Re: Breast Cancer Risk in Relation to the Interval Between Menopause and Starting Hormone Therapy

In a recent issue of the Journal, Beral et al. (1) reported on the Million Women Study (MWS) and confirmed that use of hormonal therapy either before or after menopause is not safe in terms of breast cancer risk. The false idea that hormonal therapy use before or after menopause is not associated with increased breast cancer risk has distracted from the increases in breast cancer and cancer-related mortality already described in the MWS and Women’s Health Initiative (WHI) trial (2,3). It is illogical to assume that taking hormones at any particular age is without risk because use of contraceptive estrogen–progestin increases the risk of several types of cancer, vascular diseases, and mortality in young women (4).

All hormonal contraceptives act predominantly more like progesterone rather than estrogen to avoid irregular bleeding. Combined hormonal therapy formulations also include powerful doses of progestins to avoid estrogen-induced endometrial hyperplasia and endometrial cancer in women with a uterus. Unfortunately, users of estrogen–progestin hormonal therapy have a higher risk of invasive breast cancer compared with users of estrogen–only hormonal therapy (1,5). Beral et al. (1) reported that current use of estrogen–progestin hormonal therapy approximately doubled the risk of breast cancer with less than 5 years of use (RR [relative risk] = 1.62, 95% CI [confidence interval] = 1.54 to 1.71) and more than 5 years of use (RR = 2.19, 95% CI = 2.10 to 2.27). In addition, less than 5 years of estrogen therapy use also increased the risk of breast cancer when use began either before menopause or less than 5 years after menopause (RR = 1.31, 95% CI = 1.19 to 1.43) (1). Currently, clinicians advise their patients to use hormonal therapy in the smallest doses for the shortest time period to suppress non–life-threatening menopausal symptoms. The findings reported by Beral et al. (1) indicate that this advice is potentially harmful to patients. Even so, the minor benefits of menopausal hormone use are still being lauded, although the WHI study did not find a statistically significant association between use of hormonal therapy during menopause and overall improvements in the quality of life of patients (6).

In the MWS of 1 129 025 women in the United Kingdom, the mean age at recruitment was 56 years. Nearly half (47%) of the never users of hormonal therapy who were the control subjects in the study had previously taken progestin-containing contraceptives, and 90% of users of hormonal therapy had started therapy within 5 years of menopause (7). In the WHI study of 16 608 women, the mean age at random assignment was 63 years. More than one-fourth (26%) of the women (randomly assigned as either hormone takers or placebo-taking control subjects) had been past or current users of hormonal therapy. In addition, 10.7% of the control subjects took hormonal therapy during the study. Among women with invasive breast cancer, more than one-third of users of hormonal therapy (38.7%) and control subjects (34%) had previously used hormonal contraceptives (5).

Both the MWS and the WHI study therefore underestimate all breast cancer risks associated with use of hormone therapy, including breast cancer risks for current and past users of hormonal therapy, by not having only genuine never users of hormones for baseline control subjects and by omitting the effects of total ever hormone use. Also, as breast cancer risks were highest for current users of hormones, it is important to know which women were using hormones at the time of breast cancer diagnosis, but this is not precisely known in either study.

Epidemiological studies have been underestimating breast cancer risks from hormonal therapy for decades. If current and former use of hormones were routinely included in cancer registries and death certificates, the real risks of breast cancer associated with hormone use would have been known much sooner.

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References

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