

Editorial

The Million Women Study and breast cancer

The Million Women Study recruited 1,084,110 women between 1996 and 2001 from those invited by the U.K. National Health Service Breast Screening Programme to have screening mammography every 3 years (about half had ever used postmenopausal hormone therapy) [1]. The Study data were recorded from questionnaires returned prior to mammography, and the women were followed to determine cancer incidence and death. The Study is noteworthy for its large numbers and adjustments for the well-recognized factors associated with risk of breast cancer. No increase in risk of breast cancer was measured in past users of any hormone preparation, regardless of length of time since discontinuation, from less than 5 years to 10 or more years (with the exception of discontinuation in the year previous to diagnosis), and regardless of duration of use. Based on an average follow-up of 2.6 years, the relative risks for invasive breast cancer were:

Never users	1.00 (0.96–1.04)
Past users	1.01 (0.95–1.08)
Current users	
Estrogen only	1.30 (1.22–1.38)
Estrogen-progestin	2.00 (1.91–2.09)
Tibolone	1.45 (1.25–1.67)

The risk of breast cancer increased with duration of current use:

	Current users of estrogen only	Estrogen-Progestin
Less than 1 year	0.81 (0.55–1.20)	1.45 (1.19–1.78)
1–4 years	1.25 (1.10–1.41)	1.74 (1.60–1.89)
5–9 years	1.32 (1.20–1.46)	2.17 (2.03–2.33)
10 or more years	1.37 (1.22–1.54)	2.31 (2.08–2.56)

Similar increases in relative risks were observed in users of conjugated estrogens, estradiol, oral formulations, transdermal products, and implants. Similar results were also reported comparing low and high doses of estrogen, preparations with different progestins (medroxyprogesterone acetate, norethindrone, norgestrel/levonorgestrel), and users of sequential or continuous regimens. The risk of breast cancer was increased in users of progestin only formulations; however, this analysis was based on only 9 cases in 618 users.

1. Puzzling questions

The self-reported data were compared to family physicians' records in a sample of the study revealing a 96% agreement regarding current use at baseline, 97% agreement regarding type of formulation, and 90% agreement for the specific product and dose. This is an impressive level of agreement, but when the relative risks are not large, as is the case with breast cancer and hormone therapy, will small percentages of disagreement affect the results? Furthermore, one-third of current users used more than one preparation; does this affect the analysis of specific

combinations? The participants also changed categories: the subsample analysis of 12 221 participants revealed that compared to baseline 22% were no longer current users, 19% of past users were now users, and 11% were no longer never users. The authors argue that these changes would cancel each other out, but that is a large assumption.

Never users of hormone therapy who were perimenopausal or postmenopausal had statistically significant reduced risks of breast cancer when compared to premenopausal women. This is a puzzle because the risk of breast cancer increases with age. But most importantly, did this reduced risk in never users affect the overall analysis when users were compared to never users? Of course there would be an increase in risk if the comparison is below the relative risk of 1.00. The answer to this question is not apparent to me.

Considerable space in this report is dedicated to estimating the attributable incidence of breast cancer by applying the relative risks to typical cancer rates in developed countries. This exercise, of course, assumes that the relative risks are precise, and in a cohort study this cannot be the case. The authors estimate that the past decade use of hormone therapy resulted in an extra 20 000 cases of breast cancer in the UK. Is this reflected in the national statistics? In the United States, the incidence of breast cancer increased 4% per year from 1980 to 1987, due to increasing detection because of mammography. Since 1987, the incidence rate has been very stable, with at most an increase of 0.5% per year. Because the incidence since 1987 has plateaued, the long-term increase over the past decades is attributed to lifestyle and reproductive changes [2]. A similar pattern has been recorded in the UK, with the plateau beginning in 1992 [3].

Breast cancer mortality was assessed after an average of 4.1 years of follow-up, based on a total of 517 deaths. Current users and past users were compared to the never users:

Never users	1.00 (0.88–1.14)
Current users	1.22 (1.00–1.48)
Past users	1.05 (0.85–1.34)

The increase in mortality in current users was not statistically significant. I wonder whether the increase in mortality was influenced by screening mammography performed only every 3 years. Perhaps an important contribution of the Million Women Study is documentation of the lesser efficacy with less than annual screening. The authors argue that the Million Women Study is more accurate because it includes both screening and interval tumors. They further emphasize that hormone therapy increases the probability of an interval breast cancer because of a reduction in the sensitivity of mammography. It would have been helpful to know the numbers of tumors detected at screening and those during the interval between screenings.

The authors flatly state that use of hormone therapy reduces the sensitivity of mammography and increases the diagnosis of interval cancers. Is this true? In a review of 7 studies, there were relatively few interval cancers in the user groups (from 1 to 46), nevertheless 6 of the 7 studies reported decreased mammographic sensitivity in hormone users with increases in interval cancers in users compared with nonusers, and this is the publication referenced in the report from the Million Women Study [4]. Excluding women under age 50, the relative risk for an interval cancer was summarized as 1.7 (CI 1.2–2.4). In a French study, mammographic sensitivity was reduced from 92% to 71% in users because of an incidence of interval cancers that was 3.5 times that of nonusers within the first year of the initial exam, and 1.7 times greater during the following 2 years (The odds ratio of a cancer being detected at screening among nonusers was 5.14, CI 2.5–11.8, compared with users) [5]. Most of the hormone users were on combined estrogen-progestin regimens. A Finnish study concluded that women with the most dense breasts and using hormones had the highest relative risk of breast cancer, but this conclusion was based on only 4 cases of cancer in women with dense breasts [6]. American, Scottish, and Australian studies have indicated a 15–20% decrease in mammographic sensitivity in hormone users who have dense breasts [7–10]. However, a prospective study of screening mammograms from Massachusetts General Hospital concluded that

recall rates were essentially the same comparing hormone users and nonusers, and that hormone therapy rarely causes a diagnostic dilemma [11]. Overall, studies have suggested a decrease in mammographic sensitivity with little impact on specificity (false recall rates). However, the studies are based on small numbers of interval cancers, and it is uncertain how real or how large this effect is because of the difficulty in controlling for confounding factors (for example, age, age at menopause, and time since menopause).

If the effectiveness of breast cancer screening is reduced by postmenopausal hormone therapy, one would expect an adverse impact on breast cancer mortality as reported in the Million Women Study. Instead, a study that indicated a reduction in mammographic sensitivity also reported smaller, more differentiated (Grade I) tumors among the users compared with the nonusers [12], and most of the studies that have examined breast cancer mortality rates of women who had used postmenopausal hormone therapy have documented improved survival rates [13–23]. Evidence indicates that hormone users develop smaller, better-differentiated (lower grade) tumors, evidence that is consistent with effects on pre-existing tumors, and that surveillance/detection bias is not the only explanation for better survival [24–29]. Lower grade tumors are present even when there is no difference in the prevalence of mammography comparing hormone users and nonusers, or when the data are adjusted for the method of detection [20,22,29]. The recent report from the Women's Health Initiative indicated that the tumors in hormone users were more advanced (more positive nodes and less localized disease) [30]. Does this contrary finding reflect the older age of the WHI participants?

The discussion in the report from the Million Women Study adds this piece of information: if the analysis had included women with a history of breast cancer at baseline (3% of whom were current users at recruitment), the mortality analysis would have indicated a reduced risk, a conclusion that in the opinion of the authors would be biased. The authors argue that studies indicating a lower risk of mortality from breast cancer in users at the time of diagnosis have been unable to

account for the 'bias' of breast cancer diagnosed at the beginning of a study, not during the study. The logic of this argument escapes me. An analysis of the breast cancers in our own institution revealed that more tumors in hormone users were detected by screening mammography, but when assessing outcomes in all cancers detected by mammography, hormone users had more ductal in situ tumors, more node-negative cancers, smaller tumors, and less invasive disease; and thus better survival rates [31]. After 8 years of follow-up, there was a 13% mortality rate in the nonuser group, and in the women with breast cancer who were using hormone therapy at the time of their diagnosis, there has not been a single death attributed to breast cancer.

2. Tibolone

The reported results with Tibolone are a surprise. In the rat and mouse breast cancer models (cancer induced by 7,12-dimethylbenzo[*a*]anthracene, DMBA), tibolone exerts protective effects to the same degree as tamoxifen [32]. However, tibolone is not antiestrogenic and does not inhibit aromatase. Therefore, the mechanism is explained by enzyme effects, inhibition of sulfatase and 17 β -hydroxysteroid dehydrogenase and stimulation of sulfotransferase to increase the production of inactive sulfates [33]. In addition, tibolone increases cellular differentiation and stimulates apoptosis, at least with normal breast cells in vitro [34]. Postmenopausal hormone therapy increases breast density on mammography in about 10–20% of estrogen users and about 20–35% of estrogen-progestin users, an effect that occurs within the first months of treatment. In contrast, tibolone does not increase breast density, and causes far less mastalgia than that seen with estrogen treatment [12,35–41]. It is logical to conclude that these favorable responses are a consequence of the tibolone effects on the breast tissue enzymes involved in local estrogen production.

Organon has compiled the incidence of breast cancer among 4,537 women participants in phase III and phase IV studies [42]. The incidence in the tibolone-treated women was 1.59 per 1000 woman-

years compared with 3.15 in the placebo group; however, the difference did not achieve statistical significance. It is puzzling why the Million Women Study disagrees with these results. One reason could be preferential prescribing. Clinicians, aware of the above information, may have prescribed tibolone to women at greater risk for breast cancer, but I hasten to add that the analysis found that current users of tibolone did not differ from other hormone users when assessed for breast cancer risk factors. We will have to await the outcome of the clinical trials currently underway assessing the effect of tibolone on the incidence of breast cancer and breast safety.

3. The editorial

The arrogant and inaccurate editorial [43] that accompanies the Million Women Study report requires comment. The authors claim that we have reached a low point in health care for middle-aged women, and it is the heavy promotion by the pharmaceutical industry that is responsible. Yet the health of older women in the developed world has never been better, and postmenopausal hormone therapy ranks as one of the most studied of pharmaceutical products, much of it financed by the industry. Hormone therapy is not a 'new development' that was subject to the appropriate studies of the modern era before approval, but it is a treatment that has been with us for many decades, and indeed, the present controversies reflect the enormous amount of investigation of this therapy now on-going throughout the world. To make this emotional claim and then to imply that physicians with a vested interest are to blame, and the general practitioner has been 'overwhelmed', is good theater but reflects a poor understanding of the facts and history. For example, the editorialists claim that the drug industry funded menopausal clinics; I know of no such clinics in the US. They further claim that risks were neglected, and now it is up to unbiased primary-care providers to solve the problem. I deplore this 'we vs. they' posturing. I take exception to the accusation that the many scientists and academicians interested in this subject are not

ethical, independent, and sincerely motivated to do their honest best, especially in knowing the ultimate impact on women. To do as the editorialists recommend (to categorically discourage the use of hormone therapy) is to deny women the assistance they need to make individual decisions based upon individual characteristics and needs.

4. Conclusion

We now have an increasingly impressive collection of epidemiologic data, capped by the WHI and the Million Women Study, indicating that current users of postmenopausal hormone therapy have a slightly increased risk of breast cancer. The important unanswered question is whether hormone therapy causes breast cancer or is promoting the diagnosis of pre-existing tumors. The findings that support an impact on pre-existing tumors include the impressive agreement among all studies in finding no increased risk in past users and the rapid diagnosis of breast cancer in most studies within a few years of initiating therapy.

I do not believe it is appropriate to discard the large body of evidence indicating that tumors in hormone users are better-differentiated, lower grade and stage disease, with better outcomes. The challenge is to identify the reasons for the disagreements among the studies. The results of the Million Women Study disagree with the fact that the Women's Health Initiative has reported that an increase in breast cancer has not been observed in the estrogen only arm of the clinical trial (an average follow-up has now reached about 7 years).

The current confusion and controversy that surround postmenopausal hormone therapy make it all the more important to individualize treatment. The specific objectives for each patient must be identified, and the best treatment option (formulation—hormonal or nonhormonal, dose, and route of administration, lifestyle changes, medication or no medication) that meets the patient's goals must be selected, a process that will require time-consuming patient-clinician dialogue. Because of the astounding rate at which we are accumulating new information, treatment

decisions should be short-term, at most for a year. Each year, clinician and patient together must review and evaluate the decision incorporating that year's new information, and then together forge a firm commitment to a new decision for the coming year.

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