Women’s Health Initiative: Research That Keeps on Giving

Three decades in, longstanding “team science” study continues to provide answers to health issues facing older women.

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When it comes to “team science,” the Women’s Health Initiative may be, as they say in the world of sports, the GOAT — the Greatest Of All Time.

Nationally announced in 1991 and backed by $625 million in federal funding from the National Institutes of Health, the WHI is the largest women’s health study ever conducted on the planet, recruiting more than 161,000 women ages 50 to 79 and engaging more than 5,000 scientists from the U.S. and beyond.

Some of those scientists, like Garnet Anderson, PhD, who leads the Public Health Sciences (PHS) Division at Fred Hutch Cancer Center, have been with the study since its inception. A renowned biostatistician, Anderson is the principal investigator for the WHI Clinical Coordinating Center, run by Fred Hutch. She’s also the holder of the 40th Anniversary Endowed Chair.

“There’s a reason why we’ve won two Team Science awards [from the American Association for Cancer Research, AACR, and the Association for Clinical and Translational Science, or ACTS],” Anderson told gathered investigators at the annual WHI meeting held May 1 and 2 on the Fred Hutch campus in Seattle. “WHI is definitely ‘team science,’ and I want to thank all the people who’ve helped create these data over the years, from our dedicated women participants to the people who do the data collection, the outcomes staff and adjudicators, our software engineers and statisticians and our administrative folks. All of you have participated in this and you all make it possible for everyone to have access to these data.”

And the data — painstakingly gathered, organized, analyzed and updated for the last 30 plus years — is what makes the WHI one of Fred Hutch’s outstanding research initiatives, so very valuable.

“Be part of the answer”

The WHI was created to fill in some of the knowledge gaps that existed in women’s health, specifically about chronic conditions like heart disease, cancer and osteoporosis, a big contributor to bone fractures and the mortality of older women.

Up until then, women had been primarily left out of research; the WHI was designed to make up for lost time — and data.

“Back in the late ’80s and early ’90s, the attitude in science was different,” said WHI principal staff scientist Lesley Tinker, PhD, who left her nutrition research at UC Davis in California in 1992 to join the newly established data coordinating center in Seattle. “You were encouraged to study everything in men because it was less complicated. You didn’t have to deal with all the hormonal issues that exist for women.”

Recruitment for the WHI took a few years, but participation was astonishingly high; all told, 161,808 postmenopausal women enrolled via 40 separate WHI clinic sites around the country.

Fred Hutch turns 50!

Take a look back at half a century of leading-edge research and compassionate care.

“We did millions of mass mailings to population-based lists, and we had a couple of celebrities who helped bring attention to it,” Anderson said in a PHS grand rounds lecture on WHI’s impact held in March. “The idea of legacy really resonated with women. They were doing something for their daughters and granddaughters. We were lucky it was an altruistic approach, because we only had $1 per person per year for any incentive, which doesn’t go very far.”

The women signed on to “be part of the answer,” especially for the longstanding questions addressed in the three randomized prevention trials: a two-arm study on hormone replacement therapy, widely prescribed at the time and thought to improve women’s heart health; a study on vitamin D and calcium supplementation and a diet modification trial investigating low-fat diets.

What impact — good, bad or ugly — did these “exposures” have on older women’s health, the investigators wanted to know.

The researchers also recruited women into a large observational study, tracking their medical histories and health habits over time. Researchers randomized 68,000 women to one, two or all three clinical trials. They enrolled more than 93,000 women in the observational study.

Since 2005, when the initial protocol ended, the WHI has continued via extension studies, including a 2010 extension that enrolled an additional 93,500 women. More than 42,000 participants, ages 78-108, are still actively involved.

As for findings, the WHI has produced more than 2,400 scientific publications. Read through the WHI's scientific studies.

"We wouldn't know if they hadn't started WHI"

The WHI is best known for its hormone trial, especially the arm that stopped early, in 2002, when combined hormone replacement therapy was found to increase risk of breast cancer, coronary heart disease, stroke and blood clots.

But the knowledge gained goes far, far beyond that.

Data from the WHI have paved the way for numerous advancements in cancer and chronic disease prevention and treatment, from creating more accurate polygenic risk scores to assessing T-cell response in colorectal cancers to demonstrating in long-term follow-up analysis that hormone therapy's effects on cardiovascular disease and fractures diminish rapidly after stopping the pills, to proving that a low-fat diet doesn't impact cancer incidence but does reduce long-term breast cancer mortality, to showing that calcium and vitamin D supplements reduce cancer mortality and increase cardiovascular mortality in equal measures.

At the recent annual meeting, researchers shared new insights on everything from blood-based biomarkers for Alzheimer's disease and dementia to environmental epigenetics and chronic disease risk to disparities in treatment between rural and urban populations to the association between migraine and stroke.

And crucial findings continue to come in, thanks to ancillary research studies and the thousands of dedicated participants who diligently fill out their health questionnaires year after year.

"I just finished the latest questionnaires a couple of months ago," said Joan, an 85-year-old participant from Nevada, who joked she's been involved with the WHI "since the beginning of time."

A longtime nurse and nursing teacher, Joan said she signed up because of her interest in health — her own and that of other women.

"I didn't have to work on ginning up enthusiasm for it," she said. "It fit really nicely with what I cared about."

A participant in the vitamin D and calcium supplementation trial — and other ancillary studies — Joan said she would often bring the WHI questionnaires to class along with the newsletters outlining various findings.

"Whenever I'd get a new questionnaire, I'd wave it in the air and tell my students, 'This is what I'm talking about,'" she said. "Some of my students got the message about the value of long-range studies. You can't capture that data once it's gone."

Decades after enrolling, Joan said she still appreciates the numerous health insights researchers have gleaned from the WHI questionnaires, biobank samples and other stored data.

“There have been so many stories in the news about things that have been identified that we wouldn’t know if they hadn’t started the WHI all those years ago,” she said, expressing concern over recent reports of WHI funding cuts. “I hope it doesn’t disappear. It’s a crime to lose all that history. It continues to be of daily interest to people and makes a big difference in life.”

Read the latest on WHI funding.

Investigators from the WHI held their annual meeting at Fred Hutch May 1 and 2, 2025, sharing new research conducted using samples and data from the longstanding Women’s Health Initiative.Courtesy of Robert Hood / Fred Hutch News Service

Return on investment

But as Anderson told her investigators at the annual meeting, “our future really requires us to have good plans and ideas.”

“What are the most important research questions regarding women in the ninth and 10th decades in life?” she asked. “Or another way to look at it: What would be lost if WHI didn’t continue?”

Interestingly, the Hutchinson Institute for Cancer Outcomes Research, or HICOR, posed a similar question in a 2014 study, modeling a world in which the Women’s Health Initiative never existed.

The WHI’s combined hormone replacement therapy trial alone, they found, had tremendous value, with a net economic return of $37.1 billion and a return of $140 for every dollar spent. Additionally, the researchers’ analysis projected around 4.3 million fewer women used combined hormone therapy after the findings were announced, which meant there were 126,000 fewer breast cancer cases, 76,000 fewer cases of cardiovascular disease (including coronary heart

disease and stroke) and 80,000 fewer cases of dangerous blood clots in the decade following the trial.

“That one trial saved many billions of dollars in health care costs, due to the sea change in the use of menopausal hormones that these trials induced,” said Fred Hutch professor emeritus Ross Prentice, PhD, who along with the late Maureen Henderson, MD, PhD, helped to bring the WHI’s clinical coordinating center to Fred Hutch. Prentice also served as WHI’s first principal investigator.

And, the WHI has helped in other ways.

Tinker said it facilitated years of cooperation and collaboration among researchers at other institutions, helping to forge bonds and build important connections and providing valuable training on the ins and outs of running huge prevention trials.

“We started from the ground up, so there was a lot of development of procedures and protocols,” she said. “There was a lot of good work, a lot of excitement and a lot of collegiality.”

And then there were the findings.

Tinker, who worked on the diet modification trial — where participants ate a low-fat diet that included lots of fruits, vegetables and whole grains — said a post-trial analysis found that the modified diet kept WHI participants who became diabetic from having to go on insulin right away.

“The insulin was delayed by having been in the dietary modification arm of a low fat, high vegetable and fruit and grain diet,” she said. “Anytime you can reduce, modify or delay a medication, that’s fantastic.”

When results from studies were made public, WHI researchers provided regular updates to participants to make sure they understood the findings, especially as the media began to broadcast them, sometimes accurately, sometimes not.

“We worked closely with nutritionists at the clinical centers to develop modules and implementation guides,” Tinker said. “We even developed a module of how to read and interpret news reports of scientific literature. We’d ask, ‘What was the aim of the study? What was the design?’ We broke it down simply, providing guidance on how to interpret scientific news.”

Everybody’s a critic

Since that time, interpretation (and misinterpretation) of WHI’s study results — particularly the two-arm hormone replacement trial component — have practically become a spectator sport.

“We’ve had many critiques,” Anderson said in her grand rounds lecture. “Some say we didn’t use the right hormones, when we used the exact hormones taken by the women in the studies that generated the hypothesis. Others said we raised more questions than answers. But every study

reveals more good questions."

What's most concerning, Anderson said, are those who "fail to acknowledge the original hypothesis," cherry-pick results, or just flat-out misunderstand the hormone trials.

"People think it's all one thing and it's not," she said. "It was two parallel trials. If women had their uterus, they were randomized to the combined hormone therapy arm. Women who'd had prior hysterectomy could be randomized to estrogen alone. The results of trials varied in important ways."

Still others complain that the hormone study failed to address the needs of younger women even though the entire focus of the WHI was to study chronic disease in women over 50.

Reflecting on the critiques, Anderson said she often thinks of a comment NIH director Elias Zerhouni, MD, made in his closing remarks after the special 2002 NIH symposium where the hormone study findings were shared.

"As you look through the history of science," Zerhouni told the gathered women, legislators and scientists, including Anderson, "the reaction to a new scientific finding, whatever that finding is, is really proportional to the strength of the dogma it overturns."

Building for the future

Despite all the Monday morning quarterbacking — not uncommon when an outstanding team delivers an upset — the WHI has made Fred Hutch a major player in population sciences, helping to cement the institution's reputation as a reliable and rigorous data coordinating center for large, multi-site trials.

"We were already real leaders in doing population science and large trials," Anderson said of the days before the WHI study. "We were doing major cancer prevention trials like CARET [testing vitamin A], SELECT [testing Vitamin E] and PCPT, the Prostate Cancer Prevention Trial."

Fred Hutch was also involved in the Women's Health Trial, a precursor to the WHI, and has since gone on to manage many large-scale research studies, including the Early Detection Research Network (EDRN), the Prostate Active Surveillance Study (PASS) and the Translational Liver Cancer (TLC) Consortium. Most recently, Fred Hutch was named both the Coordinating and Communications Center and the Statistics and Data Management Center for the Cancer Screening Research Network, or CSRN, evaluating liquid biopsies for their utility in cancer screening.

Anderson calls these large-scale studies "engines for discovery."

"Studies like WHI generate resources and draw people in," she said. "They support a lot of novel research and new collaborations in the population sciences. The WHI is really one of the top things to know about Fred Hutch. It's one of top things we've done."

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