Physical activity in relation to risk of hematologic cancers: a systematic review and meta-analysis

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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 8 case-control studies) and estimated summary relative risks (RRs) and 95% confidence intervals (CIs) 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 non-significant 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.
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). Amongst 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 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, 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, 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 Figure S1). After screening titles and abstracts, 911 citations were excluded; the remaining 38 full manuscripts 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), hazard ratio (HR), odds ratio (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.J.): 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.B.).

Quality assessment

Quality assessment was independently conducted by all reviewers and any disagreement was resolved by consensus. A quality score developed by Monninkhof et al. (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 relative risk (RR_i). The natural logarithms of those risk estimates log(RR_i) with their corresponding standard errors s_i=(log(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_i²+t²), where s_i denoted the standard error of log(RR_i) and t² 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, 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\(^{(21, 22, 34)}\) since 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 sub-analyses 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 relative risk 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. Based on the gender-specific relative risk estimates from the 7 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-values <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 8 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, I²=39%; Figure 1). When focusing on subtypes of non-Hodgkin lymphoma, the nine risk estimates for diffuse large B-cell lymphoma yielded a statistically non-significant relation with high versus low physical activity (RR=0.95, 95% CI=0.80-1.14, I²=0%; Figure 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; I²=2%; Figure 2). The six risk estimates available for Hodgkin lymphoma yielded a statistically non-significant risk reduction with high versus low physical activity levels (RR=0.86, 95% CI=0.58-1.26, I²=35%; Figure 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; Figure 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; I²=23%; Figure 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; I²=54%; Figure 3). By comparison, the 12 available risk estimates of high versus low physical activity and multiple myeloma showed a statistically non-significant inverse relation (RR=0.86; 95% CI=0.68-1.09, I²=38%; Figure 3).

We next investigated potential effect modification of the associations between physical activity and hematologic cancer subtypes (supplementary Tables S1 a-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-difference=0.02).

In a sub-analysis, 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 Figure 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, I²=24%).

In further sub-analyses, we found that the summary risk estimate for total hematologic cancer did not differ by study design (p-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-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-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-difference=0.02).

We conducted an exploratory dose-response meta-analysis of recreational physical activity expressed as energy-expenditure in MET-hours per week in relation to total hematologic cancer risk. The following dose-response curve was identified as the one with the best model fit: \( RR = \exp(a_1 \cdot \text{dose}^2 + a_2 \cdot \text{dose}^3) \), where \( a_1 = -0.000271 \), \( a_2 = -0.000004 \), \( \text{var}(a_1) = 1 \times 10^{-8} \), \( \text{cov}(a_1, a_2) = -2 \times 10^{-10} \), and \( \text{var}(a_2) = 3 \times 10^{-12} \) (Figure 4). That model did not indicate heterogeneity between studies (\( I^2=9\% \), p-heterogeneity=0.29). It showed an inverse association between physical activity and total hematologic cancer (Figure 4), suggesting that a risk reduction of ten percent was reached at 26 MET-hours per week (RR=0.90, 95% CI=0.83-0.97). The maximum risk reduction was detected at 41 MET-hours per 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 metabolic equivalent task (MET)-hour per week increase in recreational physical activity was associated with a five percent reduced total hematologic cancer risk (RR=0.95, 95% CI=0.91-0.99). Energy expenditure values exceeding 48 MET-hours per 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 non-significant 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 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; 4 risk estimates for Hodgkin lymphoma) and reported a statistically non-significant 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-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-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 et al. (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 five percent risk reduction of total hematologic cancer could be achieved for each 12 MET-hour per week increase in recreational physical activity (equivalent to walking at a moderate pace for 30 minutes daily) (53). Our observation of an upward trend of the dose-response curve for values exceeding 41 MET-hours per 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 non-obese 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 sub-analysis 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 sub-analysis 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 pro-inflammatory mediators such as interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-α (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 sub-analyses. A major asset is the heterogeneity of hematologic cancer subtypes included in the analysis, which enabled us to examine whether physical activity differentially impacts upon 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 relative risks of hematologic cancer associated with comparable doses of physical activity. It is possible that pre-clinical 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, non-differential 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).
were unable to distinguish between classical and non-classical 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.
Acknowledgments

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References


Table 1: Characteristics of the 15 cohort studies and 8 case-control studies of physical activity and hematologic cancer risk included in the meta-analysis.

<table>
<thead>
<tr>
<th>Authors, year, gender</th>
<th>Study region</th>
<th>Subjects</th>
<th>Cases</th>
<th>Hematologic cancer subtype</th>
<th>PA: domain, timing in life</th>
<th>Relative risk (95% CI), high vs. Low PA</th>
<th>Low PA defined as</th>
<th>High PA defined as</th>
<th>Adjustment factors (excluding sex)</th>
<th>QS (%)</th>
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<tbody>
<tr>
<td><strong>Cohort studies (N=15)</strong></td>
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<tr>
<td>Birmann et al., 2007</td>
<td>Men</td>
<td>North America</td>
<td>46,960</td>
<td>86</td>
<td>MM</td>
<td>RPA, consistent</td>
<td>0.80 [0.50, 1.50]</td>
<td>&lt; 2 h/week PA</td>
<td>≥7 h/week PA</td>
<td>Updated age, BMI</td>
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<tr>
<td></td>
<td>Women</td>
<td>North America</td>
<td>89,663</td>
<td>129</td>
<td></td>
<td>0.50 [0.20, 1.40]</td>
<td></td>
<td></td>
<td></td>
<td>73</td>
</tr>
<tr>
<td>Blair et al., 2005</td>
<td>Women</td>
<td>North America</td>
<td>37,083</td>
<td>95</td>
<td>MM</td>
<td>RPA, recent</td>
<td>0.88 [0.51, 1.49]</td>
<td>Low PA</td>
<td>High PA</td>
<td>-</td>
</tr>
<tr>
<td>Cerhan et al., 2002</td>
<td>Women</td>
<td>North America</td>
<td>37,932</td>
<td>252</td>
<td>NHL</td>
<td>RPA, past</td>
<td>0.83 [0.59, 1.11]</td>
<td>Low PA</td>
<td>High PA</td>
<td>Age</td>
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<tr>
<td></td>
<td>Leukemia</td>
<td></td>
<td></td>
<td>61</td>
<td></td>
<td>0.91 [0.45, 1.67]</td>
<td></td>
<td></td>
<td></td>
<td>60</td>
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<td>Hofmann et al., 2013</td>
<td>Men</td>
<td>North America</td>
<td>291,471</td>
<td>319</td>
<td>MM</td>
<td>RPA, recent</td>
<td>1.10 [0.82, 1.48]</td>
<td>&lt; 16.25 MET-h/week</td>
<td>≥50 MET-h/week</td>
<td>Age (at baseline), race, age-specific BMI</td>
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<td></td>
<td>Women</td>
<td>North America</td>
<td>193,578</td>
<td>152</td>
<td>MM</td>
<td></td>
<td>1.43 [0.90, 2.26]</td>
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<tr>
<td>Kabat et al., 2012</td>
<td>Women</td>
<td>North America</td>
<td>157,852</td>
<td>285</td>
<td>CLL/SLL</td>
<td>RPA, recent</td>
<td>1.03 [0.70, 1.51]</td>
<td>0 h/week strenuous PA</td>
<td>≥2 h/week strenuous PA</td>
<td>Age, smoking, servings of alcohol per week, education, ethnicity, BMI enrollment in the observational study, treatment arm assignment in the clinical trials</td>
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<td>1,071</td>
<td>NHL</td>
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<td>286</td>
<td>DLBCL</td>
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<td></td>
<td>205</td>
<td>FL</td>
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<td>1.25 [0.81, 1.94]</td>
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<td>Kabat et al., 2013</td>
<td>Men and women combined</td>
<td>North America</td>
<td>493,188</td>
<td>178</td>
<td>Leukemia</td>
<td>TPA, recent</td>
<td>0.70 [0.49, 0.99]</td>
<td>&lt;1 time/week VPA</td>
<td>≥3 times/week VPA</td>
<td>Age, BMI, smoking intensity, years of education</td>
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<td>Khan et al., 2006</td>
<td>Men</td>
<td>Asia</td>
<td>46,157</td>
<td>35</td>
<td>MM</td>
<td>RPA, recent</td>
<td>0.44 [0.21, 0.93]</td>
<td>&lt;30 min walking/day</td>
<td>≥1 hour walking/day</td>
<td>Age</td>
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<tr>
<td></td>
<td>Women</td>
<td>Asia</td>
<td>63,541</td>
<td>31</td>
<td>MM</td>
<td></td>
<td>0.58 [0.26, 1.27]</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lim et al., 2007</td>
<td>Men and women combined</td>
<td>North America</td>
<td>465,858</td>
<td>234</td>
<td>CLL/SLL</td>
<td>TPA, recent</td>
<td>0.80 [0.51, 1.25]</td>
<td>PA &lt;1 time/week</td>
<td>PA ≥5 times/week</td>
<td>Age, race, education, BMI, caloric intake</td>
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<td></td>
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<td>343</td>
<td>DLBCL</td>
<td></td>
<td>0.87 [0.61, 1.25]</td>
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<td>Study</td>
<td>Region</td>
<td>Cases</td>
<td>Controls</td>
<td>Cox HR</td>
<td>Confidence Interval</td>
<td>Physical Activity</td>
<td>Age, Smoking Status, Total Energy Intake</td>
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<td>Lu et al., 2009</td>
<td>North America</td>
<td>121,216</td>
<td>257 FL</td>
<td>0.96 [0.63, 1.46]</td>
<td>PA &lt;1 time/week</td>
<td>PA 3-4 times/week</td>
<td>Age, height, weight at cohort</td>
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<tr>
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<td>56 HL</td>
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<td>Ma et al., 2010</td>
<td>North America</td>
<td>491,163</td>
<td>338 Leukemia</td>
<td>1.09 [0.84, 1.41]</td>
<td>&lt;3 times/month VPA</td>
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<td>Age, smoking status, total energy intake</td>
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<td>Paffenbarger et al., 1992</td>
<td>North America</td>
<td>56,683</td>
<td>86 NHL</td>
<td>0.67 [0.40, 1.13]</td>
<td>&lt;5 hours of VPA per week</td>
<td>≥5 hours of VPA per week</td>
<td>Age</td>
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<td>Pukkala et al., 2000</td>
<td>Europe</td>
<td>2,269</td>
<td>6 NHL</td>
<td>0.78 [0.29, 1.79]</td>
<td>General population</td>
<td>Inclusion in athletic group</td>
<td>5-year age groups</td>
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<td>3 HL</td>
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<td>5 Leukemia</td>
<td>0.51 [0.17, 1.19]</td>
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<td>7 MM</td>
<td>1.39 [0.56, 2.85]</td>
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<td>Soll-Johanning et al., 2004</td>
<td>Europe</td>
<td>14,568</td>
<td>44 Leukemia</td>
<td>1.08 [0.78, 1.45]</td>
<td>Copenhagen population</td>
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<td>Age, calendar period</td>
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<td>North America</td>
<td>69,849</td>
<td>271 CLL/SLL</td>
<td>0.95 [0.62, 1.46]</td>
<td>≥80 MET-h/week</td>
<td>≥17.5 MET-h/week</td>
<td>Age at baseline, family history of hematopoietic cancer, education, smoking status, alcohol intake, BMI, height, sitting time</td>
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<td>1,139 NHL</td>
<td>1.02 [0.82, 1.26]</td>
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<td></td>
<td></td>
<td></td>
<td>238 DLBCL</td>
<td>1.14 [0.70, 1.88]</td>
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<td></td>
<td></td>
<td></td>
<td>143 FL</td>
<td>0.86 [0.49, 1.51]</td>
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<td>211 MM</td>
<td>0.99 [0.60, 1.64]</td>
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<td></td>
<td>211 CLL/SLL</td>
<td>0.73 [0.44, 1.20]</td>
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<td></td>
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<td>883 NHL</td>
<td>0.69 [0.54, 0.89]</td>
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<td>197 DLBCL</td>
<td>0.71 [0.44, 1.16]</td>
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<td></td>
<td></td>
<td></td>
<td>137 FL</td>
<td>0.77 [0.41, 1.43]</td>
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<td></td>
<td>132 MM</td>
<td>0.54 [0.28, 1.04]</td>
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<tr>
<td>van Veldhoven et al., 2011</td>
<td>Europe</td>
<td>127,353</td>
<td>373 NHL</td>
<td>1.05 [0.46, 2.41]</td>
<td>Sedentary activities</td>
<td>Manual/heavy manual activities</td>
<td>Age, center, hypertension, hyperlipidemia, education, diabetes</td>
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<td>1139 NHL</td>
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<td></td>
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<td></td>
<td>45 DLBCL</td>
<td>2.03 [0.38, 10.79]</td>
<td>&lt;14.25 MET-h/week</td>
<td>≥45.75 MET-h/week</td>
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<td></td>
<td></td>
<td></td>
<td>45 FL</td>
<td>2.82 [0.52, 15.23]</td>
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<td></td>
<td>77 MM</td>
<td>0.34 [0.05, 2.14]</td>
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</tbody>
</table>
Women                    216,403   402 NHL    RPA, recent
                      2.60 [0.65, 6.51] Sedentary activities Manual/heavy manual activities
                      5.03 [1.19, 21.33] Inactive Active
                      2.59 [0.54, 12.38] 75
                      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
                      0.90 [0.60, 1.40] Age, smoking
                      376
Cerhan et al., 2005
Men and women combined
North America 864   458 NHL    RPA, recent
                      0.83 [0.50, 1.38] <30 METs/week >1080 METs/week
                      0.98 [0.55, 1.74] Mostly sitting Mostly exercise
                      458
Kasim et al., 2009
Women                  North America 2,032   390 Leukemia RPA, recent
                      1.31 [0.93, 1.85] <5.9 MET-h/week ≥8 MET-h/week
                      0.97 [0.66, 1.42] ≥38.8 MET-h/week
                      1,727
Keegan et al., 2006
Women                  North America 441   187 HL     RPA, recent
                      0.56 [0.37, 0.86] Nonparticipation in ≥2 times/week strenuous PA for ≥1 month ≥2 times/week strenuous PA for ≥1 month
                      441
Kelly et al., 2012
Men                    North America 758   184 CLL/SLL RPA, recent
                      1.71 [1.08, 2.70] <615 METs/week ≥2701 METs/week Age, country of residence
                      516 NHL
                      1.37 [0.98, 1.92] 75
                      1.19 [0.64, 2.21]
                      88 DLBCL
                      0.96 [0.53, 1.72] 75
                      0.53 [0.27, 1.06]
                      113 FL
                      0.71 [0.47, 1.07] 75
                      0.38 [0.16, 0.74]
                      358 NHL
                      0.56 [0.27, 1.14] 75
                      0.27 [0.14, 0.52]
                      79 DLBCL
                      0.80 [0.38, 1.69] 75
                      0.38 [0.16, 0.74]
                      109 FL
                      0.90 [0.49, 1.67] 75
<table>
<thead>
<tr>
<th>Study</th>
<th>Sex</th>
<th>Country</th>
<th>Cases</th>
<th>NHL</th>
<th>Method</th>
<th>MET-hours/week</th>
<th>Age, Province, Education, Smoking, Alcohol Drinking, Exposure to Certain Chemicals, Occupational Exposure, BMI, Total Caloric Intake, MPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan et al., 2005</td>
<td>Men</td>
<td>North America</td>
<td>2,211</td>
<td>569</td>
<td>RPA, Recent</td>
<td>&lt;6.4 MET-h/week</td>
<td>≥37.4 MET-h/week</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td></td>
<td>1,925</td>
<td>461</td>
<td>NHL</td>
<td>&lt;6.1 MET-h/week</td>
<td>≥31.4 MET-h/week</td>
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<tr>
<td>Parent et al., 2011</td>
<td>Men</td>
<td>North America</td>
<td>748</td>
<td>215</td>
<td>NHL, Past</td>
<td>&lt;1 time/week</td>
<td>≥1 time/week</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td>OPA, Consistent</td>
<td>≤1.5 MET (at least 75% of work years in sedentary jobs)</td>
<td>≥4 METs (at least 75% of work years was spent in very active jobs)</td>
</tr>
<tr>
<td>Zahm et al., 1999</td>
<td>Men</td>
<td>North America</td>
<td>3,856</td>
<td>985</td>
<td>OPA, Recent</td>
<td>Energy expenditure ≤8 kJ/min</td>
<td>Energy expenditure &gt;12 kJ/min</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td></td>
<td>854</td>
<td>180</td>
<td>NHL</td>
<td>Energy expenditure ≤5 kJ/min</td>
<td>Energy expenditure &gt;8 kJ/min</td>
</tr>
</tbody>
</table>

Abbreviations: BMI=body mass index; MET=metabolic equivalent of task; kJ=kilojoule; min=minute; h=hour; PA=physical activity; OPA=occupational physical activity; RPA=recreational physical activity; TPA=total physical activity; MPA=moderate physical activity; VPA=vigorous physical activity; CLL/SLL=chronic lymphocytic lymphoma/small lymphocytic lymphoma; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; HL=Hodgkin lymphoma; NHL=non-Hodgkin lymphoma; MM=multiple myeloma; SES=socioeconomic status; QS=quality score.
Figure legends

- Figure 1: Forest plot of a random-effects meta-analysis including risk estimates of non-Hodgkin lymphoma and Hodgkin lymphoma. Relative risks (RRs) quantify the association between physical activity (PA) and hematologic cancer subtype risk for the highest versus lowest levels of PA, 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. Abbreviations: OPA=occupational physical activity; RPA=recreational physical activity; TPA=total physical activity.

- Figure 2: Forest plot of a random-effects meta-analysis including risk estimates of diffuse large B-cell lymphoma and follicular lymphoma. Relative risks (RRs) quantify the association between physical activity (PA) and hematologic cancer subtype risk for the highest versus lowest levels of PA, 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. Abbreviations: OPA=occupational physical activity; RPA=recreational physical activity; TPA=total physical activity.

- Figure 3: Forest plot of a random-effects meta-analysis including risk estimates of leukemia, chronic lymphocytic lymphoma / small lymphocytic lymphoma and multiple myeloma. Relative risks (RRs) quantify the association between physical activity (PA) and hematologic cancer subtype risk for the highest versus lowest levels of PA, 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.
estimate. Abbreviations: OPA=occupational physical activity; RPA=recreational physical activity; TPA=total physical activity.

- Figure 4: Dose-response analysis of MET-hours per week spent in moderate to vigorous physical activity in relation to total hematologic cancer risk.
**Figure 1**

<table>
<thead>
<tr>
<th>Authors, year (PA domain)</th>
<th>Relative risk [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non–Hodgkin lymphoma</strong></td>
<td></td>
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<tr>
<td><strong>RRs based on men</strong></td>
<td></td>
</tr>
<tr>
<td>Parent et al., 2011 (OPA)</td>
<td>0.56 [0.26, 1.20]</td>
</tr>
<tr>
<td>Pukkala et al., 2000 (OPA)</td>
<td>0.78 [0.29, 1.70]</td>
</tr>
<tr>
<td>Pan et al., 2005 (RPA)</td>
<td>0.79 [0.59, 1.05]</td>
</tr>
<tr>
<td>Brownson et al., 1991 (OPA)</td>
<td>0.80 [0.60, 1.30]</td>
</tr>
<tr>
<td>Zahm et al., 1999 (OPA)</td>
<td>1.00 [0.70, 1.30]</td>
</tr>
<tr>
<td>Teras et al., 2012 (RPA)</td>
<td>1.02 [0.82, 1.26]</td>
</tr>
<tr>
<td>van Veldhoven et al., 2011 (OPA)</td>
<td>1.05 [0.46, 2.41]</td>
</tr>
<tr>
<td>Parent et al., 2011 (RPA)</td>
<td>1.17 [0.81, 1.69]</td>
</tr>
<tr>
<td>Kelly et al., 2012 (RPA)</td>
<td>1.37 [0.98, 1.92]</td>
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<td></td>
<td>Random effects model for RRs based on men</td>
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<tr>
<td><strong>RRs based on women</strong></td>
<td></td>
</tr>
<tr>
<td>Pan et al., 2005 (RPA)</td>
<td>0.78 [0.29, 1.70]</td>
</tr>
<tr>
<td>Teras et al., 2012 (RPA)</td>
<td>0.69 [0.54, 0.89]</td>
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<tr>
<td>Kelly et al., 2012 (RPA)</td>
<td>0.71 [0.47, 1.07]</td>
</tr>
<tr>
<td>Cerhan et al., 2002 (RPA)</td>
<td>0.83 [0.59, 1.11]</td>
</tr>
<tr>
<td>Kabat et al., 2012 (RPA)</td>
<td>0.98 [0.79, 1.20]</td>
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<tr>
<td>Lu et al., 2009 (OPA)</td>
<td>1.11 [0.86, 1.44]</td>
</tr>
<tr>
<td>van Veldhoven et al., 2011 (RPA)</td>
<td>1.25 [0.49, 3.16]</td>
</tr>
<tr>
<td>Zahm et al., 1999 (OPA)</td>
<td>1.70 [0.20, 11.50]</td>
</tr>
<tr>
<td>van Veldhoven et al., 2011 (OPA)</td>
<td>2.06 [0.65, 6.51]</td>
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<td>Random effects model for RRs based on women</td>
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<td><strong>RRs based on men and women combined</strong></td>
<td>0.67 [0.40, 1.13]</td>
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<td>Cerhan et al., 2005 (RPA)</td>
<td>0.78 [0.45, 1.38]</td>
</tr>
<tr>
<td>Lim et al., 2007 (TPA)</td>
<td>0.98 [0.81, 1.16]</td>
</tr>
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<td>Cerhan et al., 2005 (OPA)</td>
<td>0.98 [0.55, 1.74]</td>
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<td>Random effects model for RRs based on men and women combined</td>
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<tr>
<td></td>
<td>Random effects model for Non–Hodgkin lymphoma</td>
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<td><strong>RRs based on men</strong></td>
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<td>Parent et al., 2011 (OPA)</td>
<td>0.84 [0.17, 4.23]</td>
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<tr>
<td>Parent et al., 2011 (RPA)</td>
<td>0.97 [0.45, 2.08]</td>
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<td>Pukkala et al., 2000 (OPA)</td>
<td>1.33 [0.27, 3.88]</td>
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<td>Random effects model for RRs based on men</td>
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<td><strong>RRs based on women</strong></td>
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<td>Keegan et al., 2006 (RPA)</td>
<td>0.56 [0.37, 0.86]</td>
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<td>Random effects model for Hodgkin lymphoma</td>
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<td><strong>RRs based on men and women combined</strong></td>
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<tr>
<td>Paffenbarger et al., 1992 (RPA)</td>
<td>0.73 [0.38, 1.39]</td>
</tr>
<tr>
<td>Lim et al., 2007 (TPA)</td>
<td>1.60 [0.72, 3.54]</td>
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<tr>
<td></td>
<td>Random effects model for RRs based on men and women combined</td>
</tr>
</tbody>
</table>

Relative Risk (log scale)
Figure 2

Authors, year (PA domain) Relative risk [95% CI]

**Diffuse large B–cell lymphoma**

RRs based on men

- Teras et al., 2012 (RPA) 1.14 [0.70, 1.88]
- Kelly et al., 2012 (RPA) 1.19 [0.64, 2.21]
- van Veldhoven et al., 2011 (TPA) 2.03 [0.38, 10.79]

Random effects model for RRs based on men 1.19 [0.82, 1.74]

RRs based on women

- Teras et al., 2012 (RPA) 0.71 [0.44, 1.16]
- Kelly et al., 2012 (RPA) 0.80 [0.38, 1.69]
- Kabat et al., 2012 (RPA) 0.89 [0.59, 1.36]
- Lu et al., 2009 (RPA) 1.00 [0.62, 1.62]
- van Veldhoven et al., 2011 (TPA) 5.03 [1.19, 21.33]

Random effects model for RRs based on women 0.90 [0.70, 1.15]

RRs based on men and women combined

- Lim et al., 2007 (TPA) 0.87 [0.61, 1.25]

Random effects model for diffuse large B–cell lymphoma 0.95 [0.80, 1.14]

**Follicular lymphoma**

RRs based on men

- Teras et al., 2012 (RPA) 0.86 [0.49, 1.51]
- Kelly et al., 2012 (RPA) 0.96 [0.53, 1.72]
- van Veldhoven et al., 2011 (TPA) 2.82 [0.52, 15.23]

Random effects model for RRs based on men 0.96 [0.65, 1.43]

RRs based on women

- Teras et al., 2012 (RPA) 0.77 [0.41, 1.43]
- Kelly et al., 2012 (RPA) 0.90 [0.49, 1.67]
- Lu et al., 2009 (RPA) 1.01 [0.57, 1.79]
- Kabat et al., 2012 (RPA) 1.25 [0.81, 1.94]
- van Veldhoven et al., 2011 (TPA) 2.59 [0.54, 12.38]

Random effects model for RRs based on women 1.05 [0.80, 1.37]

RRs based on men and women combined

- Lim et al., 2007 (TPA) 0.96 [0.63, 1.46]

Random effects model for follicular lymphoma 1.01 [0.83, 1.22]

Random effects model for follicular and diffuse large B–cell lymphoma 0.98 [0.85, 1.11]
Figure 3

Authors, year (PA domain) Relative risk [95% CI]

**Leukemia**

**RRs based on men**
- Pukkala et al., 2000 (OPA) 0.51 [0.17, 1.19]
- Brownson et al., 1991 (OPA) 0.90 [0.60, 1.40]
- Soll–Johanning et al., 2004 (OPA) 1.08 [0.78, 1.45]
- Kasim et al., 2009 (RPA) 1.31 [0.93, 1.85]

Random effects model for RRs based on men 1.06 [0.86, 1.30]

**RRs based on women**
- Cerhan et al., 2002 (RPA) 0.91 [0.45, 1.67]
- Kasim et al., 2009 (RPA) 0.97 [0.66, 1.42]

Random effects model for RRs based on women 0.95 [0.69, 1.32]

**RRs based on men and women combined**
- Kabat et al., 2013 (TPA) 0.70 [0.49, 0.99]
- Paffenbarger et al., 1992 (RPA) 0.84 [0.45, 1.58]
- Ma et al., 2010 (RPA) 1.09 [0.84, 1.41]

Random effects model for RRs based on men and women combined 0.88 [0.64, 1.21]

Random effects model for leukemia 0.97 [0.84, 1.13]

**Chronic lymphocytic lymphoma / small lymphocytic lymphoma**

**RRs based on men**
- Teras et al., 2012 (RPA) 0.95 [0.62, 1.46]
- Kelly et al., 2012 (RPA) 1.71 [1.08, 2.70]

Random effects model for RRs based on men 1.27 [0.71, 2.26]

**RRs based on women**
- Kelly et al., 2012 (RPA) 0.53 [0.27, 1.06]
- Teras et al., 2012 (RPA) 0.73 [0.44, 1.20]
- Kabat et al., 2012 (RPA) 1.03 [0.70, 1.51]
- Lu et al., 2009 (RPA) 1.50 [0.86, 2.63]

Random effects model for RRs based on women 0.91 [0.62, 1.34]

**RRs based on men and women combined**
- Lim et al., 2007 (TPA) 0.80 [0.51, 1.25]

Random effects model for chronic lymphocytic lymphoma / small lymphocytic lymphoma 0.99 [0.75, 1.29]

**Multiple myeloma**

**RRs based on men**
- van Veldhoven et al., 2011 (TPA) 0.34 [0.05, 2.14]
- Khan et al., 2006 (RPA) 0.44 [0.21, 0.93]
- Birmann et al., 2007 (RPA) 0.80 [0.50, 1.50]
- Teras et al., 2012 (RPA) 0.99 [0.60, 1.64]
- Holmman et al., 2013 (RPA) 1.10 [0.82, 1.48]
- Pukkala et al., 2000 (OPA) 1.39 [0.56, 2.85]

Random effects model for RRs based on men 0.93 [0.70, 1.22]

**RRs based on women**
- Birmann et al., 2007 (RPA) 0.50 [0.20, 1.40]
- Teras et al., 2012 (RPA) 0.54 [0.28, 1.04]
- Khan et al., 2006 (RPA) 0.58 [0.26, 1.27]
- van Veldhoven et al., 2011 (TPA) 0.65 [0.14, 3.16]
- Blair et al., 2005 (RPA) 0.88 [0.51, 1.51]
- Holmman et al., 2013 (RPA) 1.43 [0.90, 2.26]

Random effects model for RRs based on women 0.79 [0.53, 1.18]

Random effects model for multiple myeloma 0.86 [0.68, 1.09]
Figure 4

MET-hours per week

Relative risk (log scale)

0 10 20 30 40 50 60

0.5

0.6

0.7

0.8

0.9

1

1.1

1.2

1.3

1.4

1.5

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Physical activity in relation to risk of hematologic cancers: a systematic review and meta-analysis

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