Design Paper

Design of the Women's Health Initiative Clinical Trial and Observational Study

The Women's Health Initiative Study Group*

ABSTRACT: The Women's Health Initiative (WHI) is a large and complex clinical investigation of strategies for the prevention and control of some of the most common causes of morbidity and mortality among postmenopausal women, including cancer, cardiovascular disease, and osteoporotic fractures. The WHI was initiated in 1992, with a planned completion date of 2007. Postmenopausal women ranging in age from 50 to 79 are enrolled at one of 40 WHI clinical centers nationwide into either a clinical trial (CT) that will include about 64,500 women or an observational study (OS) that will include about 100,000 women. The CT is designed to allow randomized controlled evaluation of three distinct interventions: a low-fat eating pattern, hypothesized to prevent breast cancer and colorectal cancer and, secondarily, coronary heart disease; hormone replacement therapy, hypothesized to reduce the risk of coronary heart disease and other cardiovascular diseases and, secondarily, to reduce the risk of hip and other fractures, with increased breast cancer risk as a possible adverse outcome; and calcium and vitamin D supplementation, hypothesized to prevent hip fractures and, secondarily, other fractures and colorectal cancer.

Overall benefit-versus-risk assessment is a central focus in each of the three CT components. Women are screened for participation in one or both of the components—dietary modification (DM) or hormone replacement therapy (HRT)—of the CT, which will randomize 48,000 and 27,500 women, respectively. Women who prove to be ineligible for, or who are unwilling to enroll in, these CT components are invited to enroll in the OS. At their 1-year anniversary of randomization, CT women are invited to be further randomized into the calcium and vitamin D (CaD) trial component, which is projected to include 45,000 women. The average follow-up for women in either CT or OS is approximately 9 years. Concerted efforts are made to enroll women of racial and ethnic minority groups, with a target of 20% of overall enrollment in both the CT and OS.

This article gives a brief description of the rationale for the interventions being studied in each of the CT components and for the inclusion of the OS component. Some detail is provided on specific study design choices, including eligibility criteria, recruitment strategy, and sample size, with attention to the partial factorial design of the CT. Some aspects of the CT monitoring approach are also outlined. The scientific and logistic complexity of the WHI implies particular leadership and management challenges. The WHI organization and committee structure employed to respond to these challenges is also briefly described. *Controlled Clin Trials* 1998;19:61–109 © Elsevier Science Inc. 1998

INTRODUCTION

The WHI clinical trial includes three overlapping components, each a randomized controlled comparison among women who are postmenopausal and in the age range of 50 to 79 at randomization. The dietary modification (DM) component randomly assigns 48,000 eligible women to either a sustained low-fat eating pattern (40%) or self-selected dietary behavior (60%), with breast cancer and colorectal cancer as designated primary outcomes and coronary heart disease as a secondary outcome. The nutrition goals for women assigned to the DM intervention group are to reduce total dietary fat to 20% and saturated fat to less than 7% of corresponding daily calories and, secondarily, to increase daily servings of vegetables and fruits to at least five and of grain products to at least six. The hormone replacement therapy (HRT) component is a randomized, double-blind comparison among 27,500 women, with coronary heart disease as the primary outcome, with hip and other bone fractures as secondary outcomes, and with breast cancer as a potential adverse outcome. The design of the HRT component assumes that 45% of women will be post-hysterectomy at randomization, in which case there is a 1:1 randomized double-blind allocation between conjugated equine estrogen (ERT) 0.625 *mg*/day or placebo. The remaining 55% of women, each having a uterus at baseline, are randomized to 1:1 to this same preparation of estrogen plus continuous 2.5 *mg*/day of medroxyprogesterone (PERT) or placebo. Eligible women can be randomized into one or both of the DM and HRT components. At the 1-year anniversary of randomization, all women are further screened for possible randomization into the calcium and vitamin D (CaD) component, which plans to enroll 45,000 women, with hip fracture as the primary outcome and with other fractures and colorectal cancer as secondary outcomes. The CaD component is a 1:1

Table 1 Women's Health Initiative Clinical Trial Partial Factorial Design: Projected Number of Women Entering the Various Trial Components*

Dietary Modification Component		Hormone Replacement Therapy Component				
		Intact Uterus		Without Uterus		Not Randomized
		PERT+	Control	ERT+	Control	
Intervention	19,200	1210	1210	990	990	14,800
Control	28,800	1815	1815	1485	1485	22,200
Not Randomized	16,500	4538	4538	3712	3712	—
	64,500	7563	7563	6187	6187	37,000

*In each cell, approximately 70% of women are projected to be eligible and willing to be randomized to receive calcium and vitamin D supplementation or placebo (1:1 allocation).

+Pert, progestin/estrogen replacement therapy; ERT, estrogen replacement therapy.

randomized double-blind trial of 1000 *mg* elemental calcium plus 400 international units of vitamin D_3 daily, versus placebo. Table 1 shows the anticipated numbers of women in various cells of the CT.

Postmenopausal women ages 50 to 79 who are screened for the CT but prove to be ineligible or unwilling to be randomized are offered the opportunity to be one of 100,000 women enrolled in an observational study (OS). The OS is intended to provide additional knowledge about risk factors for a range of diseases, including cancer, cardiovascular disease, and fractures. It has an emphasis on biological markers of disease risk and on risk factor changes as modifiers of risk.

There is also an emphasis on the inclusion of women of racial/ethnic minority groups, with an overall target of 20% in both the CT and OS. Such a fraction will allow meaningful study of disease risk factors within minority groups in the OS, while certain CT subsamples are weighted heavily in favor of the inclusion of minority women in order to strengthen the study of intervention effects on specific intermediate outcomes (e.g., changes in blood lipids or micronutrients) within minority groups.

Age distribution goals are also specified for the CT as follows: 10%, ages 50–54; 20%, ages 55–59; 45%, ages 60–69, and 25%, ages 70–79. While the age range of 55 to 69 may be regarded as most natural for the "treatments" to be tested, there was also interest in having a sufficient representation of younger (50–54) postmenopausal women for intermediate outcome (biomarker) studies and of older (70–79) women for studies of treatment effects on quality of life measures, including aspects of physical and cognitive function.

With a projected 164,500 women enrolled in a complex program at 40 clinical centers (CCs) in the United States, the WHI is perhaps the most massive and challenging program ever undertaken. It has a budget of $628 million over the 15-year period, 1992–2007. Not surprisingly, a good deal of preliminary research and advance planning were necessary to provide sufficient bases for the development of such a program. An account of the evolution of the WHI has previously been provided [1]. Key preliminary studies included the National Cancer Institute-sponsored Women's Health Trial [2,3] and the subsequent Women's Health Trial: Feasibility Study in Minority Populations [4], which demonstrated the feasibility of recruiting postmenopausal women to a dietary intervention trial and the feasibility of such women making a major dietary change toward a low-fat eating pattern, and the National Heart, Lung and Blood Institute-sponsored Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, which examined the effects of various postmenopausal hormone replacement therapy regimens on heart disease risk factors [5], endometrial pathology [6], and bone mineral density [7].

The next section provides a description of the rationale behind the choice of the specific interventions used in each of the three CT components and of the designated clinical outcomes in both the CT and OS. The presentation then turns to a discussion of study design choices and statistical aspects of the design, followed by a brief description of CT monitoring issues. Finally, a description is given of the organizational and management approach to this complex undertaking, including mention of a committee structure designed to ensure adequate communications and decision-making procedures and to preserve investigator interest.

CHOICE OF INTERVENTIONS AND OUTCOMES IN THE WHI CT AND OS

Dietary Modification Component

Rationale for and Feasibility of a Clinical Trial of a Low-Fat Eating Pattern

Nutrition, in its broadest sense, very likely plays a fundamental role in breast and colon cancer incidence [8]. Documented breast cancer risk factors, including age at menarche, adult height, and postmenopausal body mass, suggest that adult and early nutrition each may exert its own influences. A breast cancer prevention hypothesis [9] motivated the series of NCI-sponsored feasibility studies mentioned above.

The extent to which modifications of the diet alone can reduce cancer incidence has been studied for at least 5 decades. Rodent feeding experiments dating back to the 1940s [10] indicate a promoting role for both total calorie consumption and for fat calorie consumption specifically, in mammary tumorigenesis [11–13]. Tumors are promoted in older as well as in immature female animals [14]. Consumption of both polyunsaturated and saturated fat appears to be related to mammary tumor risk [15, 16]. Increased consumption of either saturated or polyunsaturated fat increases circulating levels of reproductive hormones in older female primates [17]. In comparison, rodent feeding studies point to a more consistent role for saturated fat consumption in colonic tumorigenesis [18].

Epidemiologic study of these associations began in the 1970s. Ecologic associations were observed between national mortality rates for cancers of the breast, colon, and selected other cancer and corresponding national estimates of per capita food supply. More recent analyses of this type [19–22] indicate similar strong relationships between the cancer incidence rates of breast, colon, rectum, ovary, and endometrium among women ages 50 to 69 and per capita fat supply, with corresponding relationships among males for cancers of the colon, rectum and prostate. Such analyses also suggest an association between breast cancer risk and both saturated fat and, particularly, polyunsaturated fat, while the corresponding colon cancer association is primarily with saturated fat. These associations are supported by analyses relating changes in fat supply within countries and corresponding lagged changes in cancer incidence rates [22].

The animal experiments and ecologic studies stimulated a substantial number of case-control and cohort studies of these same associations, beginning in the middle to late 1970s. Howe et al [23] presented a combined analysis of the data from 12 breast cancer case-control studies involving several thousand cases and controls. They reported a highly significant positive relationship between postmenopausal breast cancer risk and estimated fat intake, though they interpreted the magnitude of the association to be less than that projected from the international data analyses. A recent pooled analysis of seven cohort studies [24], however, did not demonstrate any significant relationship between breast cancer risk and estimated dietary fat consumption. An overview of the colorectal cancer case-control study data [25] and specific cohort studies [26, 27] yielded somewhat variable results concerning an association with estimated fat intake.

To summarize, analysis of international variations in cancer incidence rates suggests relationships with dietary fat consumption that would have great

public health importance. For example, Prentice and Sheppard [22] project that a 50% reduction in fat consumption could eventually reduce the risk of postmenopausal breast cancer, colon cancer, and rectal cancer by 61%, 67%, and 29%, respectively, in the United States. The international comparisons are supported by animal feeding experiments and time trend studies, and they can provide an explanation for the cancer incidence experiences of first-generation migrants from low-fat- to high-fat-consuming countries [28–30]. There is even some supportive data on migrants from high-fat- to low-fat-consuming countries [31]. In contrast, analytic epidemiologic studies, which are usually regarded as yielding more reliable epidemiologic data, have often yielded weak or equivocal results.

Each of these types of observational studies has substantial methodologic limitations. The ecologic studies involve crude dietary measurements and available data have not allowed a careful attempt to control confounding. On the other hand, such studies have included populations with widely varying dietary habits and a dietary measure that reflects average nutrient availability for tens of thousands of persons in each country. In contrast, cohort and case-control studies of these associations have generally taken place within populations having a modest range of fat intake and have involved assessment instruments having substantial random measurement error [32] along with likely important systematic errors [33, 34]. These features combine to yield results of unknown reliability from both ecologic and analytic data sources [35].

In view of the preceding discussion, one can view the dietary fat reduction and breast and colon cancer prevention as strong hypotheses in the sense that there are various sources of data suggesting effects of substantial importance to public health. However, these hypotheses and, more specifically, the hypothesis that a change in the diet of postmenopausal women can influence the subsequent risk for these diseases have not yet been tested. Note that even reliable determination of dietary fat and disease associations would likely leave open the question of disease-risk reduction following a fat reduction in the middle and later decades of life and the time course of any such reduction. Hence, there is a clear need for a randomized intervention trial to test the cancer-reduction potential of a low-fat eating pattern at a predefined age. The targeted diseases are among the most common cancers among women in the United States. Specifically, among American women, breast cancer is the cancer with the greatest incidence and the second greatest mortality, after lung cancer, with more than 175,000 cases and 44,500 deaths per year, while colorectal cancer is the third leading cause of cancer incidence and mortality, with more than 75,000 new cases and 31,000 deaths per year.

In general, the data sources alluded to above suggest a stronger association of dietary fat with postmenopausal as compared to premenopausal cancer risk [22]. For this reason, as well as because of the lower incidence rates among younger as compared to older women for each of the outcomes of interest, it seem natural to focus initially on dietary change among postmenopausal women.

As noted previously, a series of NCI-sponsored feasibility studies of a low-fat intervention trial was carried out between 1984 and 1995 under the name Women's Health Trial (WHT). These studies indicated that postmenopausal women in the middle and later decades of life could be recruited in large

numbers to such a trial, could make a major change in their reported fat consumption to about 20% of daily calories from fat, and could largely maintain such a reported change over a study follow-up period of up to 2 years [2–4]. Also, a subset of the initial group of WHT women, contacted about 2 years after the end of any dietary intervention or maintenance activities, reported having retained a substantial portion of the change in their use and consumption of dietary fat [36]. Closely related feasibility studies among women of a broader range of ages took place in Canada over the same time period with similar results [37].

The dietary intervention program developed in the WHT appeared to lead to the desired maintained reduction in total fat, with evidently little change in the ratio of polyunsaturated to saturated or monounsaturated fat, according to food records supplied by participating women. Reductions in polyunsaturated as well as saturated fat was viewed as desirable in view of a potential role of polyunsaturated fats in relation to breast and other cancers. This intervention program also yielded a measurable increase in consumption of vegetables and fruits and a very modest increase in grains as natural partial replacements for high-fat foods [3]. These associated dietary changes may enhance any cancer-preventing potential of dietary intervention activities, as there is a body of analytic epidemiologic literature suggesting a possible protective effect of vegetables and fruits for breast cancer [23] and of fruits, grains, and foods containing various sources of fiber for colon cancer [38–40].

The WHI dietary intervention program refines the program used in the preceding WHT feasibility studies. In contrast to those earlier studies with the single goal of fat reduction, additional daily goals of five or more servings of vegetables or fruits and six or more servings of grain products are specified for women assigned to dietary intervention. The WHI monitors the achievement and maintenance of dietary goals using food records, food frequency questionnaires, 24-hour dietary recalls, and specific self-monitoring instruments to ensure that sufficient differences between intervention and control groups are created in relation to each dietary goal, while maintaining as the highest priority the goal of determining the percentage of calories derived from total fat. Note, however, the resulting reduced ability to attribute any observed dietary-intervention effects on breast cancer or other outcomes to specific elements of the dietary modification program. Such attribution will require an observational, analytic approach using self-reported dietary data, the limitations of which have already been indicated.

Coronary heart disease (CHD) risk reduction is a secondary goal of the dietary modification (DM) clinical trial component. International comparisons [41] and migrant studies [42] suggest an association between dietary saturated fat and coronary heart disease mortality. As for the cancers discussed above, and presumably for the same methodologic reasons, it has been difficult to demonstrate a consistent association between estimated saturated fat consumption and CHD incidence or mortality within populations in analytic epidemiologic studies. However, reductions in dietary fat and cholesterol are widely known to reduce total and low-density lipoprotein cholesterol in human clinical studies, although results appear to be somewhat less consistent in women than in men [43, 44] and no study of long-term effects has been conducted. The Women's Health Trial feasibility studies [2, 3] yielded reductions in total blood

cholesterol of about 5–6% on average among dietary intervention women at 1 and 2 years of follow-up. Furthermore, a number of cohort studies have shown a clear relationship between blood cholesterol and CHD incidence and mortality and, importantly, randomized clinical trials in men and women have shown that reductions in CHD events have been observed in relation to the use of cholesterol-lowering drugs [45–47]. While these studies do not prove the hypothesis that the low-fat eating pattern being taught in the WHI will lead to a reduction in CHD risk, WHI investigators viewed this hypothesis as somewhat too well-established to provide the primary motivation for the DM component. However, CHD results will contribute in an important manner to the assessment of overall benefits versus risks associated with the DM intervention and to an assessment of the overall public health impact that may follow from a widespread adoption of a low-fat eating pattern.

Various other clinical outcomes, including other cancers, other cardiovascular diseases, and diabetes, may be favorable impacted by a low-fat eating pattern. The WHI will monitor a broad range of clinical and behavioral outcomes in order to provide as complete a view as practical of the effects of intervention on health.

Dietary Modification Intervention Program

The WHI dietary intervention implements a change of eating behaviors rather than a prescribed diet. Several psychosocial and behavioral themes are central to the intervention program, including motivation and reinforcements, self-determination, self-management, skills training, social support, relapse prevention, self-reliance, and self-efficacy. Dietary intervention women are assigned to a permanent intervention group of, preferably, 10 to 12 members. They meet weekly with a trained nutrition interventionist for 6 weeks, every other week for an additional 6 weeks, and monthly for the course of the first year. Each intervention woman also has one individual dietary counseling session with her interventionist between 12 and 16 weeks from the beginning of intervention to ensure the nutritional balance of her new dietary pattern. Dietary maintenance sessions occur approximately quarterly after the first year of dietary intervention, along with optional, peer-led monthly meetings of the intervention groups.

Appendix I provides an outline of the objectives and content of each of the 18 group intervention sessions as well as of the individual session during the first intervention year. Appropriate concepts about nutrition and behavior are integrated into each session in a cumulative fashion. The early sessions (sessions 1–8) cover the major sources of fat in the American diet and the critical nutrition skills (shopping, recipe modification, restaurant selection) needed for major changes in fat consumption. Later topics are more specialized and emphasize behavioral skills such as problem-solving for low-fat party and holiday foods. Topics that deal with maintenance (relapse prevention, creating long-term guidelines) are included in the later sessions.

The behavioral topics are organized around strategies. The first two behavioral topics are self-management and motivation for low-fat dietary change. The core of the necessary behavior skills is self-management. The identification and reinforcement of motivations to change are included in the first session to

develop and maintain participants' interest in changing. Social influences and support are included in the next five sessions because of the critical nature of social influences on eating and on successful health-behavior change. Time management, problem-solving, and coping with stress are introduced after the initial large decreases in fat consumption have occurred to help incorporate the new low-fat behaviors into everyday living. Finally, relapse prevention is included in the last sessions to assist with long-term maintenance.

Nutrition and behavioral strategies are integrated into each session for several reasons. The intervention materials consistently focus on dietary behaviors, not nutrients, as a means of changing fat consumption. Therefore, integrating the two types of strategies in each session is important. Implementing the philosophy of a self-directed, self-controlled eating plan means that each nutritionist and participant must view dietary changes as a series of activities that will ultimately become part of everyday life. Integrating dietary plans with behavioral strategies in each session helps participants integrate them into daily life. The relative focus on nutrition is highest in the early sessions during the time of most intensive dietary change, while the emphasis on behavioral strategies to maintain the early dietary changes increases in later sessions. The nutrition and behavioral aspects of the WHI dietary modification program are described in detail in Tinker et al [48].

Hormone Replacement Therapy Component

Rationale for a Clinical Trial of HRT

The hormone replacement therapy component of the CT is intended to test the hypothesis that women assigned to estrogen replacement therapy (ERT) will have lower rates of coronary heart disease and osteoporosis-related fractures. Because progestin and estrogen (PERT) are used together in women with a uterus in order to diminish the risk of endometrial cancer, we will also assess whether the hypothesized cardioprotective effects of estrogen in preventing coronary heart disease and fractures will be retained with this regimen. The incidence of breast cancer and endometrial cancer will be monitored during and after the trial.

Coronary heart disease was selected as a primary outcome in light of recognition that heart disease is the major cause of morbidity and mortality among postmenopausal women, especially over the age of 65, and because the hypothesized cardioprotective effect of HRT cannot be proven with observational studies alone. The frequency of osteoporosis-related fractures, a major cause of morbidity in elderly women, may be reduced by a proportion similar to that for CHD.

The idea that postmenopausal estrogen replacement therapy may reduce the risk of coronary heart disease has been evolving for some time. Prior to 1980, some believed that exogenous estrogen would increase the risk of cardiovascular events based, in part, on the adverse effects of estrogen therapy in men with heart disease [49] and in those being treated for prostate cancer [50] and on the emerging evidence that oral contraceptive pills were associated with an increased risk of stroke, thromboembolic events, and coronary heart disease among women over 35 [51]. However, the role of menopause as a risk

factor for coronary heart disease was recognized during the 1980s [52–54]. Menopause has an adverse effect on the lipid profile. Low-density lipoprotein rises for approximately 10 to 15 years after menopause, and high-density lipoprotein drops [55]. Weight gain and a change in body fat distribution, increases in blood pressure, and a host of other metabolic factors are among the other changes that may affect risk.

Epidemiologic evidence for a cardioprotective effect of postmenopausal estrogen therapy began to emerge in the late 1970s and early 1980s. A majority of the more than 30 observational studies reported note a benefit from estrogen [56, 57]. Supporting this conclusion are studies showing that age-adjusted, all-cause mortality is also lower among estrogen users [58, 59]. It is important to note, however, that only one small prospective controlled trial with disease endpoints has been conducted [60].

The mechanism for the hypothesized improvement in cardiovascular risk with estrogen is not completely understood, but up to half of the effect may be explained by the beneficial lipid changes that occur with estrogen administration [59]. Exogenous estrogen increases HDL and lowers LDL [5, 61, 62]. Other factors that may play a role are changes in coagulation factors, blood pressure, insulin, body fat distribution, and direct effects on the arterial wall [5, 63].

Despite the apparent strength of the observational study reports, major questions remain. First, observational studies are always subject to potential bias. The studies of hormone replacement therapy have the potential for selection (or prescribing) bias. During the past 3 decades physicians in the United States and Europe have received many negative and contradictory messages about the safety of hormone replacement therapy, making it likely that women who received estrogen were healthier than women who did not take estrogen [64]. Estrogen users have been found to have a demographic profile associated with better health in at least two cohort studies [65, 66]. Although several investigators have reported a benefit of estrogen for heart disease after controlling for risk factors [58, 67], potential biases cannot be entirely eliminated in this post hoc fashion.

Second, the effect of the combined estrogen plus progestin replacement on coronary heart disease must be determined. Progestin is given in combination with estrogen to women with a uterus in order to reduce the increased risk of endometrial cancer that would otherwise be associated with unopposed estrogen [68]. Most epidemiologic data related to cardioprotective effect is based on women who took unopposed estrogen. Progestin can have the effect of reversing, or at least blunting, the lipid effects of estrogen that are presumed to be beneficial [5, 69, 70].

Estrogen stabilizes bone mineral density, and many observational studies support a reduction in fracture rates [57]. Estrogen replacement therapy is currently FDA-approved for both the prevention and the treatment of osteoporosis. In observational studies, current users and long-time users of estrogen appear to get the most benefit [71, 72], but concern about the potential for selection bias can again be raised [72]. Furthermore, the effect of combined therapy has not been extensively studied. Finally, an accurate assessment of the overall risks and benefits of hormone replacement therapy are especially important because of the availability of alternatives to estrogen for the treatment of osteoporosis [73].

The potential adverse effect that generates the most concern is the possibility of an increased risk of breast cancer with long-term estrogen use. The numerous observational studies have yielded results that are consistent with a modest elevation in risk that may increase with duration of use [57, 74, 75]. An additional adverse effect of progestin has also been posited, although available data sources appear to be somewhat inconsistent [76–78].

Finally, the WHI is recruiting women older than those included in typical randomized trials, with about two-thirds of the cohort over 60 years of age, and trial follow-up will be longer than any previous trial. For example, considerable evidence suggests that administration of hormones to women early in menopause stabilizes bone mineral density, but there are many fewer pertinent data about the effects of starting hormones later, especially over age 60. It is critical to determine the overall benefits and risks associated with long-term HRT because the hypothesized benefits for heart disease and fractures may accrue primarily to long-term users, and hypothesized adverse effects on breast cancer may increase with duration of use.

In summary, the potential bias introduced by the prescribing habits of the preceding decades may be important; the effects of combined hormone replacement therapy on cardiovascular disease and breast cancer must be carefully assessed; and overall benefits and risks of long-term hormone therapy need to be assessed. None of these issues can be completely resolved by additional observational studies. In fact, many expert observers have recommended that a randomized trial of hormone replacement therapy with "hard" endpoints be performed [69, 76, 79].

Exogenous ovarian steroid hormones have multiple target tissues in addition to the bone, endometrium, vascular system, and breast, and hormone replacement therapy has the potential to affect the risk of several additional conditions [57]. Epidemiologic studies suggest the following potential associations: an adverse effect on risk for cholelithiasis and systemic lupus erythematosis; a beneficial effect on risk for dementia, particularly Alzheimer's disease, as well as stroke and colon cancer; and a putative increased risk of thromboembolic disease. The WHI will monitor all of these conditions.

Selection of HRT Regimens

The WHI protocol calls for randomization of hysterectomized women to either estrogen (conjugated equine estrogens 0.625 *mg*/day) or placebo. Women with a uterus will be randomized to either estrogen (conjugated equine estrogens 0.625 *mg*/day) plus progestin (medroxyprogesterone acetate 2.5 *mg*/day continuous) or placebo.

Statistical power considerations led to the use of a single estrogen in the CT. Conjugated equine estrogens are the most widely prescribed estrogen preparations in the United States [80]. There are substantial data from both observational studies and short-term clinical trials that suggest an association of this form of exogenous estrogen with the desired level of effects on lipids and other metabolic factors; however, this choice is somewhat arbitrary in the sense that other forms of orally administered estrogens probably have similar effects. On the other hand, it is generally considered appropriate in a large-scale clinical trial to use the intervention for which there is the most extensive

preceding evidence. Partly for this reason, transdermal estrogen was viewed as inappropriate for this trial.

The dose of 0.625 *mg*/day was chosen because it is considered the minimum effective dose for the preservation of bone mineral density [81]. This dose has been demonstrated to lead to a significant rise in HDL cholesterol and drop in LDL cholesterol [5]. Cyclic administration of estrogen, typically for 25 days of the month, is still widely used in the United States, but it appears to confer no advantages over the more convenient daily administration chosen for this trial.

The original protocol called for women with a uterus to be randomized to placebo, combined estrogen and progestin, or unopposed estrogen. The rationale for this approach was the uncertainty related to the potential adverse effects of adding progestin, leading to the possibility that the overall risk-benefit ratio for unopposed estrogen, despite the increased endometrial cancer rate, might be superior to combined therapy. After the publication of the initial PEPI Trial results [5], the unopposed estrogen regimen was discontinued from the study. The PEPI Trial was not of sufficient size and duration to demonstrate an increased risk of endometrial cancer in the group using unopposed estrogen, but it did report an excess risk of serious endometrial hyperplasia (adenomatous and atypical) of approximately 40%. Although estrogen-induced endometrial hyperplasia is usually readily reversible with short-term progestin therapy, most clinicians recommend conversion to combined therapy if the woman is to remain on hormone therapy. Following this guideline and extrapolating from the incidence of hyperplasia in the PEPI study, we estimated that in the WHI, well over half of the unopposed-estrogen users might have to be converted to combined therapy within the first 5 years of WHI, and only a small proportion would remain on their original treatment assignment at the end of follow-up. The end result would be the inability to test the effects of unopposed estrogen on coronary heart disease or fractures. The approximately 300 women already randomized to the unopposed estrogen arm were informed of this change in protocol and, if they chose to remain in the trial, were converted in an unblinded fashion to the combined estrogen-progestin regimen.

Several progestins are used around the world in postmenopausal hormone therapy. Medroxyprogesterone is the most widely prescribed progestin in the United States. Compared with synthetic 19-nortestosterone, medroxyprogesterone acetate is less metabolically active yet provides the desired endometrial protection [82]. The dosage of medroxyprogesterone required depends on the regimen employed. The most well-studied regimens at 10 *mg* given for at least 12 days each month, cyclically, and 2.5 *mg* given daily.

A major decision the WHI faced was whether to administer the progestin on a cyclic or a daily regimen. First, data from most randomized trials, including the recently completed 3 year PEPI Trial, suggest that the cyclic and the daily regimens have similar metabolic effects. The daily method is somewhat more convenient than having to remember to stop and start on a particular cycle day. The major known difference between these two regimens is the pattern of vaginal bleeding. With cyclic therapy, the majority of women will experience regular cyclic bleeding in response to withdrawal of the progestin. The expectation of bleeding is a major reason women choose not to start HRT [83] and is a major reason they discontinue HRT. The daily regimen was originally developed to improve this situation. Over 90% of women who remain on combined

daily estrogen and progestin for at least 12 months will develop amenorrhea. The trade-off is that most women will have up to several months of unpredictable spotting and/or bleeding when beginning this regimen. Some evidence, however, suggests that women over 60, who constitute the majority of subjects in the WHI, experience less of this "start-up bleeding." Therefore, for reasons of convenience and a more acceptable bleeding profile and in the absence of other medical reasons to choose one over the other, the WHI adopted the daily progestin.

Calcium and Vitamin D Component

Rationale for a Clinical Trial of Calcium and Vitamin D Supplementation

This component of the WHI CT is designed to test the hypotheses that women who are randomized to receive a combination of calcium and vitamin D supplementation will have a lower risk of hip fracture and, secondarily, other fractures and colorectal cancer than women who are randomized to receive corresponding placebos. Breast cancer risk reduction is another potential benefit. To date, the effectiveness of these dietary supplements is uncertain, and evidence about their potential value has been based almost exclusively on observational studies.

About one of every six white women and one of every twenty or thirty African-American and Latina women will suffer a hip fracture during her lifetime [84]. Women with lower bone mass in the hip have a much greater risk of hip fracture [85], so interventions that increase bone mass or reduce the rate of bone loss in the hip are likely to decrease fracture risk.

Adults lose a certain amount of calcium daily through urine and other routes [86]. If the amount of calcium lost consistently exceeds the amount absorbed, a loss of bone results. A woman's capacity to absorb calcium declines with menopause and aging [87]. Estrogen replacement increases the fractional absorption of calcium [82] and appears to be capable of increasing bone mineral density [7]. It has been recommended that women consume at least 1000 *mg*/day of elemental calcium before menopause and 1500 *mg*/day of calcium after menopause to maintain the balance between calcium absorption and excretion [88]. In contrast to these recommendations, the median daily dietary calcium intakes of postmenopausal women in the United States has ranged from 352 *mg* in black women 80 years old or older to 630 *mg* in non-Hispanic white women 60 to 79 [89], all less than half of recommended levels.

Randomized trials have shown that calcium supplementation slows the rate of bone loss in women [90, 91]. A few observational studies have come to conflicting conclusions about the relationship between dietary calcium intake and risk of hip and other types of fractures [92, 93]. Therefore, it remains uncertain whether calcium supplementation will reduce the risk of hip or other fractures. Nevertheless, many women are taking calcium supplements in the hope that it will reduce their risk of osteoporotic fractures.

Previous research also suggests a potential for vitamin D supplementation in the prevention of osteoporotic fractures. Twenty-five hydroxyvitamin D, or 25(OD)D, is converted in the kidney to $1,25(OH)_2D$ which acts to increase intestinal absorption of calcium. Very low levels of 25(OH)D can limit the

formation of $1,25(OH)_2D$ and lead to osteomalacia, or secondary increases in secretion of parathyroid hormone with more rapid reabsorption of bone. It is believed that vitamin D supplementation may increase intestinal absorption of calcium, but it might also have independent effects on bone metabolism that slow bone loss [94]. One nonrandomized controlled trial [95] found that a single annual injection of 150,000 to 300,000 IU of ergocalciferol was associated with a lower risk of all fractures combined, in nursing home and geriatric clinic patients 75 years old and older. This treatment has yet to be tested in a randomized blinded trial involving community-dwelling postmenopausal women of a wider age spectrum.

The combination of calcium and vitamin D may offer greater protection against bone loss and fracture than either one alone. One randomized trial found that the combination of 1.2 g of elemental calcium (as tricalcium phosphate) with 800 IU of vitamin D_3 reduced the risk of hip and other fractures by about one-third [96]. However, the long-term care residents involved in this study had low dietary calcium intakes (511–514 mg/day) and low serum levels of 25(OH) vitamin D (13–16 ng/ml) compared with a normal range of 15–50 ng/ml. It is uncertain whether a combination of calcium and vitamin D supplementation will also reduce the risk of fractures in younger, community-dwelling women with a lower prevalence of vitamin D deficiency and a higher level of dietary calcium intake.

Most types of fractures in older women are related to low bone mass [97]. If calcium and vitamin D supplementation decreases the rate of bone loss, it may well decrease the risk of fractures other than hip fractures. In support of this concept is the study of elderly women in French nursing homes [96] where the combination of calcium and vitamin D decreased the rate of both hip and other types of fractures.

A role for calcium and vitamin D has also been proposed in the prevention of colorectal cancer. Fatty acids and bile salts stimulate the proliferation of colonic epithelium. Calcium binds to fatty acids and bile salts, forming insoluble soaps, thereby diminishing these toxic effects [98]. Some observational studies suggest that higher intakes of calcium and vitamin D may decrease the risk of colon cancer [99, 100]. In particular, one study observed significantly lower rates of colon cancer among men whose diets contained at least 1200 mg/ day of calcium. Other studies have found nonsignificant trends [101] or no association [102] between calcium intake and risk of colon cancer or occurrence of colonic polyps [103].

Some investigators postulate that vitamin D might also have an independent protective effect against colorectal cancer. An inverse relationship between serum levels of 25(OH)D and the subsequent risk of colorectal cancer has been reported [104] and disputed [105], but 25(OH)D levels also reflect the intake of dairy products and, hence, of calcium. The Health Professionals Follow-up Study and Nurses Health Study found no association between vitamin D intake and diagnosis of colorectal adenomas [103]. There have been no human trials of the effect of calcium or vitamin D supplements on the risk of colon cancer.

As mentioned above, some scientists have also hypothesized a protective effect of vitamin D on breast cancer. Most breast cancer cell lines contain receptors of $1,25(OH)_2D$ [106] and *in vitro* application of analogs of $1,25(OH)_2D$ may shrink some breast cancers [107]. However, there is very little information

about the potential effects of 25(OH)D on breast cancer. Observations of lower rates of breast cancer in regions that receive more sunlight [108, 109] have led to speculation that higher levels of 25(OH)D might reduce the risk of breast cancer.

Calcium and Vitamin D Supplementation Protocol

At their first annual visit, participants in the DM or HRT trials are asked if they are interested in joining the calcium and vitamin D trial. Willing and eligible women are randomly assigned in a double-blind fashion to the supplement or placebo group. The active tablets contain 500 *mg* of elemental calcium (as calcium carbonate) and 200 IU of vitamin D_3. Participants are instructed to take two tablets a day, for a total of 1000 *mg* of elemental calcium and 400 IU of vitamin D_3 daily. They are advised to take the tablets with meals, preferably in divided doses. Those randomized to the placebo group receive matching placebo tablets to be taken in the same fashion.

As noted previously, the primary outcome of the calcium and vitamin D component of the trial is hip fracture. Hip fractures must be confirmed by reports of X-rays or, in uncertain cases, centralized review of X-rays and other diagnostic studies. Other fractures besides hip fractures comprise a secondary endpoint, but a few types of fractures are not counted because they are difficult to diagnose from conventional X-rays (rib fractures) or have not been associated with reduced bone mass (face, skull, finger and toe fractures) [97]. Change in bone mass measured at the hip and spine by dual X-ray absorptiometry (Hologic QDR 2000, Waltham, MA) is an intermediate outcome that is measured in all WHI women who participate at one of three bone densitometry clinical centers. Urine specimens are also collected from these women and stored for studies of intervention effects on bone metabolites.

The elemental calcium is administered in the form of calcium carbonate, the most widely used supplement in the United States. Most participants in the trial are expected to have dietary calcium intakes exceeding 500 *mg*/day; thus, the addition of 1000 *mg*/day will yield an average total calcium intake exceeding 1500 *mg*/day in the active treatment group. This level is in accord with recommendations for reduction of bone loss and would, theoretically, be sufficient to reduce substantially the risk of colon cancer [100]. This dose of calcium carbonate has a low frequency of hypercalciuria, has not been associated with an increased risk of kidney stones [110], and rarely produces hypercalcemia.

A dose of 400 IU of vitamin D_3 exceeds the RDA and reliably raises 25(OH)D levels into normal ranges in vitamin D-deficient women. This dose of vitamin D_3 is safe and has not been associated with any serious side effects.

The Observational Study Component

The observational study (OS) component of the WHI will complement the clinical trial by assessing new risk indicators and biomarkers for disease in a large prospective cohort of about 100,000 postmenopausal women. The OS cohort will be comprised of clinical trial screenees who are either ineligible or unwilling to participate in the CT. Thus, the marginal costs of the OS cohort

assembly are comparatively small and the strategy takes advantage of the CT's need to screen a large number of potential participants to achieve the targeted number of randomizations.

As with the CT, OS enrollees will be followed for an average of 9 years. Minority women will be well represented, with a target enrollment of 20% minority women in the study-wide cohort. The large size of the cohort and the effort to include sizable proportions of women of racial/ethnic minority groups will permit the assessment of important exposure-disease relationships in individual minority groups. As minority women have not been well represented in most previous cohorts, the OS will provide a unique resource for exploring potential differences in risk factors for major health outcomes across ethnic groups.

Participants in the OS have a baseline screening visit that includes the following elements, which are shared by CT women: physical measurements (height, weight, blood pressure, heart rate, waist and hip circumferences), collection of blood specimens (stored as serum, plasma, and buffy coat), a medication/supplement inventory, and completion of questionnaires related to medical history, family history, reproductive history, lifestyle/behavioral factors, and quality of life. In addition, an OS questionnaire ascertains additional exposures, including geographic residence history, passive smoking exposure in childhood and adulthood, early life exposures, details of physical activity, weight and weight cycling history, and occupational exposures. The major clinical outcomes of interest in the OS are coronary heart disease, stroke, breast cancer, colorectal cancer, osteoporotic fractures, diabetes, and total mortality. Data collected at baseline will be related to subsequent clinical events, with the goal of improving risk prediction of these major health outcomes in postmenopausal women. Participants in the OS will be mailed annual forms to update selected exposures and ascertain medical outcomes, and they will return for a repeat visit, including blood collection, about 3 years after entry.

The physical measurements, questionnaire and interview data, and repository of biological specimens will permit a broad array of hypotheses to be addressed in the cohort. Most biomarker analyses will be conducted using a "nested" case-control or case-cohort design using the prospectively collected materials and specimens. The OS will provide stable estimates of the magnitude of the effects of established risk indicators (including serum cholesterol and lipoprotein subfractions, blood pressure, body weight, physical activity, diet, and reproductive history), as well as affording an opportunity to identify and test new hypotheses regarding disease etiology in women. The latter will include new potential biomarkers of disease—for example, protein polymorphisms and DNA markers. Finally, the OS is designed to elucidate the mechanisms underlying the ostensibly elevated risk of mortality at low levels of blood cholesterol [111], weight, and blood pressure. The hypothesis that underlying debility and disease are responsible will be tested by relating markers (e.g., serum albumin) of clinical and subclinical disease as well as changes in weight, cholesterol, and blood pressure between the baseline and 3-year visits to subsequent mortality in cohort.

CHOICE OF STUDY POPULATION

Eligibility Criteria

The WHI is designed to be as inclusive as it is practical to be of postmenopausal women, initially in the age range of 50 to 79, with a sufficient follow-up duration to address adequately questions of risks versus benefits and of the public health potential of the CT interventions. The diseases responsible for much of the morbidity and mortality in women are largely concentrated among women who are at least 50 years old. A focus on postmenopausal women is essential for the HRT trial component, while the motivating data for the DM component suggest initial study among postmenopausal women, as was previously mentioned. Motivating clinical trial data for the CaD component have arisen primarily from studies of women who are quite elderly [96].

It might have been considered natural to restrict the study to a somewhat narrower age range, say 55–69, to simplify the verification of postmenopausal status by excluding women under 55, and to enhance the likelihood of sufficient control over food choice and preparation and the ability to participate fully in program activities throughout the follow-up period by excluding women over 69. The HRT treatments under study are, however, of great relevance to early postmenopausal women, so information on a range of intermediate outcomes (e.g., blood lipids, antioxidants, clotting factors, and hormones) in women in the 50–54 age range was regarded as highly desirable. Correspondingly, if the study interventions turn out to be equally efficacious in terms of relative risk reduction throughout the postmenopausal age range, then older women, on average, will contribute most to the testing of study hypotheses by virtue of their higher rates of all the key clinical outcomes. Furthermore, knowledge concerning the effects of treatments on intermediate outcomes and on clinical outcomes related to physical and cognitive function were thought to be of considerable interest among older women. Since the average follow-up period is about 9 years, it seem inadvisable to enroll women older than 79 years.

In view of the differential information contribution by younger women as compared to older women under study design assumptions, and in view of the differing age-incidence curves for the diseases that may be affected by CT interventions, the WHI established target enrollment fractions of 10:20:45:25 for the respective baseline age categories of 50–54, 55–59, 60–69, and 70–79. For example, an overrepresentation in the 50–54 age category for the HRT component may unduly reduce the study's power because the incidence of the primary CHD outcome increases rapidly with increasing age; and it could distort the benefit-to-risk profile because the ratio of breast cancer to CHD incidence is higher among younger postmenopausal women than among older women.

Because the HRT component involves separate randomized comparisons for women with and without a uterus at randomization, it was necessary to specify a target fraction of hysterectomized women into this component. The fraction of 45% was established on the basis of study power and practical recruitment considerations.

As mentioned previously, the WHI plans to enroll women of racial/ethnic minority groups in at least the same proportion as such women exist in the population of women between 50 and 79; that is, 17%, according to the 1990

U.S. census. A specific target of 20% was established in both the CT and the OS. In view of the difficulty that has been experienced in enrolling minorities in some other clinical studies, various efforts are under way to enhance such recruitment. In particular, 10 of the 40 WHI clinical centers are designated as minority recruitment centers on the basis of their access to and history of interaction with large numbers of women in certain population subgroups, particularly African-Americans and Hispanic Americans.

Other eligibility criteria include the ability and willingness to provide written informed consent for the pertinent program components and an expectation of being resident in the study recruitment area for at least 3 years following enrollment.

Exclusion Criteria

Study subjects were excluded from the CT and OS if they had medical conditions predictive of a survival time of less than 3 years; if they were known to have conditions or characteristics inconsistent with study participation and adherence (alcoholism, drug dependency, mental illness, dementia); or if they were active participants in another randomized controlled clinical trial.

Women were excluded from the CT (1) for reasons of competing risks (invasive cancer in the past 10 years; breast cancer at any time or suspicion of breast cancer at baseline screening; acute myocardial infarction, stroke, or transient ischemic attack in the previous 6 months; known chronic active hepatitis or severe cirrhosis), (2) for reasons of safety (blood counts indicative of disease; severe hypertension; or currently use of oral corticosteroids), and (3) for reasons relating to adherence or retention (unwillingness or inability to compete baseline study requirements). In addition, a woman screened at any of three bone densitometry clinics was encouraged to discuss the results of her baseline bone density measurement with her primary care physician to help determine the appropriateness of continued screening for the CT. Women were excluded from the CT if they were found to have femoral neck bone mineral density of more than three standard deviations below the corresponding age-specific mean.

Each CT component incorporated specific exclusionary criteria. The DM component excluded (1) women who had special dietary requirements that were incompatible with the intervention program, (2) women who ate 10 or more main meals per week that were prepared outside the home, (3) women who were unable to complete satisfactorily a 4-day food record, (4) women who had been diagnosed with colon cancer, type I diabetes mellitus, or gastrointestinal conditions that contraindicated a high-fiber diet, (5) women who had had a bilateral prophylactic mastectomy, and (6) women whose food frequency questionnaire estimated dietary percent of calories from fat as being less than 32%. This exclusion was expected to lead to an increase in the difference in average percent of calories from fat between intervention and control groups of 2.5% to 3%, with noteworthy corresponding increases in study power for each clinical outcome.

For the HRT component, women were excluded (1) for various safety reasons (endometrial cancer or endometrial hyperplasia at baseline; malignant melanoma; pulmonary embolism or deep vein thrombosis that was nontraumatic

or that had occurred in the previous 6 months; bleeding disorder; lipemic serum and hypertriglyceridemia diagnosis; current use of anticoagulants or tamoxifen; or PAP smear or pelvic abnormalities) and (2) for reasons of adherence or retention (severe menopausal symptoms inconsistent with assignment to placebo; inability or unwillingness to discontinue current HRT use or oral testosterone use; inadequate adherence with placebo run-in; unwillingness to have baseline or follow-up endometrial aspirations).

The WHI deferred the opportunity for randomization into the CaD component of the CT until the 1-year anniversary of a woman's randomization into the DM and/or HRT trial components, primarily to avoid undue burden on study subjects. The DM intervention program, in particular, is quite time-consuming during its first several months. With this decision, the potential pool of CaD enrollees was fixed by enrollment into the other two trial components; hence it was desirable to minimize additional CaD exclusions. Accordingly, CT women were allowed to enter the CaD component regardless of their baseline calcium intake. However, women were excluded from the CaD component for reasons of safety (1) if she chose to continue vitamin D supplementation in excess of 600 IU per day, (2) if she had a history of renal calculi or hypercalcemia, or (3) if she currently used oral corticosteroids. In addition, women could be excluded at the time of screening for the CaD component for reasons of competing risk or adherence or if they were predicted to have survival expectation of fewer than 3 years.

Overlap among CT Components and OS Enrollment

Important efficiencies arise in the WHI as a result of overlap in the three CT components and because of recruitment of OS participants from the pool of CT screenees.

Overlap between the DM and HRT components will necessarily be fairly small because of the component-specific exclusionary criteria just listed, particularly the food frequency percent of calories from fat exclusion for the DM component and the intended continued use of hormone replacement therapy exclusion for the HRT component. Specifically, the less than 32% of calories from fat exclusion was expected to exclude about 40% of women otherwise eligible for the DM, although this figure turned out to be closer to 50% among women screened in the first years of the WHI. Other DM-specific exclusionary criteria were expected to come into play infrequently among women eligible and willing for the HRT, and a high percentage (e.g., 80–90%) of such women were expected to be willing to be randomized to the DM. Hence, about 40% of women randomized to the HRT component were projected to be randomized to the DM component.

Women potentially eligible for, and interested in, the DM and/or HRT components are invited to the clinic for the first of three screening visits. Women may drop out of potential CT participation as they are screened for clinical, physical, and biochemical exclusionary criteria and as they learn more about the details and demands of participation in the CT. The feasibility studies mentioned earlier suggested that one out of three women making a first screening visit would be randomized to the CT. This leaves a recruitment pool that is expected to be sufficient for the OS, although additional OS recruitment can

take place, if necessary, from the group of women initially contacted for potential CT participation who did not make a first screening visit to the clinic.

STUDY SUBJECT SCREENING AND FOLLOW-UP STRATEGY

Screening

As mentioned previously, the WHI wanted to make the eligibility criteria as broad as was practical in order to enhance the generalizability of the results to the population of postmenopausal women. Therefore, women with prevalent cardiovascular disease or a past history of bone fractures may be included, allowing the study of both primary and secondary prevention in the CT. The study cohort at each clinic can be drawn from a population-based sample, for example, using residential mailing lists; from a sample of convenience, for example, women who respond to media announcements or participate in screening programs or health maintenance organizations; or from a combination thereof. This flexibility in recruitment strategies is expected to have little impact on the generalizability of intervention effects or relative risk estimates, particularly since substantial baseline data are being collected on CT/OS enrollees that can be used to refine such estimates.

Figure 1 shows a model screening strategy for use by the WHI clinical centers. An initial mail contact provides basic information on the WHI and ascertains interest in participation. Interested women are then contacted by phone by trained interviewers or by additional mailings so the women who are ineligible for the CT can be identified. Those continuing to be eligible and interested are scheduled for a first screening visit (SV1), and a packet of materials and forms is mailed to them for their attention prior to SV1. Clinics may, at their discretion, invite such women to a prescreening visit (SV0) to provide information in relation to the personal information form and the food frequency questionnaire. A woman is typically invited for an SV1 only if she continues to be potentially eligible for the DM or HRT components, or both. Figure 1 shows some details of the content of an SV1. A woman ceasing to be willing and eligible for the CT is invited to continue being screened for possible OS enrollment. In fact, a woman fulfilling supplementary OS requirements may be enrolled in the OS at the end of SV1.

Figure 2 shows the content of screening visits 2 and 3. SV2 focuses on clinical activities, including ECG, breast examination, mammogram, and gynecologic examination for potential HRT enrollees. Women being screened for the DM component are also instructed in the completion of a 4-day food record. The third screening visit (SV3) assesses the adequacy of the completed 4-day food record (DM) and of adherence during a placebo run-in period (HRT). Cognitive and physical function status are also assessed on random subsamples of women 65 years of age or older. All CT eligibility criteria are confirmed at SV3 and, if appropriate, a woman proceeds to randomization into one or both trial components. Throughout SV2 and SV3 a woman who proves to be ineligible or unwilling to be randomized to the CT is offered the opportunity for continued screening toward OS enrollment.

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                    ┌─────────────────────────────────────────┐
                    │              Invitation:                 │
                    │  Letter of Invitation and return postcard │
                    └─────────────────────────────────────────┘
                                       │
                    ┌─────────────────────────────────────────┐
                    │           Eligibility Screen:            │
                    │  Screening and invitation of eligibles to SV1, │
                    │  followed by mailing of Personal Information Q*; │
                    │   Food Frequency Q and other materials   │
                    └─────────────────────────────────────────┘
                                       │
  ┌──────────────────────────────────────────────────────────────────────┐
  │                      SCREENING VISIT 1 (SV1)                           │
  │   ┌ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ┐       │
  │     Initial screening consent; review of Personal Information Q,      │
  │   │    Interviewer Administered Q; Physical measures;        │       │
  │     Medications and Supplements inventory; Fasting blood draw;        │
  │   │    FFQ scan and eligibility updates for HRT and DM       │       │
  │   └ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ┘       │
  │                                                                        │
  │                         CT Eligibility                                 │
  │                                                                        │
  │        Yes                                       No                     │
  │   ┌ ─ ─ ─ ─ ─ ─ ─ ─ ─ ┐           ┌ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ┐          │
  │   │       CT          │           │          OS           │          │
  │   │                   │──────────>│                       │          │
  │   │ Detailed description of │     │ OS description and consent; │      │
  │   │ pertinent CT components;│     │    complete Medical,  │          │
  │   │  ascertain willingness  │     │ Reproductive, Family History, │    │
  │   │                   │           │ Personal Habits, Psychosocial, │   │
  │   │                   │           │ and Supplementary OS Q's │        │
  │   └ ─ ─ ─ ─ ─ ─ ─ ─ ─ ┘           └ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ─ ┘          │
  │                                                                        │
  │         CT Willingness          No                                     │
  │    Yes                                                                  │
  │   ┌ ─ ─ ─ ─ ─ ─ ─ ─ ─ ┐                                               │
  │   │ Provide CT consent forms; │                                        │
  │   │    Medical History,       │                                        │
  │   │ Reproductive History, and │                                        │
  │   │ Psychosocial Qs; schedule │                                        │
  │   │          SV2              │                                        │
  │   └ ─ ─ ─ ─ ─ ─ ─ ─ ─ ┘                                               │
  └──────────────────────────────────────────────────────────────────────┘
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* Q - questionnaire. Most listed questionnaires are self-administered.

Figure 1   WHI's model enrollment activities and flow: prescreening through first screening visit.

SCREENING VISIT 2(SV2)
CT Eligible and Consenting

	HRT	DM
Review Q's*	x	x
ECG	x	x
Breast Exam	x	x
Instruct in Four Day Food Record		x
Gynecologic Exam	x	
Dispense Run-in Medication	x	
Schedule Mammogram	x	x
Provide Family History and Personal Habits Q's	x	x

Ineligible or Unwilling →

OS
Confirm OS eligibility
OS description and
consent; complete
Family History
Personal Habits, and
OS Supplementary Q's

SCREENING VISIT 3 (SV3)

	HRT	DM
Review Q's[+]	x	x
Functional Status (subsample)	x	x
Cognitive Function (subsample)	x	
Assess 4DFR adequacy		x
Assess run-in adherence	x	
Confirm CT eligibility	x	x
Randomize	x	x
Intervention	x	x

Ineligible or Unwilling →

OS
Confirm OS eligibility
OS description and
consent; OS
Supplementary Q

* Self-administered questionnaires supplied at Screening Visit 1.
[+] Self-administered questionnaires supplied at Screening Visit 2.

Figure 2   WHI's model enrollment activities and flow: second and third screening visits.

Follow-up

Women in the clinical trial are followed through regularly scheduled examinations to ensure the timely ascertainment of updated medical histories, to monitor the occurrence of possible adverse effects, to dispense study medications, and to promote adherence to the study protocol. All CT women are expected to participate in annual clinic visits, and all are to have intermediate 6-month contacts which, in the case of HRT women in their first 2 years of CT participation and women in their first year of CaD trial participation, are intended to be in the form of clinic visits, but otherwise can be by phone or mail. Rather extensive data are collected at the 1-year visit, as changes in individual characteristics or behaviors between baseline and 1 year provide the principal basis for explanatory analyses of intervention effects on study outcomes.

Some intermediate effects of trial interventions are ascertained by collecting extensive data at 3, 6, and 9 years from randomization and at study close-out on a 6% sample of CT women. To maximize component-specific information, as well as racial/ethnic-specific information, the sampling rate is higher (8.6%) among HRT than among DM women (4.3%), and minority women have odds for selection at least sixfold higher than Caucasian women have. This approach

will allow considerable precision in intermediate outcome studies among African-American and Hispanic American women and some precision for such studies among Native American and Asian-American women.

ECGs are obtained at 3, 6, and 9 years for all CT women. Follow-up mammograms are obtained annually for HRT women and biennially for non-HRT women in the CT. Additionally HRT women are contacted at about 6 weeks from randomization to discuss any concerns related to their HRT trial participation and to identify any adverse experiences they have not reported. A similar contact takes place for women participating in the CaD trial, at about 4 weeks from randomization.

Adherence in the HRT and CaD components is monitored by counting unused pills at regularly scheduled clinic visits. All DM women are asked to complete a food frequency questionnaire at 1 year, while a subsample of women provide such information in the remaining years. DM women in the 6% subsample previously mentioned are also asked to provide 4-day food records at 1 year and 24-hour dietary recalls at 3, 6, and 9 years, while an additional independent 1% sample is selected for 24-hour dietary recall data collection during each follow-up year. In addition, a range of biomarkers is measured in subsamples of CT women in an attempt to provide objective measures of adherence within each CT component.

OS study participants are contacted annually by mail to obtain updates of their medical histories and selected exposure data. They are also mailed an annual newsletter at about 6 months following each such update. At about 3 years after enrollment, all OS participants are invited to a clinic follow-up visit to update selected baseline data, to obtain additional risk factor data, and to collect a blood specimen. A 1% sample of OS participants are asked to return to the clinic between 1 and 3 months after their baseline and 3-year visits to participate in a reliability substudy, at which time blood will be drawn and the measurement of selected data items that are prone to measurement error are repeated.

Both the clinical trial and the observational study provide rich resources for ancillary studies.

SAMPLE SIZE AND POWER FOR THE CT AND OS

Data from preceding observational studies and feasibility clinical trials were used to specify a series of design assumptions for each CT component. These assumptions were then used to determine the sample size necessary to yield study powers in the range 80–95% for the primary endpoint comparisons in each trial component. In each case, power was based on a two-sided 5% level test of significance using a weighted logrank or weighted odds ratio test statistic, with weights based on the intervention-versus-control group hazard ratios, or odds ratios, under design assumptions, as elaborated below. A variety of sensitivity calculations were also carried out to determine how study power at the selected sample sizes may change under departures from design assumptions. Power calculations were also carried out for the OS cohort and for subsets thereof.

The DM Component of the CT

The design assumptions for the DM component build upon those given in Self et al [112] for a design of a full-scale women's health trial of a low-fat dietary intervention in relation to breast cancer incidence. Their calculations involve assumptions concerning the strength of relationship between percent of calories from fat and breast cancer risk, the lag in achieving an intervention effect, dietary adherence, and baseline disease rates and competing risks leading to an estimated 17% lower breast cancer incidence in the intervention-versus-control group and an 80% power for a two-sided weighted logrank test, based on a sample size of 32,000 and an average follow-up period of 8 years. In comparison, the design assumptions for the DM component of the WHI lead to an assumed 14% lower intervention-versus-control breast cancer incidence and a projected power of 86% for breast cancer alone, based on a sample size of 48,000 and an average 9-year follow-up period.

The specific design assumptions for breast cancer in the DM component can be described as follows: the international studies of correlation between diet and cancer incidence described earlier suggest a relative risk of breast cancer of about 0.4 for a lifetime 20% versus 40% of calories from fat diet. This, along with migrant study data also mentioned above, led us to assume a breast cancer relative risk function that declines linearly from unity to 0.5 over a 10-year period and is flat thereafter for an intervention woman adhering to a 20% calories from fat diet compared to a control woman consistently consuming a 40% calories from fat diet. Breast cancer risk was assumed to depend linearly on percent of calories from fat cumulated over the preceding decade.

Dietary adherence assumptions were based on feasibility study results from the Women's Health Trial [2, 3, 112]. Specifically, the difference between control and intervention group average percent of energy from fat in the Women's Health Trial was 14.7% at 1 year and 13.2% at 2 years from randomization. Because average percent of energy from fat at baseline in the WHI was about 3% less than anticipated, it was necessary to set daily fat gram goals for intervention women that were considerably more demanding than in the Women's Health Trial. Additionally, the control-minus-intervention difference in average percent of energy from fat was assumed to increase from 0 at randomization to only 13% at 1 year, and subsequently to decrease linearly to about 11% at 10 years from randomization, to allow some modest loss of adherence over time among intervention women and/or downward drift in percent of energy from fat among control group women. These assumptions were combined with age-specific breast cancer incidence rates for 1985–1989 from the SEER program, acknowledging the target WHI age distribution, to compute the power for a two-sided weighted logrank test, with weights increasing linearly from baseline to 10 years, under various assumptions concerning total sample size and average follow-up duration in the DM component. United States mortality rates were used to accommodate competing risks. The upper part of Table 2 shows selected power calculations of this type, including the design assumption 86% power at a total sample size of 48,000. Power calculations for the DM component assume a randomization ratio of 40:60 for the intervention-versus-control group. This imbalance is motivated by a desire to control total trial cost, as the cost associated with a DM intervention woman's participation considerably

Table 2 Statistical Power for the Dietary Modification Component of the CT

	Intervention Effect (%)*	Average Years of Follow-up	Disease Probability (×100)		Power % at Selected Sample Sizes		
			Placebo	Intervention	42,000	48,000	54,000
Breast Cancer	14	6	2.05	1.85	39	44	48
	14	9	2.92	2.52	81	86	89
Colorectal Cancer	20	6	1.07	0.92	40	45	49
	20	9	1.61	1.29	86	90	93
Coronary Heart Disease	14	9	3.02	2.63	68	74	79
	14	9	4.58	4.00	82	86	90

* One minus ratio of intervention versus control incidence rates at planned study termination, multiplied by 100.

☐ Power for design assumption highlighted.

exceeds that for corresponding DM control women. Note that the power for this study component would be enhanced if disease risk decreased more rapidly than is implied by our assumed linear relationship as dietary percent of calories from fat is reduced toward the 20% target.

The same data sources and assumptions were used to calculate power for colorectal cancer as a distinct primary outcome for the DM component, with the exception that the full compliance relative risk reduction (hazard ratio) was assumed to exceed that for breast cancer by a ratio of 10:7, based on somewhat stronger and more consistent epidemiologic associations, the possibility of a more rapid disease rate change following the adoption of a low-fat diet, and the possible greater contribution from the achievement of vegetable, fruit, and grain goal elements of the DM intervention. As shown in Table 2, these assumptions yield a projected power of 90% for the comparison of colorectal cancer incidence in the intervention-versus-control group at an average 9 years of follow-up at the design sample size of 48,000.

The approximate 6% reduction in total serum cholesterol observed over the first 2 years of the WHT feasibility study was used to project a coronary heart disease incidence reduction of 14% over an average 9-year follow-up period. U.S. age-specific mortality rates for the years 1980–1988 were projected forward linearly to yield CHD mortality rates for the study period. CHD incidence rates were obtained from these by multiplying by 2.5, based on incidence-to-mortality ratios in the Framingham study, and were then reduced by one-third, somewhat arbitrarily, to acknowledge an anticipated healthy volunteer effect. These assumptions led to a projected power of 86% for CHD at an average 9 years of follow-up (Table 2). Because ECGs, the basis for silent myocardial infarction diagnoses, are conducted at baseline, 3, 6, 9 years, the power just cited is based on a weighted odds ratio statistic, with incidence data grouped into 3-year periods. The weights were 0.5, 1.0, and 1.0 for the 0 to 3-year, 3- to 6-year, and 6- to 9-year periods, respectively, corresponding to an assumption of an intervention effect that is achieved linearly over the first 3 years from randomization.

In view of the large sample size (48,000) in the DM component and the broad range of possible pathophysiologic effects of a low-fat eating pattern, intervention-versus-control group power for total mortality is also of interest. Such power is dominated by the intervention effect on mortality from diseases other than breast cancer, colorectal cancer, or coronary heart disease. Specifically, if mortality rates for breast and colorectal cancer and coronary heart disease are assumed to be 25%, 35%, and 40% of corresponding respective incidence rates, and any intervention effect on mortality from other causes is assumed to occur linearly over a 10-year period, then the power for a total mortality comparison between intervention and control groups at an average 9 years of follow-up is only 29% if the intervention has no effect on deaths from other causes, but it rises to 85% if overall deaths from other causes are reduced by as little as 5% in the intervention group as compared to the control group.

The HRT Component of the CT

Observational studies, reviewed above, suggest that CHD incidence may be reduced by as much as 50% among women taking ERT over a 10-year period.

Preliminary epidemiologic data do not provide a clear basis for differing CHD relative risk assumptions for ERT versus PERT. Hence, for both ERT versus placebo and PERT versus placebo, we assume an estimated full-compliance incidence-rate reduction of 30% which is achieved linearly over the first 3 years after randomization.

PEPI data [5] and early experience in the WHI led us to assume that 6% of women assigned to ERT or PERT will stop their assigned HRT during the first year after randomization, a rate that is assumed to drop to 3% per year in subsequent years. Additionally, it is assumed that 1.5% of control group women will switch to ERT or PERT in each of the first 5 years from randomization, after which the rate will drop to 1.0% per year.

CHD incidence rates and competing risk mortality rates, as previously described, were combined with these intervention effects and adherence assumptions to project an overall 21% lower CHD incidence in intervention-versus-control groups at an average 9 years of follow-up for both ERT and PERT. The upper part of Table 3 shows CHD projected power of 88% for PERT versus placebo, based on the 55% of women having an intact uterus at randomization and a total HRT sample size of 27,500. Also shown is a projected 81% power for ERT versus placebo based on the 45% of women who are post-hysterectomy at randomization. Randomization to active-versus-placebo preparations is on a 1:1 basis for both PERT and ERT comparisons.

Hip (proximal femur) fractures constitute a subsidiary outcome for the HRT component, while power calculations were also conducted for a combined site fracture outcome consisting of proximal femur, distal forearm, proximal humerus, pelvis, and vertebra. Observational studies suggest that ERT may reduce hip and combined site fracture rates by about 50%. To accommodate biases in these studies we assumed a full-compliance relative risk of 30% that is achieved linearly over a 3-year period. Age specific fracture incidence rates were based on data from a Rochester, Minnesota, study (personal communication from Dr. L.J. Melton) with a healthy volunteer correction of 0.8. The combined fracture incidence was additionally multiplied by 0.8 to account for fractures at more than one of the five anatomical sites. When combined with the adherence and lag assumptions previously mentioned, we can project a 21% lower hip fracture and a 20% lower combined fracture incidence for ERT versus placebo. The same assumptions were applied to the PERT-versus-placebo comparisons giving the projected power shown in Table 3. WHI has moderate power for detecting an effect of PERT or ERT on hip fracture and excellent power ($> 99\%$) for combined fractures.

As previously noted, an increase in breast cancer risk is an important potential adverse effect of ERT or PERT. Because of the importance of this issue, and because an increase in breast cancer may arise later than any reduction in CHD or fractures, an additional 5 years of follow-up is planned to ascertain breast cancer incidence. Power calculations were conducted assuming full-compliance relative risks of 1.2 and 1.3 that are realized linearly over the first 10 years of HRT usage. When combined with HRT adherence, lag, and competing risk assumptions, these lead to average increases of 15% and 22%, respectively, in intervention-versus-control-group breast cancer incidence over an average 14-year follow-up period. Table 3 indicates that the HRT trial component has appreciable power to detect such a breast cancer increase, particularly at the stronger of the two relative risk specifications.

Table 3 Statistical Power for the Hormone Replacement Therapy Component of the CT

| | | | Disease Probability (×100) | | Power % at Selected Sample Sizes | | | | | |
| | | | | | Women with a Uterus (55%) PERT vs. Placebo | | | Hysterectomized Women (45%) ERT vs. Placebo | | |
	Intervention Effect (%)*	Average Years of Follow-up	Control	Intervention	25,000	27,500	30,000	25,000	27,000	30,000
Coronary Heart Disease	21	6	3.26	2.60	66	70	74	57	62	65
	21	9	5.02	3.97	85	88	90	77	81	84
Hip Fractures	21	6	1.87	1.49	47	51	54	40	43	46
	21	9	3.13	2.46	69	73	77	60	65	68
Combined Fractures	20	6	7.82	6.29	97	98	99	93	95	96
	20	9	11.83	9.46	>99	>99	>99	99	99	>99
Breast Cancer	15	14	4.53	5.21	51	55	59	44	47	50
	22	14	4.56	5.58	83	87	89	75	79	83

* Absolute value of one minus intervention versus control incidence rates at planned study termination, multiplied by 100.

□ Power for design assumption highlighted.

The above power calculations were all given separately for ERT versus placebo and PERT versus placebo. It is also of interest to consider power for overall tests of HRT versus placebo, with stratification on baseline uterine status. In particular, under the design assumptions listed above, with a 22% intervention effect there is a 79% power of detecting a breast cancer difference between HRT and placebo after an average of only 9 years of follow-up (not shown in Table 3). The corresponding projected powers (also not shown) for heart disease, hip fractures, and combined fractures are 99%, 94%, and >99%, respectively, at an average 9 years of follow-up.

The CaD Component of the CT

As noted in the previous section, about 40% of HRT women, or 11,000 women, are expected to be randomized to the DM component. This degree of overlap leads to a total CT sample size of 64,500 (48,000 plus 27,500 minus 11,000). We project about 70% of these women to be willing and eligible for the CaD component, leading to a projected sample size of 45,000 to be randomized on a 1:1 basis to active CaD versus placebo. For hip and combined fractures, the same assumptions regarding relative risk and adherence were made as with HRT. Fracture incidence rates and competing risk mortality rate assumptions were as described previously. Table 4 shows corresponding power projection for hip fractures and combined fractures at average follow-up times of 5 and 8 years, since the CaD randomization takes place 1 year into CT participation. Note the substantial power for both hip and combined fractures even at sample sizes considerably smaller than 45,000. Colorectal cancer power for the CaD comparison was calculated under the assumptions previously described, along with a relative risk assumption that leads to a 19% overall intervention effect at planned study termination. As shown in Table 4 there is a projected 85% power for detecting a reduction in colorectal cancer incidence among women receiving calcium and vitamin D as compared to the control group under these design assumptions.

Partial Factorial Aspects of Sample Size and Power

The hypothesized effects of each of the three CT interventions has some influence on the underlying disease rates upon which the other intervention effects apply. These corresponding influences on projected study power are, however, quite minor for each CT comparison. Somewhat greater power influences could occur if the relative risk change associated with a given intervention is appreciably altered by the presence of active treatment in one or both of the other CT interventions. For example, one can hypothesize a lesser fracture risk reduction associated with CaD or HRT if a woman is simultaneously assigned to the active form of the other treatment. Similarly, the HRT or DM relative risks for CHD may be less if the woman is in the active group for the other intervention, and breast cancer risk reduction associated with DM may be reduced by the use of HRT. However, the power projections given in Tables 2–4 are still approximately correct, even if the relative risk function for one intervention varies with the others, provided the hypothesized intervention

Table 4 Statistical Power for the Calcium and Vitamin D Component of the CT

	Intervention Effect (%)*	Average Years of Follow-up	Disease Probability (×100)		Power % at Selected Sample Sizes		
			Control	Intervention	25,000	35,000	45,000
Hip Fractures	21	5	1.51	1.21	60	74	84
	21	8	2.68	2.11	87	95	99
Combined Fractures	20	5	6.50	5.28	99	>99	>99
	20	8	10.48	8.38	>99	>99	≥99
Colorectal Cancer	19	5	0.86	0.75	20	27	33
	19	8	1.42	1.15	60	75	85

* One minus ratio of intervention versus control incidence rates at planned study termination, multiplied by 100.

□ Power for design assumption highlighted.

effects are interpreted as intervention effects averaged over the other treatment assignment categories.

Observational Study Power

Under the age distribution intended for the CT, annual projected incidence rates per 1000 enrollees in the OS are approximately 5.0 for CHD, 3.0 for breast cancer, 1.8 for colon cancer, and 4.0 for hip fractures. Various less common diseases, particularly other cancers, other cardiovascular diseases, and site-specific fractures, are also of interest in the OS. Hence, generic power calculations were conducted for annual incidence rates of 0.1, 0.5, 1.0, 2.0, and 5.0 per thousand.

While the characteristics or exposures to be related to disease risk may involve a variety of measurements, many analyses, especially exploratory analyses, will involve comparisons between two groups distinguished by one or more characteristics. Hence, power calculations were carried out for a binary characteristic or exposure, with exposure frequencies taking values 0.5%, 1.0%, 10.0%, 30.0%, or 50.0%.

Odds ratios relating such a binary exposure variable to a disease ranged over the values 1.25, 1.50, 1.75, 2.00, and 3.00. The smaller odds ratios are of interest in relation to exposures that are difficult to measure. For example, random measurement error for some exposures (e.g., dietary factors, physical activity measures) may severely attenuate the odds ratio toward one. For example, an odds ratio of 2.0 relating actual exposure to disease may be attenuated to an odds ratio of $\exp\{(1/3)\log 2\} = 1.26$ between the measured exposure and disease, under plausible measurement model assumptions.

Many OS analyses will involve the processing of specimens or questionnaire data from women developing a given disease along with a suitable number of time-from-enrollment matched controls (i.e., nested case-control sampling). The power of a matched case-control analysis based on a cohort of size n is approximately equal to that of a full-cohort analysis based on a sample of size $nk(k+1)^{-1}$, where k is the number of controls per case [113]. Hence, for example, a 1:1 matched case-control analysis based on a cohort of size 80,000 is approximately equal to a full-cohort analysis based on a cohort of size 40,000.

Most OS analyses will make provision by stratification, matching, or regression modeling for factors that have the potential to confound the association under study. Such control, essential to accurate odds ratio estimation, tends to yield corresponding tests of association of somewhat reduced power. As such power reductions will typically be quite minor, we have made no provision for confounding in OS power calculations.

OS power calculations were conducted for the full cohort of size 100,000 as well as for subcohorts of sizes 80,000, 40,000, 20,000, 10,000, 6,000, and 2,000. All power calculations are based on a two-sided odds ratio test at a 5% significance level [e.g., 114].

Table 5 shows power calculations for an OS subsample of size 40,000 as corresponds, for example, to comparisons between exposure variable quintiles using the entire cohort. An odds ratio as small as 1.50 for an exposure having a frequency of 0.50 can be detected with a probability (power) of 90% or greater by an average of 3 years of follow-up for diseases such as breast cancer, hip

Table 5 OS Power Calculations for a Subsample Size of 40,000

Annual Disease Incidence per 1000 Women

Average Years of Follow-up		0.1			0.5			1.0			2.0			5.0		
Exposure Frequency	Odds Ratio	3	6	9	3	6	9	3	6	9	3	6	9	3	6	9
0.50%	2.00															0.53
	3.00												0.57		0.87	0.98
1.00%	1.75															0.67
	2.00														0.70	0.89
	3.00											0.76	0.94	0.88	1.00	1.00
10.00%	1.25													0.64	0.81	0.88
	1.50											0.79	0.93	1.00	1.00	1.00
	1.75						0.66		0.66	0.79	0.79	0.95	0.98	1.00	1.00	1.00
	2.00					0.64	0.86	0.66	0.94	0.95	1.00	1.00	1.00	1.00	1.00	1.00
	3.00		0.51	0.82			1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
30.00%	1.25											0.61	0.79	0.71	0.95	0.99
	1.50					0.53	0.73	0.53	0.85	0.96	0.85	0.99	1.00	1.00	1.00	1.00
	1.75				0.51	0.84	0.96	0.84	0.99	1.00	0.99	1.00	1.00	1.00	1.00	1.00
	2.00				0.73	0.97	1.00	0.97	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	3.00		0.76	0.93	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
50.00%	1.25									0.56		0.69	0.86	0.79	0.97	1.00
	1.50					0.61	0.80	0.61	0.90	0.98	0.90	1.00	1.00	1.00	1.00	1.00
	1.75				0.59	0.89	0.98	0.89	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	2.00			0.55	0.80	0.98	1.00	0.98	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	3.00		0.81	0.95	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

fractures, or CHD having an annual incidence of at least 0.20%. Such an odds ratio can be detected with a power of 80% for much rarer diseases having an annual incidence of 0.05% by an average of 9 years of follow-up. The calculated power is omitted from Table 5 if it is less than 0.50.

Table 6 gives power calculations for a subsample of size 10,000, the approximate anticipated number of African-American women to be enrolled in the OS. Note, for example, that there will be adequate power by the end of the study to detect an odds ratio of 1.50 or larger for diseases of annual incidence of 2.0% or more, provided the characteristic or exposure arises in about one-half of the women in the subsample.

CT MONITORING

Many aspects of monitoring the WHI clinical trial are similar to those required for monitoring other randomized multicenter clinical trials. A Data and Safety Monitoring Board (DSMB), responsible for monitoring the integrity of the trial and the safety of its participants, meets at approximate 6-month intervals to review the progress of the trial. Members of the DSMB are independent scientists with expertise in women's health, including gynecology, oncology, cardiology, and bone metabolism as well as clinical trial design, statistics, and ethics.

The DSMB reviews many aspects of CT activities. It reviews the informed consent procedures [115] and other informational documents provided to the participants; data on recruitment rates of participants into the trial, focusing on both the number of women recruited and their age and ethnicity distributions; levels of participants' adherence to the interventions, as these also impact upon the trial's power; and rates of adverse events, and it compares these with the randomized groups to check for unexpected side effects. In all these activities, the methodology to be used and the issues to be confronted are similar to those that occur in other trials.

However, there is a major DSMB activity that requires special attention in the WHI, namely, the monitoring of the multiple diseases the WHI interventions may affect. A long-term prevention trial, such as the WHI, and a therapeutic trial have important differences with regard to the aims and conditions of monitoring the disease outcomes [116]. These include the involvement of healthy participants (as opposed to patients), the low mortality and morbidity rates, the potential effects (both beneficial and harmful) on several diseases, and the difficulty of repeating the trial. These considerations lead to a substantial emphasis on global assessment of health effects.

An exercise conducted with the DSMB and with the Design and Analysis Committee of WHI investigators reinforced the need for a major emphasis on global assessments of health in monitoring the WHI CT. Sets of hypothetical interim results (scenarios) of the WHI trial were constructed, and members of the above groups were asked whether, for each scenario, they would or would not recommend stopping a given CT component. The majority vote was then compared to the recommendations obtained from the application of various statistical rules to the same scenarios. We found noteworthy disagreements between the majority vote and the conventional statistical approach based on group sequential testing [117] of the primary disease endpoint. Agreement with the majority vote was much improved when we considered monitoring

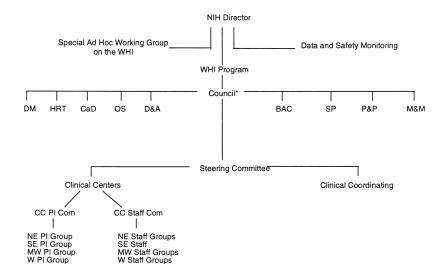**Table 6** OS Power Calculations for a Subsample Size of 10,000

Average Years of Follow-up		Annual Disease Incidence per 1000 Women											
		0.5			1.0			2.0			5.0		
Exposure Frequency	Odds Ratio	3	6	9	3	6	9	3	6	9	3	6	9
1.00%	3.00												0.69
10.00%	1.50												0.75
	1.75									0.63	0.54	0.87	0.97
	2.00						0.50		0.66	0.86	0.77	0.98	1.00
	3.00			0.65		0.82	0.96	0.82	0.99	1.00	1.00	1.00	1.00
30.00%	1.25												0.57
	1.50								0.53	0.72	0.63	0.91	0.98
	1.75					0.51	0.71	0.51	0.84	0.96	0.91	1.00	1.00
	2.00			0.58		0.73	0.90	0.73	0.97	1.00	0.99	1.00	1.00
	3.00		0.86	0.97	0.86	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
50.00%	1.25												0.64
	1.50								0.61	0.79	0.71	0.95	0.99
	1.75					0.59	0.78	0.59	0.89	0.98	0.95	1.00	1.00
	2.00			0.66		0.80	0.93	0.80	0.98	1.00	1.00	1.00	1.00
	3.00	0.58	0.90	0.98	0.90	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

algorithms that not only acknowledge the statistical significance of the primary endpoint and potential adverse outcomes, but also depend importantly on a benefit-versus-risk summary index that is responsive to differences in designated trial outcomes as well to differences in other-cause mortality between active and placebo groups. This activity also served to encourage useful discussion among DSMB members to resolve differences in their recommended actions. These exercises, along with a discussion of implications for monitoring algorithms for the WHI, have been separately described [116]. Note that the data from the ERT-versus-placebo and PERT-versus-placebo comparisons will be considered jointly in early-stoppage considerations in the HRT clinical trial component, and that otherwise, each CT component can be considered independently for early stoppage without compromising the other components.

ASPECTS OF THE ORGANIZATION AND EARLY IMPLEMENTATION OF THE WHI

By its very nature, the WHI is one of the most complex studies ever mounted. The study investigates multiple diseases in a design that includes both a multi-component clinical trial and an observational study to be carried out in two phases. In the first phase of WHI, the protocol and procedures were to be evaluated among 16 vanguard clinical centers before the second phase or entry of the final set of 24 CCs. The combined operational units include the 40 clinical centers and a clinical coordinating center having multiple subcontractors, including a clinical facilitation center to share responsibility for overseeing clinic performance; a bone densitometry center; a drug distribution and specimen storage center; a central laboratory; a central ECG-reading center, and a facility for providing the nutrient database. Within the NIH, the management scheme is also complex. The WHI was initiated within the office of the Director of the NIH under the joint oversight of the Director of the Office of Disease Prevention and the Director of the Office of Research on Women's Health. Various NIH institutes participate including the National Heart, Lung and Blood Institute, the National Cancer Institute, and the National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases.

Following an initial period of study in which the vanguard, but not the other 24, clinical centers were active, the WHI incorporated a regional aspect into study management. The clinical centers were divided geographically into four regions. This approach allowed the clinical centers' principal investigators to be active in decision-making and provided a conduit for staff to share expertise and establish close affiliation with other clinical centers. To mentor the new clinical centers, each new center was aligned with one of the vanguard clinical centers in its region. Each region elected its own chair, and one of the chairs was selected to be the national spokesperson for the clinical centers. Each region meets periodically through telephone conference calls and holds regional meetings to share common problems and solutions.

Figure 3 shows the study's organization, including the Council and Steering Committees representing the group of investigators. The Council provides overall scientific direction to WHI, is empowered to make protocol changes, and may refer management and operational issues to the Steering Committee. It is the arbiter of issues referred by the Steering Committee or the standing

* Council Committees - DM (dietary modification); HRT (hormone replacement therapy); CaD (calcium/vitamin D and osteoporosis); OS (Observational Study); D&A (Design and Analysis); BAC (Behavioral Advisory Committee); SP (special populations); P&P (presentations and publications); M&M (morbidity and mortality)

Figure 3   Organization of the Study.

advisory committees of the Council. The Council comprises the full membership of the Steering Committee, the chairs of nine standing advisory committees, two regional principal investigator group chairs who do not sit on the Steering Committee, two clinical coordinating center representatives, and two program office representatives, for a total potential membership of 18. The Council normally meets quarterly, with face-to-face meetings twice a year, one of which coincides with a WHI annual general meeting. The advisory committees include (1) Dietary Modification, (2) Hormone Replacement Therapy, (3) Calcium/ Vitamin D and Osteoporosis, (4) Observational Study, (5) Special Populations, (6) Behavioral, (7) Publications and Presentations, (8) Design and Analysis, and (9) Morbidity and Mortality.

The Steering Committee is charged with study-wide management and operational decisions. This body is empowered to approve study policy changes, including changes in the WHI manuals, that do not require amendments to the protocol. The Steering Committee has a membership of seven, including the clinical coordinating center Principal Investigator (PI) or designate, the NIH Project Officer, the Chair of the Council, two clinical center PI committee members, including the committee Chair PI, the Chair of the Clinical Center Staff Committee, and one at-large member who is the Chair of one of the standing advisory committees of the Council.

The Clinical Centers have two major committees: the Principal Investigator's Committee consists of the Chairs of each of the regional Clinical Center PI groups; the Clinical Center Staff Committee is made up of the six national

Clinical Center Staff Group Chairs. The six national staff groups are the recruitment coordinators, clinic managers, clinic practitioners, lead nutritionists, data coordinators, and outcome specialists. Initial appointments to any of these fora is for a period of 1 or 2 years; thereafter, all appointments are for 2 years to allow broad participation while maintaining continuity.

Such a large investigative group faces continuing challenges in terms of the selection of participants at national meetings and the ability to communicate rapidly with one another. E-mail through a WHI-wide area network in conjunction with newsletters, surveys, and other communication tools have facilitated communication. Also, the size and number of the various committees allow all investigators to participate to some extent in the decision-making process.

The study organization and committee structure provides the foundation for communications. Protocol policy or procedural issues or problems identified by any study personnel can be brought to the attention of an appropriate committee member or designated clinical coordinating center representative. Issues can be brought up for consideration through the regional structure or at the level of the Council Advisory Committee. Most questions of study operation are directed to the clinical coordinating center, answered directly by e-mail, and disseminated to all clinical centers.

DISCUSSION

The Women's Health Initiative Clinical Trial is a major undertaking that is designed to carefully assess interventions and treatments that have great potential for improving the health of American women. The diseases targeted for prevention, including coronary heart disease, breast cancer, colorectal cancer, and osteoporotic fractures, are among the most common causes of morbidity and mortality in middle-aged and older women. While the sample size for each component of the CT was selected to ensure sufficiently precise intervention effects, information on designated primary outcomes, CT monitoring, and reporting activities will also focus on overall benefit-to-risk assessment and on answering the questions of whether or not, and which, women should undertake the study interventions.

The low-fat eating pattern being tested in the WHI follows decades of observational study indicating that some elements of a Western lifestyle contribute to highly elevated rates of breast, colorectal, and other cancers and of coronary heart disease and other vascular diseases in women. Whether or not a high-fat eating pattern is responsible for an important fraction of such elevation is difficult to establish using nonexperimental methods, and it would be virtually impossible to determine whether or not a major dietary change in the middle and later decades of life can reduce the risk of these diseases without an appropriate randomized dietary intervention trial.

Opinions concerning the benefits and risks of hormone replacement therapy have fluctuated greatly over the past 25 years, during which time there has been substantial evolution in choice of preparation and dosages. The widespread and increasing use of HRT among postmenopausal American women and the complexity of decision-making concerning initial and continuing use of HRT

argue strongly for a randomized trial of sufficient size and duration to compare carefully risks and benefits.

Conducting the DM and HRT components of the clinical trial jointly leads to economies, particularly in such areas as study subject recruitment and clinical center staffing, even though fewer than 17% of women are expected to enroll in both CT components.

Considerably greater overlap is anticipated between the calcium and vitamin D and the other CT components, with about 70% of women enrolled in the CT projected to be randomized to the CaD component. The CaD component is as a comparatively inexpensive addition to the CT that will address critical health issues related to the prevention of osteoporosis and fractures.

The Observational Study component of the WHI is designed to provide an opportunity for participation to the large number of women coming to a WHI clinical center who are found to be unwilling or ineligible for CT randomization. The OS allows the data and specimens obtained during CT screening to be merged with limited additional baseline and follow-up data and specimens to form a large, valuable cohort of middle-aged and older women. This cohort will be used for a range of studies of the determinants of the same broad class of diseases considered in the CT, in a cost-effective manner.

The size and complexity of the WHI CT and OS pose some special logistic and organizational challenges. An organizational structure that adapts to program phases and needs and a data management system that includes a wide area network connecting program units have helped to meet these challenges. The WHI time table calls for study subject recruitment to be completed by early 1998, with follow-up and close-out visits completed by March 2005, to be followed by a period of data analysis and reporting. Of course, outcome data on any of the CT components could possibly be reported early if the accumulated data answer the corresponding public health question, and results from the OS can be anticipated throughout the follow-up period.

REFERENCES

1. Rossouw JE, Finnegan CP, Harlan WR, et al. The evolution of the Women's Health Initiative: perspectives from the NIH. *J Am Med Women's Assoc* 1995;50:50–55.
2. Insull W, Henderson MM, Prentice RL, et al. Results of a randomized feasibility study of a low-fat diet. *Arch Intern Med* 1990;150:421–427.
3. Henderson MM, Kushi LH, Thompson DJ, et al. Feasibility of a randomized trial of a low-fat diet for the prevention of breast cancer: dietary compliance in the Women's Health Trial Vanguard Study. *Prevent Med* 1990;19:115–133.
4. WHT:FSMP Investigator's Group. The Women's Health Trial: Feasibility study in minority populations. Design and baseline descriptions. *Ann Epidemiol* 1996;6:507–519.
5. PEPI Trial Writing Group. Effects of estrogen or estrogen/progestin regimes on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1995;273:199–208.
6. PEPI Trial Writing Group. Effects of hormone replacement therapy on endometrial histology in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1996;275:370–375.

7. PEPI Trial Writing Group. Effects of hormone therapy on bone mineral density: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1996;276:1389–1396.

8. Doll R. The lessons of life: keynote address to the nutrition and cancer conference. *Cancer Res* 1992;52(suppl):2024S–2029S.

9. Prentice RL, Kakar F, Hursting S, et al. Aspects of the rationale for the Women's Health Trial. *J Natl Cancer Inst* 1988;80:802–814.

10. Tannenbaum A. Genesis and growth of tumors III. Effects of a high-fat diet. *Cancer Res* 1942;2:468–475.

11. Carroll KK. Experimental evidence of dietary factors and hormone-dependent cancers. *Cancer Res* 1975;35:3374–3383.

12. Ip C, Carter CA. Requirement of essential fatty acid for mammary tumorigenesis in the rat. *Cancer Res* 1985;451:1997–2001.

13. Freedman L, Clifford C, Messina MW. Analysis of dietary fat, calories, body weight, and the development of mammary tumors in rats and mice: a review. *Cancer Res* 1990;40:5710–5719.

14. Carroll KK, Braden LM. Dietary fat and mammary carcinogenesis. *Nutr Cancer* 1985;6:254–259.

15. Newberne PM, Schrager TE, Conner MW. Experimental evidence on the nutritional prevention of cancer. In: TE Moon, MS Micozzi, eds. *Nutrition and Cancer Prevention: Investigating the Role of Micronutrients.* New York: Marcel Dekker Inc.; 1989:33–84.

16. Freedman LS, Clifford C. Meta-analysis of animal experiments: elucidating relationships between dietary fat and mammary tumor development in rodents. In: *Diet and Breast Cancer*. Advances in Experimental Medicine and Biology 1994;364:93–100.

17. Henderson M. Correlations between fatty acid intake and cancer incidence. In: Nelson GH, ed. *Health Effects of Dietary Fatty Acids*. Champaign IL: American Oil Chemist's Society; 1991:136–149.

18. Zhao LP, Kushi LH, Klein RD, Prentice RL. Quantitative review of studies of dietary fat and rat colon carcinoma. *Nutr Cancer* 1991;15:169–177.

19. Goodwin PJ, Boyd NF. Critical appraisal of the evidence that dietary fat is related to breast cancer risk in humans. *J Natl Cancer Inst* 1987;79:473–485.

20. Rose DP, Boyar AP, Wynder EL. International comparison of mortality rates of cancer of the breast, ovary, prostate and colon and per capita food consumption. *Cancer* 1988;58:2363–2371.

21. Hursting S, Thornquist M, Henderson M. Types of dietary fat and the incidence of breast cancer at five sites. *Prev Med* 1990;19:242–253.

22. Prentice RL, Sheppard L. Dietary fat and cancer: consistency of the epidemiologic data, and disease prevention that may follow from a practical reduction in fat consumption. *Cancer Causes Contr* 1990;1:81–97.

23. Howe GR, Hirohata T, Hislop TG, et al. Dietary factors and risk of breast cancer: combined analysis of 12 case-control studies. *J Natl Cancer Inst* 1990;82:561–569.

24. Hunter DJ, Spiegelman D, Adami H-O, et al. Cohort studies of fat intake and the risk of breast cancer: a pooled analysis. *N Engl J Med* 1996;334:356–361.

25. Howe GR, Aronson KJ, Benito E, et al. The relationship between dietary fat intake and risk of colorectal cancer: evidence from the combined analysis of 13 case-control studies. *Cancer Causes Contr* 1997;8:215–228.

26. Stemmerman GN, Nomura AMY, Heilbrun LK. Dietary fat and the risk of colorectal cancer. *Cancer Res* 1984;44:4633–4637.

27. Willett WC, Stampfer MJ, Colditz GA, et al. Relation of meat, fat and fiber intake to the risk of colon cancer in a prospective study among women. *N Engl J Med* 1990;323:1664–1672.

28. Kolonel LN, Hankin JH, Nomura AM, et al. Dietary fat intake and cancer incidence among five ethnic groups in Hawaii. *Cancer Res* 1981;41:3727–3728.

29. McMichael AJ, Giles GG. Cancer in migrants to Australia: extending the descriptive epidemiological data. *Cancer Res* 1988;48:751–756.

30. Ziegler RG, Hoover RN, Pike MC, et al. Migrant patterns and breast cancer risk in Asian-American women. *J Natl Cancer Inst* 1993;85:1819–1827.

31. Kliewer EV, Smith KR. Breast cancer mortality among immigrants in Australia and Canada. *J Natl Cancer Inst* 1995;87:1154–1161.

32. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol* 1985;122:51–65.

33. Lichtman SW, Pisarka K, Berman ER, et al. Discrepancy between self-reported and actual calorie intake and exercise in obese subjects. *N Engl J Med* 1992;327:1893–1898.

34. Heitmann BL, Lessner L. Dietary underreporting by obese individuals: is it specific or nonspecific? *Br Med J* 1995;311:986–989.

35. Prentice RL. Measurement error and results from analytic epidemiology: dietary fat and breast cancer. *J Natl Cancer Inst* 1996;88:1738–1747.

36. White E, Shattuck A, Kristal A, et al. Maintenance of a low-fat diet: follow-up of the Women's Health Trial. *Cancer Epidemiol Biomark Prev* 1992;1:315–323.

37. Boyd NF, Martin LJ, Beaton M, et al. Long-term effects of participation in a randomized trial of a low-fat, high-carbohydrate diet. *Cancer Epidemiol Biomark Prev* 1996;5:217–222.

38. Greenwald P, Lanza E, Eddy G. Dietary fiber in the reduction of colon cancer risk. *J Am Diet Assoc* 1987;87:1178–1188.

39. Trock BJ, Lanza E, Greenwald P. High-fiber diet and colon cancer: a critical review. In: Mettlin CJ, Aoki K, eds. *Recent Progress in Research on Nutrition and Cancer.* Progress in Clinical and Biological Research, 1990;346:145–158.

40. Howe GR, Benito E, Castelleto R, et al. Dietary intake of fiber and decreased risk of cancer of the colon and rectum: evidence from the combined analysis of 13 case-control studies. *J Natl Cancer Inst* 1992;84:1887–1896.

41. Keys A, *Seven Countries: A multivariate analysis of death and coronary heart disease.* Cambridge, MA: Harvard University Press; 1980.

42. Robertson TL, Kato H, Gordon T, et al. Epidemiologic studies in coronary heart disease and stroke in Japanese men living in Japan, Hawaii, and California: incidence of myocardial infarction and death from coronary heart disease. *Am J Cardiol* 1977;239:244–249.

43. Ernst N, Fisher M, Bowen P, Schaefer EJ, et al. Changes in plasma lipids and lipoproteins after a modified fat diet. *Lancet* 1980;2:111–113.

44. Kris-Etherton PM, Krummel D, Russell ME, et al. The effect of diet on plasma lipids, lipoproteins, and coronary heart disease. *J Am Diet Assoc* 1988;88:1373–1400.

45. The Lipid Research Clinics Coronary Primary Prevention Trial results: I. Reduction in incidence of coronary heart disease. *JAMA* 1984;251:351–364.

46. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987;317:1237–1245.

47. Scandinavian Simvastatin Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–1389.

48. Tinker LF, Burrows ER, Henry H, et al. The Women's Health Initiative: overview of the nutrition components. In: Krummel DA, Kris-Etherton PM, eds. *Nutrition in Women's Health.* Gaithersburg, MD: Aspen Publishers; 1996:510–542.

49. Canner PL, Berge KG, Wenger NK, et al. Fifteen-year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardio* 1986;8:1245–1255.

50. Sotaniemi EA, Kontturi MJ. Serum lipid levels and thromboembolic complications during estrogen therapy of prostatic cancer. *Scand J Urol Nephrol* 1975;9:89–93.

51. Petitti DB, Wingerd J, Pellegrin F, et al. Risk of vascular disease in women: smoking and oral contraceptives, noncontraceptive estrogens, and other factors. *JAMA* 1979;242:1150–1154.

52. Barrett-Connor E, Bush TL. Estrogen and coronary heart disease in women. *JAMA* 1991;265:1861–1867.

53. Korneman GS, ed. *The Menopause: Biological and Clinical Consequences of Ovarian Failure: Evolution and Management.* Norwell, MA: Serono Symposia; 1990:211–224.

54. Godsland IF, Wynn V, Crook D, et al. Sex, plasma lipoproteins, and atherosclerosis: prevailing assumptions and outstanding questions. *Am Heart J* 1987;114:1467–1503.

55. Matthews KA, Meilahn E, Kuller LH, et al. Menopause and risk factors for coronary heart disease. *N Engl J Med* 1989;321:641–646.

56. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med* 1991; 20: 47–63.

57. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992;117:1016–1036.

58. Henderson BE, Paganini-Hill A, Ross RK. Decreased mortality in users of estrogen replacement therapy. *Arch Intern Med* 1991;151:75–78.

59. Bush TL, Barrett-Connor E, Cowan LD, et al. Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the Lipid Research Clinics Program Follow-up Study. *Circulation* 1987;75:1102–1109.

60. Nachtigall LE, Nachtigall RH, Nachtigall RD, et al. Estrogen replacement therapy II: a prospective study in the relationship to carcinoma and cardiovascular and metabolic problems. *Obstet Gynecol* 1979;54:74–79.

61. Rijpkema AHM, van der Sanden AA, Ruijs AHC. Effects of post-menopausal oestrogen-progestogen replacement therapy on serum lipids and lipoproteins: a review. *Maturitas* 1990;12:259–285.

62. Walsh BW, Schiff I, Rosner B, et al. Effects of postmenopausal estrogen replacement on the concentration and metabolism of plasma lipoproteins. *N Engl J Med* 1991; 325:1196–1204.

63. Lieberman EH, Gerhard MD, Uehata A, et al. Estrogen improves endothelium-dependent, flow-mediated vasodilation in postmenopausal women. *Ann Intern Med* 1994;121:936–941.

64. Hemminki E, Sihvo S. A review of postmenopausal hormone therapy recommendations: potential for selection bias. *Obstet Gynecol* 1993;82:1021–1028.

65. Cauley JA, Cummings SR, Black DM, et al. Prevalence and determinants of estrogen replacement therapy in elderly women. *Am J Obstet Gynecol* 1990;163:1438–1444.

66. Espeland MA, Applegate W, Furberg CD, et al. for the ACAPS Investigators. Estrogen replacement therapy and progression of intimal-medial thickness in the carotid arteries of postmenopausal women. *Amer J Epid* 1995;142:1011–1019.

67. Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease: ten-year follow-up from the Nurses' Health Study. *N Engl J Med* 1991;325:756–792.

68. Persson I, Adami H-O, Bergkvist L, et al. Risk of endometrial cancer after treatment with oestrogens alone or in conjunction with progestogens: results of a prospective study. *Br Med J* 1989;298:147–151.

69. Goldman L, Tosteson ANA. Uncertainty about postmenopausal estrogen: time for action, not debate. *N Engl J Med* 1991;325:800–802.

70. Psaty BM, Heckbert SR, Atkins D, et al. A review of the association of estrogens and progestins with cardiovascular disease in postmenopausal women. *Arch Intern Med* 1993;153:1421–1427.

71. Felson DT, Zhang Y, Hannan MT, et al. The effect of postmenopausal estrogen therapy on bone density in elderly women. *N Engl J Med* 1993;329:1141–1146.

72. Cauley JA, Seeley DG, Ensrud K, et al. for the study of Osteoporotic Fractures Research Group. Estrogen replacement therapy and fractures in older women. *Ann Intern Med* 1995;122:9–16.

73. Fleisch H. New bisphosphonates in osteoporosis. *Osteoporosis Inc.* 1993;2:S15–S22.

74. Steinberg KK, Thacker SB, Smith SJ, et al. A meta-analysis of the effect of estrogen replacement therapy on the risk of breast cancer. *JAMA* 1991;265:1985–1990.

75. Dupont WD, Page DL. Menopausal estrogen replacement therapy and breast cancer. *Arch Intern Med* 1991;151:67–72.

76. Bergkvist L, Adami H-O, Persson I, et al. The risk of breast cancer after estrogen and estrogen-progestin replacement. *N Engl J Med* 1989;321:293–297.

77. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med* 1995;332:1589–1593.

78. Stanford JL, Weiss NS, Voigt L, et al. Combined estrogen and progestin hormone replacement therapy in relation to risk of breast cancer in middle-aged women. *JAMA* 1995;274:137–142.

79. Lobo RA, Pickar JH, Wild RA, et al. for the Menopause Study Group. Metabolic impact of adding medroxyprogesterone acetate to conjugated estrogen therapy in postmenopausal women. *Obstet Gynecol* 1994;84:987–995.

80. Wysowski DK, Golden L, Burke L. Use of menopausal estrogens and medroxy-progesterone in the United States, 1982–92. *Obstet Gynecol* 1995;85:6–10.

81. Lindsay R, Hart DM, Clark DM. The minimum effective dose of estrogen for preventing postmenopausal bone loss. *Obstet Gynecol* 1984;63:759–763.

82. Whitehead MI, Hillard TC, Crook D. The role and use of progestogens. *Obstet Gynecol* 1990;75:59S–76S.

83. Ferguson KJ, Hoegh C, Johnson SR. Estrogen replacement therapy: a survey of women's knowledge and attitudes. *Arch Int Med* 1989;149:133–136.

84. Cummings SR, Black DM, Rubin SM. Lifetime risks of hip, Colles' or vertebral fracture and coronary heart disease among white postmenopausal women. *Arch Intern Med* 1989;149:2445–2448.

85. Cummings SR, Black DM, Nevitt MC, et al. Bone density at various sites for prediction of hip fractures. *Lancet* 1993;341:72–75.

86. Heaney RP, Recker RR. Distribution of calcium absorption in middle-aged women. *Am J Clin Nutr* 1986;43:299–305.

87. Heaney RP, Recker RR, Stegman MR, et al. Calcium absorption in women: relationships to calcium intake, estrogen status, and age. *J Bone Miner Res* 1989;4:469–475.

88. Peck WA, Burckhardt P, Christiansen C, et al. Consensus Development Conference: Diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med* 1993;94:646–650.

89. Alaimo K, McDowell MA, Briefel RR, et al. Dietary intake of vitamins, minerals, and fiber of persons ages 2 months and over in the United States: Third National Health and Nutrition Examination Survey, Phase 1, 1988–91. *Advance Data* 1994;14:1–28.

90. Cumming RG. Calcium intake and bone mass: a quantitative review of the evidence. *Calcif Tissue Int* 1990;47:194–201.

91. Dawson-Hughes B. Calcium supplementation and bone loss: a review of controlled clinical trials. *Am J Clin Nutr* 1991;54:274S–280S.

92. Holbrook TL, Barrett-Connor E, Wingard DL. Dietary calcium and risk of hip fracture: 14-year prospective population study. *Lancet* 1988;1046–1049.

93. Paganini-Hill A, Chao A, Ross RK, et al. Exercise and other factors in the prevention of hip fracture: the Leisure World Study. *Epidemiology* 1991;2:16–25.

94. Dawson-Hughes B, Dallal GE, Krall EA, et al. Effect of vitamin D supplementation on wintertime and overall bone loss in healthy postmenopausal women. *Ann Intern Med* 1991; 115:505–512.

95. Heikinheimo RJ, Inkovaara JA, Harju EJ, et al. Annual injection of vitamin D and fractures of aged bones. *Calcif Tissue Int* 1992;51:105–110.

96. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D_3 and calcium to prevent hip fractures in elderly women. *N Engl J Med* 1992;327:1637–1642.

97. Seeley DG, Browner WS, Nevitt MC, et al. Which fractures are associated with low appendicular bone mass in elderly women? *Ann Intern Med* 1991;115:837–842.

98. Lipkin M, Newmark H. Effect of added dietary calcium on colonic epithelial proliferation in subjects at high risk for familial colon cancer. *N Engl J Med* 1985;313:1381–1384.

99. Garland C, Shekelle RB, Barrett-Connor E, et al. Dietary vitamin D and calcium and risk of colorectal cancer: a 19-year prospective study in men. *Lancet* 1985;1:307–309.

100. Slattery M, Sorenson A, Ford M. Dietary calcium intake as a mitigating factor in colon cancer. *Am J Epidemiol* 1988;128:504–514.

101. Bostick R, Potter JD, Sellers TA, et al. Relation of calcium, vitamin D, and dairy food intake to incidence of colon cancer among older women: the Iowa Women's Health Study. *Am J Epidemiol* 1993;137:1302–1317.

102. Jain M, Cook GM, Davis FG, et al. A case-control study of diet and colorectal cancer. *Int J Cancer* 1980;26:757–768.

103. Kampman E, Giovannucci E, van't Veer P, et al. Calcium, vitamin D, dairy foods, and the occurrence of colorectal adenomas among men and women in two prospective studies. *Am J Epidemiol* 1994;139:16–29.

104. Garland C, Comstock G, Garland F, et al. Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study. *Lancet* 1989;2:1176–1178.

105. Braun MM, Helzlsouer KJ, Hollis BW, et al. Colon cancer and serum vitamin D metabolite levels 10–17 years prior to diagnosis. *Am J Epidemiol* 1995;142:608–611.

106. Eisman JA, Martin TJ, MacIntyre I, et al. 1,25-dihydroxyvitamin-D-receptor in breast cancer cells. *Lancet* 1979;2:1335–1336.

107. Bower M, Colston KW, Stein RC, et al. Topical calcipotriol treatment in advanced breast cancer. *Lancet* 1991;337:701–702.

108. Gorham ED, Garland FC, Garland CF. Sunlight and breast cancer incidence in the USSR. *Int J Epidemiol* 1990;19:820–824.

109. Garland FC, Garland CF, Gorham ED, et al. Geographic variation in breast cancer mortality in the United States: a hypothesis involving exposure to solar radiation. *Prev Med* 1990;19:614–622.

110. Curhan GC, Willett WC, Rimm EB, et al. A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. *N Engl J Med* 1993;328:833–838.

111. Jacobs D, Blackburn H, Higgins M, et al. Report on the conference on low blood cholesterol: mortality associations. *Circulation* 1992;86:1046–1060.

112. Self S, Prentice R, Iverson D, et al. Statistical design of the Women's Health Trial. *Controlled Clin Trials* 1988;9:119–136.

113. Breslow NE, Day NE. *Statistical Methods in Cancer Research*, Vol 2: *The Design and Analysis of Cohort Studies*. Lyon, France: IARC Scientific Publication No. 82, International Agency for Research on Cancer; 1987.

114. Prentice RL. Design issues in cohort studies. *Stat Meth Med Res* 1995;4:273–292.

115. McTiernan A, Rossouw JR, Manson J, et al. Informed consent in the Women's Health Initiative clinical trial and observational study. *J Women's Health* 1996;5:519–529.

116. Freedman LS, Anderson G, Kipnis V, et al. Approaches to monitoring the results of long-term disease prevention trials: examples from the Women's Health Initiative. *Controlled Clin Trials* 1996;17:509–525.

117. O'Brien PC, Fleming RT. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549–556.

APPENDIX I SUMMARY of DM INTERVENTION SESSIONS

Session Number	Session Objectives	Nutrition Topics	Behavior Topics
	Weekly		
1	Review goals and objectives of the WHI trial. Discuss the benefits and responsibilities of being a participant. Identify lower-fat food choices, especially fruits, vegetables and grains. Identify the amount of fat in foods.	Awareness of fat in foods. Awareness of fruits, vegetables, and grains.	Awareness of costs/benefits of trial participants. Social support in group and home setting. Communication skills.
2	Discuss ways to reduce added fats. Use Fat Counter to calculate fat score. Use self-monitoring to evaluate dietary changes.	Awareness of current fat intake. Method to record fat intake.	Self-monitoring of dietary behavior.
3	Identify high-fat dairy foods currently used. Discuss skills for selection and use of low-fat dairy foods. Identify reasons for goal-setting as a component of behavior change. Set goals using Guidelines for Goal Setting.	High-fat dairy foods. Low-fat substitutes Low-fat calcium sources.	Definition of problem behavior. Setting goals for behavior change.
4	Identify how other people influence their eating patterns. Read and interpret nutrition labels and marketing techniques.	Nutrition label reading. Shopping skills. Food availability.	Social influences on eating. Self-control skills.
5	Identify high-fat entrees. Discuss skills for selection and preparation of low-fat entrees. Practice modification of entree recipes. Identify strategies to accommodate family and friends in the low-fat eating plan.	Low-fat entree substitutes. Vegetarian entrees. Entree recipe modification.	Support from home-eating partners. Problem solving skills. Communication skills.
6	Discuss skills and strategies for eating in social situations. Learn the skill of fat budgeting. List strategies for low-fat restaurant eating. Practice menu selection using local restaurant menus.	Fat budgeting skills. Evaluation of restaurant menus. Low-fat dining options.	Problem-solving skills. Communication skills.

APPENDIX I *Continued*

Session Number	Session Objectives	Nutrition Topics	Behavior Topics
	Bi-Weekly		
7	Learn how to use fruits and vegetables as low-fat snacks. Identify family's and friends' influences on snacking patterns. Learn ways to say "no" to high-fat snacks. Use shorter self-monitoring tool (fat scan).	High-risk foods. Fruit and vegetable snack alternatives. Short self-monitoring tool (fat scan).	Social influences on snacking. Self-monitoring. Resistance skills.
8	Discuss ways sweets are used as a reward. Select low-fat dessert alternatives. Identify social-support strategies to deal with sweets and desserts. Identify people who can help and ask for support.	High-risk food situations. Fruit dessert alternatives.	Asking for social support. Foods are reinforcers.
9	Share low-fat eating experiences with other WHI participants. Identify ways eating partners can support each other.	Low-fat recipe exchange. New food preparation ideas.	Promotion of group cohesiveness.
(I)	Individual Session: Provide individual support and feedback. Discuss dietary changes made to date. Evaluate nutrition variety and balance of current eating habits. Identify potential problems and plan for long-term maintenance.	Nutritional evaluation. Current eating habits.	Evaluation of current behavior. Reinforcing change. Planning for future change.
	Monthly		
10	Review group progress. Identify potential situations that interfere with low-fat eating. Learn how to use the skill of problem-solving. Learn the skill of problem solving.	Areas that intererfere with low-fat eating.	Barriers to change. Self-management strategies.

continued

APPENDIX I *Continued*

Session Number	Session Objectives	Nutrition Topics	Behavior Topics
11	Explain how self-talk influences actions. Identify negative thought patterns by listening to self-talk. Replace negative self-talk with positive thoughts. Identify low-fat lunch ideas.	Low-fat lunch ideas. Vegetables for lunch.	Cognitive restructuring.
12	Identify the challenges that vacations and holidays present to low-fat eating. Review strategies to handle vacations and holidays. Identify lower-fat alternaives to modify home-baked goods.	Vacation/holiday foods. Recipe modification of baked goods.	High-risk situations. Self-management strategies.
13	Discuss time-saving strategies to reduce time spent in food management activities. Plan three days of menus and make a shopping list. Identify ways to increase fish consumption.	Meal planning skills. Fish preparation ideas.	Organizational and planning strategies and skills.
14	Identify sources of complex carbohydrates. Identify and describe ways to increase complex carbohydrate intake. Discuss techniques for introducing new cuisines to eating partners.	Sources of complex carbohydrates. Tasting meatless recipes.	Communication skills. Social support.
15	Identify sources of stress that interfere with ability to change. Demonstrate strategies to cope with stress. Practice relaxation exercise. Identify methods and recipes for quick meal preparation.	Preparation of quick meals.	Stress management. Relaxation.

APPENDIX I *Continued*

Session Number	Session Objectives	Nutrition Topics	Behavior Topics
16	Explore the events and emotions that may trigger slips. Identify strategies to recover from a slip. Practice strategies to prevent setbacks. Taste new low-fat alternatives for out-of-routine situations.	High-risk foods. Low-fat alternatives for out-of-routine situations.	Relapse prevention.
17	Identify factors that help maintain dietary changes. Learn how loss of motivation can lead to "drift" in eating patterns. Identify self-monitoring ideas to maintain dietary changes. Learn ways to add flavor without fat.	Dietary variety. Fats and oils.	Reinforcement of current changes. Self-mastery. Self-help groups.
18	Review strategies that help maintain a low-fat plan. Review the progress made in WHI. Identify sources of continued support for low-fat eating.	Recipe exchange featuring new food products.	Review. Celebration. Group support.

APPENDIX II

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