Review

Physical Activity and Cancer Prevention: From Observational to Intervention Research[1]

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Abstract

The purpose of this review is to articulate how progress in epidemiological research on physical activity and cancer prevention can be made. This report briefly reviews the accumulated evidence for an etiological role of physical activity in the prevention of cancer of the colon, breast, prostate, testes, lung, endometrium, and ovary and summarizes the evidence for a causal association for each of these sites. The evidence for a causal association between physical activity and colon and breast cancers is found to be "convincing," for prostate cancer to be "probable," for lung and endometrial cancers to be "possible," and for testicular and ovarian cancers to be currently "insufficient" to make any definitive conclusions. The emerging literature on physical activity and cancer prevention intervention studies is presented, and an overview of the literature on physical activity intervention is also provided. Given the level of evidence that is currently available for the associations between physical activity and cancer, it is argued that for additional progress to be made in this field, there need to be intervention studies on physical activity and cancers of the colon and breast. For the remaining cancer sites, better designed observational epidemiological studies are needed that address the identified methodological limitations found in previous studies. These limitations include crude and incomplete physical activity assessment, lack of adequate control for confounding and effect modification, as well as a lack of consideration of the underlying biological mechanisms that are operative. This review concludes with detailed recommendations for future research in this field.

Introduction

Interest in physical activity as a means for the primary prevention of cancer is increasing as the evidence for a protective effect is accumulating. Recent reviews of physical activity and colon (1), breast (2–4), prostate (5) and all cancers (6–12) have provided detailed assessments of the levels of epidemiological evidence for these putative associations. As the evidence for a protective role of physical activity becomes more definitive, gaps in current knowledge and priorities for further research in this field can be defined more clearly. Specifically, the evidence to support intervention studies should be assessed because these types of studies would provide the next level of scientific evidence that is needed when developing public health recommendations on physical activity for cancer prevention.

The purposes of this review are to: (*a*) provide an update on the epidemiological evidence for an etiological role of physical activity in cancer causation; (*b*) identify and review the literature on physical activity and cancer prevention intervention programs; (*c*) review the literature on physical activity intervention to determine what methods are effective and could be adopted in cancer prevention programs; and (*d*) propose recommendations for future observational and intervention research in physical activity and cancer prevention. This review will document how observational epidemiological evidence has accumulated in this field and will present a rationale for further progression.

Methods

The scientific literature on the association between physical activity and cancer was reviewed. A search was conducted on Medline and PubMed for all publications on physical activity/ exercise and colon, breast, prostate, testicular, lung, ovarian, and endometrial cancers as well as cancer overall. No restrictions on language or year of publication were made. The literature search included all publications up to October 2000. For the purposes of this review, only colon and colorectal cancers and not colonic adenomas were included. To be included in this review, the studies needed to have focused on some type of physical activity assessment in relation to risk at the cancer sites listed above.

A few studies were excluded because they were preliminary publications that were later updated in a subsequent manuscript. Specifically, the cohort study on mortality and exercise by Garfinkel and Stellman (13) was excluded because it was later expanded by Thun *et al.* (14). The most recent publications of the Harvard Health Alumni study was included (15–20). The data from the cohort of longshoremen in the 1987 report by Paffenbarger *et al.* (16) and the testicular cancer data in the 1992 report from the Paffenbarger *et al.* (19) publication were nonetheless included because these data were not in the most recent 1994 publication by Lee and Paffenbarger (20). Likewise, Steenland *et al.* (21) updated the cohort follow-up initially reported by Albanes *et al.* (22) of the National Health and Nutrition Examination I Survey cohort. The report by Vetter *et al.* (23) on colon cancer was updated by Dosemeci *et al.* (24), and the report by Vihko *et al.* (25) on breast cancer was updated by Pukkala *et al.* (26). The papers by Vlanjinac *et al.* (27) on colon cancer, Kocić *et al.* (28) on breast cancer, and Ilić *et al.*

Table 1 Summary of epidemiological evidence on the association between physical activity and cancer by criteria for causality

Cancer site	Consistency of evidence for a risk reduction with increased physical activity levels			Strength of risk association		Dose-response	Temporality (time period in life associated with risk reduction)	Biological plausibility	Overall level of scientific evidence
	Cohort studies	Case-control studies	Total studies	Range of risk estimates	Average risk reduction	No. of studies			
Colon	15 of 20	23 of 26	39 of 46	0.3 to 1.0	40–50%	23 of 29	Activity throughout life?	Yes-several hypotheses	Convincing
Breast	8 of 14	16 of 22	24 of 36	0.3 to 1.6	30–40%	15 of 23	Early life? Adult life?	Yes-several hypotheses	Convincing
Prostate	10 of 16	5 of 10	15 of 26	0.5 to 2.2	10–30%	9 of 19	Early life?	Yes-some hypotheses	Probable
Lung	6 of 6	0 of 2	6 of 8	0.4 to 1.3	30–40%	4 of 6	Unknown	Unclear	Possible
Endometrial	3 of 4	5 of 7	8 of 11	0.1 to 1.0	30–40%	4 of 7	Unknown	Yes-a few hypotheses	Possible
Testicular	0 of 2	3 of 6	3 of 8	0.5 to 3.3	20%	3 of 5	Unknown	Unclear	Insufficient
Ovarian	1 of 3	1 of 2	2 of 5	0.3 to 2.1	0%	2 of 3	Unknown	Yes-a few hypotheses	Insufficient

(29) on prostate cancer were excluded because of insufficient detail in the study methods used to classify physical activity and to analyze the association with cancer. Finally, only studies that had been published were included, although it was recognized that numerous studies are in press and on-going in the field of physical activity and cancer risk.

Information on the study designs and population samples, numbers of study subjects, methods of measuring physical activity and its association with the cancer outcomes, and the main study results were extracted from these reports and tabulated. Given the high level of heterogeneity in the study designs and methods used for measuring physical activity and for analyzing the results, no attempt at estimating overall quantitative summary measures of effect was made. Rather, a summary table that highlights all of the evidence on the association between physical activity and cancer prevention was prepared. This table includes the strength, consistency, dose-response, temporality, and biological plausibility of these associations as well as an overall assessment of the level of scientific evidence for the association between physical activity and each of the cancer sites (Table 1).

The definitions of the levels of scientific evidence that exist to determine whether there is a causal association between physical activity and cancer were adapted from The World Cancer Research Fund/American Institute for Cancer Research publication Food, Nutrition and the Prevention of Cancer: a Global Perspective (30). In that report, the terms were defined as follows:

(*a*) "Convincing": means that the epidemiological evidence is conclusive. Exists when there are consistent associations from at least 20 studies that include prospective designs conducted in different populations and controlled for possible confounding factors; when the exposure data precede the cancer occurrence; when there is evidence of a dose-response relation; and when the association is biologically plausible.

(*b*) "Probable": means the evidence is strong enough to conclude that a causal relation is likely. Exists when the data from epidemiological studies are less consistent, with a number of the studies not supporting the association or else the number or type of studies is not extensive enough to make a definitive judgement; and when there are usually mechanistic and laboratory evidence that are usually or strongly supportive.

(*c*) "Possible": means that a causal relation may exist. Exists when the epidemiological studies are generally supportive but are limited in quantity, quality, or consistency. There may or may not be supportive mechanistic or laboratory data.

(*d*) "Insufficient": means that there is suggestive evidence but that it is too scanty or imbalanced to make a more definitive judgement. This level of evidence exists when there are only a few studies that are generally consistent but which only suggest a possible relation. More well-designed research is needed at this level of scientific evidence.

A review was also conducted of the literature on physical activity and cancer prevention intervention studies. A literature search was performed to identify any published or on-going cancer prevention trials in any aspect of physical activity and its association with cancer prevention. Finally, a literature search on physical activity intervention studies was undertaken. On the basis of these literature reviews, recommendations for future research were formulated.

Epidemiological Studies of Physical Activity and Cancer
Overview of the State of the Evidence
Colon, Colorectal, and Rectal Cancer. The most definitive epidemiological evidence for an association between physical activity and cancer exists for colon or colorectal cancer (1). Some of the studies have examined only colon cancer, and others have included colorectal cancers. For the purpose of this review, colon and colorectal cancer studies are combined because the evidence is essentially the same for these two cancer sites. Of the 46 colon and colorectal cancer and physical activity studies (14, 16, 20, 21, 24, 31–71) conducted worldwide to date, 38 (14, 24, 31–39, 41–44, 46–50, 52, 53, 55–61, 63–71) have demonstrated a large reduction in risk of cancer among the most physically active male and female participants in these studies (Fig. 1). Statistical significance was achieved in 32 (31–39, 41–44, 46–50, 52, 53, 55, 58–61, 63, 65–71) of the 38 studies that found risk decreases. The risk reduction has been at least 20–30%, and up to 70% reductions were found in some of the studies. The average reduction was 40–50%. Although the methods for assessing physical activity have varied among studies and have often been quite crude, a consistent reduction in risk was observed across different study designs and populations and for both occupational and recreational activity. Furthermore, a consistent dose-response relation was found in 23 (24, 32, 38, 42–44, 48–51, 53, 56–61, 66–70) of the 29 studies (20, 24, 32, 37, 38, 40, 42–44, 45, 48–51, 53, 56–61, 64–70) that examined the trend in risk. Overall, the association is strong and appears not to be confounded by diet, body mass index, and other risk factors that have been examined and controlled for in these analyses. A full evaluation of
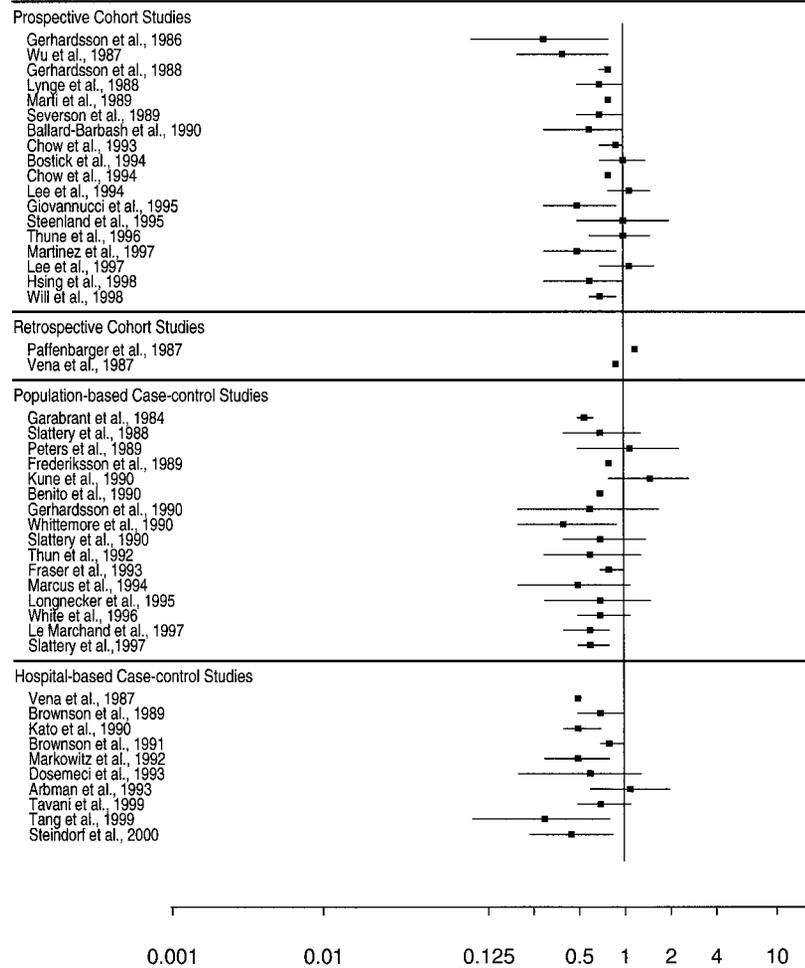
Fig. 1. Main results for epidemiological studies of physical activity and colon and colorectal cancer risk, by type of study design.

confounding has not, however, been undertaken in the majority of studies. The relation between physical activity and colon cancer is stronger for the left colon. Thus, it appears that physical activity is not merely a marker of healthier lifestyle, but that it has an independent protective effect (1). General agreement exists across these studies on a lack of association between physical activity and risk of rectal cancer, as assessed in both cohort and case-control studies. In summary, the evidence for a preventive role of physical activity in the etiology of colon cancer is convincing, and for rectal cancer, there is convincing evidence that physical activity does not have a protective etiological role.

Breast Cancer. The evidence for an association between physical activity and breast cancer, although not as strong nor as consistent as that found for colon cancer can, nonetheless, be classified as convincing (2–4). Overall, of the 36 studies (21, 24, 26, 33, 72–103) conducted thus far, 24 (33, 72, 73, 75–77, 80–84, 86–88, 90, 92, 93, 95–97, 99, 100, 102, 103) have observed a reduction in breast cancer risk among those women who were most active in their occupational and/or recreational activities (Fig. 2). These risk reductions ranged up to 70% and were statistically significant in 21 studies (33, 72, 73, 75–77, 80–82, 84, 86–88, 93, 95–97, 99, 100, 102, 103). Increased breast cancer risks were found with increased physical activity levels in two studies (26, 74). For the 24 studies that did observe a decreased risk, the reduction in risk was on average

30–40%. A dose-response relation was found in 15 (74, 76, 77, 80, 82–84, 87, 88, 92, 93, 95, 97, 99, 102) of 22 (24, 74, 76–78, 80, 82–84, 87, 88, 90–99, 102) studies that examined the trend.

The relation between physical activity and breast cancer is complex, and the relatively weak associations found may reflect some of the methodological limitations of these studies, including inadequate and possibly inappropriate measurement of physical activity, incomplete control for confounding, and lack of assessment of effect modification (2). The complicated and multiple biological mechanisms that may be operative may not have been adequately captured by the assessment methods used in these studies nor by the actual activity levels of the respondents. The levels of activity performed by the study subjects varied considerably across studies, and the inconsistencies observed may be attributable to the fact that a certain level of activity may be needed to invoke a protective effect. If the studies included only minimally active women, a reduced breast cancer risk may not be readily detectable because alterations in women's hormonal profiles may only occur with higher levels of activity. In addition, many of the studies did not adequately control for all confounding factors; hence, residual confounding may explain some of the inconsistent results. Furthermore, the relation between physical activity and breast cancer may be different among subgroups of women. Very few studies have examined the relation by menopausal status, parity, family history of breast cancer, and body mass index, to
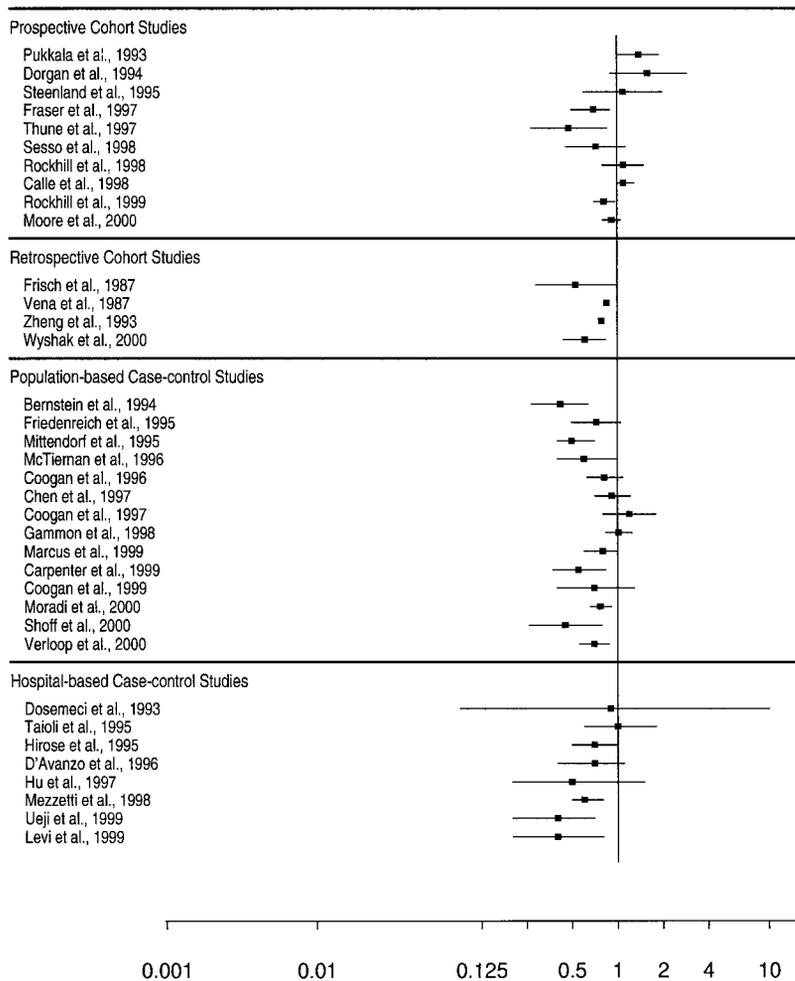
Fig. 2. Main results for epidemiological studies of physical activity and breast cancer risk, by type of study design.

name just a few of the possible effect modifiers. Several aspects of this relation remain unclear and require further investigation, including the type, time period, and level of physical activity that are associated with a reduction in breast cancer risk.

Prostate Cancer. Even less consistent but strong evidence (5) exists for prostate cancer. Of the 26 studies (16, 20, 21, 24, 33, 37, 60, 104–122) conducted to date, there is a suggestion in 15 studies (16, 21, 33, 60, 105–107, 109, 110, 112–114, 117, 120, 122) of a reduction in prostate cancer risk among the men who were most physically active (Fig. 3). This decreased risk was statistically significant in 8 of the 15 studies (60, 105, 107, 109, 110, 113, 120, 122). The magnitude of the risk reduction ranges up to 50%, with the majority of the studies observing about 10–30% decreases in risk (16, 21, 33, 60, 105–107, 109, 110, 112–114, 117, 120, 122). However, no overall association was found in 6 studies (20, 24, 37, 111, 118, 121), and an increased risk of prostate cancer was observed among the most physically active men in five studies (104, 108, 115, 116, 119). Nine (60, 105, 106, 108–110, 114, 115, 122) of the 19 (20, 24, 37, 60, 105–112, 114, 115, 117, 118, 120–122) studies that examined the trend in risk found a dose-response relation, but for only 7 (60, 105, 106, 109, 110, 114, 122) of these studies was there a decreasing risk associated with increasing levels of physical activity. The two remaining studies (108, 115) observed trends of increased risk with increasing activity levels.

As with the studies of colon and breast cancer, these prostate cancer studies were hampered by numerous methodological limitations including crude exposure assessment, variations in detection of latent disease, and inadequate control for confounding factors. The natural history of prostate cancer is still poorly understood, and the biological mechanisms and etiologically relevant time periods in prostate carcinogenesis when physical activity may be operative are unknown. In summary, the evidence for an etiological role of physical activity in reducing the risk of prostate cancer can be classified as probable.

Other Cancer Sites. Less evidence exists for the role of physical activity in reducing the risk of cancer at other sites. To date, physical activity as a risk factor has been examined in 8 studies of lung cancer (16, 20, 21, 24, 37, 60, 123, 124; Fig. 4), 8 studies of testicular cancer (19, 24, 60, 105, 125–128; Fig. 5), 5 studies of ovarian cancer (Refs. 24, 26, 73, 129, and 130; Fig. 6), and 11 studies of endometrial cancer (Refs. 26, 73, and 131–139; Fig. 7). These studies have provided some preliminary evidence that physical activity may have a role in the prevention of these cancers. Although the level of evidence is still too limited to make any statements regarding causal associations, there is, nonetheless, a suggestion that physical activity may reduce the risk of lung and endometrial cancers. Six of the eight lung cancer studies (16, 20, 21, 37, 123, 124) found reductions in risk, and four (20, 37, 123, 124) of these studies had statistically significant risk decreases. In addition, four (20,

Prospective Cohort Studies

Severson et al., 1989
Thune et al., 1994
Lee et al., 1994
Steenland et al., 1995
Oliveria et al., 1996
Cerhan et al., 1997
Hartman et al., 1998
Giovannucci et al., 1998
Liu et al., 2000
Lund Nilsen et al., 2000
Clarke et al., 2000

Retrospective Cohort Studies

Paffenbarger et al., 1987
Vena et al., 1987
Hsing et al., 1994

Population-based Case-control Studies

LeMarchand et al., 1991
West et al., 1991
Andersson et al., 1995
Whittemore et al., 1995
Villeneuve et al., 1999
Putnam et al., 2000

Hospital-based Case-control Studies

Yu et al., 1988
Brownson et al., 1991
Dosemeci et al., 1993
Sung et al., 1999
Bairati et al., 2000

0.001   0.01   0.125   0.5   1   2   4   10

Fig. 3. Main results for epidemiological studies of physical activity and prostate cancer risk, by type of study design.

Prospective Cohort Study

Severson et al., 1989
Lee et al., 1994
Steenland et al., 1995
Thune et al., 1996
Lee et al., 1999

Retrospective Cohort Study

Paffenbarger et al., 1987

Hospital-based Case-control Studies

Brownson et al., 1991
Dosemeci et al., 1993
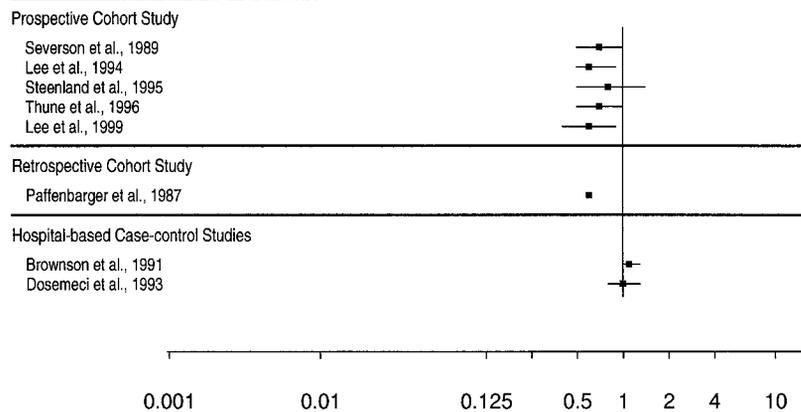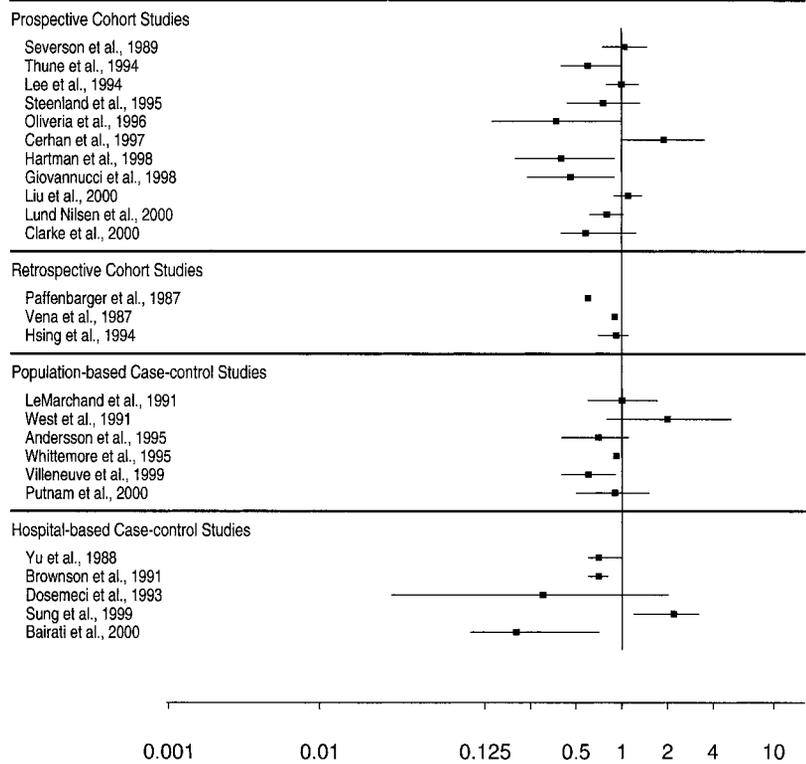
0.001   0.01   0.125   0.5   1   2   4   10

Fig. 4. Main results for epidemiological studies of physical activity and lung cancer risk, by type of study design.

37, 123, 124) of the six (20, 37, 123, 124) studies that examined the dose-response also found evidence of a trend in decreasing lung cancer risk with increasing activity levels. The remaining studies found either no effect of physical activity (24) or an increased risk (60). Likewise, 8 (73, 131–135, 137, 139) of the 11 endometrial cancer studies noted decreased risks, of which 6 (131–134, 137, 139) were statistically significant risk reductions. Three other endometrial cancer studies (26, 136, 138) observed no effect of physical activity. A dose-response effect of decreasing endometrial cancer risk with increasing physical activity was found in four studies (131, 132, 134, 139). Three (60, 126, 127) of the eight testicular cancer studies found statistically significant decreased risks with increased physical activity levels, whereas only two (73, 130) of the five ovarian cancer studies noted risk reductions for higher levels of activity.

The methodological issues that existed for the three pre-

vious sites of cancer are also relevant to these other cancer sites. These include poor physical assessment methods, incomplete assessment of confounding, inadequate examination of effect modification, and a lack of consideration of the underlying biological mechanisms that may be operative and that need to be considered when measuring exposures. In addition to these methodological issues, an insufficient number of studies have been conducted for these remaining cancer sites. More studies are needed that sample diverse populations who performed various levels of physical activity to permit a more complete evaluation of the etiological role of physical activity for those cancer sites. As discussed below, the epidemiological methods need to be improved, and these relations should be studied in other populations.

In summary, the evidence for a preventive role of physical activity in the etiology of for lung and endometrial cancers can
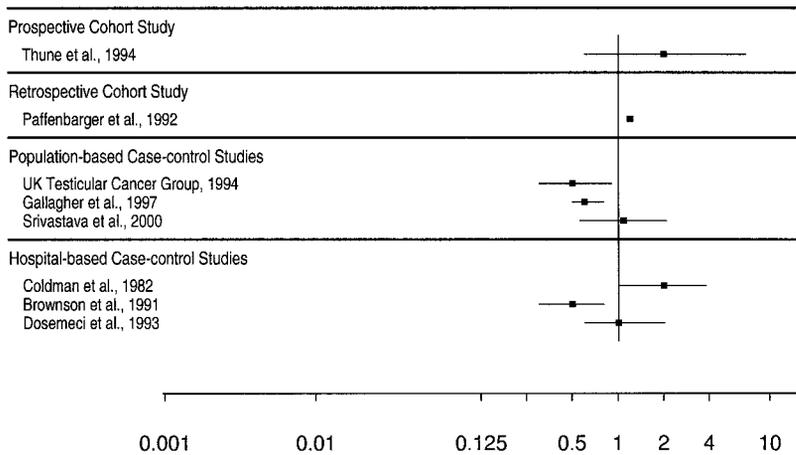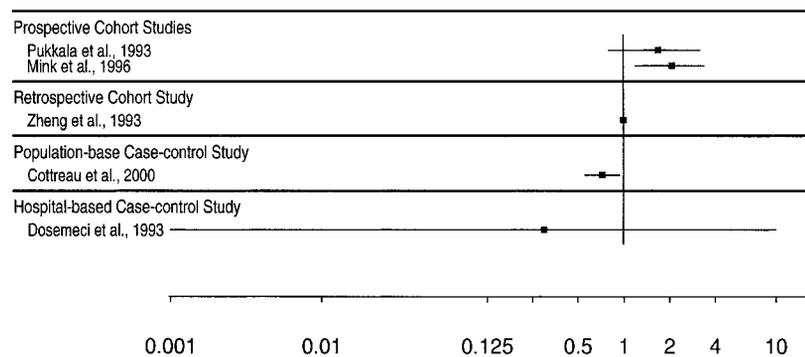
Fig. 5. Main results for epidemiological studies of physical activity and testicular cancer risk, by type of study design.

Fig. 6. Main results for epidemiological studies of physical activity and ovarian cancer risk, by type of study design.

be classified as possible, and for testicular and ovarian cancers, the evidence is currently insufficient to make any conclusions (Table 1).

Methodological Issues in the Epidemiological Studies of Physical Activity and Cancer

The methods used in these studies have varied widely. Populations have included occupational and educational cohorts and hospital-based or population-based samples. Physical activity has been defined as occupational activity, ranging from a job title to a detailed lifetime history of actual occupational activities, or as recreational activity, ranging from simple lists of activities to detailed personalized records. Physical activity data have been extracted from existing records and databases or have been measured directly from individuals using physician-, self- or interview-administered questionnaires. The time period for physical activity assessment has ranged from current activity to some attempts at lifetime assessments of activity. There has been very little standardization in the methods used for assessing physical activity and for measuring its association with cancer outcomes; hence, some of the heterogeneity in the study results is attributable to the large variations in the measurement of the exposures and in the modeling of the associations. Another possible explanation for inconsistent results is the variation across studies in the types and levels of activity that has actually been performed by the study respondents.

The main parameters of physical activity that need to be assessed are the type (occupational, household, and recreational), frequency (how many times the activity is done), duration (how long the activity is done), and intensity (how much energy is expended). These parameters have not been measured consistently. For the purposes of understanding the etiological role of physical activity in cancer causation and translating this scientific evidence into public health physical activity recommendations, data are needed on the level of risk reduction associated with these specific parameters of physical activity (140).

Another important component of these putative associations is understanding how physical activity performed in different time periods in life is associated with risk of cancer. It is unclear whether it is activity performed in early, mid-, or later life that is important for a reduction in risk of cancer. It is unknown whether a certain level of activity needs to be sustained throughout life or whether activity at key points in life is sufficient for a risk reduction. Major gaps in our understanding of the association between lifetime physical activity and cancer risks exist because so few studies have attempted to measure physical activity throughout life; hence, little empirical evidence exists on which to base any recommendations. Strategies to help respondents recall physical activity from the past (141, 142) are needed to improve the validity and reliability of long-term recall.

As mentioned previously, these studies have also been hampered by an incomplete assessment of confounding and effect modification. Residual confounding and possibly differential effects among subgroups of the study populations may explain some of the inconsistencies that have been found across these studies. Physical activity may be a marker of a healthy

Fig. 7. Main results for epidemiological studies of physical activity and endometrial cancer risk, by type of study design.
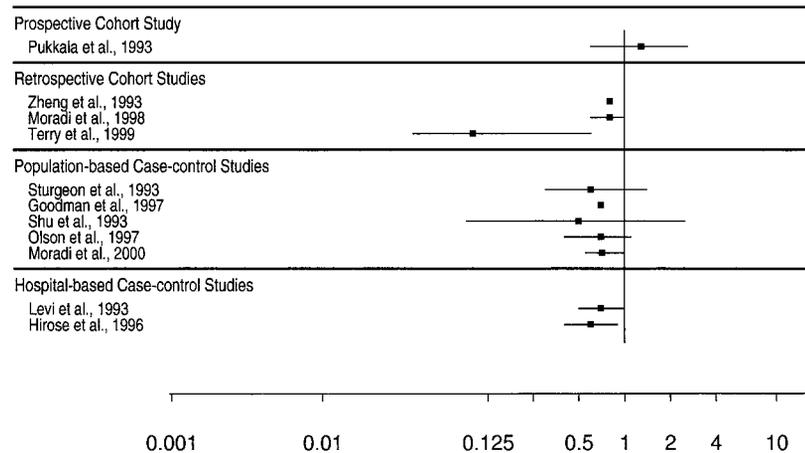
lifestyle, and the association between physical activity and cancer may be interrelated with dietary and alcohol intake, smoking habits, and other healthy behaviors including regular medical screening, maintaining appropriate weight throughout life, and psychosocial well-being. A more integrated approach to measuring the interrelations of these risk factors with physical activity and cancer risk is needed.

Finally, because the biological mechanisms for physical activity and cancer prevention are currently unknown, previous research studies were not designed to assess physical activity according to a hypothesized underlying biological model. Hence, many studies may not have measured physical activity at the appropriate periods in life and at the appropriate levels of activity.

Biological Mechanisms for Physical Activity and Cancer Prevention

Several hypothesized biological mechanisms for physical activity in cancer etiology have been proposed and are being actively researched (Table 2; Refs. 143 and 144). The main mechanisms that influence several cancer sites include modifications of endogenous sex and metabolic hormone levels and growth factors, decreased body fat content, and possibly enhanced immune function. Metabolic hormones and growth factors are hypothesized to be influenced by increased activity levels. Exercise significantly lowers insulin, glucose, triglycerides, and raises HDL cholesterol (145–147), which may also be associated with decreased cancer risk (148, 149). Several randomized clinical trials have shown a benefit of physical activity in reducing fasting insulin levels in normoglycemic and insulin-resistant populations, with the most benefit observed for those individuals that lose weight and increase physical activity levels (150–152). More specifically, exercise may affect cancer risk through its effects on IGFs[3] and their binding proteins (IGFBPs). IGF is down-regulated by increased production of its binding protein (IGFBP-3), which can occur with increased levels of physical activity, decreased caloric intake, and decreased body weight (153). High levels of circulating IGF-I and low levels of IGFBP-3 are associated with an increased risk of colorectal (154), breast (155), prostate (156), and lung (157) cancers. Lifestyle risk factors, including high-energy diets and

low physical activity, may increase IGF-I levels. More research is needed to clarify the role of IGFs in linking lifestyle factors, increased cell proliferation, suppression of apoptosis, and increased cancer risk (149).

Exercise also appears to lower biologically available endogenous sex hormones via a cascade of metabolic events that could result in a lowered risk of hormone-related cancers (*e.g.,* breast, prostate, and endometrium; Ref. 158). It is hypothesized that events of menstrual and reproductive life influence the initiation and promotion of hormonally related cancers, such as those of the breast and endometrium. Increased lifetime exposure to endogenous estrogens through an early age at menarche, late age at menopause, late age at first birth, lack of lactation, and increased number of ovulatory cycles are breast cancer risk factors (159). Girls who participate in vigorous intensity sports such as gymnastics and ballet have a higher incidence of primary and secondary amenorrhea and experience delayed menarche and irregular menstrual cycles (160–162). Physical activity may also reduce the peripheral conversion of adrenal androgens to estrogens (163) in postmenopausal women. Several investigators have shown that elevated circulating estrogens in postmenopausal women are associated with increased breast cancer risk (164–166). Increased bone mineral density, a marker for lifetime increased estrogen exposure, is related to an increased risk of breast cancer (166). The specific level and time period(s) in life when physical activity may result in decreased endogenous sex hormones are not yet established. Endogenous hormone levels may also predict prostate cancer risk. A strong linear trend of increasing prostate cancer risk with increasing levels of plasma testosterone has been observed (167), and increased physical activity is also associated with increased circulating sex hormone binding globulin in both men and women (168), which competitively binds to estrogens and androgens, thereby decreasing endogenous levels of these hormones.

Physical activity may reduce obesity, which has been associated with colon cancer, postmenopausal breast cancer, and endometrial cancer (169). Regular exercise is an important determinant of long-term maintenance of weight loss in obese individuals (170). Exercise may specifically prevent cancer development through a reduction in abdominal fat mass, which is particularly metabolically active and implicated in carcinogenesis (171). Fat mass may be part of a hypothesized hormonal causal pathway between physical activity and cancer (158).

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[3] The abbreviations used are: IGF, insulin-like growth factor; IGFBP, IGF binding protein.

Table 2   Possible biological mechanisms for physical activity and cancer prevention

Cancer site	Mechanism	Rationale
Colon	Decreased gastrointestinal transit time	Physical activity increases gut motility, reduces mucosal exposure time to carcinogens.
	Decreased ratio of prostaglandins (PGE:PGF)	Strenuous exercise may increase PGF,[a] which inhibits colonic cell proliferation and increases gut motility while not increasing PGE_2, which has the opposite effect on colonic cell proliferation from PGF.
	Lowered bile acid secretion or enhanced metabolism	Bile acid concentrations may be decreased in physically active (confounding by diet?) persons.
	Decreased circulating insulin and glucose	IGF-I and IBFBP may be decreased with increased levels of exercise.
Breast	Decreased lifetime exposure to estrogen	Physical activity delays onset of menses, prolongs menstrual cycle, reduces number of ovulatory cycles, reduces ovarian estrogen production. Physical activity reduces body fat and could reduce fat-produced estrogens and protect against breast and endometrial cancer. Physical activity increases the production of sex hormone binding globulin, which results in lower free estradiol levels and may reduce breast cancer risk.
Prostate	Reduced exposure to testosterone	Physical activity increases production of sex hormone binding globulin, which results in low free testosterone levels that may alter prostate cancer risk.
All cancers, especially breast, endometrial, and ovarian	Decreased percent body fat	Obese women have increased infertility which may increase breast cancer risk. Fat storage of carcinogens can occur in visceral fat which can be released in overweight individuals.
All cancers	Genetic predisposition of habitually active	Constitutional factors influence athletic selection or interest in physical activity and susceptibility to cancer.
	Exercise-induced increase in antitumor immune defenses	Exercise may increase number and/or activity of macrophages, lymphokine-activated killer cells, and their regulating cytokines; may increase mitogen-induced lymphocyte proliferation.
	Improved antioxidant defense systems	Strenuous exercise increases the production of free radicals, whereas chronic exercise improves free radical defenses by up-regulating both the activities of free scavenger enzymes and antioxidant levels. Extent of exercise-induced changes in oxidant defense unknown.

[a] PGF, prostaglandin F; PGE_2, prostaglandin E_2.

Immune function is enhanced with long-term endurance training, including increases in the number and activity of macrophages, natural killer cells and lymphokine-activated killer cells and their regulating cytokines, and increased mitogen-induced lymphocyte proliferation rates (144, 172, 173). There is, however, no evidence that physical activity affects risk for cancers that involve the immune system; hence, this mechanism remains speculative and requires more investigation.

Physical activity may also influence cancer risk through other correlated factors that may either act as confounders or be part of a causal pathway between physical activity and cancer risk. Other important correlated factors to consider include dietary and alcohol intake, smoking habits, medication use, family history of cancer, preclinical illness, and use of preventive medical care (158). In addition, genetic predisposition to be physically active and genetic susceptibility may also be involved in the carcinogenic process. Genetic factors influence body build, physical functioning, and capacity for conditioning and may also modify an individual's risk for certain types of cancer (144).

The level of evidence for any of these putative mechanisms is only beginning to accumulate, and much further research is needed to determine which mechanisms are operative for each type of cancer. Because several of the hypothesized mechanisms are interrelated, concerted effort is needed to model the numerous causal pathways that may be operative.

Investigation of these mechanisms should be pursued through physical activity and cancer prevention studies that are designed to examine simultaneously several of these mechanisms as well as the impact of physical activity on intermediate and long-term markers of cancer incidence. Such investigations are described in the next section.

Physical Activity and Cancer Prevention Intervention Studies

To date, no clinical trials of physical activity as a means for the primary prevention of cancer have been published. Two major studies are currently on-going (174).[4] Randomized controlled trials are recognized as the strongest type of study design to provide evidence for the effect of risk factors on disease outcomes. They are, however, the most labor and time intensive and costly of all studies to conduct. Several practical reasons exist to explain why cancer primary prevention trials are rarely conducted (175). Cancer incidence cannot be used as the primary end point, given the length of follow-up that would be needed and the loss to follow-up that would likely occur in such an intervention study. Intermediate end points that are biological markers of disease would be more feasible; however, for most cancer sites, reliable and valid intermediate end points

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[4] A. McTiernan, personal communication.

have not yet been established. The level of evidence on the role of physical activity in cancer prevention that has been accumulated to date does, nonetheless, warrant the conduct of exercise clinical trials. McTiernan *et al.* (176) have advocated that these trials be conducted and are providing leadership in this area by undertaking the first studies in this field.

The first step in the area of cancer prevention intervention trials is to conduct studies that examine the causal pathway between physical activity and cancer occurrence because larger scale, longer term studies cannot be conducted without sufficient justification for the etiological role of physical activity. Consequently, McTiernan *et al.* (174)[4] are conducting 1-year randomized controlled trials that are examining the effect of intervention of moderate intensity physical activity in two study populations. The first trial, known as the Physical Activity for Total Health Study (174), is examining postmenopausal obese women; the second trial, known as the Colon Polyp and Exercise Study,[4] includes male and female adenomatous colon polyp patients. For the Physical Activity for Total Health Study (174), the investigators hypothesize that physical activity may reduce fat mass and subsequently alter the sex hormone profile in postmenopausal women to a profile with lower risk for breast cancer. For the Colon Polyp and Exercise Study,[4] they hypothesize that physical activity will decrease the cell proliferation in the upper part of the colon and rectal crypts.

The Physical Activity for Total Health study (174) is recruiting 168 postmenopausal sedentary, overweight or obese women aged 55–75 years who are not currently taking hormone replacement therapy and randomizing them to receive either a 3-month intensively monitored and 9-month home-based exercise program or a weekly stretching class. The intervention involves five to six sessions of endurance training (30–45 min/session) plus two to three sessions of strength training (20–30 min/session) each week. The first 3 months are monitored group sessions with an exercise physiologist, whereas the last 9 months involve independent exercise. Behavioral models of exercise intervention and adherence are being applied in this study. Numerous endogenous hormones are measured at baseline and at the end of the study. Other outcomes and risk factors to be measured include various anthropometric measures, dietary intake, endocrine and reproductive factors, medications, alcohol intake, smoking, medical history, family history of cancer, and lifetime physical activity patterns. Psychosocial differences and changes associated with intervention participation are also being measured. Specifically, the psychological stages and processes of change will be monitored in these women. Several ancillary studies are also planned for the Physical Activity for Total Health study, including studies examining the effect of exercise on immune function, mammographic density, and other hormones [*e.g.,* IGFs (IGF-I)], and determining the role of genetic polymorphisms of endogenous estrogen production in the exercise-sex hormone pathway.

The Colon Polyp and Exercise Study[4] has a comparable study design to the Physical Activity for Total Health Study (174). In the Colon Polyp and Exercise Study,[4] 200 men and women of ages 40–75 years, who are sedentary and who have a diagnosis of one or more adenomatous colon polyps in the past 18 months, are randomized to either the moderate exercise intervention or the stretching control group. The exercise intervention is the same as in the Physical Activity for Total Health Study (174). The investigators will perform colon and rectal biopsies at the end of the intervention and will be measuring numerous biomarkers in their study participants including: the expression of apoptosis-related proteins, rectal prostaglandin levels, fasting serum/plasma insulin, C-peptide,

glucose, triglycerides, IGF-I, and IGFBP-3, body fat mass and distribution, s.c. abdominal and intra-abdominal fat mass, fitness (VO_2 max), and quality of life.

McTiernan *et al.* (176) have suggested that future intervention studies of exercise and breast cancer could initially repeat this same protocol in other ethnic, racial, age, and high-risk groups of women. Then, other study designs could be used that would involve modifications in the exercise intervention, including diet along with the exercise intervention, and examining other intermediate and final outcomes. The final objective of these trials would be to develop exercise prescriptions for cancer prevention that would be feasible for the population at risk.

This study has particular strengths because it is not only examining the underlying biological mechanisms that may be operative in the association between physical activity and breast cancer but because it is also examining the feasibility of implementing an exercise intervention in a population as a means for cancer prevention. This study is the beginning of comparable research endeavors that would expand the scope and duration of such investigations.

Physical Activity Intervention Studies

Despite the fact that no intervention studies have been conducted on physical activity for the primary prevention of cancer, numerous intervention studies have examined how physical activity can be increased in various population samples. Many aspects of this research are directly relevant and applicable for cancer primary prevention trials.

A systematic review by Hillsdon and Thorogood (177) of physical activity promotion strategies found that levels of physical activity can be increased, and the increase can be maintained for at least 2 years. This review included randomized controlled trials of single-factor interventions to increase activity that were conducted on apparently healthy, free-living adults for a minimum of 12 weeks duration that had exercise as the dependent variable. Interventions that encourage walking and do not require attendance at a facility were found to be the most likely to lead to sustainable increases in overall physical activity. Regular follow-up, which does not need to be time-consuming or expensive, was found to improve the proportion of people able to maintain initial increases. Furthermore, brisk walking was noted as having the greatest potential for increasing overall physical activity levels of a sedentary population and meeting current public health recommendations. These reviewers also observed that walking is the kind of exercise most likely to be adopted by a range of ages, socioeconomic, ethnic, and racial groups as well as by both sexes. They concluded by observing that walking for recreational purposes or as a mode of transport can be encouraged by paying attention to environmental factors that influence personal safety and convenience.

From this body of research, a number of gaps in current knowledge have been identified as priorities for future research (177). There is a need to perform trials on different population samples of all ages, socioeconomic classes, and ethnic and racial groups. There is a lack of properly designed, randomized controlled trials that target low income groups, ethnic minorities, and populations with disabilities. These studies need to use theoretically based interventions and validated assessment instruments to detect physical activity change. They should also include the target population or community at all steps in the design and implementation of the intervention (178). Likewise, more research needs to be done on older persons, because

Research areas	Recommendations
Physical activity assessment methods	Comprehensive measures of activity that include all types of activity, all parameters of activity (*i.e.,* frequency, intensity, and duration) for entire lifetimes. Develop and test validity and reliability of methods including self-administered *versus* interview-administered methods. Develop methods that are sensitive to different population groups. Improve early life recall methods. Develop more standardized approaches across different assessment methods.
Etiological studies	Observational epidemiological studies that measure physical activity in a comprehensive manner, which include biological mechanisms relevant to individual cancer sites and that examine different study populations. Complete assessment of confounding to assess how physical activity relates to other risk factors including obesity, dietary intake, other lifestyle risk factors, and genetic predisposition. Examination of population subgroups (effect modification). Cancer sites to be studied: breast, prostate, lung, testes, endometrium, and ovary.
Intervention studies	Randomized controlled trials of colon and breast cancers to determine the efficacy and effectiveness of various strategies to reduce risk. Steps to be followed include: identifying high-risk populations, examining several endpoints, conducting small pilot studies and small scale clinical trials, replicating the results in different populations, and then conducting large-scale studies.
Biological mechanisms	Research focused on identifying which mechanisms and how and when they are operative. Identify and test intermediate endpoints (i.e. biomarkers) for the association between physical activity and cancer risk and used in intervention studies.
Behavioral research	Studies of determinants of behavior and how these behaviors change over time and how they are inter-related. Studies of diffusion and dissemination of physical activity guidelines.
Surveillance research	Track secular changes in physical activity and changes in cancer incidence.
Health policy research	Studies of how policy, environmental, and organizational interventions influence physical activity habits.

significant gaps in scientific evidence were found for most aspects of effective interventions for this growing part of the population (179).

Lifestyle physical activity interventions have emerged recently as a means for addressing the crisis in physical activity that currently exists, particularly in North America. Lifestyle physical activity is defined as the daily accumulation of at least 30 min of self-selected activities (180). It encompasses all leisure, occupational, or household activities that are at least moderate to vigorous in their intensity and includes planned or unplanned activities that are part of everyday life (180). A review of previously tested lifestyle physical activity interventions found that they are effective in increasing and maintaining levels of physical activity that meet or exceed the public health guidelines for physical activity in representative samples of previously sedentary adults and obese children (179). The majority of these studies have used face-to-face contact in small groups, which limits their public health applicability. Most of the studies used behavior change theories (*e.g.,* Social Cognitive Theory, Transtheoretical Model, and Behavior Learning) when developing the interventions. The outstanding issues that remain for lifestyle physical activity interventions are: (*a*) their ability to be implemented on a large scale for a longer term using different media; (*b*) their cost-effectiveness for different modes of delivery; and (*c*) their efficacy in populations such as the elderly, minorities, and among low income and diseased individuals (180).

Recommendations for Research and Interventions in Physical Activity and Cancer Prevention

Future research in physical activity and cancer prevention is needed in several areas that are summarized in Table 3. Briefly,

these entail: improved physical activity assessment methods; more observational epidemiological studies for all cancer sites except colon cancer, for which there is arguably sufficient evidence regarding this association (1); intervention studies in colon and breast cancer; research into the underlying biological mechanisms; behavioral research into the determinants of physical activity; surveillance of physical activity and cancer incidence trends; and health policy studies.

This review has outlined the methodological limitations of previous epidemiological research studies, with particular emphasis on the problems with the physical activity assessment methods used. These deficiencies can be largely addressed by designing studies that incorporate improved physical activity assessment, adequate control for confounding, and consideration of effect modification. Future studies need to examine the underlying biological mechanisms that may be operative in the association between physical activity and cancer. Once sufficient evidence has been accumulated from observational epidemiological studies, randomized controlled trials of physical activity as a means for the primary prevention of cancer can be conducted.

The exact steps that need to be followed for exercise clinical trials of cancer prevention have been proposed by McTiernan *et al.* (176). These steps include identifying high-risk populations, establishing intermediate end points, conducting pilot and feasibility studies, replicating the results in different study populations and settings, and undertaking large-scale intervention trials. These investigators note that a major advantage of long-term large exercise clinical trials is that the risk and benefit of exercise for several morbidity and mortality end points can be assessed simultaneously. These trials could determine what exercise prescriptions are needed to reduce

cancer incidence and whether the recommended daily exercise guidelines prepared by national and federal agencies are appropriate for cancer outcomes. Clearly, much feasibility work and research is needed before the ultimate objective of such large-scale primary prevention trials of physical activity and cancer outcomes can be undertaken.

Because the field of physical activity and cancer prevention is still only becoming established, the area of behavioral research in promoting physical activity as a means for preventing cancer has not yet been developed. There has, however, been substantial effort in behavioral research for promoting healthy dietary habits for cancer prevention and control. A considerable component of that research is directly applicable to physical activity because these are both modifiable lifestyle risk factors. Nutrition intervention research has evolved rapidly and has become more rigorous and sophisticated. Increasingly, this research is using theoretical models from psychology and sociology and measures of cognitive and psychosocial determinants of dietary behavior such as knowledge, intentions, self-efficacy, and readiness to change (181).

Priority areas have been identified for behavioral research in dietary change that are of direct relevance to research on changing physical activity levels (181). These areas include understanding the determinants of dietary behavior and how this behavior changes over time. For physical activity and cancer prevention, research is needed that tracks secular changes in physical activity and changes in cancer incidence. Within this priority area is the issue of understanding how lifestyle behaviors are interrelated, *e.g.,* how diet, alcohol intake, tobacco and drug use, and exercise are associated. Other priority areas include health policy studies and research on diffusion and dissemination of health promotion campaigns for physical activity.

Conclusion

The evidence for a protective role of physical activity in cancer etiology is clearly accumulating rapidly and becoming increasingly convincing. A strong rationale exists for progressing from observational epidemiological studies to intervention trials in the field of physical activity and cancer. This rationale is currently most clear for colon and breast cancers. Given the strength of the risk reductions seen for most of the cancer sites, the potential for cancer prevention with increased physical activity levels is significant. Progress in this field can be made by improving understanding of the underlying biological mechanisms, enhancing physical activity assessment methods, and by conducting additional observational epidemiological studies that address the identified deficiencies in previous research. Furthermore, before definitive exercise prescriptions for cancer prevention can be made on a population basis, more evidence is needed from controlled trials of exercise interventions in at-risk populations as described above. This latter type of research can provide the necessary data on what type of physical activity performed at what intensity, duration, and frequency at which time period(s) in life are most likely to result in cancer risk reductions. Physical activity, along with dietary intake, smoking, alcohol consumption, and sun exposure are the main avenues for the primary prevention of cancer. Research in physical activity and cancer prevention has lagged behind research on other modifiable lifestyle risk factors. Considerable potential exists for significant progress in this field.

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