Cancer Epidemiology, Biomarkers & Prevention

Review

Physical Activity and Risk of Lymphoma: A Meta-Analysis

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Abstract

Background: Physical activity has a protective effect on some types of cancer. The aim of the present meta-analysis was to explore the literature on the association between physical activity and risk of lymphoma.

Methods: A meta-analysis was conducted for cohort and case–control studies examining the association between self-reported physical activity and risk of lymphoma. Depending on statistical heterogeneity, a random or fixed effects model was used to estimate the summary OR and corresponding 95% confidence interval (CI).

Results: Seven case–control studies and 5 cohort studies were included. When data from both study designs were combined, no significant influence of physical activity on risk of lymphoma was found (pooled OR = 0.90; 95% CI: 0.79–1.02; $P = 0.10$). Subgroup analysis revealed a significant protective influence of physical activity on risk of lymphoma in case–control studies (pooled OR = 0.81; 95% CI: 0.68–0.96; $P = 0.02$). In contrast, cohort studies, which have a higher level of evidence than case–control studies, confirm the results of the primary meta-analysis (pooled OR = 1.02; 95% CI: 0.88–1.19; $P = 0.76$). A subsequent subgroup analysis found no significant differences between results for Hodgkin lymphoma and non-Hodgkin lymphoma ($\chi^2 = 0.16$; $P = 0.69$), nor between results for recreational and occupational activities ($\chi^2 = 1.01$; $P = 0.31$).

Conclusions: Epidemiologic research indicates no significant influence of physical activity on risk of lymphoma.

Impact: Future research should examine the association between sedentary behavior and risk of lymphoma and investigate the dose–response and timing effect of physical activity on risk of lymphoma. *Cancer Epidemiol Biomarkers Prev; 22(7); 1173–84. ©2013 AACR.*

Introduction

Cancer is a leading cause of disease and death worldwide. In total, 7.6 million cancer deaths occurred in 2008, accounting for about 13% of all deaths (1, 2). Lymphomas are part of the hematologic cancers, arising in the lymph nodes and tissues of the body's immune system and comprising several subtypes with varied biologic and clinical features (3). The main subdivision is made between Hodgkin lymphoma and non-Hodgkin lymphoma. In 2008, about 67.000 new Hodgkin lymphoma cases and 355.000 new non-Hodgkin lymphoma cases occurred worldwide, accounting for 0.5 and 2.8% of all new cancer cases, respectively. Similar percentages were found for mortality in Hodgkin lymphoma and non-Hodgkin lymphoma worldwide in 2008: 0.4% of all cancer deaths were attributed to Hodgkin lymphoma and 2.5% to non-Hodgkin lymphoma (2, 4). In general, the incidence of lymphoma is rising in the last decades (5–7). As a consequence, more emphasis is given to implement evidence-based strategies for lymphoma prevention. To set up strategies for lymphoma prevention, understanding the modifiable risk factors for lymphoma is critical. Physical inactivity has recently received much attention as modifiable risk factor. It is well known that physical activity is effective in preventing and modifying chronic diseases, such as osteoporosis (8), obesity (9), type II diabetes (9, 10), dementia (11), hypertension (12), metabolic syndrome (13), cardiovascular (14), and respiratory diseases (15). Since the last decades, evidence is growing that physical activity also reduces the risk of some types of cancer. Evidence is convincing for a positive influence of physical activity on risk of colon (16), breast (17, 18), and endometrial cancer (19). Inconsistent evidence is found for lung (20), prostate (21), and ovarian cancer (22) with at least one-third of the studies indicating a protective effect of physical activity on risk (23). For breast, ovarian, and lung cancer, the effect seems stronger for recreational than occupational physical activity (20, 22, 24). Recently, studies were conducted to examine the association between physical activity and lymphoma. The aim of the present meta-analysis was to explore the literature on the relationship between physical activity and the risk of lymphoma.

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Materials and Methods

Search strategy and selection criteria

A search was conducted by one reviewer (N. Vermaete) in PubMed, Cochrane, PEDro, Embase, CINAHL, and Web of science up to 8 January 2013. In PubMed, Cochrane, Embase, CINAHL, and Web of Science, the following combination of key words was used: "(lymphoma OR Hodgkin) and risk ("physical activity" OR "physical fitness" OR exercise OR "cardiorespiratory fitness")". In PubMed, no limits were used. "Title" was used as field limit in Cochrane, Embase, and Web of Science, whereas "abstract" was used as field limit in CINAHL. In PEDro, only "lymphoma" was used as key word, without limits. Titles and abstracts were screened on content. For relevant articles, the full text was used. The reference lists of all selected articles were also screened for additional papers. No restrictions in date of publication, language, and group size were used. Furthermore, no restrictions in methods to assess physical activity were used. Articles with participants younger than 18 or childhood cancer were excluded. Articles were included if they met following criteria: (i) case–control or cohort study, (ii) reporting a risk estimate and corresponding SE of the relationship between recreational, occupational, or overall physical activity and lymphoma.

Data extraction and assessment of study quality

For each article, information was extracted on the study design, sample size, number of cases, gender, study region, age, physical activity domain, assessment of physical activity, timing in life of physical activity, definition of highest/lowest activity level, and adjustment for confounding factors. Methodologic quality of each study was assessed using a quality score system that was partly adopted from Monninkhof and colleagues (Supplementary Table; ref. 18). Item 12 (considering changes over time) and item 16 (influence of ductal carcinoma *in situ*) from the original quality score system were excluded, because these items were not relevant for this meta-analysis. Quality assessment was conducted independently by 2 reviewers (N. Vermaete and L. Schepers). An interrater reliability analysis using the Kappa statistic was conducted in SPSS (version 19) to determine consistency among raters. Disagreements were resolved by discussion. An independent samples *t* test was conducted in SPSS (version 19) to examine the difference in quality score between case–control and prospective cohort studies.

Analysis

The summary odds ratio (OR) and corresponding 95% confidence interval (CI) was estimated to assess the association between physical activity and risk of lymphoma, comparing highest activity level to lowest activity level. For studies reporting an OR with highest activity level as reference instead of lowest activity level, the inverse of the reported OR was used. The most adjusted risk estimate reported in each study was used. If effect estimates for physical activity were reported for more than one-life period, the most recent data were used, as most studies reported recent physical activity. If a study reported risk estimates for men and women separately, both results were included in the analysis. Statistical heterogeneity between studies was determined by using the Q and I^2 statistics (25). For the Q-statistic, a P-value below 0.05 indicates statistical heterogeneity. For the I^2 statistic, Higgins and colleagues tentatively assigned adjectives of low, moderate, and high to I^2 values of 25%, 50%, and 75% (25). In this meta-analysis, statistical heterogeneity was defined as a P-value below 0.05 for the Q-statistics or an I^2 value above 50%. When there was a discrepancy in the result for heterogeneity between both tests, the result of the I^2 value was chosen. Depending on statistical heterogeneity, a random or fixed effects model was used to estimate the summary OR and corresponding 95% CI. As randomized controlled trials are not available for this research question, it is inevitable to rely on study designs with less evidential value. In the primary analysis, case–control and prospective cohort studies were combined. The reported risk estimates for the association between total physical activity and risk of lymphoma were used in the primary analysis. For studies reporting only results for recreational or occupational physical activity, these results were included in the analysis. For studies reporting separate results for occupational and recreational physical activity, but no result for total physical activity, the results for recreational physical activity were used. It has been suggested that recreational physical activity is the major modifiable component of energy expenditure (26). Three subgroup analyses were conducted: one for study design (case–control and prospective cohort studies), one for type of lymphoma (Hodgkin lymphoma and non-Hodgkin lymphoma) and one for physical activity domain (recreational and occupational physical activity). All analyses were conducted with Review Manager version 5 (27)

Results

Study selection

The flowchart of the selection of articles is provided in Fig. 1. The literature search resulted in a total of 148 references. After reading of title, abstract, and eventually full text, 10 studies were retained. After screening of the reference lists of the selected articles, 2 more articles were included (28, 29). This resulted in a total of 12 selected publications.

Study characteristics

The main characteristics of the 7 case–control studies and the 5 prospective cohort studies are summarized in Table 1. The 7 case–control studies included a total of 5,229 non-Hodgkin lymphoma cases, 366 Hodgkin lymphoma cases, and 26,403 control subjects (28, 30–35). In the 5 prospective cohort studies, a total of 5,858 non-Hodgkin lymphoma cases and 58 Hodgkin lymphoma

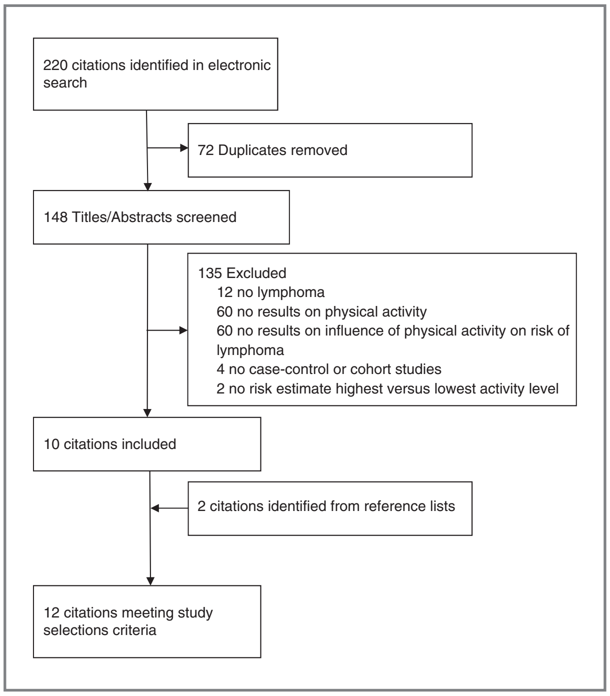

Figure 1. Flow chart of selection.

cases were identified among a total of 3,154,781 subjects (29, 36–39). Two studies involved only men (28, 34) and 3 involved only women (33, 37, 39). Seven studies involved both men and women with 5 studies reporting gender-specific results (30, 32, 35, 36, 38) and 2 reporting results for both genders combined (29, 31). Eight studies reported on recreational physical activity (31–34, 36–39), 5 studies on occupational physical activity (28, 30, 31, 34, 36), and 4 studies on total physical activity (29, 34–36). All studies used a self-reported instrument to assess physical activity. Considerable variation between studies was found with respect to the instrument used to assess physical activity, the definition of "highest activity" and "lowest activity" level and the adjustment for confounding factors.

Quality score

The total quality score, as percentage of the maximal score for cohort and case–control studies combined, ranged between 42% and 82% (median 62%). For the 5 cohort studies, the quality score ranged between 69% and 82% (median 75%), which is statistically significantly higher ($P = 0.001$) than the quality score of the 7 case–control studies, with scores ranging between 42% and 63% (median 57%; Table 2). Cohen Kappa for interrater reliability equaled 0.823 (95% CI: 0.762–0.884; $P < 0.01$).

Primary meta-analysis

The 5 cohort studies and the 7 case–control studies were included in the primary meta-analysis. Five studies reported a risk estimate for men and women separately (30, 32, 35, 36, 38), 2 studies reported results for Hodgkin lymphoma and non-Hodgkin lymphoma separately (29, 34), and 1 study reported results for 2 separate age groups (33). Consequently, 20 studied groups were included in the primary meta-analysis. The Q-statistic showed significant heterogeneity between study results ($P < 0.01$; $I^2 = 59\%$). The random effects meta-analysis found no significant influence of physical activity on risk of lymphoma (pooled OR = 0.90; 95% CI = 0.79–1.02; P = 0.10, Fig. 2 and Table 3).

Subgroup meta-analyses

Table 3 and Supplementary Fig. S1 show the sensitivity analysis of study design (prospective cohort studies versus case–control studies). The summary risk estimate derived from the cohort studies showed no significant influence of physical activity on risk of lymphoma (OR = 1.02; 95% CI: 0.88–1.19; $P = 0.76$). In contrast, the results from the fixed effects meta-analysis in the case–control studies showed a significant protective influence of physical activity on risk of lymphoma (OR = 0.81; 95% CI: 0.72–0.91; $P = 0.0006$).

Table 3 and Supplementary Fig. S2 show the sensitivity analysis of type of lymphoma (Hodgkin lymphoma vs. non-Hodgkin lymphoma). The random effects of meta-analysis showed no significant influence of physical activity on risk of Hodgkin lymphoma or on risk of non-Hodgkin lymphoma (OR = 0.82; 95% CI: 0.47–1.42; P = 0.47 and OR = 0.92; 95% CI: 0.81–1.04; $P = 0.19$, respectively).

Table 3 and Supplementary Fig. S3 show the sensitivity analysis of physical activity domain (recreational physical activity vs. occupational physical activity). The meta-analysis showed no significant influence of recreational (random effects model) nor of occupational physical activity (fixed effects model) on risk of lymphoma (OR = 0.86; 95% CI: 0.73–1.02; $P = 0.08$ and OR = 0.98; 95% CI: 0.80–1.21; $P = 0.88$, respectively).

Discussion

The aim of the present meta-analysis was to explore the literature on the relationship between physical activity and risk of lymphoma. Seven case–control studies and 5 cohort studies were included. The primary meta-analysis found no significant effect of physical activity on risk of lymphoma. Subgroup analysis for study design showed no significant influence of physical activity on risk of lymphoma in cohort studies and a significant risk reduction in case–control studies. However, the level of evidence generated by case–control studies is considerably less than that by prospective cohort studies, according to the Centre for Evidence-Based Medicine (40). Bias is less of concern in prospective cohort studies than in case–control studies, because classification of exposure is made independently of knowledge about the subject's disease status (41). As a consequence, the outcomes of prospective cohort studies should take priority in determining the relevance of our study outcomes. The results of the cohort

Table 1. Characteristics of included studies

Reference	Study design, *N*	Study region	Mean age (SD)	Physical activity domain	Assessment of physical activity	Timing in life of physical activity	Definition of highest/lowest activity level	Adjustment
Brownson and colleagues, 1991 (28)	Case–control in men 536 non-Hodgkin lymphoma 16,611 controls (other cancer type).	US (Missouri)	20 years or older at time of diagnosis (mean age not reported)	Occupational	Recorded by hospital registrars using a standardized protocol. The classification scheme of Garabrant and colleagues (50) with modifications from Missouri work requirements (49) was used to categorize occupations according to the level of physical activity	At the time of diagnosis	Physical activity required > 80% of the time versus < 20% of the time	Age, smoking
Zahm and colleagues, 1999 (30)	Case—control 1,177 non-Hodgkin lymphoma (993 M) 3,625 controls (2,918 M)	US (Iowa, Kansas, Minnesota and Nebraska)	20–75+	Occupational	Interview. Occupational job titles were coded with the 1977 Standard Occupational Classification system (51) and the 1977 Dictionary of Occupational Titles (52)	Usual occupation	Energy expenditure > 12 kJ/min versus < 8 kJ/min for men and > 8 kJ/min versus < 5 kJ/min for women	Age, state of residence
Cerhan and colleagues, 2005 (31)	Case—control 1,321 non-Hodgkin lymphoma (571 M) 1,057 controls (550 M)	US (Detroit, Iowa, Los Angeles and Seattle)	58.1 (range 20–74)	Recreational	Four self-administered questions, including one on household activity, one on moderate physical activity and one on vigorous physical activity	Before one year	> 1,080 Mets/wk versus < 30 Mets/wk	Age, gender, race, study center
				Occupational	Four self-administered questions, including one question on occupational physical activity	Before one year	Time at work characterized by mostly manual labor or exercise versus mostly sit	
Pan and colleagues, 2005 (32)	Case–control 1,030 non-Hodgkin lymphoma (569 M) 3,106 controls (1,642 M)	Canada	Cases: 58.9 (8.01) Controls: 59.6 (7.91)	Recreational	Self-administered questionnaire about recreational physical activity 2 years before interview, investigator-designed	2 years before interview	≥37.4 Met-h/wk versus <6.4 Met-h/wk	Age, province, education, pak-years of smoking, acohol drinking, exposure to some chemicals, occupational exposure, BMI, total calorie intake

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Table 1. Characteristics of included studies (Cont'd)

Reference	Study design, *N*	Study region	Mean age (SD)	Physical activity domain	Assessment of physical activity	Timing in life of physical activity	Definition of highest/lowest activity level	Adjustment
Keegan and colleagues, 2006 (33)	Case-control in women 312 Hodgkin lymphoma 325 controls	US (Greater Bay Area of northern California)	15–79	Recreational	Interview about participating in strenuous physical activity or sports. Questions were taken from an instrument used by the Collega Alumni Health Study (53)	The past year	Strenuous physical activity at least twice a week for $\geq$1 months: yes versus no	Age, race/ethnicity, education, Jewish bringing-up, single room at age 11, living in a single family home at age 8, number of miscarriages, smoking status 1 year before interview, history of first or second degree relative with lymphoma, having ever nursed children
Lim and colleagues, 2007 (29)	Cohort 285,079 M 188,905 F 58 Hodgkin lymphoma, 1,381 non-Hodgkin lymphoma	US (California, Florida, Louisiana, New Jersey, North Carolina, Pennsylvania, Atlanta, Detroit)	50–71	Total	Self-administered questionnaire: frequency of activities that lasted at least 20 minutes and caused breathing or heart rate increase or sweating	At time of enrolment	3–4 times/wk versus < 1/wk	Age, gender, race, education, BMI and caloric intake
Lu and colleagues, 2009 (39)	Cohort 121,216 F 574 B-cel non-Hodgkin lymphoma cases	US (California)	range: 19–79	Recreational	Self-administered questionnaire about strenuous and moderate recreational physical activity, investigator-designed	The past 3 years	$\geq$4 h/wk/year versus 0–0.5 h/wk/year	Height, weight, age at menarche
Van Veldhoven and colleagues, 2010 (36)	Cohort 127,353 M 216,403 F 778 non-Hodgkin lymphoma cases	Europe (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom)	M: 52.9 (9.8) F: 51 (10.9)	Total	A total physical activity index created by Friedenreich and colleagues, based on four self-administered or interview-based question about occupational, household and recreational physical activity during the past year, derived from development work undertaken in the Netherlands. Validated and repeatable index (54).	At the time of enrolment	Very high recreational physical activity ($\geq$45.75 Met-h.wk^{-1}) in combination with (heavy) manual work or standing occupation versus low or medium recreational physical activity (<27.75 Met-hr.wk^{-1}) in combination with sedentary or unknown occupation	Age, hypertension, hyperlipidaemia, education, diabetes

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Table 1. Characteristics of included studies (Cont'd)

Reference	Study design, *N*	Study region	Mean age (SD)	Physical activity domain	Assessment of physical activity	Timing in life of physical activity	Definition of highest/lowest activity level	Adjustment
				Recreational	Four self-administered or interview-based question about occupational, household and recreational physical activity during the past year, derived from development work undertaken in the Netherlands.		≥45.75 Met-h/wk versus < 14.25 Met-hr/wk	
				Occupational	Four self-administered or interview-based question about occupational, household and recreational physical activity during the past year, derived from development work undertaken in the Netherlands.		(Heavy) manual versus sedentary occupation	
Kabat and colleagues, 2011 (37)	Cohort 158,975 F 1,123 non-Hodgkin lymphoma cases	United States	63.2 (7.2)	Recreational	Self-administered questionnaire about the usual pattern of activity	At the time of enrollment	≥17.5 Met-h/wk versus <1.6 Met-hr/wk	Age, pack-years of smoking, servings of alcohol per week, education, BMI, ethnicity
Parent and colleagues, 2011 (34)	Case-control in men 215 non-Hodgkin lymphoma, 54 Hodgkin lymphoma 533 controls	Canada (Montreal)	Cases: 58.9 (8.01) Controls: 59.6 (7.91)	Total	Interview about occupational and recreational physical activity	During adult life	Intermediate level of occupational physical activity [<75% of work years spent in very active (≥4 Mets) or sedentary jobs (≤1.5 Mets)] with recreational activities, or at the high occupational physical activity level (≥75% of work years spent in very active jobs, ≥4 Mets) with or without recreational physical activity versus low occupational physical activity level (>75% of	Age, socio-economic status, educational level, ethnicity, respondent status, smoking BMI

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Table 1. Characteristics of included studies (Cont'd)

Reference	Study design, *N*	Study region	Mean age (SD)	Physical activity domain	Assessment of physical activity	Timing in life of physical activity	Definition of highest/lowest activity level	Adjustment
							work years spent in sedentary jobs (≤1.5 Mets) or intermediate occupational physical activity level without recreational physical activity	
				Recreational	Interview about recreational physical activity	During adult life	Sports and/or outdoor activities on average once a week or more for at least 6 months: yes versus no	
				Occupational	Interview about occupational physical activity	During adult life	At least 75% of work years spent in very active jobs (4 MetS or more) versus at least 75% of work years spent in sedentary jobs (≤1.5 Mets)	
Teras and colleagues, 2012 (38)	Cohort 69,849 M 77,001 F 2,002 non-Hodgkin lymphoma cases	21 states of America	62.9 (6.4)	Recreational	Self-administered question about the frequency of several leisure-time activities	The past year	≥17.5 Met-h/wk versus 0–7 Met-hr/wk	Age, family history of hematopoietic cancer, education, smoking status, alcohol intake, BMI, height
Kelly and colleagues, 2012 (35)	Case–control 950 non-Hodgkin lymphoma (550 M) 1,146 (611 M)	US (Minnesota)	Median: 63	Total	Self-administered questions on duration and frequency of walking, mild, moderate, and strenuous physical activity 2 years before case diagnosis or control selection	2 years before case diagnosis or control selection	>2,701 Mets/wk versus < 615 Mets/wk	Age, gender, county of residence

Abbreviations: BMI, body mass index; F, female; kJ, kilojoule; M; male; MET, metabolic equivalent (3.5 mlO_2/kg/min).

Table 2. Quality score of included studies

Reference	Study design[b]	Item number[a] 1	2	3	4	5	6	7	8	9	10	11	13	14	15	17	18	19	Total	Percentage
Brownson and colleagues, 1991 (28)	B	0	0	7	10	7	0	0	0	0	2	0	0	4	4	4	4	0	42	42.4
Zahm and colleagues, 1999 (30)	B	4	6	7	10	0	0	0	0	0	0	4	0	4	4	4	4	0	47	47.5
Cerhan and colleagues, 2005 (31)	B	0	6	7	10	7	0	0	5	3	2	0	0	4	4	4	4	0	56	56.6
Pan and colleagues, 2005 (32)	B	0	6	7	10	7	4	0	5	3	2	0	0	4	4	4	4	0	60	60.6
Keegan and colleagues, 2006 (33)	B	0	6	7	10	0	0	0	0	4	2	4	0	4	4	4	4	0	49	49.5
Lim and colleagues, 2007 (29)	A	8	10	7	10	7	0	4	0	3	2	4	0	7	4	4	4	0	74	74.7
Lu and colleagues, 2009 (39)	A	8	10	7	10	7	0	0	0	3	0	4	0	7	4	4	4	0	68	68.7
Van Veldhoven and colleagues, 2010 (36)	A	8	10	7	10	7	4	4	5	3	2	0	2	7	4	4	4	0	81	81.8
Kabat and colleagues, 2011 (37)	A	8	10	7	10	7	4	0	5	3	2	0	0	7	4	4	4	0	75	75.8
Parent and colleagues, 2011 (34)	B	0	6	7	10	0	0	4	0	4	2	4	0	4	4	4	4	8	61	61.6
Teras and colleagues, 2012 (38)	A	4	10	7	10	7	4	0	5	3	2	0	0	7	4	4	4	0	71	71.7
Kelly and colleagues, 2012 (35)	B	0	6	7	10	7	0	4	5	3	0	4	0	4	4	4	4	0	62	62.6

[a]The item numbers refer to the item numbers in the original Quality Score System developed by Monninkhof and colleagues (18).
[b]A, prospective cohort study; B, case–control study.

studies confirm the results of the primary meta-analysis. Subgroup analysis for lymphoma type revealed no significant differences between results found in Hodgkin lymphoma and results found in non-Hodgkin lymphoma. Similarly, subgroup analysis for the physical activity domain also revealed no significant differences between recreational and occupational activity. This conclusion was also reached in meta-analyses examining the association between physical activity and risk of endometrial (42), prostate (21), and colorectal cancer risk (43, 44).

In general, reporting of observational biomedical research is often inadequate. Therefore, the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement has been established (45). The quality score system used in this meta-analysis is consistent with these guidelines, although it does not cover all 22 items of the STROBE statement. The methodologic quality of the included studies varied. Inherent to the study design, the methodologic quality of the cohort studies was higher than that in the case–control studies. Some studies were of low quality, especially regarding the assessment of physical activity. Although a positive evolution could be expected as the establishment of the STROBE statement, no clear evolution in methodological

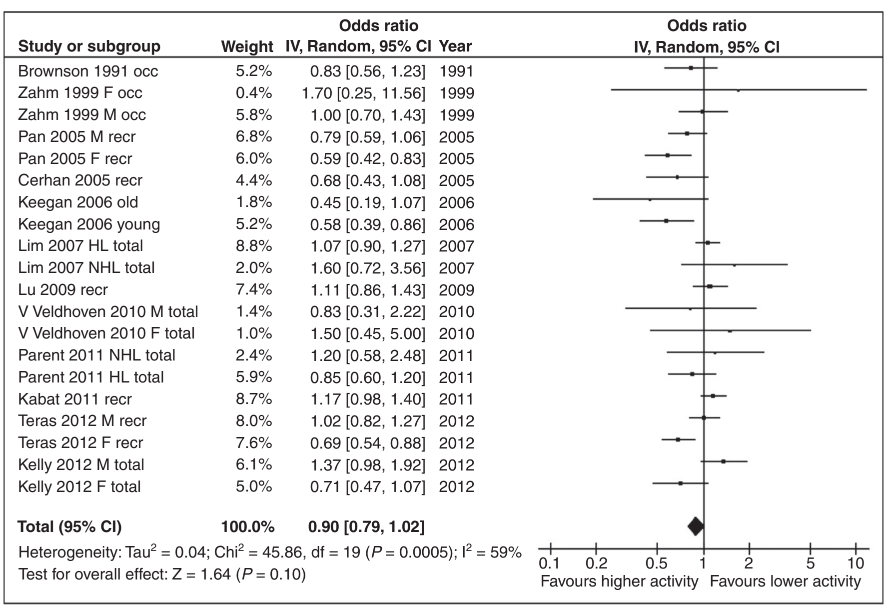

Figure 2. Primary meta-analysis: random-effects meta-analysis of the influence of physical activity on risk lymphoma. Abbreviations: F, women; M, men; occ, occupational; recr, recreational.

Table 3. Summary of results from the primary random-effects meta-analysis and the subgroup random-effects meta-analyses

	Amount of studies	OR (95% CI)	I^2	*P*
Primary meta-analysis	12	0.90 (0.79–1.02)	59%	0.10
Subgroup meta-analysis				
Study design				
Cohort studies	5	1.02 (0.88–1.19)	52%	0.76
Case–control	7	0.81 (0.68–0.96)	49%	**0.02**
Subgroup differences		–	76%	**0.04**
Type of lymphoma				
Hodgkin lymphoma	3	0.82 (0.47–1.42)	63%	0.47
Non-Hodgkin lymphoma	11	0.92 (0.81–1.04)	57%	0.19
Subgroup differences		–	0%	0.69
Physical activity domain				
Recreational	8	0.86 (0.73–1.02)	65%	0.08
Occupational	6	0.98 (0.80–1.21)	0%	0.88
Subgroup differences		–	1.1%	0.31

NOTE: Bold values indicate $P < 0.05$.

quality was observed over time. Another limitation in this meta-analysis is the methodologic and statistical heterogeneity between studies. As a consequence, the conclusion of the present meta-analysis indicating that physical activity has no effect on the risk of lymphoma, should be interpreted with caution.

Assessment of physical activity

Several methods exist to assess physical activity, with remarkable differences in validity and reliability. The two most widely used methods are objective assessment by an accelerometer and subjective self-reported assessment by a self-reported questionnaire (46). Accelerometers are more accurate than self-reported instruments, give information on the total amount, intensity, duration, and frequency of physical activity and are sufficiently sensitive to detect small movements. Disadvantages of accelerometers are the higher cost and need for additional hardware/software and technical expertise (46, 47). All 12 studies included in this meta-analysis used a self-reported instrument. Advantages of this method are that questionnaires are inexpensive, relatively reliable, and applicable in large populations (47). There are, however, also considerable limitations, including recall error, overreporting, lack of accuracy, specific focus on activities with moderate-to-vigorous intensity (46, 47), and thus a wide range of reliability and validity (48). Half of the included studies in this meta-analysis used global assessments of physical activity, without specifically considering the frequency, duration, and intensity of physical activity (28–30, 33, 34, 39). Two studies administered an investigator-designed instrument (32, 39), 2 studies used an existing classification scheme to categorize occupational activity (28, 30, 49–52), 1 study used an instrument used in a previous study (33, 53), 1 study used 4 questions derived from development work undertaken in The Netherlands (36), and in 6 studies the origin of the self-reported instrument was not reported (29, 31, 34, 35, 37, 38). The "total physical activity" index used in the study of Van Veldhoven and colleagues (36) was shown to be sufficient for ranking or classifying subjects in terms of their physical activity in large-epidemiologic studies (54) but no information was reported on the validity of the assessment of recreational and occupational activity. The validity of the self-reported instruments in the other included studies was unknown.

Level of physical activity

Remarkable differences were found in the definitions of the "highest activity level." For example, in the study of Van Veldhoven and colleagues (36), the highest activity level was defined as 45.74 MET-hours/week or more, whereas the highest activity level was defined as 17.5 MET-hours/week or more in other 2 studies (37, 38). This discrepancy in definition hampered pooling of data and thus the interpretation of the results from different studies. Conversion of the reported physical activity levels in the different studies into 2 categories using a fixed cut-off value was aimed for. The most obvious cut-off value would correspond with the public health guidelines for physical activity defined by the American College of Sports Medicine as engaging in 30 or more minutes per day of at least moderate physical activity on 5 or more days of the week, or more than 150 minutes a week (55). However, it was not possible to convert the results of each study into these dichotomous physical activity categories in an unambiguous way. Therefore, the influence of the level of physical activity on the risk of lymphoma could not be studied in more detail in the present meta-analysis. However, 8 of the included studies examined the presence of dose–response effect of physical activity on risk of lymphoma. Four of the 5 cohort studies (29, 37–39) and 4 of the 7 case–control studies (30–32, 35) reported a test of trend, with 1 cohort study (37) and 3 case–control studies (31, 32, 35) reporting a significant trend. For example, Kelly and colleagues found a significant trend of physical activity on non-Hodgkin lymphoma risk among women ($P_{\text{trend}} = 0.039$), but not among men ($P_{\text{trend}} = 0.15$; ref. 35). In the literature, convincing evidence was found for a significant dose–response effect of decreasing cancer risk with increasing activity levels for colon cancer and breast cancer (23, 56, 57).

In addition, Zahm and colleagues found no significant association between occupational sitting time (sedentary behavior) and non-Hodgkin lymphoma among men and women (30). Teras and colleagues found no significant association between leisure-time sitting and non-Hodgkin lymphoma risk in men, whereas a significant positive association was found between leisure-time sitting and risk of non-Hodgkin lymphoma in women (38). In the literature, sedentary behavior has been shown to be associated with a higher risk of ovarian, endometrial, and colorectal cancer (23, 42, 58).

Timing of physical activity

Evidence for a timing effect of physical activity on risk of cancer was shown for breast cancer, indicating a larger protective effect for physical activity after the age of 50 years than physical activity earlier in life (23, 57, 59). Inconsistent results were found in the 4 studies investigating the effect of physical activity at different age periods on the risk of lymphoma. Lu and colleagues and Lim and colleagues identified no association between physical activity at different life times and lymphoma risk (29, 39). Kabat and colleagues identified a significant association between having engaged in intense physical activity at ages 35 and 50 and non-Hodgkin lymphoma risk, whereas no significant association was found between intense physical activity at age 18 and non-Hodgkin lymphoma risk (37). Keegan and colleagues identified that strenuous physical activity in the year before diagnosis or interview, as well as sports team membership at ages 18 to 22 was significantly associated with Hodgkin lymphoma risk in young adult women, whereas no significant association was found between sports team membership in high school or strenuous physical activity throughout adult life and Hodgkin lymphoma risk (33). Since it was impossible to define 2 different timing groups in an unambiguous way, no subgroup analysis was conducted to investigate the timing effect of physical activity on risk of lymphoma.

Confounding factors

All included studies adjusted the outcome for age. Furthermore, all included studies considered gender either by adjusting for it (29, 31, 35) or by reporting results for men and women separately (28, 30, 32–34, 36–39). Other confounders that were taken into account in some but not all studies include education (7), smoking (6), BMI or weight (5), ethnicity (4), alcohol intake (3), and family history of lymphoma or hematopoietic cancer (3). Further, there were 17 factors taken into account in only 1 study (Table 1). As most studies only reported a maximal adjusted risk estimate and no minimal adjusted risk estimate, it was difficult to investigate the importance of the difference in adjustment for confounding factors. Item 18 of the quality score system questions the possibility of residual confounding. However, to assign a score on this item, it is important to know the potential confounders, or, in other words, the risk factors for lymphoma. Two well-established risk factors for lymphoma are immunosuppression and autoimmune disorders (60, 61). However, none of the included studies in this meta-analysis adjusted for these 2 confounders. Diet is also suggested to influence the risk of non-Hodgkin lymphoma. It has been shown that diary products, meat, and high fat intake are associated with an increased risk of non-Hodgkin lymphoma, whereas whole-grains and vegetables are inversely associated with risk of non-Hodgkin lymphoma (60, 62–64). Although 5 of the included studies adjusted for BMI or weight, none of the included studies adjusted for diet. As no included study adjusted for immunosuppression, autoimmune disorders, or diet, all included studies were assigned a score of 4 on the quality item about possibility of residual confounding. Differences in adjustment for confounding factors between the included studies probably did not play an important role in this meta-analysis, since every study adjusted for age and gender and none of the studies adjusted for immunosuppression, autoimmune disorders, or diet.

Biologic mechanisms

Several biologic mechanisms on how physical activity might reduce the risk of lymphoma were hypothesized in the literature. A first potential mechanism is the exercise-induced enhancement of the immune function by increasing the number and activity of macrophages, natural killer cells, lymphokine-activated killer cells, and regulating cytokines (32, 65). Indeed, there is evidence for elevated lymphoma incidence rates among subjects with immune dysregulation (30, 32, 33, 60, 65). Another possible mechanism is an exercise-induced decrease in insulin, glucose, and insulin-like growth factors (32, 33, 65), which is less favorable to the growth of tumor cells in general (17). Physical activity also prevents obesity and reduces the percentage of body fat (32, 65, 66), which serves as a storage depot for potential carcinogens. A positive association is observed between BMI and risk of lymphoma (60, 67). Finally, physical activity could reduce the risk of lymphoma by improving the antioxidant defense system and anti-inflammatory effects (32, 33, 65).

Limitations

A potential limitation of this meta-analysis is the literature search. It is possible that not all published articles concerning this topic were selected. In an attempt to reduce this limitation, the reference lists of all selected articles were screened. A second possible limitation of this meta-analysis is a publication bias. However, most included studies reported no significant results, whereas in general significant findings are more likely to be published than nonsignificant findings. Therefore, publication bias does probably not play a major role in this meta-analysis. Third, a limitation of the literature is the use of self-reported instruments to assess physical activity, which have several disadvantages compared with objective assessments.

In conclusion, epidemiologic research indicates no significant influence of physical activity on risk of lymphoma. Interesting questions for future research include whether sedentary behavior is associated with the risk of lymphoma, whether there exists a dose–response effect of physical activity on risk of lymphoma, and whether the timing of physical activity (recent physical activity vs. lifetime physical activity) influences the association between physical activity and risk of lymphoma.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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