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The Women's Health Initiative: Implications for clinicians

ABSTRACT

The Women's Health Initiative (WHI), the largest and longest randomized controlled study to date of the effect of dietary change on disease outcomes in postmenopausal women, failed to show that a low-fat diet prevents breast cancer, colon cancer, or cardiovascular disease. However, as the authors point out, the WHI Extension Study provides opportunities to assess whether nearly significant differences in breast cancer rates at 8 years become significant after 10 years of follow-up.

KEY POINTS

Colon cancer rates did not differ between the dietary intervention group and the comparison group, but the number of polyps and adenomas reported was significantly lower in the dietary intervention group.

Risk factors for coronary heart disease improved slightly with the diet, but by trial year 3, differences in overall rates of coronary heart disease and stroke in the two groups were not statistically significant.

When stratified by quartiles, those who reduced their intake of saturated and *trans*-fatty acids the most, or who increased their intake of fruits and vegetables the most, appeared to have a moderate reduction in the risk of coronary heart disease.

MORE THAN 2 YEARS have passed since we published the results of the Women's Health Initiative (WHI), which caused a storm of information—and misinformation—about the effect of long-term dietary intervention on disease outcomes in postmenopausal women. Now that the dust has long settled, what have we learned from this landmark study?

The WHI results led to numerous additional analyses of all aspects of the study.[1–7] What are the implications of all the analyses to clinical practice?

In this article, we summarize key aspects of the clinical trial, including study design, interventions, main results, and future plans. We also discuss potential clinical applications and practical considerations for public health efforts.

WHO WAS ELIGIBLE, WHO WAS NOT

A total of 48,835 postmenopausal women were randomly assigned to either no dietary intervention (n = 29,294) or a dietary intervention (n = 19,541) (see below).[7] Participants were followed at 40 clinical centers between 1993 and 2005.[4] Their mean age was 62.3 years; 18.6% were members of minorities.

Women were eligible if they were postmenopausal and had a daily dietary fat intake of at least 32% of total calories, based on assessment via a food-frequency questionnaire. They were excluded from the study if they had any of the following: a history of breast cancer, colorectal cancer, or other cancer except skin cancer during the past 10 years; type 1 diabetes; a medical condition in which the predicted survival was less than 3

years; and a potential barrier to adherence to the study regimen, including alcoholism or a lifestyle that involved often eating meals away from home.

THE WHI DIET: LESS FAT, BUT MORE FRUITS, VEGETABLES, GRAINS

The WHI dietary intervention was designed to prevent breast cancer, based on the evidence available when the study was planned. The targets included a total fat intake of less than 20% of energy (in kilocalories), increasing the intake of fruits and vegetables to at least five servings per day, and increasing the intake of grains to at least six servings per day.

Although reduction in saturated fat intake per se was not part of the WHI protocol, we assumed from previous pilot studies[8] that the reduction of total fat intake would simultaneously produce a reduction in saturated fat intake to 7% of total calories.

A simpler dietary intervention

The WHI did not recommend a specific total calorie intake or weight loss

Unlike the 2006 American Heart Association guidelines and the US Department of Agriculture's Dietary Guidelines for Americans 2005, the WHI dietary intervention had no specifications for dietary fiber, specific fatty acids (*trans*-fatty acids, omega-3 fatty acids, conjugated linoleic acid), complex carbohydrates, whole grains, vegetable protein, or other factors that have emerged as potential risk factors for cardiovascular and other chronic diseases since the study began. The WHI intervention also included no specific recommendation for total calorie intake, nor were patients in the intervention group encouraged to lose weight, as this could have confounded the results of the dietary intervention.

Education and encouragement

Those in the intervention group were each assigned a fat-gram goal, calculated on the basis of height. They were taught how to monitor their intake of total fat, fruits, vegetables, and grains. They attended intensive behavioral modification sessions to encourage them to keep to the dietary program: 18 group sessions in the first year and quarterly maintenance sessions thereafter, touching on a wide variety of nutrition- and behavior-related topics.[7,9] Specially trained and certified nutritionists supervised the dietary intervention and the behavioral modification sessions according to the WHI study protocol.

Control-group participants received a copy of the US Department of Agriculture's Dietary Guidelines for Americans[10] and other health-related materials. They had no contact with the study nutritionists.

Other arms of the study

The WHI trial design included several arms,[4,11–13] and many participants joined more than one arm: 20,592 postmenopausal women (42.2% of the total enrollment) chose dietary modification only, 8,050 (16.5%) chose diet plus hormone replacement therapy, 25,210 (51.6%) chose diet plus calcium and vitamin D supplementation, and 5,017 (10.3%) enrolled in all three.

Length of follow-up

Participants were followed from enrollment until they died, were lost to follow-up, or requested no further contact, or until the trial's planned completion date, regardless of adherence to the dietary intervention, according to intention-to-treat analysis. All participants were contacted by clinic staff at 6-month intervals to provide updates on their health outcomes.

Factors assessed

Height, weight, waist circumference, and blood pressure were measured at annual visits using standardized procedures. Fasting blood samples were collected at baseline and at year 1 from all participants and from a subsample of 2,816 women (5.8% of the study population) at years 3 and 6. This subsample was randomly chosen with oversampling of minority women, for whom the odds for selection were six times higher than for white women.

Physical activity was assessed at baseline and at years 1, 3, 6, and 9. Walking and participation in sports and hours of activity per week were calculated for each participant. Physical activity was expressed as metabolic equivalent tasks per week for the analyses.

A food-frequency questionnaire[6] to assess average dietary intake in the past 3 months

was given at baseline and at year 1 for all participants. A third of all participants completed the questionnaire each year in a rotating sample. Completion rates were 100% at baseline and 81% thereafter. Follow-up data were collected from years 5 through 7. Also, 4-day food records were provided by all women before randomization.

HOW OUTCOMES WERE ASSESSED

The primary assessments of clinical outcome[1–3] were mammographic screening, a self-reported medical history documented by a review of medical records, and electrocardiograms digitally obtained every 3 years. Mammograms and electrocardiograms were centrally adjudicated. The diagnosis of acute myocardial infarction was based on an algorithm that included cardiac pain, enzyme levels, and electrocardiographic readings.

OVERALL RESULTS

At 8.1 years, the incidence of breast cancer was 9% lower in the intervention group than in the comparison group (95% confidence interval [CI] = 0.83–1.01; P = .07, P = .09 weighted for length of follow-up).[3] Subgroup analysis further showed that women who reported higher intakes of total dietary fat at baseline reduced their risk of breast cancer by 22% (95% CI = 0.64–0.96). Whether extended follow-up will show a significant association has yet to be determined.

Colon cancer rates did not differ between groups, but the number of polyps and adenomas reported was significantly lower in the dietary intervention group.[1] The rate of colon cancer will also be included in the extended follow-up study of the WHI.

Risk factors for coronary heart disease in both groups—including levels of serum total cholesterol and serum low-density lipoprotein cholesterol, body weight, body mass index, diastolic blood pressure, and factor VIIc—improved slightly, but at year 3 of the trial, differences in overall rates of coronary heart disease and stroke in the two groups were not statistically significant.[2] In addition, the low-fat diet intervention was associated with a reduction in blood estradiol concentrations between baseline and year 1.[3] At the end of the study, however, differences in rates of breast cancer, colorectal cancer, and heart disease between the two groups were not statistically significant.

TABLE 1

Women's Health Initiative: Nutrition improved, but some improvements faded over time

DIETARY FACTORS	BASELINE	1 YEAR	6 YEARS
Total energy (kcal/day)			
Diet group	1,790.2	1,500.5	1,431.8
Comparison group	1,789.4	1,593.8	1,546.2
Total fat (% of energy)			
Diet group	37.8	24.3	28.8
Comparison group	37.8	35.1	37.0
Saturated fat (% of energy)			
Diet group	12.7	8.1	9.5
Comparison group	12.7	8.1	12.4
Fruits and vegetables (servings per day)			
Diet group	3.6	5.1	4.9
Comparison group	3.6	3.9	3.8
Grains (servings per day)			
Diet group	4.7	5.1	4.3
Comparison group	4.8	4.2	3.8

RESULTS OF DIETARY MODIFICATIONS

Fat as a percentage of total calories

At the beginning of the WHI, all participants reported consuming an average of 35% of their caloric intake from fat (TABLE 1). At 1 year from baseline, the fat intake decreased to 24.3% in the intervention group (short of the study goal of 20%); this level had risen again to 26.7% by year 3 and to 28.8% at the end of the study. Stratified by quartile, women who achieved the greatest reductions in saturated and *trans*-fatty acids or the largest increases in their intake of fruits and vegetables appeared to have a moderate reduction in the risk of coronary heart disease.[2] Women in the comparison group also decreased their fat intake initially, but to a lesser degree, and gradually increased it again thereafter. The mean net difference in self-reported total fat intake

Colon cancer rates were similar, but patients in the diet group had fewer polyps and adenomas

between the intervention group and the comparison group at 6 years was 8.2% ($P < .001$) (study goal, 13%).[1–3]

Intake of fruits, vegetables, and grains

At baseline, fruit and vegetable intake averaged 3.6 servings per day (TABLE 1). In the intervention group, this increased to 5.1 servings per day at year 1, and to 5.2 servings at year 3, but at the end of the study it had decreased to 4.9 servings.

Women in the intervention group were eating 4.7 servings of grains per day at baseline. This increased to 5.1 servings at year 1 and then decreased to 4.6 servings at year 3 and to 4.3 servings at the end of the study. It seems that as the women grew older their determination to increase servings of these foods diminished.

Proponents of some currently popular diets blame weight gain on a higher intake of carbohydrates, but the women following the WHI low-fat diet did not gain weight.[2]

Total fat vs saturated fat

A goal of < 20% of total calories from fat may not be reasonable in the general population

Intake of total fat and saturated fat decreased in the intervention group during the study, but the difference between fat intake in the intervention group and that in the comparison group did not reach the degree expected.

At year 1, total fat as a percentage of total caloric intake was 10.8 percentage points below that of the comparison group, whereas the study expected difference was 13.0. At the end of the trial, the difference was only 8.2 percentage points, whereas the expected difference was 11.0.

Intake of all fatty acids (saturated and unsaturated) decreased at year 1, but then went back up slightly by the end of the trial but did not exceed baseline levels, and saturated fatty acids remained well below baseline levels: 9.5% vs 12.5% of caloric intake at baseline.[4]

INTERPRETING THE RESULTS

It might be tempting to dismiss the results of the WHI dietary intervention trial as not significant and therefore not meaningful. This would be unfortunate. The trial had some remarkable accomplishments and offers important lessons for future investigations.

The initial reductions in total fat intake were impressive, and women who had the highest total fat intake at baseline achieved the greatest reduction of total fat (to less than 22% of total calories).[3] Nonetheless, the dietary intervention goal of less than 20% of calories from fat was not achieved despite intensive dietary counseling and a highly motivated study population. Thus, this dietary fat target may not be reasonable in the general population.

Also, despite the absence of targeted intervention on specific fatty acids, the observed blood cholesterol levels were as expected based on the well-known formula of Mensink and Katan,[14] which incorporates information on changes in saturated fat, polyunsaturated fat, and dietary cholesterol intake. The predicted reduction in low-density lipoprotein cholesterol was 2.7 mg/dL; the observed reduction was 2.3 mg/dL.[2] This illustrates that with greater modifications in specific known dietary risk factors for cardiovascular disease, such as saturated fatty acids, cholesterol, and unsaturated fatty acids, blood cholesterol levels respond in a predictable fashion. This was presumably not observed in WHI precisely because no goals and objectives were provided to participants for intake of saturated or polyunsaturated fatty acids.

Recent findings from the Optimal Macronutrient Intake Trial to Prevent Heart Disease (OmniHeart)[15] further highlight differences in the total cholesterol response to diets of varying macronutrient (carbohydrate, protein, fat) content compared with the WHI dietary intervention.[15] Participants in OmniHeart had reductions in levels of low-density lipoprotein cholesterol that were predictable from the changes reported in intake of saturated fatty acids. Presumably, the results of the WHI intervention would have been similar if the study had included this level of detail.

QUESTIONS REMAIN

Questions from the WHI that need consideration for future clinical applications include whether the study population may have already been "too old" to achieve a benefit

from dietary modification, and whether the best timing for dietary intervention might be earlier adulthood with sustained changes in saturated fat, cholesterol, and unsaturated fat intake throughout life. Future subgroup analyses based on age at baseline will need to address these questions. Likewise, a longer follow-up period may be needed for a definitive evaluation of the impact of a regular low-fat diet on different health outcomes.

As reported by Patterson et al,[16] the major contributors to total dietary fat intake at baseline were "added fats" such as sauces, gravies, butter, and margarines (25.1% of fat intake), followed by meats (20.9% of fat intake), and desserts (12.8% of fat intake). These findings highlight target areas for future interventions in women of this age group.

Another issue is how to standardize the dietary intervention from one clinical center to another—ie, to minimize differences in how each clinical center manages the study patients. Such differences were noted in WHI and other studies.[17] Despite standardized training in delivering the dietary intervention, nutritionists encountered regional and cultural differences that required tailoring the dietary intervention to their patients' needs. Staff turnover, an unavoidable phenomenon in long-term studies, has previously been reported to negatively influence dietary adherence.[18]

LIMITATIONS

A major limitation of diet modification research in general is the self-reporting of dietary intake, primarily by a food-frequency questionnaire. Although the use of a questionnaire is the most practical way to obtain dietary data for large studies, systematic biases may exist that obscure true nutrient-outcome relationships.[19] Biomarker studies of energy balance suggest that people who are overweight or obese may under-report energy intake to a greater degree than people who are not overweight.[20] Also, we still do not know how to get people to follow a healthy diet, although theories and models abound, such as social learning and cognitive-behavioral theory, and a lack of data limits our understanding of factors related to dietary adherence.[21,22]

FUTURE DIRECTIONS IN WHI

The WHI Extension Study is under way and has been funded through the year 2010. Outcomes ascertainment is the primary focus with no ongoing intervention, although the intervention group participants continue to receive a WHI newsletter that simply reiterates the importance of the study and encourages ongoing participation. As of 2006, an estimated 84% of the cohort, including both observational study and clinical trial participants, are involved. Efforts continue to recruit the remaining 16%, but many of these participants now consider themselves too old or too feeble to respond reliably.

In regard to breast cancer, the results published in 2006 are promising, albeit not statistically significant, and definitive statements cannot yet be made. However, postmenopausal women who are eating the diets highest in fat may have the greatest benefit from reductions in total fat.

Other considerations regarding the lack of statistically significant differences between groups may include the possibility that women in the intervention group may have been at lower risk for breast cancer at baseline. Likewise, although the results of the WHI dietary intervention do not include a statistically significant impact on colorectal cancer outcomes, the significant reduction in polyps and adenomas may later translate into a reduction in invasive cancer risk.

A challenge is to standardize the dietary intervention between study centers

Finally, although no significant reduction was seen in the rate of death due to cardiovascular causes, greater reductions in saturated and *trans*-fatty acid intake were associated with greater reductions in blood cholesterol and cardiovascular risk.

Numerous subgroup analyses and ongoing assessments of the long-term impact of the diet modification are planned. Further associations are expected to emerge. The current and future results will continue to provide new insights that may lead to new clinical and public health recommendations in the future.

The WHI has raised additional issues that warrant further investigation:

- Will earlier dietary intervention, eg, during premenopausal years or even childhood, alter these results?

- Does the low-fat, high-carbohydrate diet used in WHI facilitate weight maintenance or even weight loss, as proposed by Howard et al[23]?
- Do quantitative changes in physical activity and weight control attenuate morbidity and mortality rates beyond changes in diet alone?
- Do vitamin and mineral supplements or hormone therapy alter disease outcomes or quality of life?
- Which behavioral approaches are best suited to the recruitment of patients for dietary intervention trials? ■

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