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Point of View

Obesity, Social Class and Western Diet: A Link to Breast Cancer Prognosis

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INTRODUCTION

BREAST CANCER accounts for approximately 25% of all female cancers in the developed countries of Western Europe and North America. In the developing world, it is only approximately half as common but its incidence increases with increasing Westernisation of life-style [1]. When immigrants move to a high-risk country from a low-risk country, breast cancer risk increases and this may occur even in the lifetime of the immigrant generation [2]. Both this and the increased risk in women of higher socio-economic groups have led to the suggestion that the metabolic/endocrine concomitants of a more affluent life-style may predominate in its aetiology. However, most of the published studies show a worse prognosis from breast cancer associated with lower socio-economic status [3–14], and this has been taken to suggest that the metabolic/endocrine factors affecting prognosis may differ from those affecting the risk of developing breast cancer.

An explanation for the apparent inconsistency may be provided by reports of studies [15–26], almost all showing that obesity at the time of diagnosis worsens breast cancer prognosis. It is relevant that demographic surveys show that Western women of lower socio-economic status manifest relatively greater body mass [27, 28] and abdominal obesity [29] than do women of higher social status. The presence of abdominal obesity is said to be a better marker of the metabolic hazards of obesity in Western women after middle life [29].

SOCIAL CLASS AND BREAST CANCER PROGNOSIS

The risk of developing breast cancer is greater in Western women of higher socio-economic status, the observation being consistent in practically all studies [1]. Social class is identified in the studies by income, occupation and education, and social class is generally related to life-style. Thus, women of higher socio-economic status generally have their first child at an older age, have fewer children and breast-feed for a shorter period—all markers of increased breast cancer risk. However, once the disease is established, the prognosis is worse for women of lower socio-economic status. After adjusting for stage, pathology and treatment, nine published studies have shown shorter survival in women of a lower social group [3–11]. Of the three studies with dissonant results [12–14], two were in the U.S.A. and involved mixed ethnic groups. This may be a confounding factor because black women generally have a poorer survival rate from breast cancer even when the effects of socio-economic status are statistically controlled [13, 30].

In most of the aforementioned studies, hazard of death in lower social groups was increased by a factor of less than 1.5. Both pre- and postmenopausal cases showed a similar trend, but some reports showed a larger difference between social groups in the older patients [8, 10, 11]. It has been postulated that host factors that determine recurrence and metastasis may be unfavourable in deprived patients. Nutritional factors are suspected but other postulated factors include adverse environmental factors or decreased immune response.

It is possible that the worse prognosis in lower socio-economic groups could be related to increased body mass [27]. None of the aforementioned studies were controlled for obesity, but lower social status in the Western world is generally associated with a higher body mass [27, 28] and also increased abdominal obesity [29]. A higher body mass is associated with increased levels of bioavailable oestrogen, which might adversely affect the prognosis of breast cancer patients [31]. Abdominal obesity is associated with insulin resistance and hyperinsulinaemia in addition to changes in sex steroid levels. Not only is abdominal obesity a better marker of the dangers from severe obesity in women after middle age [29], but its metabolic concomitants may synergise with oestrogen in stimulating breast cancer growth [32].

OBESITY AND BREAST CANCER PROGNOSIS

Higher body mass has an adverse effect on life expectancy in general and is also associated with a worse prognosis in breast cancer. Out of 12 published studies, 11 showed increased death rates in pre- and postmenopausal women with high body mass or described as overweight or obese [15–25]. One study did not confirm this [26]. In most studies, mortality

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or recurrence were increased by a factor of less than 1.5, but some studies showed a greater effect in postmenopausal women. All studies were adjusted for stage, pathology and treatment and Senie and colleages [24] found obesity to be the only significant prognostic factor emerging from multivariate analysis controlled for stage, age and adjuvant chemotherapy. There are conflicting reports on whether the adverse prognosis in obese patients is more marked in the presence of larger breast tumours or greater axillary node involvement. Bastarrachea and colleagues [25] report that the adverse prognostic effect of obesity persists in spite of adjuvant chemotherapy.

Large abdominal fat deposits in women are associated with increased breast cancer risk [33–38]. There are no reports on the association of abdominal obesity with prognosis, but there is a report [39] that central obesity (truncal skin thickness compared with thigh skin thickness) is associated with smaller tumours, less axillary node involvement and higher oestrogen receptor levels in the tumour. Central obesity is not well-correlated with abdominal obesity and each may measure different aspects of fat distribution [40].

The mechanism generally postulated to explain the adverse prognosis associated with obesity in breast cancer is excess oestrogen production in fat tissue by aromatisation of androstenedione. In addition, the level of bioavailable oestrogen may be increased because of the lowered level of sex hormone-binding globulin (SHBG) found in obese women. However, the level of bioactive oestrogen may depend on age and body fat distribution [31]. In postmenopausal women with either generalised or abdominal obesity, higher free oestradiol levels are found to be associated with lower SHBG levels. In the case of premenopausal women, a higher free oestradiol level is associated with abdominal obesity than with generalised obesity [41]. What is more, women with abdominal obesity show hyperinsulinaemia in addition to increased levels of bioavailable oestrogen [38].

While oestrogen bioavailability probably plays a major role in stimulating growth activity in breast cancer, recent research suggests that its effect is likely to be modulated by growth-stimulating or growth-suppressive epithelial and stromal factors [42]. Hyperinsulinaemia has been shown to be a risk marker for breast cancer in both pre- and postmenopausal women [38] and breast cancer growth may be stimulated by concomitant hyperinsulinaemia, particularly a rise in the level of insulin-like growth factor 1 (IGF1). There is evidence that IGF1 may synergise with oestrogen in promoting mammary carcinogenesis [43]. Both insulin and IGF1 have been shown to stimulate growth in human breast cancer cell lines, and several investigators have shown that human breast cancers express receptors for IGF1. A recent study reports IGF1 expression in 91% of human breast cancers [44], a higher figure than in previous reports.

TESTING THE HYPOTHESIS

It is possible to test the hypothesis that breast cancer growth may be influenced by synergism between concomitant hyperinsulinaemia and increased levels of bioavailable oestrogen [45]. A high-fibre/low-fat diet could be given in a randomised trial of adjuvant dietary treatment following primary surgery in overweight women with early breast cancer. Observations on vegetarians have reported lower blood levels of oestradiol in both pre- and postmenopausal women [46, 47]. The mechanism is uncertain, but oestrogen metabolites are excreted in the bile, and intestinal flora and enzymes convert them to oestradiol, which is then partially reabsorbed. Some types of dietary fibre can diminish reabsorption in premenopausal women, thereby reducing the circulating oestrogen level [48, 49]. It is reported that without any change in dietary fat consumption, food supplements of wheat bran (but not of oat or corn bran) cause a significant fall in oestrogen levels in premenopausal women [50].

There is evidence that a high-fibre diet can also reduce insulin levels [51] and thus an adjuvant trial of a high-fibre/low-fat diet could expand the observations of a current American adjuvant trial of dietary fat reduction [52]. While a high-fat diet stimulates the development of insulin resistance, a high-fibre diet has the opposite effect [51]. Thus, raised blood insulin levels can be reduced by a diet rich in fibre and complex carbohydrates [53], and it is reported that normalisation of insulin levels can be achieved in the majority after only 3 weeks on a high-carbohydrate/high-fibre diet combined with exercise [54]. Long-term, high-fibre diet intake is more likely to improve insulin sensitivity [55] and the beneficial effect of a high-carbohydrate/low-fat diet is more closely related to its fibre content than to its carbohydrate content [56].

In the proposed adjuvant trial of a high-fibre/low-fat diet in breast cancer patients, insulin levels, free oestradiol levels and the effect on abdominal obesity could be monitored, although normalisation of such markers in the individual patient need not necessarily correlate with decreased recurrence rate. Overall correlation may lead to meaningful large-scale dietary intervention trials in the management of breast cancer patients.

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