Breast Cancer Res Treat (2015) 149:1–4
DOI 10.1007/s10549-014-3211-4

REVIEW

Reduced progesterone levels explain the reduced risk of breast cancer in obese premenopausal women: a new hypothesis

Mitch Dowsett · Elizabeth Folkerd

Received: 13 November 2014 / Accepted: 14 November 2014 / Published online: 21 November 2014

Abstract Understanding the complex relationship between obesity and breast cancer is fundamental to our knowledge of the etiology of this malignancy; changes in the composition of the hormonal milieu are implicit in this process. Estrogens are synthesized from androgens by aromatase in the gonads and in peripheral tissues, principally, adipose tissue. Obesity in women, regardless of their age, leads to more aromatase and more extra-glandular estrogen production. In postmenopausal women, in whom ovarian estrogen production is absent, the increased incidence of breast cancer in women with high body mass index has been attributed to the relatively high plasma levels of estradiol from subcutaneous fat. In contrast, obesity in premenopausal women is associated with a previously unexplained *reduced* incidence of breast cancer. In obese premenopausal women, the cumulative effect of higher levels of estrogens synthesized in the peripheral tissues, together with ovarian estrogen production, results in a negative feedback on the hypothalamic pituitary controlled release of gonadotrophins and a resultant diminution in ovarian steroid production. As a consequence, the normal balance of estrogen and progesterone levels is disrupted: while estrogen levels are normalized, progesterone production is markedly decreased. Progesterone is a promoter of proliferation in the breast. The low levels of progesterone in obese premenopausal women are consistent with, and we propose, are responsible for, the reduction in breast cancer incidence in these women.

Keywords Breast cancer · Premenopausal · Postmenopausal · Estrogen · Progesterone · Obesity · Menstrual cycle

M. Dowsett · E. Folkerd (✉)
Academic Department of Biochemistry, Royal Marsden Hospital NHS Foundation Trust, Fulham Road, London SW3 6JJ, UK
e-mail: Elizabeth.folkerd@icr.ac.uk

M. Dowsett
Division of Breast Cancer Research, Breakthrough Breast Cancer Research Centre, London, UK

M. Dowsett
Division of Molecular Pathology, The Institute of Cancer Research, University of London, London, UK

E. Folkerd
Institute of Cancer Research, University of London, London, UK

Introduction

The incidence of obesity has markedly increased in affluent countries over recent decades to the extent that many commentators refer to an "obesity epidemic". This inevitably increases the public health importance of any of the numerous adverse consequences of obesity. Among these are the multiple associations of obesity with the occurrence [1] and poor prognosis [2] of cancers. Yet one frequent observation has remained without adequate explanation for many years: obesity is associated with an increased incidence of breast cancer in postmenopausal women but conversely with a reduced incidence of breast cancer in premenopausal women [1].

Estrogen synthesis and breast cancer risk

Although there may be other contributory factors, it is widely accepted that the positive relationship between obesity and breast cancer in postmenopausal women is related to higher levels of plasma estradiol, particularly the

fraction unbound to sex hormone-binding globulin [3]. All steroidal estrogens are synthesized through the aromatase enzyme. In premenopausal women, aromatase levels are highest in the granulosa cells of the ovary but significant levels also occur in peripheral tissues, principally in subcutaneous fat. At the menopause ovarian function ceases and no further estrogen synthesis occurs in the ovaries, but aromatase activity in peripheral tissues persists and is responsible for the residual synthesis of estrogens. The greater amount of adipose-associated aromatase in women with higher BMI results in higher plasma levels of estrogen. The increased incidence of breast cancer in postmenopausal women with high BMI has been ascribed to the relatively high circulating levels of estradiol in these women [3].

Estrogen and obesity in premenopausal women

In premenopausal women, cyclical changes in plasma estrogen levels (Fig. 1) result from a complex set of stimuli, including feedback controls on ovarian steroidogenesis and follicular development mediated by gonadotrophins (Luteinizing Hormone (LH) and Follicle-stimulating Hormone (FSH)). Estrogen synthesis in subcutaneous fat also occurs in premenopausal women. Generally, this contributes on average about 5 % of the total plasma estradiol synthesis across the menstrual cycle but in cases of extreme obesity the markedly increased levels of estrogen released into the circulation from the adipose tissue activates the negative feedback in the hypothalamus pituitary axis leading to reduced gonadotrophin secretion. In such extreme cases, this can lead to a complete switch off of normal ovarian function and be reflected in amenorrhea [4]; one might view this as analogous to the impact of an oral estrogen-based contraceptive but in this case the estrogen results from endogenous synthesis. Although cessation of normal cyclical ovarian hormone production such as with ovariectomy is protective against breast cancer [5], this extreme situation cannot explain the decrease in breast cancer risk that occurs at more modest degrees of obesity where amenorrhea is uncommon.

Progesterone and obesity in premenopausal women

However, now there is a well-characterized effect of high BMI on progesterone levels in premenopausal women that

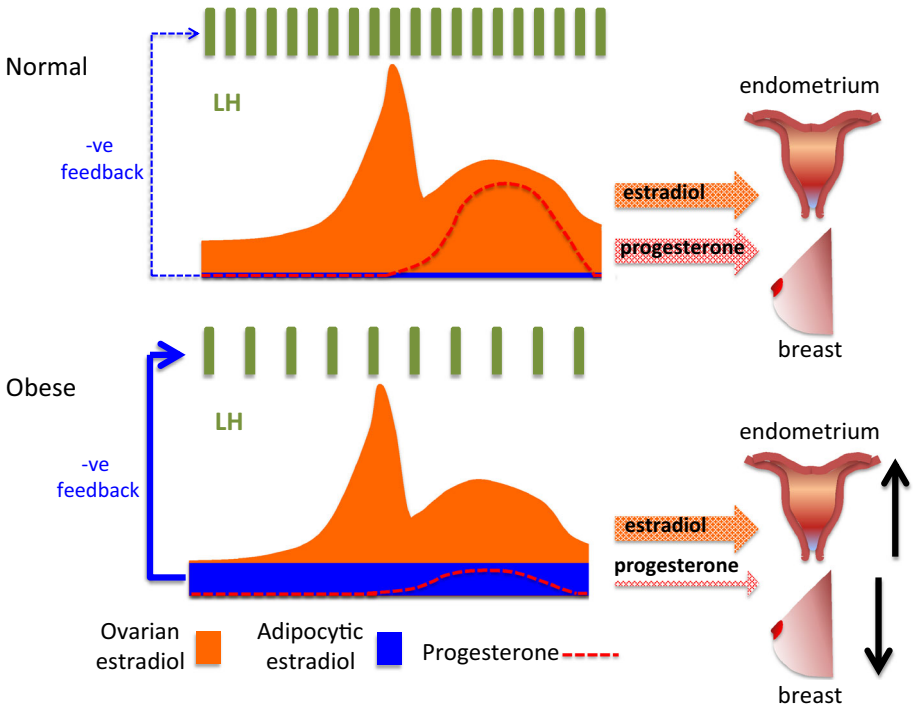

Fig. 1 Diagrammatic representation of cyclical plasma levels of estradiol and progesterone in normal weight and obese premenopausal women. In the normal weight women complex feedback-controlled ovarian steroidogenesis leads to the well-characterized cyclical exposure of the breast to estradiol and progesterone; relatively, low adipocytic estradiol production from subcutaneous fat has no significant impact on the feedback control. In obese women, higher estrogen production from subcutaneous fat leads, through negative feedback, to less frequent LH pulses and decreased ovarian estrogen and particularly luteal progesterone synthesis. We hypothesize that the decreased levels of progesterone lead to decreased risk of breast cancer and increased risk of endometrial cancer

does not appear to have been cited as a potential explanation of the reduced breast cancer risk, but is highly plausible. This is available from a detailed study, published 7 years ago [6], of steroid levels throughout the menstrual cycle of 18 eumenorrheic women with high BMI versus a group of 12 with normal BMI. Estrogen and progesterone levels were measured daily in first morning voided urine collections, as their major urinary metabolites, estrone glucuronide (E-G) and pregnanediol glucuronide (P-G), respectively. E-G levels did not differ according to BMI, but P-G levels in the obese women were between 75 and 80 % lower (38.2 ± 2.1 vs. 181.3 ± 35.1 ug/mg/creatinine, $p = 0.002$). The exact cause of this decrease in luteal phase progesterone is not clear but was associated with decreased amplitude of LH pulses and overall lower LH levels. Notably, it has been found that the low levels of luteal P-G excretion seen in morbidly obese eumenorrheic women increase following weight loss after bariatric surgery although they do not recover to the levels seen in women of normal weight [7].

Progesterone synthesis, obesity, and breast cancer risk in premenopausal women

The endocrine profile in obese premenopausal women described above is consistent with (a) high levels of estrogen secretion from the subcutaneous fat leading, by negative feedback, to reduced gonadal stimulation; (b) the lowered estrogen synthesis within the ovary effectively compensating and thereby normalizing plasma levels; and (c) reduced ovarian activity leading to markedly reduced synthesis, and hence reduced plasma levels of progesterone (Fig. 1). Progesterone is thought to have a primarily pro-proliferative role in the adult breast [8]. Compelling evidence from two major clinical studies, the Women's Health Initiative (WHI) and the Million Women study, looking at the effects of hormone replacement therapy, demonstrated that for postmenopausal women the risk for developing breast cancer was higher in women taking estrogen with progestin compared with estrogen alone therapy [9, 10]. It is also notable that increases in breast density are much greater in women using estrogen plus progestin hormone replacement therapy compared with those taking estrogen alone [11]. Each of these observations is supportive of the reduced progesterone levels in obese premenopausal women being expected to lead to a decrease in breast cancer risk.

Progesterone synthesis and endometrial cancer

It is notable that endometrial cancer risk is higher in both pre- and post-menopausal women with high BMI [1, 12]. This effect is largely ascribed to the stimulus to proliferation of the endometrium resulting from high circulating levels of estradiol yet, as noted above, in obese premenopausal women the levels of E-G are no different to those in normal weight women. In the endometrium, the actions of progesterone are regulated by local autocrine and paracrine signaling, such that, in contrast to the breast, the overall effect of progesterone in the endometrium is protective against the stimulatory effects of estrogens [13]. Thus, the reduction in normal progesterone production in obese premenopausal women can also explain their increased risk of endometrial cancer.

Conclusions

The mechanistic links between obesity and breast cancer development and progression are likely to be more complex than a simple dependence on changes in estrogen and progesterone balance. Abnormalities in inflammatory processes, lipid metabolism, chronic hyperinsulinaemia, and a disturbance in overall energy balance probably contribute to the process of carcinogenesis in, at least some, obese women. However, none of these observations provides a mechanism that changes direction at the menopause. We propose that for obese premenopausal women it is the decrease in progesterone production in the gonads, as a consequence of altered pulsatile LH secretion, that is the major determinant limiting the risk of development of breast cancer and increasing the risk of endometrial cancer. If the details of our proposed mechanistic explanation for the reduced progesterone levels were not entirely correct, the hypothesis that these lower progesterone levels result in the changes in breast and endometrial cancer remains sound.

To fully establish (or refute), this hypothesis epidemiologically is likely to need careful, comprehensive, timed collection of progesterone levels across the cycle in very large prospective studies of breast cancer. If confirmed, as well as providing a welcome explanation for a long-standing puzzle of breast cancer epidemiology, this mechanism could elicit new concepts for breast cancer prevention in premenopausal women.

Acknowledgments We are grateful for support from the Royal Marsden/Institute of Cancer Research, National Institute for Health Research Biomedical Research Centre.

Conflict of interest The authors declare that they have no conflict of interest

References

1. Bhaskaran K, Douglas I, Forbes H et al (2014) Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. Lancet 384:755–765

2. Schmitz KH, Neuhouser ML, Agurs-Collins T et al (2013) Impact of obesity on cancer survivorship and the potential relevance of race and ethnicity. J Natl Cancer Inst 105:1344–1354
3. Key TJ, Appleby PN, Reeves GK et al (2003) Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. J Natl Cancer Inst 95:1218–1226
4. Polotsky AJ, Hailpern SM, Skurnick JH et al (2010) Association of adolescent obesity and lifetime nulliparity-the study of women's health across the nation (SWAN). Fertil Steril 93:2004–2011
5. Gaudet MM, Gapstur SM, Sun J et al (2014) Oophorectomy and hysterectomy and cancer incidence in the cancer prevention study-II nutrition cohort. Obstet Gynecol 123:1247–1255
6. Jain A, Polotsky AJ, Rochester D et al (2007) Pulsatile luteinizing hormone amplitude and progesterone metabolite excretion are reduced in obese women. J Clin Endocrinol Metab 92:2468–2473
7. Rochester D, Jain A, Polotsky AJ et al (2009) Partial recovery of luteal function after bariatric surgery in obese women. Fertil Steril 92:1410–1415
8. Briskin C (2013) Progesterone signaling in breast cancer: a neglected hormone coming into the limelight. Nat Rev Cancer 13:385–396
9. Rossouw JE, Anderson GL, Prentice RL et al (2002) Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. JAMA 288:321–333
10. Beral V, Reeves G, Bull D et al (2011) Breast cancer risk in relation to the interval between menopause and starting hormone therapy. J Natl Cancer Inst 103:296–305
11. Topal NB, Ayhan S, Topal U et al (2006) Effects of hormone replacement therapy regimens on mammographic breast density: the role of progestins. J Obstet Gynecol Res 32:305–308
12. Reeves GK, Pirie K, Beral V et al (2007) Cancer incidence and mortality in relation to body mass index in the million women study: cohort study. BMJ. doi:10.1136/bmj.39367.495995.AE
13. Calle EE, Kaaks R (2004) Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 4:579–591