Overview of the Women's Health Initiative (WHI)

The Women's Health Initiative (WHI) is a long-term national health study that has focused on strategies for preventing heart disease, breast and colorectal cancer, and osteoporotic fractures in postmenopausal women. These chronic diseases are the major causes of death, disability, and frailty in older women of all races and socioeconomic backgrounds.

This multi-million dollar, 15-year project, sponsored by the National Institutes of Health (NIH), National Heart, Lung, and Blood Institute (NHLBI), involves 161,808 women aged 50 to 79, and is one of the most definitive, far-reaching clinical trials of post-menopausal women's health ever undertaken in the United States. The WHI Clinical Trial and Observational Study focused on many of the inequities in women's health research and will continue to provide practical information to women and their physicians about hormone therapy, dietary patterns, and calcium/vitamin D supplementation, and their effects on the prevention of heart disease, cancer, and osteoporotic fractures.

The WHI has two major parts: a randomized Clinical Trial and an Observational Study. The randomized controlled Clinical Trial (CT) enrolled 68,132 postmenopausal women between the ages of 50 to 79 into trials testing three prevention strategies. If eligible, women could choose to enroll in one, two, or all three of the trial components:

- **Hormone Therapy Trials (HT):** This component examined the effects of combined hormones or estrogen alone on the prevention of coronary heart disease and osteoporotic fractures, and associated risk for breast cancer. Women participating in this component took hormone pills or a placebo (inactive pill) until the Estrogen plus Progestin and Estrogen-Alone Trials were stopped early in July 2002 and March 2004, respectively. All HT participants continued to be followed without intervention until closeout.
- **Dietary Modification Trial (DM):** The Dietary Modification component evaluated the effect of a low-fat and high fruit, vegetable, and grain diet on the prevention of breast and colorectal cancers and coronary heart disease. Study participants followed either their usual eating pattern or a low-fat dietary pattern.
- **Calcium and Vitamin D Trial (CaD):** This trial evaluated the effect of calcium and vitamin D supplementation on the prevention of osteoporotic fractures and colorectal cancer. Women in this component took calcium and vitamin D pills or a placebo.

The Observational Study (OS) is examining the relationships among lifestyle, health, risk factors, and specific disease outcomes. This component involves tracking the medical history and health habits of 93,676 women. Recruitment for the Observational Study was completed in 1998 and participants were followed for 7 to 12 years.

The Fred Hutchinson Cancer Research Center in Seattle, WA, serves as the WHI Clinical Coordinating Center for data collection, management, and analysis of the WHI data. The WHI Clinical Trial and Observational Study were conducted at 40 Clinical Centers nationwide. Recruitment began in September 1993 and continued through October 1998 for the CT. The OS enrolled participants through December 1998. Closeout of the WHI occurred between April 2004 and March 2005, at which time participants were invited to join the WHI Extension Study, which involves follow-up health tracking without intervention through 2010.

The WHI Hormone Therapy Trials

Description and Overview

Between 1993 and 1998, 27,347 women aged 50 to 79 were enrolled in the WHI Hormone Therapy (HT) Trials. These trials were designed to test the effects of postmenopausal hormone therapy on women's risk for coronary heart disease, hip and other fractures, and breast cancer. The HT Trials consisted of two separate clinical trials—an Estrogen plus Progestin (E+P) Trial of combined estrogen plus progestin in women who had an intact uterus at baseline (n=16,608) and an Estrogen-Alone (E-Alone) Trial of unopposed estrogen in women who had a prior hysterectomy at baseline (n=10,739).

In the E+P Trial, participants were randomized in a 1:1 fashion to take a daily study pill with either combined hormone therapy (0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate—Prempro®) or placebo. In the E-Alone Trial, participants were randomized in a 1:1 fashion to take a daily study pill with either unopposed estrogen therapy (0.625 mg of conjugated equine estrogens—Premarin®) or placebo. After enrollment, all HT Trial participants visited a WHI study clinic once a year, during which physical and gynecological examination data were collected and reviewed for safety concerns. HT Trial participants were also required to have annual mammograms.

Following a WHI Data and Safety Monitoring Board (DSMB) review of the cumulative data, the E+P Trial was stopped early in July 2002. The DSMB determined that combined estrogen plus progestin was associated with an increased risk of breast cancer, some increased risk of cardiovascular disease, and more harm than benefit overall. The E-Alone Trial was stopped early in March 2004 because an increased risk of stroke was found in the active estrogen group with no benefit for coronary heart disease. The National Institutes of Health determined that follow-up for the remaining years would not change these overall findings, and it would not be appropriate to expose healthy women to this risk in a prevention trial.

Estrogen Plus Progestin (E+P) Trial Findings

The primary findings from the Estrogen plus Progestin Trial, "Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women," were published in the *Journal of the American Medical Association (JAMA)* in July 2002.

In July 2002, after an average 5.6 years of follow-up, participants in the E+P Trial were asked to stop taking their WHI study pills. The main findings showed that compared to women taking placebo pills:

- The number of women who developed breast cancer was higher in women taking estrogen plus progestin;
- The numbers of women who developed heart attacks, strokes, or blood clots in the lungs and legs were higher in women taking estrogen plus progestin;
- The numbers of women who had hip and other fractures or colorectal cancer were lower in women taking estrogen plus progestin; and
- There were no differences in the number of women who had endometrial cancer (cancer of the lining of the uterus) or in the number of deaths.

Another way of looking at these findings is that for every 10,000 women taking the active estrogen plus progestin pills, on average:

- 38 developed breast cancer each year, compared to 30 breast cancers for every 10,000 women taking placebo pills;
- 37 developed a heart attack each year, compared to 30 out of every 10,000 women taking placebo pills;
- 29 had a stroke each year, compared to 21 out of every 10,000 women taking placebo pills; and
- 34 had blood clots in the lungs or legs each year, compared to 16 women out of every 10,000 women taking placebo pills.

There were also some benefits. For every 10,000 women taking estrogen plus progestin pills, on average:

- 10 had a hip fracture each year, compared to 15 out of every 10,000 women taking placebo pills each year; and

- 10 developed colon cancer each year, compared to 16 out of every 10,000 women taking placebo pills.

In summary, WHI investigators found that the estrogen plus progestin combination studied in WHI does not prevent heart disease. For women taking this estrogen plus progestin combination, the risks (increased breast cancer, heart attacks, strokes, and blood clots in the lungs and legs) outweigh the benefits (fewer hip fractures and colon cancers).

Estrogen-Alone (E-Alone) Trial Findings

The primary findings from the Estrogen-Alone Trial, "Effects of Conjugated Equine Estrogen in Postmenopausal Women With Hysterectomy," were published in the *Journal of the American Medical Association (JAMA)* in April 2004.

In April 2004, after an average 6.8 years of follow-up, participants in the E-Alone Trial were also asked to stop taking their WHI study pills.

Study findings showed that compared to women taking placebo pills:

- Women taking active estrogen had more strokes;
- Women taking active estrogen had more blood clots in the legs;
- Women taking active estrogen had fewer hip fractures;
- Estrogen had uncertain effect on breast cancer; and
- Estrogen had no effect on heart attacks, colorectal cancer, and deaths.

Another way of looking at these results is that for every 10,000 women taking active estrogen pills, there were, on average:

- 12 more women with stroke compared to women taking placebo pills each year. 44 women in the active estrogen group had strokes compared to 32 women in the placebo group;
- Possibly more women with blood clots. There were more blood clots in the legs (6 more women taking estrogen compared to those taking placebo had deep vein thrombosis or DVT);
- 6 fewer women with hip fractures each year; and
- Possibly 7 fewer breast cancers. However, this effect was uncertain, and more detailed data analyses are underway.

In summary, taking into account all of the diseases studied during 6.8 years of follow-up in the WHI Estrogen-Alone Trial, no overall benefit was found and it was concluded that estrogen alone (conjugated equine estrogens) should not be used to prevent chronic disease overall, and heart disease in particular.

Conclusion

Several other findings looking at other health outcomes—colon cancer, cognitive function, urinary incontinence, diabetes, symptom experience, gallbladder disease, quality of life—in HT Trial participants have been published since the initial findings were released. WHI investigators will continue to collect data from HT Trial participants currently enrolled in the WHI Extension Study to investigate how the risks and benefits of estrogen plus progestin and estrogen alone change after women have stopped taking their WHI study pills.

The WHI Dietary Modification Trial

Description and Overview

Beginning in 1993, the Women's Health Initiative enrolled 48,835 women aged 50 to 79 in the WHI Dietary Modification (DM) Trial. The DM Trial researched the effect of a low-fat, and high fruit, vegetable, and grain diet on breast cancer, colorectal cancer, and heart disease in postmenopausal women. Women were randomized (assigned by chance) to either a Dietary Change (intervention) group or a Comparison group, making this the largest randomized clinical trial of low-fat diet ever conducted.

For the Dietary Change group, goals were to follow a low-fat dietary pattern, reducing fat intake and increasing intake of fruits, vegetables, and grains. The Comparison group followed their usual diet. The low-fat dietary pattern was not designed for weight loss and women were not asked to lose weight. DM Trial participants were followed for an average of 8.1 years, attending annual clinic visits and completing health forms. During the course of the study, Dietary Change women attended periodic group sessions with a clinic nutritionist to learn how to follow the low-fat dietary pattern.

Starting from an average of about 35 percent energy from fat at the time they joined the study, women in the Dietary Change group reduced their fat intake to 24 percent of total calories by the end of the first year. By the end of the study, their average intake was 29 percent energy from fat. Women in the Comparison group stayed at about the same level of fat intake throughout the study. The difference in fat intake between the Dietary Change and Comparison groups declined over time, from 11 percent at year one to 8 percent at the end of the study. Women in the Dietary Change group also increased their fruit/vegetable intake, but had a more challenging time with increasing grains.

Primary findings from the DM Trial on risk of breast cancer, colorectal cancer, and cardiovascular disease were published in the *Journal of the American Medical Association*, February 8, 2006.

Breast Cancer Findings

The DM Trial ended in March 2005 after an average of 8.1 years of follow-up. During that time, there were a total of 1,727 cases of invasive breast cancer in DM Trial participants. Breast cancer rates were 9 percent lower in women in the Dietary Change group compared to women in the Comparison group. This means that out of 10,000 women, 42 in the Dietary Change group and 45 in the Comparison group, on average, developed breast cancer each year. However, this difference between groups in breast cancer risk was not quite statistically significant. A difference of this size or larger could occur by chance alone, with a probability of about 7 percent, whereas scientists prefer the probability to be 5 percent or less to be considered statistically significant.

Additional analyses support the trend toward a lower risk of breast cancer among women in the Dietary Change group. Dietary Change group women who had higher levels of fat intake at the start of the study made larger reductions in fat intake than did the Dietary Change group as a whole, and had a greater reduction in breast cancer risk than did those with a lower fat intake. Also, breast cancer risk differed according to whether the breast tumor cells had receptors for estrogen or progesterone. The low-fat diet reduced blood estradiol (estrogen) levels by 15 percent. Estrogen is thought to be a risk factor for breast cancer.

Possible reasons the overall difference in breast cancer risk between the Dietary Change and Comparison groups was not statistically significant include:

- Insufficient follow-up time. Longer follow-up may be needed to see a significant reduction in breast cancer. Because diet can have lasting effects, the continued follow-up of DM Trial women in the WHI Extension Study is expected to provide the information needed for a more conclusive test of the low-fat dietary pattern.
- Dietary fat intake not low enough. Greater reductions in fat intake may be needed to achieve a significant effect. Dietary Change group participants did not lower their fat intake to the extent that scientists had hoped they would. It is possible that a lower intake than participants were able to achieve would be needed to see a significant effect on breast cancer risk.

The current findings from the WHI DM Trial are not clear enough to recommend a lower fat intake for most women to prevent breast cancer, but women who are eating a high fat diet may benefit by reducing fat intake. Women should continue to take steps to reduce their risk of invasive breast cancer, such as having regular mammograms and breast examinations.

Colorectal Cancer Findings

Results from the WHI DM Trial showed that the low-fat dietary pattern did not reduce the risk of colorectal cancer. In DM Trial participants, there were 480 cases of colorectal cancer, with similar rates in the Dietary Change (on average, 13 per 10,000 women per year) and Comparison (12 per 10,000 women per year) groups. The 8 percent difference (increase) in risk was not close to being statistically significant. The results were similar when looking at where the cancer occurred—the entire colon, upper or lower colon, or rectum. The number of women reporting polyps was 9 percent lower (significant) in the Dietary Change group (on average, 216 per 10,000 per year) than the Comparison group (235 per 10,000 per year).

Women who closely followed the low-fat dietary pattern were not found to have more benefit than those who did not, nor did women who had started with higher fat intakes at the beginning of the study show greater benefit. The data did suggest a possible reduction in colorectal cancer risk in Dietary Change women who were either taking aspirin or were on combination estrogen plus progestin hormone therapy; however, these findings may have occurred by chance.

Overall, these results suggest that a low-fat dietary pattern, with increased fruits, vegetables, and grains, is not likely to prevent colorectal cancer in postmenopausal women followed for 8 years. The reduction in polyps suggests that a benefit for colorectal cancer risk might be found when women are followed for a longer period of time.

Cardiovascular Disease (Heart Attack and Stroke) Findings

To study the effect of the WHI low-fat dietary pattern on heart disease, researchers looked at how many participants had a heart attack, heart bypass surgery, or other heart procedures (stent or balloon angioplasty). They found that the low-fat dietary pattern did not reduce the risk of heart disease, although the intervention was not designed specifically to reduce heart disease. In WHI DM Trial participants, there were 1,422 cases of coronary heart disease (fatal and non-fatal), with similar rates in the Dietary Change (on average, 35 per 10,000 women per year) and the Comparison (on average, 36 per 10,000 women per year) groups. The 2 percent difference (decrease) in risk of coronary heart disease was not statistically significant. When women who had a history of heart disease when they joined the study were removed from the analyses, there was a 6 percent reduction in heart disease, but this was not statistically significant. There was also no statistically significant effect on stroke.

There were, however, small favorable effects of the low-fat dietary pattern on some risk factors. All types of fat (saturated, mono-unsaturated, and poly-unsaturated) in the diet were reduced. There were small but significant improvements in body weight, low-density lipoprotein (LDL) cholesterol, diastolic blood pressure, and Factor VIIC (a blood clotting factor).

One important finding from the DM Trial is that a low-fat, high carbohydrate diet does not necessarily increase body weight, blood triglycerides, or indicators of increased risk of diabetes such as blood glucose or insulin levels.

There was no greater effect of the intervention on heart disease in women who participated in most of the study activities, or in women who started with higher fat intakes. Those who reached the lowest levels of saturated fat or trans fat and the highest level of fruits and vegetables had greater reductions in low-density lipoprotein (LDL) cholesterol and heart disease. However, because these analyses involved smaller groups of women, the findings are not as reliable as those which include the entire group.

The most likely explanation for the lack of a statistically significant effect on heart disease is that the dietary pattern reduced all types of fat, in order to test whether reduction in total fat prevents breast cancer. It was anticipated that reducing total fat would also lead to reductions in saturated fat with a consequent lowering of blood cholesterol. The lowering of blood cholesterol in Dietary Change participants was less

than anticipated, and therefore there was no effect on heart disease. A diet designed to reduce risk of heart disease would focus specifically on reducing saturated and trans fats, and would not reduce polyunsaturated and monounsaturated fats. Studies have shown that such a diet leads to lower blood cholesterol and reduces the risk of heart disease.

A low-fat dietary pattern is consistent with current national dietary guidelines and remains an option for generally healthy postmenopausal women. The Dietary Guidelines for Americans 2005 remain a healthy option for prevention of heart disease, especially when accompanied by physical activity and weight management. These guidelines include a mainly plant-based diet rich in vegetables, fruit, whole grains, nuts, beans, low-fat dairy products, and fish. The guidelines suggest consuming 20 to 35 percent energy from fat, with reductions in saturated and trans fats, and most fats coming from polyunsaturated and monounsaturated sources, such as vegetables and nuts. The guidelines also recommend five to nine one-half-cup servings of fruits and vegetables and three or more servings of whole grains daily. To link to the current guidelines, go to www.healthierus.gov/dietaryguidelines.

Conclusion

A low-fat dietary pattern may have some potential for reducing breast cancer risk, particularly in women consuming a high fat diet. However, the current findings are not strong enough to make a recommendation that most women should focus on low-fat dietary patterns to prevent breast cancer. These findings indicate that a low-fat diet provided no protection from colorectal cancer and should not be recommended for that purpose. The low-fat diet did not specifically focus on reducing saturated fat, had only a small effect on blood cholesterol, and did not reduce the risk of heart disease. However, the WHI results suggest that women who achieved greater reductions in saturated fat or trans fat, and higher intakes of fruits and vegetables, might experience a reduced risk of heart attacks. Overall, the WHI low-fat dietary pattern is not inconsistent with the USDA Dietary Guidelines for Americans 2005 and remains a healthy option for postmenopausal women in general.

The WHI Calcium and Vitamin D Trial

Description and Overview

Between 1995 and 2000, participants already enrolled in the WHI Hormone or Dietary Modification Trials were invited to join the WHI Calcium and Vitamin D (CaD) Trial. A total of 36,282 WHI participants joined the CaD Trial, making this the largest randomized clinical trial of calcium and vitamin D supplements ever done. The WHI CaD Trial was designed to determine the effects of calcium and vitamin D supplements on the risks for hip fractures and colorectal cancer in postmenopausal women. The effect of CaD on other fractures was also studied.

When women joined this study, a computer program assigned half of the participants, by chance alone, to be in the group given study pills containing active calcium and vitamin D. The other half were given an inactive placebo. All CaD participants were asked to take one study pill twice a day (total of two pills each day). The women could choose whether they wanted to take a chewable or "swallow-able" form of study pill, and they could switch between these two forms during the study. For those in the active group, each pill contained 500 mg of calcium carbonate and 200 IU of vitamin D3, for a total of 1000 mg of calcium and 400 IU of vitamin D in their study pills each day. The placebo study pills contained no calcium or vitamin D. Participants in both the active and placebo groups were allowed to take limited amounts of calcium and/or vitamin D supplements on their own.

CaD Trial participants were followed for an average of 7 years. They visited a WHI study clinic once a year. Every 6 months they answered questions about their health and about side effects related to study pills to monitor their safety. Participants were also asked to continue their other WHI activities (in the Hormone or Dietary Trials) as before. When the study ended in March 2005, most participants (75 percent) were still taking their study pills.

Primary findings from the CaD Trial on risk of fractures and colorectal cancer were published in the *New England Journal of Medicine*, February 16, 2006.

Fracture Findings

Over an average of 7 years, 374 CaD Trial participants had hip fractures. The study found that for every 10,000 women taking active CaD supplements each year, on average 14 had a hip fracture, compared to 16 hip fractures for every 10,000 women taking placebo pills each year. Overall, women taking active CaD had 12 percent fewer hip fractures than those taking placebo. However, this difference was smaller than expected and could have happened by chance. Women taking active CaD supplements also had 4 percent fewer total fractures (overall, including all types of fracture combined). This difference was not statistically significant.

When scientists looked only at women who took their assigned study pills regularly, they found that women taking the active supplements had 29 percent fewer hip fractures than those taking placebo (on average, 10 compared to 14 cases per 10,000 women each year), which was a statistically significant difference.

Among women 60 years of age and older, those assigned to active CaD had a 21 percent decreased risk of hip fracture compared to women 60 and over who were taking placebo (17 compared to 23 cases per 10,000 women each year). This difference was statistically significant. Further research is needed to understand the findings about differences by age.

The effect of the study pills did not differ by how much calcium women were taking or eating on their own at the time they joined the study. The findings also did not differ depending on women's levels of vitamin D measured in the blood.

Women assigned to active CaD had 17 percent more kidney stones than women on placebo (an average of 34 compared to 29 cases per 10,000 women each year). Gastrointestinal side effects such as constipation, bloating, and gas did not differ between the two groups.

During the study, participants at three of the WHI clinical centers had regular bone mineral density scans. Analysis of these scans showed that women taking active CaD supplements had significantly higher hip bone density than those taking placebo, but the difference was small (1 percent).

There are several possible explanations why participants in the active CaD group had higher bone density, but no significant difference in hip fractures. It may be that the effect of CaD supplements on bone mineral density is not enough to show a large effect on actual hip fractures. Also, many CaD Trial participants were already at a low risk for hip fractures when they joined the study and that might make finding differences less likely. Many participants had high personal calcium intake, they had higher than average weights, and many were taking postmenopausal hormone therapy. All of these factors decrease a woman's risk for hip fractures. Finally, the dose of vitamin D (400 IU) may have been too low to affect hip fracture risk. More studies are needed to determine if higher amounts of vitamin D supplements will help to prevent hip fracture.

This study found that calcium plus vitamin D supplements improved hip bone density compared to placebo and lowered the risk of hip fractures in some groups. The current national recommendations say that women over 50 years should have daily total calcium intakes of 1000 to 1200 mg/day and vitamin D intakes in the range of 400 to 600 IU.

Colorectal Cancer Findings

Over an average of 7 years of following 36,282 women in the WHI Calcium and Vitamin D Trial, a total 322 women were diagnosed with invasive colorectal cancer. When scientists compared the colorectal cancers in participants who took the active CaD supplements with those who took placebo pills, they found no differences in the rate of colorectal cancer diagnosis. The study found that for every 10,000 women assigned to take the active CaD, on average each year 13 were diagnosed with colorectal cancer compared to 12 colorectal cancers for every 10,000 women taking placebo pills.

There were also no differences between the two groups in the types of colorectal cancers themselves. For example, the cancer was not more or less advanced in one group compared to the other. In addition, there were no differences in the number of colon polyps reported by participants assigned to the active CaD group compared to the placebo group.

When scientists limited the analysis to only those taking most of their study pills, the findings about colorectal cancer did not change. Also, when scientists looked at participants' personal calcium and vitamin D intakes, the colorectal cancer findings were similar—there were no differences between the active supplement and placebo groups.

Some scientists estimate that it may take 10 to 20 years for colorectal cancer to develop. The WHI CaD Trial was limited to an average of 7 years and no women were followed for more than 10 years. It is possible that longer follow-up would be needed to find any impact of calcium and vitamin D on colorectal cancer. The WHI has an ongoing study to follow the participants 5 more years to see if findings change with longer follow-up.

The findings from the WHI Calcium and Vitamin D Trial suggest that taking calcium and vitamin D supplements for an average of 7 years will not prevent colorectal cancer and, at this time, calcium and vitamin D should not be recommended for the prevention of colorectal cancer. However, it is possible that taking CaD for a longer period of time could be of benefit.

Conclusion

We now have some very valuable answers to questions about the effects of calcium and vitamin D on the health of postmenopausal women. We know that the use of these supplements for an average of 7 years slows loss of bone density and may help protect against hip fractures. We also know that these supplements, in the dosage used for this study and for 7 years of duration, do not prevent colorectal cancer in healthy postmenopausal women.

Because the effects of CaD supplements on hip fractures and colorectal cancer may take a long time to show up, continuing to follow participants in the WHI Extension Study can help us learn more about the longer-term effects of CaD supplementation.

The WHI Observational Study

Description and Overview

Between 1994 and 1998, 93,676 women aged 50 to 79 enrolled in the WHI Observational Study (OS), making it one of the largest observational studies ever done. The OS complements the Clinical Trial (CT) by assessing new risk indicators and biomarkers for disease. The OS cohort is comprised of women who were either ineligible or unwilling to participate in the CT. OS women were followed for between 6 and 10 years, depending on when they enrolled in the study.

The major clinical outcomes of interest in the OS are coronary heart disease, stroke, breast cancer, colorectal cancer, endometrial cancer, ovarian cancer, osteoporotic fractures, diabetes, and total mortality. Routine follow-up activities consisted of annual mailings to obtain health outcomes and exposure information, and a clinic visit at 3 years after enrollment to update selected baseline data, obtain additional risk factor data, and collect a blood specimen. After an average 7.6 years of follow-up, more than 94 percent of participants were still providing annual health outcomes data.

Observational Study Findings

A number of scientific papers based on data provided by OS participants have been published over the past several years. These findings have covered a wide variety of health topics, including physical activity, high blood pressure, cancer screening, sleep habits, and mammogram use, just to mention a few. Described below are the results of some of the published scientific papers on OS participants.

Physical Activity and Cardiovascular Disease. WHI researchers looked at data from OS participants to study the links between total physical activity, walking, and vigorous exercise and risk of heart disease. They found that increased physical activity was strongly related to a lower risk of heart disease. White and African American women both had similar decreases in heart disease risk (30 to 40 percent) with increasing activity. Strenuous exercise and walking were associated with similar decreases in risk. Ethnicity, age, or body mass index did not affect this relationship. This research suggests that walking may be as beneficial as more strenuous exercise in helping protect the heart. *New England Journal of Medicine, 2002.*

Leukocyte Count and Cardiovascular Disease. WHI Investigators studied the role of a person's white blood cell (leukocyte) count as a predictor of risk for health events associated with cardiovascular disease, such as heart disease, heart attack, stroke, and death. White blood cell (WBC) counts were measured in OS women at the time they enrolled in the study. Investigators found that women with WBC counts above 6.7 had an elevated risk for a nonfatal heart attack, stroke, and death from coronary heart disease, compared with women with lower WBC counts. Even adjusting for another marker of inflammation, C-reactive protein, the WBC count was still an independent predictor of heart disease. *Archives of Internal Medicine, 2005.*

Hypertension and Its Treatment. Investigators looked at blood pressure data from WHI participants to see how many had hypertension and how it was being treated and controlled. About 38 percent of women had hypertension (equal to or above 140/90 mm HG) or were on medication for hypertension. Of those with hypertension, about two-thirds were being treated with medications, but only about one third of hypertensive women had their blood pressure under control. African American and Asian women were more likely to have hypertension than white or Hispanic women, but less likely to have it under control. Twice as many women over age 70 had hypertension (53 percent) compared to women aged 50 to 59 years (27 percent). Older women, who are most at risk for stroke and other consequences of high blood pressure, were also less likely to have their blood pressure under control. *Hypertension, 2000.*

Depression and Cardiovascular Disease. Data from OS women were analyzed to understand more about depression and cardiovascular diseases, such as heart attack, stroke, and high blood pressure. Investigators found that when they joined the study, about 16 percent of the OS women were depressed and had a higher risk for cardiovascular disease than those who were not depressed. *Archives of Internal Medicine, 2005.*

Breast Cancer and Body Weight. WHI investigators looked at weight, weight distribution, and weight

gain in OS participants who did and did not develop breast cancer in the 2 to 4 years after menopause; data were analyzed separately for those who used hormone therapy (HT) and those who did not. Among women who had never used HT, heavier women had a greater risk of getting breast cancer than slimmer women. The amount of weight gained over a woman's lifetime also predicted risk, in that greater weight gains resulted in greater risk. Weight distribution was not related to breast cancer risk in this study. For women who had used HT, none of these factors (weight, weight gain, or weight distribution) appeared to affect breast cancer risk. *Cancer Causes and Control, 2002.*

Physical Activity and Breast Cancer. WHI investigators examined physical activity and breast cancer rates in OS women, and confirmed that breast cancer risk was lower in women who were more active. Women who engaged in 1.25 to 2.5 hours per week of brisk walking had an 18 percent lower risk of breast cancer compared with inactive women. The risk was even lower for women who walked briskly for 10 hours or more per week. This study suggests that increased physical activity is related to reduced breast cancer risk, that longer duration of exercise provides more benefit, and that the activity itself need not be strenuous. *Journal of the American Medical Association, 2003.*

Physical Activity and Diabetes. Although studies in the past have shown that physical activity lowers a woman's risk for diabetes, the research has focused mainly on white women. WHI researchers looked at the effects of physical activity on risk for diabetes in African-American, Hispanic, Asian, and white women in the OS. This analysis showed that physical activity did lower diabetes risk in white women, but a lower risk was not as clear in other racial/ethnic minority groups. *American Journal of Preventive Medicine, 2005.*

Insurance Coverage and Cancer Screening. WHI investigators looked at health insurance coverage and screening for breast, cervical, and colorectal cancer among groups of OS participants. The data showed that women with prepaid health insurance were more likely to have mammograms, Pap smears, and colorectal cancer screening than were women without pre-paid health insurance. Overall, more than 80 percent of OS participants reported having a mammogram within the last two years and a pap smear within the last three years. However, only about 60 percent reported having colorectal cancer screening within the last five years. *Preventive Medicine, 2000.*

Sleep Habits of Postmenopausal Women. Looking at data provided by WHI participants at the beginning of the study, investigators found that white women reported an average of 6.9 hours of sleep each night, while minorities reported less (e.g., Hispanic women reported an average of 6.5 hours per night). Only 27 percent of women overall reported sleeping 8 hours or more each night. Waking up several times a night and waking up earlier than planned was reported by the majority of participants. Napping increased dramatically in postmenopausal women from age 50 to 54 and age 75 to 79. Those sleeping 9 or 10 hours and those sleeping 6 hours or less were more obese and more depressed than those sleeping 7 or 8 hours. *Clinical Journal of Women's Health, 2001.*

Inflammatory Biomarkers and Heart Disease. WHI scientists looked at the effect of postmenopausal hormone therapy on C–reactive protein (CRP) and cardiovascular risk in WHI participants. They looked at 304 OS women who had developed coronary heart disease and compared them to 304 women matched by age, smoking status, ethnicity, and follow-up time who had not developed heart disease. Researchers found that levels of CRP were higher among women with heart disease than women without heart disease. As expected, current use of hormone therapy was associated with higher CRP levels. However, they found that the baseline level of CRP in the blood at the time the women joined the study was a predictor of heart disease risk, whether or not the women used hormone therapy. *Journal of the American Medical Association, 2002.*

Social Support and Breast Cancer Screening. Data from OS participants were analyzed to learn more about breast cancer screening and different kinds of social support (such as having people in your life who support you emotionally or help in other ways). Researchers found that women who have emotional support are more likely to have repeat mammograms and breast exams, but having help with daily routines does not increase breast cancer screening. *Health Psychology, 2005.*

Design and Methods

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Author financial disclosure statements are listed in the relevant publications.