometric measures
Van den Brandt (2000); USA, Europe	Meta-analysis 33,819 5 years follow-up	4385 3208 post 723 prem	47–68	1.27 (1.03–10.55)	0.54 BMI 21 vs. 33	Self-reported questionnaire
Shu (2001); Chinese	Case–control	1500	25–64	2 (1.2–3.2)	NS	Medical staff
Lahmann (2002); Sweden	Cohort 12,159	245	59.9 ± 7	1.54 (1.01–2.35)	ND	Medical staff
Morimoto (2002); WHI, USA	Cohort 85,917	1030	50–79	2.52 (1.62–3.93)	ND	Medical staff
Feigelson (2004); USA	Cohort 62,756	1934	60–64	1.6 (1.22–2.12)	ND	Self-reported
Lahmann (2004); EPIC	Cohort 75,342 103,344 post	1879 Follow-up 4.7 years	45 pre 64 post	1.38 (1.08–1.76)	NS	Medical staff
Eng (2005); Long Island	Case–control 96–97	990 1006	20–98	1.6 (1.11–2.26)	ND	Self-reported
Krebs (2006); USA	Cohort 7523	350	73 ± 5	1.55 (1.13–2.13)	ND	Medical staff
Han (2006); USA	Case–control	1116 2005	35–79	1.57 (1.18–2.10)	NS	Medical staff
Tehard French (2006)	Cohort 69,116	275 prem 860 post	43 pre 52 post	RR: 1.45 (1.04–1.99)	0.61 (0.42–0.89)	Self-reported
Widerpass (2004)	Cohort 99,717	Follow-up 8 years 733 prem	40 27% >25	ND	0.62 (0.40–0.97)	Self-reported

Prem: premenopausal; post: postmenopausal.

had found a positive association between high BMI level and breast cancer before the menopause [2].

These discrepant results can be explained by different factors.

### 3. Relationship between height, BMI and BC

BMI is related to height which is an independent factor associated with BC, mainly studied in postmenopausal women [3,4]. A recent publication from the Nurses' Health Study shows that premenopausal women in the tallest group (>1.75 m) had more than a 50% greater risk of BC compared with the shortest women (<1.60 m) [5]. In taller women the BMI (the ratio of weight to height) is reduced and thus BMI may probably not be a good marker. Why would taller women have an increased risk of BC? High height is determined by many variables: genetic factors and by energy balance during childhood and adolescence, which is determined largely by caloric intake.

Breast tissues appears to be most susceptible to malignant transformation during adolescence, when undifferentiated cells are undergoing rapid proliferation and growth, a period that may be particularly important in terms of subsequent BC risk. In addition, timing and rate of growth may also influence risk. Several studies have shown a decreased premenopausal and postmenopausal BC risk in women who reached their adult height at age 18 or later compared to those who reached it before that age [6]. In girls who experience an early growth spurt, the maturing breast tissue may be exposed to high levels of growth hormone and IGF-1 at an earlier age and for a longer period of time, but this finding was not confirmed in later studies [6].

Similarly, the inverse association between high BMI and premenopausal BC risk might be explained by a slower adolescent physical growth due to prepubertal excessive body fat; this would lead to less mammary gland exposure to IGF-1 [7].

### 4. Anovulation and menstrual cycle disturbances in obese women

The principal hypothesis to explain the inverse association between high BMI and premenopausal BC is the anovulation in heavier women. Secondary to anovulation there is a lesser exposure to progesterone. It

has been suggested that a reduced number of ovulatory cycles may reduce the risk of BC. In a previous version of the Nurses' study [8], the reduced BC risk was consistent with the hypothesis that anovulation and abnormal cycles were protective against BC. However, heavier women were slightly more likely to experience long cycles or anovulation. According to other studies [9,10] the prevalence of anovulation has been shown to be increased only in a small minority of obese women. This hypothesis was not recently confirmed neither by the Nurses' study nor by the NOWAC study 2004, two large prospective studies including, respectively 113,130 and 99,717 premenopausal women [2,7]. In these reports, the association with adult BMI and BC risk was not influenced neither by the exclusion of women who reported irregular menses nor by infertility. The authors of the Nurses' [2] concluded that anovulation does not seem to be a primary explanation for the reduced BC risk and high BMI in heavier premenopausal women.

### 5. Detection bias

Finally, detection bias cannot be excluded in the observed associations. Obese women are less likely to have breast cancer screening [2]. Overweight and obese women have larger breast and thus tumor detection may be more difficult in these women simply because tumors are more difficult to palpate in larger breasts. This hypothesis is supported by several studies showing a positive relationship between breast size, BMI and later stages of breast cancer [11]. The fact that the protective effect of high BMI was retrieved in cohort studies and not in case-control studies underlines the possibility of delayed diagnosis occurring with systematic screening at the age of the menopause (Table 1). Another bias could be the lack of precision of age at menopause in obese women, due to chronic anovulatory amenorrhea. This could lead to misclassification and artificially decrease the number of premenopausal BC compared to postmenopausal overweight patients.

### 6. Heterogeneity of obesity in premenopausal women

The expression of obesity is heterogeneous in young women; the hormonal environment may be quite vari-

able. The importance of insulin resistance among obese patients is not yet very clear, especially among premenopausal women. Peripheral obesity is more prevalent in younger women and is not associated with insulin resistance. It was shown in a recent Spanish study that only 28% of an obese cohort displayed feature of polycystic ovary syndrome (PCOS) [12,13]. Anovulation and abnormal menstrual cycles are more frequently associated with upper body fat obesity than lower body fat obesity [14]. In addition, in central obesity estrogens are elevated as well as androgens. Besides that, peripheral obesity can be associated with either high, normal or low plasma levels of circulating estrogens. Thus to better establish the responsibility of obesity and insulin resistance in the BC history, it is recommended that the menstrual cycle history and the type of obesity be carefully collected in epidemiological studies.

## 7. Biological data in premenopausal women

Results from hormone assays in premenopausal women are sparse in part because of the complexity of measuring hormone levels that vary cyclically and have led to some conflicting data. Increased risk of BC was mainly associated with elevated androgens in two studies, the EPIC study (285 cases) [15] and an Italian study, the ORDET study (65 cases) [16]. In EPIC, testosterone, delta-4-androstenedione and DHEA-S were associated to BC, with an OR for highest vs. the lowest quintiles of, respectively 1.73 (95% confidence interval 1.16–2.57); 1.56 (95% confidence interval 1.05–2.32); 1.48 (95% confidence interval 1.02–2.14). In the ORDET study, elevated free luteal testosterone was associated with BC in premenopausal women, with a RR: 2.85 (95% confidence interval 1.1–7.33). Interestingly, the level of luteal progesterone was inversely associated with BC risk in these two studies, suggesting that hypothesis of protection conferred by a low progesterone level is not compelling. No significant interaction was reported between others hormones, like estradiol level, and BC in some studies, whereas in the Nurse's study II (197 cases) opposite results were reported [17]. They concluded that both the plasma levels of estrogens and androgens were associated with the risk of BC in premenopausal women. When analysis was restricted to invasive cases, the magnitude of the

association between BC and high androgen levels was similar to that reported in EPIC and ORDET studies, which included only invasive cases. The increase in androgens as a risk factor argues in favour of the predominant role of insulin resistance in the pathogenesis of breast cancer, in premenopausal women.

## 8. Central obesity

The question of whether body fat distribution contributes to the risk of breast cancer is of considerable interest. Central adiposity, a clinical marker of insulin resistance and metabolic syndrome, is associated with multiple biological metabolic changes such as hyperinsulinaemia, increase in free fatty acids level and triglycerides and hypoHDL-cholesterol. Hyperinsulinemia reduces sex hormone binding globulin (SHBG) levels resulting in an increase in free estrogen and androgen levels. Aromatisation of the androgens in adipose tissue leads to an increase in the estrogen plasmatic levels particularly in estrone in postmenopausal women. Central overweight thus may provide additional plasmatic estrogen amount to the postmenopausal mammary gland. However, some may also consider that local production of estrogens within the breast is the important factor. There are interactions between insulin and some adipokines on aromatisation. Leptin and cortisol were shown to increase aromatase activity [13]. Furthermore insulin itself can potentiate estrogen effects at the cellular level by the cross-talk between estrogen and the IGF-I pathways. In premenopausal women metabolic syndrome is often associated with features of PCO syndrome as high androgens levels and anovulation.

Insulin resistance can be assessed through clinical or biological markers. The main clinical marker used in large cohort studies in men and women was waist-to-hip ratio (WHR). Previous epidemiological studies of body fat distribution using WHR have produced contradictory results some being positively related to breast cancer, others showing no association [18]. These discrepancies can be explained by the quality and the reproducibility of clinical measures, self-reported by patients in most studies. Measurements and their significance among studies are also complicated by anthropometrics discrepancies around the world. Within studies, women are considered as insulin resis-

tant whereas others are not for the same anthropometric measures [19]. Variations between European countries exist with Southern women being more overweighted and more “android” than Northern women [20].

Another reason for these divergences is the absence of stratification by HT use in postmenopausal women. HT use partially masks the increased risk induced by central obesity. In several recent studies [21,22] a strong positive association between central obesity and postmenopausal breast cancer was only observed among postmenopausal women who never used HT.

Moreover, WHR is not the best marker for central adiposity in women. It is not well correlated to computer tomography, the gold standard technique which is better correlated to BMI and waist circumference (WC). In a small case–control study, central adiposity measured by computer tomography was significantly higher in breast cancer patients who had 45% more visceral fat [23]. In metabolic syndrome WC is a more sensitive marker to assess insulin resistance than WHR. Indeed in this ratio, hip circumference assesses a gluteofemoral repartition which seems to be a protector factor from android repartition and from insulin resistance [24,25]. This could explain why severe peripheral obesity (BMI > 40) display a less severe insulin resistant and atherosclerosis profiles than android obesity [24]. In addition, in the studies where WHR failed to demonstrate a relation with BC risk, WC displays a stronger correlation with the risk and appears to be superior to the WHR in providing assessment of visceral obesity [13]. Moreover several authors have shown an inverse relationship between large hip circumference (gynoid type) and risk of breast cancer in premenopausal women [18,21,22].

Lower body fat predominance is frequent in young women. Weight gain during pubertal years is distributed primarily on the hips and buttocks, whereas during later adult life including pregnancy and menopause, fat accumulate preferentially around the waist. It was also reported that obesity at a young age can protect from breast cancer. In the Nurses’ the strongest inverse association was observed between body fatness in childhood and adolescence and incidence of premenopausal BC with RR: 0.48 (95% confidence interval 0.35–0.55) and 0.57 (95% confidence interval 0.39–0.83), respectively [4]. Finally even if WHR is not the best marker in women, a meta-analysis from 19 studies [26] shows that it is

associated with a moderate increase of BC risk both in postmenopausal and premenopausal women.

## 9. Breast cancer in women with type 2 diabetes

A definite argument for the role of insulin resistance in breast cancer risk is the increased incidence in women with type 2 diabetes. A recent meta-analysis among type II diabetic women, including 20 studies with 5 case–control and 15 cohort studies, showed a moderate risk. According to the authors this risk is undoubtedly underestimated since type I diabetes, which accounts for 5–10% of all diagnosed cases of “type II” diabetes, is not a risk factor for BC. Among diabetic women, an increased RR: 1.2 (95% confidence interval 1.12–1.28) was observed, persisting after adjustment for BMI. HT use was assessed in only two studies. This increase in the risk was only observed and assessed in postmenopausal BC women [27].

## 10. Biological markers of insulin resistance and BC risk

There is no definite criterion for assessing insulin resistance, except the euglycemic clamp which cannot be routinely performed. As an epidemiological tool the homeostasis model assessment (HOMA) appears to be relevant. Biological markers of insulin resistance such as the insulin level, the insulin/glucose ratio, HOMA, adiponectin, leptin/adiponectin, decreased SHBG, have been associated with an increased risk of breast cancer essentially in postmenopausal breast cancer women (Table 2).

Lawlor et al. [28] observed a modest but linear increase of BC risk between the lowest and the highest quartiles of insulin level, among postmenopausal non-diabetic women (RR: 1.17 (95% confidence interval 1.01–1.36)). Similarly, Schairer and Hill found a relationship between breast hyperplasia and C-peptide level. C-peptide may be a more reliable marker because of its longer half-life [29]. Verheus et al. noticed a positive relationship between C-peptide level and breast cancer in the EPIC study, but it was restricted to women older than 60 years [30]. However, Sieri et al. showed that, in a prospective follow-up cohort of 10,786 Italian women, the highest plasma glucose levels were asso-

Table 2  
Biological markers of insulin resistance

Author	Study type	Marker	Relative risk (95% CI)
Miyoshi [35]	Case–control 102 BC 100 C	Adiponectin Between high and low tertile	3.63 (1.61–8.19)
Mantzoros [37]	Case–control 100 BC 100 C	Adiponectin Between low and high quartile	0.8 (0.71–0.99)
Tworogger [34] Nurses'	Cohort case–control 1477 BC 2916 C	Adiponectin Between low and high quartile	0.73 (0.55–0.98)
Lawlor [28]	Cross-sectional	Fast insulin Between low and high	1.34 (1.02–1.77)
Furberg [55]	Cohort of 38823 708 BC	HDL-cholesterol Between low and high group with BMI > 25	0.43 (0.28–0.67)
Verheus [30] (EPIC)	Cohort 1141 BC 2204 C	C peptide Between high and low tertile In women older than 60	2.03 (1.2–3.43)
Sieri [31]	Cohort: 8926 289 BC	Glycemic load	2.53 (4.54–4.16)

ciated with a threefold increase in premenopausal BC risk [31].

Interestingly, in a recent Italian cohort study of intervention on nutrition profile, women enrolled in the Hormones and Diet in the Etiology of Breast Tumors Study (ORDET Study) had a RR of breast cancer in the highest quintiles of glycemic index from food and glycemic load (GL) of 1.57 (95% confidence interval 1.04–2.36) and 2.53 (95% confidence interval 1.54–4.16), respectively [32]. The increased risk of dietary GL was confined to those who were premenopausal RR = 3.89 (95% confidence interval 1.81–8.34) and who had normal BMI (i.e. < 25) RR = 5.79 (95% confidence interval 2.60–12.90).

Thus, these biological markers emphasize the role of insulin resistance, both in pre- and postmenopausal breast cancer patients, and seem to be more sensitive markers than the clinical ones.

## 11. Adipocytokines as markers of insulin resistance and BC risk (Table 2)

Adipokines are a group of proteins synthesized in adipose tissue. The cells of the adipose tissue that pro-

duce the adipokines include the fat cells (adipocytes), the stromal cells (fibroblasts) and the macrophages that infiltrate the adipose cell mass [13]. Adipokines circulate in the plasma; the concentrations of most of them, including leptin, TNF- $\alpha$ , interleukin-6 (IL-6), hepatocyte growth factor (HGF), and heparin-binding epidermal growth factor-like growth factor (HB-EGF), are positively correlated with BMI. One exception is adiponectin, the relationship of which with the BMI is a negative.

Leptin: the demonstration that its plasma levels correlate positively with the BMI and that it can be a proliferative factor on breast cancer cells *in vitro* stimulated studies to correlate the levels of leptin in serum or plasma with breast cancer risk. These have produced conflicting results: three case–control studies were positive whereas seven others did not find any correlation. However, the menopausal status or the menstrual cycle phases were not mentioned; it is known that leptin levels vary according to estrogen levels.

Adiponectin: is inversely correlated with insulin resistance [33]. It seems to be a more consistent marker with a RR: 0.7 (95% confidence interval 0.5–0.9) in case–control studies [34]. In contrast to leptin, the three reported epidemiological studies on



adiponectin have all demonstrated an inverse association of the serum adiponectin levels with breast cancer risk [35–37] and cancer aggressivity [35]. It is possible that adiponectin, or the ratio leptin/adiponectin which reflects the amount of fat tissue and hyperinsulinemia, may be a marker of risk for breast cancer in the coming years.

## 12. Insulin resistance, obesity and breast cancer risk: biological plausibility

Epidemiological studies may be the object of some flaws. According to Bradford Hill the establishment of causality between the results from epidemiological observations needs a biological or mechanistic plausibility [38].

### 12.1. Insights from biology: IGF-I and breast cancer

In what concerns insulin resistance, a syndrome including central obesity and BC risk, such a biological plausibility is very consistent. Estradiol (E2) and IGFs act as mitogens in breast cancer cells. They act together and reciprocally. In addition, insulin at supraphysiologic doses may reproduce the IGF-I effects on breast cells. It was shown in breast cancer cell lines that E2 interacts with the whole transduction pathways of IGF. IGFs act through two membrane receptors: IGF type I and type II. Most of the effects of IGFs are mediated by the type I receptor. Activation by the ligand leads to an autophosphorylation and binding to signaling adaptor proteins, like insulin receptor substrate (IRS)-1 and Shc which activate the ERK and PI3-kinase pathways. The IGF binding proteins (IGF-BPs) bind IGFs and thus regulate their bioactivities. E2 upregulates in the long term IGF-RI, IRS-1 and IGF-BPs. In addition E2 increases the production of IGFs by breast cancer cell lines [39,40]. Many studies have shown that IGF-I (as well as EGF) are able to induce the phosphorylation and thus the activation of unliganded estradiol receptor (ER). Moreover, IGF-I can potentiate the genomic effects of E2 but this effect depends on the type of ER target gene. It was recently shown that IGF-I potentiated the effects of E2 on ERE-dependent genes, but not on AP-1 sites which can lead to selective activation of part of the E2 dependent genes. A

fraction of IRS-1 binds to ER alpha, translocates to the nucleus, and modulates ER alpha-dependent transcription of estrogen responsive elements (EREs). ER alpha/IRS-1 interactions are direct and involve the ER alpha AF-1/DBD domain, which is ligand independent; in the presence of E2, however, IRS-1 may act as a repressor of the hormone receptor complex [40]. However, the presence of IGF-I and its receptor as well as their role as prognostic factors in breast cancer remain controversial [41].

### 12.2. Insulin resistance and IGF-I during fetal life

Several reports have focused on a possible role of the insulin resistance environment *in utero* on the fetal mammary gland [42,43]. A stem cell burden theory has been invoked to explain how *in utero* and perinatal factors might impact the lifetime breast cancer risk. There was indication that cord blood plasma levels of IGF-I, and to a lesser extent estradiol and testosterone, are positively correlated with the density of cord blood cells, representing progenitors of hematopoietic cells, endothelial cells and possibly other cell types [42,43].

A recent publication has reviewed the available evidence from 26 studies on the association between birthweight and the risk of breast cancer [44]. The majority of studies identified a positive link between birthweight and premenopausal, but not postmenopausal breast cancer. The relative risk estimate for breast cancer, comparing women with high birthweight to women with low birthweight combining all studies including both pre- and postmenopausal breast cancer, was 1.23 (95% confidence interval 1.13–1.34). It was only significant for premenopausal risk of breast cancer when stratifying according to menopausal status RR: 1.25 (95% confidence interval 1.14–1.38). Since birthweight is strongly related to IGF-I levels in the cord blood these results emphasize the relationship between insulin-like growth factors and the risk of breast cancer.

### 12.3. Insulin resistance and IGF-I during adult life

Later in women's life, increased IGF-I levels have been associated with an increased risk mainly in premenopausal BC. However this was not confirmed in a recent publication from the Nurses' [45]. In this paper,



the authors discussed the reasons of the discrepancy between their previous results and the actual publication. No methodological explanations were apparent. It is possible that the delay between blood collection and tumor diagnosis, with an average of only 31 months, did not allow the correlation of this marker with the history of BC, in view of its long latency period. In addition, hyperinsulinemia associated with obesity decreases IGFBP1, and thus IGF-I levels. IGF-I is increased in adipose tissue but there is no definite proof of its release into the circulation, a part from the liver. Thus, it is not clear if total circulating IGF-I can reflect hyperinsulinemia; on the contrary it might be an indicator of total fat tissue.

### 13. Effects of HT on insulin resistance and IGF-I

#### 13.1. HT and insulin resistance (IR)

Low doses of oral and transdermal estrogens have been shown to improve insulin sensitivity. This effect is dose dependent for oral estrogens with 0.625 CEE it is beneficial on IR whereas with 1.25 mg CEE it is deleterious, increasing IR. Adjonction of an androgenic progestin, e.g. MPA blunts the beneficial effect of estrogens on IR. Non-androgenic progestagens have no effects on IR. Overall, the improvement of IR parameters is underlined by data showing a reduction in the onset diabetes in women receiving HT [46].

These effects could explain the slight reduced risk of breast cancer in the WHI estrogen only arm [47].

#### 13.2. HT and IGF-I plasma level

Different types of HT have different effects on the IGF-I system depending on the route of administration, estrogen dose and the type of progestin.

Oral estrogens reduce IGF-I plasma levels mainly at the hepatocellular level. This is the reason why transdermal estrogens have no effect. Androgenic progestins and MPA reverse the IGF-I decrease, whereas progestins devoid of androgenic effect do not interfere with the effect of oral estrogens [48].

Moreover, oral estrogens increase two- to three-fold the IGFBP1 levels whereas androgenic progestins

oppose the IGFBP1 increase due to oral estrogens. With oral estrogen alone free IGF-I is reduced giving another explanation for the observed low risk of breast cancer in the estrogen only arm of the WHI.

In women with the metabolic syndrome, IR is associated with reduced IGFBP1 due to a slight decrease of total plasmatic IGF-I and an increase in free IGF-I. Oral estrogens could interfere with the insulin resistance effect on IGF-I by increasing IGFBP1

### 14. The best body size predictor: weight gain along women life

In several studies BMI is highly correlated with total adult weight gain. Weight gain was a much stronger and constant predictor of breast cancer risk, with a RR reaching 2 for a WG from 25 to 30 kg between age of 20 and age at diagnosis. Furthermore, some studies found WG as a risk factor for postmenopausal BC although they did not find no relationship was found between BMI and postmenopausal BC [22,49]. WG related risk to BC was stronger or only positive among HT never users. Among HT non-users, the population attributable risk to WG of 2 kg or more reaches 32% in the largest prospective time period analysis study [50]. Moreover, an analysis to find at what time acquired WG was more strongly associated factor concluded that WG acquired later in life, after the age of 30–40 and mainly in perimenopausal period, appears to be the most deleterious [22,51–54]. BMI reflects both lean body mass and adipose mass, whereas weight gain throughout adult life reflects primarily the accumulation of peripheral and central adipose tissue. Adult weight gain is considered to be a dynamic body measure, unlike a static measure like BMI. Then, weight and weight gain appear to be the best candidates to assess the association with BC. Loss of weight, regardless of when it was initially gained during adulthood, was associated with lower risk of postmenopausal BC compared with weight maintenance [50,52,53]. This observation should serve as a strong motivation for women that loss of weight may be an effective strategy to reduce the risk of breast cancer. The major public health message is that the prevention of adult weight gain and the stimulation of overweight loss should be strongly encouraged. In addition, exercise contributes to a decrease in the risk of BC and hyper-

insulinemia. IARC suggests that 25% of cancers in the world could be attributed to obesity and sedentarism.

Thus in postmenopausal women breast cancer risk results from a subtle balance between the effect of insulin resistance and level of endogenous estrogens or exogenous estrogens in HT. In premenopausal women obesity is not so clearly related to breast cancer risk. Different bias cannot be excluded. Moreover insulin resistance is a risk factor for breast cancer in premenopausal women too. Moreover, in several studies large hip circumference associated with lower fat distribution was protective against breast cancer in premenopausal women. It is known that estradiol decreases androgen receptor in the abdominal fat and thus can oppose to the accumulation of abdominal fat which is increased by androgens in women. In addition, estrogens increase GH secretion which is a factor of decreasing abdominal fat.

## 15. Conclusions

The role of insulin resistance as a risk for BC is highly probable. Obesity is a non-specific entity that still needs to be stratified in various conditions, especially in terms of hormone environment and its link to breast cancer risk.

The main message from the available literature is that weight gain and metabolic degradation throughout life are strong promoters of the risk for breast cancer. Lifestyle factors can be modified according to individual convictions also by public health political decisions.

## Conflict of Interest

The authors confirm that there is no conflict of interest.

## References

- [1] Lahmann PH, Hoffmann K, Allen N, et al. Body size and breast cancer risk: findings from the European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer* 2004;111(5):762–71.
- [2] Michels KB, Terry KL, Willett WC. Longitudinal study on the role of body size in premenopausal breast cancer. *Arch Intern Med* 2006;166(21):2395–402.
- [3] Van den Brandt PA, Spiegelman D, Yaun SS, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. *Am J Epidemiol* 2000;152(6):514–27.
- [4] Shu XO, Jin F, Dai Q, et al. Association of body size and fat distribution with risk of breast cancer among Chinese women. *Int J Cancer* 2001;94(3):449–55.
- [5] Baer HJ, Colditz GA, Rosner B, et al. Body fatness during childhood and adolescence and incidence of breast cancer in premenopausal women: a prospective cohort study. *Breast Cancer Res* 2005;7(3):R314–25.
- [6] Baer HJ, Rich-Edwards JW, Colditz GA, et al. Adult height, age at attained height, and incidence of breast cancer in premenopausal women. *Int J Cancer* 2006;119(9):2231–5.
- [7] Weiderpass E, Braaten T, Magnusson C, et al. Prospective study of body size in different periods of life and risk of premenopausal breast cancer. *Cancer Epidemiol Biomarkers Prev* 2004;13(7):1121–7.
- [8] Garland M, Hunter DJ, Colditz GA, et al. Menstrual cycle characteristics and history of ovulatory infertility in relation to breast cancer risk in a large cohort of US women. *Am J Epidemiol* 1998;147(7):636–43.
- [9] Rich-Edwards JW, Goldman MB, Willett WC, et al. Adolescent body mass index and infertility caused by ovulatory disorder. *Am J Obstet Gynecol* 1994;171(1):171–7.
- [10] Hartz AJ, Barboriak PN, Wong A, Katayama KP, Rimm AA. The association of obesity with infertility and related menstrual abnormalities in women. *Int J Obes* 1979;3(1):57–73.
- [11] Cui Y, Whiteman MK, Flaws JA, Langenberg P, Tkaczuk KH, Bush TL. Body mass and stage of breast cancer at diagnosis. *Int J Cancer* 2002;98(2):279–83.
- [12] Garmendia ML, Pereira A, Alvarado ME, Atalah E. Relation between insulin resistance and breast cancer among Chilean women. *Ann Epidemiol* 2007;17(6):403–9.
- [13] Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. *Endocrinol Rev* 2000;21(6):697–738.
- [14] Douchi T, Kuwahata R, Yamamoto S, Oki T, Yamasaki H, Nagata Y. Relationship of upper body obesity to menstrual disorders. *Acta Obstet Gynecol Scand* 2002;81(2):147–50.
- [15] Kaaks R, Berrino F, Key T, et al. Serum sex steroids in premenopausal women and breast cancer risk within the European Prospective Investigation into Cancer and Nutrition (EPIC). *J Natl Cancer Inst* 2005;97(10):755–65.
- [16] Muti P, Stanulla M, Micheli A, et al. Endogenous sex hormones and subsequent breast cancer in premenopausal women. *Int J Cancer* 2004;112(2):312–8.
- [17] Eliassen AH, Missmer SA, Tworoger SS, et al. Endogenous steroid hormone concentrations and risk of breast cancer among premenopausal women. *J Natl Cancer Inst* 2006;98(19):1406–15.
- [18] Sonnenschein E, Toniolo P, Terry MB, et al. Body fat distribution and obesity in pre- and postmenopausal breast cancer. *Int J Epidemiol* 1999;28(6):1026–31.

- [19] Adams-Campbell LL, Nwankwo M, Ukoli F, Omene J, Haile GT, Kuller LH. Body fat distribution patterns and blood pressure in black and white women. *J Natl Med Assoc* 1990;82(8): 573–6.
- [20] Seidell JC, Cigolini M, Charzewska J, Ellsinger BM, Contaldo F. Regional obesity and serum lipids in European women born in 1948. A multicenter study. *Acta Med Scand* 1988;723(Suppl.): 189–97.
- [21] Huang Z, Willett WC, Colditz GA, et al. Waist circumference, waist:hip ratio, and risk of breast cancer in the Nurses' Health Study. *Am J Epidemiol* 1999;150(12):1316–24.
- [22] Friedenreich CM. Review of anthropometric factors and breast cancer risk. *Eur J Cancer Prev* 2001;10(1):15–32.
- [23] Schapira DV, Kumar NB, Lyman GH, Cox CE. Abdominal obesity and breast cancer risk. *Ann Intern Med* 1990;112(3): 182–6.
- [24] McCarty MF. A paradox resolved: the postprandial model of insulin resistance explains why gynoid adiposity appears to be protective. *Med Hypotheses* 2003;61(2):173–6.
- [25] Snijder MB, Dekker JM, Visser M, et al. Larger thigh and hip circumferences are associated with better glucose tolerance: the Hoorn study. *Obes Res* 2003;11(1):104–11.
- [26] Connolly BS, Barnett C, Vogt KN, Li T, Stone J, Boyd NF. A meta-analysis of published literature on waist-to-hip ratio and risk of breast cancer. *Nutr Cancer* 2002;44(2): 127–38.
- [27] Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. *Int J Cancer* 2007;121(4): 856–62.
- [28] Lawlor DA, Smith GD, Ebrahim S. Hyperinsulinaemia and increased risk of breast cancer: findings from the British Women's Heart and Health Study. *Cancer Causes Control* 2004; 15(3):267–75.
- [29] Schairer C, Hill D, Sturgeon SR, et al. Serum concentrations of IGF-I, IGFBP-3 and c-peptide and risk of hyperplasia and cancer of the breast in postmenopausal women. *Int J Cancer* 2004;108(5):773–9.
- [30] Verheus M, Peeters PH, Rinaldi S, et al. Serum C-peptide levels and breast cancer risk: results from the European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer* 2006;119(3):659–67.
- [31] Sieri S, Pala V, Brighenti F, et al. Dietary glycemic index, glycemic load, and the risk of breast cancer in an Italian prospective cohort study. *Am J Clin Nutr* 2007;86(4):1160–6.
- [32] Micheli A, Muti P, Secreto G, et al. Markers of insulin resistance and sex steroid hormone activity in relation to breast cancer risk: a prospective analysis of abdominal adiposity, sebum production, and hirsutism. *Cancer Causes Control* 2000;11(8):721–30.
- [33] Fasshauer M, Paschke R. Regulation of adipocytokines and insulin resistance. *Diabetologia* 2003;46:1594–603.
- [34] Tworoger SS, Eliassen AH, Kelesidis T, et al. Plasma adiponectin concentrations and risk of incident breast cancer. *J Clin Endocrinol Metab* 2007;92(4):1510–6.
- [35] Miyoshi Y, Funahashi T, Kihara S, et al. Association of serum adiponectin levels with breast cancer risk. *Clin Cancer Res* 2003;9(15):5699–704.
- [36] Chen DC, Chung YF, Yeh YT, et al. Serum adiponectin and leptin levels in Taiwanese breast cancer patients. *Cancer Lett* 2006;237(1):109–14.
- [37] Mantzoros C, Petridou E, Dessypris N, et al. Adiponectin and breast cancer risk. *J Clin Endocrinol Metab* 2004;89(3): 1102–7.
- [38] Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965;58:295–300.
- [39] Hamelers IH, Steenbergh PH. Interactions between estrogen and insulin-like growth factor signaling pathways in human breast tumor cells. *Endocr Relat Cancer* 2003;10(2):331–45.
- [40] Cascio S, Bartella V, Garofalo C, Russo A, Giordano A, Surmacz E. Insulin-like growth factor 1 differentially regulates estrogen receptor-dependent transcription at estrogen response element and AP-1 sites in breast cancer cells. *J Biol Chem* 2007;282(6):3498–506.
- [41] Chong YM, Williams SL, Elkak A, Sharma AK, Mokbel K. Insulin-like growth factor 1 (IGF-1) and its receptor mRNA levels in breast cancer and adjacent non-neoplastic tissue. *Anti-cancer Res* 2006;26(1A):167–73.
- [42] Baik I, Devito WJ, Ballen K, et al. Association of fetal hormone levels with stem cell potential: evidence for early life roots of human cancer. *Cancer Res* 2005;65(1):358–63.
- [43] Savarese TM, Strohsnitter WC, Low HP, et al. Correlation of umbilical cord blood hormones and growth factors with stem cell potential: implications for the prenatal origin of breast cancer hypothesis. *Breast Cancer Res* 2007;9(3):R29.
- [44] Park SK, Kang D, McGlynn KA, Garcia-Closas M, Kim Y, Yoo KY, et al. Intrauterine environments and breast cancer risk: meta-analysis and systematic review. *Breast Cancer Res* 2008;10(1):R8.
- [45] Schernhammer ES, Holly JM, Hunter DJ, et al. Insulin-like growth factor-I, its binding proteins (IGFBP-1 and IGFBP-3), and growth hormone and breast cancer risk in the Nurses Health Study II. *Endocr Relat Cancer* 2006;13:583–92.
- [46] Salpeter SR, Walsh JM, Ormiston TM, Greyber E, Buckley NS, Salpeter EE. Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. Review. *Diabetes Obes Metab* 2006;8(5): 538–54.
- [47] Michels KB, Xue F. Role of birthweight in the etiology of breast cancer. *Int J Cancer* 2006;119(9):2007–25.
- [48] Campagnoli C, Abbà C, Ambroggio S, Peris C. Differential effects of progestins on the circulating IGF-I system. Review. *Maturitas* 2003;46(Suppl. 1):S39–44.
- [49] Krebs EE, Taylor BC, Cauley JA, Stone KL, Bowman PJ, Ensrud KE. Measures of adiposity and risk of breast cancer in older postmenopausal women. *J Am Geriatr Soc* 2006;54(1): 63–9.
- [50] Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. *JAMA* 2006;296(2):193–201.
- [51] Tworoger SS, Eliassen AH, Missmer SA, et al. Birthweight and body size throughout life in relation to sex hormones and prolactin concentrations in premenopausal women. *Cancer Epidemiol Biomarkers Prev* 2006;15(12):2494–501.

- [52] Harvie M, Howell A, Vierkant RA, et al. Association of gain and loss of weight before and after menopause with risk of postmenopausal breast cancer in the Iowa women's health study. *Cancer Epidemiol Biomarkers Prev* 2005;14(3):656–61.
- [53] Eng SM, Gammon MD, Terry MB, et al. Body size changes in relation to postmenopausal breast cancer among women on Long Island, New York. *Am J Epidemiol* 2005;162(3):229–37.
- [54] Morimoto LM, White E, Chen Z, et al. Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). *Cancer Causes Control* 2002;13(8):741–51.
- [55] Furberg AS, Veierød MB, Wilsgaard T, Bernstein L, Thune I. Serum high-density lipoprotein cholesterol, metabolic profile, and breast cancer risk. *J Natl Cancer Inst* 2004;96(15):1152–60.