Negative Women’s Health Initiative Findings Stir Consternation, Debate Among Researchers

New results from the largest, most comprehensive, and most expensive study of women’s health ever conducted in the United States have run counter to some widely held beliefs.

The Women’s Health Initiative (WHI), designed to address the most common causes of death, disability, and poor quality of life in postmenopausal women, has concluded that none of the interventions for cardiovascular disease, cancer, and osteoporosis studied in this 15-year program offers a major benefit.

WHI researchers learned in 2002 that combined estrogen and progestin hormone replacement therapy (HRT) in older women hurt more than it helped, and papers published in February 2006 concluded that a low-fat diet did not reduce heart disease or colon cancer rates. Although the diet may lower breast cancer rates in some women, the overall difference was not statistically significant. A final study, reported later that month, found that calcium and vitamin D supplements also offered no overall health benefit.

The negative WHI findings produced reactions that varied widely among researchers.

Some were delighted that the $725 million large, randomized, controlled trial—the best that science has to offer—finally provided some answers. “It’s a good day whenever we learn something doesn’t work, so we can avoid wasted energy, effort, and fuzzy advice, and focus instead on things we know offer benefits,” said Russell Harris, M.D., director of the prevention program for the school of medicine at the University of North Carolina at Chapel Hill.

But it disappointed others, not least because hypotheses that were expected to be confirmed were not. “The strength of the reaction has been commensurate with the strength of the dogma it overturned,” said Jacques Rossouw, M.D., the WHI project officer.

Yet even Rossouw cannot bring himself to declare that a low-fat diet doesn’t matter to breast cancer risk, the “messiest” finding in the study. “Positive studies are easy to translate into a strong message; ambiguous studies are not,” he said. “But in striving for a balanced message, we can say that we didn’t find anything that would discourage people from using a low-fat diet.”

Ambitious Design

Before the WHI, health advice for older women was based on surprisingly few randomized trials—a point hammered home by Bernadine Healy, M.D., the first female director of the National Institutes of Health, who initiated the study that Congress authorized in 1991. In all, more than 161,000 women, aged 50–79 years, enrolled at 40 centers across the country.

Some researchers argued against launching the study. Among them was Walter Willett, M.D., Dr.P.H., who maintained that such a large randomized study was “a very difficult and very risky research investment to test the belief that you can intervene with lifestyle in a major way and reach a clear answer.” Willett, of Harvard’s School of Public Heath in Boston, said that because compliance is such an issue in trials like these, large observational studies provide more of a “real-world answer” than the WHI study.

Others defend the WHI. “This is the best study that could have been done, and the researchers who worked on it are outstanding,” declared Peter Greenwald, M.D., Dr.P.H., director of the Division of Cancer Prevention at the National Cancer Institute.

The first WHI finding on HRT set the tone for those that followed. Investigators stopped a trial of estrogen plus progestin in 16,000 women after only 5.2 years because the associated health risks outweighed the benefits. A companion trial of estrogen only in more than 10,000 women was halted 2 years later because of an increased risk of stroke and dementia and no overall heart protection. These findings, the opposite of what some smaller observational trials had reported, resulted in enormous publicity and a sharp decline in hormone therapy use in the United States.

Another bombshell hit on Feb. 8, 2006, when three WHI studies, reported in the Journal of the American Medical Association, laid asunder popular notions about low-fat diets. Among the almost 49,000 women who participated in the 8-year trial, there were no statistically significant differences in the rates of colorectal cancer, heart disease, or stroke between the group that followed a low-fat diet and the comparison group that ate normally. The reductions in breast cancer rates between the groups fell just short of statistical significance.

Other discouraging WHI findings followed February 16 in the New England Journal of Medicine. Daily supplements of calcium and vitamin D also showed no overall protection against fractures and colon cancer, contrary to what many physicians had believed.

Some researchers say that parts of the WHI were poorly designed or beset by problems, so studies failed to answer the questions they addressed. They say that the participants were healthier than...
average and too old for the interventions to make a difference and that the study period was too short to demonstrate major cancer risk reductions. The opportunity for definitive follow-up studies may have been squandered.

These researchers point to the study of calcium and vitamin D supplements. Most WHI participants, including those given a placebo, were allowed to take calcium supplements on the side. The result was that about two-thirds of the placebo group actually had high intakes of calcium. Also, 41% of the intervention group didn’t take their pills as directed.

“It’s very unusual to do a clinical trial in which you do nothing to prevent the control group from getting the intervention being studied on their own,” said John Baron, M.D., professor of medicine at Dartmouth University in Hanover, N.H., who studies colon cancer prevention. “The kind of statistical analysis that then needs to be done moves the study into the realm of observational and nonrandomized.”

Baron’s studies have shown that it takes 15 years for a daily dose of aspirin to prevent colon polyps from forming. This study was about half that long, he said, and no effort was made to use colonoscopies to check for polyp formation.

“I really hope this is not the final word on vitamin D and colon cancer,” he said.

Some cardiologists say that the way the low-fat study was designed has undermined their message that what really matters is the kind of fat a person eats. The study didn’t distinguish between “good” (mono- and polyunsaturated) fats and “bad” (saturated and trans-) fats. That was a reasonable decision to make in designing a trial at that time, but “the question cardiologists need to answer now is whether diets enriched by unsaturated fats are beneficial,” said Peter Libby, M.D., chief of cardiovascular medicine at Brigham and Women’s Hospital, Boston.

“It is very important that the public understands that this study is not a license to chow down on cheesesburgers,” he said. “From my perch, we need to have a definitive study that addresses the issue of good versus bad fats, but let’s hope the public doesn’t lose faith in us before we can do it.”

**Not Significant Now—but Later?**

Indeed, the low-fat study has caused the most consternation among researchers. On the one hand, the study demonstrates how difficult it is to lower fat intake, even among motivated study participants. From the start, women in the study group failed to achieve the goal of 20% of calories from fat, and as the study progressed, their fat intake rose to 29%—which was not so different from the 37% of calories from fat maintained by the control group. WHI trial designers had hoped to achieve an 11% spread between the two groups.

On the other hand, despite the smaller gap and difficulties with compliance, the intervention group experienced a 9% lower risk of developing breast cancer, but that was not statistically significant. Several subgroup analyses did reach statistical significance: Women who started with the highest-fat diets and reduced fat intake by 12% had a 22% lower risk; there was also a statistically significant reduction in certain tumor subtypes between the groups.

Researchers argue that if the study had gone on a little longer, the data would likely have reached statistical significance.

“I would not call this a negative trial,” said Greenwald. “The question for me is what happens in the follow-up phase of the study, because we need more time to see if the effects we are seeing are real.”

Rossouw agrees with some critics that 8 years is not enough to make a definitive conclusion about the effect of a low-fat diet on breast cancer risk. “The headlines that were written in February may be wrong in several years,” he said.

The results, even though not statistically significant at this point, dovetail nicely with conclusions reached from the Women’s Intervention Nutrition Study (WINS), according to Rowan T. Chlebowski, M.D., Ph.D., chief of the division of medical oncology and hematology at Harbor-UCLA Medical Center, Los Angeles.

In that 2,500-patient randomized trial, women with prior breast cancer who reduced fat in their diet reduced their risk of cancer recurrence compared with women who did not.

“I look at the results as being quite similar and promising,” Chlebowski said. “In both, the apparent dietary effect was greater in women with receptor-negative breast cancers. Taken together, these two randomized clinical trials, while not definitive, nonetheless provide a signal that lifestyle change can influence breast cancer clinical outcome.”

Willett begs to differ. “Even though there was not a significant reduction in breast cancer, some researchers still believe their low-fat hypotheses,” he said. “If you can’t believe the results, why do the study?”

**Communicating the Findings**

Given these conflicting perspectives, what do physicians now tell women who want to reduce their chance of developing breast cancer?

The one clear message that emerges from the dietary study is that it is difficult to cut average fat intake nearly in half and stick to it, said Suzanne
Fletcher, M.D., professor of ambulatory care and prevention at Harvard Medical School in Boston. That fact wasn’t emphasized, nor were the statistical results put in terms that nonscientists can best understand, she said.

“We have to learn to communicate better to the public, and that involves not using hazard ratios and relative risks,” she said. “Women should be told that the difference between the low-fat group and the control group was three cases of breast cancer per 10,000 women per year. “The major question for women, then, is if they want to take on a low-fat diet to reduce their risk by that much,” Fletcher said. “Some women will say that they absolutely want to, and other women who don’t want to will not be made to feel guilty.”

Greenwald regrets that the effort to communicate the WHI results quickly to the public may have resulted in largely negative reporting, with little attention to the nuances of the study.

Because of that, investigators have reached out to the media, trying to provide a more evenhanded analysis, especially of the breast cancer findings, Rossouw said. “The picture became unbalanced during the reporting of null trials, so we have made an effort to get the balance back,” he said.

But communicating the results was tricky, Rossouw conceded. “If we had stressed the positive, saying that, based on subgroup analyses and need for a longer follow-up, we think a low-fat diet will work and why, we would have gotten a strong reaction from the scientific community and would have lost credibility,” he said. “At the NIH, we need to responsibly say that the overall results from WHI were not statistically significant.”

Some oncologists are choosing to ignore that fine line. “So, the study failed the magic 95% probability rule by 4%. I think that is just about as close to a real result as there is,” said Aman Buzdar, M.D., a professor in the department of breast medical oncology at the University of Texas M. D. Anderson Cancer Center in Houston. “What this tells me is that, for the first time, women have something they can do that may help them modify their breast cancer risk, and I will tell them so.”

—Renee Twombly

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