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Review

Alcohol Intake and Late-stage Promotion of Breast Cancer

B.A. Stoll

Oncology Department, St Thomas' Hospital, London, SE1 7EH, U.K.

Breast cancer risk in women rises with increasing alcohol intake and is widely assumed to be mediated by increased oestrogen concentrations. However, observations that mechanisms and risk are likely to differ between pre- and postmenopausal women suggest that the postmenopausal disease in particular, may involve a promoting role for concomitants of hyperinsulinaemia which is commonly associated with alcoholic cirrhosis of the liver. The MEDLINE database and ongoing studies were examined for clinical, epidemiological and laboratory data on; (a) alcohol-related increase in the incidence of breast cancer in relation to menopausal status, oestrogen concentrations and the oestrogen receptor (ER) status of the tumour; (b) activation of insulin-like growth factor 1 receptor (IGF1R) in mammary tissue by alcohol-related hyperinsulinaemia; (c) interaction between ER and IGF1R in breast cancer cell systems. Epidemiological association between alcohol intake and increased breast cancer risk is more clearly seen in postmenopausal than premenopausal women, and a significant risk is associated with intake of more than two drinks (over 30 g) daily over a period of years. Alcohol-related hyperinsulinaemia is reported to increase with increasing degrees of cirrhosis and damage to liver function. Laboratory evidence suggests that hyperinsulinaemia can stimulate expression of IGF1R in mammary tissue, and this protein is likely to have a crucial role in mitogenesis and transformation to an oestrogen-independent malignant phenotype. It is postulated that in women with a history of long-term intake of moderate quantities of alcohol, the concomitants of hyperinsulinaemia may help to stimulate progression in precancerous breast lesions in the years leading up to the menopause and may increase the risk of breast cancer manifesting after the menopause. © **1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

MANY STUDIES in the past 20 years have shown that an increased breast cancer risk is associated with chronic alcohol intake in women and that the risk increases with increasing alcohol consumption [1]. Differences in the level of risk between various national populations remain unexplained. Pooled analysis of international prospective studies involving 322 647 women and 4335 breast cancer cases evaluated over 11 years [2], confirmed that risk increases with increasing intake of alcohol up to 60 g (approximately four drinks) daily but does not increase with intake beyond that amount. Alcohol intake between 30 and 60 g daily over a period of years increased the risk by 30 to 40% compared with abstainers, an increase similar to that associated with adverse reproductive history factors [2].

Considerable research has been directed towards a link between breast cancer risk and alcohol-related changes in oestrogen activity and this will be subsequently discussed below. Other mechanisms have also been considered including possible effects by carcinogenic congeners of alcohol such as acetaldehyde or plant phenols, increase in lipid peroxidase, effects on cell membrane integrity or the activation of carcinogens in the body [3]. Alcohol-related liver dysfunction may alter the metabolism of various carcinogens but experimental studies on the effects of alcohol on mammary carcinogenesis show conflicting results [4].

Reports are inconsistent on the relative frequency of alcohol-related risk of breast cancer before and after the menopause and this may be due to methodological issues or to

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biological interactions [5]. Large studies suggest that the association is considerably greater in the case of postmenopausal women [1] and that alcohol acts at a late stage in mammary carcinogenesis [6]. Risk is greater also with higher alcohol intake and its associated liver damage. The review postulates that the concomitants of hyperinsulinaemia, which is associated with alcoholic liver cirrhosis, may have a role in promoting mammary carcinogenesis, especially in the years leading up to the menopause. Other mechanisms are possible in different age groups, and one study suggests that chronic alcohol intake before the age of 30 years is associated with increased risk of premenopausal but not postmenopausal breast cancer [7].

ALCOHOL-RELATED CHANGES IN OESTROGEN ACTIVITY

In the case of premenopausal women, an association between increased breast cancer risk and long-term alcohol intake is less clear than in postmenopausal women [2]. However, both long-term and short-term alcohol intake in premenopausal women are associated with increased plasma levels of oestradiol and oestrone in the periovulatory and luteal phases, suggesting abnormal gonadotrophin release [8]. One study which failed to show alcohol-related increase in oestrogen concentrations in premenopausal women, showed instead an increase in plasma androstenedione level and suggested abnormal steroidogenesis in the ovary as a possible cause [9]. Most clinical reports agree that in premenopausal women, chronic alcohol intake is associated with ovarian failure, infertility and early menopause [10], suggesting an effect on the pituitary–ovarian axis.

In the case of postmenopausal women, the association between long-term alcohol intake and oestrogen concentrations has recently been reviewed [11]. Only three of eight studies showed significant increase in oestradiol and oestrone concentrations in the blood or urine in response to moderate alcohol intake. In the U.S.A., an association was related to consumption of wine but not beer or whisky, whilst in Europe the association with oestrogen concentrations was inconsistent [11]. Both in postmenopausal women and in men, long-term alcohol intake increases aromatisation of androgen to oestrogen in fat and skin [10]. In postmenopausal women, this effect might counteract menopausal symptoms or be associated with a reduced risk of coronary artery disease and stroke [12].

In men, chronic alcohol intake is a well-known cause of hypogonadism or even feminisation in the presence of liver cirrhosis [10]. In Egypt and other parts of North Africa, the percentage of all breast cancers that occurs in males is between 2 and 10% compared with 1% in Western countries. This has been ascribed to the high prevalence of liver cirrhosis due to bilharziasis but the relationship of male breast cancer to alcohol cirrhosis has not been studied.

The relationship between long-term alcohol intake by breast cancer patients and the oestrogen receptor (ER) status of the tumour is unclear. Two studies report a higher incidence of ER positive tumours [13, 14] whilst another reports a higher incidence of ER negative tumours [15]. Correlation between the ER status of breast cancers and the associated oestrogen concentration is generally uncertain. Whilst obese postmenopausal women with higher oestrogen concentrations are reported to show higher ER positivity in their tumours [16], users of hormone replacement therapy show a similar content in their tumours to non-users [17].

In postmenopausal, long-term alcohol users, a non-oestrogen-related mechanism may have a role in the promotion of mammary carcinogenesis. This is suggested by observations that the risk of breast cancer in women taking alcohol in addition to oestrogen replacement therapy, is higher than in abstainers on such therapy [18, 19]. In one of these studies [19], risk was increased (RR = 1.8) only if more than 5 g alcohol daily was taken. Short-term intake of alcohol by postmenopausal women has been shown to induce a temporary spurt in oestradiol levels [20] but such an effect is unlikely to influence mammary carcinogenesis.

The following evidence suggests that in a subset of women, alcohol-related hyperinsulinaemia can stimulate expression of insulin-like growth factor 1 receptor (IGF1R) in mammary tissue. This could accelerate oestrogen-independent growth in precancerous lesions in the years leading up to the menopause when oestrogen levels are falling. Such a change is likely to increase the risk of breast cancer manifesting after the menopause.

CHANGES IN PRECANCEROUS LESIONS AT THE MENOPAUSE

Screening mammography shows a peak incidence for duct carcinoma *in situ* (DCIS) at the age of 45–50 years followed by a steady decline [21, 22]. Histopathologically also, the incidence of DCIS in mastectomy specimens declines steadily after the menopause [23]. Mammographic densities reflecting abundant fibroglandular tissue with increased epithelial cell proliferation, are similarly decreased with the onset of the menopause, so that after the age of 45 years, the more favourable patterns are twice as common as in younger women [24]. In contrast, increased mammographic densities are noted in relation to the use of hormone replacement therapy [24] and also with long-term alcohol intake [25].

The above observations suggest that as the menopause approaches, a high proportion of precancerous lesions undergo spontaneous resolution presumably as a result of the falling oestrogen level. Programmed cell death (apoptosis) is involved in the regression, and histopathologically, it is seen in over 50% of DCIS cases [26]. The apoptosis index is not related to the ER status of DCIS and may be related to increased expression of the mutated *p53* oncogene [27]. In many cases, however, these foci of regression do not revert to normal growth but enter a dormant phase which can be reactivated by epigenetic factors [28]. Evidence of reactivation is seen in the increasing ER negativity associated with increasing proliferative activity [29]. Late-stage epigenetic promoting factors probably account for the high rates of postmenopausal breast cancer found in Western women. They include alcohol, obesity, oestrogen replacement therapy and specific characteristics of the Western diet [30].

As noted above, alcohol-related breast cancer risk is greater in postmenopausal than in premenopausal women and alcohol is likely to be a late stage promoter of mammary carcinogenesis. Further evidence of this is the increased mammographic density found in older premenopausal women with a high alcohol intake [25]. Overall, the evidence suggests that alcohol-related hyperinsulinaemia may counteract regression or stimulate progression in DCIS in the years leading up to the menopause. It may be associated with change from oestrogen dependence to autonomous growth [29].

Obesity is well-established as an epigenetic factor which increases the risk of postmenopausal breast cancer. Whilst breast cancer risk in women is increased to a similar degree by obesity as from long-term alcohol use, the effect of obesity on oestrogen levels in postmenopausal women is much greater than that of alcohol [31]. It has been postulated that in obese postmenopausal women, increased free oestradiol levels may synergise with the concomitants of hyperinsulinaemia in promoting mammary carcinogenesis [32].

ALCOHOL, INSULIN ACTIVITY AND BREAST CANCER RISK

Alcohol-related cirrhosis of the liver is a protein-catabolic state, and like similar states seen in critical illness, major trauma or burns and major surgery, it is associated with chronic hyperinsulinaemia and concomitant changes in the growth hormone/insulin-like growth factor 1 (GH/IGF1) axis [33, 34]. The changes in the GH/IGF1 axis in patients with alcoholic cirrhosis of the liver are thought to reflect liver dysfunction rather than malnutrition, although the latter is often associated [35]. It is relevant that case–control studies have shown chronic hyperinsulinaemia to be a risk marker for breast cancer, particularly in postmenopausal women [36–40]. The association has been confirmed even in early stage localised breast cancer cases (RR = 2.9) but has not been found in early stage cervical cancer, malignant melanoma or lymphoma [36]. One study found no association [41].

IGF1 has been shown to induce proliferative activity in cells which have undergone transformation [42]. It synergises with oestrogen in promoting growth in most human breast cancer cell lines, and most breast cancer specimens show both IGF1 and insulin receptors [43]. Circulating IGF1 is derived mainly from the liver but in addition, IGF11 is secreted by fibroblasts in the breast stroma and exerts a paracrine effect in stimulating the growth of malignant epithelial cells [44]. IGF11 expression is strongly correlated with progesterone receptor expression in the mammary epithelium [45].

The bioavailability of circulating IGF1 is regulated by a group of at least six IGF-binding proteins (IGFBPs) which are produced mainly in the liver. Whereas IGFBP1 regulates IGF1 availability in response to rapid changes in insulin levels, over 90% of circulating IGF1 is bound to IGFBP3. The latter controls long-term adaptive change to long-term hyperinsulinaemia [46]. In normal subjects, the effect of insulin is to suppress free IGF1 and IGFBP1 concentrations, but IGFBP3 concentrations are stimulated [47]. In patients with alcoholic cirrhosis of the liver, the presence of chronic hyperinsulinaemia is associated with suppression of free IGF1, but IGFBP3 concentrations are decreased whilst IGFBP1 is increased [48, 49]. The degree of these changes is correlated with the degree of damage to liver function [35, 50].

The biological effects of both IGF1 and IGF11 in mammary cells are mediated by their activation of insulin-like growth factor 1 receptor (IGF1R) and this protein is thought to have a crucial role in mitogenesis and transformation to the malignant phenotype [51, 52]. Overexpression of the mutated *p53* tumour suppressor gene is recognised in comedo type DCIS lesions which have a high likelihood of progressing to invasive breast cancer, and binding of both insulin and IGF1 to their respective receptors is significantly higher in samples of tumour showing overexpression of the mutated *p53* oncogene [53]. Increased expression of insulin and IGF receptors is likely to be associated with progression in DCIS from oestrogen-dependent to autonomous growth [54].

The mechanism by which hyperinsulinaemia associated with alcoholic cirrhosis of the liver may affect IGF1R activity in mammary epithelium is uncertain. The liver is the major source of circulating IGF1 and IGFBPs and it is thought that hyperinsulinaemia decreases IGFBP3 concentrations, resulting in increased IGF1 bioactivity which stimulates IGF1R activity in mammary tissue cells [46]. A direct effect is also possible by modulation of IGFBP3 which is secreted directly by mammary epithelial cells and has its own receptor in the cell membrane [55, 56].

Insulin receptors (IR) too may have a role in mammary carcinogenesis. Over-expression of IR has been noted in human breast cancer cells and this may make them more responsive to insulin stimulation [57, 58]. A clinical study on 584 breast cancer specimens found the IR content of the tumour cells to be a more significant predictor of prognosis than even the proliferative activity as measured by cytometry [59].

Whilst both oestrogen and IGF1 are potent mitogens for most human breast cancer cell lines, interaction between their receptors is likely to be involved in modulating the progress of mammary carcinogenesis [42]. Thus, correlation between IGF1R and ER expression has been shown in breast cancer cell lines, mastectomy specimens and animal model studies [60,61]. Higher expression of IGF1R expression is correlated with higher ER and progesterone receptor positivity [62].

In most breast cancer cell lines IGF1 stimulates ER expression [63] whilst oestrogen increases the expression of IGF1R [64]. However, prolonged overexpression of IGF1R has been shown to contribute to the development of an oestrogen-independent phenotype [42]. This observation may be relevant to a rise in the incidence of ER negative breast cancers which has been noted around the age of 50 years [65]. An increase in the oestrogen-independent phenotype at the onset of the menopause would be accentuated by the concomitants of hyperinsulinaemia. Consequent amplification of IGF1R expression in cancer precursor lesions in the breast would favour their progression to invasive cancer.

Reference needs to be made to multiple observations of lower fasting insulin levels in light drinkers compared with abstainers [66–68] and their possible association with a lower risk of coronary artery disease [69, 70]. This observation appears to contrast with evidence of hyperinsulinaemia both after acute alcohol intake [71] and also in association with long term alcohol intake. There are problems in the interpretation of studies suggesting an association between light alcohol intake and protection from coronary artery disease [70]. International comparisons suggest that diminished risk of coronary artery disease is most clearly related to wine intake and may be due to beneficial non-alcoholic components of wine or its association with leisurely meals and a healthy diet [72]. Both factors might be responsible for a decreased tendency to insulin resistance and hyperinsulinaemia [73].

THE IGF1/IGFBP3 RATIO AS A RISK MARKER IN BREAST CANCER

The balance between IGF1 and IGFBP3 concentrations might determine whether genetically damaged cells in the mammary epithelium survive and progress to carcinogenesis.

Whilst IGF1 might synergise with oestrogen in a mitogenic effect on mammary epithelium and at the same time prevent apoptosis, IGFBP3 might limit the bioavailability of IGF1 and at the same time increase apoptosis independently of IGF1. Case–control studies and also a prospective study have shown an elevated IGF1 concentration in the serum to be a risk marker for breast cancer [74–77] although other studies could not confirm this [40, 78, 79]. A protective role for IGFBP3 has been suggested in one of the studies which showed that a higher IGF1/IGFBP3 ratio was an even more significant risk marker in premenopausal women [75].

Supporting the above hypothesis is evidence that in postmenopausal women with breast cancer treated by the antioestrogen tamoxifen, IGF1 concentrations are reduced whilst IGFBP3 concentrations are increased [80]. A similar observation was made in postmenopausal patients treated by the retinoid fenretinide [81]. However, in spite of evidence that IGFBP3 can increase apoptosis and cell death in breast cancer cell lines [82], clinical studies show inconsistent results on the association between IGFBP3 concentrations and breast cancer prognosis. High levels of IGFBP3 have been shown in breast cancer specimens which are ER negative or associated with a poor prognosis [83]. The ratio of fragmented to intact IGFBP3 may need to be taken into account both for circulating and tissue measurements of IGFBP3 [82].

CONCLUSION

The review summarised evidence that long-term alcohol intake leading to hepatic dysfunction or cirrhosis is associated with hyperinsulinaemic insulin resistance. Variation between national populations may reflect consumption of different types of alcoholic spirits or else different genetic susceptibility to insulin resistance. Hyperinsulinaemia is associated with changes in circulating levels of IGF1 and its binding proteins, which can activate IGF1R in mammary epithelium. In a subset of women, interaction of IGF1R with ER may stimulate progression of precancerous to invasive lesions, particularly in the years leading up to the menopause.

The hypothesis can be tested clinically in women aged 45–55 years who are not ovariectomised or taking hormone replacement therapy. Mammographic evidence of gross dysplasia should be assessed in relation to a woman's history of long-term alcohol intake and to evidence of liver dysfunction and fasting insulin concentration.

This review has focused on possible mechanisms for the observed increase in breast cancer risk in women consuming over 30 g alcohol (that is, over two drinks) daily over a period of years. This is the level associated with a RR of 1.3–1.4 in breast cancer risk compared with abstainers [2]. These women are likely to show evidence of impaired liver function although not necessarily liver cirrhosis. A fall in the serum concentrations of IGF1 and IGFBP3 has been shown when cirrhosis develops in alcoholics and it is not associated with nutritional parameters [35]. Increased breast cancer risk in light drinkers or occasional drinkers is not discounted but is likely to be minimal, whilst a biological basis for the putative reduced risk of coronary artery disease in such women is briefly reviewed [66–72].

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