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Point of View

Impaired Ovulation and Breast Cancer Risk

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Conflicting results have been reported on the association between breast cancer risk and symptoms of luteal insufficiency, such as irregular or prolonged menstrual cycles and difficulty in becoming pregnant. Studies on the association between breast cancer risk and hormonal markers of impaired ovulation have also yielded conflicting results. Inadequate allowance for body mass and fat distribution may lead to inconsistent results when assessing the association between luteal insufficiency in premenopausal women and breast cancer risk. Ovulatory function is impaired by obesity, especially if it is predominantly abdominal in distribution. The Western diet and lifestyle favour early manifestation of hyperinsulinaemic insulin resistance in genetically-predisposed women. It is commonly associated with obesity which is predominantly abdominal in distribution. In a subset of premenopausal women, the concomitants of hyperinsulinaemia may impair maturation of ovarian follicles by a direct effect of insulin or insulin-like growth factors on ovarian tissue. Even when women are ovulating regularly, obesity may be associated with luteal insufficiency as shown by decreased levels of progestins or other changes in the sex steroid profile. Insulin resistance is likely to be involved and might explain the weak reduction in breast cancer risk associated with overweight in premenopausal Western women, in contrast with the increased risk widely reported in obese post menopausal women. © **1997 Elsevier Science Ltd.**

Key words: breast cancer, fat distribution, hyperinsulinaemia, insulin resistance, luteal insufficiency, obesity, ovulation, Western women
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INTRODUCTION

EARLY MENARCHE, nulliparity and late menopause are all risk markers for breast cancer, and it has long been postulated that the lifetime number of regular ovulations may be a determinant of breast cancer risk. Conversely, it has been suggested that chronic luteal insufficiency or anovulatory cycles might be protective [1, 2]. However, epidemiological studies on the association between a history of ovulatory dysfunction and breast cancer risk have shown conflicting results both in older [3–9] and more recent studies [1, 2, 10–14]. Differences may be due to genetic or lifestyle factors in the various populations studied, or else to methodological limitations of some of the studies. The criteria for ovulatory dysfunction varied between the studies including prolongation of cycles, lifelong irregularity, amenorrhoea and infertility. Not all the studies adjusted for age at menarche, first live birth and parity. Few of the analyses adjusted for the effect of body mass.

With regard to hormonal markers, case-control studies have yielded conflicting results on serum progesterone or urinary pregnanediol levels in breast cancer cases. Nine out of ten of the older studies (summarised in [15]) found lower levels in the cases, but later studies have not confirmed this [16–18]. Most studies used single biological samples for comparison and this might lead to questionable conclusions.

Epidemiological studies show that ovulatory dysfunction in puberty and teenage years can be associated with either excess body mass or abnormal leanness and that both are associated with decreased risk of subsequent breast cancer. Moreover, irregular menstrual cycles are more common in association with obesity beginning during adolescence [19, 20] and all studies agree that obesity in teenage years is associated with a reduced risk of premenopausal breast cancer [21]. It is relevant that in ethnic groups with a low breast cancer risk, anovulatory cycles are more common

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between the ages of 15 and 19 years [7]. With regard to abnormal leanness, child gymnasts, athletes and ballet dancers commonly manifest a delayed menarche and irregular menstruation, while they also have a reduced risk of subsequent breast cancer [22].

Until very recently, epidemiological research on the determinants of breast cancer has neglected the effect of fat distribution on ovulatory activity and ovarian steroid production [23]. This review examines several lines of evidence that in normally ovulating women, luteal insufficiency may be associated with obesity, especially if it is mainly abdominal in distribution. The latter is a common manifestation of hyperinsulinaemia. The relationship between body mass and luteal insufficiency has been clarified by recent research on the effect of insulin and insulin-like growth factors (IGFs) on normal ovarian physiology [24]. The review considers whether this mechanism may explain the weak reduction in breast cancer risk associated with being overweight in premenopausal Western women, in contrast with the increased risk widely reported in obese postmenopausal women. [21].

OBESITY AND LUTEAL INSUFFICIENCY IN PREMENOPAUSAL WOMEN

Obesity may be associated with lower mean progesterone levels in normally ovulating premenopausal women [25]. This has been confirmed in a recent study of 175 healthy women aged 21–30 years, in which several luteal phase blood collections were recorded during a single menstrual cycle [26]. A lower serum progesterone level may itself decrease proliferative activity in breast epithelial cells [27] or it may be a marker of other metabolic-endocrine sequelae of obesity which might decrease breast cancer risk.

Obese premenopausal women show a higher frequency of irregular menstrual cycles [20], but even if they are ovulating normally, they often manifest an increased serum level of free testosterone associated with a lowered serum hormone-binding globulin level [28, 29]. The association is greater in the presence of abdominal (android) obesity than with lower body (gynoid) obesity involving especially the buttocks and thighs. Premenopausal women with abdominal obesity frequently show menstrual irregularity and sometimes anovulation [30].

Abdominal obesity is more common and develops at a younger age in Western than Asian women. Apart from genetic factors, rapid weight gain or a high-calorie, high-fat, low-fibre intake and inadequate exercise all favour its development, and it is related to the manifestation of hyperinsulinaemic insulin resistance [31]. It is now recognised that the waist–hip circumference ratio may not be an adequate measure of intra-abdominal fat. Imaging, either by CAT or MRI scans, shows that large visceral deposits of fat are present in apparently lean women and provide a better guide to insulin resistance [31].

At the time of puberty, girls frequently show increased ovarian and adrenal production of androgens associated with hyperinsulinaemia and large multilocular ovaries [32] and insulin resistance is thought to be the underlying cause [33]. Although it is usually transient, hyperinsulinaemia may persist in obese adult women, particularly in the presence of genetic susceptibility. It is relevant that a combination of early-age obesity, hyperinsulinaemia, irregular menses and increased testosterone levels has been observed among Pima Indians in the U.S.A. [34]. It has been suggested as a possible factor in the low breast cancer risk found among Native American women [23].

Hyperinsulinaemia may interfere with normal ovarian follicular development and steroidogenesis by a direct effect of insulin or insulin-like growth factor 1 (IGF1) on ovarian physiology [24]. IGF1 acts synergistically with gonadotropins in stimulating follicle development and P450 aromatase activity [24]. Hyperinsulinaemia may interact with IGF1 on the ovarian follicle, impairing its maturation and causing irregular menstrual cycles and increased ovarian androgen production [35, 36]. IGF1 may also have a direct mitogenic effect on mammary epithelial cells [37]. Both IGF1 and IGFII are produced in mammary stromal tissue and may exert a paracrine effect.

Another mechanism by which hyperinsulinaemia can modulate IGF1 activity in the ovary is through insulin's effect on IGF-binding proteins (IGFBPs) and this too may impair maturation in the ovarian follicle [24]. Proteolysis of IGFBP3 in the circulation is affected by insulin levels and this can lead to changes in the bioavailability of IGF1 in the tissues [38]. Increased proteolysis of IGFBP3 has been reported in the serum of both adults and children with non-insulin-dependent diabetes mellitus [38] and this might also apply to hyperinsulinaemic insulin resistance.

A possible link has been suggested between breast cancer risk and polycystic ovary syndrome (PCOS) [39, 40]. The latter is a common gynaecological disorder which manifests typically with chronic anovulation and hyperandrogenism, while obesity is also present in approximately half the cases. PCOS involves increased ovarian production of testosterone which is associated with follicular atresia and anovulation [41]. An underlying genetic abnormality may exist either in intracellular insulin signalling or in the cytochrome P450 aromatase enzymes in the ovary, leading to increased sensitivity to insulin stimulation. Both obese and non-obese women with PCOS show hyperinsulinaemic insulin resistance and there is, in addition, an increased luteinising hormone response to gonadotropin stimulation which also is independent of obesity [42]. Studies of breast cancer risk in PCOS patients have shown a lower risk in premenopausal women [39] but a higher risk in postmenopausal women [40]. Further studies would be useful.

WESTERN LIFESTYLE AND INSULIN RESISTANCE

Westernisation of lifestyle is associated with increasing prevalence of obesity and this favours the manifestation of insulin resistance in women with a genetic predisposition [31]. The Western high-fat, low-fibre diet also favours the development of insulin resistance, while diets rich in fibre and complex carbohydrates have the opposite effect [43]. Thus insulin resistance may persist through teenage years in a subset of Western women as a result of their diet and inadequate exercise. Obesity in teenage years favours irregular menstrual cycles in later life [19, 20] and a reduced risk of premenopausal breast cancer [21].

Whereas in the case of premenopausal women, abdominal obesity is frequently associated with impaired ovulation and increased ovarian androgen activity, abdominal obesity in postmenopausal women is generally associated with increased levels of bioavailable oestrogen [44]. It is relevant that abdominal obesity in postmenopausal women has been

associated with increased breast cancer risk in seven case-control studies [45–51], although results from an eighth study [52] were discordant. One of the studies [50] reported a lesser association with premenopausal cases also.

Social stress may be an additional factor contributing to the manifestation of insulin resistance [53] and may account for the higher incidence of abdominal obesity in Western women of lower socio-economic groups [54]. The finding of increased cortisol levels in association with abdominal obesity [30, 49] has led to the suggestion that hyperactivity of the hypothalamo–pituitary–adrenal axis may be involved [55]. Cortisol has been shown to favour abdominal fat deposits [56] where oestrogen production is much lower than in upper thigh and buttock fat [57]. This corresponds to the much higher levels of P450 aromatase transcript levels in the latter sites [58].

Mortality rates from breast cancer in Asian women are only approximately one-fifth of those in women in Northern Europe and North America. The reason is not clear, but lower oestrogen levels are found in premenopausal Asian women [59]. Their diet has a higher fibre content and fibre-associated phyto-oestrogens such as isoflavones may bind to the oestrogen receptor protein in mammary target cells, thus diminishing the uptake of endogenous oestrogen. In addition, indole-3-carbinol occurs naturally in vegetables such as cabbage, broccoli and cauliflower and may have cancer-protective effects [60]. Alternative mechanisms contributing to decreased risk may involve the effect of fibre itself or the presence of antioxidant vitamins in fruit and vegetables.

An effect on oestrone metabolism by the Western diet or by obesity has been suggested as a mechanism contributing to breast cancer risk. Oestrone is normally metabolised by enzymes along two pathways—either by the 2-hydroxylase pathway to catechol oestrogens or by the 16 alpha pathway to oestriol. The latter is postulated to be a factor in mammary carcinogenesis and is said to be increased by a high-fat intake [61] or by obesity [62]. It is claimed that while overall obesity increases the C16/C2 hydroxylation ratio in premenopausal women, this does not apply to abdominal obesity [44]. If confirmed, the observation suggests that gynoid and android types of obesity may have different effects on breast cancer risk in premenopausal women.

CONCLUSION

Hyperinsulinaemic insulin resistance in women is associated with an increased body mass, but in premenopausal women the hyperinsulinaemia appears to be related more to abdominal obesity, whereas in postmenopausal women it is linked more to overall body mass [63, 64]. Recent research suggests that, in a subset of premenopausal Western women, the concomitants of hyperinsulinaemia may impair maturation of ovarian follicles. Resulting changes in sex steroid production in the ovaries may contribute to a reduction in breat cancer risk.

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