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COMMENTARY

Lack of evidence that progesterone in ovulatory cycles causes breast cancer

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ABSTRACT

A recent Perspective article asserted that progesterone secretion during ovulatory cycles is the cause of breast cancer. However, we challenge most of the evidence developed in this publication. First, there is a lack of evidence that progesterone is mutagenic for breast cells. Cause of a cancer should mean initiation by mutation, as opposed to promotion. Second, subclinical ovulatory disturbances occur rather frequently in normal-length menstrual cycles. Third, the authors attribute a potential carcinogenic effect to progesterone secreted during menstrual cycles but not to progesterone during pregnancy. They did not discuss breast cancer evidence from progesterone/progestin therapeutics. They argue that in genetic primary amenorrhea, a hypothetic lower risk of breast cancer could be due to the lack of progesterone, despite the progesterone/progestin in hormone replacements these women receive. Fourth, they advocate a regulatory effect of progesterone on several genes potentially involved in cancer genesis. In particular, they attribute a lower risk of breast cancer in women with Mayer–Rokitansky–Küster–Hauser syndrome to a defect in the progesterone-stimulated Wnt4 gene. However, this defect is only present in a small subset. Thus, the postulated progesterone breast cancer risk is unconvincing, which we discuss point by point in this commentary.

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Introduction

A recent Perspective article has proposed that progesterone from ovulatory cycles is an important cause of breast cancer [1]. We do not agree. Rather, the article is a sum of statements of which the majority are speculative and can be fundamentally challenged. The title is provocative, presented as a certainty, whereas the document, although lengthy and with multiple references, did not confirm what remains only a poorly supported hypothesis. In this commentary we outline our scientific concerns.

Clinically normal, monthly menstrual cycles are not always ovulatory

Normal ovulation (with sufficient luteal phase lengths and progesterone levels) within normal-length menstrual cycles is not inevitable. Subclinical ovulatory disturbances are normal-length cycles with either short/insufficient luteal phases or anovulation. Subclinical ovulatory disturbances by cycle-timed serum progesterone levels ≤9.5 nmol/l occurred in 24–37% of normal-length cycles in a large, ovulation point-prevalence population-based study [2]. Over 1 year in a meta-analysis of six normal-length cycle studies, 13–82% of women experienced subclinical ovulatory disturbances at least once [3]. Is there any study showing a correlation between the long-term, premenopausal frequency of ovulation and the incidence of breast cancer? We know of none.

Premenopausal progesterone levels do not predict the risk of breast cancer

Hormone-level epidemiological data also do not suggest that progesterone is involved in breast cancer pathophysiology. In one large cohort (the Nurses' Health Study) and one case–control study of premenopausal women (the Hormones and Diet in the Etiology of Breast Cancer Risk [ORDET] investigations), levels of progesterone were not correlated with the risk for breast cancer [4, 5]. Progesterone was even associated with a significantly decreased breast cancer risk in a case–control study within the large European Prospective Investigation into Cancer and Nutrition [EPIC] cohort [6]. By contrast, estradiol levels during the luteal phase and testosterone levels were related to increased breast cancer risks [4–6]. As confirmation, both estradiol and testosterone levels related to increased breast cancer risks in a large collaborative study in postmenopausal women [7].

Inconsistent statement on pregnancy

The Perspective article postulated that progesterone is mutagenic when secreted sequentially in menstrual cycles, but not

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when secreted continuously at higher levels during pregnancy [1]. No mechanism, nor even a hypothesis, is proposed to explain this astonishing contradiction. Further, this hypothesis is fully contradictory to what is known about the effect of progesterone to decrease the proliferative breast actions of estrogen receptor alpha (ERα) and prevent tumor growth in mice [8, 9], and the estradiol–progesterone-facilitated expansion of breast tissue during pregnancy which is crucial for lactation. It is also contradicts results of several randomized, controlled studies in which topical progesterone application to the normal breast (resulting in a validated breast tissue progesterone concentration) showed decreased breast cell proliferation [10].

Role of estradiol on mutagenesis instead of progesterone

The Perspective article [1] also ignored the potential roles of steroids other than progesterone in breast cancer risk [4–7]. Based on epidemiological data including younger age at menarche and older age at menopause, it is well understood that the risk of breast cancer is increased with more years of menstrual cycling. The classical interpretation is that estrogen levels, which are normal in cycles about 1 month apart, are promoting proliferation through mechanisms which have repeatedly been demonstrated. Estradiol's impact is evident in various factors involved in the control of cell cycles, and in breast cancer by promoting – in addition to proliferation – angiogenesis and inhibiting apoptosis. Catechol estrogens have also been reported to induce DNA change and, by this, to promote mutagenesis [11]. By contrast, progesterone has never been shown to have a direct mutagenic effect.

Evidence related to RANKL and breast cancer

The main argument the Perspective article makes for progesterone causing mutagenesis is through an increase of proliferation by inducing RANKL which is targeting mammographic stem cells in mice [12]. In humans, data are scarce, but the target is more likely to be breast luminal progenitor cells [13]. This system is undoubtedly a mechanism for the control of mammary gland expansion during pregnancy. RANKL is indirectly induced through the effect of estradiol to suppress osteoprotegrin in MCF-7 breast cancer cells [14]. The effect of RANKL is complex, however, since it has also been associated with better breast cancer prognosis [15]. Despite being induced in breast cancer samples at a higher level during the luteal phase than the follicular phase, RANKL is known to be inversely correlated with proliferation. Furthermore, antagonism of RANKL by denosumab in a randomized trial failed to prevent recurrence of early breast cancer [16].

The other mechanism suggested to support a carcinogenic role of progesterone is its impact on the gene, APOBEC3B, which is related to promoting mutation during the cell cycle [17]. In their publication, Coelingh Bennink et al. reported a luteal phase induction of this gene's expression [1]. However, the reference cited [17] did not even mention this gene. Rather, estradiol has been shown to be a potent inducer of the APOBEC3B gene in ER+ breast cancer cell lines [18].

Puberty and estrogen-related breast tissue expansion

From the enormous literature on gonadal effects on breast cancer genesis, it is very likely that estrogens are involved in the promotion of breast cancer and, perhaps in some cases, in its initiation (as already mentioned). The efficacy of antiestrogen therapy in the prevention of breast cancer and in the treatment of ER+ tumors sufficiently argues for the importance of estrogen in breast tumor progression. This is also suggested by data from women exposed to high radiation at Hiroshima and Nagasaki, for whom the highest breast cancer risk was at a younger age. Radiation caused sensitization before or during pubertal development; this led to rapid proliferation of the breast under the stimulation of estradiol but a progressive decrease as the gland matured with increasing age [19], and with the normally delayed appearance of ovulatory cycles. It is also plausible that progesterone is acting synergistically with estradiol to reinforce its proliferative effect and sensitize the breast tissue to the action of carcinogens, especially before the first full-term pregnancy that promotes differentiation of the breast and decreases the risk of breast tissue mutation and breast cancer [8].

Hypogonadal patients are at lower breast cancer risk

Another point we found unconvincing was the reference to hypogonadism, and the suggestion that breast cancer has a low incidence in that setting because of lower progesterone concentrations. The authors referred to primary amenorrhea, lack of spontaneous puberty and spontaneous breast development in reference to a previous article [20] as primary congenital hypogonadotropic hypogonadism, Kallmann syndrome, Turner syndrome and pure gonadal dysgenesis. So, these women primarily are lacking any estrogenic environment at the normal age of puberty. Therefore, a hormonal treatment consisting of estrogen, and subsequently estrogen plus progestin/progesterone, is usually prescribed following the diagnosis in an effort to induce mammary development. The absence of physiological breast development at puberty could be a reason to explain the lower risk; perhaps also a shorter period of an estrogenic environment. Furthermore, a recent review addressed the question of risk of breast cancer in women with premature ovarian insufficiency and stated that it was unknown (after excluding BRCA mutation carriers) [21].

Lower risk of breast cancer associated with progesterone and progesterone-like progestin therapy

Several therapy studies are important in countering this Perspective article's argument [1]. The authors neglected to report the breast cancer results from an 8-year prospective observational study with more than 80,000 participants (in France called E3N cohort) which allowed a comparison of breast cancer risk on various single and combined menopausal hormonal therapies (MHT) [22]. This study documented breast cancer risk in untreated postmenopausal women as controls versus those taking MHT with estradiol

alone (risk ratio 1.29, 95% confidence interval 1.02, 1.65) versus estradiol plus progesterone (risk ratio 1.00, 95% confidence interval 0.83, 1.22). Although there was no increased breast cancer risk with estradiol–progesterone, estradiol with synthetic progestin MHT was related to significantly increased risk (risk ratio 1.69, 95% confidence interval 1.50, 1.91) [22]. A recent review summarizes publications on a lower breast cancer risk in MHT of estradiol with micronized progesterone and dydrogesterone versus other progestins [23].

Wnt4 defect is a very rare event in Mayer–Rokitansky–Küster–Hauser syndrome

Last, the etiology of Mayer–Rokitansky–Küster–Hauser syndrome is rapidly evolving with the availability of new genome analyses. Wnt4 pathogenic variants, inferred by the authors as the mechanism of a low risk of breast cancer in these patients, are present in only a very small portion of those with this syndrome; many other genes are more strongly associated [24]. Thus, Wnt4 stimulation by progesterone, which has been demonstrated, cannot explain a decrease in breast cancer incidence in this genetic syndrome. As for other conditions, absence of data is not evidence. Indeed, we do not believe that definitive information about breast cancer risk is likely to be available for these rare diseases.

Conclusions

In summary, the Perspective article's bold and provocative title – that progesterone and premenopausal ovulation cause breast cancer – is not supported by the evidence.

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