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Impact of Physical Inactivity on Risk of Developing Cancer of the Uterine Cervix: a case-control study

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Abstract

Objective—In this study, we investigated whether physical inactivity was associated with risk of cervical cancer in women treated at an American cancer hospital.

Methods—This case-control study included 128 patients with cervical cancer and 512 controls matched on age. Controls were women suspected of having but not ultimately diagnosed with a neoplasm. Physical inactivity was defined in accordance with the 2008 Physical Activity Guidelines for Americans. Thus, participants reporting on average no moderate or vigorous recreational physical activity were classified as inactive. Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CIs).

Results—Compared to non-cancer controls, those with cervical cancer had significantly increased odds of reporting abstinence from recreational physical activity (OR = 2.43, 95% CI:

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1.56-3.80). No association was noted between occupational -related physical inactivity and cervical cancer (OR = 0.88, 95% CI: 0.58-1.36).

Conclusions—Our findings suggest that abstinence from regular recreational physical activity is associated with increased odds of cervical cancer. To our knowledge, this is the first US-based study examining these associations. Given the 2008 Physical Activity Guidelines for Americans, this study has identified yet another potential public health benefit to regular physical activity. Further investigation is needed using a larger sample and prospectively collected data to characterize dose of activity to mitigate risk and the optimal window of susceptibility.

Keywords

cervical cancer risk; physical activity benefits; physical activity guidelines; physical inactivity

Introduction

Cervical cancer is the third most common gynecologic malignancy in the United States, with 12,900 new cases and 4,100 deaths expected in 2015 [1]; the worldwide burden is even greater, where cancer of the cervix is the fourth most common cancer and the second most common cause of cancer-related death among women worldwide [2]. Established risk factors are numerous and include chronic HPV infection, immunosuppression, poverty and low socioeconomic status, early age of sexual debut, and smoking [3, 4]. The most well established protective factors include cervical cancer screening and vaccination against the most common HPV viral types. Identification of other modifiable risk factors is important to help direct public health efforts and reduce the burden of cervical cancer, not only in the United States, but around the world.

Some attention has been paid to physical activity and cervical cancer screening [5, 6], where lower levels of physical activity predicted less frequent cervical cancer screening. While screening is a protective factor against development of cervical cancer, minimal attention has been paid to the effects of physical activity on cervical cancer [7, 8]. The association between physical activity and screening has been attributed to attention to healthy lifestyle decisions; although the difficulty of undergoing screening examinations for patients who have physical disability could also play a role. However, physical activity is also associated with improved function of the immune system, which is vital for protection against development of cervical cancer [3, 9, 10].

Physical activity has been identified as a protective factor for multiple solid tumors including colon, breast, ovary, and endometrium [10-13]. This protection is independent from obesity and smoking status, which are generally associated with decreased physical activity [14, 15]. Despite a large number of studies conducted to explore the association between exposure to physical activity and risk of various types of cancer, the impact of physical activity (or inactivity) on a woman's risk of developing cervical cancer is not well investigated. The purpose of this study is to evaluate the relationship between physical inactivity on risk of cervical cancer. We hypothesized that abstinence from physical activity is associated with an increased risk of cervical carcinoma.

Methods

Patient Selection

This hospital-based case-control study was drawn from 15,430 women who received treatment at the Roswell Park Cancer Institute (RPCI; Buffalo, NY) and completed the Patient Epidemiology Data System (PEDS) questionnaire, an epidemiologic survey administered to patients receiving medical services at RPCI between 1982 and 1998. Questions relating to physical activity (PA) were added to the survey in 1990 so the sample population was limited to those 5257 women enrolled in 1990 or later.

The methods of the PEDS questionnaire have been described in detail elsewhere [16–19]. Briefly, the questionnaire was offered to all new patients at RPCI independent of diagnosis or reason for seeking care, with an approximate 50% response rate [16]. Median time from diagnosis to participation was 21 days. For the present analysis, patients who completed the PEDS questionnaire and were diagnosed with cervical carcinoma were identified through the RPCI cancer registry. Because all cancer cases reported race as “white” we limited the race of controls to white race as well. The pool of 1724 women who completed the PEDS questionnaire, were admitted for suspected neoplastic conditions not related to cervical cancer, but ultimately were not diagnosed with malignancy comprised the controls for this study. Controls were frequency matched to cases on five-year age strata with a control-to-case ratio of 4:1. Written informed consent was obtained from all participants upon recruitment and the PEDS study was approved by the RPCI institutional review board.

Exposure and Outcome Classification

Outcome of cancer vs. non-cancer was ascertained through query of the RPCI cancer registry. At the time of enrollment, all participants completed the self-administered PEDS questionnaire. Anthropomorphic features including height and weight used to calculate body mass index (BMI) were recorded at the time of enrollment. This 16-page instrument covered information on numerous exposure categories including frequency and intensity of physical activity. Because of the heterogeneity in published literature with respect to classification and quantification of physical activity [10], we selected physical inactivity as the exposure of interest. If participants answered no to the questions, “have you ever had a job that involved regular physical activity such as walking or lifting?” and “have you ever regularly exercised for health or pleasure (for example, jogging, walking, aerobics, weight lifting)?”, or if they answered yes and indicated they performed activity less than one time per week or four times per month, they were classified as inactive. Physical inactivity was assessed both over the patient’s whole lifetime, as well as limited to the 20 years prior to study enrollment. Activity 20 years prior to enrollment was ascertained by using the patient’s age at enrollment, age at starting the reported physical activity (if any), and duration (in years) of participation in the activity.

Statistical Analysis

Study size was determined according to the number of cervical cancer cases identified in the cancer registry during the study period and the selection of matching 4:1 was based on the number of available non-cancer controls who completed the PEDS questionnaire. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Bivariate statistics were calculated to describe the sample and test for differences between cases and controls. The Pearson χ^2 test was applied to categorical data and the Student's t test to continuous data. Crude and adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were estimated using unconditional logistic regression. Standard model diagnostics were performed. Potential confounders were considered based on a priori consideration of association to exposure variables, known risk factors for cervical cancer, and proxies for sexual activity. The multivariate logistic regression analyses were conducted using forward, backward, and stepwise selection of potential confounders as covariates. Only those covariates that resulted in a change in the age-adjusted OR by more than 10% were included in the adjusted model [20]. Known confounders were not forced into the final model. The final adjusted model included age at diagnosis/participation, family history of cervical cancer, and body mass index. Patients with missing exposure data were excluded from analysis.

Results

We identified 385 patients with primary incident cervical cancer diagnosed between 1982 and 1998 that were treated at our institution, 128 of whom were diagnosed after 1990 when the physical activity questions were added to the PEDS questionnaire. Of those 128 patients, 124 (96.9%) completed the physical activity portion of the PEDS questionnaire and had otherwise complete data available for analysis. The physical activity question response rate did not differ between cases and controls (96.9% vs. 94.6%, p = 0.29). There was also no difference between responders and non-responders to the physical activity questions with respect to smoking status, alcohol intake, family history of cervical cancer, or BMI. Descriptive characteristics of the cases and non-cancer controls are summarized in Table 1. The reported frequency of overall physical inactivity (no occupational or recreational physical activity) were 31.1% and 26.1% among cases and controls, respectively (p = 0.27). Cases were more likely than controls to have not completed high school, have a family history of cervical cancer, and be obese (BMI ≥ 30 kg/m^2).

The odds of cervical cancer was associated with abstinence from physical activity but not occupational physical activity as shown in Table 2. The odds of reporting no participation in recreational physical activity were more than twice as high for those with cervical cancer, compared with the controls (OR = 2.16 95% CI: 1.42 – 3.29). There was no difference in reporting occupational physical inactivity (OR = 1.02, 95% CI: 0.68-1.54).

The odds of reporting no recreational physical activity over the 20 years prior to diagnosis were also higher among those with cervical cancer compared with non-cancer controls (OR = 1.97, 95% CI: 1.28-3.04). However, abstinence from occupational physical activity 20 years prior to study enrollment was not associated with increased odds (OR = 1.00, 95% CI: 0.64-1.54) of cervical cancer (Table 3). For both current and historical domains of physical inactivity, abstinence from both recreational and occupational physical activity was not associated with risk of cervical cancer. All significant associations were robust to adjustment for age, family history, and BMI.

Discussion

In this epidemiologic case-control study, we observed a consistent association between physical inactivity and cervical cancer risk. The greatest risk is associated with abstinence from recreational physical activity; abstinence from occupational physical activity does not appear to alter the risk of cervical cancer. This study adds to the body of evidence linking physical inactivity and solid tumor risks in women. Unlike other published studies [4, 12, 21–23] the current report utilized a robust patient questionnaire administered within 6 months (median 21 days) of diagnosis. Further, the use of physical inactivity as the exposure variable may limit the impact of patient reported biases [10, 24].

Studies in other solid tumors have implicated changes in sex hormone levels, decreased BMI, decreased insulin, altered inflammatory pathways, and improved immune function as some of the protective mechanisms for physical activity [3, 10]. While several of these mechanisms may be in play with cervical cancer, altered immunity has the greatest face validity, based on the almost necessary cause of HPV infection for development of cervical cancer [25]. Multiple of these mechanisms are associated with immune function and the tumor microenvironment, suggesting that immune function or dysfunction may be a common final pathway in the development of cervical cancer.

The primary source for bias in this study is the selection of all patients from a single regional referral center for cancer care. It is possible that Berkson's bias is additionally present because non-cancer controls may have been referred to this center due to a greater number of comorbidities, which could lead to differential bias in exposure frequency. Other limitations of the study are related to the patient-reported nature of exposure ascertainment. Although the questions were standardized and administered to all patients, inherent methodological challenges associated with hospital-based study designs, in general, remain. Selection bias is of greatest concern for the present study because of the 50% response rate to the survey and our inability to ascertain how patients who declined participation may have differed from those included in the study. Recall bias is possible in any questionnaire; however, patients were enrolled on average within 3 weeks of diagnosis. Patients were matched based on age, to protect against confounding from that variable, and the significant association between recreational physical inactivity and cervical cancer persisted after adjusting for BMI. Unmeasured potential confounders for which we were not able to account include HPV status, history of Papanicolau testing, human immunodeficiency virus (HIV) status, history of hormone use, parity, age of sexual debut, and history of sexually transmitted diseases. Therefore, residual confounding could have impacted the results.

Strengths of study included that we were able to assess the potential confounding role of well-established risk factors for cervical cancer, as well as other factors that tend to parallel physical activity (or inactivity) in lifestyle patterns, including BMI, alcohol use, tobacco smoking, and education. An additional strength of our study is that our analyses included both recreational and occupational domains of physical inactivity. Further, our use of chronic, lifetime physical inactivity as the exposure of interest enabled us to identify the most sedentary individuals in population. Finally, the use of life-time activity reports decreased the likelihood of observed associations resulting from reverse causation.

Ultimately, we observed a significant association between self-reported recreational physical inactivity with odds of developing cervical cancer. If confirmed, these findings could have an important public health implication, particularly in the context of the obesity epidemic, where recommendations by national organizations are frequent and targets are escalating in both duration and intensity. However, the present study illustrates that any physical activity may reduce the risk of cervical cancer; this remained consistent when physical inactivity was considered as a pre-diagnostic chronic or even life-long risk factor. Further studies are needed to confirm the present findings and to define the optimal window of physical activity for cervical cancer prophylaxis.

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Abbreviations

OR	Odds Ratio
CI	Confidence Interval
RPCI	Roswell Park Cancer Institute
PEDS	Patient Epidemiology Data System
PA	Physical Activity
BMI	Body Mass Index

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Table 1

Baseline characteristics between cases and non-cancer controls – Roswell Park Cancer Institute, Buffalo, NY

	Cancer Cases		Non-Cancer Controls		p-value
Characteristic	**Mean**	**SD**	**Mean**	**SD**	
Age (years)	50.31	15.93	50.05	15.90	0.992
BMI	27.32	7.14	25.63	6.11	0.019
	N	%	N	%	
Education					< 0.001
At most 8th Grade	34	26.56	70	13.75	
High School Graduate	69	53.91	271	53.24	
Some Higher Education	25	19.53	168	33.01	
Family History					0.047
Yes	6	5.31	9	1.97	
No	107	94.69	448	98.03	
Smoking (pack-years)					0.357
0	52	40.94	261	51.08	
>0-31	25	19.69	85	16.63	
31-46	6	4.72	17	3.33	
46-64	5	3.94	15	2.94	
>64	39	30.71	133	26.03	

Table 2

Odds ratios and 95% confidence intervals representing the association between three domains of physical inactivity and cervical cancer risk – Roswell Park Cancer Institute, Buffalo, NY

Physical Inactivity Domain	Group	Age-Adjusted Model			Multivariable[2]-Adjusted Model		
		Cases (N[1])	Controls (N)	OR (95% CI) *p-value*	Cases (N)	Controls (N)	OR (95% CI) *p-value*
Recreational Physical Inactivity	Active	45	266	1.00	37	223	1.00
	Inactive	75	213	2.16 (1.42, 3.29) *p < 0.001*	62	160	2.14 (1.32, 3.47) p < 0.001
Occupational Physical Inactivity	Active	54	220	1.00	47	184	1.00
	Inactive	65	259	1.02 (0.68, 1.54) p = 0.92	52	198	1.15 (0.72, 1.84) p = 0.56

[1] Numbers may not sum to total, due to missing data.

[2] Multivariable models were adjusted for age, BMI, family history, alcohol consumption, smoking, and sex.

Table 3

Odds ratios and 95% confidence intervals representing the association between domains of physical inactivity activity and cervical cancer risk during the two decades prior to diagnosis/reference date – Roswell Park Cancer Institute, Buffalo, NY

Physical Inactivity Domain	Group	Age-Adjusted Model			Multivariable[2]-Adjusted Model		
		Cases (N[1])	Controls (N)	OR (95% CI) *p-value*	Cases (N)	Controls (N)	OR (95% CI) *p-value*
Recreational Physical Inactivity	Active	42	238	1.00	35	202	1.00
	Inactive	76	229	1.97 (1.28, 3.04) p = 0.002	63	171	1.95 (1.19, 3.22) p = 0.008
Occupational Physical Inactivity	Active	43	173	1.00	38	144	1.00
	Inactive	74	299	1.00 (0.64, 1.54) p = 0.99	59	231	1.01 (0.62, 1.65) p = 0.97

[1] Numbers may not sum to total, due to missing data.

[2] Multivariable models were adjusted for age, BMI, family history, alcohol consumption, smoking, and sex.