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## EDITORIAL

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# Women's Health Initiative Results: Breast Cancer Risk in Perspective

The results of the Women's Health Initiative (WHI) study are widely regarded as evidence that hormone replacement therapy (HRT) use increases breast cancer risk (1). The study's large number of subjects and randomized prospective design are cited as compelling reasons to accept its findings without further scrutiny. However, epidemiologic studies provide information about associations, not cause and effect. Their results must therefore be analyzed carefully to determine the likelihood that causality is present. When the WHI study is carefully scrutinized, it can be seen that the findings, specifically those pertaining to breast cancer risk, are by no means definitive. As discussed below, the exceedingly small and nonstatistically significant increase in breast cancer risk reported in this study may well not be due to HRT use.

### BREAST CANCER RISK AND CLINICAL RELEVANCE

Compared to nonusers, HRT users in the WHI study were reported to have a hazard ratio of 1.26, which was also called a 26% increase in breast cancer risk. In a clinical setting, the presentation of risk in a comparison format such as a hazard ratio, relative risk, or percent change is generally uninformative and may even be misleading. Because comparison formats do not provide information about a risk's actual size, their relevance to an individual or to a group is not clear. On the other hand, risks presented in an absolute (actual) format provide information that

physicians and patients can apply to an individual's situation.

In the WHI study, the absolute increase in risk to the group assigned to HRT was 8 breast cancers in 10,000 women or *eight hundredths of one percent* per year. This exceedingly small difference in breast cancer rate has been largely overlooked, perhaps because the focus has been on the comparison format. Clearly most physicians and their patients will respond differently to a 26% increase in risk than to a risk that is eight hundredths of one percent per year. As this example suggests, absolute risks are essential in any reasonable decision-making process.

### LACK OF STATISTICAL SIGNIFICANCE

The very small difference in breast cancer risk between HRT users and nonusers in the WHI study was *not* statistically significant. When differences are not statistically significant, an increase in risk may be due to causes other than the agent being studied (2). Even with statistical significance, however, there is at least a 5% chance that a difference between two groups is due to causes other than those being studied. In this, as in most other medical studies, statistical significance is calculated at the 5% level, which means that the chance of obtaining a spurious statistical significance is 5% when significance is calculated once.

As the number of statistical significance tests increases, the chance of obtaining a spurious finding also increases. For example, with four significance tests, there is a 19% chance and with 10 tests there is a 40% chance that a difference will appear to be statistically significant when it is not (3). In the WHI study, with and without correction for multiple statistical testing, HRT users did not have a significant increase in breast cancer risk.

Of interest is that another large randomized prospective study with a mean follow-up of 6.8 years also found

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no statistically significant increase in breast cancer risk to HRT users (4). We now have two large randomized prospective trials, neither of which has shown a significant increase in breast cancer risk to HRT users.

### BIOLOGY, BIOLOGY, BIOLOGY

One group has calculated that an average of at least 8 years is needed for breast cancers to reach 1 cm, with tumors in older women having a slower growth rate than those in younger women (5). Women in the WHI study had a mean age of 63 years with 68% of Prempro users and non-users having well to moderately well differentiated tumors (6).

All women in the study were followed for 3.5 years, with a mean follow-up of 5.2 years. In both groups, about 84% of the breast cancers were found in the first 5 years of the study. This means that all or nearly all of the breast cancers reported in the study were present in an undetectable state *before* the study began and so cannot be ascribed to HRT use.

### FASTER GROWTH OF BREAST CANCERS IN HRT USERS?

It is unlikely that existing breast cancers grew more rapidly in HRT users than in nonusers and so were found sooner. Not only were the breast cancers in Prempro users and non-users similar in grade, but they differed in size by only 2 mm (6). In more than 15 other studies the breast cancers detected in women who were using HRT were no larger or more aggressive than those found in nonusers. Instead, breast cancers found in HRT users were more likely to be diploid, estrogen-receptor (ER) positive, node negative, and of lower grade than those of nonusers (7–11). In these and other studies, HRT use has not been found to be associated with increased breast cancer growth.

To avoid bias due to earlier detection in HRT users, one study compared mammographically detected breast cancers in hormone users and nonusers who had equivalent screening, and so had an equal likelihood that their tumors would be found at similar stages (12). In this study, hormone users were more likely to have well-differentiated tumors and significantly less likely to have poorly differentiated tumors compared to non-hormone users (Table 1).

As a group, studies of women whose breast cancers were detected while they were using HRT show that HRT use at menopause does not in any measurable way contribute to growth or to aggressive features in breast cancers. Therefore the use of HRT in the WHI study is

**Table 1. Tumor Differentiation in HRT Users and Non-Users – Mammographic Detection**

Differentiation	HRT User	Non-User
Well	37%	30%
Moderately	35%	34%
Poorly	14%*	26%*
Unknown	14%	9%

\* significant Cheek et al. 2002

unlikely to have resulted in faster growth and so to earlier detection of breast cancers in women assigned to HRT.

### TYPE OF HRT

Women in the WHI study took a conjugated equine estrogen plus medroxyprogesterone acetate (Prempro) daily. Other HRT regimens that more closely approximate a woman's natural hormones and cycle may have different effects. To the extent that the results of the WHI study can be applied, they are for women who use Prempro, not those who use other types of HRT or other regimens.

### ADHERENCE TO PROTOCOL

The WHI study results are based on the group to which a woman was assigned, *not whether she actually took Prempro*. This is a real concern, since 42% of the women who were assigned to take Prempro discontinued its use during the course of the study. The risks to those who actually used Prempro were not given.

### POPULATION

The mean age of women in the study was 63 years, with two-thirds  $\geq 60$  years old. Only about 20% had previously used HRT. All were willing to be randomly assigned to HRT or a placebo. This study population may therefore differ from women whose genetic make-up or lifestyle produces responses to estrogen decline that lead to HRT use at menopause. Therefore the results of the study pertain to women who began taking HRT some years after menopause, not to women whose HRT use began at perimenopause or menopause.

### MORTALITY

Prempro users in the WHI study did not have a higher overall mortality rate. In fact, from about 5.5 years on,

those assigned to take Prempro had a *lower* mortality than the group assigned to take Prempro.

### CONCLUSION

In applying the results of the WHI study in a clinical setting, the following should be kept in mind:

The 5.5-years mean follow-up is not long enough to provide information about the risk of breast cancer due to Prempro use, since the average time for a breast cancer to reach 1 cm is about 8 years. This means that most or all of the breast cancers detected during the study were likely to have been present before the study began.

In the WHI study and more than 15 others breast cancers in HRT users are not of higher grade and are not growing more rapidly than those in nonusers. Therefore HRT use is unlikely to have caused faster growth and earlier detection of breast cancers in HRT users in the WHI study.

A very small difference in breast cancer risk was found between Prempro users and nonusers—8 in 10,000 per year. This difference was not statistically significant. Furthermore, the risks were calculated on the basis of assigned, not actual hormone use.

The mean age of the participants, most of whom had never used HRT before the study, was 63 years, with two-thirds  $\geq 60$  years old. This study therefore does not provide information about the risk of breast cancer to women whose HRT use starts at menopause.

When investigated fully, the WHI study and its results do not provide definitive evidence that HRT use, and specifically Prempro use, increases breast cancer risk.

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