WHI Low-Fat Diet Flawed; Some Benefit Shown

BY MITCHEL L. ZOLER
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BETHESDA, MD. — The biggest problem with the diet modification study of the Women's Health Initiative was the diet. Not enough women stuck with it, and it had an outdated design.

Despite these flaws, the trial's results, first reported in February, came close to proving that a reduced-fat diet—followed by thousands of postmenopausal women for an average of 8.1 years—could significantly reduce the incidence of invasive breast cancer.

"It's not an optimal diet; it's not feasible" for many women, commented Dr. JoAnn E. Manson at a conference on the Women's Health Initiative sponsored by the Department of Health and Human Services. The average level of fat reduction that most women achieved in their diet was not as substantial as had been planned, blunting the diet's effects.

Despite this shortcoming, the results showed "signals" that a low-fat diet produced some benefits, including a trend toward a reduced number of invasive breast cancers, a bigger reduction in breast cancers among women who had the highest level of fat in their diet at baseline, and a reduction in the incidence of colonic polyps or adenomas, said Dr. Manson, chief of the division of preventive medicine at Brigham and Women's Hospital, Boston, and a principal investigator for the WHI.

The study failed to show that the reduced-fat diet with increased consumption of fruits, vegetables, and grains could lower the incidence of cardiovascular disease.

"You need a 20%-30% decrease in low-density lipoprotein cholesterol to get an effect" on cardiovascular disease. "In this study, the effect was way too low," commented Dr. Lewis H. Kuller, professor of epidemiology at the University of Pittsburgh and a principal investigator for the WHI. The diet was also "too low in polyunsaturated fats. You blunt the LDL effect by reducing polyunsaturated fats," he said in an interview.

In this respect, the diet reflected what was known when it was designed in the early 1990s. Today, researchers have a better understanding of the benefit of polyunsaturated fat for cardiovascular disease and of the danger from saturated fat.

The diet modification study of the WHI was a companion to the hormone therapy study, as well as a third study that assessed the effect of calcium and vitamin D supplements.

One year into the study, average fat intake by the intervention group was 24% of daily calories. After 1 year, 31% had met the goal of consuming 20% fat or less.

All three of the studies enrolled women who were postmenopausal and aged 50-79 years at entry.

The diet modification study involved more than 48,000 women who, on their usual diet, got 32% or more of their calories from fat, based on a food frequency questionnaire, and who had no history of breast or colorectal cancer. More than 19,000 women were randomized to an intensive behavior-modification program designed to change their eating habits so that their fat intake would be no more than 20% of calories, their consumption of fruits and vegetables would be at least five servings a day, and their consumption of grains would be at least six servings daily. This diet did not involve a reduction in total calorie intake and had no weight loss goals. The more than 29,000 women randomized to the control arm were not asked to make any changes in their diet.

The diet intervention was modestly successful. One year into the study, average fat intake by women in the intervention group was 24% of daily calories. After 1 year of the study, 31% of women in the intervention group had met the goal of consuming 20% or less of their daily calories as fat. In the sixth year of the study, 14% of women in the intervention group were at this goal level. In addition, differences were modest between the intervention and control groups in the consumption of fruits, vegetables, and grains. One year into the study, women in the intervention group ate an average of 5.1 servings of fruits and vegetables daily and an average of 5.1 grain servings a day. The daily averages for women in the control group

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Not the Best Candidates for Trial

WHI Data *from page 1*

said Dr. Johnson, a professor of medicine at Ohio State University, Columbus, and a principal investigator of the WHI.

After the WHI's calcium and vitamin D study was designed, it was piggybacked onto the two other studies that had already begun, the hormone therapy and diet modification trials.

More than 36,000 women who were already enrolled in one or both of these ongoing WHI studies were randomized to get a daily supplement of 500 mg elemental calcium and 200 IU vitamin D or placebo, and the participants were followed for an average of 7 years.

The enrollment criteria did not contain exclusions based on calcium and vitamin D intake, and it specifically allowed women to take additional supplements of up to 1,000 mg calcium and 600 IU vitamin D per day.

At baseline, before the study began, one third of the enrolled women had a total daily calcium intake of at least 1,200 mg calcium, and another 45% of women had a daily intake of at least 1,000 mg, which meant that 78% of the participants already had a sufficient supply and were "probably not the best candidates for a calcium supplement trial," said Joan A. McGowan, Ph.D., director of the musculoskeletal diseases branch of the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

The study's primary end point was the incidence of hip fractures, with a secondary end point of incidence of all fractures. The incidence of hip fractures was 0.14% in the supplement group and 0.16% in the placebo group, a relative proportional reduction of 12%, which was not statistically significant (N. Engl. J. Med. 2006;354:669-83).

The incidence of all fractures was 1.64% and 1.70% in the intervention and placebo groups, respectively, also a nonsignificant difference.

These analyses were done on an intention-to-treat basis. During the first 3 years of the study, 60%-63% of women were adherent to the regimen, taking at least 80% of their assigned supplements. By the end of the study, 59% were still taking at least 80%.

A secondary analysis that focused only on the adherent participants showed that the incidence of hip fracture was 29% lower in the women taking calcium and vitamin D, compared with the placebo group, a statistically significant difference.

Another secondary analysis focused exclusively on women aged 60 or older, the group at highest risk of fracture. In this subgroup, the risk of hip fracture was 21% lower in the women in the active treatment arm, also a significant difference.

"We believe that this is strong enough information to support a role for calcium and vitamin D in reducing fracture risk," said Dr. Jackson in an interview at the meeting.

Calcium's main adverse effect was a 17% increased risk of having kidney stones, a significant difference.

"Although there was an increased risk of [developing] kidney stones, the possible benefits of calcium with vitamin D supplementation for the risk of fracture cannot be totally ignored," Dr. Joel S. Finkelstein, an endocrinologist at Massachusetts General Hospital, Boston, wrote in an editorial that accompanied the published findings (N. Engl. J. Med. 2006;354:750-2).

Dr. Finkelstein also commented in his editorial that "calcium with vitamin D supplementation by itself is not enough to ensure optimal bone health.

"Additional therapy with agents that have been proved to reduce the risk of fracture in women with osteoporosis, such as antiresorptive medications or teriparatide, may be indicated." ■

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were 3.9 servings and 4.2 servings, respectively.

The study's primary outcome was the incidence of invasive breast cancer, which was reduced by a relative 9% in the intervention group, compared with the control arm, a nonsignificant difference with a *P* value of .07 (JAMA 2006;295:629-42). Two secondary outcomes of the study were the rates of invasive colorectal cancer and cardiovascular disease. These rates did not significantly differ between the two study groups.

Researchers who ran the trial noted that the average follow-up was 8.1 years instead of the planned 9 years, a reduction caused by slower than expected recruitment of women into the study. The shortened follow-up limited the study's power to show a statistically significant difference in breast cancer rates.

But others said that even if the difference eventually becomes statistically significant with longer follow-up, the clinical importance of the reduction was questionable because the low-fat diet was linked with three fewer cases of invasive breast cancer for every 10,000 women followed per year.

"Even if a breast cancer effect is there, it's extremely small," said Dr. Kuller at the conference. For understanding the biology of breast cancer, proving a link to dietary fat intake is very important, "but it's a very modest clinical effect."

By contrast, Ross L. Prentice, Ph.D., lead investigator for the breast cancer analysis, said that even this small impact on breast cancer incidence is clinically meaningful. Because of the lag time in the development of breast cancer, it might take many years to see the full benefits of a reduced-fat diet, he said in an interview.

The difference in breast cancer incidence could become substantial if a reduced-fat diet was maintained over a lifetime, said Dr. Prentice, a professor of biostatistics at the University of Washington, Seattle, and a researcher at the Fred Hutchinson Cancer Research Center. "A low-fat diet is a reasonable choice for overall health, but we have not yet addressed what's the best diet to recommend." ■

HT for Hot Flashes Didn't Improve Quality of Life

BY MITCHEL L. ZOLER
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BETHESDA, MD. — Now that results from the Women's Health Initiative have shot down hormone therapy as a way to prevent coronary events, dementia, and urinary incontinence in postmenopausal women, the only indication left standing has been relief of menopausal symptoms, especially vasomotor symptoms such as hot flashes.

But even this application is on shaky ground, thanks again to results from the Women's Health Initiative (WHI).

One problem with using estrogen plus progestin, or estrogen alone to manage vasomotor symptoms is that a comprehensive quality-of-life assessment in the WHI showed no clinically significant benefit from hormone therapy, Jennifer Hays, Ph.D., said at a conference on the Women's Health Initiative, sponsored by the Department of Health and Human Services. This result carries the caveat that the WHI hormone study enrolled only women who were willing to accept randomization to placebo, which means that women with the worst symptoms were probably not included.

Despite this drawback, hormone therapy is 'clearly still the best treatment for vasomotor symptoms,' according to one WHI principal investigator.

A second problem is that 56% of women in the WHI who had hot flashes when they started hormone therapy experienced a recurrence 8-12 months after stopping hormone therapy.

The finding that symptoms recurred after hormone therapy stopped is "very important," said Dr. Hays, a developmental psychologist at Scott & White Hospital in Temple, Tex., and a principal investigator for WHI. "We now talk about treating women with estrogen for a short term, but what happens when women get taken off?"

Despite this drawback, hormone therapy is "clearly still the best treatment for vasomotor symptoms," commented Dr. Robert Brzyski, an ob.gyn. at the University of Texas Health Science Center, San Antonio, and another WHI principal investigator.

The prevalence of menopausal symptoms when women entered the WHI hormone study was related to age. Among women aged 50-54 years, the most common symptom was hot flashes, reported by about 23% of women. Vaginal dryness, headache, and mood swings were each reported by 10%-15% of women, and joint pain was noted by 20%. The prevalence of all symptoms at entry, except joint pain, was lower with increased age. For example, among women aged 55-59 years, the prevalence of hot flashes was 15%.

After 1 year of treatment with estrogen and progestin, about 85% of women with hot flashes reported that this symptom had significantly improved, compared with about 58% of women in the placebo group, a statistically significant difference. Improvement in vaginal dryness was reported by about 75% of women treated with estrogen plus progestin, compared with about 55% in the placebo group, also a significant difference, Dr. Hays said at the meeting.

But serial surveys that measured health-related quality of life using the RAND 36-Item Health Survey failed to identify any clinically meaningful improvement after 1 or 3 years of estrogen-plus-progestin treatment, compared with placebo. A similar quality-of-life assessment using the RAND 36 failed to show any clinically meaningful improvements in women treated with estrogen only, compared with placebo.

The incidence of menopausal symptoms in women who stop hormone therapy was examined by studying the 9,351 women who were still taking their prescribed estrogen plus progestin or placebo regimen when the treatment phase of this trial was stopped in July 2002.

This group constituted 56% of the participants originally enrolled, and included 4,558 in the hormone arm and 4.793 in the placebo group.

During the first 8-12 months after stopping, hot flashes occurred in 56% of women who had this symptom when they began hormone therapy, compared with a 21% incidence in women who had hot flashes when they entered the placebo arm of the study (JAMA 2005;294:183-93). In women who had hot flashes at any time before entering the WHI study, the symptom occurred after treatment stopped in 22% of women who had been on estrogen plus progestin vs. 4% of women from the placebo group.

The results suggest that hormone therapy only postpones certain menopausal symptoms, and it may eventually make the symptoms worse, said Dr. Hays in an interview.

Several management options are alternatives to hormone therapy for menopausal symptoms, including drugs such as clonidine or selective serotonin reuptake inhibitors, treatment with various supplements or herbal agents, or modified forms of hormone therapy that involve different dosages, duration of treatment, hormone formulations, or routes of administration. But these alternatives are all limited by a lack of information on their safety and efficacy, said Dr. Margery Gass, an ob.gyn. at the University of Cincinnati and a principal investigator for the WHI.