



Frequently Asked Questions

The Women's Health Initiative (WHI) is an ongoing large national health study involving more than 160,000 women aged 50–79. It has both an *observational* and a *clinical trial* part, and focuses on heart disease, breast and colorectal cancer, and osteoporotic fractures in postmenopausal women. The hormone therapy (HT) component of the study consisted of *randomized controlled trials* (see FAQ #1) and we will refer to them as “the WHI trials.” There were two arms to these trials:

- the estrogen-only arm for women who have had a hysterectomy and
- the estrogen-progestin arm for women with an intact uterus

The trials were conducted from 1997 to 2002 for estrogen-progestin, and from 1997 to 2004 for estrogen-only. The participants continue to be followed to determine the impact of HT. Below, we outline some of the statistical topics useful for understanding the results of the WHI trials, as well as the current understanding of HT and its impact on women's health based on the WHI trials and other studies. We finish with some summaries of media coverage of the topic from 2002 to 2007.

1. What is the difference between the WHI trials and other scientific studies on HT during or after menopause?

The WHI trials were *randomized controlled trials*. This study design is the gold standard for ascertaining the effect(s) of treatment. Approximately 16,600 women enrolled in the estrogen and progestin component of the WHI trials, and they were randomly assigned to take either hormones (estrogen and progestin) or a placebo (sugar pill). Another 10,700 were enrolled in the estrogen-only component, and they also were randomly assigned to take either hormones (estrogen) or placebo. Over the period of the trials, clinicians tracked the health of the women in the study. Ultimately, in each component, the two groups (those receiving hormones and those receiving placebo) were compared. Since the women themselves did not choose whether to receive hormones or a placebo, bias resulting from *who* decides to take hormones and *who* decides not to was eliminated.

The question of who decides to pursue hormone therapy (HT) is an important issue when comparing groups outside of a controlled environment. For example, if women who are less likely to use HT are also more likely to be vegetarians, then a benefit that could be due to vegetarianism might be incorrectly attributed to non-use of HT, and the lack of benefit among non-vegetarian HT users interpreted as a risk of HT. One of the concerns about observational studies was that the observed benefit to heart disease was actually due to the fact that women who use HT were healthier than women who do not. Similarly, if those who have HT are more likely to be aggressive about medical care, then a benefit attributed to HT may in fact be due to better medical attention. As large randomized controlled trials, the WHI trials were not subject to these kinds of biases.

Other studies reporting on the effects of HT, such as the Nurses' Health Study (NHS), were *observational*. That is, researchers compared women who chose to undergo HT and compared them to similar women who did not. Because there is a potential for many kinds of bias, they tried to control for *confounding factors* (see FAQ #3). These include other health issues that may have an impact on long-term health, such as body mass index and smoking status.¹

One of the limitations of the WHI data is that the women in the study were not necessarily the "typical" women who initiate hormone therapy on their own. For example, the average participant in WHI was 63 years old, so the overall, aggregated results of the WHI trials have limited meaning for younger women interested in HT for treatment of hot flashes. This is one of the reasons that the data collected by the WHI trials has been re-analyzed by many researchers trying to quantify the risks and benefits of HT for certain subgroups of women.

2. Why was there a widespread belief before the WHI that HT during or shortly after menopause would be beneficial? Did the WHI change doctors' minds? If so, how could the science have gotten it wrong earlier?

The WHI trials were randomized controlled trials (see FAQ #1), also called clinical trials. Before the WHI trials, there were some smaller clinical trials, most notably the Heart and Estrogen/Progestin Replacement Study (HERS), which enrolled just under 2,800 women, and its follow-up, HERS II, with about 2,300 women continuing to participate. These two trials were conducted from 1993 to 2000. Before then, doctors relied on *observational studies*, some of which were much larger than the WHI trials and suggested a benefit from HT, especially in preventing coronary heart disease. These included the Nurses' Health Study (NHS), which included over 70,000 women and ran from 1976 to 2000. One analysis of the NHS data found that those taking estrogen alone reduced their risk of heart attacks by almost 40 percent compared to those who never used HT, though it increased their risk for stroke. A follow-up look at the same women a few years later found that women beginning HT near menopause were *only two-thirds* (for estrogen alone) to *three-quarters* (for estrogen and progestin) as likely to have coronary heart disease compared to those who never

¹ Barrett-Connor, 2003.

used HT.² Other observational studies also found a relative benefit of HT for coronary heart disease among postmenopausal women using estrogen.³

These results appeared contrary to the findings of the WHI trials. In the initial analysis of the WHI data, the use of HT was correlated with an *increase* in coronary heart disease by almost 25 percent.⁴ Considering that heart disease is the leading cause of death for women in the United States, this finding was significant and initiated a change in medical recommendations regarding HT. Women are no longer prescribed HT as a heart-protective measure.

However, the initial analysis of data from the WHI trials did not break the women into subgroups to see if HT had a different effect on younger women (compared to young women not taking HT) than on older women (compared to older women not taking HT). A secondary analysis of both the NHS data and the WHI data suggested that younger women who underwent HT compared to those who did not were subject to less risk than older women on HT compared to older women who did not use HT. This age-related difference was especially important for heart disease. The overall data from the WHI trials pointed to an increased risk of heart disease among women taking estrogen and progestin, compared to women who were in the placebo group. However, when the clinicians only considered those women who had gone through menopause less than 20 years before starting HT or who were under 70 years old, there was no statistically significant increase in heart disease⁵ (see FAQ #5 for more on statistical significance) for women on HT, compared to similar women in the placebo group. However, the NHS data suggested a *benefit* for heart disease, while the WHI trials did not.

There are many reasons why different studies can have different outcomes, and many of these have been proposed to explain the discrepancy between the observational studies and the clinical trials. First of all, the WHI included women of all ages, and the average age was 63. In contrast, many of the women who are beginning HT are between the ages of 50 and 59, at the onset of menopause. An observational study such as the NHS will take a picture of the *actual* way in which people, on average, go about getting hormone therapy. Typically speaking, those NHS women who took hormones began them close to the onset of menopause. In contrast, in the WHI study, women were assigned hormones or a placebo without regard to their age; in theory it is possible that the older women who started HT long after menopause clouded a benefit to beginning HT close to menopause. On the other hand, there are many possible confounding factors in any observational study (see FAQ #3), and it is possible that some of these were not collected and adjusted for in the observational data analysis. Because of the scope of the WHI trials and the strength of a randomized controlled trial, it is now accepted medical advice *not* to use HT for protection against coronary heart disease.

Figure 1 compares the hazard ratio (see FAQ #4) associated with estrogen and progestin hormone therapy for women in the WHI trials to those participating in NHS. A hazard ratio greater than 1.0

² Grodstein et al., 2000.

³ Barrett-Connor et al., 1991.

⁴ Manson et al., 2003.

⁵ Rossouw et al., 2007.

suggests that the hormone therapy is harmful, while one less than 1.0 suggests it is helpful. All results in this chart are statistically significant (see FAQ #5). For heart disease, data from the NHS suggest that women using HT are at less risk than women who do not, while WHI data suggest that women using HT are at higher risk. For both sets of data, HT is associated with higher risk of breast cancer.

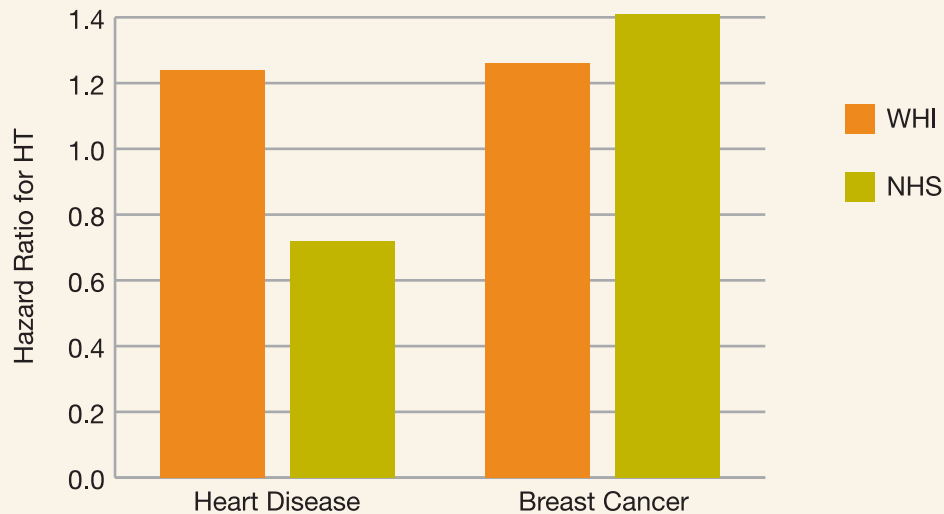


Figure 1. Comparison of hazard ratios using different data

3. What are confounding factors and how do they affect scientific research on HT and menopause?

Confounding factors are especially important to consider in observational studies. A potential confounding factor (or confounder) is any variable that could be related to HT and to a health outcome, such as heart disease or breast cancer. An illustration of this concept is that women who take HT tend to have lower body mass index (BMI) than women who do not. BMI is a confounding factor, since high BMI is associated with increased heart disease and increased breast cancer. Without worrying about this confounder, the group of women taking HT may seem healthier than those not taking HT—and we cannot know if this is because they have a lower BMI or because they are taking HT. In the NHS, adjusting for confounding factors can explain much (though not all) of the perceived benefit due to HT. Women participating in the NHS tended to be “white, educated, upper middle class, and lean, thereby at lower risk of heart disease than women without estrogen replacement therapy.”⁶ Because the demographics of women taking HT are not the same as the demographics of women not taking HT, we cannot determine the health benefits

⁶ Barrett-Connor et al., 1991.

and risks from HT without adjusting for confounding factors. This is one of the reasons that statisticians say that HT is “associated with” or is “correlated with” breast cancer, rather than causes it.

The problem in determining cause and effect lies in determining which factors are confounding—and unfortunately, sometimes there are confounders that have not been, or cannot be, measured when the data is collected, such as dietary habits. For heart disease alone, the major confounders include cigarette smoking, age, weight, history of hypertension, diabetes, elevated cholesterol, parental heart history, alcohol use, vitamins, aspirin use, physical activity, and family income.⁷ The more confounders considered, the larger the data sample needs to be to account for these appropriately. Because we can never know if we have addressed all the confounding factors in an observational study, randomized controlled trials are considered the standard for establishing causality.

Since the WHI trials were large randomized controlled trials (see FAQ #1), confounding factors such as age were not an issue. An older woman was just as likely to be assigned to the group of people taking hormones as to the group of those who were not. Similarly, smokers were just as likely to be assigned to the hormone group as to be assigned to the placebo group. Since the study was so large, it would be very unlikely that one group would have a disproportionately large group of smokers compared to the other, and that this would inadvertently confound the study. This is one of the primary advantages of a randomized controlled trial; with confounding factors unlikely to make a difference in the HT and the placebo groups, we can look at the outcome (whether it be breast cancer, colon cancer, or cardiovascular disease) and assume that *the only difference between the people in the HT and the placebo groups is which group they are in*. As a natural conclusion, any differences in outcome (provided there is statistical significance) are due to HT.

4. What is the difference between absolute and relative risk or hazard ratio, and why does it matter in reporting on WHI?

In the WHI trials, the *hazard ratio* is a comparison of risk between two different groups. The hazard ratio approximates a mathematically simpler concept, called *relative risk*. The relative risk of HT is the ratio of the risk of a disease if you are assigned HT, compared to the risk of a disease if you are assigned the placebo. If the risks are the same, then the ratio of these two risks is 1. Mathematically, if p is the risk of breast cancer for the HT group, and q is the risk of breast cancer for the placebo group, then the relative risk is p/q . If p and q are equal, this ratio is 1. On the other hand, if p is greater than q , suggesting that the risk is higher for those in the HT group, then the relative risk p/q will be greater than 1. Similarly, if the risk for breast cancer in the HT group were lower than the risk in the placebo group, then the relative risk p/q would be less than 1. The hazard ratio is a continuous version of relative risk that takes time into account. Relative risk and the hazard ratio are important ways to compare two different choices.

⁷ Grodstein et al., 2006.

In the case of breast cancer, the WHI trials found that among those in the estrogen and progestin arm of the trials the hazard for invasive breast cancer was 1.24 compared to those in the placebo group. Since the value is over 1.0, HT was 24 percent more likely to result in breast cancer than not taking hormones. For those in the estrogen-only arm of the trial, the hazard ratio for invasive breast cancer was 0.80, suggesting that taking hormones was 20 percent *less* likely to result in breast cancer compared to the placebo group. However, the increase in the estrogen-progestin arm of the study was statistically significant, while the reduction for those using estrogen only was not (see FAQ #5 on statistical significance) in comparison to the placebo group.

Many women would like to know what their actual risk is. This kind of risk is called *absolute risk*. It quantifies the likelihood that any individual will actually get breast cancer. A similar notion is what is called *attributable risk*, which quantifies the absolute risk that you can attribute to a particular cause. In the case of breast cancer, for a woman with an intact uterus, the absolute risk of breast cancer for women not on HT is about 33 cases per 10,000 women in a year, or approximately a third of a percent per year. The absolute risk for such a woman on HT is approximately 41 per 10,000, which is under a half a percent per year. The attributable risk for HT is approximately eight additional cases for every 10,000 women in one year; there is less than a tenth of a percent chance that a woman on HT would get breast cancer as a result of the HT.

It is often helpful to put these numbers in perspective, especially in lifestyle choices that increase risk of cancers. The estimated additional risk of breast cancer incurred by delaying childbirth after age 23 is approximately eight percent per year, suggesting that a relative risk of 24 percent, such as taking HT, is similar to the risk of waiting three years to have a baby.⁸ However, over a large population, the small but significant increase in breast cancer associated with HT can translate into a large number of deaths.

It is essential that media report on both absolute and relative risks; they are complementary, and one cannot be derived from the other. In the coverage of HT from 2002 to 2007, the media did mention both absolute and relative risks, with attributable risk cited about twice as often as relative risk; absolute risk of various diseases was generally not mentioned.

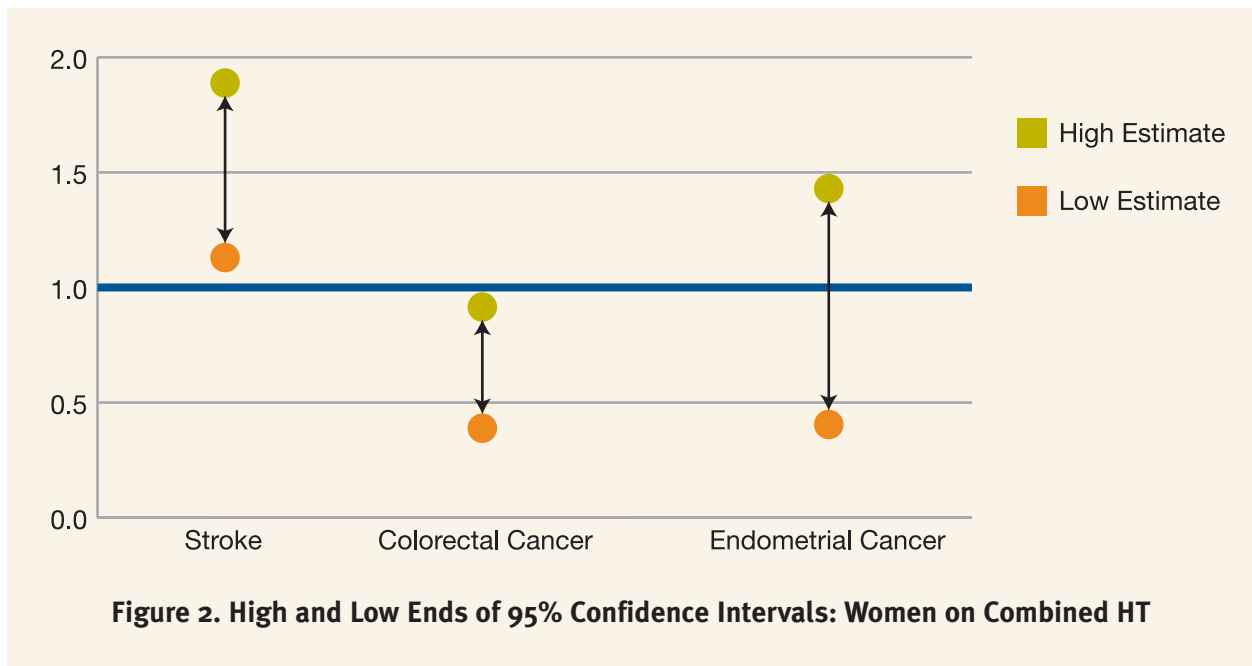
5. What does it mean that some of the results regarding HT were not statistically significant in the WHI trials? What can be understood from the confidence interval?

For any designed study involving health risks and benefits, we have to settle for a “sample” of the population—in the case of the WHI trials on HT, there were approximately 27,000 participants across the United States. However, there are millions of women who take HT, which is considered the “whole population” of those on HT. The goal of a study on HT is to use the sample to extract information about the whole population. The “true value” of risk, which is the risk in the whole population, cannot be measured easily, but we can estimate it based on what we see in the sample population. The larger the sample, the better an estimate we can get.

⁸ Lee et al., 2003.

The *confidence interval* is the best estimate of where the true value of risk lies. A 95 percent confidence interval is a range that we can be 95 percent certain contains the true risk for the whole population, based on what is happening with the sample. For example, the WHI trials found that, for women on estrogen and progestin, the relative risk for stroke was 1.41 (1.07–1.85) with 212 cases, and for colorectal cancer, was 0.63 (0.43–0.92) with 112 cases. The way to understand these results is that we can be 95 percent sure that the hazard ratio (see FAQ #4) of stroke for anyone taking HT is somewhere between 1.07 (a seven percent increase) and 1.85 (an 85 percent increase).

While a seven percent increase and an 85 percent increase seem like a wide range of values, the main point is that they both say that there is an *increase* in stroke for women on HT. In other words, we can be at least 95 percent confident that HT is associated with an increase in stroke. The most likely level of increase is 41 percent, since the hazard ratio was estimated to be 1.41. On the other hand, we can be at least 95 percent confident that colon cancer *decreased* among HT users. This is because the confidence interval is from 0.43 (suggesting a 57 percent reduction) to 0.92 (an eight percent reduction). Again, both of these numbers are below “1”. Graphically, these confidence intervals are represented below. We can be 95 percent confident that the true risk for these diseases among HT users (compared to the placebo group) lies along the arrows between the low estimate and the high estimate. These estimates are the low and the high ends of the confidence interval, respectively.



A closely related notion is that of *statistical significance*. Statistical significance is an important standard for research involving statistics. Technically speaking, statistical significance usually means that the result that was found was less than five percent likely to have occurred by chance. Since we can be 95 percent confident that the true value is in the confidence interval, we can conclude that “the WHI trials found a statistically significant increase in stroke from HT” since “1” is not in the confidence interval. Similarly, the WHI trials found a statistically significant decrease in colon cancer, since its confidence interval also does not cover the value 1.

The likelihood that an outcome occurs by chance alone is called the *p-value*. When the *p-value* is 0.05 or less, the result is referred to as statistically significant. Sometimes results are described in terms of *p-values* rather than in terms of confidence intervals. For example, the WHI trials found that “The hazard ratio (HR) for probable dementia was 2.05 (95% confidence interval [CI], 1.21–3.48; 45 vs. 22 per 10,000 person-years; P=.01).”⁹ What this means is that we can be 95 percent confident that the hazard ratio for probable dementia is between 1.21 and 3.48. The *p-value* of 0.01 states that it is less than 1 percent likely that we would see these data by chance alone, i.e., if HT was not associated with dementia. The *p-value* does not quantify the *amount* of increase. It quantifies the chance of seeing this increase randomly and not because of HT.

There were some “results” from the WHI trials that were not statistically significant. If a hazard ratio (see FAQ #4) is less than one, but the confidence interval contains the value 1, the results should not be viewed as scientifically definitive because there was a good possibility (meaning over five percent) that they occurred randomly. For example in the WHI trials, the hazard ratio of endometrial cancer of those on HT compared to the placebo group was found to be 0.83 with a confidence interval of 0.47–1.47¹⁰; see Figure 2. This means that among the women involved in the WHI trials, women taking hormones were on average less likely to get endometrial cancer than those who were in the placebo group; however, we can’t be sure that this is true of the whole population of women taking hormones compared to those who do not. The result was not statistically significant, because the value “1” is in the confidence interval. The correct way to read this result is that we can be 95 percent sure that the risk of endometrial cancer for those on HT is anywhere from 0.47 (about half as likely) to 1.47 (about fifty percent more likely) as those not on HT. In other words, we cannot say that the risk is definitely less or definitely more for endometrial cancer. We simply say that we do not have enough evidence to suggest that HT and endometrial cancer are correlated, either positively or negatively.

⁹ Shumaker et al., 2003.

¹⁰ Writing Group for the WHI Investigators, 2002.

6. What were the results of the WHI trials on HT?

The WHI trials were deigned to evaluate the effect of HT on a variety of diseases. The hazard ratios of these diseases for women using estrogen and progestin are charted in Figure 3, below. All of the numbers can be found in the publications resulting from the WHI trials listed in the bibliography of the Report on Select Literature.

These results can be quantified by saying that, for women in the estrogen and progestin arm of the study, there was a statistically significant increase in stroke, heart disease, breast cancer, and venous thrombosis (and the more serious event, pulmonary embolism). There was a statistically significant decrease in colorectal cancer and hip fracture. There was no observed difference between the HT and the placebo groups for endometrial cancer and death by other causes.

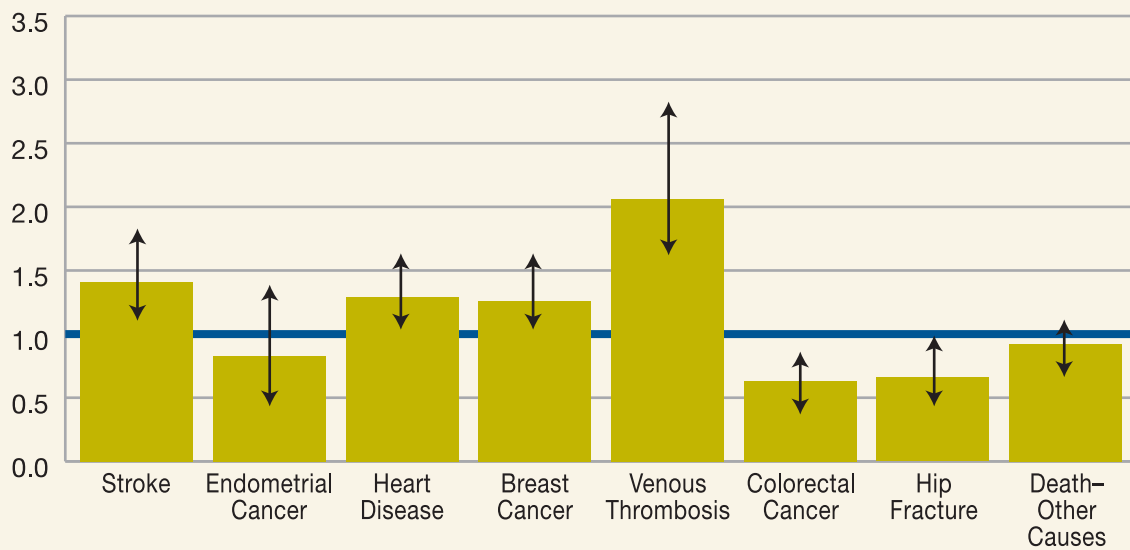


Figure 3. Hazard Ratios with 95% Confidence Intervals for Women on Estrogen and Progestin

A similar analysis can be done for women on estrogen alone, resulting in Figure 4. For these women, stroke stands out as the only statistically significant risk, with a confidence interval that does not contain the value 1. However, venous thrombosis is a category that also covers deep venous thrombosis, which by itself had a higher hazard ratio of 1.47 and a statistically significant 95 percent confidence interval of 1.06–2.06. Similarly, hip fracture was the only observed benefit.

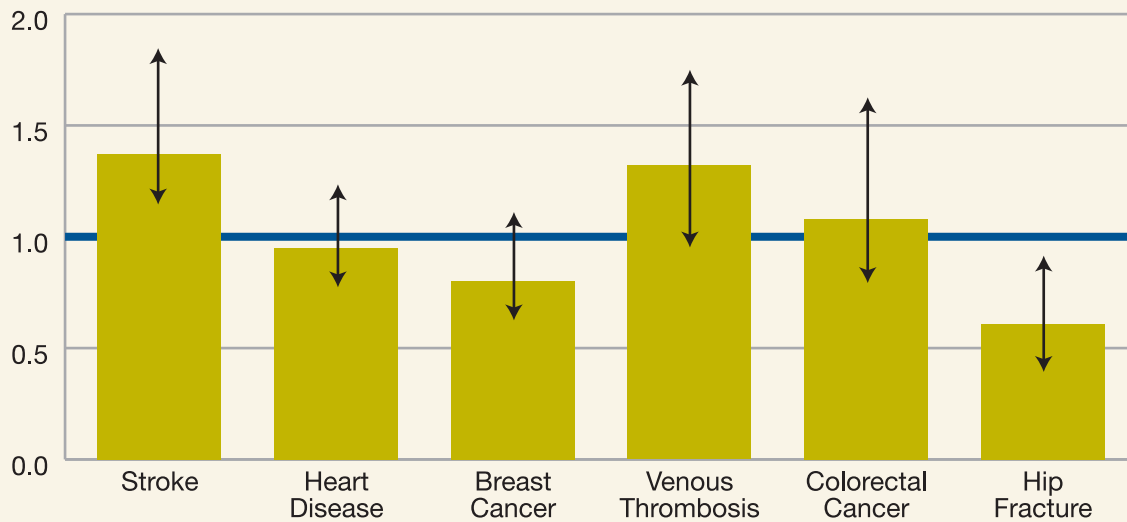


Figure 4. Hazard Ratios with 95% Confidence Intervals for Women on Estrogen Alone

7. Do the increased risks mean that no women should take HT? How much increased risk is “a lot”?

The level of risk that is considered “a lot” is obviously personal in nature. Generally speaking, relative risks that exceed 2.0 are considered serious, though for some in the medical community, the threshold is even higher. In recent years, a plethora of medical articles have appeared showing small but statistically significant risks.

The main message of the WHI trials is not that women who have taken HT are at great risk of these diseases: they are at only slightly increased risk. Even before the WHI trials began, the risk of breast cancer was recognized and considered to be an acceptable level. The point of the trials is that HT should not be prescribed to *prevent* heart disease.

While risks for individual women are personal, as a public health measure recommendations are made to whole populations. The current consensus is that women should not be taking HT to prevent heart disease, but women who are close to menopause may be able to use HT to help control symptoms. This decision should be taken in the context of a particular woman’s health history and her tolerance for risk. Women with high blood pressure, for example, would be at higher risk for pulmonary embolism and stroke; HT may be contraindicated in this case. On the other hand, women who have no history of hypertension and who are under 60 might consider HT if they have hot flashes and/or vaginal dryness. Ultimately the choice is one that needs to be made between a woman and her treating physician.

8. What did the media get right?

The media did a good job at describing the confusion over HT. In particular, among those stories expressing the opinion that the results were surprising, 22 percent specifically mentioned that the results regarding heart attacks were surprising.

For those stories that attempted to quantify the risk, a full 37 percent of opinions stated that the risks were “small” or “miniscule.” The media also pointed out that risks were not immediate and that symptom relief could justify the risk for some women.

Those stories that described absolute risks had correct figures. These absolute risks were typically stated with less precision than the hazard ratios, so the updated hazard ratios that were incorrectly reported (see FAQ #9) did not change their accuracy.

Some media stories discussed alternative treatments for menopausal symptoms, and correctly noted that the research was not conclusive or nonexistent. Black cohosh, soy products, and red clover were all mentioned as unconfirmed alternative treatments, with unknown risks and benefits.

9. What did the media miss?

Perhaps the biggest “media miss” regarded the discussion of heart disease for women on hormone therapy. While the WHI trials were conducted to see if there was a general heart benefit, some media sources reported the lack of heart-protective effect in terms of “risk of harm.” This citation of possible harm was especially misleading when it came to those women who had had a hysterectomy, or those women without a hysterectomy and were under 70 years old. While the WHI trials showed that HT should not be prescribed for prevention of heart disease, it did not show that HT was categorically risky for women to use.

The media occasionally quantified results, without updating these results as the figures were themselves updated on follow-up with the women of the study. For example, the press reported a 38 percent increase in stroke when the final data suggested a 31 percent increase.¹¹ The media reported on a 40 percent reduction in colon cancer, when the final figure was 44 percent.¹² In contrast, there were four references that HT increases breast cancer risk 26 percent, and three references to the final number of 24 percent.¹³ The reports of these lower figures included results over an additional four months of follow-up, and are therefore considered the more accurate and final results.

¹¹ Wassertheil-Smoller et al., 2003.

¹² Chlebowski et al., 2004.

¹³ Chlebowski et al., 2003.

The media also did not provide context on which the WHI trial findings were predicated. Very large observational studies such as the NHS, as well as a wealth of basic science data, had led researchers to the hypothesis on which the WHI was based. It was therefore surprising to find that observational studies were mentioned explicitly only 134 times, compared to the 1,109 mentions of the WHI trials. There were also over 200 mentions of a generic body of research.

While the media did discuss the risk attributed to HT accurately (e.g., eight additional breast cancer cases per 10,000 women), there was no discussion of the actual risk of the diseases. This would have helped keep some perspective on health issues; for example, it would have helped invalidate the myth that breast cancer kills more women than heart disease.

The general media miss was the contextual or conditional references to the subtleties of the data. The numbers were cited without qualification, as if they applied to all postmenopausal women. The focus on the failure of HT in the WHI to prevent chronic diseases of aging clouded the practical use of HT for symptom relief in young, recently postmenopausal women. Furthermore, when the results were first reported there was little mention of possible differences among different groups of women. The media did not lay the groundwork for the later scientific results that looked at health effects of HT on young women.

10. How did the media coverage change?

Media coverage of HT use changed in ways both obvious and subtle. Most dramatic and obvious was a marked decline in the amount of coverage over time. In the last six months of 2002 we found 139 stories discussing HT (see the Media Analysis). Coverage fell 65 percent in 2003 to 49 stories. Coverage did not exceed 50 stories a year over the next four years. Over the course of the six years studied, stories became shorter as the very long, highly detailed pieces written by veteran reporters like Gina Kolata, Jane Brody, and David Brown disappeared. This left behind relatively brief pieces highlighting new research findings and other aspects of the HT debate.

The topic or focus of media coverage also shifted over time as new aspects of HT use made news. This is seen most clearly in the assertions of harm and benefit connected with HT use. In 2002, discussions focused on the outcomes that were explored in the WHI trials: heart attacks, strokes, blood clots, and breast cancer. In 2003, these concerns were augmented by discussions of Alzheimer's disease and research suggested that HT did not help protect women from the disease. As a result of the findings from the estrogen-only trials in the WHI, 2004 coverage included proportionally more discussion of stroke risk. The final years of the study period brought a handful of news reports on class action litigation against Wyeth, and that coverage drew attention back to the initial areas of concern in the WHI trials.

As the years went by, discussion of the harms and benefits of HT use was less likely to cite specific numbers (e.g., eight additional cases of breast cancer per 10,000 women using HT). Instead, stories came to rely on general assertions that HT increased the risk of heart attack, stroke, breast cancer, and blood clots.

11. Where is menopause research going? What should journalists expect looking forward?

Reworking the data. Data that was collected through the WHI trials and the NHS still hold information that has not been analyzed yet by researchers. Just as the results of the WHI trials were significantly different when a secondary analysis of the data stratified women by age, we expect that other insights into the health benefits and risks will emerge over time as researchers apply new statistical techniques to evaluate the observations that were made. These include comparing different groups of women, so that the results can be more narrowly applied in specific circumstances; even now, for example, women over 70 who use combined hormone therapy are taking on an increased risk of heart disease, whereas women under 60 are not taking on any additional risk. Similarly, what can be said for women who have had children, women who have a history of breast cancer, women with certain genetic markers, overweight versus normal weight women? There are many possible ways to slice and dice the data, and journalists should expect that this will occur over the next few years. Already, in 2008, a new study was published suggesting that the results of the WHI trials do not disagree with the Nurses' Health Study (see "Menopause Research: A Report on Select Literature" for a discussion of these recent analyses).

Hormone therapy in small quantities or by different delivery method. Another important ongoing area of research involves the quantity of estrogen/progestin women receive, and the method of delivery of these hormones. The WHI trials involved oral HT. Some new hormonal therapies' delivery methods include vaginally inserted rings and gels, dermal patches, sprays or gels whose quantities can be self-regulated based on need for alleviating symptoms, and even implants. The route of exposure—and the amount of exposure—could have a significant impact on health benefits and risks. Many experts theorize that low doses of hormone therapy may provide most of the necessary symptom relief without any increased risk of breast cancer or heart disease.

Bioidenticals and alternatives to hormone therapy. The term "bioidentical hormones" usually refers to hormone supplements prepared by compounding pharmacies. In a pure sense of the word, however, a number of FDA-approved hormone therapies are bioidentical, that is, the chemical structure of the hormones are identical to those manufactured by the body. These include oral estradiol, all transdermal estrogens, and micronized progesterone.

Bioidenticals from compounding pharmacies have become a popular alternative to HT. However, the lack of standardization of these individually compounded treatments and their use in the face of FDA-approved bioidentical hormones is not only illogical, it is potentially dangerous, with potential for both over- and under-dosing. The Endocrine Society has issued a statement against the prescription of non-FDA-approved hormone therapy and has requested that the FDA take a more active role in the regulation of the "bioidentical" movement.

Some have argued that bioidenticals are in fact the same as their synthetic counterparts, while others insist that they are a safe alternative (i.e., have no associated risks). Many women are turning to bioidenticals for the same reason that women still turn to HT: to relieve symptoms. Bioidenticals consist of a variety of different substances, so as with the many forms that HT can come in, it is hard to do one overarching study and make a definitive conclusion about all bioidenticals. Some experts believe that bioidenticals will have the same health effects as the

pharmaceutical counterparts, and others believe that there is great variability in the quality of bioidenticals because they are not sufficiently regulated. Some claim that they have changed many peoples' lives, but there have been no large double-blind clinical trials, leaving us with little evidence to evaluate the anecdotal evidence. In the future, research on bioidenticals will continue to appear, and journalists should certainly be aware of the need to establish efficacy and safety for bioidenticals.

Similarly, non-hormonal alternatives to estrogen and progestin for the treatment of menopausal symptoms will continue to be developed. How well these medications compare to estrogen in terms of their ability to relieve hot flashes, vaginal dryness, and other symptoms of menopause will be the topic of much future research.

Testing the New Hypotheses. The KEEPS (Kronos Early Estrogen Prevention Study) is a multicenter trial that will examine the role of early initiation of hormone therapy (within three years of a woman's final menses) to help establish whether or not early initiation has the potential to protect women from cardiovascular disease. Unlike the WHI, which relied on heart attacks and even deaths from heart disease to make conclusions, KEEPS is a shorter and much smaller study that will examine the intermediate outcomes of carotid artery thickening and coronary calcium accumulation—two new, powerful markers of future heart disease. ■

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COLLABORATING ORGANIZATIONS

The Hormone Foundation

www.hormone.org

Established in 1997 by The Endocrine Society as its non-profit public education affiliate, The Hormone Foundation serves as a resource for the public by promoting the prevention, treatment and cure of hormone-related conditions through outreach and education. The Hormone Foundation draws from the expertise of The Endocrine Society, the oldest and most influential organization of endocrinologists in the world, to develop and implement authoritative and reliable educational programs on endocrine disorders for the public.

The Endocrine Society

www.endo-society.org

Founded in 1916, The Endocrine Society is the world’s oldest, largest and most active organization devoted to research on hormones and the clinical practice of endocrinology. Today, The Endocrine Society’s membership consists of more than 14,000 scientists, physicians, educators, nurses and students in more than 100 countries. Society members represent all basic, applied and clinical interests in endocrinology. The Endocrine Society is based in Chevy Chase, Maryland.

Center for Media and Public Affairs

www.cmpa.com

The Center for Media and Public Affairs (CMPA) is a non-partisan research and educational organization that conducts scientific studies of news and entertainment media. CMPA’s goal is to provide an empirical basis for ongoing debates over media coverage and impact through well-documented, timely, and readable studies. Since its formation in 1985, CMPA has emerged as a unique institution that bridges the gap between academic research and the broader domains of media and public policy. CMPA campaign news studies have played a major role in the ongoing debate over improving the election process. CMPA is also one of the few groups to study the role the media plays in communicating information about health risks and scientific issues.

Statistical Assessment Service

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Since its founding in 1994, the non-profit, non-partisan Statistical Assessment Service (STATS) has become a much-valued resource on the use and abuse of science and statistics in the media. The goals of STATS are to correct scientific misinformation in the media resulting from bad science, politics, or a simple lack of information or knowledge; and to act as a resource for journalists and policy makers on major scientific issues and controversies. STATS’ work has been featured on NBC’s “Nightly News,” “The News Hour with Jim Lehrer,” and ABC’s “20/20,” and in publications such as *The New York Times*, *The Wall Street Journal*, *The Washington Post*, *U.S. News and World Report*, *New Scientist*, and *New England Journal of Medicine*.