Physical Activity, Weight Control, and Breast Cancer Risk and Survival: Clinical Trial Rationale and Design Considerations

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Substantial observational epidemiological evidence exists that physical activity and weight control are associated with decreased risk of postmenopausal breast cancer. Uncertainty remains regarding several aspects of these associations, including the effect of possible confounding factors on these associations. We present the rationale and design for two randomized controlled trials that can help resolve this uncertainty. In a 5-year prevention trial conducted among women at high risk of breast cancer, the primary endpoint would be breast cancer incidence. For a comparable survivorship trial, the primary endpoint would be the disease-free interval and secondary endpoints would be breast cancer recurrence–free interval, second primary breast cancer, and total invasive plus in situ breast cancer. A set of inclusion and exclusion criteria is proposed for both trials. Intervention goals are the same for both trials. Goals for the weight control intervention would be, for women whose body mass index (BMI) is greater than 25 kg/m^2, to lose 10% of body weight and, for women whose BMI is less than or equal to 25 kg/m^2, to avoid weight gain. The goal for the physical activity intervention would be to achieve and maintain regular participation in a moderate-intensity physical activity program for a total of 150–225 minutes over at least 5 days per week. Sample size calculations are based on alternative assumptions about hazard ratio, adherence, follow-up duration, and power and are presented for the primary prevention and survivorship trials. Although both studies could enhance our understanding of breast cancer etiology and benefit public health, practical considerations, including smaller sample size, ease of recruitment, and reduced likelihood of early termination, favor the survivorship trial at this time.

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Breast cancer is the most commonly diagnosed cancer and the second most common cause of cancer deaths among women in the United States (1). Although the etiology of breast cancer remains unclear, several risk factors have been identified. The primary risk factors are nonmodifiable and include age, family history, and race. Only a few factors have been identified that are modifiable. These factors are alcohol intake, dietary intake, physical activity, and body weight. Although several dietary trials have been funded for prevention of several types of cancers and for improving survival in patients with breast cancer, little attention has been given to potential trial designs in the areas of physical activity, weight control, and cancer.

It is only within the last decade that major cancer organizations have begun to recommend physical activity as a preventive measure for breast cancer. In 2002, both the American Cancer Society (ACS) (2) and the International Agency for Research on Cancer of the World Health Organization (3) recommended regular physical activity as a strategy for individuals to reduce their risk of developing breast cancer and further advocated for community action to support increased physical activity. The revised ACS guidelines released in 2006 (4) have further emphasized the sound better potential benefit of physical activity in the prevention of breast and several other cancers. In addition, the revised 2006 ACS guidelines for cancer patients and survivors (5) suggest ways to increase physical activity to improve cancer outcomes. These recommendations come in the context of data indicating that US adults are not achieving recommended amounts of physical activity (6–8).

Maintaining normal body weight also has been recommended as a strategy for reducing cancer risk. As early as 1996, the ACS recommended maintaining a healthy body weight as a strategy to reduce cancers in general, but the specific recommendations for breast cancer focused more on food choices than on weight reduction among overweight or obese women. In 2002 (2), these guidelines were strengthened to specifically recommend that individuals maintain a healthy weight throughout life by balancing caloric intake, engaging in physical activity, and losing weight if overweight or obese. Most recently, in 2006 (4), the ACS published updated guidelines for prevention that further emphasized the

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importance of maintaining a healthy weight throughout life and being physically active. The ACS guidelines for cancer survivors (5) also addressed the benefits of weight control and physical activity. These recommendations were made as the proportion of overweight and obese US adults was increasing (9).

Although the observational epidemiological evidence is strong and consistent that physical activity and weight control are associated with reduced risk of breast cancer, uncertainty persists about whether the apparent association is attributable to confounding from other factors. Obtaining an accurate understanding of a possible benefit in the absence of confounding factors can be achieved only within the context of a controlled clinical trial. Such evidence can be extremely valuable in promoting the broad-scale adoption of new prevention and treatment management approaches within clinical and public health practice. Results of several large randomized trials, including the Diabetes Prevention Program (DPP), the Dietary Approaches to Prevent Hypertension (DASH), and the current Look Action for Health in Diabetes (AHEAD) trial, show that it is feasible to achieve complex diet and physical activity changes among high-risk groups in trials (10–12).

Given this context, the National Cancer Institute (NCI) convened a 2-day workshop in March 2006 that included experts in energy balance, physical activity, weight control, and trial design with expertise in biological mechanisms of action for how these factors may influence cancer-related biology, epidemiology, and large community-based behavioral interventions. The purpose of the workshop was to assess whether current evidence is sufficient to justify a randomized controlled trial to test the efficacy of a physical activity and weight control intervention in reducing the incidence of breast cancer among high-risk women or improving prognosis among survivors. Furthermore, because of differences in rates of obesity between racial and ethnic groups, experts also addressed the evidence of differences in participation, compliance, or success in randomized controlled trials of these factors among different racial and ethnic groups.

During this workshop, data on the strength of evidence for and nature of associations between physical activity, weight control, and breast cancer risk and prognosis were presented and discussed. The characteristics of relevant clinical and community-based trials and their associated interventions also were reviewed. These presentations and reviews set the stage for debate about optimal trial design and trade-offs among various trial characteristics as well as current readiness for a large randomized controlled trial related to breast cancer.

Evidence Review

Physical Activity

In general, epidemiological studies have found an inverse relationship between physical activity and breast cancer incidence. Across some 50 studies, the risk of developing breast cancer is 20% lower among the most active women than among the least active. Similar reductions were seen regardless of menopausal status, with the risk reduction in postmenopausal women (30%) being slightly greater than that in premenopausal women (13). Many different levels of physical activity have been shown to be associated with reduced breast cancer risk. Evidence suggests that 4–7 hours per week of moderate- to vigorous-intensity physical activity is required for adequate risk reduction (13). Although there is a large body of evidence supporting an inverse relationship between breast cancer incidence and physical activity, limited evidence is available about factors other than menopausal status that might modify this relationship. No clear evidence suggests that this inverse relationship differs by age or weight.

Few studies (13) have investigated the role of physical activity among patients with breast cancer in improving breast cancer prognosis, but preliminary evidence (14–16) suggests that physical activity both before and after a diagnosis of breast cancer is associated with improved prognosis. In addition, evidence from randomized controlled trials that was presented at an NCI workshop in 2002 (17–20) documented consistent beneficial effects of physical activity on both quality of life and levels of several hormones associated with breast cancer.

Weight Control

There is extensive evidence linking body weight, weight change over time, and various alternative measurements of body size to breast cancer risk (3,21). Many studies have further explored the role of effect modifiers on this association, predominantly factors reflecting exposure to estrogen, such as menopausal status, age, hormone receptor status of the tumor, and use of hormone therapy (HT).

Menopausal status is a clear modifier of the effects of body weight on breast cancer risk, with an increased breast cancer risk demonstrated for overweight and obese postmenopausal women and no increased risk for comparable premenopausal women (22). In a meta-analysis of prospective cohort data, among postmenopausal women, a higher body mass index (BMI) was associated with an increased risk for breast cancer (for BMI of 28 vs 21 kg/m^2, relative risk [RR] = 1.26, 95% confidence interval [CI] = 1.09 to 1.46) (23). This meta-analysis, however, did not examine how this risk may have been modified by exposure to HT. BMI is not associated with risk of breast cancer among women currently using HT, whereas among women who have never used HT, risk estimates for breast cancer among women with an elevated BMI are much higher than the relative risk of breast cancer observed in the meta-analysis (23) and in previous studies (24–28). For example, in the Women's Health Initiative (WHI) cohort study, which had measured weight and height, increased risk of breast cancer (RR = 2.52, 95% CI = 1.62 to 3.93) was observed among postmenopausal obese (BMI = 31.1 kg/m^2) women who had never used HT, in contrast to no increased risk (RR = 0.96, 95% CI = 0.73 to 1.27) among postmenopausal obese women who had used HT (27). In addition, in the limited number of studies that have examined whether the association of BMI varies by hormone receptor status of the tumor, an increased risk has been shown for estrogen receptor (ER)– and progesterone receptor (PR)–positive tumors but not ER- or PR-negative tumors among obese women (22,29).

Several studies have reported that BMI-associated breast cancer risk increases with age at diagnosis, even when controlling for menopausal status. In one study (30), among postmenopausal women, the risk of breast cancer for obese women, compared with women of normal weight, was lower for those younger than 60 years (RR = 1.1, 95% CI = 0.8 to 1.4) than for those older than 65 years (RR = 1.8, 95% CI = 1.3 to 2.5).

Among premenopausal women, however, breast cancer risk decreases with increases in body weight (in general among overweight and obese premenopausal women, average RRs = 0.6 and 0.7) respectively (22). Evidence about the role of other potential modifying factors is less clear. Data for premenopausal women are limited or inconclusive with respect to variations in associations of obesity with breast cancer risk by family history of breast cancer (22).

Most studies find that higher weight or BMI during teenage and young adulthood (18–20 years) is associated with a 10%–30% decrease in breast cancer risk for both pre- and postmenopausal breast cancer. During the middle decades of life (ie, between 20 and 50 years of age), this inverse relationship between breast cancer and BMI persists for premenopausal breast cancer. Weight gain also appears in most studies (22) to be associated with a reduced or no statistically significant increase in risk of premenopausal breast cancer. However, the relationship between weight gain and breast cancer risk changes for postmenopausal women in a manner that is consistent with the patterns observed for body weight or BMI. Adult weight gain in the range of 20–50 pounds has been associated with a twofold increase in postmenopausal breast cancer risk—a relationship that is sustained regardless of baseline BMI (22). Among women who have not taken HT, the relative risk of postmenopausal breast cancer associated with adult weight gain increases to threefold or greater (22,25,26,28).

Extensive evidence also suggests that obesity and being overweight have an adverse effect on disease-free interval, breast cancer–specific interval, and overall survival (22). In addition, substantial weight gain after diagnosis and treatment for breast cancer may be adversely associated with breast cancer prognosis. Obesity appears to double the risk of recurrence and death among breast cancer survivors, and this adverse association remains irrespective of menopausal status and after adjusting for stage and treatment (22,31). Risk of distant recurrence has been observed in some studies to be higher among overweight and/or obese women (22,31). Recent studies suggest that the degree of weight gain after treatment for breast cancer is less than what was previously reported (32). A decrease in energy expenditure, as a consequence of reductions in both resting energy expenditure [attributable to a decrease in lean mass (33)] and physical activity (34), may account for this weight gain. This evidence, combined with results from small controlled studies of physical activity among breast cancer patients (31), indicates that physical activity may prevent weight gain. Few studies have examined in detail possible interactions between physical activity and diet either among asymptomatic women or among breast cancer survivors (22).

Trial Endpoints and Participant Eligibility

Potential primary and secondary endpoints for primary prevention and survival trials include breast cancer–specific endpoints (46) (primary endpoints include incident breast cancer for the primary prevention trial and disease-free interval for the survival trial; secondary endpoints for the survival trial include occurrence of invasive and in situ breast cancer, breast cancer recurrence, and second primary breast cancer) and other disease endpoints that are likely to be affected by a physical activity and weight control intervention (such as all-cause mortality, coronary artery disease, stroke, or diabetes mellitus) (Table 1). Several potential mechanisms that are related to physical activity and weight control have been and continue to be actively explored—from initiation to micrometastases in basic, animal, and human studies. Although sex steroids (especially estrogen), insulin, and insulin-like growth factors have been explored most extensively, other mechanisms under investigation pertain to immune function, angiogenesis, oxidative stress, DNA repair, and growth factors. It is likely that the relative importance of these mechanisms is likely to differ depending on whether the development of new primary breast cancer, recurrence, or metastatic disease is examined. However, there is little evidence of whether specific differences exist by type of physical activity or weight control intervention for each of these mechanisms. In the area of primary prevention, there remains substantial debate on whether there are particularly important periods during the life cycle, including exposures in utero and during puberty, when physical activity and weight may be more important than other periods. However, evidence from observational and animal studies (13,22) suggests that

Table 1. Specific and common trial endpoints for physical activity and weight control trials addressing breast cancer risk and survival*

Endpoints	Primary prevention	Survival	Common to both
Primary	Breast cancer	Disease-free interval†	
Secondary	None specific to primary prevention	Total invasive and in situ breast cancer‡	Hormone receptor status
		Breast cancer recurrence–free interval	In situ breast cancer (DCIS and LCIS)
		Breast cancer recurrence	Breast cancer death
		Second primary breast cancer	
Other			All-cause mortality (35,36)
			Cancer incidence and non–breast cancer death (4,13)
			Hospitalized, coronary artery disease (37–40)
			Hospitalized, stroke (40–43)
			Diabetes mellitus (10,44)
			Functional status, mood disorders, and quality of life (17–20)
			Cost–benefit analysis (45)

* Items in the "Primary prevention" column are relevant only to that trial, items in the "Survival" column are relevant only to that trial; items in the column labeled "Common to both" are relevant to both trials. DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ.

† Disease-free interval is defined as not having breast cancer recurrence, contralateral breast cancer, a second primary cancer, death from breast cancer, or death from any cause (44,46).

‡ Calculated from the number of invasive and ductal carcinoma in situ and lobular carcinoma in situ cancers.

increases in physical activity and improvements in weight control later in life are beneficial.

Potential eligibility criteria for participants in primary prevention and survival trials include risk and prognostic characteristics as well as factors that may influence a participant's ability to comply with the intervention (Table 2). Criteria that are of higher importance include breast cancer diagnosis, use of selective ER modulators (SERMs), systemic treatment, diabetes, and changes in weight and physical activity.

Breast Cancer Diagnosis

A focus of recruitment to the survivorship trial will be women with nonmetastatic invasive breast cancer (TNM staging system (47) T1–3, pN0–pN3, M0) that has been completely resected with mastectomy or with lumpectomy followed by breast radiation. Inclusion of women with invasive breast cancers that have a favorable prognosis, such as tumor size of less than 1 cm in diameter, grade 1, and no lymph node involvement, may increase sample size requirements. Consideration of additional exclusion criteria that are based on prognostic characteristics may be needed. Recent evidence from the Women's Intervention Nutrition Study (48) of a potentially greater effect of dietary fat reduction (coupled with modest weight loss) in ER-negative vs ER-positive breast cancer not only requires replication but also merits consideration in trial planning.

Selective Estrogen Receptor Modulators

Women who have taken and who are taking SERMs, such as tamoxifen or raloxifene, may need to be excluded because treatment with SERMs lowers breast cancer risk and would likely reduce the size of the intervention effect. Thus, a larger trial sample size would be required if these women were included. Although trials have demonstrated the benefit of SERMs, use of these agents for primary prevention is currently low at the population level (49). However, if use increases markedly, it may be difficult to recruit a large enough group of high-risk women who do not use SERMs. Given the large reduction in risk demonstrated with newer agents, such as raloxifen, it is hypothesized that physical activity or weight control would need to have a large added benefit to demonstrate an effect among women taking these agents.

Systemic Treatment

Systemic treatment decisions for each patient with breast cancer must be made before random assignment. Because chemotherapy may reduce compliance with the intervention, requiring completion of chemotherapy before study entry could enhance compliance.

Diabetes Mellitus

Women who have insulin-dependent diabetes would be excluded because the management of their diabetes might not allow full participation in the intervention. Because of the growing incidence of non–insulin-dependent diabetes mellitus (NIDDM), which is estimated to have doubled during the past 30 years (50), and the rapid rise in US obesity rates, excluding women with NIDDM may not be feasible. Standard clinical care for managing NIDDM includes recommendations to reduce body

Table 2. Specific and common eligibility criteria for physical activity and weight control trials addressing breast cancer risk and survival*

Criteria	Primary prevention	Survival	Common to both
Inclusion	Age 45–75 years†	Up to age 75 years	Female
	Postmenopausal‡	Breast cancer diagnosis	All races and ethnicities§
	High risk for breast cancer (using Gail model for risk)	Completion of treatment	Medical clearance‖
			BMI of ≥24 kg/m^2 (≥23 kg/m^2 for Asians) but ≤45 kg/m^2¶
Exclusion	Invasive breast cancer	Pending systemic treatment decision	Cardiovascular disease#
	Diagnosis of DCIS		
	Use of SERMs		
			Insulin-dependent diabetes
			Current weight-loss medication or surgical procedure
			Recent weight loss of ≥10 pounds or enrollment in active weight-loss program
			Factors potentially limiting intervention adherence:
			Other medical contraindication
			Mental illness
			Substantial travel time to intervention site

* Items in the "Primary prevention" column are relevant only to that trial, items in the "Survival" column are relevant only to that trial; items in the column labeled "Common to both" are relevant to both trials. BMI = body mass index; DCIS = ductal carcinoma in situ; SERMs = selective estrogen receptor modulators.

† The upper age limit of 75 years was selected to identify women with an expected lifespan of 5 or more years and the capacity to fully comply with the physical activity and weight control requirements of the intervention.

‡ Although physical activity has been associated with reduced breast cancer risk in both pre- and postmenopausal women, the strongest evidence of a relationship between weight control and breast cancer incidence exists among postmenopausal women. For the survivorship trial, because breast cancer treatment often induces menopause, most women either will be postmenopausal or will become postmenopausal during their participation in the trial.

§ Oversampling may ensure sufficient representation among racial and ethnic groups.

‖ Further exploration of medical clearance requirements from other trials may help to inform the extent of and process for meeting clearance requirements.

¶ These lower limits for BMI ensure that all women in the trial will benefit from weight loss, thus precluding the need for two interventions (weight maintenance and weight loss). Obesity would not be a reason for exclusion as long as a woman was able to complete the physical activity component of the intervention. An upper BMI limit of 45 kg/m^2 is suggested because of unique physical activity intervention requirements.

\# Women who have had a heart attack or stroke within the past 6 months would be excluded.

weight through diet and exercise. These recommendations are common to the control arm of current weight-loss trials, and participants who are randomly assigned to the comparison group would receive no less than this current standard of care. Women with NIDDM who are stable and well managed without insulin would be eligible.

Changes in Weight and Physical Activity

Two other potential exclusion criteria, lifetime weight changes and lifetime changes in physical activity, were considered and dismissed because they are difficult to assess and there is no evidence that they would alter response to the intervention. Some evidence suggests that weight loss among women who are enrolled in a structured weight control program is further enhanced by individually tailored weight control interventions, similar to the intervention proposed (51).

Determining High Risk for Breast Cancer

A modified Gail model or other validated model for risk assessment could be used to identify women at high risk for developing breast cancer. Although we do not propose a specific cut point, the cut point used in the Study of Tamoxifen and Raloxifene (STAR) trial (52) was a composite increased breast cancer risk score of at least 1.66% in 5 years. The Gail model (53) assesses the following factors: medical history of breast cancer, ductal carcinoma in situ, lobular carcinoma in situ, age, age at menarche, age at first live birth, number of first-degree relatives with breast cancer, race and/or ethnicity, number of previous breast biopsy examinations, and history of atypical hyperplasia. Breast density has not been proposed as a measurement to select high-risk women, although recent research (54) suggests it may be as effective for assessing risk when compared with multiple factors, such as reproductive history, history of breast biopsy, and other breast cancer risk factors used with the Gail model. Assessment of breast density would require having a woman's mammogram before enrollment and thus could increase trial costs and logistic difficulty. Breast cancer risk modeling is an active area of research, and it is anticipated that enhancements in risk modeling would be incorporated into a final trial design.

Eligibility Assessment

Eligibility and consent procedures are nearly identical for primary prevention trials and survival trials. Both include a multistep process that allows for assessment of eligibility compliance as well as likelihood of adherence to intervention and assessment protocols. The eligibility assessment steps include initial risk assessment and baseline screening as well as secondary screening. The purpose of the initial risk assessment and baseline screening step is to complete an eligibility screening, including self-reported height and weight for calculation of BMI and obtaining data for calculating risk for primary prevention trial participants. The purpose of the secondary screening step is to complete all consent forms and requirements as well as a demographic and health history questionnaire and to evaluate a woman's capacity to participate, adhere to the intervention, and perform dietary and physical activity assessments.

Enrollment and Baseline Evaluation

All participants who remain eligible after completion of the first and second screenings and who provide written informed consent will be enrolled in the trial and complete a baseline evaluation. Enrollment will include verification of eligibility, baseline evaluation, randomization, and scheduling of the initial and 6-month visits. Baseline evaluations will not differ for primary prevention and survivorship trials. Baseline measurements will be used as a comparison point for assessing individual progress and intervention effects. A baseline evaluation will include assessment of trial endpoints, mentioned in Table 1, and a physical evaluation. The physical evaluation will include a clinical breast examination and mammogram, anthropometrics, and a dietary and physical activity assessment. Annual mammograms will be required and intensive efforts will be made to avoid differential screening by study arm. Breast density will be estimated from the baseline mammogram by use of the latest technology in quantitative breast density assessment. Anthropometrics will include height, weight, calculation of BMI, and waist and hip circumferences. Dual-energy x-ray absorptiometry (DXA) may be considered in a subset to further evaluate changes in body composition. Dietary assessment measurements will include a combination of food-frequency questionnaires, 24-hour recalls, and perhaps food diaries in a subsample. Objective measurements of some dietary components, such as serum carotenoid measurements that are associated with fruit and vegetable intake, may also be considered. Physical activity assessments will include self-reported and objective measurements with sealed pedometers or accelerometers. Objective measurements of physical fitness, such as step tests, may also be considered.

In addition, fasting blood and normal breast tissue samples may be used to assay several biological measurements of interest, such as DNA expression, or biomarkers. Consideration will be given to obtaining fasting blood and breast tissue samples to evaluate the role of intermediate markers, such as oxidative stress and DNA repair, target tissue markers and metabolism detoxification factors, noninflammatory aspects of immune function, inflammation, growth factors, and hormones—particularly estrogen and insulin and insulin-like growth factors. The importance of such measurements has been demonstrated by research that has identified possible differential responses to interventions that are based on analysis of genetic characteristics from stored samples in large-scale randomized controlled trials.

Intervention

Changes in both calorie intake and expenditure are critical for weight loss and maintenance, and it is well documented that physical activity is important to promoting weight control and maintaining weight loss. The study intervention would therefore integrate two behavioral components, physical activity and diet. Regular physical activity is defined as 150–225 minutes of moderate-intensity activity over 5 or more days per week. A calorie-controlled diet consistent with general health recommendations, such as that used in the DPP, would be used to reduce energy intake relative to expenditure to promote weight loss in overweight or obese (BMI of $\geq$25 kg/m^2) participants and to maintain a healthy energy balance among normal-weight (BMI of 24–24.9 kg/m^2)

women. Both the prevention and survivorship trials will be designed to test intervention efficacy rather than evaluate logistical or cost aspects of disseminating an intervention.

Goals

The trial goal for women whose BMI is greater than 25 kg/m^2 is to lose 10% of body weight. In addition to this individual goal of 10% weight loss, the overall trial goal will be an average weight loss of 5%–7% because not all participants will achieve the 10% goal. The evidence to support this 10% goal is drawn from previous trials of weight loss (10,11) that demonstrate that this level of weight loss normalizes several metabolic parameters that are adversely affected by obesity and is feasible to achieve. Because evidence to date on weight loss and cancer outcomes is drawn from observational studies that cannot distinguish between disease-related vs intentional weight loss, there is no conclusive evidence for the level that is needed to reduce cancer risk or improve survival. The goal for women whose BMI is less than or equal to 25 kg/m^2 will be to avoid weight gain. The goals of the physical activity component of the intervention are to achieve and maintain regular participation in a moderate-intensity physical activity (ie, 3–5 metabolic equivalents [METs]) program of 150–225 minutes for at least 5 days per week. This corresponds to a range of 7.7–19 MET-hours per week, which is consistent with the midrange for which benefit has been observed in observational studies (12,14–16).

Cognitive and Behavioral Foundation

Cognitive and behavioral strategies that are grounded in social learning theory (55) and interpersonal health education and behavior theories (56) form the theoretical foundation of the intervention. These theories of action have been used successfully to design and implement interventions for physical activity, dietary change, and weight loss (57,58). The specific techniques to be implemented include achievable goal setting, developing plans of action, self-monitoring, accountability, problem solving, decisional balance, stimulus control, social support, and enhancing self-efficacy. Each participant will work individually with a health counselor to set his or her own goals and to develop and apply cognitive and behavioral strategies to achieve both physical activity and dietary targets.

Intervention Phases

Initial intervention efforts, tailored to individual needs, generally involve more frequent and intensive contact (in person, by telephone, or by e-mail) with participants to provide training and feedback to stimulate the behavior change process. Group contact is a more cost-effective approach than one-on-one contact to providing participants with the information they will need to adopt physical activity and dietary behaviors (59,60). Group contact also provides social support but typically restricts the intervention to large centers. Individual and group sessions available during the day and evenings may maximize participation and afford flexibility for participants.

The presentation of physical activity and the dietary intervention components at both individual and group sessions allows equal emphasis to both behaviors. The trial will use a combination of individual and group counseling designed to maximize compliance with the intervention that will be based on the evolving evidence on this issue.

The specific details of frequency and type of contact for the intervention were drawn from recent successful large National Institutes of Health (NIH) trials in weight control, diet, and physical activity (58,61,62) and may change as new research evidence emerges. The Activity Counseling Trial demonstrated that physical activity and fitness can be increased in women without extensive face-to-face contact (58), and similar approaches may be used in the proposed trial in the interest of cost efficiency. Additional evidence on the use of telephone counseling for physical activity adoption suggests that these approaches may be effective during critical early stages of behavioral change adoption (58,63). Telephone counseling also has been effective in recent dietary interventions to increase intake of fruits and vegetables (63,64) but has not been studied extensively in weight control. It is clear, however, that ongoing continued contact with participants is needed to maintain changes in body weight.

These intervention components are commonly implemented in three phases (termed initiation, action, and maintenance) over the duration of a 5-year trial. These phases are designed to provide more frequent contact initially when participants are learning new behaviors and a reduced schedule of continuing contact for the duration of the trial to assist participants in maintaining their behavior changes. However, ongoing contact will be needed throughout the duration of the trial to help participants maintain their behavior changes. Self-monitoring by intervention participants is anticipated to be more frequent as they are initiating and adopting new behaviors and will decrease once behaviors are adopted. Monitoring for relapse or failure to achieve goals would trigger temporary increases in contact and self-assessment among intervention participants until goals are achieved. Activity logs, questionnaires, and/or pedometers have been used effectively for self-monitoring and compliance enhancement in recent large trials. Details on the frequency and specific issues to be addressed in each phase of the intervention have been described for previous trials (10,65).

For a survivorship trial, existing evidence does not address the issue of whether a physical activity and weight control intervention should be initiated before, during, or after completion of the first course of treatment. Planning when the intervention should begin will be an important issue for discussion in finalizing the trial design. Issues to be considered include whether initiation of the intervention will affect patient participation, safety, and differential response to the intervention as a function of the phase of treatment. For example, disruptions in patients' lives in the early period of cancer diagnosis and treatment may reduce the likelihood of participation in such a trial until intensive treatment is completed. In addition, some evidence suggests that the cardiac response to exercise is different in patients who are being treated and in those who have completed treatment. However, other evidence suggests that patients who are active throughout treatment also have a better quality of life. Because it is likely that effects may vary depending on when in the course of treatment the intervention is initiated, a defined period for initiation is necessary. For example, random assignment could occur by 12 months after definitive treatment (ie, surgery, radiation, and/or chemotherapy, excluding HT).

Physical Activity

The target of 150–225 minutes of physical activity per week is consistent with current literature (13–21) concerning the levels of activity associated with decreased risk for breast cancer and improved prognosis. In the future, new evidence on the duration and intensity of physical activity achievable by women, coupled with emerging data on physical activity and breast cancer, may help to further define the type, intensity, and duration of activity for the intervention.

Three specific elements of the intervention will be addressed in designing the physical activity intervention, with explicit goals that have been formulated on the basis of currently available evidence, including reducing sedentary behaviors, exercise sessions, and the type and intensity of physical activity. For reducing sedentary behaviors, such as watching TV or playing video games, women will be encouraged to spend less time sitting and to be more active, even at low intensity and for short periods. Initially, the physical activity intervention would involve frequent contacts with participants, including individual and/or group counseling. Although research indicates that supervised physical activity sessions enhance program adoption (66), research on nonsupervised, home-based interventions also demonstrates success in some populations (58,66–69). In some smaller scale trials, supervised physical activity sessions have been provided during the first 6–12 months of intervention. Some of these trials have also offered monthly group-supervised physical activity sessions to enhance program adoption and maintenance. As for the type and intensity of activity, women who are willing and able would be encouraged to increase the intensity and/or duration of their physical activity. Some women may wish to take up vigorous sports, such as cycling or running. For those who do not progress to more vigorous activity, the focus would be on maintaining moderate-intensity activities, such as walking. Evolving research on the effect of other types of exercise, such as strength training, will be considered in designing the physical activity intervention.

Diet

The diet intervention for this trial will focus on individualized food choices and meal patterns consistent with managing energy intake to promote weight loss among overweight and obese women or to avoid weight gain among women within recommended BMI ranges. For normal-weight women, maintaining a healthy energy balance is the primary dietary focus. For overweight and obese women, among whom weight loss is the goal, a reduced-calorie diet would be recommended to produce a weight loss of 1–2 pounds per week. This rate of weight loss has been shown to be safe and achievable and allows participants to reach the 10% weight-loss goal within the first 6 months of the intervention (65). After achieving the 10% weight-loss goal, those who wish to lose more weight will be assisted to achieve these objectives, but, for those who do not, the calorie levels will be adjusted and strategies for maintaining weight will be presented.

Food choices would emphasize increased vegetables, fruits, and fiber intake, as well as sustainable choices that provide recommended nutrient intakes and do not result in excessive dietary restrictions. The diet and food choices that result from encouraging the consumption of more vegetables, fruits, and fiber are consistent with the dietary approaches used in recent NIH trials (DPP and DASH), the 2005 Dietary Guidelines for Americans, and current recommendations for cancer prevention (4). Energy density, which is influenced by dietary fiber, water, fat, and other dietary constituents (such as sugar), has emerged as a dietary characteristic that can be manipulated to maintain volume and satiation despite reduced energy intake (59,67,70). In particular, high-fiber vegetables, fruits, and whole grains add bulk and volume to a meal and reduce energy density.

Individual Tailoring

In addition to the general intervention strategies for encouraging increased physical activity, calorie restriction (where appropriate), and maintenance of a healthy diet, emphasis should be placed on innovative approaches that meet unique participant needs and help participants overcome barriers to achieving intervention goals. These tailored strategies, referred to as the "intervention toolbox," are used primarily for individuals having difficulty achieving or maintaining physical activity or weight loss (65,66). The toolbox is designed to add new strategies to enhance adherence and address the barriers being reported by the individual participant. Toolbox approaches include, for example, awarding items of nominal value for achieving specific behavioral goals, using structured eating plans, or instituting meal replacement products.

Implementation

Implementation of the physical activity and diet components of the weight control intervention will include a combination of individual and group contacts over the course of 5 years. Recent trials have demonstrated success with the use of centrally trained lifestyle counselors who have expertise in nutrition, exercise, or behavior modification and experience leading group lifestyle programs and individual counseling that follow a standardized curriculum. Performance of counselors would be commonly monitored centrally and counselors would be retrained as needed. Participants would be assigned a specific counselor for all individual sessions.

Written lesson plans and leader guides that are developed for all group treatment sessions and used by all centers would ensure standardization. Participants would be weighed privately at the start of each session. Sessions would begin with a review and discussion of the previous week's assignments and their successes and difficulties with behavior change, with the remainder of the session being devoted to new topics. Goals for the next week and specific activities would be provided at the end of each session.

Comparison Group

To determine the effects of the intervention, it is necessary to compare the outcomes among women randomly assigned to the intervention and comparison groups. Women in the comparison group would be given general but not individual and specific physical activity and diet recommendations. The intensity of activities in the comparison group would be low to reduce the likelihood that women in this group would adopt intervention behaviors. Topics to be discussed in comparison group sessions would be developed centrally and include issues of importance to the women, such as stress reduction, yoga, menopause, use of vitamin and mineral supplements, and specific women's health problems,

such as urinary incontinence. Additional topics that are specifically relevant to cancer patients might be added for a survivorship trial. Sessions for the comparison group would not cover topics related to diet, physical activity, or weight control but would provide an introduction to each topic, and topics would not be repeated in other sessions. Some studies have used periodic newsletters effectively with comparison groups, and this approach may also be considered.

Adherence

Adherence to the intensive lifestyle intervention is commonly assessed by measuring attendance at group and individual counseling sessions, exercise sessions, completion of self-monitoring records, measured weights, and changes in aerobic fitness. Changes in physical activity and diet over time in both intervention and comparison groups will be evaluated with self-report physical activity and dietary questionnaires as well as objective measurements such as weight, accelerometer, or blood nutrient levels that are associated with increased fruit and vegetable intake. Self-monitoring records that are completed by intervention group participants and evaluated by the lifestyle interventionist can be useful in monitoring adherence to treatment goals.

Participant Follow-up

All trial participants would receive follow-up examinations including measurements of height, weight, BMI, and waist and hip circumference. Fasting blood tests would be included every 6 months as well as clinical breast examinations, mammograms, and measurement of mammographic breast density every 12 months. Measurements to accurately assess body composition, such as DXA or computed tomography scans, would provide additional valuable data, but cost may allow use of such measurements only in a subset of participants. A subsample would receive assessments including all baseline measurements at 24, 36, and 48 months. Participants in a survivorship trial also would be evaluated every 6–12 months to determine breast cancer recurrence and progression.

Substantial attrition can jeopardize study power and potentially introduce bias into results. Attrition appears to be determined primarily by the relationship between study staff and participants and the desire of participants to be part of a well-run study (71–73). Other factors that have been shown to influence participant attrition include frequency of contact with participants, emphasis given to intervention sessions, notification about upcoming intervention sessions, use of study newsletters to share information with participants, and aggressiveness of follow-up for nonresponse (74); randomization and speed of intervention start-up (75); and age, race, and marital status (76).

Monetary incentives and various forms of appreciation [stamp books, gift cards, and Valentine's Day or birthday cards (73)] have been shown to improve study retention (69,73–75,77,78). However, most assessments of the effect of incentives have been in short-term studies and survey studies in which incentives can double response rates (78). Reimbursement for transportation, child care, and parking costs (57) also reduce attrition. The Lifestyle Interventions and Independence for Elders trial, which was designed to increase physical activity among elderly women and men with mobility disability (69), achieved a retention rate of 94% at 12 months; therefore, high retention is possible in multicenter trials, even those with unhealthy participants.

Monitoring

Ongoing data and safety monitoring is necessary to determine whether to stop the trial early to protect the well-being of trial participants or make information of immediate public health benefit available to the public. It is anticipated that risk for some health conditions, such as diabetes, will be decreased by the intervention. Participants will be notified of anticipated health effects during informed consent and of trial effects in response to monitoring throughout the trial. Monitoring rules, including the frequency and timing of data review, need to be clearly established at the beginning of the trial. These rules would preserve the overall statistical significance level of the trial and take into account the fact that the data are examined repeatedly.

Decisions are needed on how to balance the impact of various health outcomes other than trial endpoints in determining whether or not to stop a trial early. Perhaps the most difficult aspect of monitoring a prevention trial is dealing with multiple health outcomes of interest, more than one of which may be affected by the intervention at any given point in time. Freedman et al. (79) propose several approaches for dealing with this problem. One method is to focus on a primary endpoint and ignore other events. Depending on the nature of the other health outcomes affected, this approach may raise ethical issues. Another approach is to focus on a global endpoint, such as total mortality; this strategy, however, may not reflect the intervention effects on the particular outcomes of interest, such as breast cancer incidence or death. Another approach, which the WHI used (79), is to develop an index that summarizes the intervention effects on several health outcomes, with different weights assigned to each outcome. The frequency and seriousness of endpoint events, which may differ between prevention and survivorship trials, would play a major role in determining the optimum approach. However, in the specific instance of the proposed trial on physical activity and weight control, substantial evidence suggests that such an intervention would result in benefit to other disease endpoints, such as heart disease, diabetes, and hypertension. Because breast cancer is a relatively rare and later endpoint compared with these other chronic diseases, it is likely that a trial of physical activity and weight loss would be stopped before evidence on the intervention's effect on breast cancer. In contrast, a trial evaluating physical activity, weight control, and breast cancer survival would not have to be ended prematurely because of benefit to other disease endpoints because breast cancer events are not rare in women with breast cancer and occur more frequently than other chronic disease endpoints.

Sample Size Estimates

Sample size calculations for the prevention and survival trials show that much larger sample sizes are required for studies of breast cancer prevention than for studies of survivorship (Tables 3–5). For both the prevention and survivorship trials, we assumed all tests were performed at the one-sided α level of .025, with a 3% annual loss to follow-up. A one-sided test was used because the trial is designed to test the benefit of the intervention; data from

Table 3. Sample size estimations for a primary prevention trial of invasive breast cancer that evaluates physical activity and weight control

Hazard ratio (control vs treatment 5-year disease-free interval rate)	Power, %	Minimum follow-up of 5 years		Minimum follow-up of 3 years	
		Length of accrual, y	No. of patients	Length of accrual, y	No. of patients
0.75 (98.4 vs 98.8)	90	6.5	25 998	7.7	30 802
	85	5.7	23 094	6.9	27 690
	80	5.2	20 836	6.3	25 266
0.80 (98.4 vs 98.7)	90	9.1	36 406	10.4	41 700
	85	8.1	32 490	9.4	37 640
	80	7.3	29 450	8.6	34 448
0.85 (98.4 vs 98.6)	90	13.9	55 798	15.3	61 686
	85	12.5	50 066	13.9	55 821
	80	11.3	45 598	12.7	51 230

randomized controlled trials of similar physical activity and weight-loss interventions do not indicate any substantial adverse effects from such interventions in noncancer patients. Other assumptions about event rate, power, alpha level, accrual and loss to follow-up rates, intervention effect size, and compliance rates differ for the two trial designs.

The effect of noncompliance was estimated similarly for both trials using the following assumptions. With perfect compliance, we estimated that the reduction in risk from increased physical activity would be 18% and the reduction in risk from weight control would be 12%. The effect of the two components was assumed to be additive; therefore, the effect of the intervention would give a 30% reduction in risk. We also assumed that compliance would be directly related to the reduction in risk. For example, a compliance of 50% would result in 50% of the expected reduction in risk.

Two scenarios of noncompliance were examined. In the first scenario we assumed that one-third of patients did not comply at all for both the physical activity and weight control components, one-third complied 50% of the time, and one-third complied fully. Under these assumptions, the observed reduction in risk would be 15% rather than 30% (the effect with perfect compliance). In the second scenario, we assumed that 50% did not comply at all and 50% complied fully with the physical activity and weight control components. Under these assumptions, the observed reduction in risk would be 21% rather than 30%.

For the primary prevention trial, sample size calculations were performed for two different endpoints. In one case the primary endpoint included only invasive cancers, and in the second case the primary endpoint included both invasive and noninvasive cancers. The following assumptions were used in the calculations of the sample size for a primary prevention trial. The rate of invasive cancers was 1.7% over 5 years, on the basis of the Gail model. The rate of noninvasive cancers was based on the placebo arm rates from the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention P1 Trial. The ratio of noninvasive to invasive cancers was 0.366, and so the noninvasive cancer rate over 5 years was 1.7 × 0.366. It was also assumed that 10% of patients would use antiestrogenic therapy with an improvement in the hazard rate of 0.5. The monthly accrual was assumed to be 335, which was based on the STAR trial. We estimated the length of accrual and sample sizes required for 90%, 85%, and 80% power using three different hazard ratios and two different lengths of follow-up for the primary endpoint of invasive and nonivasive cancers combined (Table 4).

The following assumptions were made for the survival trial. The rate of 3-year disease-free interval for the control arm was assumed to be 89.4% (5-year value was assumed to be 83%), and the accrual rate was assumed to be 209 patients per month. Both of these assumptions were based on the Arimidex, Tamoxifen, Alone or in Combination study (80). The length of accrual and sample sizes required for 90%, 85%, and 80% power by use of three different hazard ratios and two different lengths of follow-up (Table 5).

Conclusions

A substantial body of observational epidemiological evidence suggests that 1) a physically active lifestyle among both pre- and

Table 4. Sample size estimations for a primary prevention trial of invasive and noninvasive breast cancer to evaluate physical activity and weight control

Hazard ratio (control vs treatment 5-year disease-free interval rate)	Power, %	Minimum follow-up of 5 years		Minimum follow-up of 3 years	
		Length of accrual, y	No. of patients	Length of accrual, y	No. of patients
0.75 (97.8 vs 98.4)	90	5.1	20 638	6.2	25 052
	85	4.5	18 262	5.6	22 468
	80	4.1	16 350	5.1	20 442
0.80 (97.8 vs 98.3)	90	7.3	29 190	8.5	34 174
	85	6.5	25 974	7.6	30 774
	80	5.8	23 472	7.0	28 108
0.85 (97.8 vs 98.1)	90	11.3	45 246	12.7	50 874
	85	10.1	40 502	11.4	45 976
	80	9.2	36 807	10.5	42 146

Table 5. Sample size estimations for a trial of breast cancer survival among patients with breast cancer to evaluate physical activity and weight control

Hazard ratio (control vs treatment 5-year disease-free interval rate)	Power, %	Minimum follow-up of 5 years		Minimum follow-up of 3 years	
		Length of accrual, y	No. of patients	Length of accrual, y	No. of patients
0.75 (83.0 vs 86.9)	90	1.4	3380	1.9	4642
	85	1.2	2928	1.6	4074
	80	1.0	2588	1.5	3634
0.80 (83.0 vs 86.1)	90	2.0	5108	2.7	6744
	85	1.8	4444	2.4	5946
	80	1.6	3936	2.1	5330
0.85 (83.0 vs 85.3)	90	3.6	9070	4.5	11 270
	85	3.2	7954	4.0	10 026
	80	2.8	7104	3.6	9060

postmenopausal women can lower breast cancer risk and improve prognosis among survivors and that 2) achieving and maintaining normal body weight by postmenopausal women can also lower risk and improve prognosis. The question remains, however, whether these consistently observed protective associations are causal—which would imply a practical public health strategy for reducing breast cancer incidence and death rates—or merely reflect confounding by other lifestyle or biological factors. This question can be optimally answered with a randomized trial. Although other trials have evaluated physical activity and weight control (eg, DPP and Look AHEAD) from the standpoint of primary prevention of other chronic diseases, no trials have addressed this issue for breast cancer risk or survival.

Several large clinical trials (48,61,62,64,81) have demonstrated that it is feasible to recruit asymptomatic high-risk women and cancer survivors to behavioral intervention trials. Moreover, several large trials (10–12,62,65,67–69) have demonstrated success in implementing and fostering adherence to physical activity and/or weight control interventions. These trials also suggest that no specific intervention differences are needed between a primary prevention trial and a survival trial (Table 6). Both proposed types of trial offer an opportunity to evaluate several biomarkers that potentially mediate the relationships between physical activity, body weight, and breast cancer. Examples of such markers include hormones (particularly estrogen), insulin, and insulin-like growth factors; oxidative stress and DNA repair; target tissue markers; metabolisms; detoxification factors; noninflammatory aspects of immune function; inflammation; and growth factors.

The public health impact of either trial could be great, particularly given the current paucity of modifiable breast cancer risk factors and the increasing number of women older than 50 years. Definitive evidence from a primary prevention trial would be relevant to a larger population—all asymptomatic women older than 45 years of age. Definitive evidence from a survivorship trial, however, would be directly referable to a smaller population of all women diagnosed with breast cancer, although it could be argued that such trial findings provide valuable insights about late-stage breast cancer events in general. In terms of intervention adoption, no evidence exists to suggest differences across asymptomatic and diagnosed women, and this area might be an important one for follow-up investigation.

Several considerations, however, may weigh in favor of a survivorship over prevention trial, at least as a first step in a challenging fiscal environment. First, the endpoints for a survivorship trial, such as disease-free interval, breast cancer recurrence, and second primary breast cancer, occur more frequently and sooner than invasive breast cancer among asymptomatic women in a primary prevention trial. This difference has implications for sample size, trial duration, and ultimately cost. The estimates of sample size requirements for primary prevention vs survivorship trial indicate very large differences of four- to sixfold in the numbers needed for these two trials. For example, if a 5-year follow-up is planned, a relatively conservative assumption of a reduction in risk of 20%, and a power of 85%–90%, sample size requirements for a primary prevention trial are in the range of 26 000–36 000. In contrast, sample size requirements for a survivorship trial are in the range of 4500–5000. Although the number of participants required is larger for a trial limited to 3 years of follow-up, the very large difference in sample size requirements for the two types of trials is unchanged.

Second, it may be easier to identify women who have breast cancer through registries and medical records than to identify asymptomatic women at high risk for the disease. Hence, recruitment to a survivorship trial is likely to be more efficient and less costly than recruitment for a primary prevention trial.

Third, the eligibility rates for a prevention trial may be lower than those for the survival trial. For example, the requirement that women in a primary prevention trial are postmenopausal may exclude some women at the lower end of the eligible age range of 45–75 years. Moreover, given the prevalence of HT, it is expected that the exclusion of women having used SERMs would considerably reduce eligibility rates among women recruited to a prevention trial. For either type of trial, additional evidence may be required to inform specific components of trial recruitment, such as audience-specific recruitment strategies, recruitment among racial and ethnic minorities, or timing of trial enrollment among newly diagnosed breast cancer patients.

Fourth, early termination of the trial (before a definitive breast cancer result) because of an observed reduction in the incidence or mortality from conditions other than breast cancer is a more likely scenario for a primary prevention than a survival trial because the time to diagnosis of cardiovascular disease, diabetes, or stroke endpoints is shorter among women with breast cancer than that for cancer among women without breast cancer.

Table 6. Comparison of primary prevention and survivorship trial characteristics*

Characteristic	Common to both trials	Primary prevention trial	Survivorship trial
Endpoints			
Primary		Invasive breast cancer	Disease-free interval
Secondary	Hormone receptor status of invasive breast cancer		Breast cancer recurrence–free interval
	In situ breast cancer (DCIS and LCIS)		Second primary breast cancer
	Breast cancer deaths		
Other	All-cause mortality		
	Non–breast cancer incidence and death		
	Hospitalized coronary artery disease		
	Hospitalized stroke		
	Diabetes mellitus		
	Functional status and quality of life		
	Cost–benefit analysis		
Recruitment and enrollment	Centrally prepared material, promotional tools, and training	To the extent possible, target recruitment to high-risk populations	Target recruitment using tumor registries, medical records, support groups, and so on
	Locally tailored recruitment plans and strategies		
	Eligibility rates lower among racial and ethnic minorities compared with whites	Eligibility and participation rates lower than those for a survivorship trial	May be able to identify eligible participants as EMRs become widespread
	Participation rates lower among racial minorities compared with whites and Hispanics/Latinos		
Participant eligibility			
Inclusion criteria	Female	Age 45–75 years	Up to 75 years
	All races and ethnicities	Postmenopausal	Breast cancer diagnosis
	≥24 kg/m^2 BMI (≥23 kg/m^2 among Asian women) and not >45 kg/m^2		
	Medical screening	High risk for breast cancer	Completion of treatment
Exclusion criteria	Cardiovascular disease	Invasive breast cancer or DCIS	Pending systemic treatment decision
	Type 1 diabetes mellitus		
	Current weight-loss medication or surgical procedure		
	Medical condition limiting adherence	Use of SERMs	
	Mental illness		
	Travel time exceeding 1 h		
Eligibility assessment	Initial risk assessment and baseline screening		
	Secondary screening		
Enrollment and baseline evaluation	Final review of eligibility		
	Baseline assessment		
	Clinical breast examination, mammogram, breast density		
	Anthropometrics: height, weight, BMI, waist circumference		
	Fasting blood sample		
	Normal breast tissue		
	Randomization and study number assignment		
	Schedule initial intervention visit and 6-mo medical visit		
Intervention goal	Avoid weight gain among women with BMI ≤25 kg/m^2		
	Lose 10% body weight among women with BMI >25 kg/m^2		

(Table continues)

Table 4 (continued).

Characteristic	Common to both trials	Primary prevention trial	Survivorship trial
Components	Three-phase intervention: initiation, action, and maintenance Regular participation in moderate physical activity (approximately 3–5 METs) of 150–225 min over at least 5 or more d/wk (equivalent to 7.5–19 MET-hours per week) Reduce energy intake relative to expenditure among overweight or obese women and maintain energy balance among normal-weight women Improve food choices and meal patterns consistent with USDA dietary guidelines Implement tailored approaches to meet individual needs and overcome barriers		
Implementation	Implement using trained health counselors Provide a combination of individual and group contacts over 5 years		
Comparison group	Women retained in the trial but not given specific physical activity or diet recommendations Provide four weekly meetings followed by sessions every 6 mo through the end of the trial		
Adherence	Measure attendance Completion of self-monitoring records Measure changes in aerobic fitness		
Participant follow-up	6-mo examinations including height, weight, BMI, waist circumference, and fasting blood sample 12-mo examinations including CBE, mammogram, DXA		Evaluation by treating oncologist every 6–12 months
Monitoring	Ongoing monitoring of accumulated evidence to determine if trial should be stopped to protect the well-being of trial participants or make information available to the public		
Sample size	Assuming 5-year follow-up, risk reduction of 20%, power of 85%–90%	26 000–36 000	4400–5100

* Items in the column labeled "Common to both trials" are items common to both trials. DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; EMRs = electronic medical records; BMI = body mass index; SERMs = selective estrogen receptor modulators; METs = metabolic equivalents (a MET is defined as the ratio of a person's working metabolic rate relative to the resting metabolic rate; 1 MET is the caloric consumption of a person while at complete rest); USDA = US Department of Agriculture; CBE = clinical breast examination; DXA = dual-energy x-ray absorptiometry.

In conclusion, given the magnitude of the public health problem and the amount of accumulated evidence in support for this next level of scientific evidence, it is now appropriate to explore in detail the feasibility and timing of a large randomized trial to assess the effects of physical activity and weight control on breast cancer risk and/or prognosis—and the trade-offs in moving toward the prevention vs the survival trial.

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This commentary was initiated following the March 2006 NCI conference titled "Feasibility of a Physical Activity, Weight Control and Breast Cancer Risk Trial" and incorporates presentations and reviews from the conference as well as contributions from members of two postconference working groups: the Populations and Questions Working Group and the Interventions Working Group. Members of these working groups contributed substantively to the debate about optimal trial design and trade-offs among various trial characteristics.

The NCI Workshop Steering Committee Cochairs were Rachel Ballard-Barbash and Arthur Schatzkin (NCI); members included Emily Dowling, Sally A. Hunsberger, Victor Kipnis, Anna Levy, Worta McCaskill-Stevens, Lori Minasian, Sheila Prindiville, Julia Rowland, Ashley Wilder Smith, and JoAnne Zujewski (NCI).

The Populations and Questions Working Group Cochairs were Pam Goodwin (University of Toronto Mount Sinai Hospital) and Anne McTiernan (Fred Hutchinson Cancer Research Center); members included Elizabeth Barrett-Connor (University of California, San Diego); Leslie Bernstein (Norris Comprehensive Cancer Center at the University of Southern California); Diana Buist (Group Health Cooperative); Wendy Demark-Wahnefried (Duke University Medical Center); Jennifer Eng-Wong, Mitchell Gail, Larissa Korde, and Worta McCaskill-Stevens (NCI); Cynthia Thomson (The University of Arizona); Inger Thune (Ullevál University Hospital); and Yvonne Vargas (NCI).

The Intervention Working Group Cochairs were Rena Wing (The Miriam Hospital) and Steven Blair (University of South Carolina); members included Kerry Courneya (University of Alberta); Marian Fitzgibbon (University of Illinois at Chicago); Melinda Irwin (Yale School of Public Health); Michael Leitzman (NCI); Charles Mathews (Vanderbilt University); Jill Murphy Hall (Georgia Cancer Coalition); Cheryl Rock (University of California, San Diego); Ashley Smith (NCI); and Victor Stevens (Kaiser Permanente Center for Health Research).

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