

# The New York Times

**EARLY EDIT**  
New York: Today, som  
27. Tonight, mostly cle  
Tomorrow, partly clou  
Weather map is on

53,495

Copyright © 2006 The New York Times

NEW YORK, SUNDAY, FEBRUARY 19, 2006

\$4.50 beyond the greater New York metropolitan area.

## Women's Health Studies Leave Questions in Place of Certainty

By DENISE GRADY

So what do women do now? The results of two major studies over the past two weeks have questioned the value of two widely recommended measures: calcium pills and vitamin D to prevent broken bones, and low-fat diets to ward off heart disease and breast and colon cancer.

Should women abandon hope, since it looks as if nothing works? Abandon guilt and assume diet makes no difference? Or muddle on with salad and supplements anyway, just in case?

The studies — part of the same government research project that in 2002 found hormone treatment for menopause did more harm than good — have confused women and prompted renewed examination of the regimens that many have been carefully following. Researchers find themselves parsing the results, and debating about how far the scientific rules can be stretched when it comes to measuring results and searching for evidence in smaller groups of patients within a large study.

The researchers admit that the findings were an unexpected and puzzling challenge to firmly held, almost religious beliefs about nutrition and health.

And though some experts said the results meant women should look for

other ways to prevent heart disease, cancer and bone loss, the scientists who conducted the studies insisted that hints of benefit in parts of the data could not be ignored.

"We just didn't come out with as strong a finding as everyone expected," said Dr. Marcia L. Stefanick, head of the study's steering committee. "The results weren't clear enough, weren't black and white."

"We're still debating amongst our-

*Continued on Page 20*

# Health Studies Leave Questions in Place of Certainty

Continued From Page 1

selves," Dr. Stefanick said.

The studies, which involved thousands of women and cost hundreds of millions of dollars, were the largest and most rigorous look ever at the effects of diets and supplements, and are unlikely to be repeated.

News of the findings spread rapidly, and women interviewed in several cities were aware of them.

Pouran Zamani-Hariri, 68, of Chicago, said she had been taking calcium and vitamin D every day for five years and planned to ask her doctor about the calcium study. But the results did not surprise her, she said, because despite taking the supplements, she has broken her shoulder and her leg within the last two years.

"Maybe it proves that it doesn't work," she said.

Kim Curtis, 39, a portfolio accountant from Winthrop, Mass., said she chose full-fat foods over reduced-fat products because she worried about sugars and preservatives being used to replace fat in processed food.

"The way things are, you're going to get cancer anyway," Ms. Curtis said.

But the researchers who conducted the study said their findings were not a signal to binge on bacon cheeseburgers.

"I was a little uncomfortable with some of the reactions," said Dr. Jacques Rossouw, the project officer for the Women's Health Initiative, the program that has created the stir. It worries him, he said, that some people think the studies mean dietary fat and calcium do not matter.

"It's not what we say, and I don't think it's what the papers say," Dr. Rossouw said.

"For folks who are on a low-fat diet, by all means continue," he said. "If you're on a high-fat diet, certainly get it down. That's the message we would like to send."

As for calcium and vitamin D, he said, the recent study had "enough hints" of benefit that women whose diets do not provide adequate amounts should take supplements.

The studies were part of the health initiative, which started in the 1990's. The one on the low-fat diet, which included nearly 49,000 women ages 50 to 79, found that overall, after 8 years, the diet had no effect on the rates of breast cancer, strokes, heart attacks or colon cancer.

Similarly, the calcium study, which included more than 36,000 women, found that taking supplements for 7 years did not prevent broken bones or colorectal cancer,



Mark Lyons for The New York Times

Connie Elsaesser, 76, of Cincinnati, said she had no intention of resuming her old eating habits. "I've been brainwashed," she said.

but it did produce a 1 percent increase in bone density in the hip.

Given the findings, then, how can researchers like Dr. Rossouw still recommend low-fat diets and supplements?

The answer depends on how one interprets data. These studies included women who were treated and a control group that took placebos or, in the diet study, simply ate whatever they wanted. The researchers tracked the women's health, comparing the groups.

## Trying to decide how to treat the findings of a major initiative.

According to standard rules based on probability, the difference in results between the groups has to be of a certain size to qualify as a genuine, or statistically significant, difference, and not something that could happen by chance.

In the diet study, the difference in breast cancer rates was not statistically different. But Dr. Rossouw said it was so close — a 9 percent reduction in risk, whereas 10 percent would have been significant — that if the study had gone on longer, it might well have become significant. That was one of his main reasons for continuing to defend a low-fat diet. In addition, he said, the women who started out eating the most fat and then reduced their intake seemed to

have the biggest reduction in risk.

Dr. Larry Norton, a breast cancer expert at Memorial Sloan Kettering Cancer Center in New York, also said the reduction in breast cancer risk came too close to significance to ignore. "Any minute now that study could turn positive," Dr. Norton said.

He added, "It's a trend, a strong hint that something is happening and we need to follow these patients longer." The patients are still being monitored.

Dr. Norton is an author of a study in which a 50 percent reduction in dietary fat reduced the risk of cancer recurrence in women who had already had breast cancer.

A participant in the government study, Connie Elsaesser, 76, of Cincinnati, said she had mostly given up butter and cut way back on cheese and desserts. At times she had cravings, but, she said, she had no intention of resuming old eating habits.

"I've been brainwashed," Ms. Elsaesser said.

The debate about the studies stems from findings in subgroups of patients, a kind of result considered questionable by many scientists.

A basic rule in setting up experiments is that a study must be designed specifically from the very beginning to look for certain effects in a certain type of patient. It is generally not considered legitimate for researchers to go back over the data afterward and slice it up into smaller and smaller groups — sometimes called data snooping — until they find a result they like. That result could be false because it arose from chance.

In addition, if there is no statis-

tically significant finding in the larger group, it is considered even worse to dig around in subgroups.

"Subgroup analyses can get you in trouble," Dr. Norton said. "They don't prove anything." But, he added, effects found in subgroups can lead to further studies.

In the calcium study, the researchers noticed intriguing differences in certain subgroups. The ones who took most of their calcium, 80 percent of the pills, had a 29 percent reduction in hip fractures. Women over 60 also had a reduction, 21 percent.

Those findings persuaded Dr. Rossouw and Dr. Elizabeth G. Nabel, the director of the health initiative and of the National Heart Lung and Blood Institute, to recommend supplements for women whose diets did not include enough calcium.

"I think those are fair health messages," Dr. Nabel said. "I don't think it's overstating the data or cheating."

But statisticians say that subgroup analyses are seductive and perilous, and that the danger is in believing too much.

The health initiative investigators are cautious and conservative in their analyses, Dr. Rossouw said. They decide ahead of time on subgroups they plan to examine — women of different ages, women who did and did not follow their assigned treatment, women of different races, for example — and give greater weight to those analyses than to ones they decide to do after the study is completed.

But what does it mean when, as happened in this study, the subgroup analysis found that women in their 50's had more hip fractures if they took calcium and vitamin D? What does it mean if the women who were deficient in calcium were not helped by the supplements?

The temptation, statisticians say, is to pick the subgroup analyses that support a favored hypothesis and disregard the ones that do not.

"The probability that you will see a spuriously positive effect gets very big very quickly," said Dr. Susan Ellenberg, a former Food and Drug Administration official who is now a statistician at the University of Pennsylvania.

The health initiative investigators say they are aware of the pitfalls.

One way to decide whether to use a subset, Dr. Rossouw said, is "the reality check." He explained: "For a person knowledgeable in this field and knowing what is likely to be plausible, what do you believe?"

That, for example, is why the health initiative investigators emphasized their analysis of women

## Clinical Trials On Women's Health

The largest osteoporosis clinical trial before the W.H.I.

Total participants **3,000**



### CALCIUM AND VITAMIN D

Total participants **36,282**

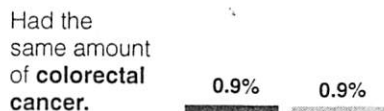
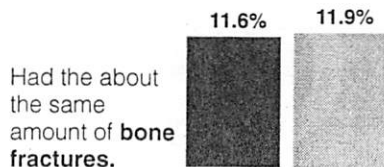
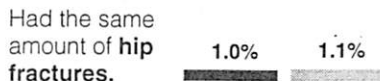
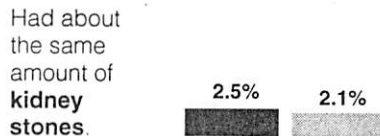


Took calcium and vitamin D supplement  
**18,176**

Took placebo  
**18,106**

### RESULTS Feb. 16, 2006

Women who took calcium and vitamin D supplements ...



The Women's Health Initiative, begun in 1991, followed more than 100,000 postmenopausal women to test the effects of low-fat diets and calcium and vitamin D supplements on heart disease, fractures and cancer. By comparison, most clinical trials today follow 1,000 to 5,000 people.

### DIET MODIFICATION

Total participants **48,835**

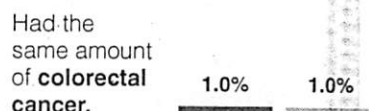
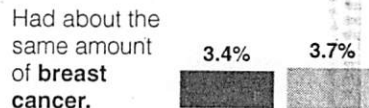
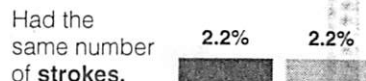
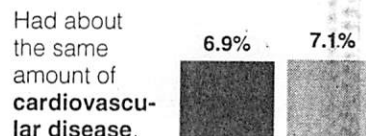


Put on low-fat diet  
**19,541**

Left on usual diet  
**29,294**

### RESULTS Feb. 8, 2006

Women who followed a low-fat diet ...



Sources: Dr. Jacques Rossouw, Women's Health Initiative; Dr. Clifford J. Rosen, Maine Center for Osteoporosis Research and Education

David Constantine/The New York Times

who complied with their assigned treatment, be it placebos or calcium and vitamin D supplements.

Donald Berry, a statistician at M. D. Anderson Cancer Center in Houston, said he would not be so critical of the analysis of women who took most of their pills, although he was not overwhelmed by the effect. The annual rate of hip fractures in women who adhered to the regimen was 10 per 10,000 as compared with 14 per 10,000 in adherent women taking placebos.

"One thing that is absolutely clear," Dr. Berry said. "If there is a benefit, it's not great, no matter which subgroup we're talking about."

Dr. Ellenberg quoted another statistician, Richard Peto of Oxford University, who said of subgroups, "You should always do them but you should never believe them."

Dr. Nabel acknowledged that statisticians often frowned on using subgroups, but, she said: "Medicine is an art. You take the data you have in hand and do your best to interpret it for the individual sitting across the table from you."

These studies are not the last word from the health initiative. There will be more reports and analyses, many based on subgroups, Dr. Nabel said.

Dr. Rossouw said, "Probably 15 to 20 papers a year for the next 5 years would be a conservative estimate."