

# Lifetime Physical Activity and the Risk of Non-Hodgkin Lymphoma

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## Abstract

Research regarding the association between physical activity and the risk of non-Hodgkin lymphoma (NHL) is limited and inconsistent, and few studies have investigated whether the intensity and timing of physical activity influence the association. A case-control study of NHL was conducted in British Columbia, Canada, in 2000 to 2004. Data were collected on various NHL risk factors, including moderate-intensity and vigorous-intensity physical activity performed over the lifetime. Logistic regression was used to estimate the association between physical activity and the risk of NHL. This analysis included 818 controls and 749 cases. Lifetime vigorous-intensity physical activity was inversely associated with NHL risk. Participants in the second, third, and fourth quartiles of lifetime

vigorous-intensity physical activity had an approximately 25% to 30% lower risk of NHL than those in the lowest quartile [adjusted odds ratios, 0.69 (95% confidence interval [CI], 0.52–0.93); 0.68 (95% CI, 0.50–0.92); and 0.75 (95% CI, 0.55–1.01), respectively]. No consistent associations were observed for total or moderate-intensity physical activity. There were no apparent age periods in which physical activity appeared to confer a greater risk reduction. In this study, we found that lifetime vigorous-intensity physical activity was associated with a significantly reduced risk of NHL. Given this finding, more research on physical activity intensity and timing in relation to NHL risk is warranted. *Cancer Epidemiol Biomarkers Prev*; 24(5); 873–7. ©2015 AACR.

## Introduction

Non-Hodgkin lymphoma (NHL) accounted for approximately 3% of worldwide incident cancers in 2012 (1). NHL has few well-established risk factors, and little is known about its etiology (2). As such, the identification of modifiable risk factors is particularly important for the prevention and control of NHL (3).

Physical activity is convincingly associated with a reduced risk of several cancers, including colon, postmenopausal breast, and endometrial cancers (4). There is limited and inconsistent research regarding the association between physical activity and NHL risk; only 13 previous studies have investigated this association. Two recent meta-analyses of these studies indicate that people with the highest physical activity levels may have a slightly lower risk of NHL than people with the lowest physical activity levels (5, 6). Although there is no established etiologic pathway that explains how physical activity may reduce NHL risk, several plausible mechanisms have been suggested. Physical activity reduces obesity and increases immune function, both of which

are hypothesized to play a role in NHL development (3, 5). Physical activity may also influence NHL risk by reducing inflammation, improving insulin sensitivity, and improving antioxidant defense systems (3, 5).

Research indicates that the intensity and timing of physical activity may influence the association between physical activity and cancer risk (7–9); however, few studies have investigated these issues in relation to NHL risk (5, 6). Only two studies have considered different levels of intensity when examining the association between physical activity and NHL risk, and there is limited research regarding the association between long-term or lifetime physical activity and NHL risk.

The aims of this study were to investigate the associations between (1) lifetime total, moderate-intensity, and vigorous-intensity physical activity and NHL risk; and (2) total, moderate-intensity, and vigorous-intensity recreational physical activity performed during specific age periods and NHL risk.

## Materials and Methods

To investigate these aims, we used data from a case-control study that was conducted between 2000 and 2004 in British Columbia (BC), Canada (10). The study recruited 820 incident NHL cases (78.7% response rate) from the BC Cancer Registry and 848 randomly selected age group-, sex-, and residential location (Greater Vancouver Regional District or Capital Regional District) matched controls (45.7% response rate) from the Client Registry of the BC Ministry of Health. The Registry contains contact information for virtually the entire BC population, including all members of the mandatory provincial health insurance plan. All incident NHL cases were confirmed by a pathologist. NHL subtype was categorized as diffuse large B-cell lymphoma, follicular lymphoma, other B-cell lymphomas, and T-cell lymphomas (11).

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

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doi: 10.1158/1055-9965.EPI-14-1303

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A questionnaire (administered by self-report or computer-assisted telephone interview) was used to collect information about demographic characteristics and various possible NHL risk factors, including lifetime recreational physical activity. The study received approval from the BC Cancer Agency–University of BC Research Ethics Board. All participants gave written informed consent.

#### Assessment of physical activity

For each decade of life (i.e., 10–19 years, 20–29 years, and so on, to 70–79 years), participants were asked to record the average number of days/week and hours/day that they performed each of "mild," "moderate," and "vigorous" physical activity (see Supplementary Fig. S1). Participants were asked not to include job-related activities. "Mild" activities were defined as those that increase heart and breathing rates above resting level (example activities included gardening and heavy housework). Moderate activities were defined as those that increase heart rate moderately, and vigorous activities were defined as those that increase breathing and heart rates to a high level. No example moderate or vigorous activities were included on the questionnaire. A metabolic-equivalent (MET) value was assigned to each activity type (3.3, 4.0, and 8.0 for mild, moderate, and vigorous, respectively).

On the basis of these data, the average number of hours/week spent in each activity type in each age period was calculated. We then calculated the average MET-hours/week for each activity type in each age period by multiplying the average number of hours/week by the relevant MET value. These totals were summed to create a MET-hour/week total for each age period (i.e., mild plus moderate plus vigorous). We also combined the mild and moderate MET-hour/week totals to create a measure of moderate-intensity physical activity (i.e., activities with a MET value between 3 and 5.9), while the vigorous totals were considered to be a measure of vigorous-intensity physical activity (i.e., activities with a MET value of 6 or greater).

To investigate the association between lifetime physical activity and NHL risk, we calculated the average MET-hours/week over the lifetime for each of total, moderate-intensity, and vigorous-intensity physical activity, and then classified participants into quartiles, based on the distribution among controls. To investigate the association between NHL risk and physical activity in specific age periods, in each age period we classified participants into quartiles of total and moderate-intensity physical activity, based on the distribution among controls; and categorized participants as having done none or some vigorous-intensity physical activity.

#### Statistical analysis

Sixty participants were excluded due to large amounts of missing physical activity data, and a further 41 participants with missing ethnicity information were excluded, leaving 1,567 participants (818 controls and 749 cases) in this analysis.

Logistic regression was used to estimate the association between physical activity and NHL risk, and multinomial logistic regression was used to determine whether the association between physical activity and NHL risk differed by NHL subtype.

The frequency-matching variables (age group, sex, and residential location) were included as covariates in all analyses. A directed acyclic graph (causal diagram) was used to inform the choice of other covariates (12). The following known or possible NHL risk factors were included on the causal diagram: alcohol consumption, autoimmune disorders, educational attainment (as a proxy

for socioeconomic status), energy intake, ethnicity, family history of NHL, immune function, obesity, smoking, sun exposure, and vitamin D intake (see Supplementary Fig. S1). Associations between these variables, and the direction of the associations, were based on the published literature. Immune function, sun exposure, and obesity were assumed to be on the causal pathway. Ethnicity, educational attainment, and autoimmune disease were identified as a minimal sufficient set of confounders, and a model containing these three variables and the frequency-matching variables was considered the "fully-adjusted" model. To increase precision, we then used the backward deletion strategy to remove confounders until the change-in-estimate from the "fully adjusted" model was greater than 5% (13). Ethnicity (along with the frequency-matching variables) was the only covariate that remained in the model following this procedure. Moderate-intensity and vigorous-intensity physical activity were mutually adjusted. Trend tests were conducted by entering the relevant ordinal variable into the model as a continuous variable.

We tested for nonlinearity in the associations between NHL risk and lifetime total, moderate-intensity, and vigorous-intensity physical activity using fractional polynomial regression, with the exposure variables entered into "fully adjusted" models as continuous MET-hours/week variables. There was no significant evidence that any of these associations were nonlinear (i.e., models including first- or second-degree fractional polynomials were not a significantly better fit than linear models). A significance level of  $P = 0.05$  was used in all analyses. All analyses were performed using Stata 13.1 (StataCorp).

## Results

Demographic characteristics of the participants are shown in Table 1. Cases were more likely than controls to be male, be in an older age group, live in the Greater Vancouver Regional District, to have not completed high school, and to have had autoimmune disease. The distribution of the lifetime physical activity variables by sex and NHL subtype is shown in Supplementary Table S1.

There was no clear association between lifetime total physical activity (lifetime average MET-hours/week) and overall NHL risk, and lifetime moderate-intensity physical activity did not appear to be associated with NHL risk (Table 2). For lifetime vigorous-intensity physical activity, participants in the second, third, and fourth quartiles of average MET-hours/week had an approximately 25% to 30% lower risk of NHL than those in the lowest quartile [adjusted odds ratios, 0.69; 95% confidence interval (CI), 0.52–0.93; 0.68; 95% CI, 0.50–0.92; and 0.75; 95% CI, 0.55–1.01, for the second, third, and fourth quartiles respectively;  $P_{\text{Trend}} = 0.072$ ]. An inverse association between lifetime vigorous-intensity physical activity and overall NHL risk was observed in both males and female, although among males the largest risk reduction was found in the second and third quartiles, while in females the greatest risk reduction was observed in the highest quartile ( $P_{\text{Trend}} = 0.228$  and 0.144 for males and females, respectively).

For lifetime vigorous-intensity physical activity, an inverse association was observed for all NHL subtypes (Table 3). Stronger associations were observed for follicular lymphoma and other B-cell lymphomas than for diffuse large B-cell lymphoma and T-cell lymphoma; however, these differences were not statistically significant. Neither lifetime total nor moderate-intensity physical activity was associated with the risk of any NHL subtype.

**Table 1.** Characteristics of the participants in a case-control study of NHL, British Columbia, Canada, 2000-2004

Characteristic	Controls (n = 818) n (%)	Cases (n = 749) n (%)
Sex		
Male	435 (53.2)	441 (58.9)
Female	383 (46.8)	308 (41.1)
Age, y		
20-39	114 (13.9)	64 (8.5)
40-49	117 (14.3)	86 (11.5)
50-59	172 (21.0)	182 (24.3)
60-69	211 (25.8)	198 (26.4)
70+	204 (24.9)	219 (29.2)
Residential location		
Greater Vancouver Regional District	634 (77.5)	615 (82.1)
Capital Region District	184 (22.5)	134 (17.9)
Ethnicity		
White	645 (78.9)	612 (81.7)
Asian	93 (11.4)	75 (10.0)
South Asian	43 (5.3)	27 (3.6)
Other/mixed	37 (4.5)	35 (4.7)
Education		
Did not complete high school	111 (13.7)	140 (18.8)
High school only	191 (23.6)	189 (25.4)
Vocational qualification	188 (23.2)	145 (19.5)
Some university	74 (9.1)	58 (7.8)
Undergraduate university degree	154 (19.0)	126 (16.9)
Postgraduate university degree	91 (11.2)	87 (11.7)
Autoimmune disorder		
No	707 (86.7)	612 (81.8)
Yes	109 (13.4)	136 (18.2)

There were no specific age periods in which physical activity appeared to confer a greater risk reduction (Supplementary Tables S2 and S3).

## Discussion

In this study, we found that vigorous-intensity lifetime physical activity was associated with a significantly reduced risk of NHL. An inverse association was seen in both males and females and for all

NHL subtypes. No consistent associations were observed between NHL risk and total or moderate-intensity physical activity.

We found that lifetime vigorous-intensity physical activity was more strongly associated with NHL risk than moderate-intensity physical activity or physical activity in any specific age period. Only one previous study has examined lifetime non-occupational physical activity in relation to NHL risk, with the results indicating no association (14). In regard to physical activity intensity, although it is possible that vigorous-intensity physical activity is required to reduce NHL risk, another explanation is that measures of vigorous-intensity physical activity are better able to distinguish between active and inactive participants. Measures of vigorous-intensity physical activity are more reliable than measures of moderate-intensity physical activity (15), so may result in less exposure misclassification. Only two previous studies have considered different intensity levels when examining the association between physical activity and NHL risk (16, 17). One study found a slightly stronger inverse association for vigorous-intensity physical activity than for moderate-intensity physical activity (16), while the other found the opposite for females and no difference for males (17). There are too little data to draw any firm conclusions regarding whether intensity and/or timing influence the association between physical activity and NHL risk.

In NHL subtype analyses, we found a stronger association for physical activity and the risk of follicular lymphoma and other B-cell lymphomas than for diffuse large B-cell lymphoma and T-cell lymphoma, although these differences were not statistically significant. Although two studies have found that physical activity may have a greater influence on follicular lymphoma risk than diffuse large B-cell lymphoma risk (17, 18), most studies have found little variation between physical activity and the risk of different NHL subtypes (14, 16, 19-23). It remains unclear whether the association between physical activity and NHL risk varies by subtype.

This study had several limitations that should be considered. First, the validity and reliability of the physical activity questionnaire is unknown, although the questions are similar to those in widely used questionnaires used to measure recent physical activity (24). While research indicates that physical activity

**Table 2.** Associations between lifetime total, moderate-intensity, and vigorous-intensity physical activity and the risk of NHL in a case-control study conducted in British Columbia, Canada, 2000-2004

Lifetime physical activity	Controls (n = 818) n (%)	Cases (n = 749) n (%)	All participants AOR <sup>a</sup> (95% CI)	Males AOR <sup>a</sup> (95% CI)	Females AOR <sup>a</sup> (95% CI)
Total					
0-35.9 MET-hours/week	205 (25.1)	208 (27.7)	1.00	1.00	1.00
36-58.9 MET-hours/week	208 (25.4)	165 (22.0)	0.79 (0.59-1.06)	0.87 (0.60-1.26)	0.66 (0.41-1.05)
59-84.9 MET-hours/week	208 (25.4)	154 (20.6)	0.73 (0.54-0.99)	0.75 (0.50-1.11)	0.64 (0.40-1.03)
85+ MET-hours/week	197 (24.1)	222 (29.6)	1.16 (0.87-1.55)	1.14 (0.78-1.68)	1.07 (0.68-1.68)
<i>P</i> <sub>Trend</sub>			0.332	0.661	0.591
Moderate intensity					
0-18.9 MET-hours/week	209 (25.6)	205 (27.4)	1.00	1.00	1.00
19-35.9 MET-hours/week	201 (24.6)	172 (23.0)	0.86 (0.64-1.15)	0.79 (0.55-1.12)	1.02 (0.60-1.75)
36-55.9 MET-hours/week	202 (24.7)	163 (21.8)	0.86 (0.63-1.17)	0.90 (0.61-1.34)	0.77 (0.46-1.27)
56+ MET-hours/week	206 (25.2)	209 (27.9)	1.15 (0.84-1.57)	1.06 (0.68-1.65)	1.14 (0.71-1.83)
<i>P</i> <sub>Trend</sub>			0.375	0.807	0.062
Vigorous intensity					
0-4.9 MET-hours/week	199 (24.3)	220 (29.4)	1.00	1.00	1.00
5-18.9 MET-hours/week	212 (25.9)	177 (23.6)	0.69 (0.52-0.93)	0.58 (0.38-0.89)	0.79 (0.52-1.18)
19-36.4 MET-hours/week	204 (24.9)	165 (22.0)	0.68 (0.50-0.92)	0.51 (0.33-0.78)	0.99 (0.64-1.53)
36.5+ MET-hours/week	203 (24.8)	187 (25.0)	0.75 (0.55-1.01)	0.71 (0.47-1.09)	0.62 (0.38-1.01)
<i>P</i> <sub>Trend</sub>			0.072	0.228	0.144

Abbreviation: AOR, adjusted odds ratio.

<sup>a</sup>Adjusted for the frequency matching variables (age group, sex, and residential location) and ethnicity. Moderate-intensity and vigorous-intensity physical activity are mutually adjusted.

**Table 3.** Associations between lifetime total, moderate-intensity, and vigorous-intensity physical activity and the risk of NHL subtypes in a case-control study conducted in British Columbia, Canada, 2000–2004

Lifetime physical activity	Diffuse large B-cell (n = 202) AOR <sup>a</sup> (95% CI)	Follicular (n = 188) AOR <sup>a</sup> (95% CI)	Other B-cell (n = 268) AOR <sup>a</sup> (95% CI)	T-cell (n = 70) AOR <sup>a</sup> (95% CI)
Total				
0–35.9 MET-hours/week	1.00	1.00	1.00	1.00
36–58.9 MET-hours/week	0.70 (0.44–1.11)	0.93 (0.59–1.49)	0.87 (0.58–1.30)	0.65 (0.31–1.35)
59–84.9 MET-hours/week	0.80 (0.51–1.28)	0.73 (0.44–1.19)	0.81 (0.54–1.23)	0.58 (0.27–1.24)
85+ MET-hours/week	1.22 (0.79–1.88)	1.26 (0.80–1.99)	1.04 (0.69–1.57)	1.19 (0.61–2.32)
<i>P</i> <sub>Trend</sub>	0.256	0.450	0.883	0.648
Moderate intensity				
0–18.9 MET-hours/week	1.00	1.00	1.00	1.00
19–35.9 MET-hours/week	0.70 (0.44–1.11)	0.89 (0.55–1.44)	1.12 (0.75–1.69)	0.72 (0.36–1.43)
36–55.9 MET-hours/week	0.97 (0.62–1.53)	0.96 (0.59–1.55)	0.82 (0.53–1.29)	0.54 (0.24–1.20)
56+ MET-hours/week	1.00 (0.62–1.61)	1.08 (0.66–1.77)	1.48 (0.96–2.28)	0.91 (0.44–1.86)
<i>P</i> <sub>Trend</sub>	0.704	0.697	0.178	0.635
Vigorous intensity				
0–4.9 MET-hours/week	1.00	1.00	1.00	1.00
5–18.9 MET-hours/week	0.58 (0.36–0.93)	0.59 (0.37–0.93)	0.78 (0.52–1.15)	0.88 (0.45–1.72)
19–36.4 MET-hours/week	0.72 (0.45–1.15)	0.64 (0.40–1.02)	0.77 (0.51–1.16)	0.48 (0.22–1.06)
36.5+ MET-hours/week	0.94 (0.60–1.49)	0.71 (0.44–1.14)	0.59 (0.38–0.92)	0.80 (0.39–1.67)
<i>P</i> <sub>Trend</sub>	0.859	0.207	0.028	0.323

Abbreviation: AOR, adjusted odds ratio.

<sup>a</sup>Adjusted for the frequency matching variables (age group, sex, and residential location) and ethnicity. Moderate-intensity and vigorous-intensity physical activity are mutually adjusted.

performed in the past can be recalled reliably (15, 25), asking participants about their physical activity levels in early adulthood is likely to result in some exposure misclassification. This exposure misclassification was likely to have been nondifferential, so any possible bias was likely to have been in the direction of the null. Second, the low response rate among controls means we cannot rule out selection bias as a possible explanation for the observed results. It is possible that controls who participated in the study were more physically active than nonparticipants, so we may have overestimated the possible inverse association between physical activity and NHL risk. Another possible explanation for the results is recall bias. Physical activity is not a well-known risk factor for NHL, so recall bias is unlikely to have had a large influence; however, we cannot rule it out as an explanation.

In conclusion, in this case-control study, we found that lifetime vigorous-intensity physical activity was associated with a significantly reduced risk of NHL. Given this finding, more research on physical activity intensity and timing in relation to NHL risk is warranted.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

### Authors' Contributions

Conception and design: R.P. Gallagher, J.J. Spinelli

Development of methodology: R.P. Gallagher, J.J. Spinelli

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R.P. Gallagher, R.D. Gascoyne, J.M. Connors, J.J. Spinelli

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 Writing, review, and/or revision of the manuscript: T. Boyle, R.P. Gallagher, R.D. Gascoyne, J.M. Connors, N.D. Le, J.J. Spinelli  
 Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): R.P. Gallagher  
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### Acknowledgments

The authors thank Agnes Lai and Zenaida Abanto (Cancer Control Research, British Columbia Cancer Agency) for their contributions to this study.

### Grant Support

This study was supported by the National Cancer Institute of Canada (grant to R.P. Gallagher, R.D. Gascoyne, J.M. Connors, N.D. Le, and J.J. Spinelli), the Canadian Institutes of Health Research (grant to R.P. Gallagher, R.D. Gascoyne, J.M. Connors, N.D. Le, and J.J. Spinelli; fellowship #300068 to T. Boyle), the Michael Smith Foundation for Health Research (Postdoctoral Fellowship #5553 to T. Boyle), The University of British Columbia (Honorary Killam Postdoctoral Research Fellowship to T. Boyle), and the Australian National Health and Medical Research Council (Early Career Fellowship #1072266 to T. Boyle).

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Received November 19, 2014; revised February 3, 2015; accepted February 16, 2015; published online May 1, 2015.

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*Cancer Epidemiol Biomarkers Prev* 2015;24:873-877.

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