Obesity and breast cancer risk

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Being overweight appears to be associated with a higher risk of post-menopausal breast cancer in most studies. Although the relative risk of breast cancer related to Quetelet’s index is generally weak (range 1.1–1.9 in the major cohort studies), some studies have found that timing of weight gain and body fat distribution could be more significant factors of an increased risk. Conversely, obesity appears to be slightly correlated with a decreased risk of breast cancer in pre-menopausal women. These contrasting effects of excess weight on breast cancer incidence according to menopausal status, and the lack of a strong association between obesity and breast cancer in some studies, could be due to a number of confounding factors. Among these factors, age, country of origin, family history, alcohol consumption, nutrition, and hormonal treatment could account for the differences observed, and are reviewed in the present study. Obesity and central fat distribution are believed to act through endocrine intermediates such as hyperinsulinaemia and steroid hormones. Since obesity is one of the few breast cancer risk factors that can be modified, the influence of weight loss, particularly in women at high risk, deserves to be further investigated.

Key words: breast cancer/fat distribution/obesity/weight gain

Introduction

Obesity has been found to be associated with the risk of breast cancer in several, but not all, studies. In post-menopausal women, overall obesity is generally related to an increased risk of breast cancer, whereas an inverse relationship has been reported in pre-menopausal women (Ballard-Barbash et al., 1994). These contrasting effects of excess weight on breast cancer incidence according to menopausal status and the lack of a strong association between obesity and breast cancer in some cohort studies could suggest that obesity has little effect on breast cancer risk. However, a number of clinical and epidemiological factors related to obesity, such as body fat distribution and timing of weight gain, may influence the association between obesity and breast cancer. Other confounding factors could include age, country of origin, family history, alcohol consumption, nutritional events, or hormonal treatment. We have undertaken a review of the literature on the relationship between obesity and breast cancer risk.

Excess weight and menopausal status

The major cohort and case-control studies published over the last decade relating excess weight to breast cancer risk are summarized in Tables I and II respectively. Most studies have found that heavier post-menopausal women are at increased risk of breast cancer (Figure 1A). It is noteworthy that, to our knowledge, none of the case-control or the cohort studies have reported a decreased risk of breast cancer in post-menopausal obese women. The increased risk of breast cancer with weight excess has been found in the late menopause but not in the early post-menopause (Choi et al., 1978; Le Marchand et al., 1988; London et al., 1989). In addition to the fact that overweight could be associated with a decreased risk in pre-
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menopause, this could suggest an age-dependent effect of obesity on the risk of breast cancer.

In several prospective cohort studies, pre-menopausal obese women have a slightly decreased risk of developing breast cancer than lean women (Figure 1B; Le Marchand et al., 1988; London et al., 1989; Tretli et al., 1989; Vatten et al., 1992; Moller et al., 1994; Tornberg et al., 1994). This inverse relationship between overweight and risk of breast cancer is also found in most of the case-control studies (Willet et al., 1985; Swanson et al., 1989; Pathak and Whittemore, 1992; Brinton et al., 1992; Harris et al., 1992). However, some studies have found either no association at all (La Vecchia et al., 1987) or a positive relationship (Chu et al., 1991) between pre-menopausal overweight women

<table>
<thead>
<tr>
<th>References</th>
<th>Patients (n)</th>
<th>Menopausal status or age</th>
<th>Anthropometric indices</th>
<th>Cut-off</th>
<th>Relative risk</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Ballard-Barbash, 1990</td>
<td>2201</td>
<td>pre and post</td>
<td>QI</td>
<td>4th versus 1st quartile</td>
<td>NS</td>
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<tr>
<td>Chu et al., 1991</td>
<td>4323</td>
<td>pre post</td>
<td>QI</td>
<td>&gt;32 versus &lt;20</td>
<td>1.3</td>
<td>0.9–2.0</td>
</tr>
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<td>Pre-mens</td>
<td>post weight gain</td>
<td>&gt;32 versus &lt;25</td>
<td>1.8</td>
<td>1.2–2.6</td>
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<td>16 355</td>
<td>post</td>
<td>QI</td>
<td>&gt;28 versus &lt;23</td>
<td>1.6</td>
<td>0.9–2.8</td>
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<td>Den Tonkelaar et al., 1994</td>
<td>9746</td>
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<td>weight gain</td>
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<td>1.2–3.9</td>
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<td>Folsom et al., 1990</td>
<td>41 837</td>
<td>post</td>
<td>WHR</td>
<td>&gt;94 versus &lt;67</td>
<td>1.3</td>
<td>0.9–1.9</td>
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<tr>
<td>Garfinkel, 1985</td>
<td>419 060</td>
<td>pre and post</td>
<td>%IBW</td>
<td>&gt;140% versus &lt;100%</td>
<td>1.5</td>
<td>NA</td>
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<tr>
<td>London et al., 1989</td>
<td>111 534</td>
<td>pre early post</td>
<td>QI</td>
<td>&gt;30 versus &lt;25</td>
<td>1.4</td>
<td>1.2–1.6</td>
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<tr>
<td>Moller et al., 1994</td>
<td>43 965</td>
<td>&lt;50 weight gain</td>
<td>&gt;29 versus &lt;21</td>
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<td>0.4–0.8</td>
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<tr>
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<td>37 105</td>
<td>post</td>
<td>QI</td>
<td>&gt;30 versus &lt;22.9</td>
<td>1.5</td>
<td>1.1–2.0</td>
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<td>Swanson et al., 1988</td>
<td>7149</td>
<td>pre and post</td>
<td>WHR</td>
<td>&gt;0.9 versus &lt;0.7</td>
<td>1.2</td>
<td>0.8–1.6</td>
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<td>Tornberg and Carstensen, 1994</td>
<td>47 003</td>
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<td>QI</td>
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<td>Tretti, 1989</td>
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<td>&gt;1g/cm²</td>
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<td>0.7–0.9</td>
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<td>Vatten and Kvinsland, 1992</td>
<td>25 967</td>
<td>pre post</td>
<td>QI</td>
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<td>0.6</td>
<td>0.5–0.8</td>
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<tr>
<td>Willet et al., 1985</td>
<td>121 964</td>
<td>pre post</td>
<td>QI</td>
<td>&gt;30.3 versus &lt;20.5</td>
<td>0.6</td>
<td>NA</td>
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QI = Quetelet's index (kg/m²); WHR = waist-to-hip ratio; %IBW = percentage of ideal body weight; SF = skinfold; *Skinfold ratio (evaluation of central body fat by trunkal skinfolds/extremity skinfolds ratio); **suprailiac/thigh skinfold ratio; VO = visceral obesity assessed by computerized scan (threshold: visceral-to-total fat area ratio); NA = not available; NS = not significant.

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*Skinfold ratio (evaluation of central body fat by trunkal skinfolds/extremity skinfolds ratio); **suprailiac/thigh skinfold ratio; 
VO = visceral obesity assessed by computerized scan (threshold: visceral-to-total fat area ratio); NA = not available; NS = not significant.

aCurrent weight minus weight at age 18 (kg).

bSubscapular.

Related to weight.

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Table II. Association between body size and breast cancer risk: case-control studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. patients</th>
<th>Menopausal status</th>
<th>Anthropometric indices</th>
<th>Cut-off</th>
<th>Relative risk</th>
<th>95% CI</th>
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</thead>
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<td>Harris et al., 1992</td>
<td>604</td>
<td>pre</td>
<td>QI^a</td>
<td>&gt;27 versus &lt;22</td>
<td>0.6</td>
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<tr>
<td></td>
<td></td>
<td>post</td>
<td>QI</td>
<td>–</td>
<td>1.5</td>
<td>1.0-2.3</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>weight gain^c</td>
<td>–</td>
<td>2.6</td>
<td>1.5-4.6</td>
</tr>
<tr>
<td>Ingram et al., 1989</td>
<td>513</td>
<td>pre and post</td>
<td>QI</td>
<td>&gt;26 versus &lt;20</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Schapira et al., 1990</td>
<td>216</td>
<td>pre and post</td>
<td>WHR</td>
<td>&gt;0.81 versus &lt;0.73</td>
<td>5.2</td>
<td>2.8-9.6</td>
</tr>
<tr>
<td>Schapira et al., 1994</td>
<td>40</td>
<td>pre and post</td>
<td>SF**</td>
<td>&gt;0.71 versus &lt;0.42</td>
<td>5.2</td>
<td>3.8-7.2</td>
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<td>Segala et al., 1991</td>
<td>450</td>
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<td>QI</td>
<td>&gt;10 versus &lt;10</td>
<td>2.1</td>
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<td></td>
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<td>QI</td>
<td>&gt;74 versus &lt;56</td>
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<td>1.3-3.3</td>
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<td>Swanson et al., 1989</td>
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<td>pre</td>
<td>VO</td>
<td>0.24</td>
<td>9.5</td>
<td>2.8-31.5</td>
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<td></td>
<td>post</td>
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<td>&gt;24 versus &lt;21</td>
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<td></td>
<td></td>
<td>QI</td>
<td>&gt;30 versus &lt;20 NS</td>
<td>1.3</td>
<td>1.0-1.7</td>
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</table>

CI = confidence interval; QI = Quetelet’s index (kg/m^2); WHR = waist-to-hip ratio; SF = skinfold; ^Skinfold ratio (evaluation of central body fat by trunkal skinfolds/extremity skinfolds ratio), **suprailiac/thigh skinfold ratio; VO = visceral obesity assessed by computerized scan (threshold: visceral-to-total fat area ratio); NS = not significant.

^Related to weight.
^bCurrent weight minus weight at age 18 (kg).
^cCurrent QI vs QI at age 18.

and breast cancer risk. The relative risks of breast cancer for the highest level of Quetelet’s index (kg/m^2, QI) in pre-menopausal women are shown in Figure 1B.

The inverse relationship between body mass and breast cancer risk in obese pre-menopausal women has particularly been observed in patients with small tumours (Willet et al., 1985; London et al., 1989; Swanson et al., 1989). Therefore, it has been suggested that the observed association between relative weight and breast cancer risk might be due to a bias resulting from easier detection in these women. However, in a large prospective study, London et al. (1989) concluded that earlier detection does not suffice to explain the inverse association between relative weight and breast cancer among pre-menopausal women.

Key and Pike (1988) proposed a mechanism for the differential effect of obesity among pre-menopausal and post-menopausal women. They postulated that increased exposure to progesterone and oestrogen raises the risk of breast cancer more than increased exposure to oestrogen alone. Since pre-menopausal obesity has little effect on free oestradiol but is associated with a decreased progesterone production, this hypothesis could explain the decrease in risk of breast cancer in pre-menopausal women. On the other hand, obese post-menopausal women are exposed to higher oestrogen concentrations than their lean counterparts, whereas progesterone has negligible values in both groups.

Numerous other risk factors appear to behave differently according to the age of the women, such as physical activity, fat distribution, associated metabolic disorders, oral contraceptive use or oestrogen replacement therapy. Some data suggest that in post-menopausal women, hyperinsulinaemia is related to overall obesity, whereas in pre-menopausal women it would rather be related to abdominal localization of fat (Zimmet, 1993). This hypothesis could also explain why an overall increase in body mass index is a risk marker for breast cancer in post-menopausal but not in pre-menopausal women.

**Body fat distribution**

The distribution of body fat may also play an independent role in breast cancer. In most studies, upper body adiposity has been found to be correlated with the risk of post-menopausal breast cancer independently of overall obesity (Ballard-Barbash et al., 1990; Folsom et al., 1990; Bruning et al.,...
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**A**

**Cohort**
- Tornberg 1994
- Tretli 1989
- London 1989
- Moller b 1994
- Vatten 1992
- Le Marchand 1988

**Case-control**
- Willet 1985
- Swanson 1989
- Chu 1991
- Harris 1992

![Figure 1. Quetelet's index and breast cancer risk according to menopausal status. (A) pre-menopausal women; (B) post-menopausal women. Plain circles represent the relative risk for the highest category of QI versus the lowest. Error bars represent the 95% confidence intervals. a <55 years; b <50 years; c ≥50 years; d ≥55 years; e >55 years.](image)

1992; Sellers et al., 1992; Schapira et al., 1994). However, Den Tonkelaar et al. (1992) have reported that overall obesity but not fat distribution, as measured by different groups of subscapular and triceps skinfold thickness, is related to breast cancer. This discrepancy may be explained by the differences in fat distribution assessment used in this study compared to the anthropometric indices used in the other studies such as thigh skinfold (Schapira et al., 1990), waist-to-hip ratio (WHR; Folsom et al., 1990; Sellers et al., 1992), or visceral adiposity measured by computerized scan (Schapira et al., 1994).

Excess amounts of circulating free steroids may be responsible for the association between fat distribution and post-menopausal breast cancer. The elevation of oestrogen production results from the conversion of androstenedione to oestrone in peripheral adipose tissue (Deslypere et al., 1982). In addition, central adiposity decreases sex hormone-binding globulin (SHBG) concentrations (Schapira et al., 1991), which in turn increases free oestrogen and free androgen fractions. In a study on post-menopausal women, a negative association between WHR and SHBG was observed although no relationship was found between WHR and free oestradiol concentrations (Kaye et al., 1991). These authors also observed a relationship between WHR and free testosterone concentrations. Since increased androgenicity has been found to be associated with an increased risk of breast cancer in some studies (Secreto et al., 1994; Berrino et al., 1996), it could be postulated that the increased risk of breast cancer in women with central adiposity could be mediated in part by androgens. The associations of circulating steroids and SHBG with breast cancer in obese women are summarized in Table III.

In addition, some data suggest that hyperinsulinaemia related to insulin resistance could be a significant marker of increased breast cancer risk (Bruning et al., 1992). The potential effect of hyperinsulinaemia related to increased risk of breast cancer in women with central obesity deserves further studies. Other unknown metabolic
disturbances related to central adiposity could also play a role in breast tumourgenesis.

**Timing of weight gain**

The studies analysing the effect of timing of weight gain on the risk of breast cancer are presented in Table IV. Weight gain has been shown to increase the risk of post-menopausal breast cancer in several studies (Le Marchand et al., 1988; London et al., 1989; Ballard-Barbash et al., 1990; Folsom et al., 1990; Brinton et al., 1992; Bruning et al., 1992). This increased risk is observed even in the absence of relationship between basal weight and breast cancer risk (London et al., 1989; Ballard-Barbash et al., 1990; Folsom et al., 1990). The effect of adult weight gain also appears to be independent of QI (London et al., 1989; Ballard-Barbash et al., 1990; Folsom et al., 1990). Timing of weight gain has been assessed differently depending upon the authors. Some authors have studied overall weight gain or QI gain over time, whereas the dynamics of weight gain have been analysed for different periods of time ranging from 5–30 years before diagnosis of breast cancer. Few studies have analysed weight at various ages during the follow-up (Le Marchand et al., 1988; Ingram et al., 1989; Brinton et al., 1992).

Stoll (1995) proposed that hyperinsulinaemia related to insulin resistance at critical period of life, such as puberty or menopause, may be a metabolic link between weight gain and the risk of breast cancer in Western countries.

**Exogenous hormones**

There are little data to analyse how oral contraceptive use or oestrogen replacement therapy
could influence the association between obesity and breast cancer risk. Some authors (Kaufman et al., 1991; Harris et al., 1992) have observed an increased risk in lean post-menopausal women receiving oestrogen replacement therapy compared with obese women receiving such therapy. In the Nurses’ Health study, a positive relationship between relative weight and breast cancer risk was observed in post-menopausal women who have never used oestrogen replacement therapy, but not in the whole population (London et al., 1989).

However, the interpretation of a potential effect of oestrogen replacement therapy and body mass on breast cancer risk is difficult since some data suggest that a lower body mass could be associated with an increased use of oestrogen replacement therapy (Garcia Rodriguez et al., 1990). A greater follow-up for women treated by oestrogen replacement therapy has also been suggested. This could also be a confounding factor, since the increase incidence of breast cancer in post-menopausal women receiving oestrogen replacement therapy could be expect to be greater in lean women because of an easier detection compared to obese women.

**Nutritional factors: alcohol**

Nutritional factors could also be confounding for the analysis of the relationship between breast cancer and obesity. Case-control and prospective studies, however, have generally failed to show associations between dietary fat and breast cancer risk or have given conflicting results (for review, see Byers et al., 1994, and Hunter and Willet, 1996). However, a meta-analysis found a relative risk of 1.4 for fat intake in the upper quintile compared with the lower quintile (Howe et al., 1990).

In contrast to the lack of a strong association between dietary fat intake and breast cancer risk, a more consistent association has been observed with alcohol intake and breast cancer risk (Willet et al., 1985; Garfinkel et al., 1985; La Vecchia et al., 1987; Harris et al., 1992). In a meta-analysis, alcohol consumption has been found to be correlated with the risk of breast cancer (Longnecker et al., 1988). As alcohol consumption also appears to be inversely correlated with weight (Colditz et al., 1993), alcohol could be another confounding factor in the relationship between obesity and breast cancer risk. However, in the study by London et al. (1989), adjustment for alcohol intake did not appreciably change the relation between relative weight and breast cancer risk. Further studies are needed to examine the potential confounding effect of alcohol intake and nutrition on breast cancer risk.

In a study analysing hormone concentrations in relation to alcohol consumption in a subset of post-menopausal participants of the Nurses’ Health study, alcohol intake was positively associated with oestrone sulphate concentrations (Hankinson et al., 1995). QI was also associated with oestrone and oestradiol. These observations could support the hypothesis that the association of alcohol consumption and post-menopausal obesity with breast cancer risk might be mediated though a similar effect on plasma oestrogen concentrations.

**Infertility**

The link between female infertility and breast cancer risk has recently been reviewed by Meirow and Schenker (1996). Several studies have found no association between infertility and the risk of breast cancer (Coulam et al., 1983; Ron et al., 1987; Brinton et al., 1989; Le et al., 1989). Conversely, a positive association between anovulation or infertility and an increased risk of breast cancer has been found by others (Cowan et al., 1981; Gammon and Thompson 1990; Sellers et al., 1992). The studies by Sellers et al. (1992, 1993), showed that in patients with a family history of breast cancer, an increased risk was associated with a high WHR and a low parity. Since the association between high WHR and infertility has been documented (Zaadstra et al., 1993), the interrelationships between central fat, infertility and hormonal status could act in a complex way on the risk of developing breast cancer.

**Country of origin**

Pathak and Whittemore (1992) have studied the effect of body size and breast cancer incidence in several countries. They found that the risk of breast
cancer decreases with body mass among pre-menopausal women in high-risk countries, but increases in all other groups of pre- or post-menopausal women. These data suggest that body mass exerts a similar effect on breast cancer incidence regardless of breast cancer rates in the country of residence, except for pre-menopausal women living in high-risk countries.

**Family history**

In a study by Sellers *et al.* (1992), obese post-menopausal women with a family history of breast cancer were found to have a greater risk of developing breast cancer than obese women without a family history. Interestingly, the follow-up analysis of this cohort showed that the combination of a high WHR with a family history of breast and ovarian cancer was associated with an increase in the risk of breast cancer, whereas in the absence of a high WHR, a family history of breast cancer was not associated with a significantly increased risk (Sellers *et al.*, 1994). Parent *et al.* (1996) recently reported an inverse relationship between parental obesity and pre-menopausal breast cancer risk, concordant with the protective effect of obesity on early-onset breast cancer reported at the individual level. Family breast cancer syndrome related to *BRCA1* gene, the major gene of susceptibility to breast and ovarian cancer, is known to have incomplete penetrance. The cumulative risk of breast cancer for women carrying a *BRCA1* mutation is 44–63% before the age of 70 (Easton *et al.*, 1994). Since the reasons for this lack of penetrance are unknown, it could be suggested that obesity may be an interesting environmental risk factor to study in these families.

**Potential factors related to obesity influencing breast cancer risk**

- Timing of weight gain
- Body fat distribution
- Alcohol, nutrition
- Exogenous hormones
- Familial history
- Infertility

**Potential biological intermediates**

- Oestrogens
- SHBG
- Oestrogen receptor
- Progesterone
- Androgens
- Insulin, IGF1

**Figure 2.** Potential factors influencing the relationship between obesity and breast cancer risk, and potential biological intermediates. Arrows indicate the relationships between obesity and the other potential factors influencing breast cancer risk. The factors related to obesity could also act directly on biological intermediates of breast cancer risk. SHBG = sex hormone-binding globulin; IGF1 = insulin-like growth factor-I.
Conclusion

There is an emerging body of evidence that obesity is positively correlated with breast cancer risk in post-menopausal women. However, the relative risk of breast cancer appears weak when overall obesity is considered. This association might be more significant if factors such as timing of weight gain or fat distribution are taken into account.

A model of the relationships between obesity and the other potential factors influencing breast cancer risk is presented in Figure 2. A number of these factors related to obesity could also act directly on biological intermediates, explaining the complexity of the risks analysis. Oestrogens, androgens and hyperinsulinaemia are potential metabolic intermediates between overweight and breast cancer risk. Hyperinsulinaemia with insulin resistance could be particularly involved in the mechanism of the increased risk observed in central obesity.

The increased breast cancer risk in post-menopausal women with hyperinsulinaemia and abdominal obesity is particularly observed in women with a family history of breast cancer (Sellers et al., 1992, 1994). It may be postulated that his feature could explain in part the lack of penetrance of breast cancer in women carrying BRCA1 gene mutations. Since obesity could be one of the few breast cancer risk factors that can be modified throughout life, the influence of weight loss, particularly in women at high risk, deserves further studies.

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References


