Exercise and Biomarkers for Cancer Prevention Studies\textsuperscript{1,2}
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Abstract
The International Agency for Research on Cancer estimates that 25\% of cancer cases worldwide are caused by overweight or obesity and a sedentary lifestyle. These lifestyle patterns may increase cancer risk by several mechanisms including increased estrogens and testosterone, hyperinsulinemia and insulin resistance, increased inflammation, and depressed immune function. Several randomized clinical trials have shown that physical activity and diet interventions can change biomarkers of cancer risk. In a controlled physical activity trial, we found decreases in serum estrogen, testosterone, and insulin in overweight, sedentary postmenopausal women with a 1-y exercise program consisting of moderate-intensity aerobic exercise, 45 min/d, 5 d/wk. In another controlled trial in middle-aged to older persons, we found that a 1-y exercise intervention of 60 min/d, 6 d/wk, reduced colon crypt cell proliferation in men who adhered closely to the program. Only 1 trial, the Women’s Health Initiative Dietary Modification Trial, has published results of a dietary intervention on breast cancer incidence and reported a statistically nonsignificant 9\% reduction in invasive breast cancer incidence in postmenopausal women following a low-fat dietary pattern for 8–12 y. Other trials under way are testing effects of weight loss, physical activity, and dietary patterns on other cancer biomarkers. The NCI-funded Transdisciplinary Research on Energetics and Cancer centers are exploring novel research into mechanisms linking energy balance with cancer risk and prevention. The worldwide trends toward increasing overweight and obesity and decreasing physical activity may lead to an increased incidence of several cancers unless other means of risk reduction counteract these effects. Thus, adoption of lifestyle changes by individuals and populations may have a large impact on the future incidence of cancer. J. Nutr. 137: 161S–169S, 2007.

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American adults are overweight, 22.1\% are obese, and 24.4\% report little or no physical activity (2). These lifestyle patterns may increase cancer risk by several mechanisms including increased estrogens and testosterone leading to increased risk of breast and endometrial cancers; hyperinsulinemia and insulin resistance leading to increased risks of colon, breast, and pancreatic cancers; and increased inflammation and depressed immune function leading to several cancers (3).

Determining the mechanisms by which these lifestyle patterns influence cancer risk will not only illustrate biological plausibility for the observed association but also provide evidence of causality to inform the optimal exercise prescription for cancer risk reduction. However, how overweight and obesity, sedentary lifestyle, and cancer are associated is complicated. Diet and physical activity are complex behaviors to measure, accurate measurement of body composition in large population studies is often unfeasible, and the etiology of cancer is multifactorial (4–6). The long latency of cancer development also adds to the difficulty of studying these associations because the time between an important exposure and a disease diagnosis can be many years.

A current avenue of research has focused on generating a better understanding of how lifestyle patterns influence cancer risk by using biomarkers as surrogate outcomes rather than the disease itself as the outcome. Biomarkers are biological factors...
thought to be involved in the causal pathway between exposure and cancer development. Rundle (6) outlined the case for cancer biomarker studies involving physical activity that could be expanded to other lifestyle behaviors. The use of biomarkers proposed to be associated with lifestyle and cancer risk is the focus of several ongoing cancer prevention-related studies.

**Proposed biomarkers for the associations among physical activity, overweight or obesity, and cancer**

The proposed biomarkers for the observed associations among physical activity, overweight or obesity, and cancer initially focused on sex steroid hormones (i.e., estrogens and androgens). However, additional biomarkers have recently been proposed, such as hyperinsulinemia and insulin resistance, other metabolic hormones (i.e., leptin, adipokines), increased inflammation (i.e., prostaglandin, C-reactive protein), depressed immune function (i.e., natural killer cells, leukocytes, T helper cells), and oxidative stress (i.e., reactive oxygen species). Physical activity and energy balance have the potential to affect all of these biomarkers, and their contribution may overlap or be synergistic.

**Sex steroid hormones.** Women with elevated levels of estrogens and androgens have increased risk of developing breast cancer (7), and those with elevated estrogen concentrations (unopposed by progesterone) are at an increased risk for endometrial cancer (8). In men, antiandrogen therapy improves prostate cancer survival (9) and reduces overall incidence of the disease when tested as a preventive agent (10).

The effects of physical activity on age at menarche, menstrual cycle function, and level of endogenous sex steroid hormone levels in girls and young women are often cited as potential mechanisms for reduced breast cancer risk (11). Exercise may cause minor shifts in the hormonal milieu of premenopausal women (12,13), but exercise of significant frequency and intensity is needed to induce menstrual dysfunction sufficient to result in significantly decreased exposure to sex-steroid hormones (14). Recent research suggests that exercise and other stressors have no disruptive effect on reproductive function beyond that of their energy cost on energy availability (15–17).

In premenopausal women, observational research points to the presence of delayed age at menarche (18), a continuum of menstrual dysfunction (amenorrhea, anovular cycles, luteal phase deficiency), longer menstrual cycles, and lower progesterone and estradiol levels in athletes compared with control subjects (19–25). However, the individual effects of weight control and physical activity are difficult to discern (26). Prospective intervention studies have been few, have used small sample sizes, and results were mixed. Two of these studies found that a moderate-intensity running intervention did not disrupt reproductive function (27,28). Other studies reported minor changes in measures of reproductive function (12,13) or induced menstrual dysfunction with significant exercise frequency and intensity (14).

In postmenopausal women, increased physical activity is associated with decreased serum concentrations of estradiol, estrone, and androgens after adjustment for BMI in some (29,30) but not other studies (31). The beneficial effect of physical activity is closely linked to body composition because the primary source of estrogen in postmenopausal women is from aromatization of androgen precursors in peripheral tissue, mainly adipose tissue (32). In a recent study using a random subsample of women in the Women’s Health Initiative Dietary Modification Trial (33), women with a high BMI and low self-reported physical activity had higher levels of estrone, estradiol, and free estradiol and lower levels of sex hormone binding globulin (SHBG) than women with a similar BMI who were active or with low BMI in either activity category (Fig. 1) (30).

Few cross-sectional studies have examined the association of physical activity levels with sex hormones in men, although chronically lower testosterone concentrations are reported in athletes (34–37), but such changes may require a threshold amount or intensity of physical activity (37). The association of obesity with lowered testosterone in men further complicates the issue of the effect of physical activity, if any, on testosterone (32). The effects of a moderate-intensity aerobic exercise intervention on sex steroid hormones in previously sedentary middle-aged or older men is not known, and studies are underway to examine this issue.

For premenopausal women, being overweight or obese lowers the risk of breast cancer, possibly because of a higher frequency of anovular menstrual cycles (38,39). This may result in less exposure to estrogens, which may subsequently reduce breast cancer risk. However, overweight or obesity also results in lower progesterone levels, which may play a key role in the increased endometrial cancer risk for overweight or obese premenopausal women because of unopposed estrogens (32). For postmenopausal women who are overweight or obese, an observed higher risk of postmenopausal breast cancer is attributed primarily to greater amounts of adipose tissue, where estrogen is produced via aromatization (40). The production of estrogen is no longer under feedback regulation as in premenopausal women. Postmenopausal women who are obese have up to 2-fold higher serum concentrations of estradiol than lean postmenopausal women (32). Increasing BMI is also associated with a drop in SHBG, resulting in a notable increase in levels of free estradiol in women (32). Among men, a higher BMI is associated with lower SHBG and total testosterone, but there is little difference in free testosterone by BMI (32).

Alterations in metabolism of estrogens may be linked to cancer development, particularly breast cancer. Estrogens are metabolized primarily through 2 mutually exclusive pathways to produce 16α-hydroxyestrone (16α-OHE1), which acts like estrogen, and 2-hydroxyestrone (2-OHE1), which has little or no estrogenic effect. Prospective cohort studies have reported a statistically nonsignificant reduction in breast cancer risk among women with higher ratios of 2-OHE1 to 16α-OHE1, especially premenopausal women (41–43). Physical activity is suggested to favorably alter estrogen metabolism (i.e., toward higher levels of 2-OHE1). Observational studies found higher ratios of 2-OHE1 to 16α-OHE1 in athletes compared with control subjects (44); with high-intensity training, resulting in the development of menstrual dysfunction (44–46); with self-reported daily physical activity (47,48); and with higher aerobic fitness (VO_{2max}) (49).

![Figure 1](https://academic.oup.com/jn/article-abstract/137/1/161S/4664325) (30). Low BMI < 29.0; high BMI ≥ 29.0; low physical activity ≤ 6.5 MET-hours per week; high physical activity > 6.5 MET-hours per week.
Metabolic hormones. Insulin resistance (defects in insulin action; a reduction in the rate of glucose disposal elicited by a given insulin concentration) is characterized by hyperinsulinemia (elevated blood levels of insulin), hyperglycemia (elevated fasting blood levels of glucose), hypertension, and dyslipidemia and is estimated to affect 22% of U.S. adults (52). Insulin resistance has been linked to increased risk of breast, colon, pancreas, endometrium, and stomach cancers (53,54). Higher cancer incidence (55,56) and mortality (57) were also noted in those with type 2 diabetes mellitus or impaired glucose tolerance. Insulin can enhance tumor development by stimulating cell proliferation or inhibiting apoptosis, regulating the synthesis and biological availability of sex steroid hormones, and inhibiting hepatic synthesis of SHBG (53).

Acute bouts of physical activity improve insulin sensitivity and increase glucose uptake by skeletal muscle for up to 12 h even in those with type 2 diabetes mellitus (58). These improvements may differ in physically trained vs. untrained individuals (59) and with age (60). Chronic exercise training results in prolonged improvements in insulin sensitivity (61) even in individuals with impaired glucose tolerance (62). However, higher-intensity exercise may prove to be more effective than exercise of longer duration (63). Although body composition has been strongly associated with insulin sensitivity, exercise-induced changes in insulin sensitivity can occur independent of the changes in body weight or body composition associated with physical activity (64–66). An additive effect of resistance training to improve insulin sensitivity and glycemic control has also been proposed because skeletal muscle is the primary site of insulin resistance (54). Resistance training has been shown to be beneficial alone or in combination with aerobic physical activity (67–69).

Overweight and obesity are strongly linked to insulin resistance and hyperinsulinemia. Central adipose tissue is more metabolically active than peripheral tissue and is independently correlated with glucose disposal and insulin sensitivity (70). The effect of equivalent diet- or exercise-induced weight loss and exercise without weight loss was compared with control subjects for both men (71) and premenopausal women (72). All treatment groups showed a decrease in total, abdominal, and subcutaneous abdominal fat. Improvements in insulin resistance for the exercise-induced weight loss group alone were observed in women (72); similar improvements for the diet-induced or exercise-induced weight loss groups were seen in men (71).

The insulin-like growth factor (IGF) family is also implicated in cancer risk. IGF-1 bioavailability is regulated by at least 6 binding proteins (IGFBPs). IGF-1 enhances division of normal cells and inhibits cell death, actions also related to tumor proliferation, and IGFBP-3 is responsible for binding the majority of IGF-1 (1,73). High circulating levels of IGF-1 and low levels of IGFBP-3 were associated with increased risk of some cancers, such as breast, colon, and prostate, but overall the evidence is conflicting (73,74). Recent large nested case-control studies failed to see a significant association among IGF-1, IGFBP-3, and breast cancer (75–77).

Physical activity is suggested to affect IGF-1 and IGFBP-3 levels. However, a systematic review found that the majority of studies showed no difference in IGF-1 with increasing activity; the remaining studies showed higher levels of IGF-1 with increasing activity except for a few that showed lower levels with increasing activity (78). For IGFBP-3, the studies were split between no difference and increasing levels with increasing physical activity, with a small number of studies showing lower levels of IGFBP-3 with increasing activity (78). Overall, the effect of exercise on IGF-1 and IGFBP-3 concentrations and their relation to cancer risk are unclear and require further investigation.

Inflammation. Systemic inflammation is linked to numerous chronic health conditions, including cancer (79–81). Proinflammatory factors, such as C-reactive protein, serum amyloid A, interleukin-6, and tumor necrosis factor-α and antiinflammatory factors, such as adiponectin, are now being investigated as makers of disease risk and prognosis (82–84). Physical activity may reduce systemic inflammation alone or in combination with body weight or composition (85).

Although cross-sectional studies support an association between chronic physical activity and lower levels of C-reactive protein, serum amyloid A, interleukin-6, and tumor necrosis factor-α in both men and women (86–98), intervention studies of exercise alone or exercise and diet combined showed an effect on C-reactive protein in some (99–101) but not all (85,102,103) studies. The results for interleukin-6 and serum amyloid A are similarly conflicting (84). Body composition appears to have a significant influence on markers of inflammation, with association from cross-sectional studies dependent on lower BMI or body fat found in more highly active individuals and effects of physical activity intervention studies related to significant weight loss (98,99).

Cross-sectional studies reported lower levels of adiponectin, an antiinflammatory factor, associated with higher BMI (96,104,105), higher percentage body fat (106,107), larger waist circumference (108), and more visceral fat (107,109). Increases in adiponectin were seen with physical activity interventions in the presence of significant weight loss (99). Shorter prospective physical activity and weight loss studies have failed to alter adiponectin levels despite modest changes in body weight and body composition (85,105).

Immune function. The immune system is suggested to play a role in reducing cancer risk by recognition and elimination of abnormal cells or through immune system components—acquired, innate, or both (110,111). An impaired immune system has been associated with increased cancer risk, such as AIDS patients who show increased risk of not only AIDS-related malignancies (e.g., Kaposi’s sarcoma) but also other cancers, such as lung and colon (112,113). Lifestyle factors also enhance both the functionality and number of innate immune cell components, such as cytokotic T lymphocytes, natural killer cells, lymphokine-activated killer cells, and macrophages (114).

Bouts of exercise result in acute increases in a number of components of immune function (e.g., neutrophils, monocytes, eosinophils, lymphocytes) followed by a dip below preexercise levels lasting up to 1–3 h (115). For chronic physical activity, the proposed relation between intensity of physical activity and immune function is an inverted J-shaped dose-response relationship. Moderate physical activity results in enhanced immune function, whereas exhaustive exercise, overtraining, or high-intensity exercise may lead to immunosuppression, such as increased susceptibility to upper respiratory tract infections (116–118). However, the current evidence on the effects of moderate-intensity physical activity from randomized controlled trials is inconclusive; differences in components of the innate immune system were noted in some cross-sectional studies comparing exercisers with nonexercisers (84).
Evidence from clinical research (i.e., higher risk of infection after surgical procedures) and animal models suggest that overweight and obesity are associated with impaired immune function. However, in human research, overweight and obesity were associated with impaired immune function in some (119–121) but not all studies (122).

**Effect of lifestyle interventions on biomarkers of cancer risk**

**Dietary interventions.** Numerous dietary factors have been examined for a role in cancer prevention. Two recent meta-analyses report the strongest evidence for the consumption of fruits and vegetables and whole grains (123,124). Dietary fat has also been identified as a possible risk factor, but the largest randomized controlled dietary cancer prevention intervention study to date found only a modest statistically nonsignificant 9% decrease in invasive breast cancer (125) and no reduction in invasive colon cancer (126) in over 48,800 postmenopausal women following a low-fat diet for 8–12 y. At baseline both groups consumed a diet with ~38% of energy from fat and 3.6 serving per day of fruits and vegetables. The difference between the intervention and control group for percentage of energy from fat was −10.7% in y 1 and −8.1% at y 6, and for servings of fruits and vegetables was +1.2 servings at y 1 and +1.1 servings at y 6. The authors note that the majority of participants did not achieve the dietary target of 20% of energy from fat, and a longer intervention may be needed to determine the effects of this as a habitual dietary pattern. After y 1, the intervention group lost an average of 2.4 kg compared with a 0.4-kg weight loss in the control group, and the intervention group maintained a lower body weight through an average of 7.5 y of follow-up (mean difference in change between groups at 6 y, −0.8 kg (33)). This amount of weight loss was shown in a recent observational study to lower breast cancer risk (127).

**Physical activity interventions.** There is strong epidemiologic evidence for reduced risk of some cancers with increasing physical activity (128,129). The strongest evidence exists for colorectal and postmenopausal breast cancer, with possible associations for prostate, endometrial, and lung cancer (128). However, an understanding of the amount, type, and intensity of activity needed has not been fully elucidated. In addition, these associations are based on cohort and case-control studies of self-reported physical activity. The impact of physical activity on reducing cancer risk in previously sedentary individuals is not known (26). To date a randomized controlled trial of physical activity with primary cancer prevention has not been undertaken, but 2 published randomized clinical trials examined the effect of physical activity on biomarkers of cancer risk.

A controlled physical activity trial in 173 overweight, sedentary postmenopausal women (BMI ≥ 24 and percentage body fat > 33%) consisted of a moderate-intensity aerobic exercise, 45 min/d, 5 d/wk, for 12 mo. The exercise group had a reduction in body weight, total body fat, intraabdominal fat, and subcutaneous fat compared with the control group, and a significant dose response for greater body fat loss was observed with increasing duration of exercise (130). A significant decrease in estradiol, estrone, and free estradiol was seen from baseline to 3 mo with an attenuation of the effect at 12 mo (131). However, in women who lost body fat, the exercise intervention resulted in a statistically significant decrease in these estrogens at 12 mo (Fig. 2) and a statistically significant decrease in testosterone and free testosterone (Fig. 3) (132). No changes in IGF-1 and IGFBP-3 (133) were seen, but the exercise group had a 4% decrease in insulin concentrations from baseline to 12 mo compared with a 12% increase in the control group, along with an improvement in insulin resistance, measured using homeostasis model assessment scores, compared with a worsening in controls (134). Consistent with the finding of other biomarkers, a greater decrease in insulin levels was seen in those who lost body fat (134). Overall, the protective changes in biomarkers were particularly striking in participants who lost body fat.

In another controlled trial in middle-aged to older men (n = 102) and women (n = 100), the effects of a 1-y exercise intervention of 60 min/d, 6 d/wk, on biomarkers of colon cancer risk was examined (135). The intervention resulted in significant decreases in colon crypt cell proliferation indices (Ki67" nuclei) in men who adhered closely to the program (exercised a mean ≥250 min/wk or whose VO2max increased by ≥5%) but no change in women. Exercisers also had a reduction in body weight, BMI, waist circumference, and total fat mass, with greater decreases in these anthropometric measures seen with greater increases in pedometer-measured steps per day, minutes of exercise per day, and aerobic fitness (136). Analyses of other biomarkers of interest—colon crypt cell apoptosis patterns, prostaglandin levels, serum sex-steroid hormones, metabolic hormones, and markers of inflammation—are under way.

**Weight loss interventions.** Just as the impact of obesity on a variety of health conditions (e.g., type 2 diabetes, cardiovascular disease, and stroke) has been extensively reported, an association with cancer has received increasing attention. In 2002 the IARC Working Group reported sufficient evidence for avoidance of weight gain for cancers of the colon, (postmenopausal) breast, endometrium, kidney, and esophagus (1). Cancer of the pancreas,

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**Figure 2** Percentage change in estradiol by percentage change in body fat in a randomized controlled trial of 1-y moderate-intensity exercise in postmenopausal women (131). Statistically significant difference in estradiol level in exercisers who lost 0.5–2% body fat ($P = 0.02$) and for those who lost >2% body fat ($P = 0.008$).

**Figure 3** Percentage change in testosterone by percentage change in body fat in a randomized controlled trial of 1-y moderate-intensity exercise in postmenopausal women (132). Statistically significant difference in testosterone level in exercisers who lost 0.5–2% body fat ($P < 0.05$) and for those who lost >2% body fat ($P < 0.05$) compared with control subjects at 12 mo.
gallbladder, ovary, cervix, liver, and prostate and certain hematopoietic cancers have also been linked to body weight and body composition (137).

A higher risk of colorectal cancer for men and women is associated with being overweight (138). The association appears to be stronger for colon rather than rectal cancer, in men compared with women, in larger adenomas compared with smaller ones, and for obesity ($BMI \geq 30$) compared with overweight ($BMI \geq 25$) (138). Although higher BMI has consistently been shown to increase the risk of premenopausal breast cancer, being overweight or obese increases the risk of postmenopausal breast cancer (relative risk of 1.26, 95% confidence interval 1.09, 1.46) (139). Obesity-related risk appears to be higher among women who have never used hormone replacement therapy (40). Higher waist-to-hip ratio, percentage body fat, and adult weight gain also were strongly associated with increased postmenopausal breast cancer risk (140). A linear increase in endometrial cancer risk with increasing body weight and BMI has consistently been reported, with a 2- to 3-fold increased risk for overweight women ($BMI > 25$) (1). However, some studies show an increase in risk only for those in the highest BMI categories (i.e., BMI $\geq 30$), especially among premenopausal women (137,141). Adult weight gain was also associated with endometrial cancer risk, whereas an association with waist-hip ratio has generally not contributed additional risk beyond that of BMI (1). A linear increase in kidney (renal cell) cancer with increasing weight and BMI was reported in both men and women, with a 1.5- to 2.5-fold higher risk in those who are overweight or obese (1,137). Associations of adult weight gain and waist-hip ratio were also observed (1). Higher BMI is associated with a 2-to 3-fold increased risk of esophageal adenocarcinoma, but the association is stronger for men than women (137). Adult weight gain is also implicated in risk of esophageal cancer, suggesting the duration of obesity may be an important etiologic factor (142). An increase in incidence of gastric reflux, a proposed precursor of cancer, seen with obesity is the prime suggested mechanism for this association (142).

Currently, there are no published weight loss intervention trials specifically examining cancer prevention biomarkers, although weight loss trials have shown significant decreases in insulin and insulin resistance (54).

**Upcoming results from ongoing trials.** Four controlled physical activity intervention trials are under way. The ALPHA Trial (Alberta Physical Activity and Breast Cancer Prevention Trial) is a randomized controlled trial examining the effects of a 12-mo aerobic exercise intervention compared with usual sedentary lifestyle on proposed biomarkers of breast cancer risk in 330 sedentary, postmenopausal women (143). The NEW Trial (Nutrition and Exercise for Women) is a 4-arm randomized controlled trial examining the effects of diet- and exercise-induced weight loss on biomarkers of breast cancer risk in 503 sedentary, postmenopausal women randomly assigned to dietary weight loss alone, exercise alone, dietary weight loss plus exercise, or usual lifestyle control (144). The WISER Trial (Women In Steady Exercise Research) is a 4-mo exercise intervention trial examining the effect on estrogen metabolites and other breast biomarkers in 320 premenopausal women (145). The SHAPE Trial (Sex Hormones And Physical Exercise) is a 1-y exercise trial examining the effect on estrogen and other biomarkers in 180 postmenopausal women. In addition, the NCI-funded Transdisciplinary Research on Energetics and Cancer (TREC) Centers are exploring novel research into mechanisms linking energy balance with cancer risk and prevention (146).

**Future directions**

Future exercise interventions should expand on current knowledge by testing different types of exercise in different populations and in persons at different risk of developing cancer (147). Further research should also be undertaken to confirm that proposed biomarkers do indeed lie on the causal pathway between physical activity and cancer development and examine the role of genetic polymorphisms related to biomarkers of interest.

In summary, the completion of 2 randomized exercise trials demonstrated that lifestyle intervention trials are feasible and produce less-biased effects of the association of exercise with breast and colon cancer biomarkers. Moderate-intensity physical activity has biological effects that may reduce breast and colon cancer risk. However, the additional positive effect of weight loss in sedentary, overweight postmenopausal women on biomarkers of breast cancer risk suggests the need for future diet- and exercise-induced weight loss trials.

**Literature Cited**


Detailed study description. Available at: http://www.cancerboard.ab.ca/alphatrial/detailed.html.


