Low-Fat Diet and Chronic Disease Prevention: the Women's Health Initiative and Its Reception

Alice Ottoboni, Ph.D.
Fred Ottoboni, M.P.H., Ph.D.

ABSTRACT

The Women's Health Initiative Randomized Controlled Dietary Modification Trial was designed to study a low-fat diet, a nutritional approach to prevention of chronic diseases that was considered promising. The negative findings from the trial were both unexpected and disappointing to nutrition authorities. The authors' public responses to the findings articulated an unwillingness to believe the finding that a low-fat diet did not prevent breast or colon cancer or heart disease. The negative results should stimulate work on alternate hypotheses, and reconsideration of the long-standing proscription against dietary fat.

Introduction

The Women's Health Initiative (WHI) was launched in 1991 with the purpose of addressing the most common causes of death, disability, and impaired quality of life in postmenopausal women: heart disease, breast cancer, colorectal cancer, and osteoporotic fractures. Three randomized controlled clinical trials were proposed to test promising approaches to prevention of these chronic diseases. The three trials were hormone therapy, calcium plus vitamin D supplementation, and dietary modification.

The WHI program was the largest federally funded study of women's health ever undertaken, with the expenditure of more than $700 million since its inception in 1991. To put the massive WHI effort in more personal terms: "After 12 years, 7.5 million forms, and 1 million clinic visits, we have reached the most exciting phase of the Women's Health Initiative—the results!"[1] The results from the hormone therapy trial were published earlier, in 2002.[2] Results from the calcium plus vitamin D supplementation trial[3,4] and the dietary modification trial were published in 2006.[5,6,7] A WHI Extension Study through 2010 has been funded to follow participants through the next four years.

The WHI Randomized Controlled Dietary Modification Trial was designed to study a low-fat diet, a dietary approach to prevention of cardiovascular disease, colorectal cancer, and breast cancer. Although unproven, nutrition scientists thought the approach was promising. The findings were published simultaneously in three separate scientific papers, the first dealing with breast cancer,[5] the second with colorectal cancer,[6] and the third with cardiovascular disease.[7]

All three papers from the dietary modification trial presented findings that were not only a surprise to the nutritionists, but also in sharp disagreement with its long-held dietary recommendations, as diagrammed in the Food Guide Pyramid[8] (now known as MyPyramid[9]).

"The Low-Fat Diet Doesn't Prevent Chronic Disease—or Does It?"[10] is the title of one of the many responses that attempted to explain the disappointing findings. It summarizes the conundrum that the trial presented to the nutrition authorities.

The dietary trial was designed in accordance with the prevailing expert opinion of international nutrition authorities, who believed that a reduction in total fat intake would reduce the risks of breast and colorectal cancers. There was less agreement on how reducing total fat intake would affect heart disease, even though saturated fat was a generally accepted risk factor for heart disease. Thus, the heart-disease component of the study was added to the protocol because it was anticipated that a reduction in total fat would be accompanied by a reduction in saturated fat. Fruits, vegetables, and grains were also considered to have a role in chronic disease prevention, but this hypothesis also had not been tested in a long-term, randomized trial.

Design of the Trial

The dietary modification trial[5,6,7] enrolled 48,835 postmenopausal women aged 50 to 79 years, recruited between 1993 and 1998 from 40 clinical centers throughout the United States. Each clinical center had its own principal investigator and staff. The women were randomly assigned to the dietary modification group, referred to as the intervention group (n = 19,541; 40%), or the comparison group (n = 29,294; 60%). The women in the intervention group were asked to lower their fat intake to 20% of their total calories, and to eat five or more fruit/vegetable servings and six or more grain servings a day. The comparison group was asked not to make any dietary changes. Both diet groups were followed closely during the 8.1 years of the study with clinic visits and periodic questionnaires. The intervention group also participated in an intensive behavioral modification program using group sessions, self-monitoring techniques, and other strategies aimed to motivate and support reductions in dietary fat and increase consumption of vegetables, fruit, and grains.

Results of the Trial

Diet Compliance: Dietary fat intake was significantly lower in the intervention group than in the comparison group. The difference between groups in change from baseline for percentage of energy from fat was 10.7% at year 1, and this difference between groups was mostly maintained throughout the trial, although by year 6, the difference in mean fat intake between the two groups decreased somewhat, to 8.2% of energy intake. The intervention group also achieved statistically significant increases in vegetable, fruit, and grain servings. Vegetable and fruit consumption was higher in the intervention group by at least one serving per day, and grain consumption was higher by half a serving per day.[5,6,7]

Breast Cancer: The number of women who developed invasive breast cancer (annualized incidence rate) was 665 (0.42%) in the intervention group and 1,072 (0.45%) in the comparison group. It was concluded that among postmenopausal women, a low-fat dietary pattern did not result in a statistically significant reduction in invasive breast cancer risk over an 8.1-year mean follow-up period. However, because some of the findings, although not statistically significant, indicated that there might be a reduced risk associated with a low-fat dietary pattern, the authors suggested that the planned longer nonintervention follow-up might yield a more definitive comparison.[5]

Colorectal Cancer: Despite dietary changes, there was no evidence that the intervention reduced the risk of invasive colorectal cancer. There were 201 women with invasive colorectal cancer (0.13% per year) in the intervention group and 279 (0.12% per year) in the comparison group. These results led to the conclusion that a low-fat dietary intervention did not reduce the risk of colorectal cancer in postmenopausal women during the mean 8.1 years (SD, 1.7) of follow-up.[6]

Cardiovascular Disease: Low-density lipoprotein cholesterol levels and diastolic blood pressure were significantly reduced by 3.55 mg/dL and 0.31 mm Hg, respectively, in the intervention vs. the comparison group. However, high-density lipoprotein cholesterol, triglycerides, glucose, and insulin did not significantly differ between the groups. The number who developed coronary heart disease (CHD), stroke, or cardiovascular disease (CVD) (annualized incidence rates) were 1,000 (0.63%), 434 (0.28%), and 1,357 (0.86%) in the intervention group, and 1,549 (0.65%), 642 (0.27%), and 2,088 (0.88%), respectively, in the comparison group. It was concluded that over a mean of 8.1 years, dietary intervention (reduced total fat intake and increased intake of vegetables, fruits, or grains) did not significantly reduce the risk of CHD, stroke, or CVD in postmenopausal women.[7]

Responses to the Trial from Nutritionists

As might be expected when strongly held beliefs are called into question, nutrition experts responded to the results of the WHI diet study quickly and vigorously. Because so many of the responses were negative, officials at the National Institutes of Health, under whose aegis the study was conducted, rejected criticism that they mishandled the study with the following comment:

> … [P]eople are upset only because it took controversial topics and upset accepted notions. "The strength of the reaction has been commensurate with the strength of the dogma it overturned," says Jacques Rossouw, WHI project officer for the NIH.[11]

"Many of the principal investigators emphasized that in many ways, the project was very well conceived, designed, and executed, and has produced valuable information," according to a report in the *Washington Post*.[12] However, the general agreement that the study was properly conducted did not mute dissatisfaction with the outcome. Nor did it persuade nutritionists to change the advice they will give to clients. As Jean Wactawski-Wende, one of the authors of the breast and colorectal cancer papers, remarked, there is no question that a diet low in fats and high in fruits, vegetables, and grains is a very healthy diet. Lack of proved effect on chronic diseases "does not mean that anyone should abandon a proven healthy diet."[13]

Responses of nutrition experts can be grouped into four major categories: disappointment and/or disbelief, criticism of study design, attribution of results to participant noncompliance, and statements that findings were incomplete or immaterial**.**

Disappointment and/or Disbelief: Many of the principal investigators as well as other health scientists expressed feelings of disappointment and/or disbelief about the lack of statistically significant benefits. Tim Byers, WHI principal investigator, University of Colorado Health Sciences Center in Denver, said, "We are scratching our heads over some of these results."[12]

Margery Gass, principal investigator for the University of Cincinnati clinical center said, "The women [in the study] worked very hard to change their eating patterns. That is another reason the finding are disappointing…. We really hoped the dietary modification would produce a major benefit in their health."[14]

In an effort to assuage the almost universal feelings of disbelief in the results of the study, Rossouw, the WHI project officer, offered a ray of hope: "Scientists will observe the women until 2010, when we could hear a whole new message. I would not worry about the headlines of today as far as low fat and breast cancer are concerned. They may be wrong."[15]

Flawed Study Design: Criticisms of the study cited its duration, size, selection of participants, failure to distinguish between "good fat" and "bad fat," and inadequate lifestyle change (e.g. no exercise).

Jacques Rossouw, WHI project officer, suggested that "some of the hypotheses used to design the project may have been flawed, or become outdated while the project was underway" and it "may have been too short, or studied women who were too old or just too healthy."[13]

Ruth Kava, Director of Nutrition at the American Council on Science and Health, asked: "The activity levels weren't described—if they had increased their exercise, would that have increased their weight loss and thus decreased at least their risk of heart disease? Would the results have been different with a longer follow-up period?" She added that perhaps a greater degree of supervision and/or education would have made a difference.[10]

Kelly Brownell, director of Yale's Rudd Center for Food Policy and Obesity, said that members of the WHI committee who designed the trial had serious questions: "Cancer and heart disease can take decades to develop. Would an eight-year trial be long enough? Would the women in the test group fully report their eating habits? Self-reports of dietary intake are notoriously inaccurate."[15]

Participant Noncompliance: The women in the intervention group achieved only a modest though statistically significant reduction in their percentage of energy from fat, from 38% to 29%. A statement issued by the Harvard School of Public Health (HSPH) Department of Nutrition cited the view of some nutrition experts that benefits from the low-fat approach may have become more apparent had the women reached the target of 20%.[16]

Findings Incomplete or Immaterial: Elizabeth Mayer-Davis, director of the Center for Research in Nutrition and Health Disparities, University of South Carolina, wrote: "My view is that for several reasons the WHI results are not entirely negative or positive; they are simply incomplete."[17]

Marcia Stefanick, chair of the WHI steering committee, said that additional studies that distinguish between "good fats" and "bad fats" need to be done.[18] In another interview, Stefanick noted that "the women weren't asked to differentiate between 'good fats' and 'bad fats,' which is emphasized in current guidelines for heart disease reduction."[19]

The Lipid Hypothesis

The lipid hypothesis, the label for the diet-heart connection that attributes heart disease to consumption of animal fats, has a long history. It had its origins in the 1950s when nutrition pioneer Ancel Keys and his wife Margaret discovered the cuisine of southern Italy and Greece, which they named the Mediterranean diet. The Keyses assumed wrongly that their Mediterranean diet was low in animal fats because it was largely pastas, olive oil, vegetables, fruits, and wine.[20] Convinced that the Mediterranean diet was responsible for low rates of coronary heart diseases (CHD) because it was low in animal fat, they set out to obtain statistics on fat consumption and CHD in other countries, including those that bordered the Mediterranean, for which there were such statistics.

The studies of Keys and his followers became widely popular, and the nutrition and medical communities enthusiastically embraced the diet-heart connection of the lipid hypothesis. Later, laboratory reports showing an association between blood cholesterol levels and CHD, plus reports that cholesterol was found in coronary artery occlusions in people who died of heart disease, strengthened the credibility of the lipid hypothesis, because cholesterol is a lipid found only in association with animal fats. Thus, cholesterol became accepted as a major risk factor for the lipid hypothesis.

Many large, long-term prospective studies that examined the question of a link between dietary fat and chronic disease, beginning with the Framingham Heart Study of the post-World War II era, have been conducted in the United States and abroad in the last five decades. Despite this tremendous expenditure of time and money, a statistically significant association between dietary fat intake and chronic disease still eludes proponents of the lipid hypothesis.[21]

The epidemiology on which the low-fat diet was based had a number of early critics, but scant attention was paid to them until the late 1980s, when a Scandinavian cardiologist began to question the purported relationship between cholesterol and cardiovascular disease. The result was a thoughtful, factual, and thoroughly referenced book describing cholesterol myths, in which Uffe Ravnskov explains the flaws in the studies that led to the lipid hypothesis and the fallacies that have supported it.[20]

There is ample scientific evidence that the lipid hypothesis is not a valid theory, but rather a creature of misused and/or incompetent epidemiology. A new book by Colpo[21] explains the misuses of epidemiology in the genesis of the lipid hypothesis, and describes how and why politics and the food and pharmaceutical industries actively promote the very profitable lipid hypothesis. This exhaustive treatise, with more than 1,400 references to major scientific journals, builds on the work of Ravnskov in exposing the fiction of the lipid hypothesis.

Reflections on Reactions to the WHI Study

The response to the WHI diet study results make it clear that traditional nutritionists are still wedded to the concept of the lipid hypothesis, despite the fact that arbiters of official nutrition policy had been aware of problems with the low-fat diet for many years. The HSPH Department of Nutrition wrote:

> The dietary fat reduction arm of the WHI was controversial from the beginning. Members of the HSPH Department of Nutrition argued that the hypothesis that a reduction in total fat would have major health benefits was not supported by existing data…. The findings from the Women's Health Initiative Dietary Modification Trial came as a surprise to many Americans who have been hearing for years that reducing fat is important for long-term health. Yet long-term follow-up studies such as the Nurses Health Study have consistently found little relation between the percentage of calories from fats and risks of breast cancer, colon cancer, or coronary heart disease. Such studies are one reason why major reviews of diet and health in the last five years, including those conducted by the U.S. Institute of Medicine and the U.S. Dietary Guidelines Committee, have moved away from advocating low fat intake to emphasis on the type of fat.[15]

In order to retain the lipid hypothesis as a foundation for official dietary policy, something that will excuse the failure of studies to confirm the concept, without lessening its validity, is required. This requirement could be met by new data showing that it is not total dietary fat that is the culprit, but rather only the saturated fat and trans fat components of total fat that are to blame for heart and other chronic diseases. Walter Willett, in Chapter Four of a Harvard Medical School diet guide, summarizes traditional nutrition's rationale for why dietary fat restriction should apply only to saturated and trans fats, and not to total fat.[22]

It seems incomprehensible that authorities in a scientific discipline would be unaware of the wealth of data in the scientific literature that contradict the basis for its official position on dietary fat intake. Thus, the responses suggest an unwillingness to look objectively at all relevant data, plus a lack of motivation to reexamine long-held nutrition dogma.

The lesson to be drawn from the WHI study is the importance of a fundamental principle of scientific inquiry: Believe the data. If a well-designed study yields results that negate the hypothesis being tested, the data must not be rejected until a valid reason for doing so is found. If no errors of omission or commission can be found, the possibility exists that some unsuspected variable may have been operating. Hence, negative results could give important direction to future research.

Instead of simply reaffirming support for a low-fat diet, nutritionists might ask whether the role of some other macronutrient and/or micronutrient might be worth exploring.

Implications for Chronic Disease Prevention

Academic nutrition experts like to believe that they have been engaged in prevention of chronic diseases since the mid-1950s with the publication of their government-sponsored dietary guidelines. These guidelines, based on the lipid hypothesis, ushered in an era of fat-phobia that is still with us today. Now, five decades after adoption of these guidelines as official nutrition policy, we have a generation of obese Americans, beset with chronic diseases. Not only have the guidelines failed to keep their promise of preventing cardiovascular diseases, but they may well have played a role in causing an exceptionally large increase in the incidence of lipid abnormalities, type II diabetes, and metabolic syndrome.

As Dr. Sylvan Weinberg, former president of the American College of Cardiology, observed:

> This [low-fat] diet can no longer be defended by appeal to the authority of prestigious medical organizations or by rejecting clinical experience and a growing medical literature suggesting that a much-maligned low-carbohydrate, high-protein diet may have a salutary effect….[23]

Yet it appears that the only change in official recommendations will be an inconsequential redefinition of dietary fat.

A basic flaw that led nutritional science to the detour down the lipid-hypothesis path was neglect of hard science to confirm associations. Even the most competent of epidemiologic studies can only determine association. Other scientific disciplines are required to prove cause-effect relationships. Validation of epidemiologic associations must involve laboratory investigations of biochemical and physiologic mechanisms, and clinical studies. Unfortunately, nutritionists seem to have little interest in how biochemistry, physiology, and other medical sciences might provide nutritional studies with a solid scientific foundation.

Prevention of nutritionally based chronic diseases is a long-term strategy. It cannot replace the current diagnose-and-treat scenario in the near term for palliation of today's nutritional diseases. However, as a start, an objective, scientifically based nutrition program that educates the public about the true relationship among macro/micronutrients, health, and disease may eventually eliminate or at least delay the onset of the modern nutritional diseases that are devastating today's health and the medical system. A failure of prevention is a serious blow to any chance of alleviating the growing economic burden of medical care.

Implications for Physicians

Medical education covers such a tremendously wide range and volume of information necessary to the diagnosis and treatment of disease that ancillary subjects such as nutrition are given only superficial treatment. Physicians rightfully have assumed that nutritional science can provide whatever information they require. Medical organizations must serve their members by demanding current, unbiased, accurate information from nutrition scientists. As patients look to their physicians for all manner of advice on health, including nutrition, physicians will ultimately be held responsible for errors. Physicians must also recognize that there is no drug that will cure a nutritional disease.

Conclusion

An op-ed article in *The Wall Street Journal*, from a physician critical of alternative therapies, presents some thoughts that nutritional scientists who continue to promote the low-fat diet, despite negative results from scientific studies, should bear in mind. This prophecy may well predict the fate of the lipid hypothesis:

> There are the conflicting tides of belief and fact, and each has its own chronology. Things don't change quickly, but over time a cumulative body of evidence becomes compelling. I reflected on this when I read that one major vendor of saw palmetto asserted that he would continue to promote the herb despite the new data [that it was ineffective]. As science spreads in his world, doubt will chip away at blind faith, and he will find a shrinking group of believers.[24]

Fred Ottoboni, M.P.H., Ph.D., and **Alice Ottoboni, Ph.D.**, are retired public health scientists. E-mail: ottoboni@775.net.

REFERENCES

1. WHI—the results are in! *WHI Matters: A Publication of the Women's Health Initiative* 2006;11:1.
2. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progesterone in healthy postmenopausal women. *JAMA* 2002;288:321-333.
3. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006;354:669-683.
4. Wactawski-Wende J, Kotchen JM, Anderson GL, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancers. *N Engl J Med* 2006;354:684-696.
5. Prentice RL, Caan B, Chlebowski RT, et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA* 2006;295:629-642.
6. Beresford SA, Johnson KC, Ritenbaugh C, et al. Low-fat dietary pattern and risk of colorectal cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA* 2006;295:643-654.
7. Howard BV, Van Horn L, Hsia J, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA* 2006;295:655-666.
8. Ottoboni A, Ottoboni F. The Food Guide Pyramid: will the defects be corrected? *J Am Phys Surg* 2004;9:109-113.
9. U.S. Department of Agriculture. MyPyramid.com. Available at: www.mypyramid.gov. Accessed Dec 20, 2006.
10. Kava R. Low-fat diet doesn't prevent chronic disease—or does it? *ACSH in Action,* Spring 2006, p 2.
11. Parker-Pope T. In study of women's health, design flaws raise questions. *Wall Street Journal*, Feb 28, 2006, p A1.
12. Stein R. New data on health: studies in confusion. *Washington Post*, Feb 19, 2006, p A1.
13. Baker L. Diet study finds little effect on chronic disease in women. *UB Reporter* 2006;37(20):1. Available at: www.buffalo.edu/reporter. Accessed Jan 31, 2007.
14. Davis J. Low-fat, high-fruit diet may not stop disease. *HealthNEWS* March 2006. Available at:www.healthnews.uc.edu/publications/findings/?/1552/1554. Accessed Dec 20, 2006.
15. Kantrowitz B, Kalb C. Food news blues. *Newsweek,* Mar 13, 2006, pp 44-50.
16. Harvard School of Public Health Nutrition Source. Low-fat diet not a cure-all. Available at: http://www.hsph.harvard.edu/nutritionsource/low_fat.html. Accessed Dec 20, 2006.
17. Mayer-Davis E. Yes, diet matters. Surprising findings of WHI are not cause to abandon nutrition. *DOC News* 2006;3(Apr):3. Available at: http://docnews.diabetesjournals.org. Accessed Jan 31, 2007.
18. The real scoop on the women's health studies. *Stanford Magazine* 2006;34(May/June):31. Available at: www.stanfordalumni.org/news/magazine. Accessed Jan 31, 2007.
19. Low-fat diet's benefits for women less than expected, Stanford researcher says. Stanford press release, Feb 7, 2006.
20. Ravnskov U. *The Cholesterol Myths: Exposing the Fallacy that Saturated Fats and Cholesterol Cause Heart Disease.* Washington, D.C.: New Trends Publishing; 2000.
21. Colpo A. *The Great Cholesterol Con.* Lulu Press; 2006. Available at: www.lulu.com. Accessed Dec 20, 2006.
22. Willett WC. Chapter four. *Eat Drink, and Be Healthy: the Harvard Medical School Guide to Healthy Eating*. New York, N.Y.: Free Press, Simon & Schuster; 2003.
23. Weinberg SL. The diet-heart hypothesis: a critique. *J Am Coll Cardiol* 2004;43:731-723.
24. Groopman J. No "alternative." *Wall Street Journal*, Aug 8, 2006, p A12.