



# Progesterone Exposure and Breast Cancer Risk—Addressing Barriers

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Exposure to endogenous sex hormones has long been recognized as an important (albeit unavoidable) source of risk for cancer, particularly of reproductive organs. Studies addressing the breast cancer risk associated with endogenous hormone exposures have reported the increased breast cancer risk experienced by postmenopausal women who have higher than average serum levels of estradiol and its androgenic precursors. For example, in the European Prospective Investigation into Cancer and Nutrition cohort, the relative risk of breast cancer per doubling of serum estradiol in women sampled when postmenopausal was 1.31 (95% CI, 1.08-1.58).<sup>1</sup> Of note, the European Prospective Investigation into Cancer and Nutrition investigators did not measure progesterone levels in postmenopausal women “as ovarian progesterone synthesis ceases after menopause.”<sup>1(p4183)</sup> The understudied possibility that progesterone exposure may be associated with breast cancer risk is highly relevant, particularly because efforts are under way to develop natural progesterone as a safe alternative to progestins in menopausal hormone therapy regimens.<sup>2</sup>

Although the major focus for more than 50 years has been on estrogens, progesterone and progestin exposure is increasingly recognized as instrumental in the breast cancer risk associated with exposure to the reproductive hormones. The evidence supporting an important promoting role for progesterone<sup>3</sup> includes data regarding risk associated with increasing number of ovulatory cycles,<sup>4</sup> and on high cell proliferation rates during the luteal phase of the menstrual phase.<sup>5</sup> These and other data together suggest a specific protumorigenic role of progesterone, at least in the premenopausal breast. However, studies of endogenous progesterone exposure have faced both biological and technical barriers. In premenopausal women, research has been hampered by the cyclical variation of serum progesterone levels, so that even when studied, no clear trends emerge.<sup>1</sup> In postmenopausal women, the extremely low concentrations of circulating progesterone renders it below the level of detection in studies using classical methods; and methods using liquid chromatography and mass spectrometry have not yet been widely applied.

For these reasons, the data reported by Trabert and colleagues<sup>8</sup> are of particular interest. Improvements in methods for measurement of hormones now allow questions regarding progesterone exposure to be addressed in postmenopausal women. Trabert et al<sup>8</sup> used blood samples and data collected from the Breast and Bone Follow-up to the Fracture Intervention Trial, to perform a case-cohort analysis that included 405 incident breast cancer cases diagnosed during 12 follow-up years and a subcohort of 495 postmenopausal women not using exogenous hormones. They measured circulating concentrations of pregnenolone, progesterone, and their major metabolites, and used estradiol data measured for previous analyses of this cohort. They found progesterone concentrations displayed a mean (SD) of 4.6 (1.7) ng/dL. Higher circulating progesterone levels were associated with a modestly increased breast cancer risk, with a hazard ratio of 1.16 (95% CI, 1.00-1.35) per SD of serum progesterone. The association with progesterone was linear and stronger for 267 women with invasive breast cancers, where the hazard ratio was 1.24 (95% CI, 1.07-1.43;  $P = .004$ ). Trabert et al<sup>8</sup> also examined estradiol and progesterone together, and found that higher progesterone concentrations were associated with reduced breast cancer risk among women in the lowest quintile of circulating estradiol (<6.30 pg/mL). Here, they observed that the hazard ratio per SD was 0.38 (95% CI, 0.15-0.95);  $P = .04$ . Conversely, risk was increased among women in the second to fifth quintiles with estradiol greater than or equal to 6.30 pg/mL, where they found a hazard ratio of 1.18 (95% CI, 1.04-1.35)  $P = .01$ ;  $P = .04$  for interaction.

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The findings reported by Trabert et al<sup>8</sup> are in contrast to those from a case-control study nested within the Nurses Health Study reported by Missmer et al.<sup>6</sup> This study included 322 cases and twice this number of controls. Although hormones were measured using radioimmunoassay, the progesterone concentration was very similar to that observed by Trabert et al<sup>8</sup> (4.0 ng/dL), and was similar across cases and controls, leading to a hazard ratio for progesterone that approximated unity. However, the level of detection of the radioimmunoassay was higher, leading to one-third of women having undetectable levels. Trabert et al<sup>8</sup> suggest that this is an explanation for the null findings relative to progesterone, but the lower sensitivity of the detection method does not invalidate the findings of the Nurses Health Study. If levels are too low for detection, this still means that they are low; and the null findings suggest that women in the lowest (undetectable) category are equally distributed across cases and controls. Another discrepancy between the Breast and Bone Follow-up to the Fracture Intervention Trial and Nurses Health Study findings is with regard to the strength of the association with invasive versus in situ disease. In the former, the association strengthened when restricted to invasive cases, whereas in the latter it was stronger for duct carcinoma in situ. Further work is clearly needed to resolve these discrepancies.

In both studies, participants were not using menopausal hormone therapy, but in both studies, they may have been using this in the recent past. The Nurses Health Study authors specify that hormones had not been used in the prior three months, and Trabert et al<sup>8</sup> report that participants were not using menopausal hormone therapy at the time of study entry. Because risk associated with menopausal hormone therapy use dissipates slowly over several years, an imbalance in recent menopausal hormone therapy use may have produced a lingering high-risk environment as a factor in case status. In contrast, both studies find that women with a combination of high progesterone and low estradiol levels experience a lower breast cancer risk: in the Nurses Health Study population, relative risk was 0.5 (95% CI, 0.2 to 1.3) and in the Breast and Bone Follow-up to the Fracture Intervention Trial report the hazard ratio was 0.38. These data reinforce the context-specificity of progesterone effect, which appears to require a minimal estrogen presence to initiate the biologic consequences that promote cancer development.

An intriguing aspect of the study by Trabert et al<sup>8</sup> is an examination of the relationships of breast cancer risk with progesterone metabolites, because previous data suggests a differential effect of 5 $\alpha$ -dihydroprogesterone (5 $\alpha$ P) and 3 $\alpha$ -dihydroprogesterone (3 $\alpha$ HP) with risk of breast cancer. If validated in humans, this suggests the possibility that 5 $\alpha$ -reductase, the enzyme responsible for conversion of progesterone to 5 $\alpha$ P, may be targeted for breast cancer therapy,<sup>7</sup> although its toxicity profile may preclude its use in cancer prevention. Trabert et al<sup>8</sup> saw no association of these metabolites with risk, except among women in the lowest tertile of 3 $\alpha$ HP and the highest tertile of 5 $\alpha$ HP, but the hazard ratio in this extreme group was 1.96 (95% CI, 1.01-3.81). At first sight, these data do not support the hypothesis that 5 $\alpha$ P exposure is associated with breast cancer risk, but serum measurements may not tell the whole story because intramammary concentrations may differ by local enzyme activity, which itself may be associated with genetic variation.

The further development and application of these findings in postmenopausal women will require larger studies that use highly sensitive assay methods and address prior menopausal hormone therapy use more fully. The role of progesterone metabolites does require further attention, but such studies should be accompanied by an analysis of genetic variation in enzyme activity. In addition, researchers must turn their creativity towards addressing the barriers that hinder the study of progesterone exposure in premenopausal women, where progesterone exposure is highest, and where data on risk will best guide the development of breast cancer prevention strategies.

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#### ARTICLE INFORMATION

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