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Review
Western nutrition and the insulin resistance syndrome: A link to breast cancer

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Objective: The incidence of breast cancer in the Western world runs parallel to that of the major components of the insulin resistance syndrome—hyperinsulinaemia, dyslipidaemia, hypertension and atherosclerosis. Evidence is reviewed that the growth of breast cancer is favoured by specific dietary fatty acids, visceral fat accumulation and inadequate physical exercise, all of which are thought to interact in favouring the development of the insulin resistance syndrome.
Design: Clinical, epidemiological and experimental studies linking breast cancer risk with evidence of insulin resistance and its concomitants, were searched for in the MEDLINE database since 1985.
Results: Clinical and epidemiological evidence suggests that both breast cancer and the metabolic disorders comprising the insulin resistance syndrome are polygenic and multifactorial in origin. Experimental evidence suggests that hyperinsulinaemia and its concomitants can increase the promotion of mammary carcinogenesis and the mechanism is likely to involve increased bioactivity of insulin-like growth factor 1 (IGF-1). Case-control and cohort studies have shown that higher serum levels of IGF-1 are associated with increased breast cancer risk. Pharmacological agents which lower IGF-1 concentrations are under clinical trial for breast cancer prevention.
Conclusions: Nutritional and lifestyle modifications that improve insulin sensitivity may not only decrease a tendency to atherosclerosis but also reduce breast cancer risk in women. In addition to a reduced fat intake, the dietary regimen might involve a reduced n-6/n-3 ratio of polyunsaturated fatty acids and should be associated with avoidance of obesity and regular physical exercise. Interventions to decrease breast cancer risk in first-degree relatives of breast cancer patients need to begin at an early age.
Descriptors: atherosclerosis; breast cancer; insulin-like growth factor; insulin resistance; nutrition; obesity; unsaturated fatty acids; Western diet; physical exercise

Introduction

Western women have the highest breast cancer rates in the world and it is widely assumed that nutrition and lifestyle play a significant role in determining this high risk. The mechanism is likely to involve an increased level of bioavailable oestrogen but it has recently been postulated that the concomitants of hyperinsulinaemia may also be involved (Stoll & Secreto, 1992).

The insulin resistance syndrome, previously called Syndrome X, is characterised by hyperinsulinaemia, dyslipidaemia, hypertension and atherosclerosis, and the incidence of the syndrome runs parallel to that of breast cancer in Western populations. They are both polygenic and multifactorial in origin but evidence is increasing that, in both cases, their development is favoured by high fat intake, obesity and inadequate physical exercise. These aetiological factors are likely to interact in their effect on insulin activity.

The study reviewed the literature from 1985 linking breast cancer risk with evidence of insulin resistance and its concomitants. In relation to the components of the insulin resistance syndrome, it examines separately (1) clinical data linking dyslipidaemia, hyperinsulinaemia, hypertension and atherosclerosis with breast cancer risk; (2) clinical data linking diet, obesity and physical exercise with breast cancer risk; (3) experimental and clinical data linking the bioactivity of insulin-like growth factor with carcinogenesis in the human breast.

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Associations between breast cancer and insulin resistance syndrome

Of the various components of the insulin resistance syndrome, dyslipidaemia has been the most frequently studied for its epidemiological association with breast cancer risk. Dyslipidaemia has a strong genetic basis but the levels of cholesterol, triglycerides and lipoproteins in an individual are strongly correlated with obesity and dietary intake of saturated fat. An association between a raised cholesterol level and increased breast cancer risk has long been suggested but was not confirmed in prospective studies (Hiatt *et al*, 1982). More recently, studies have focused on high-density lipoprotein cholesterol (HDL-C) and its ratio to total cholesterol as a risk marker (Boyd & McGuire, 1990). Most studies have reported lower HDL-C levels in breast cancer cases compared to healthy controls or those with benign breast disease, but some disagree. Decreased

HDL-C levels in the insulin resistance syndrome are usually associated with increased VLDL-C and triglyceride levels.

Failure to distinguish between pre- and postmenopausal status in women may explain some of the inconsistencies in the reports of an epidemiological association between breast cancer risk and HDL-C levels. A recent cohort study reports that premenopausal cases showed lower mean HDL-C levels than controls (Moorman *et al*, 1998) and it is relevant that the cholesterol profile differs between female relatives of sporadic breast cancer cases and those with a strong family history (Boyd *et al*, 1995). Evidence of genetic linkage is greater in pre- than in postmenopausal breast cancer and it is possible that lipid-regulatory genes may also differ between the two groups.

Hyperinsulinaemia is believed to contribute directly to the other components of the insulin resistance syndrome. As many as 25% of Western populations show evidence of glucose intolerance or fasting hyperinsulinaemia. Although its incidence increases with aging, hyperinsulinaemia may begin in childhood and it is reported in obese prepubertal children in association with dyslipidaemia (Bao *et al*, 1996).

The diet of the industrialised West favours earlier onset of menarche and this is associated in epidemiological studies with an increased breast cancer risk. Earlier menarche is also associated with earlier manifestation of hyperinsulinaemic insulin resistance in obese genetically susceptible girls (Stoll *et al*, 1994). Case-control studies have shown hyperinsulinaemia in adult women to be a marker of increased breast cancer risk (Bruning *et al*, 1992; Tekden *et al*, 1996; Gamayunova *et al*, 1997; Muti *et al*, 1997; Del Giudice *et al*, 1998), although not all studies agree (Byrne *et al*, 1998). The mechanism by which hyperinsulinaemia helps to promote carcinogenesis is uncertain, but hyperinsulinaemia is associated with decreased levels of sex hormone-binding globulin and this leads to increased availability of free oestradiol. A second mechanism involving an increased level of bioactive insulin-like growth factor 1 (IGF-1) is discussed below.

Epidemiological association between hypertension and breast cancer risk was suggested about 25 years ago but was not confirmed in older studies. More recent studies are rare, but a positive association has been reported in African-American women (Muss *et al*, 1992) and this group is well known to have an increased incidence of insulin resistance. A positive association between breast cancer risk and hypertension has also been reported from Japan (Land *et al*, 1994).

Association between atherosclerosis and breast cancer risk has not been confirmed directly (Dreyer & Olsen, 1998) and is likely to be affected by hormone replacement therapy and its formulation. Both atherosclerosis and breast cancer risk are related to obesity, high dietary fat intake and inadequate exercise—all factors in the development of the insulin resistance syndrome. A positive association between atherosclerosis and hyperinsulinaemia is well established although its precise mechanism is uncertain.

Genetic susceptibility is a significant factor both in breast cancer risk and in the insulin resistance syndrome. Multiplicity of contributing genes and mutations and the effect of environmental factors make it impossible to predict with any certainty the risk of breast cancer in an individual with hyperinsulinaemia. However, a focused review of the association may provide clues to: (a) metabolic mechanisms promoting mammary carcinogenesis in women and (b) lifestyle modifications that may protect women from breast cancer.

Insulin-like growth factor activity and breast cancer risk

Nutritional intake is a strong determinant of IGF-1 levels in the blood. Recent case-control studies (Peyrat *et al*, 1993; Barni *et al*, 1994; Bruning *et al*, 1995) and a prospective study (Hankinson *et al*, 1998) have reported an increased breast cancer risk associated with higher IGF-1 levels, but other studies do not confirm it (Favoni *et al*, 1995; Del Giudice *et al*, 1998). The prospective study reports an up to seven-fold increased risk in postmenopausal women.

The ductal epithelium of normal breast tissue contains abundant IGF-1 receptors and it can express both IGF-1 and IGF-11 and their binding proteins. Experimental studies show that the proliferative activity of breast cancer cells in vitro are stimulated either by increased production of IGF-1, overexpression of IGF-1 receptors (Kaleko *et al*, 1990) or changes in the level of IGF-binding proteins (IGFBPs) (McGuire *et al*, 1992). Insulin plays a major role in regulating the production of IGFBPs, which can either enhance or inhibit the effect of IGF-1. While IGFBP-1 reduces IGF-1 bioactivity in the tissues, IGFBP-3 is thought to maintain the circulating pool of IGF-1.

Synergism between IGF-1 and oestradiol has been confirmed in stimulating the growth of human mammary cancer cell lines (Thorsen *et al*, 1992). Oestradiol may sensitise mammary cells to the proliferative effect of IGF-1 either by increasing IGF-1 receptor expression or by increasing cellular IGFBPs (McGuire *et al*, 1992). Evidence of growth stimulation by oestradiol of normal breast tissue grafted into nude mice, associated with upregulation of the IGF-1 receptor, supports a role for the IGF receptor system in the promotion of human mammary carcinogenesis (Clarke *et al*, 1997).

The anti-oestrogen tamoxifen is widely used in the treatment of breast cancer patient and its administration is associated with a lowering of the IGF-1 level in the blood (Pollak, 1998). A similar effect is reported for somatostatin analogues (Pollak & Schally, 1998) and also for the retinoid fenretinide (Torrisi *et al*, 1993), both under trial in the treatment and prevention of breast cancer.

Diet, breast cancer and insulin resistance

High-fat diets increase the growth of spontaneous and chemically induced mammary tumours in rodents, but in the human the results of numerous epidemiological studies are inconsistent. Dietary fat intake has not been shown to be an independent risk factor for breast cancer. Recent research suggests that the inconsistent findings on the association may result in part from uncertainties as to the relative intake of different fatty acids (Stoll, 1998).

Populations of industrialised Western countries consume a diet with a relatively high proportion of n-6 polyunsaturated fatty acids (PUFAs) such as linoleic acid. Cheap vegetable oils such as corn and sunflower oils contain a high ratio of n-6 PUFAs, whereas fish oils and flaxseed oil are rich in n-3 PUFAs. In general, PUFAs provide a substrate for lipid peroxidation but whereas n-6 PUFAs tend to aggravate insulin resistance and hyperinsulinaemia (Yam *et al*, 1996), higher intake of n-3 PUFAs has been

shown to improve insulin sensitivity, the effect being independent of any change in adiposity (Feskens *et al*, 1994). In obese pubertal children, insulin levels are lower in those with higher plasma levels of n-3 PUFAs (Agostoni *et al*, 1994) but higher in those with higher n-6 PUFA levels (Decsi *et al*, 1996).

An inverse correlation is reported in ecological studies between breast cancer rates and per capita consumption of fish oils with a high n-3 PUFA content, the association being greatest in countries with a high animal fat intake (Caygill *et al*, 1996). Studies on carcinogen-induced mammary tumours in rat show that feeding with saturated fats has a weak promoting effect, n-6 PUFAs have a strong promoting effect, and n-3 PUFAs have an inhibiting effect on tumour growth (Carroll, 1991). In the case of human mammary cancer cells, n-6 PUFAs stimulate their growth *in vitro*, and corn oil supplements (rich in n-6 PUFAs) stimulate growth and metastasis in explants (Rose *et al*, 1993). In contrast, long chain PUFAs of the n-3 series inhibit the growth of human mammary cancer cells *in vitro* while fish oil supplements (rich in n-3 PUFAs) inhibit growth and metastasis in explants (Rose & Connolly, 1993).

Obesity, breast cancer and insulin resistance

Obesity is commonly associated with insulin resistance in skeletal muscle and it has been postulated that a high intake of saturated fatty acids may increase predisposition to abdominal adiposity, hyperinsulinaemia and insulin resistance (Storlien *et al*, 1996). It is likely that high fat intake and obesity interact in causing insulin resistance. A study on the effect of high dietary fat intake on insulin levels in US ethnic groups showed that fasting insulin levels were increased more in obese than in non-obese individuals (Mayer-Davis *et al*, 1997).

Obesity is consistently associated with increased breast cancer risk in postmenopausal women although not in premenopausal women in Western populations. The increased risk is widely attributed to high levels of aromatisation of androgen to oestrogen in excessive adipose tissue. Extra-ovarian aromatisation accounts for most of the circulating oestrogen after the menopause, whereas in premenopausal women its contribution is relatively small compared to ovarian oestrogen. This hypothesis, however, fails to explain why a high body mass is associated with *increased* breast cancer risk in premenopausal women belonging to populations with a moderate or low breast cancer incidence (Pathak & Whittemore, 1992).

Body fat *distribution* may be a better marker of breast cancer risk. Thus, abdominal adiposity, both visceral and subcutaneous, is more closely correlated with breast cancer risk than is body mass, the relationship being clearer in postmenopausal than in premenopausal women (den Tonkelaar *et al*, 1994). The accumulation of abdominal fat is associated with the insulin resistance syndrome and the concomitants of hyperinsulinaemia may contribute to the risk of breast cancer (Stoll & Secreto, 1992).

Hypertension is more closely associated with hyperinsulinaemia in obese than in non-obese patients (Modan *et al*, 1985) and demonstration of visceral fat by CAT scan is a variable distinguishing hypertensive from non-hypertensive women. A high-risk cardiovascular lipid profile (low HDL-C) is associated with abdominal obesity and hyperinsulinaemia in premenopausal women who show no evidence of clinical cardiovascular disease (Igea *et al*, 1998).

Physical exercise, breast cancer and insulin resistance

Epidemiological studies investigating the association between breast cancer risk and physical exercise have yielded inconsistent results, possibly reflecting the variety of assessment methods. In a large case-control study, moderate exercise was associated with a reduced breast cancer risk independently of body mass and reproductive variables (Bernstein *et al*, 1994). In another study, decreasing risk was correlated with increasing physical activity in the daily occupation (Coogan *et al*, 1997). A review of the role of physical activity in reducing oestrogen-dependent cancer risk in women concludes that the inverse association is stronger for occupational than for leisure exercise (Kramer & Wells, 1996).

For members of families at increased risk to breast cancer, a protective regimen should include regular physical exercise both for adolescents and for adult women (Bernstein *et al*, 1994). A lower incidence of breast cancer has been shown in ballet dancers and gymnasts and this has been related to their exercise and delayed onset of menarche (Frisch *et al*, 1987). In the case of postmenopausal women, obesity is clearly associated with increased breast cancer risk. Regular physical exercise may reduce risk by the reduction of higher oestrogen levels derived from aromatisation of androgens in the excessive adipose tissue.

Another mechanism by which regular physical exercise may reduce breast cancer risk is by improving insulin sensitivity. Such an effect is independent of obesity and manifests even without any change in body weight (Bjorntorp *et al*, 1970). Physical exercise is associated with a reduction in the plasma insulin level, and even moderate non-vigorous exercise can improve insulin sensitivity (Mayer-Davis *et al*, 1998). Aerobic training involving walking, jogging or swimming two or three times weekly is reported to decrease the fasting insulin level in healthy middle-aged men and is associated with an increased fasting level of IGFBP-1 (Hellenius *et al*, 1995).

Daily aerobic exercise associated with restriction of dietary fat intake is reported to decrease insulin levels in patients with atherosclerosis and also to normalise insulin and lipid levels in patients with dyslipidaemia. A recent study reports that while a combination of aerobic exercise and reduced fat diet led to normalised cholesterol levels in individuals with high-risk lipoprotein levels, diet by itself was not effective (Stefanick *et al*, 1998).

Conclusion

Globalisation of the Western lifestyle and diet involves parallel globalisation of diseases such as hypertension, atherosclerosis and cancers of the breast, endometrium and colon. Obesity is no longer a marker of affluent populations. It is increasingly prevalent in less affluent countries associated with increase in coronary artery disease and diabetes. It is now common in adults in the large cities of China where it is ascribed to decreased physical activity in addition to increased consumption of cheap vegetable oils and refined grains.

Bioactive IGF-1 levels and hyperinsulinaemia are strongly influenced by diet and lifestyle and it is

hypothesised that regimens that decrease IGF-1 and insulin levels may help to protect female members of families at increased risk to breast cancer. Such intervention might involve dietary supplements of n-3 PUFAs combined with regular exercise (Stoll, 1998). Increased consumption of PUFAs is said to require increased intake of antioxidants such as vitamin E (Suarez *et al*, 1994). Since promotion of mammary carcinogenesis is likely to begin in adolescence, protective interventions need to begin at an early age.

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