The Women’s Health Initiative (WHI) randomized trials of menopausal hormone therapy have provided insights that have dramatically changed clinical practice and led to reduced breast cancer incidence at a population level. In this issue of JAMA Oncology, Chlebowski et al present a detailed analysis of the impact of estrogen plus progesterone (E + P) therapy or estrogen alone on breast cancer incidence during the intervention as well as early (first 2.75 years) and late (beyond 2.75 years) postintervention periods of the WHI trials. While a significant increase in invasive breast cancer risk occurred during the E + P intervention, Chlebowski et al report a “sharp decrease in breast cancer risk” in the early postintervention period for E + P, although risk, as defined by hazard ratios, remained higher than 1, followed by a sustained increased risk higher than 1 in the late postintervention period with a median additional follow-up of 5.5 years (Figures 1 and 3 in the article by Chlebowski et al). The decrease in risk during the early postintervention period compared with the intervention period was postulated to reflect modulatory effects of a changed hormonal environment on preclinical breast cancer lesions. In contrast, the use of estrogen alone was associated with lower breast cancer risk during the intervention, an even lower risk during the early postintervention period with subsequent attenuation of this risk reduction during the late postintervention period. There were suggestions of different patterns of breast cancer subtypes and stage at presentation over time with E + P therapy vs estrogen alone, including a potential increased risk of progesterone receptor (PR)-negative or triple-negative cancers during the intervention and early postintervention period with E + P therapy.

The contrast between effects of E + P therapy vs estrogen alone is striking—breast cancer risk is persistently elevated with E + P therapy, while risk is persistently decreased with estrogen alone therapy. Thus, an important message underlying the study is that the progesterone inclusion during a median hormone therapy intervention period of 5.6 years not only increases the breast cancer risk during intervention but results in a continued elevated risk for several years after stopping this regimen. Recent advances in understanding the biological basis of hormone effects on normal mammary epithelial cell populations and breast carcinogenesis shed light on this contrast and provide insight on how progesterone may exert its cancer-promoting effects (Figure). In animal models, E + P therapy, but not estrogen alone, stimulates expansion of the number of mammary stem and progenitor cells, generating new, denser, and more complex mammary morphology that is also recapitulated during the natural progesterone surge of the mouse reproductive cycle. Estrogen is instrumental for breast development during puberty, but its primary role during adult mammary growth cycles is to induce PR expression to facilitate progesterone’s proliferative effects in this tissue. The human breast also exhibits increased complexity, density, and mitotic activity during the progesterone-high luteal phase of the menstrual cycle. Indeed, mammogram diagnostic performance was hindered in the E + P WHI trial in the first years of intervention, likely owing to increased breast density with E + P therapy. It is important to consider whether mammary stem and progenitor cells that trigger these morphological changes in the breast underlie the increased risk associated with E + P exposure.

Breast cancer animal models incorporating medroxyprogesterone acetate, the same compound used in the WHI trials, have shown its potent capacity to promote mammary tumors through key mitogenic signals that stimulate the mammary epithelium. Accumulating evidence suggests that mammary stem cells and progenitors are the likely “cells-of-origin” for different breast cancer subtypes, and thus research geared toward deciphering the fundamental biological processes of these cells provides important insight into their potential function in breast cancer development. Because mammary stem and progenitor cells are largely hormone receptor negative, the E + P-exposed mammary stem cell niche is thought to drive an increase in their cell number via a paracrine cross talk. Here, PR-positive cells can act as progesterone-sensing cells and deliver mitogenic signals to PR-negative stem/progenitor cells. This effect of progesterone on the expansion of hormone receptor-negative cells may explain how E + P therapy increases the risk of PR-negative and triple-negative breast cancers seen in the WHI trial reported by Chlebowski et al. Hormone receptor-positive tumors observed could stem from a PR-positive cell or a PR-negative progenitor that subsequently acquires hormone receptor expression.

It is plausible that a sudden decline in progesterone levels within the stem cell niche would mitigate further development of early cancer lesions that are still dependent on progesterone, resulting in the decreased breast cancer risk during the early postintervention period. However, breast cancer risk still remained elevated (hazard ratio >1), and the cancers that may have formed during this early postintervention period were likely to have already progressed to an advanced preclinical stage prior to stopping treatment and thus no longer
The human breast is a well-organized ductal network ending in terminal ductal lobular units, which are hormone sensitive. The mammary epithelium is home to a heterogeneous populations of cells that contain basal and myoepithelial cells, stem cells, luminal differentiated cells, and luminal progenitors, some of which contain hormone receptors (PR). Progesterone is thought to act through PR-positive (PR+) luminal cells and activate PR-negative (PR-) cells via paracrine signals, such as receptor activator of nuclear factor κB ligand (RANKL) and wingless-int (WNT), expanding the number of stem/progenitor cells to generate a more complex and denser epithelium. Estrogen + progesterone (E + P) exposure during hormone therapy is likely to harness these cellular and mitogenic mechanisms, thus increasing breast cancer risk. New data from the Women's Health Initiative clinical trials have provided further insight into the early and late postintervention effects of progesterone exposure on breast cancer risk. Plausible underlying biological mechanisms for these time-varying risk alterations are illustrated.

Emerging detailed analyses from the WHI trials such as that reported by Chlebowski et al1 reveal new compelling evidence for the significance of progesterone in breast cancer, where it has traditionally taken a backseat to estrogen. Progesterone inclusion during hormone therapy intervention leads to a persistent increase in breast cancer risk after intervention and leads to the development of hormone receptor–negative tumors in addition to those that are hormone receptor positive. Although the WHI trials relate to the menopausal setting, lessons learned from them continue to provide additional value in appreciating a potential role of progesterone even in premenopausal breast cancer. Furthermore, investigation into the cellular and mechanistic underpinnings of progesterone's impact on the normal breast and breast cancer may provide new opportunities for knowledge translation and therapeutic intervention in breast cancer.
REFERENCES


11. Tomasetti C, Vogelstein B. Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. Science. 2015;347(6217):78-81.

CORRECTION

Error in Text: In the Original Investigation titled “Association Between NRAS and BRAF Mutational Status and Melanoma-Specific Survival Among Patients With Higher-Risk Primary Melanoma,” by Thomas et al, published online in JAMA Oncology April 9, 2015 (doi:10.1001/jamaoncol.2015.0493), there was an error in wording in the Statistical Methods subsection of the Methods section. In the fourth paragraph, fourth sentence, the word “lower” should have read “better.” The corrected sentence reads “TIL grade was included because higher TIL grade of primary melanoma is associated with better melanoma-specific survival.” This article has been corrected online.