Leukemia Research 69 (2018) 7–11

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Lifetime physical inactivity is associated with increased risk for Hodgkin and non-Hodgkin lymphoma: A case-control study

John Lewis Etter[a,1], Rikki Cannioto[a,1], Kah Teong Soh[b], Emad Alquassim[a], Hani Almohanna[a], Zachary Dunbar[c], Janine M. Joseph[a], Sophia Balderman[d], Francisco Hernandez-Ilizaliturri[d], Kirsten B. Moysich[a,*]

[a] Department of Cancer Prevention and Control, Roswell Park Comprehensive Cancer Center, Buffalo, NY, United States
[b] Department of Flow and Image Cytometry, Roswell Park Comprehensive Cancer Center, Buffalo, NY, United States
[c] Department of Health Behavior, Roswell Park Comprehensive Cancer Center, Buffalo, NY, United States
[d] Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY, United States

ARTICLE INFO

Keywords:
Hodgkin lymphoma risk
Non-Hodgkin lymphoma risk
Physical inactivity

ABSTRACT

Background: Although physical activity is a well-established risk factor for several cancer types, studies evaluating its association with lymphoma have yielded inconclusive results. In such cases where physical activity is not clearly associated with cancer risk in a dose-dependent manner, investigators have begun examining physical inactivity as an independent exposure of interest.

Methods: Associations of self-reported, lifetime physical inactivity with risk of developing Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) were evaluated in a hospital-based case control study using data from the Patient Epidemiology Data System at Roswell Park Comprehensive Cancer Center. Participants included 87 patients with HL and 236 patients with NHL as well as 348 and 952 cancer-free controls, respectively. Multivariable-adjusted logistic regression models were fit to calculate odds ratios (OR) and 95% confidence intervals (CI) estimating the association between physical inactivity and lymphoma risk.

Results: We observed significant, positive associations between lifetime recreational physical inactivity and risk of both HL (OR = 1.90, 95% CI: 1.15–3.15) and NHL (OR = 1.35, 95% CI: 1.01–1.82).

Conclusions: The current analysis provides evidence for a positive association between physical inactivity and risk of both HL and NHL. These results add to a growing body of research suggesting that lifetime physical inactivity may be an important independent, modifiable behavioral risk factor for cancer.

1. Introduction

The two most common subtypes of lymphoma, Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), are estimated to account for 0.5% and 4.3% of all new cancer cases and 0.2% and 3.4% of all cancer deaths respectively in the United States in 2017 [1,2]. Well-established unmodifiable risk factors for both HL and NHL include immunosuppression, immunodeficiency, age and sex, with men being disproportionately affected. Additional NHL risk factors include autoimmune disorders, such as rheumatoid arthritis and Sjögren syndrome, as well as bacterial infections, such as Helicobacter pylori [3,4]. Lastly, a family history of HL is associated with increased risk of HL, however only 5% of cases have a family link.

Because few modifiable risk or protective factors for HL and NHL have been identified, several studies have investigated the role of physical activity in HL and NHL risk; however, these studies have yielded mixed and inconclusive results [5,6]. In situations where investigations have yielded inconsistent evidence representing the associations of risk of certain cancer types with incrementally higher levels of physical activity exposure, researchers have begun to examine *physical inactivity* as a potentially valuable independent exposure of interest for several important reasons [7–11]. First, despite recommendations by the 2008 Physical Activity Guidelines for Americans to avoid physical inactivity, approximately 50–79% of Americans are insufficiently active [12]. Further, evidence suggests that physically inactive individuals will derive the greatest benefit from exercise interventions

Abbreviations: HL, Hodgkin lymphoma; NHL, Non-Hodgkin lymphoma; PEDS, Patient Epidemiology Data System; OR, odds ratio; CI, confidence interval

* Corresponding author at: Department of Cancer Prevention and Control, Roswell Park Comprehensive Cancer Center, 352 Carlton House, Elm and Carlton Streets, Buffalo, NY 14263, United States.
E-mail address: Kirsten.moysich@roswellpark.org (K.B. Moysich).

[1] These authors contributed equally to this work as co-first authors.

https://doi.org/10.1016/j.leukres.2018.03.014
Received 9 May 2017; Received in revised form 23 March 2018; Accepted 26 March 2018
Available online 27 March 2018
0145-2126/

and are least likely to self-misclassify their physical activity level [13,14]. It has recently been shown that even the smallest amounts of physical activity associate with decreased mortality [15]. Lastly, physical inactivity may associate with cancer endpoints via pathways that are, at least in part, independent of obesity [16–18].

Nevertheless, because physical inactivity has conventionally been identified as a referent group in epidemiologic studies, our understanding of the independent associations between physical inactivity and cancer risk, including those of HL and NHL, remains poor. To date, no studies have evaluated the independent associations of lifetime physical inactivity with HL or NHL risk. As such, in the current hospital-based case-control analyses, we sought to examine the associations of HL and NHL with lifetime, self-reported physical inactivity. We hypothesized that those with HL or NHL would be more likely to report a history of lifetime physical inactivity than controls without cancer.

2. Material and methods

2.1. Epidemiologic questionnaire and study population

The study population for this hospital-based, case-control analysis was composed of individuals who participated in the Patient Epidemiology Data System (PEDS) and completed an epidemiologic questionnaire while receiving medical services at Roswell Park Comprehensive Cancer Center between 1989 and 1998. The PEDS questionnaire was a self-administered epidemiologic survey offered to all patients receiving medical service at Roswell Park and was completed within 6 months of diagnosis (median: 21 days) with a 50% response rate [19–22]. The Roswell Park Institutional Review Board approved the conduct of the study and all participants provided informed consent.

Both HL and NHL cases were identified through the Roswell Park tumor registry. Cases included 87 individuals with primary, incident HL and 236 individuals with primary, incident NHL. Among NHL cases, 134 (56.78%) were diffuse NHL, 97 (41.10%) were follicular NHL, and five (2.12%) were categorized as other or unspecified types of NHL. Controls were sex- and age-matched via nearest neighbor sampling at a 1:4 case-control ratio [23]. Controls included 348 individuals for HL analyses and 952 individuals for NHL analyses identified from a pool of 10,642 potentially eligible controls who were seen at Roswell Park Comprehensive Cancer Center under suspicion of malignant disease but who were ultimately diagnosed with non-malignant conditions.

2.2. Lifetime recreational physical inactivity

The PEDs questionnaire included a section on recreational physical activity with questions assessing age of initiation of activity, total duration of the activity in years, and frequency of the activity in times per week or month. The questionnaire defined 'recreational physical activity' as exercising for health or pleasure in activities such as jogging, walking, or aerobics.

Congruent with the Physical Activity Guidelines for Americans, we defined physical inactivity, our exposure of interest, as the absence of regular, weekly, recreational physical activity [24]. Thus, participants reporting less than one weekly session of exercise, spanning all of the years preceding study enrollment, were classified as physically inactive. Conversely, those reporting at least one regular session of physical activity per week on average were classified as physically active.

2.3. Covariates and assessment of confounding

Age, sex, body mass index (BMI), family history of lymphoma and smoking (pack-years) were identified *a priori* as important variables for adjustment. Potential confounding effects of additional variables such as decade of study enrollment and education level were assessed by the ten percent change-in-estimate method as described by Maldonado et al. [25]. For HL analyses, education level (less than high school, high school graduate, some higher education) met this criterion and was included as a covariate in the multivariate model. In NHL analyses, all additional variables failed to meet this criterion and were thus omitted from the multivariate model.

2.4. Statistical analyses

Two tailed *t*-tests and Pearson's χ^2 tests were used to compare descriptive characteristics between cases and controls. Unconditional multivariate logistic regression models were fit to estimate the odds ratios (OR) and 95% confidence intervals (CI) describing the association between physical inactivity and risk of HL and NHL. Multivariate models were adjusted for age, sex, BMI, education level, family history and smoking (pack-years) for HL analyses and age, sex, BMI, family history, and smoking (pack-years) for NHL analyses. Despite small stratified sample sizes, exploratory analyses were stratified by BMI (normal-weight versus overweight/obese) and smoking status (never, former, current) to evaluate for possible effect modification and formal tests for interaction between physical inactivity and these stratifying variables were conducted utilizing a cross-product term in multivariable models, with effect modification declared at $p < 0.01$. All statistical analyses were performed using R version 3.2.2 [26]. All tests were two-sided and considered statistically significant at $p < 0.05$. All analyses were confirmed by a second data-analyst using SPSS version 21.

3. Results

Comparisons between descriptive characteristics of HL and NHL cases and controls are shown in Table 1. Both HL and NHL cases were more likely to report a lifetime of physical inactivity. No additional significant differences were observed between cases and controls.

Age- and multivariable- adjusted ORs representing the associations between lifetime physical inactivity and HL risk are shown in Table 2. Overall, in multivariable analyses, there was a strong, positive association between physical inactivity and risk of HL (OR = 1.90, 95% CI: 1.15–3.15). After stratifying by BMI (normal weight vs. overweight/obese), the observed associations remained positive. We observed a strong association among overweight/obese individuals (OR = 2.79, 95% CI: 1.29–6.23) and a similar trend among normal weight individuals (OR = 1.29, 95% CI: 0.62–2.64). Likewise, after stratifying by smoking status, we observed a positive association among never-smokers (OR = 3.30, 95% CI: 1.63–6.75) and a signal suggestive of a positive association among ever smokers (OR = 1.20, 95% CI: 0.58–2.50). Despite significant measures of association, stratified analyses were limited by small sample sizes and interaction terms for both BMI and smoking status were not statistically significant in multivariable-adjusted models (0.749, 0.140, respectively).

Table 3 contains age- and multivariable- adjusted ORs representing the associations between physical inactivity and NHL. Overall, a strong, positive association was observed between physical inactivity and NHL risk (OR = 1.35, 95% CI: 1.01–1.82). After stratifying by BMI, we observed a positive association among normal-weight individuals (OR = 1.84, 95% CI: 1.13–3.01) and a similar trend among overweight/obese individuals (OR = 1.17, 95% CI: 0.80–1.72). In subgroup analyses by smoking status, we observed positive signals among ever-smokers (OR = 1.37, 95% CI: 0.92–2.05) and never smokers (OR = 1.32, 95% CI:0.85–2.07). Again, despite statistically significant stratified results, these analyses were limited by small sample sizes and interaction terms for both BMI and smoking status were not statistically significant in multivariable-adjusted models (p = .399, p = .709, respectively).