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Hypothesis

The potential for oxytocin (OT) to prevent breast cancer: A hypothesis*

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Key words: ductal obstruction, functional breast behaviour, microvessel ischemia, oxytocin, prolactin

Abstract

This hypothesis proposes that carcinogens in the breast are generated by the action of superoxide free radicals released when acinal gland distension, under the influence of unopposed prolactin, causes microvessel ischaemia. Inadequate nipple care in the at-risk years leads to ductal obstruction preventing the elimination of carcinogens from the breast. The regular production of oxytocin (OT) from nipple stimulation would cause contraction of the myoepithelial cells, relieving acinal gland distension and aiding the active elimination of carcinogenic fluid from the breast.

Mechanical breast pump stimulation causes an increase in plasma OT levels in the luteal but not in the follicular phase of the menstrual cycle. OT production upon nipple stimulation in the luteal phase of premenopausal, non-lactating women may be protective against the high rates of mitotic breast cell division noted at this time via the potential to block the effect of oestrogen.

The epidemiology of breast cancer suggests that lengthy lactation time is beneficial. Sexual activity in nulliparous women also protects and OT levels have been shown to rise with orgasm in women and in men. OT systems in the brain are intricately linked to oestrogen and progesterone levels, and it is possible that these hormones may modify the OT secretory response both centrally and through an effect on the sensitivity of the breast.

OT production with nipple care and in sex and lactation, and the reduction in cycling ovarian hormones that occurs with pregnancy, may all be important preventative factors in the development of breast cancer both pre- and post-menopausally.

Hypothesis

This theory states that inadequate nipple care in the at-risk years, leads to ductal obstruction which prevents the elimination of carcinogens from the breast. It is proposed that carcinogens are generated by the action of superoxide free radicals released when acinal gland distension, under the influence of unopposed prolactin, causes microvessel ischemia [1].

Nipple care is an accepted practice during lactation and could be extended into the post-reproductive, premenopausal and postmenopausal years. The regular production of OT from nipple stimulation is a key factor in this notion of breast cancer prevention [2] (Fig. 1).

Historical evidence

Hippocrates associated the origin of breast cancer with the cessation of menstruation. Such suppres-

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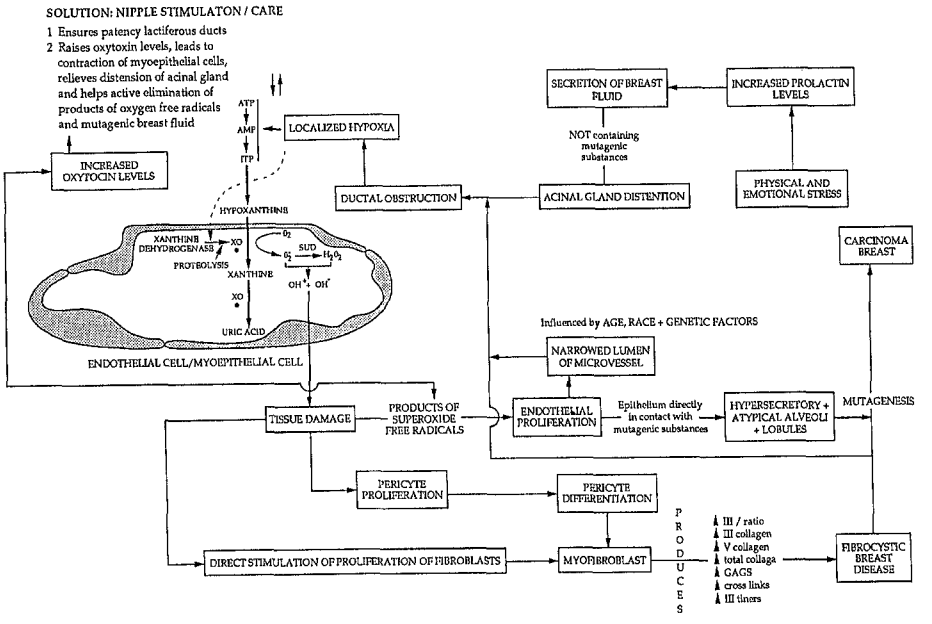

Fig. 1. A conceptual model for the pathogenesis of fibrocystic and cancerous breast disease. Upper R and L sections modified from: Murrell *et al.* [22]. Centre and bottom R sections modified from: Murrell *et al.* [23].

sion would lead to breast engorgement nodules and 'hidden' cancer [3]. He and Soranus also advocated the 'cupping' of the breasts to produce uterine contractions to treat postpartum bleeding, heavy periods and engorged breasts [4, 5].

In the sixteenth century, Wilhelm Fabry believed that the cancer began with a drop of milk curdling within the breast [6]. This ushered in ideas about scirrhus and cancer being the outcome of a sluggish thick humour of bile which originated outside the liver. Notions of ductal obstruction appeared following Harvey's discovery of the circulation in the seventeenth century. Bartholin discovered the lymph flow and Dionis attributed cancer to a stagnation of lymph in the breast [6]. This stasis could be brought about by external trauma or internal noxious constituents in the blood. Many of Dionis's patients were nuns. It was Ramazinni in 1700 who showed that nuns had a high risk [7].

In the early eighteenth century a Lancashire physician, Edward Baynard, complained that women who wanted to be fashionable with squashed breasts and flattened nipples due to their hard lacing, were at risk from scirrhous cancers and hard tumours [8]. Charles White of Manchester equated tight boned dresses with flat non-responsive nipples with breast disease ' the tightness of the stays is alone to do much harm. Hence it would appear evident why women of rank meet difficulty in giving suck to children – and why hard working labouring women, who are obliged to go very loose about their breasts, generally make good nurses –' [8]. So it would seem that the social class differences then were as relevant for functional breast behaviour as they are today.

Clinical evidence

An important clinical finding in some women who present for routine breast examination is a flat, atrophic, and sometimes scaly nipple [9]. This sign indicates that nipple care or stimulation has been absent for at least a year with the likelihood of lactiferous duct obstruction high. Studies in Adelaide suggest that the pain and lumps of hormonal mastopathy can be resolved in about three menstrual cycles with appropriate counselling which advocates options of various kinds of nipple care, particularly when there is a partner [10]. Another clinical observation from this work is that young women who wear tight bras for twenty-four hour periods and

longer tend to develop hyperprolactinemia. This reinforces the historical notions on causality from the wearing of compressing apparel. It may also explain the latitude differences in breast cancer incidence in the US and Australia.

The physiological basis of these clinical observations has been provided by the work of Leake *et al.* [11] (Fig. 2). Mechanical pump stimulation evoked a significant increase in plasma OT level during the luteal but not follicular phase of the mentrual cycle. This causes contraction of the myoepithelial cells of the acinal gland, thus eliminating any static fluid which may be potentially carcinogenic with lead times from two years or longer. Oestrogen may well be acting indirectly as a promoter of carcinogen production [12]. OT levels have also been shown to rise with orgasm in women and in men [13].

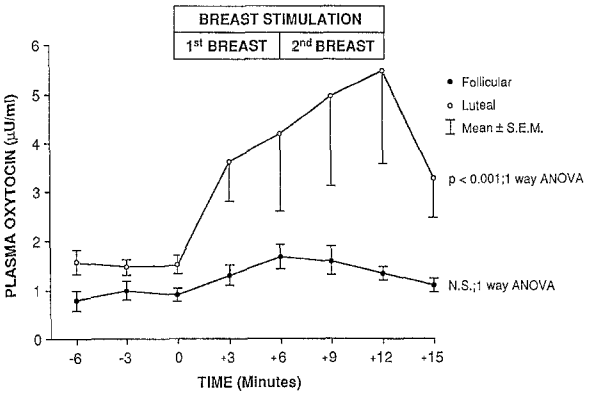

Fig. 2. Mean (± SEM) plasma oxytocin concentrations during mechanical breast pump stimulation in nine women studied serially during the follicular and luteal phases of the menstrual cycle. (Reproduced with permission, Leake *et al.* [11].

Biochemical evidence

It is proposed that prolactin secretion in the absence of OT leads to fluid pressure on the secretory epithelium. Hyperprolactinaemia may be a result of stress [14]. Mammary stimulation can also cause prolactin secretion in non-lactating women [15], although this is not the case with clinical examination of the breast [16]. Although OT is generally thought to be a stimulator of prolactin secretion at the level of the pituitary, it has been shown to inhibit prolactin secretion within the hypothalamus [17].

Despite a plethora of data on the role of oestrogen in breast cancer origins, the case for or against this association remains open [18]. However, it is possible that oestrogen and progesterone may modify the OT secretory response through an effect on the sensitivity of the breast or through effects on the central adrenergic mechanism of OT secretion [19, 20]. Opioid peptides inhibit OT in stressful situations and there is a relationship between ovarian function and these peptides in the hypothalamus, the peptides rising during puberty and falling after menopause [21]. Additionally, oestrogen and progesterone have been shown to increase the circulating levels of beta-endorphin during the luteal phase of the mentrual cycle [21].

The pathogenetic cascade which results in carcinogens is shown in Fig. 1 and is based on a hypoxic model responsible for the fibrosis of Dupuytren's contracture [22–24]. During localised ischemia, ATP is degraded to hypoxanthine and xanthine dehydrogenase to xanthine oxidase. The latter is found in microvessel endothelial cells and catalyses the conversion of hypoxanthine to xanthine and xanthine to uric acid [25]. Both reactions generate oxygen free radicals which may chemically modify or damage proteins, lipids, carbohydrates, and nucleotides [26]. An important free radical mediated process is lipid peroxidation. Generation near DNA may result in damage to the nucleotides leading to mutation, altered biological activity, and cancer [27]. Fibrosis in the early phase of this reaction creates ductal obstruction, thus aggravating the microvessel ischemia. Positive tests for presumptive mutagenic substances have been found in nipple aspirates from 6.7% of women attending breast screening clinics [28].

Epidemiological evidence

There are strong indicators from epidemiology that the macro-ecology of breast cancer involves a major issue of functional breast use where a woman's reproductive and sexual history are key determinants. Early this century, investigations noted that

nulliparity and a negative history of lactation were more prevalent with the disease [29].

Recent work has clarified the effect of pregnancy on risk [30]. There is a strong and highly significant inverse association between the number of full term pregnancies and risk which could not be confounded by age at first birth. The protective effect of high parity was strongest in groups with an early first birth. Women with many late pregnancies and those with a few widely spaced pregnancies had a higher risk than nulliparous women. There is now doubt about the sole importance of age at first full term pregnancy. Instead, length of breast feeding may appear to be the important variable, although this has yet to be established conclusively [31, 32]. This reduction in risk by lactation time is in premenopausal rather than postmenopausal females with breast cancer [33, 34].

Studies have shown that a negative association between lactation and subsequent risk appears independent of parity and is present in both pre- and post-menopausal cancers [35]. It was also reported from Hong Kong that the Tanka women had a disproportionate incidence of breast cancer in the left breast because of their practice of nursing solely with the right breast [36]. The low incidence among certain racial groups can be attributed to aggregate lactation. The higher age specific incidence in postmenopausal women means that prophylaxis by nipple care during the premenopausal years may be important.

Latitude differences in incidence appear consistent for USA, the former USSR, and Australia. Differences in vitamin D production have been used to explain this phenomenon [37]. However, an alternative explanation may be the absence of compressive clothing in hotter climates with lower levels of prolactin.

There has only been one study on sexual behaviour and risk and this supports the proposed hypothesis. A recent case-control study has shown that in age-matched nulliparous women the incidence, and therefore risk, was much lower in the sexually active group when compared with the celibate group [38]. Of note again here, is the effect of orgasm on oxytocin levels [12]. Nothing is known of OT levels in post-menopausal women.

Conclusion

There is no general concensus on the environmental or hormonal factors responsible for the genesis of human breast cancer. In the ecology of breast cancer it seems that the important variable missing from the present scenario is functional breast behaviour in the non lactating years – and, herein lies a controversy. Sensitivity in collecting the information required to prove the hypothesis will be matched by the difficulties in mounting an intervention study. The way around this issue may be to examine the role that nipple care may play in prophylaxis and the effect on oxytocin secretion as an extension of an acceptable practice for nursing mothers in addition to manual breast palpation as a screening manoevre in later life.

All the historical, clinical (which in this paper is only descriptive), biochemical, and epidemiological evidence points to a theory of ductal obstruction and trapped carcinogens as a basic notion of pathogenesis. Studies on the role that OT may play in the post-reproductive, premenopausal, and postmenopausal lives of women at risk will be crucial to the outcome of the thesis along with laboratory data which target the effects of OT on breast cancer cell live cultures *in vitro*. Much is known about the role of prolactin and OT from animal studies of the lactating mammal, but there is little information available in the non-lactating situation [39].

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