”Risks and Benefits of Estrogen Plus Progestin in Healthy, Postmenopausal Women: Principal Results from the Women's Health Initiative Randomized Controlled Trial” (2002), by Jacques Rossouw, Garnet Anderson, Ross Prentice, Andrea LaCroix, Charles Kooperberg, Marcia Stefanick, Rebecca Jackson, Shirley Beresford, Barbara Howard, Karen Johnson, Jane Morley Kotchen, and Judith Ockene

In 2002, the Writing Group for the Women's Health Initiative Investigators published the article ”Risks and Benefits of Estrogen Plus Progestin in Healthy, Postmenopausal Women: Principal Results from the Women's Health Initiative Randomized Controlled Trial” in The Journal of the American Medical Association. In the article, the authors report on the Women's Health Initiative, which was a study initiated by the National Institutes of Health to determine the effects of hormone therapy in postmenopausal women, or women whose menstrual cycles have stopped, from the ages of fifty to seventy-nine. The researchers attempted to determine if a link existed between a common type of hormone therapy, a combination of estrogen and progestin, and prevalent diseases in postmenopausal women, including cardiovascular disease and cancer. As reported by the authors in their article, the researchers discontinued the study after five years when they found that there were many risks associated with the use of estrogen plus progestin hormone therapy, including increased risks of breast cancer and heart diseases.

During the twentieth century, physicians began using hormone therapies to treat women hormonal deficiencies. One of the first hormone therapies was known as Premarin, a form of estrogen supplementation derived from the urine of pregnant horses, and was used primarily in postmenopausal women beginning in the 1960s. Doctors prescribed Premarin among other drugs as a means to prevent heart disease and cancer in their female patients. Between 1960 and 1975, annual estrogen prescriptions doubled in female patients. Women used it to combat symptoms associated with menopause, including flushing, insomnia, low libido, and weight gain. However, little was known about the long-term effects of hormone therapy, until researchers conducted clinical trials to study that at the end of the twentieth century.

In 1991, Bernadine Healy, the first female director of the National Institutes of Health in Bethesda, Maryland, established the Women's Health Initiative to study major causes of death in postmenopausal women. The researchers of the Women's Health Initiative defined postmenopausal women as women age fifty to fifty-four who had not had a menstrual cycle in at least twelve months, women age fifty-five and above, up to seventy-nine years old, who had not had a menstrual cycle in six months, women who had had their uteri removed, and women who had begun to take postmenopausal medications.

The Women's Health Initiative included three clinical trials and one observational study. ”Risks and Benefits of Estrogen Plus Progestin in Healthy, Postmenopausal Women: Principal Results from the Women's Health Initiative Randomized Controlled Trial,” authored by the Writing Group for the Women's Health Initiative Investigators, reported on the results of one of the clinical trials. The

Writing Group included Jacques Rossouw, Garnet Anderson, Ross Prentice, Andrea LaCroix, Charles Kooperberg, Marcia Stefanick, Rebecca Jackson, Shirley Beresford, Barbara Howard, Karen Johnson, Jane Morley Kotchen, and Judith Ockene. Those researchers were responsible for compiling the data and conducting the primary clinical study that was the focus of ”Risks and Benefits.” They all contributed to the final report.

The purpose of the clinical trial, according to the authors, was to determine the risks and benefits of the use of hormone therapy. Hormonal therapy is the supplementation of naturally occurring hormones that decline during menopause in women. At the time of the study's commencement, hormone therapy was commonly used to treat symptoms of menopause, such as hot sweats and vaginal dryness. Additionally, hormone therapy was used to prevent the incidence of heart disease, breast and colorectal cancer, and bone fractures in postmenopausal women. To determine if there were any negative effects of hormone therapy on women, the researchers involved in the WHI enrolled over 16,000 postmenopausal women in the study between 1993 and 1998. The trial studied the effects of estrogen and progestin, which were the specific hormones commonly used together in hormone therapy. Estrogen is a female sex hormone associated with the menstrual cycle that is excreted by the ovary. Progestin is a synthetic hormone that is the artificial equivalent to the female sex hormone progesterone and is responsible regulating the uterine lining.

”Risks and Benefits” was organized into four parts, an introduction section, a methods section, a results section, and a further comments section. Within the introduction, the authors detail the purposes and background of the WHI and the hormone therapy clinical trial parameters, and they mention that the primary purpose of the study was to determine the safety of hormone therapy. In the methods section, the authors describe how they chose participants based on criteria including overall good health, age, and absence of menstruation. They set up the trial to have an experimental group receive the hormone therapy and to have a placebo group receive a placebo. In the results section, the Writing Group documents the outcomes of the study, including their findings that the use of hormone therapy may result in an increased risk of breast cancer of up to twenty-six percent of women, and an increased risk of cardiovascular disease of twenty-nine percent of women. In the final comments section, the authors describe their conclusions that hormone therapy increases a postmenopausal woman's likelihood of developing a chronic disease. In ”Risks and Benefits,” the authors concluded that there were more risks than benefits associated with the use of hormone therapy in postmenopausal women in regard to breast cancer and heart disease risks.

The authors highlight the purpose of the study in the introduction section, stating that they wanted to determine the direct effects of hormone therapy on heart disease and cancer in women, and whether it could be safe to use to prevent those diseases. The research team first provide a brief overview of the study, along with an immediate disclaimer that the particular study was supposed to last fifteen years but was stopped after five years due to unforeseen health risks as a result of the treatment. While 168,000 women were potential candidates for the study, the researchers developed baseline qualities each participant had to have to maintain a cohesive population sample for the study. Those qualities included a woman's previous experience with heart disease or cancer and prior usage of hormone therapy unrelated to the study.

The authors also discuss the treatment groups. In the original experimental group, healthy postmenopausal women were given estrogen plus progestin hormone therapy or estrogen only hormone therapy. The authors note that they changed the experimental group to only include the estrogen plus progestin therapy after they obtained results showing that the estrogen-only therapy wasn't feasible. The placebo group included healthy women who received a sugar pill.

The authors then describe the goals of the study in the context of the aims for the Women's Health Initiative. They distinguish ”Risks and Benefits” as being the first study to determine the effects of hormone therapy on women before they ever showed signs of coronary heart disease. That was an important marker because the team wanted to determine if hormone therapy could prevent or cause the disease. The authors describe other illnesses that commonly affect postmenopausal women, including osteoporosis and breast cancer, which are also related to hormones. The authors emphasize that one of the main goals of the study was to determine if hormone therapy could prevent postmenopausal women from developing those diseases. To compile their evidence in a cohesive manner, they organized the final report's section on methods into separate categories.

The authors divide their methods section into eight subsections. The first three subsections focus on the selection of patients and the study's randomization techniques. To be selected for the study, women had to be between the ages of fifty and seventy-nine and had to have been considered post-menopausal at the time. The authors describe other factors that affected a woman's likelihood of being selected for the study. Those factors included the potential for the patient's relocating and the woman's previous disease history. The researchers selected women who had not taken any hormonal medications for three months before the study began to ensure that it was the trial's hormone therapy causing any observable effects. The researchers designated eligible women to either receive the combined estrogen-progestin hormone therapy pill or a placebo pill, which served as a control for the experiment. The researchers kept in contact with the women throughout the study, and assessed their adherence to the medication protocol and any side effects the women were experiencing. In order to measure specific health outcomes of the participants, the researchers required that the participants receive annual mammograms along with electrocardiograms every three years. The mammogram is a type of x-ray used to diagnose breast cancer, and an electrocardiogram is a test that diagnoses different forms of heart disease.

The authors then detail their use of statistics and safety monitoring in determining negative health outcomes throughout the study in the remaining five sections of the methods. They used statistical analysis to determine the significance of change seen in health outcomes among the women who had received the hormone therapy and the women who had received the placebo. They defined negative outcomes as being an occurrence of cancer, heart disease, or osteoporosis-related bone fracture that may have been caused by the use of hormone therapy. Some women stopped participating in the study before it concluded, because they had developed cancer or blood clots in their legs. Other women temporarily discontinued the medications for a short period of time if they had encountered health problems such as a heart attack or stroke. The researchers derived their results after five years of experimentation, beginning the study in 1993.

In the results section of the article, the authors discuss the weaknesses of the study, the final outcomes, and the effects of hormone therapy on heart disease and cancer. They state that almost half of all the women involved in both the treatment group and the placebo group had to stop taking their therapies for either an acute illness or voluntary withdrawal from the medication regimen. Of all the participants, 2.7 percent died before the authors ended the trials. Dropout rates and death rates exceeded what the authors had anticipated at the start of the study, meaning they had less data to use than they originally expected.

The authors further discuss the results of the study. Women in the estrogen-progestin treatment group experienced lower cholesterol levels than women in the placebo group. However, the authors also state that women in the treatment group were twenty-nine percent more likely to experience a cardiovascular event such as a stroke or heart attack than the women receiving the placebo. The authors mention that women in the treatment group experienced a twenty-eight percent increased risk for invasive breast cancer. They state that it was those differences that led to the premature end of the clinical trial in 1998. Women in the treatment group experienced a thirty-seven percent reduction in colorectal cancers and no difference in lung cancers. The authors state that bone fractures were reduced by ten percent in the women in the treatment group. The authors conclude that the participants' non-adherence to the study protocols and the increased amount of dropout and death rates may have affected the conclusions of the study.

In the final section of ”Risks and Benefits,” the authors describe that there were more negative outcomes associated with the study than positive outcomes. The team reiterate one of the goals of the study was to determine if hormone therapy using estrogen and progestin could be used to prevent coronary heart disease, cancer, and bone fractures. The authors note that the use of estrogen plus progestin hormone therapy increased the risk of heart disease and breast cancer in all racial and age groups. However, they also note that it reduced risks of colorectal cancers and bone fractures. The researchers conclude that risks associated with the use of estrogen plus progestin hormone therapy hormone therapy outweigh the benefits, which led them to end the trial after five years, ten years earlier than they originally anticipated. The researchers call for further observation before reporting on patient mortality associated with the use of hormone therapy.

As of 2017, ”Risks and Benefits” had been cited over 12,200 times. Historian Elizabeth Siegel

Watkins, who studies the history of hormone therapy, cited that over half of the women who had been taking the common hormone therapy drug, Premarin, ceased their treatments after the results of the study were published in 2002. A further study by the Women's Health Initiative found that estrogen plus progestin hormone therapy also led to an increased risk of stroke and dementia.

In 2013, National Public Radio interviewed Joann Manson, director of the Women's Health Initiative. Manson stated that women should not use hormones for chronic disease prevention, but that younger women with moderate or severe symptoms of menopause may consider hormone therapy as they are less likely to experience negative side effects. Manson also stated the purpose of the clinical trials was not to dissuade women from ever using hormone therapy, but to determine the effects of hormone therapy as a treatment for chronic disease prevention.

Sources

1. Parker-Pope, Tara. ”The Women's Health Initiative and the Body Politic.” The New York Times, April 9, 2011. http://www.nytimes.com/2011/04/10/weekinreview/10estrogen.html (Accessed July 2, 2017).
2. Shumaker, Sally A., Claudine Legault, Stephen R. Rapp, Leon Thal, Robert B. Wallace, Judith K. Ockene, Susan L. Hendrix et al. ”Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial.” Journal of American Medical Association 289 (2003): 2651–2662. http://www.npr.org/sections/health-shots/2013/10/04/229171477/the-last-word-on-hormone-therapy-from-the-womens-health-initiative (Accessed July 2, 2017).
3. Shute, Nancy. ”The Last Word On Hormone Therapy From the Women's Health Initiative (interview with Joann Manson).” National Public Radio, October 4, 2013. http://www.npr.org/sections/health-shots/2013/10/04/229171477/the-last-word-on-hormone-therapy-from-the-womens-health-initiative (Accessed July 10, 2017).
4. Watkins, Elizabeth Siegel. The Estrogen Elixir: A History of Hormone Replacement Therapy in America. Baltimore: Johns Hopkins University Press, 2007.
5. Writing Group for the Women's Health Initiative Investigators. ”Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial.” Journal of the American Medical Association 288 (2002): 321–33. http://jamanetwork.com/journals/jama/fullarticle/195120 (Accessed July 2, 2017).