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The Association of Lifetime Physical Inactivity with Head and Neck Cancer: A Hospital-based Case-Control Analysis

Alexis J. Platek^{1,*}, Rikki A. Cannioto^{1,*}, John Lewis Etter¹, Jae Kim², Janine M. Joseph¹, Nicholas R. Gulati¹, Kristina L. Schmitt¹, Emily Callahan¹, Edgar Khachatryan¹, Ryan Nagy¹, Albina Minlikeeva¹, J. Brian Szender³, Anurag K. Singh⁴, Iris Danziger², and Kirsten B. Moysich¹

¹Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263

²Department of Otolaryngology, University at Buffalo Jacobs School of Medicine and Biomedical Sciences, 1237 Delaware Avenue, Buffalo, NY 14209

³Department of Gynecology, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263

⁴Department of Radiation Medicine, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263

Abstract

Objective—Despite mounting epidemiological evidence suggesting an inverse association between recreational physical activity and cancer risk, evidence associated with head and neck cancer is scant. We conducted a case-control analysis to examine the associations of lifetime physical inactivity with the risk of head and neck squamous cell carcinoma (HNSCC).

Methods—We utilized data from the Patient Epidemiology Data System at Roswell Park Cancer Institute (RPCI). Participants included 246 patients with HNSCC and 504 cancer-free controls who received medical services at RPCI between 1990 and 1998. Participants were considered physically inactive if they did not participate in any regular, weekly recreational physical activity throughout their lifetime, prior to diagnosis. Multivariate logistic regression models were utilized to estimate odds ratios (OR) and 95% confidence intervals (CI) representing the association between lifetime physical inactivity and HNSCC risk.

Results—We observed a significant positive association between recreational physical inactivity and HNSCC risk (OR=2.73, 95% CI: 1.87–3.99, $p<0.001$). In subgroup analyses by body mass index (BMI) (underweight/normal-weight: OR=3.40, 95% CI: 1.89–6.12, $p<0.001$; overweight/obese: OR=2.40, 95% CI: 1.43–4.02, $p<0.001$) and smoking status (former smoker: OR=3.12,

Corresponding Author: Dr. Kirsten B. Moysich, Department of Cancer Prevention and Control, Roswell Park Cancer Institute, 352 Carlton House, Elm and Carlton Streets, Buffalo, NY 14263, Phone: 716-845-8004, Fax: 716-845-1126, Kirsten.moysich@roswellpark.org.

*These authors contributed equally as first authors

Ethics approval and consent to participate

The RPCI Institutional Review Board approved the conduct of this study, and all participants provided informed consent

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95% CI: 1.89–5.14, $p < 0.001$; never smoker: OR=2.71, 95% CI: 1.21–6.05, $p = 0.020$; current smoker: OR=1.61, 95% CI: 0.66–3.95, $p = 0.300$) significant positive associations were also observed.

Conclusion—Results of the current analyses suggest that lifetime physical inactivity associates with HNSCC independent of BMI. In addition, physical inactivity may be a modifiable risk factor among never smokers. These data add to the growing body of evidence suggesting that physical inactivity may be an independent risk factor for cancer.

Keywords

head and neck cancer; physical activity; physical inactivity; recreational physical activity; cancer epidemiology

INTRODUCTION

Head and neck cancers are the seventh most common cancers worldwide and the ninth most common cancers in the United States [1]. These tumors are comprised of the anatomic sites of the upper aerodigestive tract and most commonly present as squamous cell carcinoma [1]. In 2015, there were approximately 59,349 newly diagnosed cases and approximately 12,290 deaths attributed to head and neck cancer in the United States [2].

The well-established risk factors for head and neck squamous cell carcinoma (HNSCC) include tobacco use, alcohol consumption, and human papillomavirus (HPV) infection [3] [4]. Tobacco use has declined in recent years in the U.S., suggesting that there may be a decline in tobacco-related HNSCC, while HPV-associated HNSCCs have increased [4]. In an era of potentially shifting risk factors associated with HNSCC, there is continued interest in identifying additional modifiable risk factors associated with these cancers. Recreational physical (in)activity represents a potentially modifiable factor that has been associated with risks of ovarian [5], cervical [6], lung [7], endometrial, breast, and colon cancers [8,9]. However, physical activity is not currently recognized as a protective factor for HNSCC, and the independent association of physical inactivity with HNSCC remains unknown.

Despite national guidelines encouraging Americans to avoid physical inactivity [10], current reports suggest that 50 to 79% of Americans are insufficiently physically active during their leisure time [11]. To this end, researchers have called for more investigations of the associations between physical *inactivity* and cancer endpoints [12], yet inactivity remains a behavioral risk factor which has not been routinely investigated as an exposure of interest in the current literature. Rather, under the prevailing paradigm, inactive participants are typically identified as the referent group and the independent associations of physical inactivity with cancer endpoints often remain unreported. From a public health perspective, we argue that inactive individuals could be a particularly important group to study, especially given the high prevalence of inactivity at the population level and the hypothesis that the greatest protective benefits can be achieved by increasing activity levels among inactive individuals [13]. Furthermore, there is a body of literature suggesting that self-reported physical inactivity is assessed with less exposure misclassification in comparison to

incrementally higher levels of self-reported physical activity exposure [13,14], and that inactivity may associate with cancer endpoints independently of obesity [15] [12].

As such, we conducted a hospital-based case-control analysis designed to systematically evaluate the association between HNSCC risk and lifetime physical inactivity. We also evaluated these associations according to subgroups based upon body mass index (BMI) classification, smoking status, and sex.

METHODS

Study Population

The study population included individuals who received medical services at Roswell Park Cancer Institute (RPCI) between 1990 and 1998 and participated in the Patient Epidemiology Data System (PEDS), a comprehensive data collection effort aimed at identifying epidemiological risk factors for cancer. The PEDS collection effort ended in 1998 when RPCI transitioned to a more comprehensive epidemiologic data bank and biorepository system. Nonetheless, the PEDS data remain a rich source of epidemiologic analysis opportunities, and analysis of these legacy data is ongoing. Participants in the current study were predominantly Caucasian (94%) and ranged from 25 to 90 years of age. Cases included 246 individuals diagnosed with primary, incident cancers of the head and neck region of squamous cell histology, who were identified from the RPCI tumor registry and Diagnostic Index. Controls included 504 individuals and were frequency matched to cases by five-year age strata with a control-case ratio of 2:1. Controls came to RPCI with a suspicion of malignant disease but were diagnosed with non-malignant conditions, including diseases of the genitourinary system (23%), circulatory system (26%), gastrointestinal system (18%), respiratory system (7%), and infectious and parasitic diseases (26%). The RPCI Institutional Review Board approved the conduct of this study, and all participants provided informed consent.

Epidemiological Questionnaire

The PEDS questionnaire was a self-administered questionnaire offered to all new patients receiving medical service at RPCI between 1980 and 1998 as part of the admission process. A physical activity questionnaire (PAQ) was added to the instrument in 1990 (Table 1). The questionnaire was offered independent of diagnosis and had an overall response rate of approximately 50% [16]. The questionnaire assessed detailed information on demographic background, health history, BMI, diet, tobacco use, alcohol consumption, and additional epidemiological variables.

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 [10]. Thus, individuals reporting no

regular, weekly, recreational physical activity throughout adulthood (on average, less than one session per week or less than four sessions per month) were classified as inactive. Conversely, participants reporting, on average, at least one regular, weekly session of physical activity throughout adulthood were classified as active.

Identification of Confounding Variables

We pre-specified age, sex, smoking history, and alcohol consumption as important variables for adjustment in multivariable logistic regression models. To examine additional potential confounding variables, we followed the methods described in Maldonado et al [17]. Variables identified as being significantly associated with HNSCC in univariate logistic regression models were subsequently tested in an age-adjusted model. If age-adjusted estimates changed by more than 10%, the variable was considered a confounder and included in the multivariate model. Based upon these criteria, BMI and level of education did not meet the definition of confounding and therefore were excluded from multivariable-adjusted models.

Statistical Analysis

T-tests and Pearson's χ^2 were conducted to evaluate differences between case and control groups for continuous and categorical variables, respectively. Next, we utilized age-adjusted and multivariable-adjusted binary logistic regression models to estimate the odds ratios (OR) and 95% confidence intervals (CI) representing the associations of lifetime physical inactivity with HNSCC. Multivariable models were adjusted for age, smoking, alcohol consumption, and sex. In exploratory analyses, we conducted subgroup analyses by smoking status, BMI classification (BMI < 25 kg/m² and BMI ≥ 25 kg/m²), and sex. All statistical analyses were performed using Statistical Analysis System (SAS) for Windows, version 9.4 and all tests were two-sided and considered statistically significant at $p < 0.05$.

RESULTS

Descriptive characteristics of the study population are displayed in Table 2. Anatomical sub-sites for HNSCC cases included the oral cavity (30.49%), the pharynx (29.27%), paranasal/accessory sinuses, middle ear and nasal cavity (3.66%), the larynx (33.74%), parotid gland (0.41%), and other or ill-defined sites of the head and neck (2.44%). As expected due to matching, we observed no significant differences in age between cases and controls ($p = 0.958$). Further, controls had a significantly higher education level ($p < 0.001$), consumed significantly fewer alcoholic drinks per week ($p < 0.001$), and were less likely to be current or former smokers in comparison to cases ($p < 0.001$). Lastly, cases had a significantly higher proportion of participants that were physically inactive throughout their lifetime ($p < 0.001$).

In multivariable logistic regression analyses we observed a significant association between recreational physical inactivity and HNSCC risk overall (OR = 2.73, 95% CI: 1.87–3.99, Table 3). In subgroup analyses by sex, we observed similar associations among both males and females as those observed in the overall study population: (OR = 2.08, 95% CI: 1.29–3.37) and (OR = 4.00, 95% CI: 2.07–7.73), respectively (Table 3). In sub-group analyses by smoking status, we observed positive associations between recreational physical inactivity

and HNSCC risk across all groups, but the association did not reach statistical significance among current smokers: former smokers (OR=3.12, 95% CI:1.89–5.14); never smokers (OR=2.71, 95% CI:1.21–6.05); and current smokers (OR=1.61, 95% CI: 0.66–3.95) (Table 3). Lastly, in subgroup analyses by BMI classification (<25 kg/m² and ≥25 kg/m²), we observed similar significant positive associations as those observed in the overall study population: BMI <25 kg/m² (OR=3.40, 95% CI: 1.89–6.12) and BMI ≥25 kg/m² (OR=2.40, 95% CI: 1.43–4.02) (Table 3).

DISCUSSION

In this case-control analysis, we observed evidence of a significant positive association between lifetime recreational physical inactivity and HNSCC risk. The observed association for recreational physical inactivity was robust to adjustment for relevant confounders, including smoking status and alcohol consumption, and the positive association was consistently observed in subgroup analyses by sex, smoking status, and BMI classification.

While no previous studies have systematically examined recreational physical inactivity as a potentially modifiable behavioral exposure relative to HNSCC, five published studies of the association between physical activity exposure and HNSCC risk have yielded inconclusive results [18–21,9]. In a prospective cohort study, Hashibe et al (2013) found that increasing hours of physical activity per week were associated with a decreased risk of head and neck cancer, with three or more hours per week associated with a 40% decrease in risk [18]. Similarly, in a pooled analysis of four case-control studies utilizing evidence from the International Head and Neck Cancer Epidemiology Consortium (INHANCE) moderate recreational physical activity was associated with a 22% reduction in risk for head and neck cancers [20]. A recent study by Moore et al (2016) also observed a moderate protective effect of leisure time physical activity on head and neck cancer risk [9]. Conversely, two additional studies reported no association between physical activity and HNSCC risk [19,21].

Inconsistencies in how individual studies examined physical activity exposure in relationship to cancer risk may be due to insufficient statistical power, a mixture of participants with different activity levels in the referent groups [22], or inherent measurement limitations when examining associations between incrementally higher levels of self-reported physical activity [23–25]. Not only is physical inactivity likely measured with less exposure misclassification than physical activity, it is an exceedingly important public health exposure which is scarcely examined as an independent behavioral construct. In fact, under the prevailing paradigm of examining dose-response associations of activity exposure, we often overlook an important segment of the activity continuum in terms of identifying those individuals who may be at greatest risk of cancer and, therefore those who may benefit the most from a public health intervention.

Although observational studies have suggested that the incidence of several types of cancer is reduced by regular physical activity, the biological mechanisms relating physical activity (or inactivity) and cancer risk are not entirely understood [26]. The most commonly cited potential mediators of these associations include changes in body fat, circulating

reproductive hormone levels, alterations in cytokine and growth factor milieus, and alterations in immune function [26]. Physical activity may increase the levels of certain immune cells, including natural killer cells, monocytes, neutrophils, lymphocytes and eosinophils, leading to enhanced immune function [27]. Physical activity has also been shown to improve function of antioxidant pathways and improve tissue resistance to reactive oxygen species, decreasing DNA damage as a result of oxidative stress [27]. Interestingly, physical activity may also influence salivary immunoglobulin A (IgA) concentration. Physical activity has been associated with an increased concentration of salivary IgA and a decreased incidence of upper respiratory infections [28] [29]. Salivary IgA plays an important role in the immune system's first line of defense by protecting the mucosal epithelium from toxins and pathogenic colonization [29]. Therefore, it is possible that the increase in salivary IgA concentration observed with exercise also plays a role in inhibiting carcinogenesis of the head and neck.

In sub-group analyses by sex, the association between HNSCC risk and recreational inactivity was stronger for females than for males. However, the observed confidence intervals were wide for females, suggesting that there was imprecision associated with estimates for females, likely owing to a smaller number of active cases. This relationship is contrary to the INHANCE results in which a stronger association was observed for males [20]. Females have a lower incidence of HNSCC [2] which may largely be attributed to a lower prevalence of smoking among females [30]. It should be noted that within this population of non-smoking females, HPV infection may contribute to the development of their HNSCC [4]. Nevertheless, some females with no tobacco history and who are HPV negative develop HNSCC, suggesting that recreational physical inactivity represents a modifiable risk factor that may be particularly effective in lowering females' risk for HNSCC, especially in the population of females with no tobacco history.

In sub-group analyses by smoking status, a positive association between recreational physical inactivity and HNSCC risk was observed for never and former smokers, with a stronger relationship among former smokers. Our data coincide with a previous study that also reported a stronger inverse relationship between physical activity and head and neck cancer among ever smokers [20], thereby underlining the strength of association between physical (in)activity and head and neck cancer. We failed to observe a statistically significant association within current smokers, possibly due to the smaller sample size of current smokers (n=138) compared to former smokers (n=367) and never smokers (n=244). It is also plausible that in this population, smoking accounts for the largest proportion of risk, and therefore any effect of physical inactivity is masked. Notably, among never smokers, after adjustment for alcohol consumption, there remained greater than two-fold odds that cases were inactive throughout their lifetime. It should be noted that among never smokers HPV infection is an increasingly important cause of HNSCC [4]. Therefore, within this population of never smokers physical inactivity may not be the sole cause of their HNSCC, but may contribute to at least some portion of their risk for HNSCC. Recreational physical inactivity may represent an important modifiable risk factor among not only former smokers, but also among never smokers who lack any other major risk factors, including HPV infection, for HNSCC.

Lastly, in subgroup analyses by BMI classification we observed a significant positive association between recreational physical inactivity and HNSCC risk in both underweight/normal-weight and overweight/obese participants, with a stronger relationship among underweight/normal-weight participants. Our data somewhat conflicts with data from a pooled analysis suggesting that a BMI ≥ 25 kg/m² was associated with a decreased risk of HNSCC [31]. It is possible that physical inactivity represents an exposure that exerts an effect on carcinogenesis via biological mechanisms that are at least partly independent of BMI, while at the same time working synergistically with BMI.

A key strength of this study is our use of lifetime inactivity as the exposure variable of interest. This approach allowed us to identify the most sedentary segment of the population and to systematically examine the association between lifetime recreational physical inactivity and HNSCC risk. In addition, the use of lifetime inactivity minimizes the probability that the associations observed in this study are due to a reverse causality bias. Another strength of this study is the careful examination of the potential effects of known risk factors of HNSCC and other potential confounders that could be closely associated with physical inactivity.

An important limitation of this retrospective analysis is that HPV testing, an established risk factor of head and neck cancer [32], was not available at the time of this study. Additionally, we are limited by the self-reported nature of physical inactivity data. We also recognize the potential for misclassification as a result of a referent group containing individuals who may have participated in a wide range of activity. However, using physical inactivity, rather than activity, as the exposure of interest is likely associated with less misclassification [14]. Further, the use of hospital-based controls diagnosed with non-malignant diseases could limit the likelihood of differential misclassification occurring between cases and controls because all controls were diagnosed with non-malignant conditions that may impact an individual's physical activity, or recall of activity, in a way similar to a cancer diagnosis. Although the use of hospital-based controls may limit the potential for differential misclassification, this approach could also result in a control population that is unhealthier than the general population. Therefore, it is possible that unhealthy controls with non-malignant diseases would be more likely to report physical inactivity than the general population, which would have attenuated the observed associations between inactivity and HNSCC.

The current findings are also limited because we did not consider physical inactivity in other behavioral domains. While our primary focus was to examine recreational physical inactivity because it is a modifiable behavior, we did examine associations for occupational inactivity in exploratory analyses (results not presented). These findings were insignificant and similar with results of a previous study which determined that adjusting for occupational physical activity did not change the inverse association between recreational physical activity and HNSCC risk [20]. We also cannot account for explicitly sedentary behavior (i.e., hours of television viewing or reading) in these analyses, a distinct behavioral construct which is likely associated with cancer endpoints via similar physiological pathways as recreational physical inactivity.

CONCLUSIONS

The results of the current analyses suggest that lifetime recreational physical inactivity associates with HNSCC after adjustment for additional well-established modifiable risk factors. Notably, our data suggest that lifetime recreational physical inactivity associates with HNSCC among never- and former- smokers. We also observed consistent associations between recreational inactivity and HNSCC across both strata of BMI (BMI <25.0 kg/m² and BMI ≥ 25.0 kg/m²). These data add to the growing body of evidence suggesting that physical inactivity may be an independent, modifiable risk factor for cancer.

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Abbreviations

HNSCC	Head and neck squamous cell carcinoma
HPV	Human Papilloma Virus
BMI	Body Mass Index
RPCI	Roswell Park Cancer Institute
PEDS	Patient Epidemiology Data System
PAQ	Physical Activity Questionnaire
SAS	Statistical Analysis System
OR	Odds Ratio
CI	Confidence Interval
IgA	Immunoglobulin A
INHANCE	International Head and Neck Cancer Epidemiology Consortium

References

1. Rettig EM, D'Souza G. Epidemiology of head and neck cancer. *Surg Oncol Clin N Am*. 2015; 24(3):379–396. DOI: 10.1016/j.soc.2015.03.001 [PubMed: 25979389]
2. American Cancer Society: Cancer Facts and Figures 2015. Atlanta: American Cancer Society; 2015.
3. Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, Curado MP, Dal Maso L, Daudt AW, Fabianova E, Fernandez L, Wunsch-Filho V, Franceschi S, Hayes RB, Herrero R, Koifman S, La Vecchia C, Lazarus P, Levi F, Mates D, Matos E, Menezes A, Muscat J, Eluf-Neto J, Olshan AF, Rudnai P, Schwartz SM, Smith E, Sturgis EM, Szeszenia-Dabrowska N, Talamini R, Wei Q, Winn DM, Zaridze D, Zatonski W, Zhang ZF, Berthiller J, Boffetta P. Alcohol drinking in never users of

tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *J Natl Cancer Inst.* 2007; 99(10):777–789. DOI: 10.1093/jnci/djk179 [PubMed: 17505073]

4. Chaturvedi AK, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol.* 2011; 29(32):4294–4301. [PubMed: 21969503]
5. Cannioto R, LaMonte MJ, Risch HA, Hong C, Sucheston-Campbell LE, Eng KH, Szender JB, Chang-Claude J, Schmalefeldt B, Klapdor R, Gower E, Minlikeeva AN, Zirpoli GR, Bandera EV, Berchuck A, Cramer D, Doherty JA, Edwards RP, Fridley BL, Goode EL, Goodman MT, Hogdall E, Hosono S, Jensen A, Jordan S, Kjaer SK, Matsuo K, Ness RB, Olsen CM, Olsen SH, Pearch CL, Pike MC, Rossing MA, Szamreta EA, Thompson PJ, Tseng C, Vierkant RA, Webb P, Wentzensen N, Wicklund KG, Winham SJ, Wu AH, Modugno F, Schildkraut JM, Terry KL, Kelemen LE, Moysich KB. Chronic Recreational Physical Inactivity and Epithelial Ovarian Cancer Risk: Evidence from the Ovarian Cancer Association Consortium Cancer Epidemiol Biomarkers Prev. 2016; 25(7):1114–1124. DOI: 10.1158/1055-9965.epi-15-1330 [PubMed: 27197285]
6. Szender JB, Cannioto R, Gulati NR, Schmitt KL, Friel G, Minlikeeva A, Platek A, Gower EH, Nagy R, Khachatryan E, Mayor PC, Kasza KA, Lele SB, Odunsi K, Moysich KB. Impact of Physical Inactivity on Risk of Developing Cancer of the Uterine Cervix: A Case-Control Study. *J Low Genit Tract Dis.* 2016; 20(3):230–233. DOI: 10.1097/LGT.0000000000000210 [PubMed: 27105330]
7. Brenner DR, Yannisos DH, Farris MS, Johansson M, Friedenreich CM. Leisure-time physical activity and lung cancer risk: A systematic review and meta-analysis. *Lung Cancer.* 2016; 95:17–27. DOI: 10.1016/j.lungcan.2016.01.021 [PubMed: 27040847]
8. Kushi LH, Byers T, Doyle C, Bandera EV, McCullough M, McTiernan A, Gansler T, Andrews KS, Thun MJ, American Cancer Society N, Physical Activity Guidelines Advisory C. American Cancer Society Guidelines on Nutrition and Physical Activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin.* 2006; 56(5):254–281. quiz 313-254. [PubMed: 17005596]
9. Moore SC, Lee I, Weiderpass E, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. *JAMA Intern Med.* 2016; 176(6):816–825. DOI: 10.1001/jamainternmed.2016.1548 [PubMed: 27183032]
10. USDHHS. 2008 Physical Activity Guidelines for Americans. Office of Disease Prevention and Health Promotion; Washington, D.C.: 2008.
11. USDHHS. Prevalence and Trends Data: Nationwide Physical Activity - 2013. US Department of Health and Human Services, Centers for Disease Control and Prevention; 2014. Accessed November 1, 2014
12. Sanchis-Gomar F, Lucia A, Yvert T, Ruiz-Casado A, Pareja-Galeano H, Santos-Lozano A, Fiuza-Luces C, Garatachea N, Lippi G, Bouchard C, Berger NA. Physical inactivity and low fitness deserve more attention to alter cancer risk and prognosis. *Cancer Prev Res (Phila).* 2015; 8(2): 105–110. DOI: 10.1158/1940-6207.capr-14-0320 [PubMed: 25416409]
13. Bull, FC., Armstrong, TP., Dixon, T., Ham, S., Neiman, A., Pratt, M. Physical Inactivity. In: WHO. , editor. Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to selected Major Risk Factors. Vol. 1. WHO; 2004. p. 729-881.
14. Celis-Morales CA, Perez-Bravo F, Ibanez L, Salas C, Bailey ME, Gill JM. Objective vs. self-reported physical activity and sedentary time: effects of measurement method on relationships with risk biomarkers. *PloS one.* 2012; 7(5):e36345.doi: 10.1371/journal.pone.0036345 [PubMed: 22590532]
15. Byers T. Physical activity and gastric cancer: so what? An epidemiologist's confession. *Cancer Prev Res (Phila).* 2014; 7(1):9–11. DOI: 10.1158/1940-6207.capr-13-0400 [PubMed: 24346343]
16. Baker JA, Odunuga OO, Rodabaugh KJ, Reid ME, Menezes RJ, Moysich KB. Active and passive smoking and risk of ovarian cancer. *Int J Gynecol Cancer.* 2006; 16(Suppl 1):211–218. DOI: 10.1111/j.1525-1438.2006.00473.x [PubMed: 16515593]
17. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *Am J Epidemiol.* 1993; 138(11):923–936. [PubMed: 8256780]
18. Hashibe M, Hunt J, Wei M, Buys S, Gren L, Lee YC. Tobacco, alcohol, body mass index, physical activity, and the risk of head and neck cancer in the prostate, lung, colorectal, and ovarian (PLCO) cohort. *Head Neck.* 2013; 35(7):914–922. DOI: 10.1002/hed.23052 [PubMed: 22711227]

19. Leitzmann MF, Koebnick C, Freedman ND, Park Y, Ballard-Barbash R, Hollenbeck AR, Schatzkin A, Abnet CC. Physical activity and head and neck cancer risk. *Cancer Causes Control*. 2008; 19(10):1391–1399. DOI: 10.1007/s10552-008-9211-0 [PubMed: 18704714]
20. Nicolotti N, Chuang SC, Cadoni G, Arzani D, Petrelli L, Bosetti C, Brenner H, Hosono S, La Vecchia C, Talamini R, Matsuo K, Muller H, Muscat J, Paludetti G, Ricciardi G, Boffetta P, Hashibe M, Boccia S. Recreational physical activity and risk of head and neck cancer: a pooled analysis within the international head and neck cancer epidemiology (INHANCE) Consortium. *Eur J Epidemiol*. 2011; 26(8):619–628. DOI: 10.1007/s10654-011-9612-3 [PubMed: 21842237]
21. Dosemeci M, Hayes RB, Vetter R, Hoover RN, Tucker M, Engin K, Unsal M, Blair A. Occupational physical activity, socioeconomic status, and risks of 15 cancer sites in Turkey. *Cancer Causes Control*. 1993; 4(4):313–321. [PubMed: 8347780]
22. Cannioto RA, Moysich KB. Epithelial ovarian cancer and recreational physical activity: A review of the epidemiological literature and implications for exercise prescription. *Gynecol Oncol*. 2015; 137(3):559–573. DOI: 10.1016/j.ygyno.2015.03.016 [PubMed: 25797080]
23. Bull, FC., Armstrong, TP., DixON, T., Ham, S., NEiMAN, A., Pratt, M. Comparative Quantification of Health Risks Global and Regional Burden of Disease Attributable to Selected Major Risk Factors Geneva. World Health Organization; 2004. Physical inactivity; p. 729-881.
24. Troiano, R. Limitations of Self-Report in Physical Activity and Obesity Research. In: Bouchard, CK,PT., editor. *Physical Activity and Obesity*. 2nd. Champaign, IL: Human Kinetics; 2010. p. 34-37.
25. Troiano R. Differences between objective and self-report measures of physical activity. What do they mean? *J Kir Sic Meas Eval*. 2008; 10:31–42.
26. Walsh NP, Gleeson M, Shephard RJ, Gleeson M, Woods JA, Bishop NC, Fleshner M, Green C, Pedersen BK, Hoffman-Goetz L, Rogers CJ, Northoff H, Abbasi A, Simon P. Position statement. Part one: Immune function and exercise. *Exerc Immunol Rev*. 2011; 17:6–63. [PubMed: 21446352]
27. Kruk J, Czerniak U. Physical activity and its relation to cancer risk: updating the evidence. *Asian Pac J Cancer Prev*. 2013; 14(7):3993–4003. [PubMed: 23991944]
28. Francis JL, Gleeson M, Pyne DB, Callister R, Clancy RL. Variation of salivary immunoglobulins in exercising and sedentary populations. *Med Sci Sports Exerc*. 2005; 37(4):571–578. [PubMed: 15809554]
29. Trochimiak T, Hubner-Wozniak E. Effect of exercise on the level of immunoglobulin a in saliva. *Biol Sport*. 2012; 29(4):255–261. DOI: 10.5604/20831862.1019662 [PubMed: 24868115]
30. National Center for Health Statistics. National Health Interview Survey 2015, Survey Description. Hyattsville, Maryland: 2016.
31. Gaudet MM, Olshan AF, Chuang SC, Berthiller J, Zhang ZF, Lissowska J, Zaridze D, Winn DM, Wei Q, Talamini R, Szeszenia-Dabrowska N, Sturgis EM, Schwartz SM, Rudnai P, Eluf-Neto J, Muscat J, Morgenstern H, Menezes A, Matos E, Bucur A, Levi F, Lazarus P, La Vecchia C, Koifman S, Kelsey K, Herrero R, Hayes RB, Franceschi S, Wunsch-Filho V, Fernandez L, Fabianova E, Daudt AW, Dal Maso L, Curado MP, Chen C, Castellsague X, Benhamou S, Boffetta P, Brennan P, Hashibe M. Body mass index and risk of head and neck cancer in a pooled analysis of case-control studies in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium. *Int J Epidemiol*. 2010; 39(4):1091–1102. DOI: 10.1093/ije/dyp380 [PubMed: 20123951]
32. Chung CH, Gillison ML. Human papillomavirus in head and neck cancer: its role in pathogenesis and clinical implications. *Clin Cancer Res*. 2009; 15(22):6758–6762. DOI: 10.1158/1078-0432.CCR-09-0784 [PubMed: 19861444]

Table 1

Physical Activity Questionnaire (PAQ), section E of the Patient Epidemiology Data System (PEDS) questionnaire

1. Have you ever had a job that involved regular physical activity such as walking or lifting? ☐ yes ☐ no If yes, <ul style="list-style-type: none"> a. At what age did you begin this type of work? ____ years old b. For how many years did you do this type of work? ____ years c. Describe the nature of this physical activity? _____ 	
2. Other than in school, have you ever regularly participated in an active sport such as golf, tennis, or a team sport? ☐ yes ☐ no If yes, <ul style="list-style-type: none"> a. What was the sport? _____ b. At what age did you begin this sport? ____ years old c. For how many years did you do this sport? ____ years d. How many times a month did you usually do this? ____ /month 	
3. Have you ever regularly exercised for health or pleasure (for example, jogging, walking, aerobics, weight lifting)? ☐ yes ☐ no If yes, <ul style="list-style-type: none"> a. What was the exercise activity? _____ b. At what age did you begin this exercise? ____ years old c. For how many years did you do this exercise? ____ years d. How many times a month did you usually do this? ____ /month 	
4. Compared to other people your age, how would you rate the level of your usual physical activity? (If currently ill, think about your activity during the years before your illness) ☐ much more active ☐ more active ☐ about the same ☐ less active ☐ much less active	

Table 2

Descriptive Characteristics of 246 HNSCC Patients and 504 Hospital-Based Controls

Characteristic	Cases (N=246) Mean (SD) or N(%)	Controls (N=504) Mean (SD) or N(%)	p-value ²
Age (years)	60.94 (11.96)	60.90 (11.77)	0.958
BMI (kg/m²)	25.38 (4.33)	26.56 (5.27)	0.001
Alcohol Consumption (drinks per week)	8.56 (25.12)	3.53 (5.57)	<0.001
Sex			
Male	173 (70.33%)	219 (43.45%)	<0.001
Female	73 (29.67%)		
Education¹			
At most 8 th Grade	84 (34.15%)	93 (18.45%)	<0.001
High School	123 (50.00%)	287 (56.94%)	
Some Higher	39 (15.85%)	121 (24.01%)	
Smoking¹			
Never Smoker	40 (16.26%)	204 (40.48%)	<0.001
Former Smoker	142 (57.72%)	225 (44.64%)	
Current Smoker	64 (26.02%)	74 (14.68%)	
Recreational Physical Inactivity¹			
Active	67 (27.24%)	253 (50.20%)	<0.001
Inactive	176 (71.54%)	250 (49.60%)	
Stage at Diagnosis			
Unknown	9 (3.66%)		
Localized	83 (33.74%)		
Regional	132 (53.66%)		
Distant	22 (8.94%)		
Head and Neck Sites			
Oral Cavity	75 (30.49%)		
Pharynx	72 (29.27%)		
Paranasal and accessory sinuses, middle ear, and nasal cavity	9 (3.66%)		
Larynx	83 (33.74%)		
Parotid Gland	1 (0.41%)		
Other/ill-defined sites of head and neck	6 (2.44%)		

¹ Numbers may not sum to total due to missing data

²Chi square test for independence was performed for categorical variables; t-test was performed for age, BMI, and alcohol consumption

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Table 3

Associations of lifetime physical inactivity with HNSCC

	Physical Activity Status	Age-Adjusted Model				Multivariable-Adjusted Model ³			
		Cases (N ^I)	Controls (N ^I)	OR (95% CI)	p-value ²	Cases (N ^I)	Controls (N ^I)	OR (95% CI)	p-value ²
Overall	Active	67	253	1.00		59	228	1.00	
	Inactive	176	250	2.67 (1.91, 3.72)	<0.001	152	200	2.73 (1.87, 3.99)	<0.001
Sex	Male	49	105	1.00		44	94	1.00	
	Inactive	122	114	2.28 (1.49, 3.50)	0.0002	103	90	2.08 (1.29, 3.37)	0.003
Female	Active	18	148	1.00		15	110	1.00	
	Inactive	54	136	3.11 (1.73, 5.60)	0.0002	49	134	4.00 (2.07, 7.73)	<0.001
Never Smoker	Active	12	109	1.00		11	94	1.00	
	Inactive	28	94	2.73 (1.31, 5.67)	0.007	22	77	2.71 (1.21, 6.05)	0.020
Former Smoker	Active	40	116	1.00		34	107	1.00	
	Inactive	101	109	2.69 (1.71, 4.22)	<0.001	92	88	3.12 (1.89, 5.14)	<0.001
Current Smoker	Active	15	27	1.00		14	27	1.00	
	Inactive	47	47	1.69 (0.77, 3.70)	0.191	38	35	1.61 (0.66, 3.95)	0.300
Underweight/Normal-weight	Active	33	118	1.00		29	107	1.00	
	Inactive	89	93	3.39 (2.09, 5.985)	<0.001	77	76	3.40 (1.89, 6.12)	<0.001
BMI	Active	34	135	1.00		30	121	1.00	
	Inactive	87	157	2.21 (1.39, 3.49)	<0.001	75	124	2.40 (1.43, 4.02)	<0.001

¹Numbers may not sum to total, due to missing data.²Italicized p-values are statistically significant at an alpha of 0.05³Multivariable models were adjusted for age, smoking, alcohol consumption, and sex.