Progestins and Recurrence in Breast Cancer Survivors

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Menopausal hormone therapy use in breast cancer survivors is controversial, and clinical trials of this issue have proven difficult. Eight years ago, two separate randomized trials of this question were begun, but accrual difficulties led to development of a merger with a joint analysis plans. In 2004 the trials were stopped early after an interim combined analysis of the pooled data found an increased risk for breast cancer recurrence in the hormone group (hazard ratio [HR] = 1.8, 95% confidence interval [CI] = 1.03 to 3.1) relative to the control group. One study, the Hormone Replacement Therapy After Breast Cancer—Is It Safe (HABITS), then reported substantially increased breast cancer recurrences with hormone use (HR = 3.3, 95% CI = 1.5 to 7.4). However, risk of breast cancer recurrence in this comparison in the Stockholm trial was lower (HR = 0.8, 95% CI = 0.4 to 1.9), with statistically significant heterogeneity between the study results ($P = .02$) *(1)*. Von Schoultz and Rutqvist *(2)* now provide details of the Stockholm trial results and pose a hypothesis that is based on progestin exposure to explain outcome differences between the two trials.

Both investigative groups are to be congratulated for addressing this question by use of a randomized study design. Nonetheless, study limitations, including the nonblinded design, flexibility in the actual regimens administrated, accrual problems, and the paucity of breast cancer recurrences (a total of only 58 recurrences across both trials), preclude these studies from providing definitive results that can by applied in clinical practice. The results, however, do raise a biological hypothesis regarding exogenous hormone use and breast cancer risk.

Since the initiation of these trials, the context for considering menopausal hormone therapy in breast cancer survivors has changed. The Women's Health Initiative provided evidence from randomized clinical trials that menopausal hormone therapy, either estrogen alone *(3)* or estrogen plus progestin *(4)*, does not reduce overall chronic disease risk. Because bisphosphonates provide an alternative approach to bone loss, the use of menopausal hormone therapy in breast cancer survivors should be now based on vasomotor and vaginal–vulvar symptom effects and breast cancer safety. Nonetheless, this question remains of clinical relevance because women with diagnosed breast cancer commonly are menopausal and/or experience estrogen deficiency symptoms related to amenorrhea induced by ovarian suppression or chemotherapy *(5)* or by hormone therapies including tamoxifen and/or aromatase inhibitors *(6)*.

Although they were analyzed together, the HABITS and Stockholm trials had differences not limited to frequency of concurrent tamoxifen use. For entry, the HABITS trial required menopausal symptoms sufficient to "need treatment," whereas the Stockholm trial did not list menopausal symptoms as an entry requirement. Specific hormone therapy was not mandated by the protocol in either trial. In the HABITS trial, the hormone therapy was directed by local practice and tibolone, a steroid compound available in Europe for vasomotor symptoms management, was not allowed. In the Stockholm trial, hormone therapy was recommended: continuous oral estradiol at 2 mg daily for women who had a hysterectomy and a "spacing out" regimen of estradiol at 2 mg for 84 days plus 20 mg of medroxyprogesterone acetate during the last 14 days, followed by 7 days off therapy for those 55 years old or older. Because 73% of the women in the Stockholm hormone group were offered either estradiol alone or the "spacing out" regimen with progestin, it was proposed that the shorter-duration progestin exposure was associated with the lower breast cancer recurrence risk observed in the Stockholm compared with the HABITS trial, in which longer-duration progestin regimens were more commonly used.

How does this hypothesis, which associates longer progestin exposure with increased breast cancer recurrence risk, fit with current evidence regarding the larger question of hormone exposure and breast cancer risk? Although a comprehensive review of the issue exceeds the scope of this commentary, there is strong observational evidence relating increased breast cancer risk to reproductive history factors that are associated with greater endogenous estrogen exposure and to exogenous estrogen use when combined with progestin *(7,8)*. A randomized trial within The Women's Health Initiative among women with an intact uterus reported *(9)* similar results with statistically significantly more breast cancers in the group receiving combined estrogen plus progestin than in placebo groups. The evidence relating exogenous estrogen alone to breast cancer risk, as described by the Stockholm investigators, is "much more uncertain" *(2)*. The preponderance of observational studies do report an association between use of exogenous estrogen alone and increased breast cancer risk *(7,10)*, in some cases only after long-duration (many years) exposure *(11)*. However, in a randomized trial within the Women's Health Initiative among women with prior a hysterectomy, use of conjugated equine estrogens alone resulted in no breast cancer increase after about 7 years of use, with the suggestion of a decreased risk of breast cancer compared with that in placebo groups *(3)*. More recently, Kerlikowske et al. *(12)* reported a statistically significant decreased risk of breast cancer among women using estrogen alone for less than 5 years compared with nonusers in a cohort of 374 465 women in community-based mammography practices. Such evidence thus suggests a determinate role for progestins in this process. The role of exogenous estrogens in breast cancer risk will be further clarified in the near future by ongoing analyses of the breast cancers reported in the estrogen-only group of the Women's Health Initiative trial and analyses combining breast cancer results from the two randomized hormone trials in the Women's Health Initiative (involving more than 27 000 participants) with results from the Women's Health Initiative observational study and from the Women's Health Initiative non–hormone-based clinical trials (with an additional 133 000 participants).

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DOI: 10.1093/jnci/dji100

Observational studies of menopausal hormone therapy on the risk of breast cancer recurrence among breast cancer survivors have consistently reported safety and sometimes benefit for hormone therapy *(13,14)*. However, such nonrandomized reports have design limitations that preclude reliable conclusions. For example, balanced restaging of breast cancer survivors at the initiation of hormone use was rarely conducted, the cancer stage at diagnosis was not uniformly reported, and many studies were based on "clinical experiences" in which trial investigators also provided the hormone therapy, raising the potential of reporting bias *(14)*.

Given the current uncertainties, what can be done for a woman diagnosed with breast cancer who has limiting estrogen deficiency symptoms? For vaginal–vulvar symptoms, topical estrogens are commonly recommended for breast cancer survivors and were permitted on the control arm of the Stockholm trial. However, short-term estradiol vaginal ring use (i.e., Estring) results in lipid changes comparable to those of full-dose oral estrogens *(15),* and so the safety of such preparations with respect to breast cancer risk should not be assumed. Although less effective, non–estrogen-based vaginal lubricants and moisturizers provide alternatives. For vasomotor symptoms, several selective serotonin reuptake inhibitors, including venlafaxine and paroxetine, provide substantial relief in approximately half of the users *(5,16)*. However, even with these inhibitors, caution is needed because concurrent use of paroxetine with tamoxifen has been associated with a statistically significant decrease in concentrations of an active tamoxifen metabolite, a problem that could compromise anticancer efficacy *(17)*. Finally, nonprescription remedies, such as phytoestrogens or black cohash, have limited efficacy data and no credible safety data regarding breast cancer recurrence risk, a concern raised by a recent report that low-dose dietary phytoestrogen abrogates mammary tumor prevention of tamoxifen *(18)*.

Tibolone, an agent with high efficacy against vasomotor symptoms and purported absence of endometrial and breast stimulation, is widely prescribed in Europe but is not currently approved for use in the United States. On the basis of a hypothesis of breast cancer safety, a randomized clinical trial comparing tibolone with placebo among breast cancer survivors with vasomotor symptoms has completed accrual with more than 3000 participants. Follow-up for the study end points of breast cancer recurrence and of vasomotor symptoms continues, with results anticipated in a few years *(19)*.

In summary, the results from these two trials, although limited by several design and implementation features, provide additional evidence that progestin use is associated with an increased breast cancer risk, compared with its nonuse. The lack of direct evidence for the effects of estrogen alone from these two trials, especially in the context of divergent data on the effects of exogenous estrogen, emphasizes the need to design subsequent studies to address questions for specific agents. For breast cancer survivors, however, current evidence supports non–hormone-based interventions for vasomotor and vaginal–vulvar symptom control in most circumstances. The possibility that use of estrogen alone in symptomatic breast cancer survivors with a hysterectomy may represent an option with a favorable risk/benefit balance warrants further clinical attention.

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