

Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Poststopping Phase of the Women’s Health Initiative Randomized Trials

(Manson et al., 2013)

Executive Summary and Questions and Answers

Table of Contents

Executive Summary.....	2
Questions and Answers.....	4
What did you set out to find; what was your objective?	4
Who did you study and what did you look at?	5
What were the results of your study?.....	5
1. Heart Disease.....	5
2. Breast Cancer.....	6
3. Stroke and Blood Clots	7
4. Hip Fracture	7
5. Colorectal Cancer	8
6. Endometrial Cancer.....	8
7. Overall Illness and Death (Global Index).....	8
Were there other results that could be important to women considering hormone therapy ...	9
How does this information help women who are considering hormone therapy?	10
What does the study tell women who previously used hormone therapy and then stopped?	12
What does this analysis add to what was already known?	13
What is the "take home" or "bottom line" message of this? How do these findings help women and physicians make decisions about hormone therapy?.....	14
Why is this study important?	17
Is there anything else that should be brought to light?	18
The findings for younger women on estrogen-alone are intriguing. What further research is planned to follow-up on the possible protection against heart disease?.....	18

Executive Summary

The Women's Health Initiative (WHI) was planned and launched in the 1990s, when there was substantial evidence that estrogen with or without a progestin might prevent disease in postmenopausal women. The WHI Hormone Therapy Trials included 27,347 women ages 50-79 who were followed during active treatment (5.6 years in the *estrogen-plus-progestin* trial, 7.2 years in the *estrogen-alone* trial) and for an extended period with no treatment, for a total follow-up of 13 years.

This study summarizes comprehensively and for the first time over 117 different publications and a wealth of WHI data on overall health risks and benefits of hormone therapy for postmenopausal women. The study shows a side-by-side comparison of the findings in the two Hormone Therapy Trials during treatment, after stopping, and by age group. We compare rates of coronary heart disease, stroke, breast cancer, blood clots in the lungs, hip fracture, colorectal cancer, endometrial cancer, and death among women assigned to the hormones and women assigned to placebo study pills. These illnesses and death were also combined in a global index to measure the balance of harm and benefit. Other important outcomes were also studied. The study showed differences and similarities in the effects of *estrogen-plus-progestin* and *estrogen-alone*:

- **Heart Disease:** *Estrogen-plus-progestin* increased coronary heart disease risk by 80% during the first year but only by 18% over the entire treatment period; this risk did not differ by age. *Estrogen-alone* did not increase coronary heart disease risk during this time, but there was a decreased risk among women in their 50s which became significant over the total 13-year follow up period.
- **Breast Cancer:** *Estrogen-plus-progestin* progressively increased breast cancer risk to 24% over the entire treatment period, with cancers diagnosed at a more advanced stage. This risk remained elevated over the total follow-up time of 13 years. *Estrogen-alone* decreased breast cancer risk, an effect that became statistically significant over the total follow-up time of 13 years.
- **Stroke and Blood Clots:** Both *estrogen-plus-progestin* and *estrogen-alone* increased stroke risk by about one-third during the treatment period.

These regimens also increased the risk of blood clots in the legs or lung, although this effect was greater for *estrogen-plus-progestin* than for *estrogen-alone*. The increased risks of stroke and blood clots were not seen after women stopped treatment and did not differ by age group.

- **Hip Fracture:** Both *estrogen-plus-progestin* and *estrogen-alone* decreased hip fracture risk by 33% during the treatment period. After stopping, this risk slowly increased, but was still lower in women who had taken *estrogen-plus-progestin* and similar in women who had taken *estrogen-alone*.
- **Colorectal Cancer:** *Estrogen-plus-progestin* decreased colorectal cancer risk, with cancers diagnosed at a more advanced stage; differences by age were not seen. *Estrogen-alone* had no overall effect on colorectal cancer risk, but the risk was increased in older than younger women. After stopping, there were no hormone effects in either trial.
- **Overall Illness and Death (Global Index):** *Estrogen-plus-progestin* increased the global index of combined illness and death by 12% during the treatment period. *Estrogen-alone* had no effect on overall illness and death, although risk was reduced for women in their 50s and increased for women in their 70s. After stopping, there were no hormone effects in either trial.
- **Other Results:** Probable dementia in women 65 years and over was increased by *estrogen-plus-progestin* and to a lesser extent by *estrogen-alone*. Memory was not affected in women aged 50-54. Gallbladder disease and urinary incontinence increased by 50-60% during both trials, and diabetes decreased by 14-19%. Hot flashes and night sweats were decreased in women ages 50-54 years in both trials.

These findings provide the strongest evidence base available to guide individualized counseling and personal decisions about hormone therapy. *Estrogen-alone* in women who have had a hysterectomy, particularly younger women, has a very different and more favorable risk-benefit profile than *estrogen-plus-progestin* in women with an intact uterus.

Taking all of the study effects into account, hormone therapy is not recommended for prevention of chronic disease, but it remains a reasonable option for managing menopausal symptoms short-term in younger women.

Questions and Answers

What did you set out to find; what was your objective?

In the early 1990s when the Women's Health Initiative was planned and launched, there was substantial evidence that estrogen drugs with or without a progestin might be good for disease prevention long-term in postmenopausal women – that they might prevent heart disease, hip fracture, and colorectal cancer among other conditions. We were concerned about a possible increased risk of breast cancer but, based on observational studies, we couldn't be sure if that risk was real.

That WHI Trial of estrogen-plus-progestin was stopped three years early (in 2002) because of an increased risk of breast cancer, heart disease, stroke, blood clots, and overall harm, when taking many risks and benefits into consideration. The trial of estrogen-alone (in women with no uterus) was stopped one year early in 2004 because of increased risk of stroke and no overall benefit. Looking beyond the end of the trials is important, because medications can continue to affect our bodies long after we take the last pill. It is also important to take into account the many effects that the pills might have and whether these effects differ by age.

Previous findings from the WHI trials have been reported in 117 different publications, and it is difficult to make sense of the wealth of data. This publication, for the first time, summarizes comprehensively the overall health risks and benefits for postmenopausal women who had been followed during the active treatment period (5.6 years in the *estrogen-plus-progestin* trial and 7.2 years in the *estrogen-alone* trial) and then followed afterwards for an extended period with no treatment. The total average follow-up time for these women was 13 years. These data are important because most women use hormone therapy for only a short period, but until now we have not been certain what might be the long-term consequences of previous use. For the first time, we show a side-by-side comparison of the findings in the two trials and can explore the effects by age group in detail for all the outcomes studied.

Who did you study and what did you look at?

We studied the 27,347 US women ages 50-79 who enrolled in the Women's Health Initiative Hormone Therapy Trials between 1993 and 1998. There were 16,608 women with a uterus in the trial of *estrogen-plus-progestin* and 10,739 without a uterus in the trial of *estrogen-alone*. Everyone was told to stop taking their study medication after the trials ended in 2002 (*estrogen-plus-progestin*) and 2004 (*estrogen-alone*). 81% of these women agreed to continue follow-up after the planned end of those trials.

We compared the rates of coronary heart disease including a heart attack (myocardial infarction), stroke, breast cancer, blood clots in the lungs, colorectal cancer, endometrial cancer, hip fracture, and death among women who had been assigned to the hormones and women who had been assigned to placebo study pills. These chronic diseases and death were also combined in a global index to provide an overall measure of the balance of harm and benefit. We also studied several other important outcomes such as dementia, other cancers, other fractures, diabetes, gallbladder disease, urinary incontinence, hot flashes and other symptoms, and quality of life.

What were the results of your study?

Among the many results presented in this article, the major points include:

1. Heart Disease

- Prevention of coronary heart disease was the major objective for doing the WHI Hormone Therapy Trials.
- Specific results for heart disease differed between the two trials.
 - In the *estrogen-plus-progestin* trial coronary heart disease risk increased by 80% during the first year, but was only slightly increased (by 18%) over the entire treatment period.
 - In the *estrogen-alone* trial there was no difference in rates of heart disease for women taking estrogen versus placebo during the treatment period.

- There was no overall indication that hormone therapy prevents heart disease.
- Some findings differed for women by age group and years since menopause.
 - Although not statistically significant, the rates of coronary heart disease by age show that for every 10,000 women taking *estrogen-plus-progestin* over a one-year period, there would be 5 *extra* diagnoses of coronary heart disease among women in their 50s and 19 extra diagnoses among women in their 70s. Age affected absolute risk (number of coronary events) because older women have more events.
 - The findings suggested that age mattered in the *estrogen-alone* trial: For every 10,000 women taking *estrogen-alone* over a one-year period, there would be 11 *fewer* diagnoses of coronary heart disease among women in their 50s and 7 extra diagnoses among women in their 70s. For women in their 50s taking *estrogen-alone*, the 40% reduction in heart attack compared to placebo became more pronounced when examined over the whole 13-year time period.

2. Breast Cancer

- Knowing the truth about the safety of hormone therapy in terms of breast cancer was another major objective for the trials.
- Results for breast cancer differed between the two trials.
 - During the *estrogen-plus-progestin* trial, breast cancer risk progressively increased to 24% overall. For every 10,000 women taking estrogen-plus-progestin for one year, there were 9 extra cases of breast cancer. These cancers were at a more advanced stage than in the placebo group. During the post-intervention follow-up period, the risk remained elevated.
 - In the *estrogen-alone* trial, we observed a *reduced* risk of breast cancer among women assigned to estrogen compared to placebo.

For every 10,000 women taking estrogen-alone for one year, there were 7 fewer cases of breast cancer. The effect was present but not statistically significant during the intervention phase, but it persisted after stopping, and the risk of breast cancer was significantly reduced (by 21%) over the 13-year follow-up.

- The effect of hormones on breast cancer did not differ by age group or time since menopause in either trial.
- WHI does not have data on what would have happened to breast cancer risk if the treatments had been continued longer.

3. Stroke and Blood Clots

- Both *estrogen-plus-progestin* and *estrogen-alone* increased the risk of stroke by about one-third during the trial. For every 10,000 women taking estrogen-plus-progestin, there were 9 extra cases of stroke and for estrogen-alone there were 11 extra cases of stroke.
- Both *estrogen-plus-progestin* and *estrogen-alone* increased the risks of blood clots in the legs or lungs, but the risks were greater for estrogen-plus-progestin than for estrogen-alone.
- The increased risks of stroke and blood clots seen while women were taking pills during the trial were not seen after they stopped taking the pills. These risks diminished after stopping.
- In both trials the effects of hormones on stroke and blood clots were the same in every age group.

4. Hip Fracture

- Effects on hip fracture were similar for *estrogen-plus-progestin* and *estrogen-alone*. During the trial, the women assigned to either estrogen-plus-progestin or estrogen-alone had fewer hip fractures (about a 33% reduction or 6 fewer cases for every 10,000 women treated for one year).
- An important point here is that stopping neither estrogen-plus-progestin nor estrogen-alone resulted in an astronomical increase in hip fracture

rates. After stopping, the rates slowly increased, becoming similar to those of women who did not take hormones.

- Over the 13-year follow-up, rates were still lower in women who had taken estrogen-plus-progestin than in the placebo group, while rates in women who had taken estrogen-alone were similar to those in the placebo group.

5. Colorectal Cancer

- Results differed between the two trials.
 - For *estrogen-plus-progestin* colorectal cancer risk was reduced, but the cancers were diagnosed at a more advanced stage. Differences by age were not seen.
 - *Estrogen-alone* had no overall effect on colorectal cancer risk for all age groups combined, but it *increased* risk in older compared to younger women.
- After stopping, there were no effects of hormones on colorectal cancer in either trial.

6. Endometrial Cancer

- During the *estrogen-plus-progestin* trial, there were no effects on endometrial cancer, but a benefit emerged after stopping treatment.

7. Overall Illness and Death (Global Index)

- Results differed between the two trials.
 - In women taking *estrogen-plus-progestin*, rates of illness overall (among the major illnesses we studied) and death were 12% higher than in women taking placebo pills during the trial. For every 10,000 women, there were 20 extra adverse events per year. After stopping, there were no effects on overall illness and death. These results were similar in each age group.
 - In women taking *estrogen-alone*, rates were similar to those for placebo during and after the trial. However, these results differed

importantly by age. For women taking estrogen-alone in their 50s, there were reduced risks of overall illness and death, whereas for women in their 70s there were increased risks of overall illness and death. During the trial, the rates per year showed 19 fewer illnesses and deaths (including 11 fewer deaths) per 10,000 women in their 50s taking estrogen-alone compared to 51 extra illnesses and deaths (including 26 extra deaths) per 10,000 women in their 70s taking estrogen-alone.

Were there other results that could be important to women considering hormone therapy?

Some of the more important other results were:

- ***Dementia*** was studied in women 65 and older. We found that probable dementia was increased 2-fold by estrogen-plus-progestin and to a lesser and non-significant extent by estrogen-alone. Cognitive function (memory) in younger women ages 50-54 was not affected by hormones in either trial.
- ***Diabetes*** risk decreased by 14-19% or 16-21 fewer cases per 10,000 women per year. After stopping treatment, the diabetes risk increased in the estrogen-plus-progestin trial but the risk was more neutral in the estrogen-alone trial. Overall the combined 13-year period, there were no effects of the two regimens on diabetes risk.
- ***Gallbladder disease and urinary incontinence*** both increased by 50-60% during the trials. These risks diminished after stopping treatment.
- ***Hot flashes and night sweats*** in women ages 50-54 years were decreased by 64% on estrogen-plus-progestin and 28% on estrogen-alone. After stopping treatment, these symptoms increased again in the estrogen-alone group but not the estrogen-plus-progestin group.

- **Breast tenderness** increased 2-to 4-fold during the treatment phase of the trials but disappeared after stopping treatment.
- **Joint pain** decreased during treatment and increased after stopping in both trials.
- Effects on **other symptoms and quality of life** outcomes were mixed. Mood and depression were not affected. Vaginal dryness was relieved, but vaginal discharge increased. Physical functioning improved a small amount, but headaches increased. In the estrogen-plus-progestin group vaginal bleeding (mostly spotting) was common in the first year, and the risk of hysterectomy was increased.

How does this information help women who are considering hormone therapy?

We conclude that it is important women receive individual counseling about hormone therapy, depending on their age and whether or not they have had a hysterectomy.

- **Estrogen-plus-progestin:** For women who have an intact uterus and need the addition of progestin to protect against endometrial cancer, the picture that emerges is one of risks that exceed benefits, even in younger women. These results pertain to a trial period of 5.6 years (and about 3 years of actual hormone use) and then no hormone use for 8 or more years. WHI does not have data on longer durations of use.
 - Stroke, blood clots, coronary heart disease (at least initially), and breast cancer increased, while hip fracture and colorectal cancer decreased. The global index of major chronic diseases and death showed that overall harm exceeded benefit.
 - During the trial, risk of diabetes decreased, but risks of gallbladder disease and urinary incontinence increased.
 - For women in their 50s, these risks and benefits were similar, and the global index of major chronic diseases and death was unfavorable.

- Estrogen-plus-progestin can still be used for the relief of hot flashes and night sweats in younger women, but because of the increasing risk of breast cancer over time, the duration should generally be limited to no more than 4 or 5 years.
- Estrogen-plus-progestin cannot be recommended for the long-term prevention of chronic disease.
- **Estrogen-alone:** For women who have had a hysterectomy and can safely take estrogen without progestin, the results indicate that the benefit-to-risk profile of estrogen-alone is much more favorable than estrogen-plus-progestin, especially in younger women. These results pertain to a trial period of 6.8 years (and about 4 years of actual hormone use) followed by 7 or more years without treatment. We still do not know about the risks and benefits of taking estrogen for 10 or more years, even when it is started in the 50s or close to the time of menopause.
 - Stroke and blood clot risks were elevated during treatment.
 - Breast cancer rates were not elevated overall or in any age group of women taking estrogen; in fact there may have been a small reduction in risk. This finding is a major contrast to the increased risk of breast cancer when taking estrogen-plus-progestin.
 - Risk of diabetes was decreased but risks of gallbladder disease and urinary incontinence were increased.
 - Women starting estrogen for treatment of hot flashes in their 50s have a relatively good benefit-to-risk profile. Their risks of heart attack, overall illness and death tend to be reduced, especially when compared to the increased risks in older women.
 - For women over 60, these findings did not show overall benefit for prevention and in women in their 70s there was a trend towards harm for colorectal cancer and overall chronic disease and death.
 - Estrogen-alone remains a valuable short-term treatment for relief of hot flashes and night sweats in younger women. Because of

limited information about longer term effects, treatment should generally be limited to no more than 5 years.

- However, estrogen-alone cannot be recommended for prevention of chronic disease because of the increased risks of stroke, blood clots, gallbladder disease, and urinary incontinence in addition to the lack of reliable knowledge from randomized trials about long-term effects if treatment is continued.

What does the study tell women who previously used hormone therapy and then stopped?

This is an important question, because the findings do apply to the vast majority of prior hormone users who stopped either because of the WHI findings or for other reasons. We have talked at length about the findings during the period women were taking study drugs. After women stopped taking hormones, the picture differed for estrogen-plus-progestin and estrogen-alone.

- After stopping *estrogen-plus-progestin*, the increased risks of coronary heart disease, stroke, and blood clots were no longer present, but some increased risk of breast cancer continued. We do not yet know for how long the increased risk of breast cancer continues to be a concern. On the other hand, the benefits for hip fracture and colorectal cancer diminished, as did the benefit for diabetes. Overall risks for chronic disease and death became neutral after stopping treatment. Risks for gallbladder disease and urinary incontinence lessened but did not go away after women stopped.
- After stopping *estrogen-alone*, the benefit for breast cancer observed during the treatment period became statistically significant over the entire period of follow-up. The risks of stroke, blood clots, gallbladder disease, and urinary incontinence lessened during the follow-up period, as did the benefit for hip fracture and diabetes. In women in their 50s the benefits seen for coronary heart disease, heart attack, and the global index of chronic diseases and death during the treatment period also became statistically significant during the entire period the women were followed.

These data suggest that there may be some advantage to short-term treatment followed by stopping estrogen-alone. On the other hand, we do not know what would have happened if treatment had continued beyond the 3-4 years of actual use that occurred in these trials.

What does this analysis add to what was already known?

WHI Hormone Therapy Trial findings had previously been reported in 117 different publications. This paper brings together all of the richness of these findings in one place. In some cases the findings have been updated because a few more fully investigated cases of disease have now been entered into the database. Showing the data for estrogen-plus-progestin and estrogen-alone side by side allows for the first time direct comparisons of the effects of these drugs. This paper also adds more detailed information on drug effects according to age and over a longer follow-up than before. Finally, this is the first time that the data from the extended follow-up period has been presented. Below are some examples of what we have learned from this undertaking:

- *Estrogen-alone* in women who have had a hysterectomy has a very different and more favorable profile of benefits versus risks than *estrogen-plus-progestin* in women with an intact uterus. This is particularly true for coronary heart disease (including heart attack) and breast cancer.
- Both regimens increase risks of stroke and blood clots and decrease risk of hip fracture.
- The differences between *estrogen-alone* and *estrogen-plus-progestin* are even more striking in younger women. Women in their 50s who received estrogen-alone had lower risks of heart attack, death, and combined chronic disease and death than older women. This difference by age was not observed in the trial of estrogen-plus-progestin.
- On the other hand, these analyses make it very clear that the risk profiles for both regimens are unfavorable in older women.

- The data also highlight important drug effects on common conditions that affect postmenopausal women's health and quality of life. Diabetes risk is decreased by both regimens but risks of gallbladder disease and urinary incontinence are increased.
- The data from the extended follow-up add important new information that is highly relevant to the large number of women who used hormone therapy in the past and then stopped.
 - For both regimens the increased risks of stroke and blood clots decreased after stopping, while the benefit for hip fracture was reduced or abolished.
 - Of great interest, the reduced breast cancer risk observed during the *estrogen-alone* trial period persisted and became statistically significant during the overall 13-year period. On the other hand, some increased risk of breast cancer persisted in women who had taken *estrogen-plus-progestin* compared to placebo.
 - The reduced risks of coronary heart disease, heart attack, and combined chronic disease and death seen during the *estrogen-alone* trial also persisted during follow-up and, for younger women, became statistically significant over the entire 13-year period.

What is the "take home" or "bottom line" message of this? How do these findings help women and physicians make decisions about hormone therapy?

Decisions about hormone therapy are not easy, but these findings provide the strongest evidence base available to guide personal decisions. Hormone therapy affects many organ systems in the body and changes the risks of many diseases—some in good ways, others in bad ways. Depending on hysterectomy status, age, and other individual factors, the consequences can vary dramatically.

WHI was designed to obtain reliable evidence about the use of hormone therapy to prevent chronic disease, in particular coronary heart disease, and obtain reliable information about overall risks and benefits. The findings about heart disease do not support long-term use for prevention. Taking all the effects on

chronic disease and death into account, hormone therapy is no longer considered useful for long-term prevention of chronic disease.

However, the short-term use of hormone therapy to treat the symptoms of menopause, such as hot flashes and night sweats, remain relevant because there are few effective alternatives.

Some factors that may help in making a decision about short-term treatment are:

- **Hysterectomy status**

- The majority of postmenopausal women has an intact uterus and needs to take a progestin to protect against endometrial cancer. However, the combination of *estrogen-plus-progestin* has an unfavorable risk-benefit profile. In particular the risk of breast cancer increases progressively after about 4 years of treatment. Therefore, treatment for as short a duration as possible to manage symptoms seems advisable. This regimen remains a reasonable option for women who have intolerable symptoms and who are not at elevated risk otherwise (see below).
- Women who have had a hysterectomy do not need the progestin. *Estrogen-alone* does not increase the risks of coronary heart disease or breast cancer, though there are still some risks of stroke and blood clots. Since the risk-benefit profile appears more favorable for women in their 50s and neutral for women in their 60s, the WHI data support greater flexibility about duration of therapy. However, the WHI data mostly reflect a short duration of actual use, so 5 years is a good reference point for considering how long treatment might be continued. While decisions about continuing treatment beyond 5 years can be individualized, there are no reliable trial data to support longer term use.

- **Age**

- For older women it is clear is that hormone therapy, whether *estrogen-plus-progestin* or *estrogen-alone*, is inadvisable. Firstly,

older women have higher risk of disease to start with. Any added risk from hormone therapy will be magnified in terms of numbers, as seen in the large number of excess global index of chronic disease and death in women ages 70 and older in both trials. For estrogen-plus-progestin the major contributors to this excess risk are coronary heart disease, breast cancer, stroke, and pulmonary embolism. For estrogen-alone the major contributors are stroke, colorectal cancer, and overall death. A noteworthy finding is that older women with moderate to severe hot flashes and night sweats are at very high risk of coronary heart disease if they take hormone therapy—so hot flashes and night sweats should NOT be treated with hormones in older women.

- For younger women in their 50s with hot flashes and night sweats, these results are largely reassuring. While *estrogen-plus-progestin* in younger women with an intact uterus does confer some risk of coronary heart disease, stroke, blood clots, and breast cancer, the numbers are small at least in the short term. Therefore, short-term use to manage these symptoms remains a reasonable option. The options are clearer for younger women who have had a hysterectomy, since there are no excess risks of coronary heart disease or breast cancer with *estrogen-alone*—in fact the findings are in the direction of benefit. However, small adverse effects on stroke and blood clots remain a concern. As noted previously, there are no reliable data on longer-term use of estrogen-alone.

- **Other factors**

- The health profile of an individual woman should be taken into account when considering hormone therapy. Similar to age, other risk factors could increase her risk of a particular disease whether or not hormone therapy is taken. Even a modest further increase in risk from hormone therapy could cause a worrisome increase in the numbers of excess events. For example, women with

hypertension and smokers are already at increased risk of stroke, and hormone therapy will increase that risk further. Similarly, women with a personal or family history of heart attack or blood clots will be at increased risk for heart disease with hormone therapy. Women with a high risk score for breast cancer will further increase their risk of breast cancer. On the other hand, women at high risk of hip fracture because of low bone mineral density might be more likely to consider short-term treatment with hormones for relief of menopause symptoms prior to starting first-line treatments such as bisphosphonates.

- High blood cholesterol is a special case, because the findings indicate that women with high blood cholesterol are at particularly high risk of coronary heart disease if they take hormone therapy. Similarly, women with metabolic syndrome (a combination of increased waist circumference, blood glucose, blood pressure, triglycerides, and decreased “good” cholesterol) are at particularly high risk. Conversely, women who do not have high blood cholesterol or metabolic syndrome do not appear to be at increased risk of coronary heart disease if they take hormones.
- The take-away message is to assess a woman’s individual risk status before considering hormone therapy and treat any risk factors discovered.

Why is this study important?

This study is important because when women reach the menopause, they face decisions about whether or not to use hormone therapy for treatment of hot flashes and other menopausal symptoms. When considering the use of a medicine that alters risks of many diseases, it is important to have accurate and complete information about the long-term health consequences of taking that medication. This study advances what we know about the long-term health consequences of taking estrogen with or without progestin.

Is there anything else that should be brought to light?

Another important detail about the study is that about half of the women had stopped taking their study pills before we told them to stop. So the average time of study pill adherence (taking 80% of the study pills assigned) was actually shorter than 5.6 years in the *estrogen-plus-progestin* trial – more like 3 years. And in the *estrogen-alone* trial, which lasted for 7.2 years, the duration of adherent therapy was only about 3.5 years. When you think about these findings in the context of only about 3-4 years of treatment, the results seem even more remarkable. Just a few years of treatment with hormone therapy, followed by stopping, produced all of these differences in disease rates. In analyses taking into account women discontinuing their study pills before the trial was stopped, the effects were even stronger. For example, in the estrogen-plus-progestin trial there was an increase in coronary heart disease by one-third, while there was a 15% decrease in the estrogen-alone trial. For breast cancer the estrogen-plus-progestin trial showed a 52% increase and the estrogen-alone trial a 42% decrease.

The findings for younger women on estrogen-alone are intriguing. What further research is planned to follow-up on the possible protection against heart disease?

A definitive trial in younger women, with heart attack as the outcome, is unlikely to be feasible, because very large numbers of women in their 50s would need to be enrolled (given their low rates of heart attack), making costs prohibitive. Smaller trials are looking at the effects of hormone therapy on the arteries of younger women, but thus far the results have been inconclusive. If results from small studies show evidence of benefit on the arteries, these results are still unlikely to change practice. Current practice is focused on evidence-based treatments of the risk factors for heart disease such as high blood cholesterol and high blood pressure using non-hormonal medications like statins and antihypertensives.