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Randomized Controlled Trials of Physical Activity and Breast Cancer Prevention

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IRWIN, M.L. Randomized controlled trials of physical activity and breast cancer prevention. *Exerc. Sport Sci. Rev.*, Vol. 34, No. 4, pp. 182–193, 2006. *Observational studies demonstrate that women who exercise have a lower risk of developing breast cancer compared with sedentary women, but clinical trials are necessary to demonstrate a decreased effect of exercise on breast cancer. This review presents a rationale for randomized controlled exercise trials for breast cancer prevention and proposes a construct for designing such trials.*
Key Words: exercise, fitness, body weight, obesity, chronic disease, clinical trials

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer among American women (217,000 new cases in 2005), and incidence rates continue to rise (1). Approximately 39,000 women in the United States die of breast cancer each year, and an estimated 2.3 million breast cancer survivors in the United States alone are living with the long-term and late effects of the disease (1). Although advances in therapy have led to improvements in survival in recent years, new therapies are costly, are associated with significant side effects, and may benefit only subsets of those with breast cancer. Alternative approaches are needed to help diminish the morbidity and mortality of breast cancer, as well as its cost to society.

Multiple studies during the past 20 yrs, coming from North America, Europe, Asia, and Australia, have demonstrated that women who exercise regularly have a decreased risk of developing breast cancer compared with sedentary women (6). This association has been observed in various racial/ethnic minorities as well as in non-Hispanic white women (6). The evidence for the association between higher levels of physical activity and lower risk of breast cancer has been classified as "convincing," with the degree of protection estimated at about 30 to 40% with 3 to 4 $h \cdot wk^{-1}$ of moderate- to vigorous-intensity physical activity (6). Furthermore, recent findings from the Nurses' Health Study cohort and the Health, Eating, Activity and Lifestyle Study show that women who are physically active after a breast cancer diagnosis are at lower risk of a recurrence and death caused by breast cancer (8,9). Numerous observational studies also have demonstrated that obesity and weight gain adversely affect primary and secondary breast cancer risk, adding further evidence to the hypothesis that physical activity, one of the critical components of energy balance, influences breast cancer risk and prognosis (2,8,9).

Although observational studies have provided an important base of evidence for inferring that physical activity has a protective effect against breast cancer development, these studies cannot, by definition, show a protective "effect" of physical activity against breast cancer development. At this point, clinical trials are needed to (i) determine whether the independent effect of physical activity prevents the primary and secondary occurrence of breast cancer and (ii) elucidate the biological mechanisms by which physical activity protects healthy women from developing breast cancer and breast cancer survivors from experiencing recurrence and breast cancer–related mortality. To date, no human intervention studies have examined the effect of physical activity on primary and secondary breast cancer prevention. Conducting such a trial presents many challenges, including the need for a very large sample size, long study duration, and participation from multiple research institutes (Table 1). Nevertheless, the Women's Health Initiative Trial provides a model for such a study and suggests that such an undertaking is feasible (15). In addition, two large National Institutes of Health–funded multicenter clinical trials, the Women's Healthy Eating and Living Study and the Women's Intervention Nutrition Study, both of which are

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TABLE 1
Strengths and limitations of randomized controlled trials versus observational studies of physical activity and breast cancer risk

	Randomized Controlled Trials	Observational Studies
Strengths	Strongest design to establish causal relationships	May be less expensive
	Can study multiple outcomes	Can study multiple outcomes (if prospective cohort study)
	Blinding research staff minimizes measurement bias	Easier recruitment
	Random assignment avoids confounding	Minimal recall bias (if prospective cohort study)
	Less measurement error	No intervention
	Can measure dose	Larger sample size
	Can assess change in physical activity	Study of disease with many different physical activity patterns
	Can assess effect on intermediate endpoints	
	Minimal recall bias	
Limitations	Expensive	Cannot establish causality
	Long study duration	Difficult to measure change in physical activity
	Recruitment challenges	Measurement bias
	Control group issues	Incomplete control of confounders
	Adherence/compliance issues	Recall bias
	Large sample size to show effect on disease endpoint	
	Labor intensive	
	Not always ethical	
	Only able to examine one or 2 exercise prescriptions	

testing the effect of a change in dietary composition on recurrence and survival in breast cancer survivors, further demonstrate the feasibility of lifestyle intervention trials in this population (3,14).

Based on the epidemiological data and current understandings of how physical activity affects several specific biological processes involved in the primary and secondary occurrence of breast cancer, we hypothesize that physical activity has a direct causal role in breast cancer incidence, recurrence, and death and argue that randomized controlled physical activity trials are required to test this hypothesis, despite the challenges and limitations of this study design.

BIOLOGICAL MECHANISMS/ INTERMEDIATE ENDPOINTS

A number of potential physiological responses to physical activity have been postulated to be intermediate markers or endpoints in the development and progression of breast cancer (2). The evidence for each of these effects is summarized in Table 2. We hypothesize that exercise may reduce the risk of breast cancer occurrence/recurrence through a reduction in fat mass, leading to a more beneficial metabolic and sex hormone profile in terms of breast cancer risk, as depicted in Figure 1. Other mechanisms for a protective effect of exercise on breast cancer risk could exist. For example, exercise may improve immune status, which could in turn decrease risk for breast cancer.

Obesity and Weight Control

Of the possible biological mechanisms mediating an association between physical activity and breast cancer, body fat, or weight control may be most important (2,10,12). Maintenance of normal body weight throughout a woman's adult years is one of the few known modifiable risk factors for breast cancer, and many studies have shown positive associations between obesity and breast cancer risk (2). However, the influence of obesity on breast cancer risk varies by menopausal status: obesity has a protective effect against breast cancer in premenopausal women but is associated with increased risk in postmenopausal women. The biologic rationale for this difference in effect of obesity on breast cancer risk is based on the source of endogenous estrogen before and after menopause (2). Although menopausal status may modify the effect of obesity on breast cancer risk, recent studies have shown a positive association between weight gain during premenopausal or postmenopausal years and breast cancer risk (2). Epidemiological studies have also shown that premenopausal and postmenopausal women who are overweight or obese when they are diagnosed with breast cancer are more likely to experience a recurrence or die of breast cancer than women who are of a normal weight (2). Furthermore, some, but not all, studies suggest that women who gain weight after breast cancer diagnosis, regardless of menopausal status, are at increased risk for breast cancer recurrence and death as compared with women who maintain their weight after diagnosis (2). This is especially worrisome given the fact that most women who are treated for breast cancer gain a significant amount of weight in the year after breast cancer diagnosis, and return to prediagnosis weight rarely occurs (10).

Physical activity and obesity are highly interrelated. Obese individuals generally exhibit a lower level of habitual physical activity than the nonobese, and physically active individuals may be less likely to become obese (2). In the treatment of obesity, adding exercise to a calorie-reduction program enhances weight loss, and regular exercise is a powerful predictor of long-term maintenance of weight loss. No randomized trials have examined the effect of weight loss, established via increases in physical activity and/or dietary changes, on primary and secondary breast cancer risk. Such trials are necessary to (i) establish a causal relationship between weight loss and breast cancer risk and (ii) better understand the mechanisms mediating the relationships among physical activity, weight loss, and breast cancer risk (*e.g.*, does physical activity with or without weight loss decrease the risk of primary or secondary breast cancer?).

TABLE 2
Potential biological mechanisms involved in the association between physical activity and breast cancer

Possible Mechanism Involved	Effect of Mechanism on Breast Cancer	Effect of Physical Activity on Mechanism
Decreased sex hormones	Increases cell proliferation	Delays menarche
	Decreases apoptosis	Reduces number of ovulatory cycles
		Reduces ovarian estrogen production
		Reduces fat-produced estrogens
		Increases SHBG, resulting in less biologically available estrogen and testosterone
Decreased body fat	Fat storage of carcinogens	Decreases visceral and subcutaneous body fat
	Increases sex hormones	Prevents weight gain/promotes weight maintenance
	Increases insulin levels	
Decreased insulin and IGFs	Increases sex hormones	Increases post–receptor insulin signaling
	Increases cell proliferation	Increases glucose transporter protein and mRNA
		Increases clearance of free fatty acids
		Increases muscle glucose delivery
		Changes muscle composition favoring increased glucose disposal
Increase in immune function	Recognizes and eliminates abnormal cells	Increases no. and activity of macrophages
		Increases lymphokine-activated killer cells
		Increases lymphocyte proliferation
Decreased adipocytokines	Promotes angiogenesis	Decrease TNF-α, leptin, CRP, and IL-6 and increases adiponectin via decreases in body fat and insulin
	Stimulates estrogen biosynthesis	
Decreased mammographic density	Increases cell proliferation	Decreases sex hormones, insulin, and IGFs, which in turn, may decrease mammographic density
Improved antioxidant defense systems	Free radicals produce DNA damage	Improves free radical defenses and DNA repair by up-regulating free radical scavenger enzymes and levels of antioxidants

SHBG indicates sex hormone–binding globulin; IGFs, insulinlike growth factors; TNF-α, tumor necrosis factor α; CRP, C-reactive protein; IL-6, interleukin 6.

Insulin and Insulinlike Growth Factors

Physical activity and obesity also both influence circulating concentrations of insulin (2,7) which, in turn, may affect breast cancer risk and prognosis (2,7). In a study of women with early-stage breast cancer, higher insulin levels were associated with a two and three times higher risk of recurrence or breast cancer death, respectively (7), and in preclinical studies, insulin has a mitogenic effect in normal breast tissue and can stimulate growth of breast cancer cell lines. High insulin levels produce an increase in circulating insulinlike growth factor I (IGF-I) and a decrease in IGF-binding proteins (increasing the availability of IGF present). Insulinlike growth factor I is thought to have a major role in promoting breast cancer (2). However, the few trials that have assessed the effect of exercise on IGFs have had variable results (2). Randomized controlled trials testing the effect of exercise on insulin and IGFs are needed to elucidate the biological mechanisms by which physical activity protects against the development of primary or secondary breast cancer.

Sex Hormones

Obesity, a high insulin level, and altered IGF levels are also associated with a less favorable sex hormone profile (2). Sex steroid hormones have powerful mitogenic and proliferative influences and are strongly associated with the development of breast cancer (2,5). A recent pooled analysis of nine cohort studies showed that the risk for breast cancer in postmenopausal women increased significantly with increasing concentrations of estradiol, free estradiol, and estrone (5). Women who were in the highest quintile for these sex hormones had a twofold increased risk for breast cancer compared with women in the lowest quintile. Other findings from epidemiological studies further support the etiologic role of estrogen in breast cancer, showing that breast cancer risk is associated with early menarche, late menopause, low parity, and use of exogenous estrogens, all of which are linked to prolonged or extensive exposure of breast tissue to estrogen stimulation (2,5). Finally, a number of clinical trials show that estrogen ablation increases survival after a diagnosis of breast cancer. Changes in sex hormones are perhaps the most consistently cited potential mechanism for the association between physical activity and breast cancer.

Girls who participate in athletics tend to have a later age of menarche and a delay in establishing normal ovarian cyclicity. Later age of menarche and slowed establishment of cycling would decrease the total steroid hormone exposure to the breast (2). In adult premenopausal women, exercise has been associated with decreased levels of circulating estrogen and progesterone, shortened luteal phase, increased frequency of anovulation, and an increased incidence of oligomenorrhea and amenorrhea (2). In postmenopausal women, physical activity has been found to be associated with decreased serum estrogens and androgens (2,13). Increased physical activity also has been associated with increased sex hormone–binding globulin resulting in lower amounts of free active sex hormones in circulation (2,13).

The primary mechanism of physical activity influencing sex hormones in postmenopausal women is via decreased

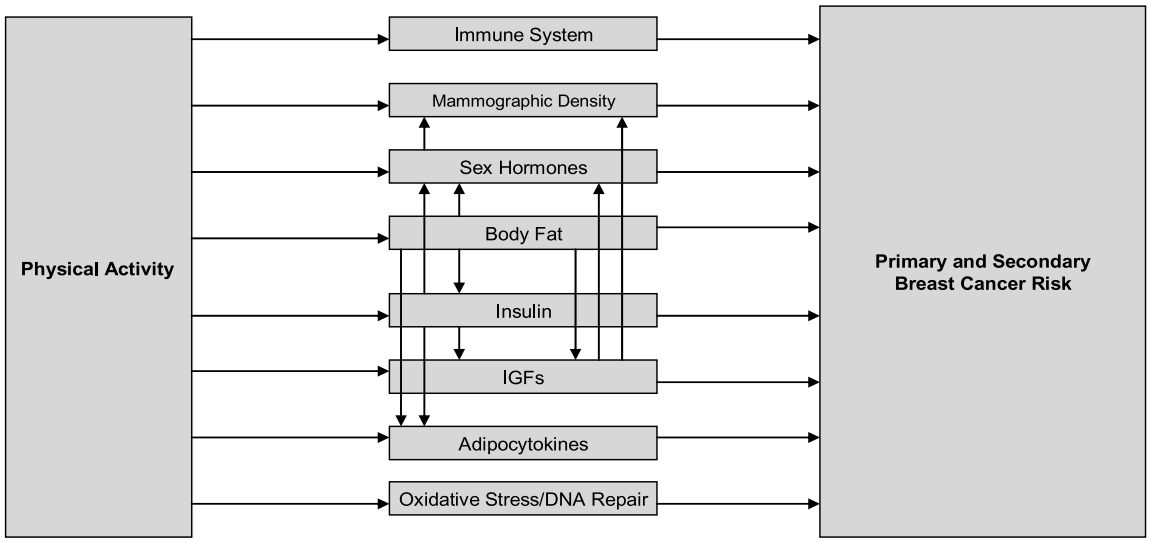

Figure 1. Hypothesized relationship between physical activity and primary and secondary breast cancer risk.

body fat, a substrate for estrogen, and testosterone production, which results in less tissue capable of aromatization of the adrenal androgens to estrogens. Only one randomized controlled exercise trial has been published examining the effect of exercise on sex hormone concentrations (13). Although an overall effect of exercise was significantly associated with decreased sex hormone concentrations in healthy postmenopausal women, a stronger effect was observed among women who lost body fat with exercise compared with women who did not lose body fat with exercise. Because of the paucity of randomized controlled trial data, it is not yet established that change in physical activity can affect sex hormone concentrations independently of an effect of physical activity on adiposity. More randomized trials are required to determine the associations among physical activity, body fat, sex hormones, and breast cancer risk and prognosis.

Immune Function

Changes in immune function may also mediate the relationship between physical activity and breast cancer risk and prognosis (2). The immune system is thought to play a role in protecting against breast cancer by recognizing and eliminating abnormal cells. A growing literature of small exercise intervention studies shows that physical activity improves immune function, both functionally and numerically (2). Physical activity appears to enhance proliferation of lymphocytes, increases the number of natural killer cells and increases lymphokine-activated killer cells activity.

Other Biological Mechanisms/ Intermediate Endpoints

Other intermediate endpoints have been proposed, such as mammographic density (2,11), adipocytokines (tumor necrosis factor α [TNF-α], leptin, and adiponectin) (2), and oxidative stress (2). Strong evidence exists that the characteristics of breast tissue as seen on a mammogram, measured as mammographic density, provide information about breast cancer risk. Women with high levels of mammographic density have a fourfold to sixfold greater risk of developing breast cancer than women with lower levels of mammographic density; thus, mammographic density is a stronger predictor of breast cancer risk than most traditional risk factors. Mammographic density reflects proliferation of the breast epithelium and stroma, in response to growth factors induced by current and past circulating sex hormone levels. Mammographic density may vary throughout lifetime, with the pattern reflecting the accumulated breast cancer risk at the time the mammogram was obtained. Factors that change mammographic density may also change breast cancer risk. Physical activity may influence mammographic density by favorably changing certain hormones associated with mammographic density and breast cancer risk. Both mammographic dense area and percent density have been found to be inversely related to physical activity in obese postmenopausal women (2,14).

Adipocytokines exhibit strong associations with body mass index, abdominal fat mass, and hyperinsulinemia. In addition, several adipocytokines, including interleukin 6 (IL-6), TNF-α, and leptin, promote angiogenesis, which is essential for breast cancer development and progression and can stimulate estrogen biosynthesis by the induction of aromatase activity. C-reactive protein is not an adipocytokine *per se*, but its production is promoted by TNF-α and IL-6. C-reactive protein is a well-known systemic marker for inflammation that is produced by the liver and is only present during episodes of chronic inflammation. Thus far, varying effects of physical activity for the different adipocytokines have been observed (2). For postmenopausal women, the evidence most strongly supports physical activity decreasing circulating leptin, IL-6, and C-reactive protein. The evidence is mixed on TNF-α, and no studies have yet found an association between exercise and adiponectin.

Lastly, reactive oxygen species (*i.e.*, free radicals) can play a significant role in breast cancer via their ability to produce DNA damage as well as damage to other cellular components

which interact with DNA (2). Acute exercise may promote free radical production, whereas chronic exercise improves free radical defenses by up-regulating both the activities of key free radical scavenger enzymes and levels of antioxidants (2). To date, there are few studies that have examined reactive oxygen species–related damage or relevant antioxidant enzymes in the context of exercise in a cancer model.

Conclusions

With numerous publications showing statistically and clinically significant associations between obesity, fasting insulin levels, sex hormones, and breast cancer risk, recurrence, and death, more effective treatment strategies to reduce body fat, insulin, and sex hormone levels in healthy women and breast cancer survivors should be explored. Although much further research is needed to determine the effect of physical activity on these intermediate endpoints/biomarkers, we posit that physical activity decreases primary and secondary breast cancer risk directly and indirectly through multiple interrelated actions of body fat levels and/or hormonal concentrations and actions. Only randomized controlled exercise trials are able to determine whether physical activity directly prevents the primary and secondary occurrence of breast cancer and what the biological mechanisms are by which physical activity protects against primary or secondary breast cancer.

RANDOMIZED TRIALS OF EXERCISE AND INTERMEDIATE ENDPOINTS/BIOLOGICAL MECHANISMS

Because of the cost and logistical difficulties involved with a trial that has breast cancer as the outcome, many breast cancer researchers have advocated for trials of short-term responses that may be early disease markers (*e.g.*, atypical benign breast disease before development of *in situ* or invasive breast cancer) or, more specifically, biomarkers, such as serum sex hormones, which can be measured in fresh or stored biological specimens. To the extent that these intermediate endpoints and biomarkers are valid and reliable measures of breast cancer risk, trials that examine the effects of exercise on these endpoints provide important clues about the causal pathway between physical activity and breast cancer occurrence, recurrence, and death. The few existing exercise interventions in humans that have examined these effects are summarized in Table 3. Despite the positive results of the intermediate outcome trials discussed in Table 3, favorable intermediate outcome changes may or may not convey meaningful benefits in terms of disease prevention. Thus, randomized trials with disease occurrence outcomes are still considered the gold standard for testing breast cancer prevention hypotheses.

DESIGNING AN EXERCISE TRIAL FOR PRIMARY OR SECONDARY BREAST CANCER PREVENTION

Because randomized controlled exercise trials with breast cancer prevention outcomes are very costly, only a few trials can be conducted. Consequently, a well thought out design is needed before initiating a large-scale, multisite prevention trial. Table 4 lists essential steps needed for the successful delivery of exercise and breast cancer trials. We discuss some of the essential steps in more detail below.

Study Investigators

A team of investigators must be assembled representing a variety of scientific disciplines such as exercise science, epidemiology, and oncology. Breast cancer survivors should also be active participants in the collaborative team. Preliminary/pilot data from exercise trials in healthy women or breast cancer survivors are necessary.

Study Design

A two-arm comparison of exercise versus control or two alternative types of exercise are necessary. Given the established benefits of physical activity for cardiovascular disease, the ethics of having a nonexercise control group may be questioned. Researchers also need to consider ways to make randomized assignment palatable for participants, including use of a delayed intervention or alternative intervention (*e.g.*, health education or two different exercise prescriptions).

Recruitment and Eligibility Criteria

Because randomized trials are expensive and require a high level of staff involvement, it is most efficient to recruit individuals at high risk for developing breast cancer or breast cancer survivors. Recruitment may take 2 to 4 yrs, and approximately fewer than 10% of those approached may eventually be randomized. Pilot data on recruitment rates are critical before initiating a full-scale trial, as well as a plan for how participants will be recruited. A population-based approach is ideal; however, this approach may need to be supplemented with physician referrals and/or mass media. Whatever recruitment approached is used, demographic, behavioral, and physiological data need to be collected on all participants during a screening visit (phone call or mailing) to compare characteristics between women eventually randomized and women not randomized to the study (either because of ineligibility or lack of interest). An ethnically/racially diverse sample must be recruited that is at least similar to the ethnic/racial distribution in the general population of the study areas. To observe a maximal effect of the exercise intervention on the disease outcome, only physically inactive women would be eligible. Other eligibility criteria worth considering are age, menopausal status, body mass index, and breast cancer disease stage (if studying survivors) (Table 5).

Study Population

Because of differences in incidence rates and outcomes being assessed, a trial needs to be conducted separately for healthy women and breast cancer survivors. A trial among healthy women will require a significantly larger sample size and longer study duration to examine the effect of exercise on preventing primary breast cancer compared with a trial in breast cancer survivors on preventing secondary breast

TABLE 3

Randomized controlled trials examining the effect of exercise on biological mechanisms/intermediate endpoints of breast cancer risk or prognosis

Principal Investigator	Study Objectives	Study Design	Participants	PA Prescription/Intervention	PA Measures	Outcome Measures	Results/Comments
McTiernan	Randomized clinical trial of exercise vs stretching control (the Physical Activity for Total Health Study) investigated the effect of exercise on biomarkers of breast cancer risk	Two-arm randomized trial design: (i) moderate-intensity aerobic exercise, (ii) stretching control	173 Healthy overweight, physically inactive, postmenopausal women not using HRT with no previous cancer diagnosis	At least 45 min of moderate-intensity exercise 5 $d \cdot wk^{-1}$ for 12 months; participants attended 3 exercise physiologist-supervised sessions per wk and exercised 2 $d \cdot wk^{-1}$ at home Facility sessions consisted of treadmill walking, stationary bicycling, and use of other aerobic machines; a variety of home exercises were suggested and encouraged, including walking, aerobics, and bicycling	• Completion of weekly facility activity logs • Completion of weekly home activity logs • All participants completed baseline and end-of-study VO_2max; baseline, 6-month, and end-of-study 7-d pedometer log; and baseline and follow-up physical activity questionnaire	• Serum estrogens, androgens, insulin, IGF-I and IGFBP-3, mammogram density, and body composition via DEXA and CT scans	• Women randomized to exercise lost 5.9% intra-abdominal body fat compared with a slight increase in controls ($P < 0.05$) • Decreased estrogen concentrations by 7.7% in exercisers vs no change in controls ($P < 0.05$) • Exercisers whose body fat decreased by at least 2% had decreases of 13.7% in estradiol ($P < 0.05$)
McTiernan	Randomized clinical trial of exercise or caloric restriction ("New Trial") investigating the independent and combined effects of changes in energy balance through exercise and/or caloric restriction on biomarkers of breast cancer risk	Four-arm randomized trial design: (i) moderate-intensity aerobic exercise, (ii) reduced-calorie diet, (iii) both moderate-intensity aerobic exercise + reduced-calorie diet, and (iv) control (neither intervention)	503 Healthy overweight, physically inactive, postmenopausal women not using HRT with no previous cancer diagnosis	***Exercise intervention.*** At least 45 min of moderate-intensity exercise 5 $d \cdot wk^{-1}$ for 12 months; participants required to attend 3 exercise physiologist-supervised sessions per wk and to exercise 2 $d \cdot wk^{-1}$ at home Facility sessions consist of treadmill walking, stationary bicycling, and use of other aerobic machines; a variety of home exercises are suggested and encouraged, including walking, aerobics, and bicycling ***Calorie reduction intervention.*** Modification of the diabetes prevention program lifestyle intervention with 7% goal weight loss The diet intervention is conducted by nutritionists with training in behavior modification; the nutritionists	***Exercise intervention*** • Completion of weekly facility activity logs • Completion of weekly home activity logs • All participants complete baseline and end-of-study VO_2max; baseline, 6-month, and end-of-study 7-d pedometer log; and baseline and follow-up physical activity questionnaire ***Diet Intervention*** • Weekly weigh-in's • Weekly food journaling	• Serum estrogens, androgens, insulin, IGF-I and IGFBP-3, mammogram density, and body composition via DEXA scans • Biomarkers of inflammation (CRP, serum amyloid A, and IL-6) • DNA damage sensitivity and DNA repair capacity in response to challenges by H_2O_2 and γ-irradiation, as measured by single-cell gel electrophoresis (Comet assay) • Gene expression of DNA repair enzymes	McTiernan *et al.* hypothesized that both the exercise intervention and the reduced-calorie diet intervention will result in decreases in sex hormones, insulin, IGF-I, mammographic density, body fat, and up-regulation of DNA repair enzymes, increased DNA repair capacity, and reduced mutagen sensitivity Results are expected in 2009

TABLE 3 (*continued*)

Principal Investigator	Study Objectives	Study Design	Participants	PA Prescription/Intervention	PA Measures	Outcome Measures	Results/Comments
				meet weekly with participants in groups of 8–15 women in the first 24 wk and contact each participant at least monthly thereafter (with in-person contacts at least every 2 months throughout the remainder of the diet program to help participants to maintain weight loss); the goal caloric intake will be based on baseline weight; the goal ranges from 1200–1800 kcal·d^{-1}	• Monitored attendance to individual and group nutrition sessions • All participants complete baseline and follow-up food frequency questionnaires		
Friedenreich	Randomized clinical trial of exercise vs control (ALPHA) investigating the effect of exercise on biomarkers of breast cancer risk	Two-arm randomized trial design: (i) moderate-intensity aerobic exercise, (ii) control	320 Healthy physically inactive, postmenopausal women aged 50–74 yrs, BMI >22 to <40, not using HRT with no previous cancer diagnosis	60 min of moderate-intensity exercise 5 d·wk^{-1} for 12 months; participants attend 3 exercise physiologist-supervised sessions per wk and exercise 2 d·wk^{-1} at home Facility sessions consist of treadmill walking, stationary bicycling, and use of other aerobic machines; a variety of home exercises are suggested and encouraged, including walking, aerobics, and bicycling	• Completion of weekly physical activity logs • All participants complete baseline and end-of-study $\dot{V}O_2$max; baseline, 6-month and end-of-study 7 d-pedometer log; and baseline and follow-up questionnaires on physical activity, diet, well-being, predictors of adherence to exercise	• Serum estrogens, androgens, insulin, IGF-I and IGFBP-3, adipocytokines, mammographic density, body composition via DEXA and CT scans	Friedenreich *et al.* hypothesized that the exercise intervention will result in decreases in sex hormones, insulin, IGF-I, mammographic density, body fat, and adipocytokines Results are expected in 2007
Schmitz	Randomized controlled trial of weight training vs control group (WGPS) to investigate effects of resistance training on body composition, insulin, and the IGF pathway among healthy midlife women	Two-arm randomized trial design: (i) twice weekly progressive overload weight training, (ii) no exercise control	60 Healthy, sedentary midlife women (aged 30–50 yrs) with no previous cancer diagnosis	Twice weekly 1-h progressive overload weight training for 9 months, first 15 wk was supervised; all activity occurred in a fitness facility; no intervention for control group; all participants asked not to change their diet	• Completion of workout logs at each session, logs checked weekly by trainers • All participants complete self-reported physical activity survey and 1-RM strength testing pre- and postintervention	* Body composition, insulin, IGF-1, IGFBP-1, IGFBP-3	* Weight training resulted in significant increases in lean mass and decreased body fat percentage * Weight training resulted in significant decreases in IGF-1, but no changes in IGFBP-1 or IGFBP-3

TABLE 3 (*continued*)

Principal Investigator	Study Objectives	Study Design	Participants	PA Prescription/Intervention	PA Measures	Outcome Measures	Results/Comments
Schmitz and Kurzer	Randomized controlled trial of aerobic exercise vs control (WISER) on oxidative stress and estrogen metabolism	Two-arm randomized controlled trial design: (i) 5 times weekly 30 min of moderate- to vigorous-intensity aerobic exercise, (ii) no exercise control	400 Healthy, sedentary, eumenorrheic women aged 18–30 yrs who have not taken hormonal contraceptives during the past 6 months	Five times weekly 30 min of moderate- to vigorous-intensity aerobic exercise, with intensity monitored by heart rate monitor; four menstrual cycles of exercise; all activity will occur in a fitness facility; no intervention for control group; all participants asked not to change diet and to avoid losing weight	• Completion of workout logs, which will be checked daily by trainers • All participants will complete a self-reported physical activity survey and a submaximal treadmill exercise test pre- and postintervention	• Oxidative stress: F2-isoprostanes • Estrogens: E_1, E_2, E_3, 2-OHE_1, 2-OHE_2, 4-OHE_1, 4-OHE_2, 2-MeE_1, 2-MeE_2, 4-MeE_1, 4-MeE_2, and 16-αOHE_1	Schmitz and Kurzer *et al.* hypothesized that aerobic exercise will reduce oxidative stress and alter estrogen metabolism in a manner consistent with reduced breast cancer risk Results are expected in 2010
Schmitz	Randomized controlled trial of weight training vs control group (WTBS) to investigate effects of resistance training on body composition, insulin, and the IGF pathway among recent breast cancer survivors	Two-arm randomized trial design: (i) twice weekly progressive overload weight training, (ii) no exercise control; partial crossover design: after 6 months, treatment group kept weight training, and control group began weight training for months 7–12	85 Healthy, sedentary breast cancer survivors who were 4–36 months post–adjuvant therapy	Twice weekly 1-h progressive overload weight training for 6 months, first 13 wk was supervised; all activity occurred in a fitness facility; no intervention for control group; all participants asked not to change their diet	• Completion of workout logs at each session, logs checked weekly by trainers • All participants complete self-reported physical activity survey and 1-RM strength testing pre- and postintervention	* Body composition, insulin, IGF-1, IGF-II, IGFBP-1, IGFBP-3	* Weight training resulted in significant increases in lean mass and decreased body fat percentage * Weight training resulted in significant decreases in IGF-2, but no changes in IGF-1, IGFBP-1 or IGFBP-3
Schmitz	Randomized controlled trial of weight training vs control group (Physical Activity and Lymphedema Trial) to investigate effects of resistance training on inflammation, adipocytokines, insulin, and the IGF pathway in breast cancer survivors, comparing effects among those who are vs are not taking hormone therapy	Two-arm randomized trial design: (i) twice weekly progressive overload weight training, (ii) no exercise control	288 Healthy, sedentary breast cancer survivors 1–15 yrs after diagnosis	Twice weekly 1-h progressive overload weight training for 12 months, first 13 wk was supervised; all activity will occur in a fitness facility; no intervention for control group; all participants asked not to change their diet	• Completion of workout logs at each session, logs checked weekly by trainers • All participants complete self-reported physical activity survey and 1-RM strength testing pre- and postintervention	• Body composition, insulin, IGF-1, IGFBP-1, IGFBP-3 • Cytokines • Adipocytokines	Schmitz *et al.* hypothesized that the exercise intervention will result in decreases in insulin, IGF-I, body fat, cytokines, and adipocytokines; furthermore, the effect on insulin and the IGF pathway will differ according to whether the participant is taking hormone therapy during the trial Results are expected in 2008

TABLE 3 (*continued*)

Principal Investigator	Study Objectives	Study Design	Participants	PA Prescription/Intervention	PA Measures	Outcome Measures	Results/Comments
Irwin	Randomized clinical trial of exercise vs control (the Yale Exercise and Survivorship Study) investigating the effect of exercise on biomarkers of breast cancer recurrence and death	Two-arm randomized trial design: (i) moderate-intensity aerobic exercise, (ii) usual care	75 Physically inactive, postmenopausal breast cancer survivors who have completed adjuvant treatment	30 min of moderate-intensity exercise 5 d·wk^{-1} for 12 months; participants attend 3 exercise physiologist-supervised sessions per week and exercise 2 d·wk^{-1} at home Facility sessions consist of treadmill walking, stationary bicycling, and use of other aerobic machines; a variety of home exercises are suggested and encouraged, including walking, aerobics, and bicycling	• Completion of weekly physical activity logs • All participants complete baseline, 6-month, and end-of-study 7-d pedometer log; and baseline and follow-up physical activity questionnaire; and 7-d logs	• Serum estrogens, androgens, insulin, IGF-I and IGFBP-3, mammogram density, body composition via DEXA scans, and adipocytokines	Irwin *et al.* hypothesized that the exercise intervention will result in decreases in sex hormones, insulin, IGF-I, mammographic density, body fat, and adipocytokines Results are expected in 2007
Irwin	Randomized clinical trial of exercise vs control (IMPACT Study) investigating the effect of exercise on biomarkers of breast cancer recurrence and death	Two-arm randomized trial design: (i) moderate-intensity aerobic exercise, (ii) usual care	50 Physically inactive, postmenopausal, newly breast cancer survivors who are receiving adjuvant treatment (*e.g.*, chemotherapy and/or radiation)	30 min of moderate-intensity exercise 5 d·wk^{-1} for 6 months; home-based intervention; participants receive weekly phone calls from exercise physiologist/psychologist A variety of home exercises are suggested and encouraged, including walking, aerobics, and bicycling	• Completion of weekly physical activity logs • All participants complete baseline and end-of-study 7-d pedometer log; and baseline and follow-up physical activity questionnaire; and 7-day logs	• Serum estrogens, androgens, insulin, IGF-I and IGFBP-3, mammogram density, body composition via DEXA scans, and adipocytokines	Irwin *et al.* hypothesized that the exercise intervention will result in decreases in sex hormones, insulin, IGF-I, mammographic density, body fat, and adipocytokines Results are expected in 2007
Courneya	Randomized clinical trial of exercise vs control (REHAB) investigating the effect of exercise on biomarkers of breast cancer recurrence and death	Two-arm randomized trial design: (i) moderate-intensity aerobic exercise, (ii) control	53 Postmenopausal, nonsmoking, breast cancer survivors between the ages of 50 and 68 yrs who completed adjuvant treatment	35 min of moderate-intensity exercise 3 d·wk^{-1} for 15 wk on recumbent or upright cycle ergometers	• Facility attendance • Participants complete baseline and end-of-study $\dot{V}O_2$max testing	• Serum insulin, IGF-I and IGFBP-3, CRP, and immune function	CRP decreased in the exercise group, whereas it increased in the control group Exercise training increased natural killer cell cytotoxic activity Exercise training decreased IGF-I and increased IGFBP-3

TABLE 3 (*continued*)

Principal Investigator	Study Objectives	Study Design	Participants	PA Prescription/Intervention	PA Measures	Outcome Measures	Results/Comments
Ligibel	Randomized clinical trial of exercise vs control (Study of the impact of an exercise intervention on insulin levels in breast cancer survivors) investigating the effect of exercise on biomarkers of breast cancer recurrence and death	Two-arm randomized trial design: (i) moderate-intensity aerobic and strength training exercise; (ii) usual care	100 Physically inactive, pre- and postmenopausal breast cancer survivors who have completed adjuvant treatment	The exercise intervention consists of a 16-wk cardiovascular and strength training regimen; participants attend two 50-min supervised weight training sessions each week and complete three 30-min cardiovascular exercise sessions at home Facility sessions consist of lower body and core training exercises; a variety of home exercises are suggested and encouraged, including walking, aerobics, and bicycling	• Completion of weekly physical activity logs • All participants complete follow-up physical activity questionnaires at 3 and 9 months after completion of the intervention	• Serum insulin, glucose, leptin, and estrogen levels • Body weight, fat mass as determined by bioelectric impedance monitor, and waist and hip measures	Ligibel *et al.* hypothesized that the exercise intervention will result in decreases in insulin, glucose, leptin and sex hormone levels. Results are expected in 2006

HRT indicates hormone replacement therapy; $\dot{V}O_2$max, maximal oxygen uptake; IGF-I, insulinlike growth factor I; IGFBP, insulinlike growth factor binding protein; DEXA, dual-energy x-ray absorptiometry; CT, computed tomography; CRP, C-reactive protein; IL, interleukin; "New Trial", Nutrition and Exercise for Women; ALPHA, Alberta Physical Activity; WGPS, Weight Gain Prevention Study; WISER, Women In Steady Exercise Research; WTBS, Weight Training for Breast Cancer Survivors Study; IMPACT, Increasing or Maintaining Physical Activity during Cancer Treatment; REHAB, rehabilitation exercise for health after breast cancer.

cancer. However, both trials are necessary to determine the optimal dose of exercise necessary to prevent either primary or secondary breast cancer.

Exercise Intervention

Choosing an appropriate exercise intervention is critical for a study's success. If null results are observed, it may be difficult to distinguish an intervention's lack of effect from inadequate exercise training or loss of power from poor adherence. Similarly, differential adherence reporting between intervention and control groups could lead to inaccurate recommendations following a positive trial result. A number of different types of exercise interventions could be implemented. A supervised program has advantages over a "lifestyle" or home-based program in that participants' adherence to exercise can be directly observed. However, home-based programs may result in better long-term adoption and maintenance of exercise, especially if the participants find cost-effective ways to incorporate exercise into their daily routine. Another approach could involve an exercise intervention consisting of a combined home exercise and supervised program. Women randomized to exercise may be taught exercise techniques and principles in an initial in-person visit at a local health club with the exercise trainer and then weekly via the telephone. A telephone counseling protocol could be the principal instrument used to promote exercise adherence in the exercise group, as was done in the Women's Health Initiative, Women's Intervention Nutrition Study, and Women's Healthy Eating and Living Studies (3,14,15). In addition to the telephone counseling and in an effort to maximize adherence to the exercise intervention and provide more variety or different options for exercising, participants could also be offered access to a health club, allowing them to exercise during inclement weather and in the evenings. The successful Diabetes Prevention Program protocol required that each clinical center offer supervised exercise sessions at least two times per week throughout the trial (4).

Exercise Prescription

The type of exercise prescribed depends on the outcome. For primary or secondary breast cancer prevention, observational data recommend 3 to 4 $h \cdot wk^{-1}$ of moderate-intensity aerobic activity such as brisk walking. However, until this dose of exercise is tested using a randomized design, the optimal amount of exercise necessary to decrease breast cancer risk is unknown. The amount of exercise prescribed in other exercise trials (*e.g.*, randomized trials of exercise and breast cancer intermediate endpoints or cardiovascular disease) may provide some guidance as to what dose to prescribe. Although many questions remain concerning the optimal duration, frequency, intensity, and type of exercise (*e.g.*, aerobic exercise vs strength training), as well as when (*e.g.*, after completing breast cancer treatment) and for how many years to intervene, no doubt remains that only randomized controlled exercise trials will provide direct answers as to the recommended amount of physical activity necessary for primary and secondary breast cancer prevention. However, a limitation of

TABLE 4
Essential steps needed for the successful delivery of exercise and breast cancer trials

1) Study investigators
   a) Multidisciplinary team including exercise scientists, epidemiologists, and oncologists
   b) Breast cancer survivors
2) Study design
   a) Randomized controlled trial
      i) Two-arm
      ii) Four-arm
      iii) Ethical issues related to control group
3) Eligibility and recruitment
   a) Locating subjects—cancer registries, physician referral, mass media
   b) Ethnic variation
   c) Eligibility criteria
4) Randomization
   a) Willingness of subjects to be randomized
   b) Block on potential effect modifiers (*e.g.*, study site, menopausal status, body mass index, disease stage, hormone receptor status)
   c) Blinding of study staff
   d) Adherence to exercise intervention
   e) Compliance to randomization group
5) Intervention
   a) When to intervene (*e.g.*, after completing breast cancer treatment)
   b) Study duration
   c) Exercise prescription (type, duration, frequency, and intensity)
   d) Supervised vs unsupervised
   e) Theoretical approach
6) Assessment of physical activity and covariates
7) Assessment of outcome variables
   a) Primary breast cancer
   b) Secondary breast cancer
      i) Recurrence
      ii) New breast primary
      iii) Breast cancer death
      iv) Death from any cause
8) Other issues
   a) Assessment of intermediate markers
   b) Effect modifiers
   c) Data management
      i) Development of tracking systems
      ii) Data entry
      iii) Development of final analytic data sets
   d) Quality control
      i) Detailed manual of operations
      ii) Staff training
      iii) Survey design
      iv) 10% repeat measure of all forms
   e) Power and sample size
      i) Appropriate effect size
      ii) Adherence and compliance rates
   f) Statistical analyses
      i) Intent-to-treat analyses
      ii) Survival analyses accounting for variable lengths of follow-up
      iii) Adherence and compliance
      iv) Covariates and effect modifiers
   g) Data safety and monitoring committee

randomized trials is that only one or two exercise prescriptions can be prescribed per trial.

Assessment of Physical Activity and Covariates

To assess accurately the effect of physical activity on breast cancer risk and prognosis, reliable, valid, and comprehensive physical activity measures, as well as measures of other potential covariates, must be used at baseline and follow-up. All components of physical activity must be assessed (type, frequency, duration, and intensity) via multiple measures, for example, physical activity questionnaire, physical activity logs, accelerometers, and maximal oxygen uptake ($\dot{V}O_{2max}$) treadmill testing. After each exercise session, subjects would complete a physical activity log, recording the type of exercise, duration, average heart rate, and perceived heart rate. The physical activity log could be used as a measure of exercise adherence. For measuring study compliance, ideally, all study participants would complete physical activity questionnaires and a weekly physical activity log at baseline and follow-up visits. Participants would also wear an accelerometer for a week at baseline and follow-up visits to assess physical activity levels objectively. Lastly, participants would complete a $\dot{V}O_{2max}$ treadmill test at baseline and follow-up as an indirect measure of physical activity. Physical activity would then be compared between participants randomized to exercise versus control.

Assessment of Breast Cancer Outcome

Outcome data must be collected at semiannual or annual follow-up visits, with medical history update questionnaires collected from participants every 6 months with questions regarding hospitalizations and procedures to detect occurrence of breast cancer or any recurrences/new primaries. Investigators would then obtain medical records for any tests or hospitalizations that occurred during the study period. An outcomes committee must be formed who will review records and decide if the event is a new primary or a recurrence or death (from any cause) has occurred.

Other Essential Steps

Other issues to consider for the successful delivery of exercise and breast cancer trials include data management,

TABLE 5
Potential eligibility criteria for a randomized controlled exercise trial on primary or secondary breast cancer risk

Inclusion criteria

- Age
- Menopausal status
- Ethnicity/race
- Sedentary activity pattern
- Physically able to exercise and physician consent to start an exercise program
- Body mass index
- Agrees to be randomly assigned to either of exercise or usual care
- Gives informed consent to participate in all study activities
- Able to come for baseline and follow-up visits
- Accessible by telephone
- English speaking
- Mentally competent
- Disease stage (secondary prevention trial only)
- Completed adjuvant therapy (secondary prevention trial only)
- Hormone therapy (secondary prevention trial only)
- Hormone receptor status (secondary prevention trial only)
- Diagnosis date (secondary prevention trial only)

Exclusion criteria

- Diagnosis of primary or recurrent invasive cancer ever except for nonmelanoma skin cancer or *in situ* cervical cancer
- Pregnant or intending to become pregnant in the next 5 yrs
- Cardiovascular disease

quality control, statistical analyses, and power and sample size calculations. Lastly, a Data and Safety Monitoring Committee needs to be formed. This committee is responsible for monitoring the data and safety of all study participants.

Physical activity trials with disease prevention outcomes have great potential to lead to reductions in primary and secondary breast cancer risk. One benefit of a full-scale trial is that it can focus specifically on the health benefits and risks of a prescribed change in physical activity over a specific period. However, establishing the criteria for the initiation of a full-scale disease prevention trial is itself an important methodologic goal.

CONCLUSIONS

If randomized controlled exercise trials demonstrate that exercise can significantly decrease primary and secondary breast cancer risk, exercise could be prescribed as an integral part of primary care and breast cancer therapy. Exercise could possibly even replace toxic and costly treatments in some patients for whom chemotherapy is not very beneficial. This would, in turn, lower both breast cancer mortality and the morbidity that many patients experience from the disease and its treatment. One can even imagine a time when health club fees and physical activity counseling for primary and secondary breast cancer prevention would be reimbursed by health insurance companies.

There are, clearly, many questions to be answered concerning who, in terms of breast cancer prevention, would benefit from increasing physical activity, when physical activity would be most beneficial, and how much physical activity would be optimal. Given the high level of physical inactivity in the population and the heavy burden that breast cancer creates for the individual and for the society, the need for well-designed randomized trials of exercise on primary and secondary breast cancer prevention is an urgent public health priority.

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