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CLINICAL PERSPECTIVE

Why does hormonal contraception and menopausal hormonal treatment have such a small effect on breast cancer risk?

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Oestrogen is considered by many to be a major cause of breast cancer, and yet hormonal contraception and menopausal hormonal therapy have a paradoxically small effect on breast cancer risk. Also, in the oestrogen-only arm of the Women's Health Initiative, subjects given oestrogen had a reduced risk of breast cancer compared to controls. Initiation of breast cancer likely begins early in life, in the long-lived ER^-PR^- breast stem cell. The main mitogen of ER^+PR^+ breast cancers is oestrogen derived from local breast fat and the tumour itself, rather than circulating oestrogens. Progesterone is relatively breast neutral, but progestins in the laboratory have been shown to expand malignant breast stem cell number.

KEYWORDS

breast cancer, causality, contraception, menopausal hormone therapy, risk factor

INTRODUCTION

Breast cancer is a common malignancy in women, and the majority of tumours are oestrogen receptor positive (ER^+) and often progesterone receptor positive (PR^+). The epidemiology of breast cancer is well studied[1,2] and summarised in Table 1. Oestrogen is often described as a prime mitogen for breast cancer.[1,2] If this was true, then it would follow that prolonged use of hormonal contraception or menopausal hormonal therapy (MHT) should substantially increase the risk of ER^+ breast cancer and worsen prognosis. This is not the case.[1–4] Even more surprising were the results from the oestrogen-only arm of the Women's Health Initiative (WHI)[3] reported in 2020.[3] A total of 10,739 women with prior hysterectomy were randomly assigned to oestrogen or placebo, treated for 7.2 median years and had a 20-year follow-up. The treatment group had a lower risk of developing breast cancer (Hazard Ratio (HR): 0.78, 95% confidence interval (CI): 0.65–0.93, $P = 0.005$) and a lower risk of dying of the disease (HR: 0.60, 95% CI: 0.37–0.97, $P = 0.04$). Yu *et al*.[4] performed a systematic review of MHT studies and showed that pre-diagnosis MHT usage was associated with a reduced risk of death from breast cancer (HR: 0.88, 95% CI: 0.81–0.97) or any cause (HR: 0.79, 95% CI: 0.69–0.90).

Another interesting paradox is that in the past, ovarian removal or irradiation was an effective treatment for advanced breast cancer but so too was giving a potent oestrogen such as stilboestrol.[5]

The aim of this study is to attempt to explain these apparent contradictions and to review the impact of sex hormones on breast cancer aetiology. Over the past 30 years, there has been a substantial increase in our knowledge of the initiation and progression of breast cancer. The first was the discovery of the breast stem cell as the likely site of initiation of breast cancer.[6–10] The second is that breast fat and the malignant tumour itself actively make oestrogens locally, within the breast,[11–13] and these locally

produced oestrogens seem to be more important than the impact of MHT or other exogenous hormones.

EPIDEMIOLOGY OF BREAST CANCER

Breast cancer is a common malignancy, much more prevalent in women than men and linked to many reproductive markers, implying a major role for female sex hormones in the aetiology of this disease. The underlying risk factors for breast cancer are presented in Table 1.[1,2]

Normal and malignant breast cell biology studies typically study the pathogenesis of breast cancer in two parts. First, there are factors that commence the malignant process (initiation) and then factors that cause the malignant cells to proliferate (progression). There is now considerable evidence that the breast malignant process is driven by a small population of breast stem cells.[6–10]

NORMAL BREAST STEM CELLS

Normal breast tissue comprises many different cell types, including fat, vascular, fibrous, ductal and lobular cells.[6–10] Breast stem cells are unspecialised cells with an ability to self-renew almost indefinitely and yet also able to differentiate into all the cell types found within the breast.[11] Breast stem cells represent between 1/200 and 1/1000 cells within the breast; they are located in a niche along the breast duct and are under tight control, mostly quiescent in the G_0 phase. Stem cells are able to divide symmetrically into stem cells or asymmetrically producing a progenitor that goes down the path of differentiation.[6,10] These progenitors cannot self-renew and have limited scope for differentiation. Adult or 'somatic' stem cells persist throughout adult life and aid in tissue repair. Breast stem cells are multipotent, typically ER^-PR^- and have specific surface markers, including CD10, CD44, CD24 and ALDH1.[5]

Within the breast niche, the long-lived ER^-PR^- stem cell is surrounded by a population of short-lived ER^+PR^+ stem cells or progenitors that produce the breast duct cells. There is now considerable evidence that most breast cancers are initiated in the breast stem cells.[6–10] These long-lived cells have been around for many years and can potentially acquire sufficient genetic and epigenetic damage to escape the control of its niche.

TABLE 1 Risk factors for breast cancer

High-risk factors (RR > 4)
Female sex
Increasing age
Caucasian (vs Asian)
Specific genes (eg BRCA1/2 mutations)
Cancer in the other breast
Breast atypical hyperplasia/DCIS
High-density mammogram
Age at first pregnancy
The Western diet (compared with the Japanese diet)
Moderate-risk factors (RR > 2)
Tall (vs short)
Obese
Young age at menarche
Late age at menopause
Alcohol intake (two drinks daily, RR: 2)
Minimal-risk factors (RR < 2)
Recent hormonal contraceptive usage
Recent/prolonged MHT (progestin)
High birth weight
Late first pregnancy
Low physical activity
Ionising radiation
Working on an aeroplane

DCIS, ductal carcinoma in situ; MHT, menopausal hormonal therapy.

ONCOGENIC INFLUENCES IN UTERO AND INFANCY

When one reviews the risk factors in Table 1, several factors point to an intrauterine and/or early childhood, early adulthood aetiology. These include the impact of diet, early first pregnancy and high birth weight.

Early-life oncogenic influences have been reviewed[1,2,6–10] and will now be summarised. This process may begin in utero. Breast stem cell number is likely, at least in part, determined in utero. Birth weight, for example, links to the number of fetal stem cells found in cord blood.[14] Some peptide growth factors such as insulin and the insulin-like growth factors (IGFs) are known to stimulate stem cells.[6–10] There is abundant evident too that diet, weight and height (all three of these link to insulin and/or IGFs) strongly predict breast cancer risk. Dietary studies strongly suggest an early (first 20–30 years of life) impact on breast cancer risk.[6–10]

BREAST LOBULE DEVELOPMENT

This area was pioneered by Russo and Russo[15] and recently reviewed by Fu *et al*.[16] A cluster of acini extending from a terminal duct and surrounded by myoepithelial tissue is termed a terminal duct lobular unit (TDLU). These are the major sites of breast cancer rather than the ducts themselves.[16] Russo and Russo described four lobular types: lob 1, lob 2, lob 3 and lob 4. They also described ten stages of in utero breast development resulting in lob 1 ducts. After puberty lob 2 ducts are found too and perhaps a few lob 3. Full breast development is achieved only after the first full-term pregnancy.[9,15]

Lob 1 unit has the highest proliferative index and the highest concentration of ER and is the most vulnerable to carcinogenesis in animal studies.[9] Lob 3 and lob 4 are much less vulnerable to carcinogenesis.[9]

PREGNANCY AND THE BREAST

Pregnancy has complex effects on breast cancer risk.[1,2,6–10] In the short term, risk increases, probably due to stimulation of an existing tumour, especially in women aged over 35 years. In contrast, early first, full-term pregnancy reduces long-term risk (eg first full-term pregnancy around age 25 years halves future breast cancer risk). Breast feeding only slightly reduces breast cancer risk (Relative Risk (RR) < 1.3, 1).

Only during the first full-term pregnancy do significant numbers of lob 3 and lob 4 appear, and these types are less vulnerable to carcinogenesis as stated earlier (7–98). Also, breast stem cell number is reduced by the first full-term pregnancy, and the breast stem cells are more resistant to carcinogenesis.[7,9]

THE MENSTRUAL CYCLE AND THE BREAST

The normal breast undergoes extensive changes throughout the menstrual cycle. In 1984, Anderson[17] examined 116 breast biopsy samples and showed that both mitosis and apoptosis peak in the luteal phase. Oestrogen's effects on the breast are well known. Progesterone and progestins have a complex effect on the breast.[18] Typically, short bursts of progestins or progesterone stimulate breast cell proliferation, whereas high-dose progestins or progesterone tend to down-regulate the breast. These effects are mediated through PR, altered local oestrogen production and impacts on ER.

THE MASS OF UNDETECTED BREAST CANCER AND DUCTAL CARCINOMA IN SITU

Welch and Black[19] reviewed seven autopsy studies, some hospital based and others forensic, in the 1990s to try and discover the background rate of ductal carcinoma in situ (DCIS) and invasive breast cancer. The median prevalence of invasive breast cancer and DCIS was 1.3 and 8.9%, respectively. Many of these lesions were too small to show on a mammogram. Prevalences were higher in women aged 40–70 years. They concluded that a substantial reservoir of DCIS is undetected in life.

Santen and Yue[20] have reviewed clinical and lab data and have developed some mathematical models of the impact of different MHTs on breast cancer risks. They have suggested that MHT does not cause breast cancer, but some types, especially those with progestins, stimulate small existing tumours. In contrast, in the conjugated equine oestrogen (CEE) arm of WHI, the CEE induced cellular apoptosis. These are intriguing theories; however, the biology is even more complex. For example, it has been known for decades that the breast itself makes large amounts of oestrogens locally.[11–13,21]

BREAST OESTROGEN PRODUCTION

The breast cancer stem cell (CSC) driving the malignant process is usually $ER^{-}PR^{-}$; however, their progenitors are usually $ER^{+}PR^{+}$, and these and their offspring form the bulk of the tumour. As such, one would expect giving MHT would substantially increase the growth of these progenitors. This is not the case. Their growth is certainly driven by oestrogen. As will now be shown, the major oestrogenic drive to these tumour cells is locally produced oestrogens. Local breast fat and associated parenchyma make high amounts of oestrogens, both before and after menopause.[11–13,21]

Typically, normal breast levels of oestradiol (E2) are about 20 times that of serum. Breast fat has high levels of not just the enzyme aromatase but also sulphatase which converts oestrone sulphate into oestrone.[11] These weak oestrogens are converted into E2 by 17β-hydroxysteroid dehydrogenase. Most ER^{+} breast cancers (about 70%) have enhanced aromatase activity around them, even more than fat in other quadrants of the breast. Thus, the ability of the tumour microenvironment to make oestrogens is likely to be more important than systemic or exogenous oestrogens.[6–9,13,21]

There are many other microenvironmental factors that can also promote breast cancer growth.[9,21,22] These include local peptide growth factors, cytokines and angiogenesis (new blood vessel formation). There is also some evidence that some breast cancers can recruit other stem cells (fat, fibroblast, haematological) into the tumour mass.[9]

PROGESTINS AND BREAST CANCER PROMOTION

The effects of progesterone and progestins differ based on type, dose and delivery frequency.[3,4,23] With regard to MHT, the data seem clear that MHTs containing progestins are associated with a slightly higher breast cancer risk than oestrogen alone or regimens containing progesterone. In the French E3N study[23] MHTs containing progesterone had a lower breast cancer risk than those regimens containing synthetic progestins. Paradoxically, high-dose medroxyprogesterone acetate (MPA) is an effective treatment for some breast cancers, probably by down-regulating ER and PR.[24]

Over the past 20 years, Horwitz and Sartorius[25] and Brisken and Scabia[26] have studied these effects in detail. A summary of their findings follows. Progesterone has a key role in the maturation of the normal breast. In Horwitz's view, progesterone in physiological doses is incapable of causing breast cancers but may play

a role in promotion.[25] Her group has studied, in the laboratory, cells derived from ER^+PR^+ (lumen A type) breast cancers. When progestins are added to the cell culture, the malignant stem cell number expands, and because the malignant stem cell is the main driver for tumour mass expansion, a slight increase in tumour growth occurs. The bulk of the tumour is comprised of daughter cells derived from these CSC, and their main mitogen is oestradiol. The main source of oestradiol that stimulates tumour growth is the local breast fat and other parenchymal cells.[6–9,13,21]

MHT AND IMPROVED BREAST CANCER SURVIVAL

The oestrogen-only arm of the WHI was associated with a reduced risk of diagnosis of and death from breast cancer.[3] The combined MHT arm showed a slightly increased risk of breast cancer (HR: 1.28, 95% CI: 1.13–1.45, $P = 0.001$) and no effect on death rate from breast cancer. The authors explained this by citing the apoptosis theory already mentioned and suggested, as earlier, that MPA expanded the CSC population. They offered no explanation for the null impact of combined MHT on breast cancer mortality. The review of Yu *et al*.[4] found that MHT usage reduced the risk of death from breast cancer, and current users had the most benefit. They found that the MHT users who were diagnosed with breast cancer had tumours more likely to be ER^+ and lower grade than the control group. These observations could, at least in part, explain the improved survival rates observed in the MHT users.

SUMMARY AND CONCLUSIONS

MHT has a small impact on breast cancer risk (RR < 2) compared with consuming two alcoholic drinks per day (RR > 2), increasing age (RR > 4) and being tall or obese.[1–3] It has been shown that the factors for initiating most breast cancer occur in utero, and during childhood and young adulthood. For example, the impact of diet, peptide growth factors such as insulin and IGFs are highest in the young. It has also been shown that nulliparous women mostly have lob 1 TDLU, which are more vulnerable to carcinogenesis, at least in animal models, than lob 3 and lob 4.

Initiation of breast cancer is likely due to accumulated genetic and epigenetic damage to the long-lived breast stem cells. Once this has occurred, the malignant CSC must escape the control of its niche and begin to produce malignant offspring. These progenitor cells acquire ER and PR, and they and their offspring form the bulk of the tumour. Oestrogen is the main mitogen for these ER^+ breast cancer cells, but the main source of E2 is the local breast fat and its parenchyma,[12,13,21] not systemic or exogenous oestrogens. It has been known for decades that many ER^+ breast cancers have high levels of aromatase in the malignant tissue itself and surrounding tissues.[21,22] These locally produced oestrogens would likely be the main drivers of tumour growth. Low-dose progestins tend to expand breast CSC number and therefore may act as a minor promotor of small existing luminal A breast cancers.[25,26]

In the combined oestrogen–progestin arm of the WHI where MHT was given to women aged on average 64 years (an older group than those who usually take MHT), the slight increased risk of breast cancer (8/10,000/year; HR: 1.28, 95% CI: 1.13–1.45, $P < 0.001$ [3]) was likely due to a small promotor effect on existing tumours that would have been detected anyway a year or so later, if the subject had not taken MHT. In contrast, the reduced risk of breast cancer observed in the oestrogen-only arm of the WHI (HR: 0.78, 95% CI: 0.65–0.93 [3]) was likely due in part to an apoptotic effect of giving oestrogen to older postmenopausal women.

Menopausal patients are reticent to take MHT because of their concern it may increase their risk of developing breast cancer. The evidence presented in this review would suggest that MHT does not cause breast cancer but rather might slightly stimulate an existing tumour to appear sooner. In this respect, oestrogen-only MHT is breast safer than oestrogen and progestin therapy. Progesterone seems safer than a synthetic progestin.[3,23] It is reassuring to note as well that women who are taking MHT when their breast cancer is diagnosed have improved survival.[4]

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