Cancer Treatment and Research Communications 14 (2018) 37–45

Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

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

Lifetime physical inactivity is associated with lung cancer risk and mortality

Rikki Cannioto[a,1], John Lewis Etter[a,1], Michael J. LaMonte[b], Andrew D. Ray[c], Janine M. Joseph[a], Emad Al Qassim[a], Kevin H. Eng[d], Kirsten B. Moysich[a,*]

[a] Department of Cancer Prevention and Control, Roswell Park Comprehensive Cancer Center, Elm and Carlton Streets, Buffalo, New York 14263, United States
[b] Department of Epidemiology and Environmental Health, University at Buffalo, 273 Farber Hall, Buffalo NY 14214, United States
[c] Department of Rehabilitation Science, University at Buffalo, 632 Kimball Tower, Buffalo NY 14214, United States
[d] Department of Biostatistics, Roswell Park Comprehensive Cancer Center, Elm and Carlton Streets, Buffalo, New York 14263, United States

ARTICLE INFO

Keywords:
Lung cancer epidemiology
Lung cancer risk
Lung cancer survival
Lung cancer mortality
Physical inactivity

ABSTRACT

Introduction: Investigations of the independent associations of physical inactivity with cancer endpoints have been mounting in the epidemiological literature, in part due to the high prevalence of physical inactivity among cancer patients and to evidence that inactivity associates with carcinogenesis via pathways independent of obesity. Yet, physical inactivity is not currently recognized as a well-established risk or prognostic factor for lung cancer. As such, we examined the associations of lifetime physical inactivity with lung cancer risk and mortality in a hospital-based, case-control study.

Presentation of case: materials and methods: The analyses included data from 660 lung cancer patients and 1335 matched cancer-free controls. Multivariable logistic regression analyses were utilized to assess the association between lifetime physical inactivity and lung cancer risk, and Cox proportional hazards models were utilized to estimate the association between lifetime physical inactivity and mortality among lung cancer cases.

Results: We observed a significant positive association between lifetime physical inactivity and lung cancer risk: [Odds ratio (OR) = 2.23, 95% confidence interval (CI): 1.77–2.81]; the association remained significant among never smokers (OR = 3.00, 95% CI:1.33-6.78) and non-smokers (OR = 2.33, 95% CI: 1.79–3.02). We also observed a significant positive association between lifetime physical inactivity and lung cancer mortality [Hazard ratio (HR) = 1.40, 95% CI: 1.14–1.71]; the association remained significant in non-smokers (HR = 1.51, 95% CI: 1.16–1.96).

Discussion/conclusion: These data add to the body of evidence suggesting that physical inactivity is an independent risk and prognostic factor for cancer. Additional research utilizing prospectively collected data is needed to substantiate the current findings.

Introduction

In 2018, lung cancer will account for over 234,000 new cancer diagnoses and 154,000 cancer deaths in the United States, making it the second most commonly diagnosed, and the most deadly, cancer in the U.S.[1] Active cigarette smoking is the most well-established behavioral risk factor for lung cancer, accounting for as much as 90% of newly diagnosed lung cancer cases [2]. Thus, the majority of efforts to prevent lung cancer and improve prognosis are focused on smoking cessation. However, given the high burden of lung cancer incidence and the poor survival outcomes, the identification of additional behavioral risk and prognostic factors for lung cancer could be of significant public health importance, especially among never-smokers. In fact, lung cancer among never smokers represents the seventh most common cancer globally [3], and lung cancer rates among female never-smokers are rising [4].

While a recently published meta-analysis of epidemiological evidence reported an inverse association between the highest level of recreational physical *activity* exposure and lung cancer risk [2], data representing the associations between physical activity and lung cancer endpoints among women, non-smokers, and among the individual subtypes of lung cancer is limited [2,4]. Importantly, physical activity

Abbreviations: OR, odds ratio; HR, hazard ratio; CI, confidence intervals; RPCI, Roswell Park Cancer Institute; PEDS, Patient Epidemiology Data System; BMI, body mass index; RERI, Relative Excess Risk due to Interaction; FEV, Forced Expiratory Volume; FVC, Forced Vital Capacity

* Correspondence to: 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 first authors.

https://doi.org/10.1016/j.ctarc.2018.01.001
Received 10 July 2017; Received in revised form 9 January 2018; Accepted 16 January 2018

exposure is not currently recognized by the National Cancer Institute or the American Cancer Society as a well-established protective or prognostic factor for lung cancer [5,6], and little is known about the independent association of physical *inactivity* with lung cancer risk and prognosis.

Despite national guidelines encouraging Americans to avoid physical inactivity [7], current reports suggest that 50 to 79% of Americans are insufficiently physically active during their leisure time [8]. As a result, researchers have called for more investigations of the associations between physical *inactivity* and cancer endpoints [9]. Yet, under the prevailing paradigm of epidemiological physical activity research, the "no-activity", or the lowest activity level, is typically identified as the referent group. Thus, the independent associations of physical inactivity with cancer risk and survival often remain unreported. This may be an important public health oversight due to a recently published report suggesting that even the smallest amounts of physical activity associate with decreased mortality [10]. Thus, investigations emphasizing physical inactivity as an independent exposure of interest may be especially impactful for disease sites in which physical activity exposure has not been identified as a well-established protective or prognostic factor. That is, a lack of a consistent association between incrementally higher quantities of physical activity with cancer endpoints should not preclude additional investigations of the independent associations of inactivity with cancer risk and mortality merely due to convention. Rather, given the high prevalence of physical inactivity at the population level and the hypothesis that the greatest protective benefits can be achieved by increasing activity levels among those at the low end of the activity continuum [11], physically inactive individuals could be a particularly important group to study from a public health perspective. Further, there is also a body of literature suggesting that self-reported physical inactivity is assessed with less exposure misclassification in comparison to self-reported incrementally higher levels of activity exposure [11,12], and that inactivity may associate with cancer endpoints independently of obesity [9,13].

Based on this collective knowledge, we sought to investigate the associations of lifetime recreational physical *inactivity* with lung cancer risk and mortality. We hypothesized that lung cancer patients would be more likely to report a history of lifetime physical inactivity in comparison to controls without cancer and that physically inactive patients would have poorer survival outcomes. To address additional gaps in the literature [2,4], we also examined the associations of physical inactivity with lung cancer endpoints in subgroups based upon sex, smoking status, body mass index (BMI) and lung cancer histology.

Materials and methods

Study Population

The study population for the current analyses included individuals who received medical services at Roswell Park Cancer Institute (RPCI) between 1990 and 1998 who also agreed to complete a comprehensive epidemiological questionnaire and participate in the Patient Epidemiology Data System (PEDS). Lung cancer cases were identified from the RPCI Tumor Registry and Diagnostic Index and included 660 individuals diagnosed with primary, incident lung cancer. Controls were age-frequency matched to cases on five-year age strata and included 1,335 individuals identified from a pool of 10,642 potentially eligible controls. Control participants came to RPCI with a suspicion of cancer but were diagnosed with conditions that included non-malignant diseases of the circulatory system, genitourinary system, gastrointestinal system, respiratory system, or other conditions. The RPCI Institutional Review Board approved the conduct of the study and all participants provided written informed consent.

Epidemiological Questionnaire

The PEDS questionnaire, including a lifetime recreational physical activity assessment, was a self-administered epidemiological questionnaire offered to patients receiving medical service at RPCI. The PEDS questionnaire was offered to all new patients upon admission, regardless of diagnosis or reason for seeking care at RPCI. All questionnaires were completed within six months from date of diagnosis (median 21 days), with a 50% response rate among all admitted patients [14]. The detailed content and administration methods associated with the PEDS questionnaire have been previously described [15–17].

Physical Inactivity

The recreational physical activity section of the PEDS questionnaire was comprised of items assessing the age of onset of regular activity, the total years of regular activity, and the frequency of the activity (i.e., number of times per week or month). Recreational activity was defined as regularly exercising for health or pleasure in activities such as jogging, walking, or aerobics. We defined recreational physical *inactivity* in accordance with The 2008 Physical Activity Guidelines for Americans [7]. Thus, individuals reporting no regular, weekly, recreational physical activity throughout their adult lifetime (on average, less than one session per week or less than four sessions per month) were classified as physically inactive. Conversely, participants reporting, on average, at least one regular, weekly session of physical activity were classified as active. In exploratory analyses, we also examined physical inactivity during the time period spanning two decades prior to study enrollment, as this may be a more relevant exposure window relative to carcinogenesis.

Identification of confounding variables

We pre-specified age, sex, BMI, family history of lung cancer, and smoking (pack years) as important variables for adjustment in risk analyses. For survival analyses, we pre-specified age, sex, stage, grade, smoking (pack years), and BMI as important adjustment variables. We also examined the potential confounding effects of additional putative epidemiological risk and prognostic factors (i.e., education, race, treatment regimen, etc.) by applying the ten percent change-in-estimate method described by Maldonado et al.[18].

Statistical analysis

Physical inactivity and lung cancer risk

In descriptive analyses, differences in demographic and risk factor characteristics between lung cancer cases and controls were evaluated with two-tailed t-tests and Pearson's Chi-square. In risk analyses, we utilized age-adjusted and multivariable-adjusted binary logistic regression models to estimate the odds ratios (OR) and 95% confidence intervals (CI) representing the association between lifetime physical inactivity and lung cancer risk. We estimated associations of inactivity with lung cancer risk overall, and also by subgroups based upon sex, BMI status (normal weight versus overweight/obese), smoking status (never-smoker, former-smoker, current-smoker, non-smoker) and histological subtype (adenocarcinoma, squamous-cell carcinoma, small-cell carcinoma and 'other histology,' which consisted of all additional histological subtypes of lung cancer). In subgroup analyses by smoking status, the non-smoker group was defined as those participants who were not smoking at the time of study entry, and included never smokers and former smokers who had quit at least one year prior to study enrollment.

For all subgroup analyses, if we observed evidence that point estimates varied considerably across strata based upon sex, BMI, or smoking status, we evaluated the potential for statistical interaction via the inclusion of a physical inactivity cross-product term in