Review

Physical Activity and Endometrial Cancer Risk, a Systematic Review of Current Evidence

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Abstract

Objective: **To assess the epidemiologic evidence for the association between physical activity and endometrial cancer risk, taking into account the methodologic quality of each study.**
Design: **Systematic review, best evidence synthesis.**
Data Sources: **Studies were identified through a systematic review of literature available on PubMed through December 2006.**
Review Methods: **We included cohort and case-control studies that assessed total and/or leisure time and/or occupational activities in relation to the incidence of endometrial cancer. The methodologic quality of the studies was assessed with a comprehensive scoring system.**
Results: **The included cohort (n = 7) and case-control (n = 13) studies consistently show that physical activity is associated with a decreased risk of endometrial cancer. The best evidence synthesis showed that the majority (80%) of 10 high-quality studies found risk reductions of >20%. Pooling of seven high-quality cohort studies that measured total, leisure time, or occupational activity showed a significantly decreased risk of endometrial cancer (summary estimate: OR, 0.77; 95% CI, 0.70-0.85) for the most active women. Case control studies with relatively unfavorable quality scores reported divergent risk estimates, between 2-fold decreased and 2-fold increased risk. Effect modification by body mass index or menopausal status was not consistently observed. Evidence for an effect of physical activity during childhood or adolescence was limited.**
Conclusions: **Physical activity seems to be associated with a reduction in the risk of endometrial cancer, which is independent of body weight. Further studies, preferably prospective cohort studies, are needed to determine the magnitude of the risk reduction and to assess which aspects of physical activity contribute most strongly to the reduced risk and in which period of life physical activity is most effective.**
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Introduction

Endometrial cancer is the eighth most common cancer in women worldwide. An estimated 200,000 cases occur yearly, accounting for 1.8% of all new cases of cancer worldwide and 4% to 8% in Western industrialized countries (1). Known risk factors for endometrial cancer include obesity, postmenopausal estrogen replacement, ovarian dysfunction, type II diabetes, infertility, nulliparity, and tamoxifen use (2, 3). Recently, physical inactivity has received increasing attention as a potential risk factor for endometrial cancer (4-6). Physical activity together with maintenance of a healthy body weight would provide women with a powerful strategy for the prevention of endometrial cancer and possibly other cancers as well (7).

The majority of studies on the association between physical activity and cancer have focused on breast cancer. About 50 observational studies have been conducted on total or leisure time activities, in which both null results and inverse associations between physical activity and breast cancer have been observed (8). By contrast, much fewer studies examined the association between physical activity and endometrial cancer, and the results seem to point rather uniformly to risk reduction from physical activity. By systematically reviewing all the evidence from observational epidemiologic studies, we aim to estimate the magnitude of the effect of physical activity on endometrial cancer risk and to examine the level of evidence, taking into account the methodologic quality of the studies including those on total, leisure time, and occupational activities. Because obesity is a strong risk factor for endometrial cancer, we have paid special attention to a possible role for body weight as a confounder, effect modifier, or intermediary factor in the association between physical activity and endometrial cancer.

Methods

Search and Selection of Literature. Studies were identified through a systematic review of published literature available on PubMed literature databases through December 2006. The databases were searched using the following terms: (''physical activity'' OR ''physical inactivity'' OR ''exercise'' OR ''sedentary lifestyle'') AND (''endometrial cancer'' OR ''cancer, endometrium'' OR ''neoplasms, endometrium'' OR ''cancer, corpus uteri'' OR ''neoplasms, corpus uteri'' OR ''cancer, uterus'' OR ''neoplasms, uterus''). From relevant publications, the bibliographic lists were hand searched for additional articles.

The criteria for inclusion of studies in the review were as follows: case-control or cohort studies investigating the association between physical activity and endometrial cancer; with incidence, prevalence, or mortality as end point; >10

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Note: This review was undertaken as part of the activities of the Task Force Physical Activity and Cancer of the Signalling Committee of the Dutch Cancer Society.

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Table 1. Characteristics and results of the cohort studies stratified by source of activity (total, leisure time, occupational)

Author (reference)	Cohort name and country	Baseline	Age (y)	Follow-up (y)	Cohort size
Total activity					
Colbert et al. (13)	Breast Cancer Detection Demonstration Project (United States)	1987-1989	61 ± 8	8.2	23,369
Friberg et al. (6)	Swedish Mammography Cohort	1997	50-83	7.2	33,723
Leisure time activity					
Terry et al. (12)	Swedish Twin Registry (Sweden)	1967	42-81	20.4	11,659
Furberg and Thune (14)	Norwegian Women Cohort (Norway)	1974-1981	45 ± 7	15.7	24,460
Schouten et al. (4)	Netherlands Cohort Study on Diet and Cancer (Netherlands)	1986	55-69	9.3	62,573
Friberg et al. (6)	Swedish Mammography Cohort	1997	50-83	7.2	33,723
Occupational activity					
Pukkala et al. (15)	Teachers cohort (Finland)	1958-1973, 1984-1991	20-75+	24	10,118
Moradi et al. (16)	Swedish Cancer Environment Registry (Sweden)	1960-1970	16-95	19	989,270
Furberg and Thune (14)	Norwegian Women Cohort (Norway)	1974-1981	45 ± 7	15.7	24,460
Friberg et al. (6)	Swedish Mammography Cohort	1997	50-83	7.2	33,723

*Printed in italic if contrast is low versus high activity levels.
†Trend: subjective assessment (P value for trend test if available).

cancer cases included in the analysis; published in English. We included studies assessing leisure time activity or total activity or occupational activity.

Data Extraction and Quality Assessment. The data extraction and study quality assessment were independently done by two reviewers (D.W.V. and E.M.M.). Any disagreement was resolved by consensus or by consultation with a third reviewer (F.E.v.L.). Details of the standardized data extraction are described elsewhere (8). We documented study size, characteristics of the study population, components of physical activity assessment, and methodologic characteristics.

A quality scoring system was developed that captured both generic methodologic issues and issues specific to our subject (see Appendix A; ref. 8). The items of the scoring system were categorized according to three important sources of error in observational studies (the major headings): selection bias, misclassification bias, and confounding bias. Criteria for physical activity assessment methods were partly adopted from Powell et al. (9). The quality scoring system contained 19 items (selection, 5; misclassification, 11; and confounding, 3). The members of the Task Force Physical Activity and Cancer assessed which aspects of quality are more important and therefore should be weighted more in the overall quality score. In this research area, the potential for confounding bias is judged less important. Studies that adequately adjusted for potential confounders show that the magnitude of the risk estimates does not materially change after adjustment, whereas biases due to selection or misclassification are expected to lead to larger effects on risk estimates. Thus, the major headings were weighted 2:2:1. The maximum attainable score is 105 (see Appendix A), and the quality score of the studies is presented as percentage of the maximum attainable score.

Analysis. We assessed statistical heterogeneity across studies using a formal test (10) and found statistical evidence for heterogeneity for total, leisure time, and occupational activities combined, both in cohort and case-control studies. Summary estimates were calculated using a general variance–based method using confidence intervals (11).

A qualitative summary of all studies was undertaken according to a best evidence synthesis, taking into account the methodologic quality of the studies and the consistency of the available evidence (see Appendix B). An inverse association between physical activity and endometrial cancer risk within a study was defined as a risk estimate for the highest versus the lowest level of activity of <0.8, irrespective of statistical significance. In our best evidence synthesis, the evidence for an inverse association was defined as ''strong'' if ≥75% of the high-quality studies reported an inverse association. Studies were categorized as high or low quality based on the median quality score of all studies combined. Graphical displays were used to investigate whether the risk estimates from studies with a relatively low methodologic quality differed systematically from those with relatively high quality. Possible publication bias was investigated by funnel plots.

Results

We identified 20 relevant articles on physical activity and endometrial cancer risk. The main characteristics and results of the 7 cohort studies (4, 6, 12-16) and 13 case-control studies (5, 17-28) are summarized in Tables 1 and 2, respectively. All studies were published between 1993 and 2006. Two cohort studies and four case-control studies assessed total activity whereas the other studies reported only leisure time activities and/or occupational activities. The number of endometrial cancer cases ranged from 49 to 5,287 in the cohort studies and from 31 to 832 in the case-control studies. There was considerable variation among the studies with respect to age of the participants, physical activity assessment, and the length of follow-up (cohort design).

Quality Score. The total quality score, as a percentage of the maximum score, ranged between 61% and 87% (median, 71%) for the cohort studies and between 33% and 80% (median, 55%) for the case-control studies. The median quality score of all studies combined was 60.5%. All seven cohort studies and three case-control studies were thus categorized as high-quality studies (i.e., quality score above the median). Especially cohort studies scored very favorably on issues about selection bias (range, 83-100%; median, 100%) as compared with case-control studies (range, 26-90%; median,

Table 1. Characteristics and results of the cohort studies stratified by source of activity (total, leisure time, occupational) (Cont'd)

No. cases	Activity measure—life period	Contrast	Risk estimate (95% CI)*; trend †	Quality score (% of max)
253 postmeno	MET—recent	Highest activity quintile vs lowest	HR, 0.8 (0.5-1.1) Residual confounding: no	75
199 postmeno	MET—recent	Highest activity quintile vs lowest	RR, 0.79 (0.53-1.17); trend: no (P = 0.27) Residual confounding: partly	87
133 pre- and post-meno	Subjective—recent	Hard physical exercise vs none (4 cats)	HR, 0.1 (0.04-0.6); trend: yes (P < 0.01) Residual confounding: yes	61
130 pre- and post-meno	Subjective—recent	Grade 3 + 4 (sports) vs grade 1 (sedentary)	HR, 0.79 (0.43-1.45); trend: no (P = 0.39) Residual confounding: yes	75
226 postmeno	Duration (h/wk)—recent	Total nonoccupational activity; ≥90 min/d vs <30 min/d (4 cats)	HR, 0.54 (0.34-0.85); trend: yes (P = 0.002) Residual confounding: partly	68
199 postmeno	Hours/d—recent	High (≥20 min/d) vs low (<20 min/d)	RR, 0.99 (0.73-1.32); trend: n.a. Residual confounding: partly	87
49 pre- and post-meno	Subjective—lifetime	Physical exercise teachers vs language teachers	SIR_{PE}/SIR_{L}: 0.85; trend: n.a. Residual confounding: partly	68
5,287 post- and post-meno	Subjective—1970	Sedentary vs high/very high (4 cats)	*RR, 1.32 (1.17-1.50)*; trend: yes (<0.001) Residual confounding: yes	71
130 pre- and post-meno	Subjective—recent	Grade 3 + 4 (manual) vs grade 1 (sedentary)	HR, 0.61 (0.35-1.05); trend: no (P = 0.09)	75
199 postmeno	MET—recent	High (standing/manual) vs low (sedentary)	RR, 1.01 (0.75-1.37); trend: n.a. Residual confounding: partly	87

71%). Case-control studies scored moderately on misclassification issues (range, 24-83%; median, 57%) and even less favorably on confounding (range, 0-100%; median, 19%). Cohort studies scored similarly, for misclassification between 43% and 78% (median, 60%) and for confounding between 19% and 76% (median, 38%). Among case-control studies, there was a tendency for larger studies (i.e., greater number of endometrial cancer cases) to have a more favorable quality score than smaller studies (Fig. 1).

Magnitude of Risk and Strength of Evidence. Four cohort studies reported on leisure time activity, of which three found a decreased risk of endometrial cancer (based on our definition; see Methods) for women in the highest activity versus the lowest activity category (Table 1; Fig. 2; refs. 4, 12, 14). Risk reductions ranged between 20% and 90%, and two of three studies showed evidence for a dose-response effect (trend test, $P < 0.01$; refs. 4, 12). Terry et al. (12) found that the highest activity level (i.e., ''hard physical training'') was associated with a very strong decrease in risk of endometrial cancer compared with having no leisure time activities [hazard ratio (HR), 0.1; 95% confidence interval (95% CI), 0.04-0.6]. However, this was based on only two cases in the most active group. Only one cohort study assessed total activity and found a 20% endometrial cancer risk reduction (HR, 0.8; 95% CI, 0.5-1.1; ref. 13). In two of four studies that assessed occupational activity, a decreased risk of endometrial cancer was found in women in the highest versus the lowest category of occupational activity (e.g., manual/standing work versus sedentary work; refs. 14, 16).

Of the 13 case-control studies, 4 assessed total activity and 9 assessed leisure time activity (3 studies assessed both). Ten case-control studies included some assessment of occupational activities. Of the nine studies assessing leisure time activity, five observed a decreased risk of endometrial cancer (based on our definition; see Methods) for the most active group compared with the least active group (Table 2; Fig. 2; refs. 5, 19-21, 24). Three of these nine studies also showed evidence for a dose-response effect (P values between <0.01 and 0.06 for trend test; refs. 5, 21, 24) and one study reported a significant trend test although no obvious trend could be observed (19). All four studies that assessed total activity found a markedly decreased risk of endometrial cancer (HRs between 0.1 and 0.5) for the most active women compared with the least active women (17-19, 23). None of these studies clearly showed a dose-response effect, although a trend test suggested differently in two studies (trend test, $P \leq 0.01$; refs. 19, 23). Six of 10 studies reporting on occupational activity found a decreased risk of endometrial cancer (based on our definition; see Methods; refs. 17, 19, 22, 24, 26, 28). Two of these studies also showed some evidence for a dose-response effect; however, no P values were reported (26, 28). Dosemeci et al. (27) reported on the only study to find a 2-fold increased risk of endometrial cancer for women with active jobs as compared with women with sedentary jobs. The reported odds ratio (OR) was not statistically significant, based on only 31 cases, and the study had an unfavorable quality score.

Based on our best evidence synthesis, there is strong evidence for an inverse association between physical activity and endometrial cancer risk. Eight of 10 high-quality studies reported a risk reduction of >20% for the highest category of total, leisure time, or occupational activity. Seven of eight (88%) high-quality studies reporting on total or leisure time activities found an inverse association with either of these physical activity assessments. Only 3 of 7 (43%) high-quality studies on occupational activity found a reduction in risk for women with active jobs as compared with women with inactive jobs.

Statistical Heterogeneity and Pooling. The effect estimates of eight case-control studies that investigated leisure time activities and reported 95% CIs were not found to be statistically heterogeneous. Pooling resulted in a summary estimate of a 27% decreased risk of endometrial cancer for the most active women compared with the least active women (summary OR, 0.73; 95% CI, 0.62-0.86). Similarly, effect estimates of eight case-control studies that reported on occupational activities and included 95% CIs were also not found to be statistically heterogeneous (summary OR, 0.80; 95% CI, 0.66-0.96). Pooling of all total, leisure time, and occupational activity effect estimates, irrespective of statistical heterogeneity, suggested an at least 20% decrease in endometrial cancer risk for the most active women compared with the least active women [cohort summary relative risk (RR), 0.77; 95% CI, 0.70-0.85; case-control summary OR, 0.71; 95% CI, 0.63-0.80; Fig. 2].

Effect Modification by Body Mass Index and Menopausal Status. Four of seven cohort studies assessed whether body

Table 2. Characteristics and results of the case-control studies stratified by source of activity (total, leisure time, occupational)

Author (reference)	Country	Activity assessment	Age (y)	No. cases	No. controls	Study base (cases/controls)
Total activity						
Sturgeon et al. (17)	United States	1987-1990	20-74	405	297	Hospital/population
Shu et al. (18)	China	1988-1990	18-74	268	268	Population/population
Levi et al. (19)	Switzerland/Italy	1988-1991	31-75	274	572	Hospital/hospital
Salazar-Martinez et al. (23)	Mexico	1995-1997	?	85	668	Hospital/hospital
Leisure time activity						
Sturgeon et al. (17)	United States	1987-1990	20-74	405	297	Hospital/population
Shu et al. (18)	China	1988-1990	18-74	268	268	Population/population
Levi et al. (19)	Switzerland/Italy	1988-1991	31-75	274	572	Hospital/hospital
Hirose et al. (20)	Japan	1988-1993	18-80+	145	26,751	Hospital/hospital
Olson et al. (21)	United States	1986-1991	40-85	232	631	Hospital/population
Goodman et al. (22)	Hawaii (United States)	1985-1993	18-84	332	511	Population/population
Moradi et al. (24)	Sweden	1994-1995	50-74	709 ‡	3,368	Population/population
Littman et al. (25)	United States	1985-1991	45-74	822	1,111	Population/population
Matthews et al. (5)	China	1997-2001	30-69	832	846	Population/population
Occupational activity						
Sturgeon et al. (17)	United States	1987-1990	20-74	405	297	Hospital/population
Shu et al. (18)	China	1988-1990	18-74	268	268	Population/population
Levi et al. (19)	Switzerland/Italy	1988-1991	31-75	274	572	Hospital/hospital
Zheng et al. (26)	China	1980-1984	≥30	452	?	Population/population
Dosemeci et al. (27)	Turkey	1979-1984	all	31	244	Hospital/hospital
Kalandidi et al. (28)	Greece	1992-1994	all	145	298	Hospital/hospital
Olson et al. (21)	United States	1986-1991	40-85	232	631	Hospital/population
Goodman et al. (22)	Hawaii (United States)	1985-1993	18-84	332	511	Population/population
Moradi et al. (24)	Sweden	1994-1995	50-74	709 ‡	3,368	Population/population
Matthews et al. (5)	China	1997-2001	30-69	832	846	Population/population

Abbreviation: n.a., not applicable; SIR, standard incidence ratio; PE, physical exercise teachers; L, language teachers; high: <12 kJ/m; low: <8 kJ/m.
*Printed in italic if contrast is low versus high activity levels.
†Trend: subjective assessment (*P* value for trend test if available).
‡ Includes only postmenopausal women.

mass index (BMI) had a modifying effect on the association between physical activity and endometrial cancer risk and did not find any statistical evidence for interaction (at the multiplicative level; refs. 4, 6, 13, 14). Of all case-control studies, six assessed effect modification by BMI. Four studies found no differences in stratum-specific risk estimates (5, 18, 24, 25). Sturgeon et al. (17) found that the decrease in risk found with leisure time activity was limited to those with a BMI >25. Levi et al. (19) also observed stronger associations with physical activity in those with a high BMI; however, these analyses were not adjusted for potential confounders. Most studies adjusted for BMI as a confounding factor but found only slightly attenuated risk estimates.

Very few studies specifically assessed whether the association between physical activity and endometrial cancer risk differed by menopausal status. Colbert et al. (13) found no significant interaction between menopausal status and total activity. Furberg and Thune (14) stratified by age and found that the effect of physical activity was stronger in women aged ≥50 years (not statistically significant). Of the case-control studies, only two studies examined effect modification by menopausal status. Both Sturgeon et al. (5) and Matthews et al. (17) found no significant difference in effect between premenopausal and postmenopausal women.

Association with Physical Activity in Different Life Periods. The association between endometrial cancer risk and physical activity in different periods of life was only assessed in five case-control studies (5, 18, 19, 21, 24). The association with physical activity levels in recent years of life (above age 50, or years before physical activity assessment) was generally somewhat stronger than the association with physical activity in adolescence or young adulthood (18, 19, 21, 24). None of these studies adjusted for physical activity levels in other periods of life. Matthews et al. (5) specifically studied physical activity patterns in adolescence and adulthood in relation to

Table 2. Characteristics and results of the case-control studies stratified by source of activity (total, leisure time, occupational) (Cont'd)

Activity measure—life periods	Contrast	Risk estimate (95% CI)* trend †	Quality score (% of max)
Subjective—recent	Global assessment: very inactive vs very active (5 cats)	*OR, 2.5 (0.7-8.7)*; trend: no Residual confounding: no	60
Subjective—age 50-59	Very inactive vs very active (5 cats)	*OR, 2.1 (0.6-7.1)*; trend: no Residual confounding: no	80
Subjective—age 55	Lowest vs highest (4 cats)	*OR, 8.6 (3.0-25.3)*; trend: no (P < 0.01) Residual confounding: yes	42
MET-h/wk—recent? leisure?	≥38 MET-h/wk vs ≤29 (3 cats)	OR, 0.47 (0.26-0.86); trend: no (P = 0.01) Residual confounding: yes	44
Subjective—recent	Lowest quintile vs highest	*OR, 1.2 (0.7-2.2)*; trend: no Residual confounding: no	60
MET—age 50-59	Lowest quartile vs highest quartile	*OR, 1.0 (0.6-1.7)*; trend: no Residual confounding: no	80
Subjective—recent	Sporsts and leisure: lowest vs highest (4 cats)	*OR, 1.9 (0.9-4.0)*; trend: no (P < 0.01) Residual confounding: yes	42
Frequency—recent	Exercise for health: ≥3-4×/wk vs no activity (3 cats)	OR, 0.63 (0.34-1.11); trend: no Residual confounding: yes	48
Duration—recent	Vigorous activity: ≥100 h/y vs none (3 cats)	OR, 0.67 (0.42-1.09); trend: yes (P = 0.06) Residual confounding: yes	47
Duration—lifetime	Lifetime hours: >3,339 vs 0 h (4 quartiles)	OR, 0.9 (CI incl 1); trend: no (P = 0.34) Residual confounding: yes	55
Duration—recent	Exercise/sports: 0 h/wk vs >2 h/wk	*OR, 1.3 (1.1-1.7)*; trend: yes (P = 0.01) Residual confounding: partly	70
Duration—recent	Any recreational activity: >6 h/wk vs none (4 cats)	OR, 0.83 (0.59-1.15); trend: no (P = 0.31) Residual confounding: yes	58
Calorie expenditure—lifetime	Highest quartile vs none (5 cats)	OR, 0.60 (0.42-0.86); trend: yes (P < 0.01) Residual confounding: no	74
Frequency—recent	Rarely/never vs daily	*OR, 1.4 (1.0-2.1)*; trend: no Residual confounding: no	60
Caloric expenditure—lifetime	Lowest quartile vs highest quartile	*OR, 1.0 (0.6-1.7)*; trend: no Residual confounding: no	80
Subjective—recent	Very low vs high (4 cats)	*OR, 1.5 (1.0-2.2)*; trend: no (P < 0.05) Residual confounding: yes	42
Job category—recent	High (>12 kJ/m) vs Low (<8 kJ/m)	SIR_{high}/SIR_{low}: 0.72; trend: yes Residual confounding: yes	55
Job category—lifetime	Sedentary (<8 kJ/m) vs active (>12 kJ/m)	*OR, 0.5 (0.0-9.3)*; trend: yes (P = 0.27) Residual confounding: yes	33
Job category—recent	Manual vs nonmanual (3 cats)	OR, 0.41 (0.18-0.91); trend: yes Residual confounding: no	45
Caloric expenditure—recent	Highest vs lowest tertile	OR, 1.19 (0.76-1.87); trend: no (P = 0.39) Residual confounding: yes	47
Duration—lifetime	Lifetime hours: >20,089 h vs 0 h (4 quartiles)	OR, 0.7 (CI incl 1); trend: no (P = 0.08) Residual confounding: yes	55
Job category—recent	Sedentary vs high/very high	*OR, 1.3 (0.9-1.9); trend*: no (P = 0.05) Residual confounding: partly	70
Calorie expenditure—lifetime	Highest quartile vs none	OR, 0.86 (0.63-1.18); trend: no (P = 0.70) Residual confounding: no	74

premenopausal and postmenopausal endometrial cancer risk. They reported that being physically active only in adulthood (i.e., nonactive during adolescence) was associated with a decrease in postmenopausal but not in premenopausal endometrial cancer risk. Higher levels of physical activity in adolescence were associated with a decreased risk of premenopausal endometrial cancer only. However, being physically active in adolescence only (i.e., nonactive during adulthood) was associated with marginally decreased risk of both premenopausal and postmenopausal endometrial cancer (not statistically significant).

Exploring Causes of Heterogeneity in Study Results. We next examined whether methodologic issues can explain heterogeneity in the magnitude of the estimated endometrial cancer risk. Substantial variation between studies was observed in exposure quantification and categorization. The reference category of leisure time activities varied from ''none'' to 2-3 h of (moderate) activity per week, whereas the highest activity category varied from 2 h of (vigorous) activities per week to >6 or even 9 h of moderate/vigorous activities per week. We did not observe a pattern or trend of studies with higher activity categories or a larger contrast finding stronger associations between physical activity and endometrial cancer risk (data not shown).

Besides these issues relating to exposure assessment, we also examined whether study quality could explain heterogeneity in magnitude of the risk estimates. In Fig. 2 studies are

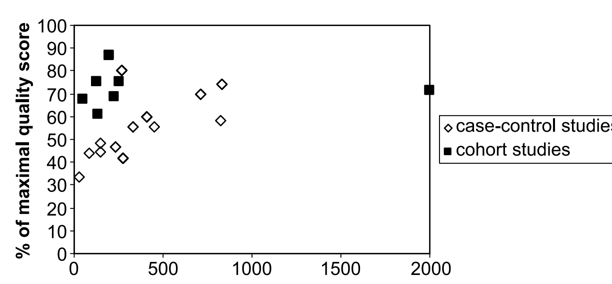

Figure 1. The relation between quality score and study size in cohort and case-control studies. One cohort study [Moradi et al. (16)] includes 5,287 cases, but is depicted at 2,000 for presentation purposes.

ordered according to total quality score, showing the relation between the total quality score and the magnitude of the estimate of the highest versus the lowest level of activity. Studies with an unfavorable total quality score tended to report more divergent risk estimates, ranging from a >2-fold decreased risk to a 2-fold increased risk. In particular, high variability in the magnitude of the risk estimates was found in case-control studies with a relatively unfavorable ''selection bias score'' (Fig. 3). In cohort studies, selection bias was not an issue as six of seven cohort studies attained the maximum score. The magnitude of the risk estimates in cohort and case-control studies did not correlate strongly with quality scores for ''misclassification'' or ''confounding'' (data not shown).

Exploring Publication Bias. Figure 4 represents a funnel plot for cohort and case-control studies combined. The funnel plot shows that risk estimates of the larger studies cluster around a risk reduction of 20% to 50%, comparing the lowest and highest levels of physical activity, in both cohort and case-control studies. Studies with relatively small numbers of cases show a larger diversity in risk estimates, both strong risk reductions and some increased risks. These results suggest that no major bias has occurred by selective publication.

Discussion

This is the first systematic and standardized review of epidemiologic studies of the association between physical activity and endometrial cancer. Considerable variation among studies was observed with respect to design, exposure assessment, and study quality (scores ranging between 33% and 87% of the maximum attainable score). The best evidence synthesis showed that the majority of high-quality studies

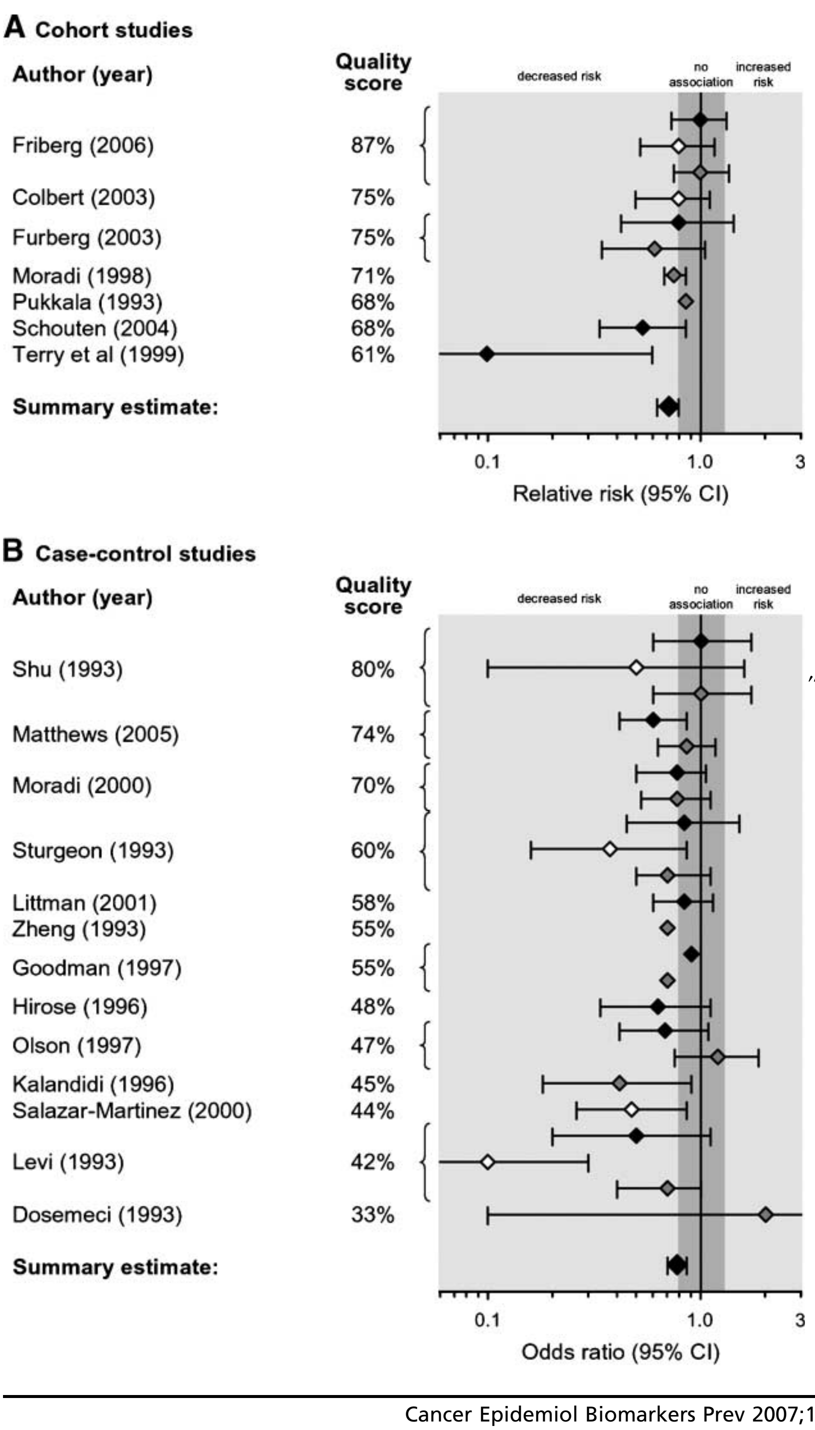

Figure 2. Risk estimates of studies on physical activity and endometrial cancer risk, ordered according to study design and total quality score. **A.** Cohort studies. **B.** Case-control studies. ♦, leisure time activity; ◇, total activity; ⋄ occupational activity. Risk estimates from Sturgeon et al. (17), Shu et al. (18), and Levi et al. (19) were reported for inactive versus active group and have been converted for presentation purposes.

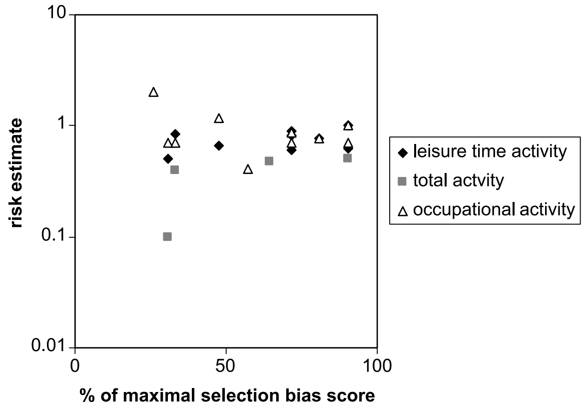

Figure 3. Relation between selection bias score and magnitude of the association between physical activity and endometrial cancer risk.

found strong evidence for an inverse association between physical activity and endometrial cancer risk. The pooled estimate of seven high-quality cohort studies showed a statistically significantly decreased risk of endometrial cancer (OR, 0.77; 95% CI, 0.70-0.85) for the most active women compared with the least active women. We found some evidence that study quality was inversely associated with the estimated magnitude of the risk reduction, particularly with regard to selection bias in case-control studies. Therefore, several more high-quality cohort studies are needed for a definitive conclusion on the association between physical activity and endometrial cancer risk.

Most of the studies included in this review controlled for confounding factors to some extent. On the other hand, neither cohort nor case-control studies scored very favorably on study quality with respect to confounding. The incomplete assessment of confounders does not automatically imply, however, that the results of the included studies are biased. In those studies that adequately adjusted for potential confounders and reported both adjusted and unadjusted risk estimates, the magnitude of the risk estimates did not materially change by adjusting for confounding factors. An important issue with respect to confounding is the role of BMI. Body weight or BMI could be in the causal pathway between physical activity and endometrial cancer risk (i.e., hypothetically, the apparently protective effect from physical activity might be wholly due to a lower body weight in physically active women). If this is the case, adding BMI as a confounding factor to the regression models would strongly attenuate the effect of physical activity. Three of five cohort studies and 6 of 13 case-control studies specifically reported on the effect of adding BMI to the model adjusted for other confounding factors. Most studies found only slightly attenuated risk estimates, providing evidence that physical activity is associated with lower endometrial cancer risk independently of BMI. Furthermore, no convincing evidence was found for differences in the association between physical activity and endometrial cancer risk after stratification for BMI.

This review shows that only few studies assessed total physical activity. All four studies that assessed both total physical activity and leisure time activity found that the association with endometrial cancer risk was stronger for total than for leisure time activity. Overall, the evidence was less consistent for occupational activity than for total and leisure time activities. Most studies on occupational activity used crude methods for exposure assessment (i.e., job title) and a large number of women were not, or only shortly, engaged in paid employment. This may have resulted in errors in the measurement of physical activity and consequently risk estimation for risk of endometrial cancer. Although leisure time activity has become more important in Western countries and may reflect an individual's total physical activity level in most societies, this assumption does not hold for all populations. Therefore, future studies should aim at measuring both total and leisure time activities, and special attention should be paid to household activities.

Several issues have not received sufficient attention in the epidemiologic studies thus far. Some studies have used very rough assessments of physical activity, without specifically taking into account the frequency, duration, and intensity of physical activities, and the different periods in life during which activity patterns may have changed. In addition, the association of physical activity and premenopausal endometrial cancer risk has been insufficiently studied. Future epidemiologic studies will need to address these issues to specify the association between physical activity and endometrial cancer risk.

The mechanisms by which physical activity may protect against endometrial cancer are not fully understood. Obesity is one of the main risk factors for endometrial cancer and is estimated to account for ~40% of endometrial cancer incidence in Europe (29). Although lack of physical activity is known to be associated with an increased risk of obesity (30, 31), the studies described in this systematic review show that physical activity is associated with a decreased risk of endometrial cancer in both normal weight and obese women. The combined effects of endogenous hormones, such as sex steroid hormones, insulin, and insulin-like growth factor-I, are also known to play an important role in the development of endometrial cancer, and may well relate to the mechanism underlying the effect of physical activity on endometrial cancer risk (32). Many of the effects of known risk factors for endometrial cancer can be explained by the unopposed estrogen hypothesis (2). This hypothesis proposes that endometrial cancer risk is increased in women who have high plasma bioavailable estrogens insufficiently counterbalanced by progesterone, which would result in stimulation of proliferation and induction of genetic damage in endometrial cells (2, 33). Both hormones also affect levels of insulin-like growth factor-I, possibly in opposite directions. Hyperinsulinemia is also associated with increased risk of endometrial cancer (34, 35). Although the effects of physical activity on insulin-like growth factor-I are unclear (36), physical activity is known to decrease the levels of serum estrogens (37) and serum insulin (38).

In conclusion, physical activity seems to be associated with a significant reduction in the risk of endometrial cancer. However, the number of high-quality prospective cohort studies is still limited. Based on 20 observational studies, evidence suggests that physical activity is associated with a 20% to 40% decreased risk of endometrial cancer. Further studies are needed to assess which aspects (i.e., frequency, intensity, duration) of physical activity are most strongly

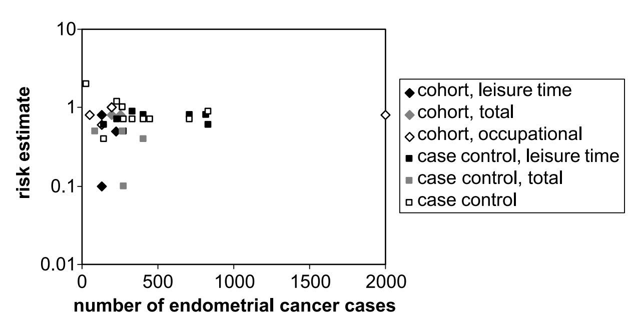

Figure 4. Funnel plot of cohort and case-control studies, relating study size to magnitude of the risk estimate. One cohort study (Moradi et al.) includes 5,287 cases, but is depicted at 2,000 for presentation purposes.

related to the risk of endometrial cancer; which amount of physical activity is necessary; and in which period of life physical activity contributes most to the risk reduction. Both observational epidemiologic studies, preferably prospective in design, and intervention studies should be designed to examine interactive effects of physical activity, diet, and body weight. Intervention studies should help elucidate the causal pathway through which these effects occur.

Appendix A

Methodologic quality score—cohort and case-control studies

Criteria	Score	Comments
Selection bias		
1a. Percentage loss to follow-up? Only applicable to cohort studies		
>20% or unknown or unclassifiable	0	The percentage is unclassifiable if the total eligible cohort is not clear.
5-20%	4	
<5%	8	
1b. Percentage response of the cases and controls? *Only applicable to case-control studies*		
<75% or unknown or unclassifiable	0	Response = [1 − (refusal of subject/physician, contact problems, death before interview) / eligible subjects) × 100. Judging the response of cases and controls, the lowest percentage counts. Unclassifiable if the complete eligible group is not clear.
75-90%	4	
>90%	8	
2. Was the absolute difference in percentage response <20% between cases and controls?		
Not applicable (cohort study)	10	
No or unknown	0	
Yes	6	
3. Percentage incident cases?		
<75%	0	Some studies include prevalent and/or fatal cases without information about the date of diagnosis, which may introduce bias, as physical activity may also be associated with survival.
75-99% or unknown	4	
100%	7	
4. Did the cases and controls originate from the same source population?		
Not applicable (cohort study)	10	
No or unknown	0	
Yes	10	
5. Were the same exclusion/inclusion criteria applied to cases and controls?		
Not applicable (cohort study)	7	
No or unknown	0	
Yes	7	
Maximal selection bias score	42	
Misclassification bias		
Determination of physical activity		
6. Was the measure of leisure time activities that was analyzed complete enough?		
No	0	Activity may have been assessed extensively whereas only few components where included in the analysis. Judgement of the item was based on reviewers' consensus.
Yes	4	
7. Was total activity assessed?		
No	0	Total activity means leisure time activity and job/household activity. These should be combined in one effect measure.
Yes	4	
8. Did the measure of physical activity include intensity, frequency and duration?		
One component or unknown	0	
Intensity + frequency/duration per week	5	
9. Type of administration of physical activity questionnaire		
By proxy	0	By proxy means that physical activity is not individually assessed (e.g., a family member was asked); classification was based on college registration of athletics.
Self-administered	3	
Interview-administered	4	
10. Was the operationalization of the physical activity score understandable?		
No or partly	0	
Yes	2	
11. Did the physical activity measure include past physical activity?		
No, only recent	0	A physical activity measure covering more periods of life is supposed to be more accurate.
Yes, more life periods	4	

Appendix A. (Cont'd)

Methodologic quality score—cohort and case-control studies

Criteria	Score	Comments
12. Did the authors consider changes over time in physical activity pattern in the analyses?		
No	0	Yes: e.g., when two measurements of physical activity several years apart were used to classify participants in consistently active or inactive.
Yes		
13. Was the physical activity questionnaire validated or was reliability tested?		
No or unknown	0	
Yes	2	
14. Was physical activity level assessed before endometrial cancer diagnosis?	0	
No, but physical activity level was assessed the same way for cases and controls	4	When physical activity is measured after the diagnosis of endometrial cancer, there is a possibility of recall bias.
Yes	7	
Outcome		
15. Was the case diagnosis valid?	0	Endometrial cancer self-report may be valid, especially if confirmed by medical report.
No or unknown		
Yes	4	
16. Could benign endometrial disease (carcinoma *in situ*) in any way have influenced the results?		
Yes or unknown	0	Any influence seems unlikely if <5% of cases have carcinoma *in situ* and/or if separate analyses/exclusion did not result in different estimates.
No	2	
Maximal misclassification bias score	42	
17. Were confounders adjusted for in a correct way (statistically)?		
No or unknown	0	
Yes	4	
18. Could residual confounding be a problem?		
Yes	0	Potential confounders: age, BMI, parity, age at menopause (and/or smoking), oral contraceptive use, hormone replacement therapy; Residual confounding could also be a problem when (*a*) continuous variables were crudely categorized or (*b*) BMI or hormone replacement therapy were not measured within 5 y of diagnosis.
Partly	4	
No	9	
19. Were the effects of leisure time activities adjusted for occupational/household activities?		
No or unknown	0	
Yes	8	
Maximal confounding bias score	21	

Maximal total score: 105

Patients and controls are not from the same source populations when:

- hospital-based controls are used and it is unlikely that the controls would be referred to the same hospital in case of cancer;
- cases are recruited from a specialized cancer hospital (e.g., subgroup of patients with more advanced disease) and controls are population based and it is quite uncertain whether they would be referred to the same hospital if they had become a case;
- controls are not a random sample of the source population;
- cases and controls are selected from different areas/countries.

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Appendix B. Levels of Evidence for an Inverse Association between Physical Activity and Endometrial Cancer Risk

Level of evidence	Study results[(a)]
Strong evidence for an inverse association	≥75% of all high-quality studies[(b)] reporting a decreased risk,[(c)] or ≥60-75% of all high-quality studies reporting a decreased risk and <10% of all high-quality studies reporting an increased risk[(c)]
Moderate evidence for an inverse association	≥60-75% of high-quality studies reporting a decreased risk and <25% of all high-quality studies reporting an increased risk, or ≥50-60% of all high-quality studies reporting a decreased risk and <10% of all high-quality studies reporting an increased risk
Indecisive evidence	inconsistent findings defined as all other findings not applicable to strong, moderate or no evidence for an inverse association, or there are <4 high-quality studies available
Nil	≥60% of all high-quality studies reporting no association or an increased risk, or ≥40% of all high-quality studies reporting an increased risk

(a) At least four studies are necessary to define the evidence as strong, moderate, or no evidence. When less than four studies are available, the evidence will be defined as inconclusive.

(b) A high-quality study was defined as a study with a total quality score above the median quality score of all studies (i.e., >60.5% of the maximal attainable score).

(c) A decreased risk was defined as a risk estimate of <0.80 for the highest versus the lowest level of activity; no association as a risk estimate between 0.8 and 1.25; and an increased risk as a risk estimate >1.25.

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