

*Hypothesis/Commentary***Ovarian Cancer and Menopausal Hormone Therapy: More Data and New Questions**

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The key message on the use of unopposed estrogen and estrogen plus progestin after menopause is clear: increased risks of stroke, coronary heart disease, pulmonary embolism, and breast cancer outweigh reduced risks of fractures and colorectal cancer. Individual risk-benefit profiles will, of course, vary, but current clinical guidelines emphasize use for symptom relief only, at low doses and for short durations. After the 2002 announcement of the main findings from the Women's Health Initiative estrogen-plus-progestin trial (1), which clarified those risks, use of menopausal hormone therapy decreased by ~50% (2). Today, however, symptom relief apparently trumps potential risks: many postmenopausal women are continuing to use hormone therapy or are having difficulty discontinuing use (3).

The increased risks associated with unopposed estrogen therapy use now include ovarian cancer, based largely on recent evidence indicating that current or long-duration use increases risk by 50% to 100%. Fortunately, ovarian cancer is rare. A 2-fold higher relative risk only increases a woman's absolute lifetime risk of developing ovarian cancer from ~1.5% to 3.0%. Unfortunately, ovarian cancer is often lethal because it typically evades early detection. A 3.0% absolute risk means more women will face grim prognoses, difficult treatments, and low survival odds. Whether the ovarian cancer risks will influence decision-making about unopposed estrogen is uncertain because women and their physicians presumably will heavily weight elevated risks of common conditions, such as coronary heart disease or stroke, and discount even quantitatively similar increased risks of rare outcomes such as ovarian cancer.

The association between ovarian cancer and estrogen plus progestin is less clear. Ovarian cancer studies published through 2002 included too few exposed women to provide reliable measures of association. The new case-control data from Rossing et al. (4), published in this issue of *Cancer Epidemiology, Biomarkers & Prevention*, are therefore especially informative. Its large case group, appropriate controls, and extensive risk-factor data from a population with substantial menopausal hormone therapy use offer an opportunity to directly compare

associations between ovarian cancer and both unopposed estrogen and estrogen plus progestin.

Compared with no menopausal hormone therapy use, unopposed-estrogen use for ≥ 10 years was statistically significantly associated with increased risk of ovarian cancer. Use for ≥ 5 years was associated with increased risk among both former and current users, but that increase disappeared 3 years after cessation of use. These data generally match most of the recently published results and nicely expand the available data on risk among former users. In contrast, estrogen-plus-progestin use was inversely associated with ovarian cancer. Most of the odds ratios for specific exposures were close to the null, but short-duration (< 5 years) and former use were both associated with a statistically significant 50% reduction in risk, which persisted among women whose last use occurred at least 3 years before their diagnosis or interview.

Rossing et al. succinctly summarized the relevant published literature, offering reasonable explanations of the inconsistent results. However, important consistencies went unnoticed. The largest cohort study to date (5) replicated recent findings from a U.S. cohort (6) and the Women's Health Initiative estrogen-plus-progestin clinical trial (7). Together, these three prospective studies suggest an increased risk among current, long-duration estrogen-plus-progestin users that is similar to that among long-duration unopposed-estrogen users. Almost all of the case-control studies, however, observed null associations. Rossing et al.'s study is the third (8, 9) to report inverse associations with estrogen plus progestin use, but the first in which the association is statistically significant. In each of these studies, reduced risk seen among short-duration or former users was absent among long-duration and current users. Inconsistent findings typically resolve themselves over time, even when first-pass explanations, like chance or small sample size, do not fit. Contradictory findings that are each separately replicated are more puzzling.

Rossing et al. propose that estrogen and progesterone play opposing mechanistic roles in ovarian carcinogenesis, the former as a promoter and the latter encouraging apoptosis. For estrogen plus progestin to be truly protective, progestin should both negate estrogen-associated (risk-increasing) proliferation and leave the ovaries better off than they were before menopausal hormone therapy was used (because users' risk was lower than nonusers' risk). By extension, progestin-only hormone therapy would offer the best possible protection. The few studies with data on this uncommon exposure did not observe reduced risks among progestin-only

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users. Rossing et al. noted that the interaction with body mass index (BMI)—strongest inverse associations for estrogen plus progestin occurred among women with above-normal BMI—has also been seen with endometrial carcinoma. That analogy, however, is tenuous because continuous estrogen plus progestin only attenuates the hugely increased endometrial carcinoma risk associated with high BMI, such that the absolute risk of endometrial carcinoma remains higher among estrogen-plus-progestin users with above-normal BMI than in never-users with normal BMIs (10). In addition, unlike endometrial carcinoma, BMI increases the risk of ovarian cancer only slightly, if at all.

The estrogen-as-promoter, progestin-as-counter-proliferator mechanism also does not fit Rossing et al.'s data on recency and duration. This model predicts classic dose-response relationships. Endometrial carcinoma (11) and breast cancer (12) data operate that way: associations are strongest for current and long-duration use, but increased risks steadily diminish after cessation of use. How then can short-duration estrogen-plus-progestin use truly decrease ovarian cancer risk if long-duration use does not? Can estrogen-plus-progestin use indeed reduce a woman's risk of ovarian cancer only after she stops taking it? There is little precedent for a lesser exposure decreasing risk when a greater exposure generates a null association. Additional data that describe risk across a longer time span since last use would be especially informative here.

As noted above, Rossing et al. are not the only group to observe these odd associations. The rarity of ovarian cancer and the tremendous challenges of studying hormone therapy mean that no single study will be sufficient to capture the complexity of the true patterns of risk. More than ever, we need replication using consistent analytic approaches in different populations with diverse experiences. As that occurs, two issues deserve particular attention. First, why do the published studies have so few former and short-term users? Estrogen-plus-progestin use greatly expanded in the decade before 2002, but up to one-half of new users reportedly stopped within a few years of starting (13). This should generate similar numbers of former, short-duration users and current, long-duration users, but current users outnumbered former users in most studies. Are former users systematically missing from case-control studies, perhaps because of participant nonresponse, changes in hormone therapy use around the time of diagnosis, imperfect operational definitions of current versus former use, or participants' inaccurate recall of timing of use? Do cohort studies that do not update exposure information enough to capture changing use misclassify recency so much that the results are ungeneralizable? Better data on who stopped, why they stopped, and when they stopped should be a priority for current and future studies.

The second issue concerns what happens after cessation of use. The Rossing et al. data stand out because former users outnumber current users. Almost all participants were enrolled after the Women's Health Initiative estrogen-plus-progestin findings were published, when overall use in the United States decreased rapidly. However, few data fully describe contemporary

patterns of use (14). Which quitters resumed their previous hormone therapy, and when? How many others tried different preparations or different treatment altogether? Fewer women are using hormone therapy, but is overall duration of use shorter? And do the factors that lead women to initiate use or continue use because of persistent symptoms, patient preferences, or other reasons reflect underlying ovarian changes that are related to ovarian carcinogenesis? More precise data on who is taking what—and why—are also needed.

Future studies can address these inconsistencies. Individual decisions about whether to use menopausal hormone therapy or not are unlikely to depend solely on potentially increased ovarian cancer risks. For women who choose to use menopausal hormone therapy, regardless of what influences their decisions, uncertainty about ovarian cancer risks might be as worrisome as small actual increases in absolute risk. Our challenge is to describe, as precisely as possible, the specific potential risks associated with specific patterns of contemporary menopausal hormone therapy use.

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