

Research Article

**Physical Activity in Relation to Risk of Hematologic Cancers:
A Systematic Review and Meta-analysis**

Carmen Jochem, Michael F. Leitzmann, Marlen Keimling, Daniela Schmid, and Gundula Behrens

Abstract

Background: Despite the existence of numerous biologic pathways potentially linking increased physical activity to decreased risk of hematologic cancers, the associations between physical activity and subtype-specific hematologic cancers have not been comprehensively quantified.

Methods: We conducted a systematic review and meta-analysis of physical activity in relation to subtype-specific hematologic cancers. We summarized the data from 23 eligible studies (15 cohort and eight case-control studies) and estimated summary relative risks (RR) and 95% confidence intervals (CI) using random-effects models.

Results: When comparing high versus low physical activity levels, the RR for non-Hodgkin lymphoma was 0.91 (95% CI, 0.82–1.00), for Hodgkin lymphoma it was 0.86 (95% CI, 0.58–1.26), for leukemia it was 0.97 (95% CI, 0.84–1.13), and for multiple myeloma it was 0.86 (95% CI, 0.68–1.09). When focusing on subtypes of non-Hodgkin lymphoma, the RR for diffuse large B-cell lymphoma was 0.95 (95% CI, 0.80–1.14) and for follicular lymphoma it was 1.01 (95% CI, 0.83–1.22). In an exploratory analysis combining all hematologic cancers, high versus low physical activity levels yielded a statistically significant RR of 0.93 (95% CI, 0.88–0.99).

Conclusions: Physical activity showed statistically nonsignificant associations with risks of non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, and leukemia. These findings may not represent a true lack of associations given the variation in high versus low physical activity definitions, the quality of physical activity assessments, and the variability in hematologic cancer classification schemes in individual studies.

Impact: Physical activity is unrelated to risks of subtype-specific hematologic cancers. *Cancer Epidemiol Biomarkers Prev*; 23(5); 833–46. ©2014 AACR.

Introduction

Hematologic cancers represent a heterogeneous group of malignant neoplasms of the hematopoietic and lymphoid tissues and they comprise non-Hodgkin lymphoma, Hodgkin lymphoma, leukemia, and multiple myeloma. In 2008, 6.9% of cancer incidence and 7.3% of cancer mortality worldwide were due to hematologic cancers (1). Non-Hodgkin lymphoma and leukemia rank among the top 10 cancer sites globally, and in developed countries, non-Hodgkin lymphoma is the seventh most frequently diagnosed cancer (1). Among non-Hodgkin lymphoma, diffuse large B-cell lymphoma is the most common subtype.

Obesity has been suggested to be a risk factor for non-Hodgkin lymphoma, Hodgkin lymphoma, leukemia, and multiple myeloma (2–4). Similarly, a deficient or suppressed immune system is a recognized risk factor common to non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, and leukemia (5–8). Physical activity is inversely linked to adiposity (9) and is positively associated with immune function (10) and thus, may play a role in the prevention of hematologic cancer. Physical activity may also prevent the development of hematologic cancer independently of body weight control through enhancements of insulin sensitivity, anti-inflammatory mechanisms, and antioxidant defense systems (11–16).

Despite the existence of numerous biologic pathways potentially linking increased physical activity to decreased risk of hematologic cancer, the epidemiologic evidence relating physical activity to hematologic cancer has been mixed, and the results of a recent meta-analysis on physical activity and lymphoma were not statistically significant (17). Thus, the relation between physical activity and hematologic cancer remains inconclusive.

The purpose of the current systematic review and meta-analysis was to quantify the association between physical activity and hematologic cancer subtypes. To our knowledge, the current investigation is the first meta-analysis to

Authors' Affiliation: Department of Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, Germany

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

Corresponding Author: Carmen Jochem, Department of Epidemiology and Preventive Medicine, University of Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany. Phone: 49-941-944-5216; Fax: 49-941-944-5202; E-mail: carmen.jochem@ukr.de

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include a comprehensive investigation of physical activity in relation to hematologic cancer subtypes.

Materials and Methods

Systematic search strategy and study selection

Studies were identified through a systematic search of PubMed from inception to June 2013 using the following search terms for physical activity: physical activity, exercise, cardiorespiratory fitness, cardiovascular fitness, resistance training, endurance training, aerobic, sport, athletes, players, lifestyle, and anthropometric. Those terms were combined with the following (truncated) terms for hematologic cancers using an AND operator: hematologic malignancy, hematologic neoplasm, hematopoietic malignancy, hematopoietic neoplasm, lymphoid, leukemia, lymphoma, multiple myeloma, and cancer. Cancer outcomes other than hematologic cancers were excluded. The search was limited to studies in humans and no language restrictions were imposed.

Using that search, 949 citations were identified (Supplementary Fig. S1). After screening titles and abstracts, 911 citations were excluded; the remaining 38 full articles were given a more detailed assessment. Studies that met the following criteria were considered further: observational cohort or case-control studies of physical activity and hematologic cancers that provided an effect estimate [relative risk (RR), HR, OR, or standardized incidence ratio (SIR)], with 95% confidence intervals (CI) or sufficient information to calculate those values. Fifteen citations were excluded after full-text screening and two additional articles were found by a manual search. Of the 25 studies (18–42) on physical activity and hematologic cancers, two studies (41, 42) were removed because they did not provide a risk estimate for a hematologic cancer subtype. The remaining 23 studies (18–40) were included in the meta-analysis.

Data extraction

For each study, the following data were extracted by the principal reviewer (C. Jochem): first author's last name, year of publication, sample size, number of cases, study geographic region, type of physical activity assessment, domains and intensities of physical activity, timing in life of physical activity, definition of the highest and the lowest categories of physical activity, reported physical activity effect estimates with corresponding 95% CI, adjustment variables, and information needed to assess the methodological quality of each study. All data extraction was double-checked by a second reviewer (G. Behrens).

Quality assessment

Quality assessment was independently conducted by all reviewers and any disagreement was resolved by consensus. A quality score developed by Monninkhof and colleagues (43) and previously used in several meta-analyses of physical activity and specific cancers (17, 43–46) was applied to assess the methodological

quality of the selected studies (supplementary Materials and Methods).

Statistical analysis

Effect estimates were interpreted as estimates of the RR_i . The natural logarithms of those risk estimates [$\log(RR_i)$] with their corresponding standard errors $s_i = [\log(\text{upper 95\% CI bound or RR}) - \log(RR)]/1.96$ were calculated using a random-effects model to determine the weighted average of those $\log(RR_i)$ s while allowing for effect measure heterogeneity. The $\log(RR_i)$ s were weighted by $w_i = 1/(s_i^2 + I^2)$, where s_i denoted the standard error of $\log(RR_i)$ and I^2 denoted the restricted maximum likelihood estimate of the overall variance (47).

The main meta-analysis included one risk estimate per hematologic cancer subtype (non-Hodgkin lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, Hodgkin lymphoma, leukemia, and multiple myeloma), per gender, and per physical activity domain for each study. If risk estimates were available separately for each sex as well as for men and women combined, the latter were not included in the main meta-analysis. If risk estimates were provided for different numbers of adjustment factors, the maximally adjusted risk estimate was used. If a study presented several risk estimates for physical activity at various time periods in life, the risk estimate for the most recent time period was chosen (21, 22, 34) as most studies provided risk estimates for recent physical activity.

The 23 underlying studies used varying definitions of hematologic cancer subtypes, sometimes without providing information about the specific classification scheme used. In our meta-analysis, the hematologic cancer groups of non-Hodgkin lymphoma, Hodgkin lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, chronic lymphocytic lymphoma/small lymphocytic lymphoma, and multiple myeloma included all risk estimates that were available for those specific subtypes. Our group of non-Hodgkin lymphoma did not include histologic subtypes of non-Hodgkin lymphoma. No study provided information on the specific subtype of Hodgkin lymphoma. Our group of leukemia included risk estimates that were either classified as all leukemia or specific leukemia subtypes, such as acute or chronic myeloid leukemia. Our groupings are consistent to the extent possible across studies included in the meta-analyses.

Publication bias was assessed using a funnel plot and Begg's rank correlation test (48). Statistical heterogeneity between risk estimates was estimated using the Q - and I^2 statistics (47).

For each subsite-specific hematologic cancer, *a priori* determined subanalyses were performed that were stratified by study design, gender, study quality score, physical activity domain, type of physical activity assessment, timing in life of physical activity, number of adjustment factors, adjustment for smoking, adjustment for alcohol consumption, adjustment for adiposity, and study geographic region. Potential heterogeneity of the physical

activity and hematologic cancer subtype associations was assessed according to those factors using random-effects meta-regression, where the model that included the current factor of interest as a single explanatory variable was compared with the null model that included no explanatory variable.

An exploratory dose-response meta-analysis was conducted using fractional polynomials based on a modified version (Supplementary Materials and Methods) of the method proposed by Rota and colleagues (49). For that analysis, we considered seven studies (19, 20, 22, 23, 29, 39, 40) that investigated recreational physical activity expressed as metabolic equivalent task (MET)-hours or MET-minutes per week in relation to hematologic cancer subtypes. The midpoint of each physical activity category was used as the dose associated with the RR for that category. Because the highest categories of physical activity in the underlying studies were open-ended, the dose corresponding to the highest category was defined as 1.5 times the value of the lower bound of that category. The reference level (lowest category) was set to 0 MET-hours. On the basis of the gender-specific RR estimates from the seven included studies, a total of 27 individual dose-response relationships were summarized using multivariate random-effects meta-analysis.

All statistical analyses were performed with R version 2.12.2 (50) using the packages "metafor" (51) and "mvmeta" (52). All risk estimates are reported with 95% CI and $P < 0.05$ were considered statistically significant.

Results

The current meta-analysis comprised a total of 1,648,601 subjects and 19,334 hematologic cancer cases. Table 1 presents the main characteristics and results of the 15 cohort studies (26–40) and eight case-control studies (18–25) included. Three studies investigated more than one physical activity domain (19, 24, 40) and nine studies provided results stratified by gender (20, 22, 23, 25, 26, 29, 32, 39, 40).

Comparing the highest versus the lowest level of physical activity, the 23 risk estimates for non-Hodgkin lymphoma were consistent with a borderline statistically significant inverse association (RR, 0.91; 95% CI, 0.82–1.00; $I^2 = 39%$; Fig. 1). When focusing on subtypes of non-Hodgkin lymphoma, the nine risk estimates for diffuse large B-cell lymphoma yielded a statistically nonsignificant relation with high versus low physical activity (RR, 0.95; 95% CI, 0.80–1.14; $I^2 = 0%$; Fig. 2). Similarly, the summary risk estimate of the nine available risk estimates for physical activity and follicular lymphoma was null at 1.01 (95% CI, 0.83–1.22; $I^2 = 2%$; Fig. 2). The six risk estimates available for Hodgkin lymphoma yielded a statistically nonsignificant risk reduction with high versus low physical activity levels (RR, 0.86; 95% CI, 0.58–1.26; $I^2 = 35%$; Fig. 1). An analysis of all risk estimates available for non-Hodgkin lymphoma and Hodgkin lymphoma combined ($N = 29$) showed a statistically significant

reduction in lymphoma risk with high versus low physical activity level (RR, 0.90; 95% CI, 0.81–0.99; Fig. 1).

Nine risk estimates were available for high versus low physical activity and leukemia and resulted in a summary risk estimate of 0.97 (95% CI, 0.84–1.13; $I^2 = 23%$; Fig. 3). Similarly, seven risk estimates for physical activity and chronic lymphocytic lymphoma/small lymphocytic lymphoma yielded a null summary risk estimate of 0.99 (95% CI, 0.75–1.29; $I^2 = 54%$; Fig. 3). By comparison, the 12 available risk estimates of high versus low physical activity and multiple myeloma showed a statistically nonsignificant inverse relation (RR, 0.86; 95% CI, 0.68–1.09; $I^2 = 38%$; Fig. 3).

We next investigated potential effect modification of the associations between physical activity and hematologic cancer subtypes (Supplementary Tables S1A–G). No statistically significant effect modification was observed for any of the variables studied for any of the hematologic cancer subtypes, apart from apparent effect modification of the physical activity and diffuse large B-cell lymphoma relation by study geographic region. Specifically, physical activity was positively associated with diffuse large B-cell lymphoma in studies from Europe (RR, 3.41; 95% CI, 1.14–10.18), whereas it was unrelated to diffuse large B-cell lymphoma in studies from North America (RR, 0.92; 95% CI, 0.77–1.10; $P_{\text{difference}} = 0.02$).

In a subanalysis, we combined 75 risk estimates and noted a statistically significant 7% reduced risk of total hematologic cancer when comparing the highest versus the lowest level of physical activity (RR, 0.93; 95% CI, 0.88–0.99; Supplementary Table S2). No evidence for publication bias was found in a funnel plot (Supplementary Fig. S2). Begg's rank correlation test also indicated no publication bias ($P = 0.82$). In contrast, the Q -statistic indicated heterogeneity of study results ($P = 0.04$; $I^2 = 24%$).

In further subanalyses, we found that the summary risk estimate for total hematologic cancer did not differ by study design ($P_{\text{difference}} = 0.72$). In contrast, the relation of physical activity to total hematologic cancer varied according to gender, showing an inverse relation with physical activity in women (RR, 0.88; 95% CI, 0.79–0.98), but not in men (RR, 1.03; 95% CI, 0.94–1.01; $P_{\text{difference}} = 0.03$). Furthermore, studies with a large number of adjustment factors yielded a more pronounced inverse relation of physical activity to total hematologic cancer (RR, 0.85; 95% CI, 0.76–0.95) than studies with an intermediate (RR, 1.03; 95% CI, 0.94–1.12) or low number of adjustment factors (RR, 0.92; 95% CI, 0.82–1.04; $P_{\text{difference}} = 0.04$). Also, studies that adjusted for smoking showed a stronger inverse association between physical activity and total hematologic cancer (RR, 0.86; 95% CI, 0.78–0.95) than studies that did not adjust for smoking (RR, 1.00; 95% CI, 0.93–1.07; $P_{\text{difference}} = 0.02$).

We conducted an exploratory dose-response meta-analysis of recreational physical activity expressed as energy-expenditure in MET-hours/week in relation to total hematologic cancer risk. The following dose-response curve was identified as the one with the best model fit: $RR = \exp(a_1 \text{dose}^2 + a_2 \text{dose}^3)$, where

Table 1. Characteristics of the 15 cohort studies and eight case-control studies of physical activity and hematologic cancer risk included in the meta-analysis

Authors, year, gender	Study region	Subjects	Cases	Hematologic cancer subtype	PA: domain, timing in life	RR (95% CI), high vs. low PA	Low PA defined as	High PA defined as	Adjustment factors (excluding sex)	QS (%)
Cohort studies (N = 15)										
Birmann et al., 2007										
Men	North America	46,960	86	MM	RPA, consistent	0.80 (0.50–1.50)	<2 h/wk PA	≥7 h/wk PA	Updated age, BMI	73
Women	North America	89,663	129	MM		0.50 (0.20–1.40)				73
Blair et al., 2005										
Women	North America	37,083	95	MM	RPA, recent	0.88 (0.51–1.49)	Low PA	High PA	—	48
Cerhan et al., 2002										
Women	North America	37,932	252	NHL	RPA, past	0.83 (0.59–1.11)	Low PA	High PA	Age	60
Hofmann et al., 2013										
Men	North America	291,471	319	MM	RPA, recent	1.10 (0.82–1.48)	<16.25 MET-h/wk	≥50 MET-h/wk	Age (at baseline), race, age-specific BMI	65
Women	North America	193,578	152	MM		1.43 (0.90–2.26)				65
Kabat et al., 2012										
Women	North America	157,852	285	CLL/SLL	RPA, recent	1.03 (0.70–1.51)	0 h/wk strenuous PA	≥2 h/wk strenuous PA	Age, smoking, servings of alcohol per week, education, ethnicity, BMI enrollment in the observational study, treatment arm assignment in the clinical trials	82
			1,071	NHL		0.97 (0.79–1.20)				82
			286	DLBCL		0.89 (0.59–1.36)				82
			205	FL		1.25 (0.81–1.94)				82
Kabat et al., 2013										
Men and women combined	North America	493,188	178	Leukemia	TPA, recent	0.70 (0.49–0.99)	<1 time/wk VPA	≥3 times/wk VPA	Age, BMI, smoking intensity, years of education	62
Khan et al., 2006										
Men	Asia	46,157	35	MM	RPA, recent	0.44 (0.21–0.93)	<30 min walking/d	≥1 hour walking/day	Age	64
Women	Asia	63,541	31	MM		0.58 (0.26–1.27)				64
Lim et al., 2007										
Men and women combined	North America	465,858	234	CLL/SLL	TPA, recent	0.80 (0.51–1.25)	PA <1 time/wk	PA ≥5 times/wk	Age, race, education, BMI, caloric intake	65
			1,340	NHL		0.97 (0.81–1.16)				65
			343	DLBCL		0.87 (0.61–1.25)				65
			257	FL		0.96 (0.63–1.46)				65
			56	HL		1.60 (0.72–3.54)	PA <1 time/wk	PA 3–4 times/wk		65
Lu et al., 2009										
Women	North America	121,216	124	CLL/SLL	RPA, recent	1.50 (0.86–2.63)	0–0.50 h/wkly strenuous PA plus MPA	≥4 h/wkly strenuous PA plus MPA	Age, height, weight at cohort entry, age at menarche long-term strenuous PA plus MPA	61
			574	NHL		1.11 (0.86–1.44)				61
			155	DLBCL		1.00 (0.62–1.62)				61
			121	FL		1.01 (0.57–1.79)				61
Ma et al., 2010										
Men and women combined	North America	491,163	338	Leukemia	RPA, recent	1.09 (0.84–1.41)	<3 times/mo VPA	≥3 times/wk VPA	Age, smoking status, total energy intake	69

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Table 1. Characteristics of the 15 cohort studies and eight case-control studies of physical activity and hematologic cancer risk included in the meta-analysis (Cont'd)

Authors, year, gender	Study region	Subjects	Cases	Hematologic cancer subtype	PA: domain, timing in life	RR (95% CI), high vs. low PA	Low PA defined as	High PA defined as	Adjustment factors (excluding sex)	QS (%)	
Paffenbarger et al., 1992 Men and women combined	North America	56,683	86	NHL	RPA, past	0.67 (0.40–1.13)	<5 hours of VPA per week	≥5 hours of VPA per week	Age	57	
		52		HL		0.73 (0.38–1.39)				57	
		81		Leukemia		0.84 (0.45–1.58)					57
Pukkala et al., 2000 Men	Europe	2,269	6	NHL	OPA, past	0.78 (0.29–1.70)	General population	Inclusion in athletic group	5-year age groups	57	
		3		HL		1.33 (0.27–3.88)				57	
		5		Leukemia		0.51 (0.17–1.19)					57
		7		MM		1.39 (0.56–2.85)					57
Soll-Johanning et al., 2004 Men	Europe	14,568	44	Leukemia	OPA, past	1.08 (0.78–1.45)	Copenhagen population	Mail carrier	Age, calendar period	45	
Teras et al., 2012 Men	North America	69,849	271	CLL/SLL	RPA, recent	0.95 (0.62–1.46)	≤0 MET-h/wk	≥17.5 MET-h/wk	Age at baseline, family history of hematopoietic cancer,	65	
		1,139		NHL		1.02 (0.82–1.26)			education, smoking status,	65	
		238		DLBCL		1.14 (0.70–1.88)			alcohol intake, BMI, height,	65	
		143		FL		0.86 (0.49–1.51)			sitting time	65	
		211		MM		0.99 (0.60–1.64)				65	
		211		CLL/SLL		0.73 (0.44–1.20)				65	
		863		NHL		0.69 (0.54–0.89)				65	
		197		DLBCL		0.71 (0.44–1.16)				65	
		137		FL		0.77 (0.41–1.43)				65	
		132		MM		0.54 (0.28–1.04)				65	
van Velthoven et al., 2011 Men	Europe	127,353	373	NHL	OPA, recent	1.05 (0.46–2.41)	Sedentary activities	Manual/heavy manual activities	Age, center, hypertension, hyperlipidemia, education, diabetes	67	
				NHL	RPA, recent	1.11 (0.49–2.52)	<14.25 MET-h/wk	≥45.75 MET-h/wk		71	
		45		DLBCL	TPA, recent	2.03 (0.38–10.79)	Inactive	Active		75	
		45		FL		2.82 (0.52–15.23)				75	
		77		MM		0.34 (0.05–2.14)				75	
		402		NHL	RPA, recent	1.25 (0.49–3.16)	<14.25 MET-h/wk	≥45.75 MET-h/wk		71	
				NHL	OPA, recent	2.06 (0.65–6.51)	Sedentary activities	Manual/heavy manual activities		67	
				DLBCL	TPA, recent	5.03 (1.19–21.33)	Inactive	Active		75	
		49		FL		2.59 (0.54–12.38)				75	
		88		MM		0.65 (0.14–3.16)				75	
Case-control studies (N = 8) Brownson et al., 1991 Men	North America	17,147	462	NHL	OPA, recent	0.80 (0.60–1.30)	PA required <20% of the time	PA required >80% of the time	Age, smoking	45	
		376		Leukemia		0.90 (0.60–1.40)				45	

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Table 1. Characteristics of the 15 cohort studies and eight case-control studies of physical activity and hematologic cancer risk included in the meta-analysis (Cont'd)

Authors, year, gender	Study region	Subjects	Cases	Hematologic cancer subtype	PA: domain, timing in life	RR (95% CI), high vs. low PA	Low PA defined as	High PA defined as	Adjustment factors (excluding sex)	QS (%)	
Cerhan et al., 2005 Men and women combined	North America	864	458	NHL	RPA, recent	0.83 (0.50–1.38)	<30 METs/wk	>1,080 METs/wk	Age, race, study center, alcohol use, height, BMI	58	
			458	NHL	OPA, recent	0.98 (0.55–1.74)	Mostly sitting	Mostly exercise			49
Kasim et al., 2009 Men Women	North America	2,032	390	Leukemia	RPA, recent	1.31 (0.93–1.85)	<5.9 MET-h/wk	≥38.8 MET-h/wk	10-year age group, BMI, educational years, total fruits and vegetables consumption, occupational exposure to benzene and ionizing radiation	58	
		1,727	263	Leukemia		0.97 (0.66–1.42)	<5.6 MET-h/wk	≥38.8 MET-h/wk	Age, race/ethnicity, education, Jewish upbringing, having a single room at age 11 years, living in a single family home at age 8 years, living in a rented family home at age 8 years, having ever nursed children, number of miscarriages, smoking status 1 year before diagnosis/interview, history of first or second degree relative with lymphoma	63	
Keegan et al., 2006 Women	North America	441	187	HL	RPA, recent	0.56 (0.37–0.86)	Nonparticipation in ≥2 times/wk strenuous PA for ≥1 mo	≥2 times/wk strenuous PA for ≥1 mo		58	
Kelly et al., 2012 Men Women	North America	758	184	GLL/SLL	RPA, recent	1.71 (1.08–2.70)	<615 METs/wk	≥2,701 METs/wk	Age, country of residence	58	
			516	NHL		1.37 (0.98–1.92)					58
			88	DLBCL		1.19 (0.64–2.21)					58
			113	FL		0.96 (0.53–1.72)					58
			591	94	CLL/SLL		0.53 (0.27–1.06)				58
				358	NHL		0.71 (0.47–1.07)				58
Pan et al., 2005 Men Women	North America	2,211	569	NHL	RPA, recent	0.79 (0.59–1.05)	<6.4 MET-h/wk	≥37.4 MET-h/wk	Age, province, education, smoking, alcohol drinking, exposure to certain chemicals, occupational exposure, BMI, total caloric intake, MPA	67	
		1,925	461	NHL		0.59 (0.42–0.81)	<6.1 MET-h/wk	≥31.4 MET-h/wk		67	

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Table 1. Characteristics of the 15 cohort studies and eight case-control studies of physical activity and hematologic cancer risk included in the meta-analysis (Cont'd)

Authors, year, gender	Study region	Subjects	Cases	Hematologic cancer subtype	PA: domain, timing in life	RR (95% CI), high vs. low PA	Low PA defined as	High PA defined as	Adjustment factors (excluding sex)	QS (%)
Parent et al., 2011 Men	North America	748	215	NHL	RPA, past	1.17 (0.81–1.69)	Sports or outdoor activities <1 time/wk	Sports or outdoor activities ≥1 time/wk	Age, SES, educational level, ethnicity, respondent status, smoking, BMI, sports, outdoor activities	75
		54	54	HL	OPA, consistent	0.97 (0.45–2.08)	≤1.5 MET (at least 75% of work years in sedentary jobs)	≥4 METs (at least 75% of work years spent in very active jobs)		75
		215	215	NHL		0.56 (0.26–1.20)				66
		54	54	HL		0.84 (0.17–4.23)				66
Zahm et al., 1999	North America	3,856	985	NHL	OPA, recent	1.00 (0.70–1.30)	Energy expenditure <8 kJ/min	Energy expenditure >12 kJ/min	Age, state of residence	51
		854	180	NHL		1.70 (0.20–11.50)	Energy expenditure <5 kJ/min	Energy expenditure >8 kJ/min		51

Abbreviations: CLL/SLL, chronic lymphocytic lymphoma/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; MM, multiple myeloma; MPA, moderate physical activity; NHL, non-Hodgkin lymphoma; OPA, occupational physical activity; PA, physical activity; QS, quality score; RPA, recreational physical activity; SES, socioeconomic status; TPA, total physical activity; VPA, vigorous physical activity.

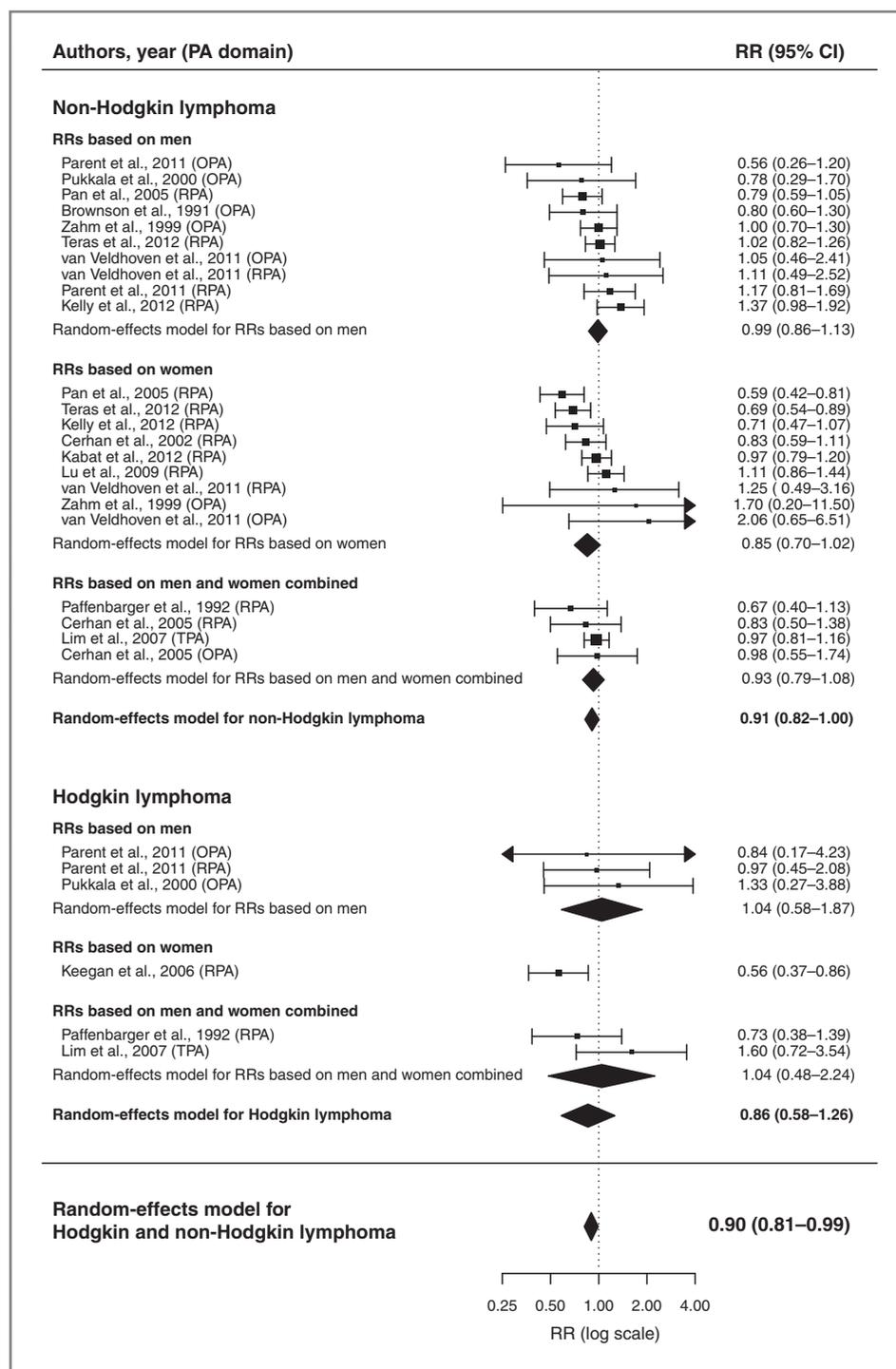
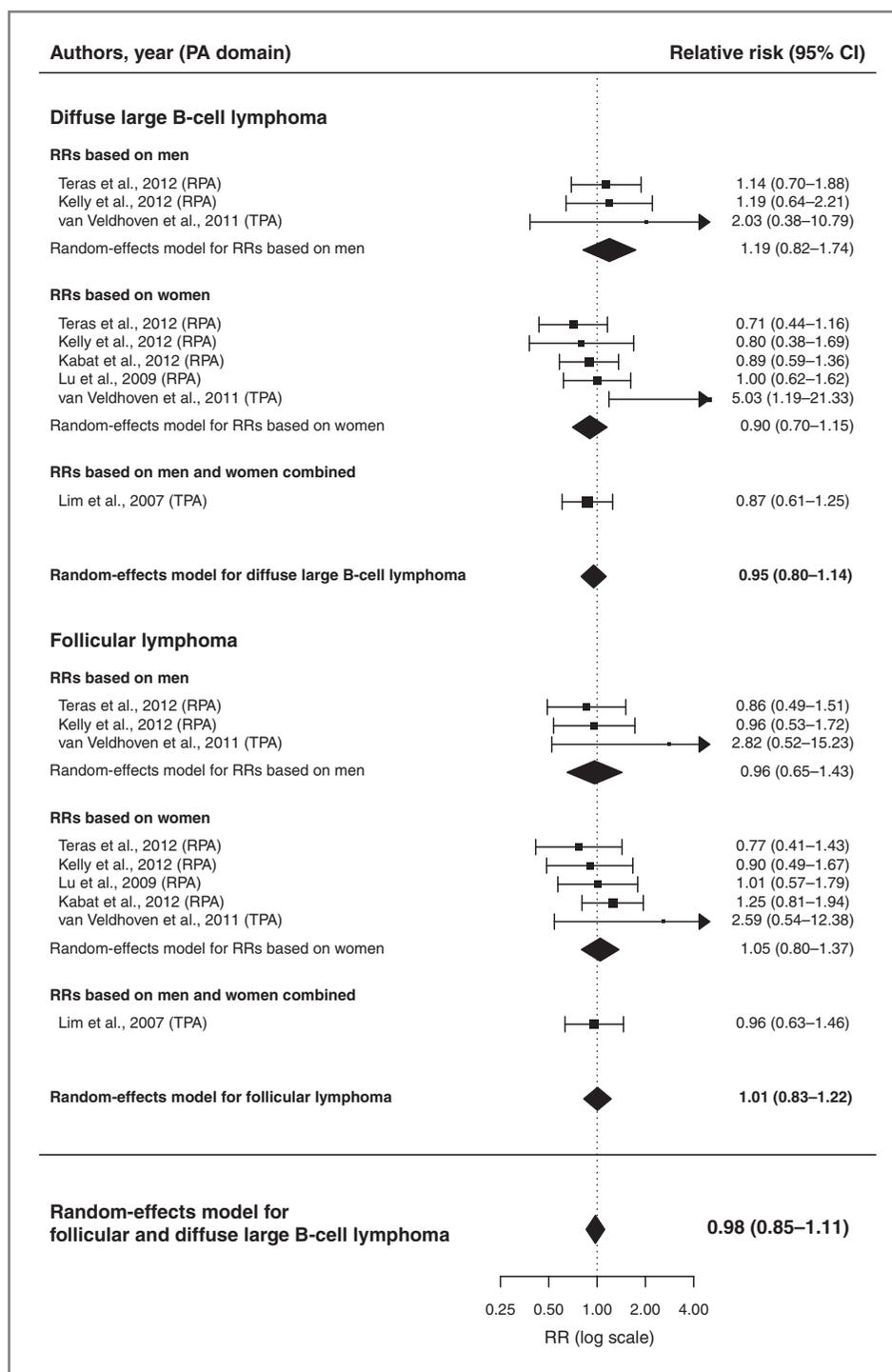


Figure 1. Forest plot of a random-effects meta-analysis including risk estimates of non-Hodgkin lymphoma and Hodgkin lymphoma. RRs quantify the association between physical activity (PA) and hematologic cancer subtype risk for the highest versus lowest levels of physical activity, grouped by men, women, and men and women combined for non-Hodgkin lymphoma and Hodgkin lymphoma. The size of each box is proportional to the weight the risk estimate contributed to the summary risk estimate. OPA, occupational physical activity; RPA, recreational physical activity; TPA, total physical activity.

$a_1 = -0.000271$, $a_2 = -0.000004$, $\text{var}(a_1) = 1 \times 10^{-8}$, $\text{cov}(a_1, a_2) = -2 \times 10^{-10}$, and $\text{var}(a_2) = 3 \times 10^{-12}$ (Fig. 4). That model did not indicate heterogeneity between studies ($I^2 = 9\%$; $P_{\text{heterogeneity}} = 0.29$). It showed an inverse association between physical activity and total hematologic cancer (Fig. 4), suggesting that a risk reduction of 10% was reached at 26 MET-hours/week (RR,

0.90; 95% CI, 0.83–0.97). The maximum risk reduction was detected at 41 MET-hours/week (RR, 0.86; 95% CI, 0.76–0.97). A linear dose-response meta-analysis including all physical activity doses up to 41 MET-hours indicated that each 12 MET-hour/week increase in recreational physical activity was associated with a 5% reduced total hematologic cancer risk (RR, 0.95;

Figure 2. Forest plot of a random-effects meta-analysis including risk estimates of diffuse large B-cell lymphoma and follicular lymphoma. RRs quantify the association between physical activity (PA) and hematologic cancer subtype risk for the highest versus lowest levels of physical activity, grouped by men, women, and men and women combined for diffuse large B-cell lymphoma and follicular lymphoma. The size of each box is proportional to the weight the risk estimate contributed to the summary risk estimate. OPA, occupational physical activity; RPA, recreational physical activity; TPA, total physical activity.



95% CI, 0.91–0.99). Energy expenditure values exceeding 48 MET-hours/week were no longer related to a statistically significant risk reduction.

Discussion

This is the first meta-analysis to comprehensively examine physical activity in relation to hematologic

cancer subtypes. We found that high versus low physical activity showed statistically nonsignificant relations to non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, and leukemia. The relations of physical activity to hematologic cancer subtypes were not modified by study design, gender, study quality score, physical activity domain, type of physical activity assessment, timing in life of physical activity, number

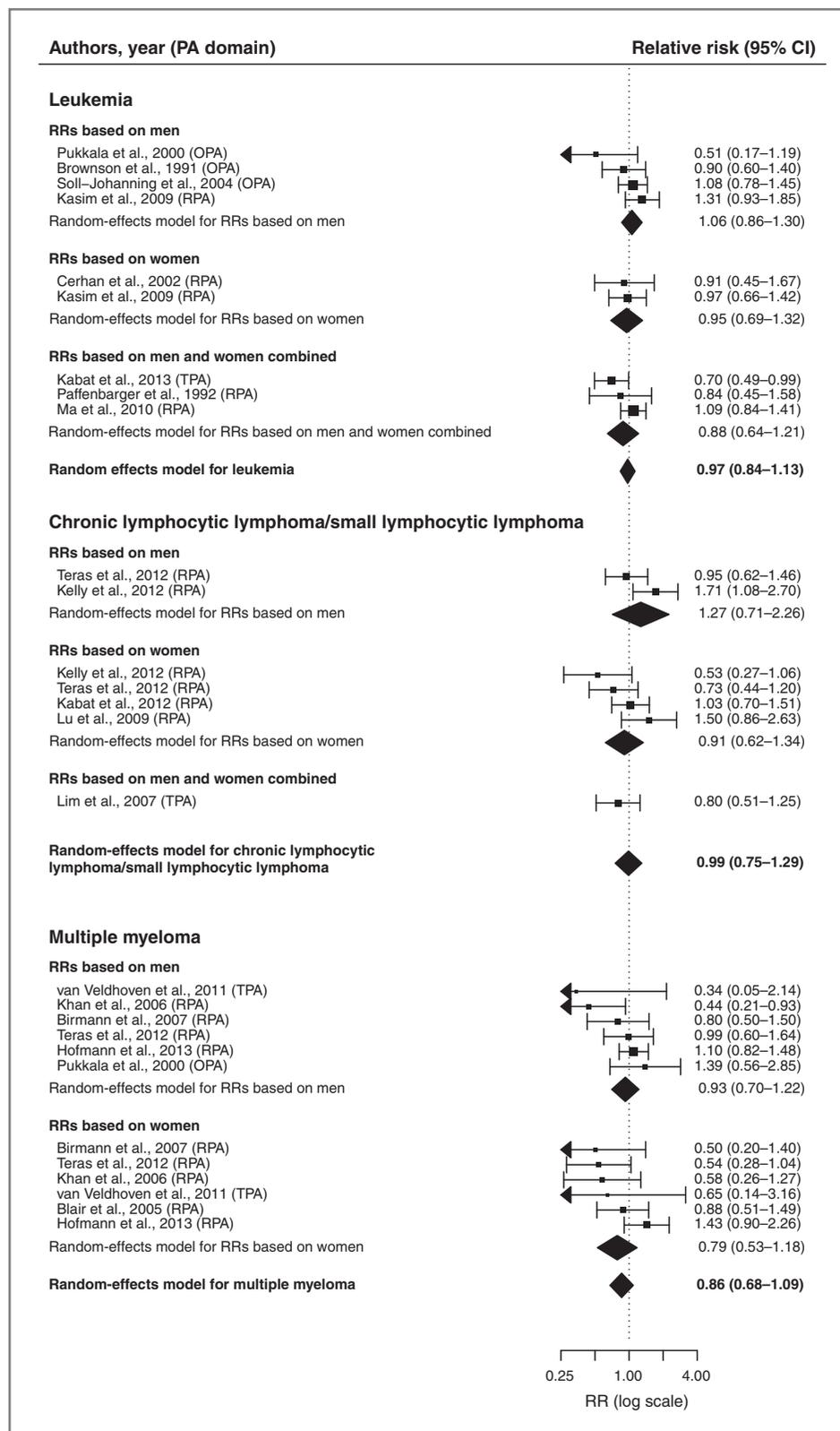
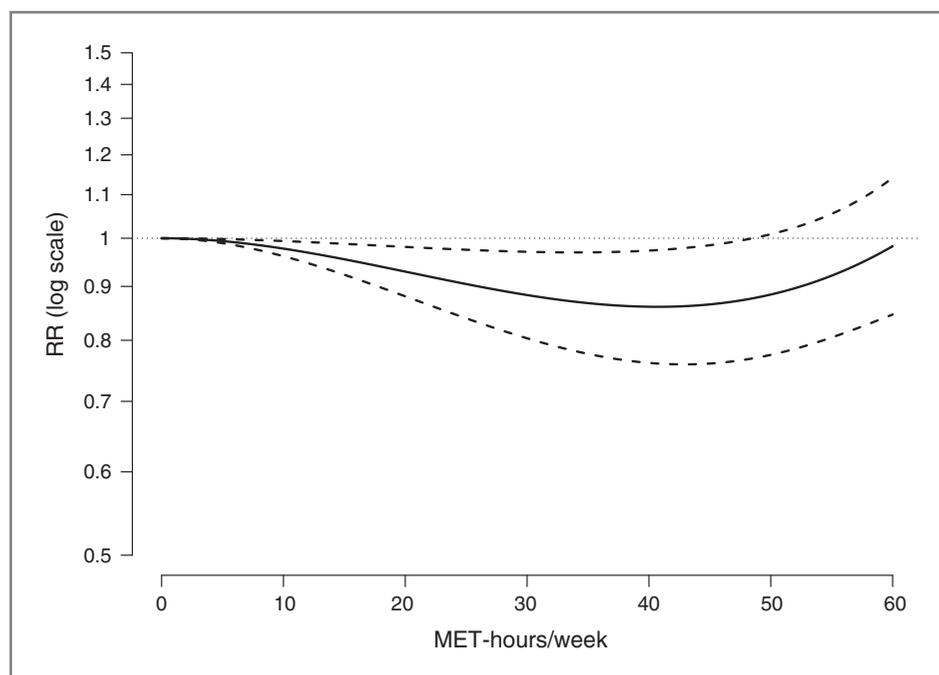


Figure 3. Forest plot of a random-effects meta-analysis including risk estimates of leukemia, chronic lymphocytic lymphoma/small lymphocytic lymphoma, and multiple myeloma. RRs quantify the association between physical activity (PA) and hematologic cancer subtype risk for the highest versus lowest levels of physical activity, grouped by men, women, and men and women combined for leukemia and chronic lymphocytic lymphoma/small lymphocytic lymphoma. The size of each box is proportional to the weight the risk estimate contributed to the summary risk estimate. OPA, occupational physical activity; RPA, recreational physical activity; TPA, total physical activity.

of adjustment factors, adjustment for smoking, adjustment for alcohol consumption, and adjustment for adiposity.

A recent meta-analysis (17) that focused on non-Hodgkin lymphoma and Hodgkin lymphoma pooled the data from 12 studies (16 risk estimates for non-Hodgkin lymphoma;

Figure 4. Dose–response analysis of MET-hours/week spent in moderate to vigorous physical activity in relation to total hematologic cancer risk.



four risk estimates for Hodgkin lymphoma) and reported a statistically nonsignificant reduction in lymphoma risk with high versus low levels of physical activity (RR, 0.90; 95% CI, 0.79–1.02), with observed heterogeneity by study design ($P_{\text{difference}} = 0.04$). Our meta-analysis included nine additional risk estimates for lymphoma and yielded an identical point estimate that was statistically significant (RR, 0.90; 95% CI, 0.81–0.99) and showed no effect modification by study design ($P_{\text{difference}} = 0.72$).

In contrast to the previous meta-analysis (17), the present meta-analysis considered all main hematologic cancer subtypes (non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, and leukemia). In addition, it incorporated one additional study by Paffenbarger and colleagues (36) that provided risk estimates for physical activity and both non-Hodgkin lymphoma and Hodgkin lymphoma, in addition to leukemia. The current meta-analysis also examined the potential for publication bias.

Our exploratory dose–response meta-analysis indicated that a 5% risk reduction of total hematologic cancer could be achieved for each 12 MET-hour/week increase in recreational physical activity (equivalent to walking at a moderate pace for 30 minutes daily; ref. 53). Our observation of an upward trend of the dose–response curve for values exceeding 41 MET-hours/week indicates that there may be an upper level of physical activity that no longer provides protection against total hematologic cancer risk. In this context, it is interesting to note that extremely high levels of physical activity are thought to impair the immune system (54). Particular caution is needed in interpreting our findings for total hematologic cancer because of etiologic heterogeneity for individual hematologic cancer subtypes.

Two case–control studies on physical activity and hematologic cancer (20, 23) presented results stratified

by body mass index (BMI). In one study (20), physical activity showed a more pronounced inverse association with adult leukemia among obese than overweight or normal weight men and women, although the test for interaction was not statistically significant. In the other study (23), an inverse relation of physical activity to non-Hodgkin lymphoma was seen only among obese or normal weight men, whereas no association with physical activity was noted among overweight men. In contrast, physical activity displayed inverse associations with non-Hodgkin lymphoma among nonobese women, whereas the relation of physical activity to non-Hodgkin lymphoma among obese women was null (23). Those inconsistent gradients in hematologic cancer risk associated with physical activity across categories of BMI suggest that physical activity and adiposity affect hematologic cancer risk through distinct etiologic mechanisms. In support of the notion that the inverse association between physical activity and hematologic cancer is not mediated by healthy body mass among physically active persons, in our meta-analysis the magnitude of the summary risk estimates of physical activity and hematologic cancer subtypes that were adjusted for BMI were similar to the risk estimates that were unadjusted for BMI.

In our study, the associations between physical activity and hematologic cancer subtypes were not modified by gender. However, in a subanalysis of total hematologic cancer, we noted that the relation with physical activity was statistically significantly inverse in women but null in men. Possible explanations for the observed difference between women and men include reproductive factors and exogenous estrogens, but relevant biologic pathways of hematologic cancer risk as they interact with physical activity are not well investigated.

Although the relations of physical activity to hematologic cancer subtypes did not vary according to smoking, in a subanalysis of total hematologic cancer, we found that studies that adjusted for smoking showed a stronger inverse association with physical activity than studies that did not adjust for smoking. Smoking is inversely related to physical activity (55) and positively associated with all investigated hematologic cancer subtypes (56–58) except multiple myeloma (59). Thus, adjustment for smoking would be expected to produce a less pronounced inverse association between physical activity and total hematologic cancer than not adjusting for smoking. However, because studies that adjusted for smoking also tended to include a large number of additional adjustment factors, we were unable to discern the effects of controlling for smoking from those controlling for a large number of other adjustment factors, the latter variable of which also represented an effect modifier of the physical activity and total hematologic cancer relation.

Our observation that European studies yielded a positive association between physical activity and diffuse large B-cell lymphoma was based on only two RR estimates. Multiple comparisons could have yielded such a finding by chance because we evaluated a large number of potential effect modifiers.

The etiologic pathways linking increased physical activity to decreased risk of hematologic cancer are not established, but several plausible mechanisms exist. Immunodeficiency is a risk factor for non-Hodgkin lymphoma and Hodgkin lymphoma (5, 8), and physical activity enhances the immune system by increasing the number and activity of natural killer cells, macrophages, lymphokine-activated killer cells, and regulating cytokines (16). Physical activity may also decrease hematologic cancer risk by reducing insulin resistance (12) and decreasing levels of insulin and insulin-like growth factors (11, 60, 61). A further potential mechanism is an exercise-induced reduction of proinflammatory mediators such as interleukin-6 (IL-6), C-reactive protein (CRP), and TNF- α (16), factors that have been positively associated with hematologic cancer (62, 63). Physical activity may also increase the production of antioxidant enzymes, thereby improving DNA repair capacity (15, 16). Finally, physical activity may indirectly decrease hematologic cancer risk by preventing adiposity and reducing body fat (13) because obesity represents a risk factor for non-Hodgkin lymphoma, Hodgkin lymphoma, leukemia, and multiple myeloma (2–4).

Strengths of the present meta-analysis are its large sample size, which provided substantial statistical power and permitted extensive subanalyses. A major asset is the heterogeneity of hematologic cancer subtypes included in the analysis, which enabled us to examine whether physical activity differentially affects specific hematologic cancer subtypes. Also, we comprehensively assessed effect modification of the relation of physical activity to subtype-specific hematologic cancers. In addition,

we applied a study quality score that addressed potential selection bias, misclassification, and confounding. Reassuringly, we found no heterogeneity of the risk estimates between higher and lower quality studies.

Limitations of the current meta-analysis are the heterogeneous study designs and the variability in the definitions of high and low levels of physical activity in the underlying studies. However, we addressed the heterogeneity in high and low levels of physical activity in an exploratory dose-response meta-analysis in which we combined RRs of hematologic cancer associated with comparable doses of physical activity. It is possible that preclinical symptoms of hematologic cancer influenced physical activity habits at baseline. Our analyses were limited in that we were unable to remove cases diagnosed in the time period proximal to physical activity assessment. Thus, we may have overestimated any possible inverse association between physical activity and hematologic cancers in our study.

A further potential shortcoming of our study is measurement error in physical activity assessment because studies used self-reports or interview methods to assess physical activity rather than objective instruments such as accelerometers. However, nondifferential misclassification of physical activity levels would have tended to underestimate but not overstate risk estimates. Notwithstanding, the common use of accelerometers might have increased comparability between studies.

Comparability of studies would also have been enhanced if all studies had used a uniform hematologic cancer classification scheme. Some studies did not specify the classification scheme used, whereas other studies provided detailed information about the use of common classification schemes such as the second or third editions of the International Classification of Diseases for Oncology (ICD-O-2/-3) or the InterLymph classification scheme (64). We were unable to distinguish between classical and nonclassical histologic types of Hodgkin lymphoma or between younger adult and older adult Hodgkin lymphoma because of lack of such data.

In summary, our meta-analysis indicates that physical activity is unrelated to risk of subtypes of hematologic cancer. Future studies should include standardized, high-quality physical activity assessments to refine our knowledge regarding whether specific intensities, durations, and frequencies of physical activity may be potentially relevant for protection from hematologic cancers. In addition, mechanistic research is needed to delineate the biologic mechanisms underlying the possible relations of physical activity to hematologic cancer subtypes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: C. Jochem, M.F. Leitzmann, G. Behrens
Development of methodology: C. Jochem, M.F. Leitzmann, G. Behrens
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C. Jochem, M.F. Leitzmann, G. Behrens
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C. Jochem, M.F. Leitzmann, G. Behrens

Writing, review, and/or revision of the manuscript: C. Jochem, M.F. Leitzmann, M. Keimling, D. Schmid, G. Behrens
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C. Jochem
Study supervision: M.F. Leitzmann, G. Behrens

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Cancer Epidemiology, Biomarkers & Prevention

Physical Activity in Relation to Risk of Hematologic Cancers: A Systematic Review and Meta-analysis

Carmen Jochem, Michael F. Leitzmann, Marlen Keimling, et al.

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