Commentary

Exercise Clinical Trials in Cancer Prevention Research: A Call to Action

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Abstract
The experimental study design can yield valuable information in measuring the association between physical activity and occurrence of cancers. Randomized clinical exercise trials can provide insight into the avenues through which physical activity might affect cancer development and can provide experience with diffusing an exercise intervention into certain populations. This report describes the potential utility of the randomized clinical trial design in providing answers about bias, mechanisms, behavior change, and dose-response in defining the causal pathway between physical activity and cancer. The challenges and limitations of exercise clinical trial are discussed. The research experience in cardiovascular disease and exercise is used as a model for developing a research agenda to explore the potential role of physical activity as a cancer-prevention modality. We recommend that a series of small clinical trials of exercise interventions be conducted to measure exercise change effects on biomarkers for cancer risk, to learn about exercise behavior change in individuals at risk for cancer, and to serve as feasibility studies for larger randomized controlled trials of cancer and precursor end points and for community intervention studies.

Introduction
Considerable observational data have accrued linking physical activity to a reduced risk of several cancers. Observational methods can give important pieces of information about links between lifestyle factors. There are some aspects to the epidemiological discovery process, however, that can be best extended and clarified with the experimental model. This report describes the potential utility of the randomized clinical trial design in providing answers about bias, mechanisms, behavior change, and dose-response in defining the causal pathway between physical activity and cancer. It also discusses the challenges and limitations to conducting exercise intervention studies in cancer prevention research. Finally, a research agenda is proposed to use the unique opportunities afforded through the human experimental research method in defining cost-effective, workable ways for individuals to reduce their lifetime risk of developing cancer.

Role of Exercise Clinical Trials in Other Chronic Diseases
The scientific discovery process for the role of physical activity in coronary heart disease prevention provides one model for the role of physical activity in cancer prevention. In 1953, Morris et al. (1) studied 31,000 male employees of the London Transport Executive and reported a 30% lower rate of heart disease in tram conductors (who were active in their jobs) compared with drivers (who spent most of their job hours sitting). Similar observations were made in over 191,000 United States railroad workers, showing that men who were active on the job had a 50% lower mortality rate from atherosclerotic diseases compared with sedentary workers (2). Numerous excellent observational studies confirmed the association between increased physical activity on the job or in leisure time and reduced risk of cardiovascular disease and death (3). Parallel discovery of a link between blood cholesterol levels and risk of heart disease led to interest in identifying lifestyle factors that could prevent atherosclerosis and its sequelae (4). Observational studies were useful here as well; athletes and men and women who followed a regular high-intensity aerobic exercise program were noted to have favorable cholesterol levels (later refined to a beneficial lipid subfraction ratio), blood pressure, and body fat mass and distribution (5).

It was noted, however, that men and women who engaged in regular leisure-time physical activity were lighter weight, were less likely to be smokers, and had diets that were lower in saturated and total fats, compared with sedentary persons (6–8). Furthermore, the effect of change in exercise behavior was difficult to quantify with observational data. If individuals who exercise have lower risk for cardiovascular disease, will the same protection apply to sedentary individuals who adopt an active lifestyle? The need for controlled experimental studies was soon appreciated. A series of controlled clinical trials followed, measuring exercise effects on intermediate markers for coronary heart disease, including lipid profiles, hypertension, weight and fat distribution, insulin, clotting factors, and angiographically measured coronary atherosclerosis (9–12). A clinical trial of an exercise intervention on coronary heart disease itself (myocardial infarction and coronary death) has not been conducted.

These clinical trials of exercise effect on intermediate markers for cardiovascular disease were of great benefit in several ways: (a) they gave evidence that change in physical activity results in measurable change in cardiac risk factors (9–13); (b) they provided experience and data on how to best effect change in physical activity habits in various populations (14, 15); (c) they increased knowledge about specific exercise...
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explored.2 The effects of vitamin and mineral supplements on fruits and vegetable diet on rectal cell proliferation has been on risk of recurrent colorectal polyps (25). The effect of a high Prevention Trial is testing the effect of a low-fat, high fiber diet been assessed in several small clinical trials (23, 24). The Polyp endogenous estrogens in pre- and postmenopausal women have experiments (22). The effects of low-fat or high-fiber diets on areas led several investigators to measure the effect of dietary homogeneity nature of diet in many cultures and geographic factors relating to cancer provides an example. Difficulties with accurately categorizing population diet is unusual and the ho- other interventions

Cancer Prevention Trials Using Dietary and Other Interventions

There is considerable precedent for undertaking clinical trials using intermediate markers as end points. The area of dietary factors relating to cancer provides an example. Difficulties with accurately categorizing population diet is unusual and the homogeneity nature of diet in many cultures and geographic areas led several investigators to measure the effect of dietary manipulation on cancer biomarkers or risk factors with human experiments (22). The effects of low-fat or high-fiber diets on endogenous estrogens in pre- and postmenopausal women have been assessed in several small clinical trials (23, 24). The Polyp Prevention Trial is testing the effect of a low-fat, high fiber diet on risk of recurrent colorectal polyps (25). The effect of a high fruits and vegetable diet on rectal cell proliferation has been explored.2 The effects of vitamin and mineral supplements on cancer biomarkers and intermediates have been tested in several human experimental studies. An observed association between increased dietary and supplemental calcium intake on decreased risk of colorectal cancer was experimentally supported with the placebo controlled double-blind trials of calcium supplementation on colonic crypt cell proliferation (26, 27). Controlled clinical trials of medication effect on colon cancer intermediates and biomarkers have been done or are ongoing using aspirin (28), sulindac (29), calcium (30), and antioxidant vitamins (31). The effect of a low-fat dietary pattern on mammographic density patterns was measured in a clinical trial of women with high levels of breast density (32). These trials have led to trials testing dietary, vitamin, and mineral effects on cancer end points (33–38) and to trials testing dietary effects on cancer recurrence (39).

Utility of Exercise Clinical Trials with Intermediate or Biomarker End Points

Small randomized clinical trials of exercise effects on biomarkers for cancer can add to the body of knowledge of cancer prevention in several ways (Table 1). Clinical trials can focus on one or two specific interventions, so that the effect of a given level of exercise for a defined period of time can be assessed. The specific physiological aspects of physical activity can be assessed. Many of the difficulties associated with measuring exercise exposure in observational studies can be avoided, because direct observation of subjects exercising and physiologi- cal measures of fitness can be used. Properly designed and executed randomization can minimize bias. Homogeneity of exercise exposure can be avoided, because the trial design would include one or more groups with defined exercise prescriptions and, usually, a control condition. Measuring change in exercise exposure is difficult in observational settings because: (a) most people do not undergo significant changes in exercise habits; and (b) recall of changes in physical activity are problematic. Clinical trials can be designed such that change in physical activity or fitness is prescribed and maximized to allow assessment of effect. The randomized trial can focus on specific populations, such as high-risk individuals, who may be highly motivated to make changes in exercise behaviors. The clinical trial design allows assessment of physical activity effect on intermediate end points and biomarkers, which is difficult to do in some observational designs (such as case-control studies). Synergistic effects with other factors can be studied in clinical trials, especially with factorial designs with two or more interventions. Finally, multiple end points can be measured in a single trial.

Determining the Pertinent Aspects of Movement

There are several physiological effects of movement that might be associated with promoting health and preventing cancer. Aerobic exercise acutely causes a cascade of events including increased pulse and blood pressure and various neuroendocrine responses (40). Sustained regular aerobic exercise causes changes in cardiopulmonary capacity and reserve, resulting in increased cardiac stroke volume, decreased resting pulse, and decreased resting blood pressure (41). Sustained aerobic exercise, if not countered with an overcompensation of caloric intake, results in loss of fat mass, including the highly meta- bolic intraabdominal fat mass (12). Weight training (isometrics) results in gradual increase in muscle bulk, which results in increased metabolic rate and decreased fat mass (42). Exercise can be done at various intensities, duration, and frequency. Determining the needed components of these for impacting cancer incidence on a population level will first require having

Table 1

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<thead>
<tr>
<th>Strengths</th>
<th>Randomized clinical trials</th>
<th>Observational studies</th>
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<tr>
<td>Strengths</td>
<td>Minimal bias</td>
<td>Relative simplicity to administer</td>
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<td>Less measurement error</td>
<td>Inexpensive</td>
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<td>Can measure high intensity</td>
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<td>Can assess effect of change</td>
<td>Ease of recruitment</td>
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<td>Minimize confounding</td>
<td>Subgroup analyses possible</td>
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<td>Determine pertinent aspects of movement</td>
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<td>Avoid within-population homogeneity of exercise exposure</td>
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<td>Can focus on specific populations</td>
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<td>Can assess effect on intermediate endpoints and biomarkers</td>
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<td>Able to examine synergy with other factors</td>
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<td>Measure effects of exercise on multiple endpoints</td>
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<td>Weaknesses</td>
<td>Expensive</td>
<td>Homogeneity of exposures (usually low-high intensity exercisers)</td>
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<td>Multidisciplinary team required</td>
<td>Difficult to measure change</td>
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<td>Exercise facilities needed</td>
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<td>Recruitment challenges</td>
<td>Incomplete control of confounders</td>
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<td>Control group issues</td>
<td>Colinear covariates</td>
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<td>Adherence/retention issues</td>
<td>Show definitive effects on disease endpoints</td>
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<td>May require very large sample size and long-term follow-up</td>
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2. J. Potter, personal communication.
knowledge of mechanisms through which physical activity exerts its effect on cancer occurrence (43) so that appropriate public health messages can be crafted and delivered.

Minimizing Confounding
Observational studies can assess associations between risk factors and disease, and analyses can account for potential confounding or affect modifying factors, if the confounding factors are known. The statistical techniques of adjustment, however, lose robustness when the potential confounding variables are highly correlated with the risk factors being assessed. This becomes a particular problem with behavioral factors that cluster such as diet, alcohol use, cigarette smoking, and physical activity. Men and women who are physically active, compared with sedentary individuals, are more likely to have diets that are lower in fat and higher in fiber, fruits, and vegetables and are more likely to use vitamin supplements (7, 44, 45). Similarly, persons who are more physically active are more likely to be nonsmokers and to refrain from excessive alcohol use (45, 46).

Dietary intake is difficult to assess accurately; it has been shown that obese individuals, particularly women, systematically underestimate intake of total calories, fats, and carbohydrates (47). Obese individuals may overreport amount and frequency of physical activity (48, 49). The inaccurate measurement of physical activity, coupled with inaccurate dietary intake measurement, may lead to inadequate measures of association for these factors with cancer risk and to inadequate control for confounding effects of diet on physical activity effects and vice versa. In a clinical trial, the potential confounding can be minimized and much more readily quantified. When asked not to change their diets when starting on our exercise interventions, women have a small increase in caloric intake and men have no measurable diet changes.

Avoiding Physical Activity Measurement Errors
In an observational study, the investigator relies on the ability of subjects to report timing, frequency, and intensity of a variety of physical activities over time periods as long as a lifetime. It has been estimated that the lack of association between dietary fat intake and breast cancer risk seen in cohort studies (50) might be explained by systematic error in reporting dietary fat and total caloric intake in some individuals (47). Similarly biased reporting of physical activity by obese or overweight individuals has been suggested (48). There is little correlation between reported level of physical activities and objective measures of fitness in older populations (51).

In a clinical trial, the investigator develops and can directly monitor the exercise intervention, thus reducing the need for the subject to recall activities. A typical intervention study is done in an exercise physiology laboratory, where a physiologist works closely with study subjects individually or in small groups. Participants log in their activity time and intensity, and the logs are checked by the physiologist for accuracy. Nonetheless, if the intervention includes activities done outside of the controlled laboratory setting, there is a potential for measurement error due to inaccurate or biased recall. Other objective measures of exercise adherence can be used, however, including doubly-labeled water, activity monitoring devices to measure muscle movement objectively, and maximal (VO₂ max) or submaximal oxygen consumption, which can provide valid and reliable measures of current (i.e., past month) moderate to intense physical activity and of change in activity (52–54).

Overcoming Within-Population Homogeneity of Risk Factors
A clinical trial can correct for problems encountered with homogeneity of risk factor exposure in a population. Observational studies are limited to assessing the types and intensities of physical activity experienced by subjects in the population being studied. In some populations, very few individuals engage in certain types and intensities of physical activity. Several population surveys have shown that fewer than 25% of U.S. adults engage in regular, sustained exercise at moderate or greater intensity (3). Thus, comparisons of cases and noncases with respect to level of activity will be limited to small numbers at the higher levels of activity intensity or duration with resulting unstable estimates of association. In a clinical trial, the intervention can be low, moderate, or high intensity, depending on the purposes of the study and the characteristics and ability of the study participants. The investigator can observe effects of levels of exercise that are higher and more consistent than usually observed in the general population.

Measuring Effect of Change in Physical Activity or Fitness
It is difficult to assess the effect of change in physical activity or fitness within the setting of an observational study. Measuring change in exercise exposure is difficult in observational settings because most people do not undergo significant changes in exercise habits, except for a usual gradual decline in activity level with increasing age (6). The inaccuracies of recall are compounded when the investigator attempts to compare reported activities at different life periods if the subjects are reporting retrospectively. True change (or lack of change) in activity may be masked by subjects’ improvements in using the instrument. Change in activities can be assessed in cohort studies that update exposure measurements at regular intervals, although such updates add to costs. In a clinical trial, the investigator can enroll individuals in intervention programs that represent significant changes in activity over their usual levels. Several recent trials in middle-aged and older individuals have recruited sedentary individuals and randomized them to usual activity or to a structured or home-based moderate or high-intensity exercise intervention (13, 55, 56).

Focusing on Specific Populations
As with other focused intervention studies, clinical trials of exercise interventions can focus on high-risk individuals (such as individuals having precursor lesions or diagnosed cancer, individuals with established genetic predisposition, or those with particular risk factors or exposures). Focusing on high-risk groups can have several benefits, such as ease of recruitment (26), high motivation for subject adherence (26), and high incidence of intermediate and clinical end points (25, 30, 33), with smaller sample sizes needed as a result. In population studies, the prevalence and type of physical activities vary greatly by age (6). It may be difficult, therefore, to assess the effect of some types and intensity of exercise in certain age groups. For example, older individuals are very unlikely to engage in vigorous physical activity on their own (6, 46). Numerous trials have shown, however, that older men and women can adopt and maintain intensive vigorous exercise programs as part of trial or programmatic interventions, with meaningful significant changes in disease biomarkers (12, 56). In our own studies, older men have exercised safely at 85% of heart rate reserve for 6 months (12).
The prevalence of certain types of physical activities varies greatly among United States ethnic and racial groups (3, 6). Furthermore, reporting of activities varies by ethnicity and culture. For example, African-American men and women have been found to be less likely to report activities of daily living (such as walking to the store, housework, and others) as physical activity compared with Caucasian men and women (57). An exercise intervention study can provide important information on biological effects of a given type and intensity of exercise in diverse or specific ethnic and racial populations.

The prevalence, types, and biological effects of exercise differ between the sexes. In the United States at all ages, men report a higher level of recreational physical activities compared with women, whereas women report more time spent in low-level activities such as housework (58). Of those women who do engage in physical activities, the most common activities are walking, gardening, and aerobic dancing (6, 45). Older men who exercise most often report walking and gardening (6). The effects of physical activity may differ by gender. A recent factorial-design clinical trial showed that a Step II low-cholesterol diet alone did not achieve increases in HDL cholesterol levels in either men or women (13). In women, daily physical activity alone (but not with the Step II diet) was needed to raise HDL to a beneficial level, whereas in men, either exercise alone or with diet raised HDL.

Assessing Effects of Physical Activity on Intermediate End Points and Biomarkers

The progression to clinical cancer is widely recognized to be a long-term process for most cancers. Some cancers are preceded by early disease markers, for example, adenomatous polyps prior to colorectal cancer formation, CIN I and CIN II lesions prior to development of cervical cancer, and atypical benign breast disease before development of in situ or invasive breast cancer. “Biomarker” is used to describe a factor associated with disease risk that can be measured in fresh or stored biological specimens. Examples include serum sex hormones and breast cancer risk (59, 60), prostate-specific antigen and prostate cancer risk (61), and crypt cell proliferation and colorectal cancer risk (26). Because of the difficulties with quantifying physical activity and with ensuring adequate sample size to assess high levels of exercise, observational studies are ill equipped to precisely quantify the effect of various types and levels of exercise on cancer risk factors with precision. Clinical trials can measure the effect of a given exercise exposure and can help establish a target level of a cancer biomarker. This will be helpful in designing larger clinical efficacy trials, community intervention trials, and clinical and public health practice guidelines. Clinical trials can be designed to assess directly the exercise effects on recurrence or progression of intermediate disease markers, as for example, an exercise intervention trial in colorectal polyp patients.

Assessing Synergistic Associations

Several lifestyle and genetic factors might interact in the etiology of cancer. For example, the consistent association between increased body mass index and risk of postmenopausal breast cancer (62) could be due to specific macronutrients, caloric intake, lack of physical activity, genetic polymorphisms associated with propensity to weight gain, other related factors, or any combination of these. Measurement errors in these factors may not be independent. As stated above, individuals who are obese are more likely to underreport total caloric intake (47, 49). If those same individuals overreport levels of physical activity, then observational studies will give systematically biased results on the individual and combined effects of diet, exercise, and body mass. Factorial designs in clinical trials can control some of the correlations between diet and exercise. An example might be a four-arm trial design involving an exercise program, dietary change, and a nonintervention group (usual diet and exercise).

Challenges

There are several challenges to overcome in the conduct of exercise trials. Such studies tend to be costly because of the staff-intensive nature of data collection and intervention delivery. The successful design and implementation of an exercise trial requires expertise in medicine, clinical trials, behavioral science, exercise physiology, epidemiology, and statistics. The development of such a multidisciplinary team takes some time and effort prior to initiation of a research agenda. The implementation of an exercise intervention will often require access to specific equipment, depending on the intensity of the intervention. Depending on subjects' cardiovascular risk profiles, interventions that require subjects to exercise aerobically to >70% of maximal heart rate may require preintervention screening for cardiovascular risk factors and an exercise tolerance test to ensure cardiovascular safety of study subjects (63). Adherence to a high intervention requirement requires attention and innovation in clinical trials.

Exercise trials using intermediate end points require that such end points and cancer biomarkers are valid and reliable markers of cancer risk. The biomarkers/intermediate markers must be associated with the disease occurrence, be potentially modifiable by exercise, and lie in the causal pathway. The biomarker may be weakly linked to disease, or association with disease may be biased. If the biomarker pathway to disease is different from the pathway of the intervention to disease, change (or lack of change) in the biomarker may give false leads to a cancer prevention method (64). Trials with biomarker and intermediate marker end points that are short-term also do not address long-term adherence and safety issues, which may also give false leads to efficacy of an intervention in preventing cancer development.

Issues surrounding using a control group in exercise clinical trials must be addressed in the study design. There are many known benefits of exercise, including control of obesity and improvement in cardiopulmonary function, thus the “ethics” of using a control group might be questioned. However, the risk/benefit profiles of certain exercise interventions are not known in all population groups, especially older and minority individuals. Potential risks to exercising include injury (muscular-skeletal strains and breaks, accidents including accidental deaths), sudden cardiac death, and economic costs. Individuals volunteering for an exercise clinical trial may not be willing to be randomized to a control group. There are several ways to make randomized assignment more attractive to potential participants, including use of a “minimal” movement control (e.g., stretching, slow dance); a delayed aerobic intervention (i.e., starting the control group on an exercise program at a later time point or using a cross-over design); or comparing two different exercise interventions (e.g., aerobic versus resistance exercise). For end points that can be changed by minimal social interven-

3 The abbreviation used is: HDL, high-density lipoprotein.
tions (such as quality of life), care must be made in choice of control condition.

There are several challenges common to clinical trials that can affect the conduct or results of exercise clinical trials. The intensive nature of trials requires a high level of staff involvement, making them costly. Recruitment of eligible, motivated individuals who are willing to be randomized, adopt and maintain an intervention, and be followed closely is difficult. Maintaining intervention adherence, especially in long-term trials, requires intensive commitment of investigators, staff, and participants and requires diligence in screening of appropriate study participants. Determination of study end points requires close follow-up of all participants, minimizing dropouts, and assurance that staff and investigators who are adjudicating end points are unaware of participants’ study condition.

Proposed Research Agenda

The first step in building a research agenda is to identify cancers most likely to be associated with physical activity from observational data that can be targeted for intervention studies. A growing body of data are available from case-control and cohort studies of leisure-time and occupational physical activity and occurrences of cancers of the breast, colon, and prostate (43). Limited data are available for cancers of the endometrium, ovary, lung, and testes (43). Of these cancers, consistent observational data for a reduced risk associated with increased physical activity exists only for colon cancer.

The second step is to identify groups of individuals who might be at high risk for developing cancer and who would be likely to benefit from adopting an exercise program. Such groups might include persons who are sedentary, overweight or obese, or who have other characteristics of risk that might be affected by physical activity, such as persons with precancerous conditions (e.g., benign breast disease, colon polyps) or with biomarkers of cancer risk (e.g., genetic polymorphisms, serum markers, radiographic markers, or tissue markers of proliferation). Other high-risk individuals might include persons who have been successfully treated for primary cancer but who are at risk for developing future second primary cancers (e.g., breast and colon). Such individuals may be highly motivated to volunteer for an exercise intervention study and to adopt and maintain an exercise intervention (65).

To optimize efficiency, intervention studies should be designed to test exercise effect on more than one marker for cancer risk. This can be done in the initial design of the trial or through ancillary study uses of stored biological specimens. Thus, for example, a single exercise clinical trial can test the exercise effect on hormones and growth factors, tissue proliferation markers, fat mass and distribution, RNA activity for various metabolic parameters, psychosocial and quality of life measures, and subjective symptoms.

Pilot testing of various exercise interventions will give clues to types of exercise interventions needed. If a substantial amount of fat mass loss is needed to affect a cancer marker, for example, it may be necessary to design an exercise intervention that includes aerobic exercise that is high intensity, frequent, and long duration to observe an effect. Small-scale behavioral trials should be done to translate biological goals (for example, 10% reduction in body fat mass) into appropriate and functional behavioral goals (for example, 30-min walks six times per week).

We suggest that a series of small clinical trials be conducted to measure exercise change effects on biomarkers, to learn about exercise behavior change in individuals at high risk for cancer, and to serve as feasibility studies for larger randomized controlled trials. These larger trials can test exercise effect, for instance, on recurrence of a cancer marker, such as recurrence of colon polyps, similar to the ongoing trial of diet effect on polyp recurrence in the Polyp Prevention Trial (25). The benefits of doing these small trials include lower cost, smaller sample size, and shorter duration, compared with larger primary prevention trials (22). The shorter duration has benefits not only in terms of cost but also in terms of likelihood of achieving high compliance to intervention and more complete retention. We are presently conducting a randomized, controlled clinical trial to test the effect of a 1-year moderate level exercise program (versus stretch control) in postmenopausal women on potential biomarkers of breast cancer risk: serum and urine estrogens, serum androgens and binding globulins, insulin, growth factors, and immune function markers (66).

An important part of the research agenda will be to test various exercise interventions on similar populations and to test single interventions on diverse populations, such as age groups, genders, ethnic and racial minorities, and individuals of various physical and athletic ability. A particular exercise prescription may need to be modified in terms of how it is delivered. In other words, a single goal of amount of exercise done in an intervention might be reached by different means, and those means may differ between populations.

Finally, when large-scale, long-term trials of disease end points are planned, it will be more efficient to include multiple end points (e.g., cancer, cardiovascular disease, diabetes, cognition and memory, psychosocial and quality of life outcomes). For such trials, it will be best to have completed preliminary and feasibility studies, so that an intervention that is simple to implement and adopt, with a simple data collection process, can be used. That primary prevention trials can give important information on ways to decrease cancer risk (or identifying modalities that are of no benefit) has been shown by the BCPT Breast Cancer Prevention Trial (placebo-controlled trial of Tamoxifen; Ref. 67), the Carotene and Retinol Efficacy Trial and other trials testing retinoids to prevent lung cancer (36–38), and the trial of selenium to prevent cutaneous malignancies (35). The ongoing Women’s Health Initiative is testing the effect of a low-fat, high fruits, vegetables, and grain diet on the primary prevention of breast and colorectal cancers (33).

A large-scale, long-term exercise trial with cancer morbidity and mortality end points will provide important answers about overall benefit versus risk to individuals. For example, would an increased risk of sudden death with adoption of a vigorous activity program in a sedentary middle-aged man outweigh a decreased risk of colon cancer mortality? Would the current Centers for Disease Control-NIH recommended level of exercise (30 min/day of moderate or greater level exercise for most days of the week; Ref. 3) be sufficient to reduce cancer incidence? Much groundwork is necessary, however, before conducting a full-scale primary cancer prevention trial or a large-scale community intervention to increase physical activity at the population level to reduce cancer morbidity and mortality.

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