Recreational Physical Activity and Differentiated Thyroid Cancer Risk: A Pooled Analysis of Two Case-Control Studies

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Key Words

Recreational physical activity · Pooled case-control study · Thyroid cancer · Risk factors

Abstract

Purpose: Physical activity has been hypothesized to influence cancer occurrence through several mechanisms. To date, its relation with thyroid cancer risk has been examined

in relatively few studies. We pooled 2 case-control studies conducted in Cuba and Eastern France to assess the relationship between self-reported practice of recreational physical activity since childhood and thyroid cancer risk. **Methods:** This pooled study included 1,008 cases of differentiated thyroid cancer (DTC) matched with 1,088 controls (age range 9–35 and 17–60 years in the French and Cuban studies, respectively). Risk factors associated with the practice of recreational physical activity were estimated using OR and 95%

CI. Logistic regressions were stratified by age class, country, and gender and were adjusted for ethnic group, level of education, number of pregnancies for women, height, BMI, and smoking status. **Results:** Overall, the risk of thyroid cancer was slightly reduced among subjects who reported recreational physical activity (OR = 0.8; 95% CI 0.5–1.0). The weekly frequency (i.e. h/week) seems to be more relevant than the duration (years). **Conclusion:** Long-term recreational physical activity, practiced since childhood, may reduce the DTC risk. However, the mechanisms whereby the DTC risk decreases are not yet entirely clear.

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Introduction

Over the last few decades, the differentiated thyroid cancer (DTC) incidence has grown rapidly in many countries [1]. The study of DTC risk factors is therefore of great importance to understand this observed increase in incidence. In addition to exposure to ionizing radiation during childhood or adolescence, which is the main established risk factor for DTC, a number of other risk factors are now well documented. These include anthropometric factors like height, BMI or body surface area, and obesity [2–4] and, among women, hormonal and reproductive factors such as a high parity [3, 5–8].

Physical activity has been hypothesized to influence cancer risk through several mechanisms [9]. Specifically, physical activity may affect the thyroid cancer risk via DNA repair [10–12], hormonal [13–15], metabolic [15–17], and anti-inflammatory [18, 19] pathways.

Nevertheless, to date, the sparse epidemiologic data concerning the relation between physical activity and DTC risk are inconclusive. Two cohort studies and 1 case-control study found a slight decrease in DTC risk related to the practice of physical activity [20–22]. A pooled study of 5 prospective studies provided evidence of a slight increase in DTC associated with the practice of physical activity [23], while the other studies were inconclusive [24–29]. However, only 3 of these studies examined the association between long-term physical activity and DTC risk [20, 22, 25].

In our study, we pooled individual data from 2 case-control studies conducted in Cuba and Eastern France to examine the association between self-reported practice of recreational physical activity since childhood and DTC in men and women.

Methods

Study Population

Cases and controls from 2 studies using identical methodologies were included. The Cuban case-control study was approved by the Clinical Research Ethics Committee of the National Institute of Oncology and Radiobiology (INOR), Havana, Cuba. The French case-control study was approved by the French Data Protection Authority (agreement No. 05-1120, April 5, 2005). Written informed consent was obtained from all participants in each study. The study population and the methods used for data collection have previously been reported in detail [8, 30], while the main characteristics of the 2 population-based case-control studies are summarized in table 1. The Cuban study was conducted between 2009 and 2011 and included 203 cases diagnosed before the age of 60 years between 2000 and 2011, matched with 212 controls. The French study was conducted between 2009 and 2010 and included 805 cases diagnosed before the age of 35 years between 2002 and 2006, matched with 876 controls.

Analyzed Parameters

The 2 studies used the same standardized questionnaire, which elicited information on demographics, anthropometry, dietary intake, and medical, reproductive, and family history, as well as life-style factors including smoking history, alcohol consumption, and recreational physical activity. The questions related to recreational physical activity were strictly identical in both questionnaires. All types of recreational physical activities were taken into account, but only those reported outside of school time. In this study, we summed all reported physical activity in order to obtain the duration (years) and frequency (h/week) from childhood until 1 year before the diagnosis (for cases) or 1 year before the reference year (for controls). Duration and frequency were separated into 3 categories: childhood and adolescence (age <18 years), adulthood (age ≥18 years), and total lifetime.

Quartiles for each variable were then calculated in accordance with their distribution among controls.

Statistical Analysis

Data were analyzed using logistic regression with SAS software, version 9.3 (SAS Institute, Cary, N.C., USA). Analyses were stratified by 5-year age class, area of residence or country, and gender and were adjusted for ethnic group, level of education, number of pregnancies for women, height (3 tertiles for each gender and study), BMI (3 categories in accordance with the WHO classification), and smoking status. Analyses were also conducted separately for women and men because risk factors may vary by sex. Interaction tests were performed to assess whether the association of recreational physical activity with thyroid cancer risk was modified by characteristics such as height, BMI, smoking status, number of pregnancies, oral contraceptive use, and age at menarche.

Results

A total of 1,008 cases and 1,088 controls were included in the pooled study (table 1). Approximately 91% of the cases were of papillary carcinoma, and women represented 70% of cases.

Table 1. Characteristics of the 2 case-control studies

	Eastern France	Cuba
Case/control subject ratio	805/876	203/212
Women, %	78.0	84.8
Diagnostic period	2002–2006	2000–2011
Median age at diagnosis (range), years	28 (9–35)	39 (17–60)
Identification of cases	Three main sources by region: (i) General Cancer Incidence Registry in Champagne-Ardenne, Alsace, and Rhône-Alpes; (ii) National Childhood Cancer Registry (which contains information on children <15 years of age) in all regions, and (iii) private and public hospitals in Lorraine, Franche-Comté, Corse, and Provence-Alpes-Côte d’Azur	National Cancer Registry and cross-referenced with the INOR Pathology Registry
Case eligibility	Residents of 1 of the 7 regions of Eastern France and under 35 years of age in the reference year	Residents of Havana City or its surroundings, between 17 and 60 years of age
Papillary histology, %	90.3	93.1
Microcarcinoma ^a , %	18.5	2.0
Type of control subjects	General population	General population
Control selection	Randomly selected from the landline telephone directory ^b	Randomly selected from primary care unit patient consultation files
Matching criteria	Sex, date of birth, and region	Sex and date of birth (± 5 years)
Type of matching	Individual	Frequency
Type of interviews	Face-to-face	Face-to-face

^a Defined as unifocal tumors <10 mm without tumor extension. ^b Or related persons of contacted people from the landline directory.

No significant interaction (*p* value for interaction >0.05) was apparent between country and any variable used as an adjustment variable (educational level, ethnicity, smoking status, BMI, height, or number of pregnancies for women) in the risk of thyroid cancer, enabling us to pool the results of these 2 studies.

Recreational physical activity is common in France (77% of subjects) but rare in Cuba (32% of subjects). Cases were less likely than controls to report any regular recreational physical activity (OR = 0.7; 95% CI 0.6–0.9). This ratio was identical among women (OR = 0.7; 95% CI 0.6–1.0) and was not significant among men (OR = 0.9; 95% CI 0.5–1.5) (table 2). Because the proportion of microcarcinomas was higher in the French study than in the

Cuban study (18.5 vs. 2%), analyses were also been done without microcarcinomas, and the results remained similar with or without taking into account microcarcinomas (for having practiced any physical activity: OR = 0.8; 95% CI 0.6–1.0).

When excluding nonpractitioners, this decrease in risk was not significantly associated with the duration, in years, of the recreational physical activity, either when considering whole lifetimes or when investigating physical activity separately for up to and beyond 18 years (table 2).

Conversely, the frequency of recreational physical activity, as measured by the weekly number of hours of practice, was significantly associated with a lower risk of DTC in all subjects, in both men and women, up to 18

Table 2. OR of DTC by aspects of recreational physical activity

	All subjects					Women only					Men only				
	cases (n = 1,008)	controls (n = 1,088)	OR	95% CI	p for trend ^b	cases (n = 812)	controls (n = 852)	OR	95% CI	p for trend ^b	cases (n = 196)	controls (n = 236)	OR	95% CI	p for trend ^b
No physical activity	356	302	1.0	Ref.		321	261	1	Ref.		35	41	1	Ref.	
Any physical activity	652	786	0.7	0.6–0.9	<0.01	491	591	0.7	0.6–1.0	0.01	161	195	0.9	0.5–1.5	0.66
Duration of practice, years															
Under 18 years															
0	393	347	1.0	Ref.		351	294	1.0	Ref.		42	52	1.0	Ref.	
1–2	96	119	0.8	0.5–1.0		78	97	0.7	0.5–1.0		18	23	1.1	0.5–2.5	
3–5	175	176	0.9	0.7–1.2		142	138	0.9	0.7–1.2		33	38	1.0	0.5–2.0	
6–9	176	229	0.8	0.6–1.0		124	173	0.7	0.5–1.0		52	56	1.1	0.6–1.9	
≥10	168	217	0.8	0.6–1.0	0.05	117	150	0.7	0.5–1.0	0.04	51	67	0.9	0.5–1.6	0.61
18 years and over															0.45
0	706	698	1.0	Ref.		613	575	1.0	Ref.		93	123	1.0	Ref.	
1	53	78	0.7	0.5–1.0		39	60	0.6	0.4–0.9		14	18	1.0	0.5–2.3	
2–3	77	102	0.7	0.5–1.0		56	77	0.7	0.5–1.0		21	25	0.9	0.5–1.9	
4–7	76	106	0.7	0.5–1.0		55	77	0.7	0.5–1.0		21	29	0.8	0.4–1.5	
≥8	96	104	0.9	0.6–1.3	0.08	49	63	0.8	0.4–1.2	0.02	47	41	1.4	0.8–2.5	0.55
Total															0.94
0	356	302	1.0	Ref.		321	261	1.0	Ref.		35	41	1.0	Ref.	
1–3	147	161	0.8	0.6–1.1		123	136	0.8	0.6–1.0		24	25	1.3	0.6–2.8	
4–7	182	218	0.7	0.6–1.0		141	166	0.7	0.5–1.0		41	52	0.8	0.4–1.6	
8–11	139	175	0.7	0.5–1.0		114	129	0.8	0.6–1.1		25	46	0.6	0.3–1.2	
≥12	184	232	0.7	0.5–0.9	0.02	113	160	0.7	0.5–0.9	0.02	71	72	0.9	0.5–1.7	0.53
Time per week ^a , hours															
Under 18 years															
0	393	347	1.0	Ref.		351	295	1.0	Ref.		42	52	1.0	Ref.	
1	122	118	1.1	0.7–1.6		106	108	1.0	0.7–1.6		16	10	1.9	0.6–5.7	
2	195	207	0.9	0.6–1.3		158	178	0.9	0.6–1.3		37	29	1.8	0.7–4.5	
3–4	152	218	0.7	0.5–1.0		111	153	0.7	0.4–1.1		41	65	0.8	0.3–2.0	
≥5	146	198	0.7	0.5–1.1	<0.01	86	118	0.7	0.4–1.1	0.02	60	80	1.0	0.4–2.5	0.30
18 years and over															0.06
0	706	698	1.0	Ref.		613	575	1.0	Ref.		93	123	1.0	Ref.	
1	49	54	0.7	0.4–1.2		42	48	0.7	0.4–1.3		7	6	0.9	0.2–3.6	
2	86	999	0.7	0.4–1.1		59	80	0.6	0.4–1.1		27	19	1.1	0.4–2.9	
3–5	91	140	0.5	0.3–0.8		57	96	0.5	0.3–0.8		34	44	0.6	0.2–1.6	
≥6	76	97	0.5	0.3–0.9	0.01	41	53	0.6	0.3–1.1	0.03	35	44	0.6	0.2–1.7	0.20
Total															0.27
0	356	302	1.0	Ref.		321	261	1.0	Ref.		35	41	1.0	Ref.	
1	132	120	1.1	0.7–1.5		114	112	1.0	0.7–1.5		17	8	2.4	0.8–7.5	
2	198	225	0.8	0.6–1.1		158	189	0.8	0.5–1.1		41	36	1.3	0.5–3.2	
3–4	163	225	0.7	0.5–1.0		120	161	0.7	0.4–1.0		43	64	0.8	0.3–1.9	
≥5	159	216	0.6	0.4–1.0	<0.01	99	129	0.7	0.4–1.0	0.01	60	87	0.8	0.3–2.0	0.10
OR were stratified by sex, region or country, and age and adjusted for educational level, ethnicity, smoking status, BMI, height, and number of pregnancies for women. Ref. = Reference values. ^a OR were also adjusted for the number of years of physical activity practice. ^b When excluding subjects who did not report any recreational physical activity.															

OR were stratified by sex, region or country, and age and adjusted for educational level, ethnicity, smoking status, BMI, height, and number of pregnancies for women. Ref. = Reference values. ^a OR were also adjusted for the number of years of physical activity practice. ^b When excluding subjects who did not report any recreational physical activity.

years of age, for age 18 years and over, and for the lifetime weekly frequency (p for trend for lifetime intensity <0.01 both in all subjects and in women, and 0.04 in men; table 2).

In total, 31% of the subjects declared having never practiced any physical activity, 4% declared having practiced physical activity only after 18 years of age, 36% only practiced before 18 years of age, and 29% practiced during their entire lifetime, and these percentages were the same for cases and controls. Hence, subjects who had not reported any physical activity before the age of 18 years were not likely to practice during adulthood. Conversely, 36% of the subjects practiced physical activity only during childhood.

No significant interactions between each tested variable (any physical activity, years of duration, h/week) and height, BMI, smoking status, number of pregnancies, oral contraceptive use, and age at menarche were apparent.

Discussion

Our study found a slightly decreased DTC risk associated with the practice of recreational physical activity (OR = 0.7; 95% CI 0.6–0.9), and a higher association with the weekly frequency of practice rather than its duration.

Lifetime recreational physical activity is difficult to measure, and available epidemiologic data regarding the relation between physical activity and thyroid cancer risk are sparse. Only a few studies have been published on this subject, and the majority of them have not found any positive or negative association between recreational physical activity and DTC risk [24–29].

In our study, the duration and weekly frequency of practice of recreational physical activity were examined both during whole lifetimes and separately for childhood/adolescence and adulthood. Concerning the lifetime duration of physical activity practice, a significant association was found both in all subjects and in women only. But no significant association remained when the age groups were examined separately.

We found a slight negative association between weekly frequency of practice of physical activity during the entire lifetime and DTC risk (OR per h/week = 0.9; 95% CI 0.9–1.0). A more frequent practice of recreational physical activity during childhood and adolescence could be more protective than during adulthood, because adolescence or early adulthood could be a more biologically relevant time period. This has also been shown for anthropometric factors during young adulthood, which play a

significant role in DTC risk [4]. Some authors also examined the practice of recreational physical activity separately for early ages, the whole lifetime, or just a few years before the diagnosis [20, 22]. However, they did not find any significant risk differences by age, and they reported that the early practice of recreational physical activity is associated with a lower DTC risk (practice between 12 and 21 years of age [20] or whole-lifetime practice since high school [22]).

The results for women only were not different from those for all subjects, except for years of practice after 18 years of age. For men, the only significant association was with the intensity of lifetime practice. DTC affects mostly women, and several studies have focused only on women [20, 22, 27]. This higher incidence may be explained by hormonal exposure, especially with regard to the role of estrogens and estrogen receptors in thyroid tumorigenesis, reprogramming, and progression [8]. Hence, some other risk factors may act differently according to the sex of the subjects. However, no difference between men and women was reported for the association of practice of recreational physical activity and thyroid cancer risk in an analysis of the NIH-AARP Diet and Health Study, which included 171 cases in men and 181 in women [25].

The mechanisms whereby the DTC risk might decrease with the practice of recreational physical activity may involve several pathways, including DNA repair and anti-inflammatory and hormonal mechanisms [22], but these mechanisms are not yet entirely clear. Another hypothesis is that the practice of physical activity may influence the DTC risk by reducing obesity, which is known to be positively related to DTC risk [26]. However, this last hypothesis was not supported by the absence of an interaction between the practice of recreational physical activity and BMI in our pooled study.

Our pooled study has several strengths, including its large sample size, the use of strictly identical questionnaires across the 2 studies, and the adjustment of analyses for confounding covariates. Even though the Cuban and French populations are different, the absence of an interaction between the aspect of practice of recreational physical activity and the country of origin has enabled us to pool the 2 studies. Nevertheless, the Cuban case-control study does not itself have sufficient statistical power to be analyzed alone for studying the influence of recreational physical activities.

There are also some limitations. The main limitation of our study is that physical activity, BMI, and other covariates are self-reported and thus subject to reporting errors or recall bias. Imprecise estimation of physical ac-

tivity levels may consequently have occurred. The validity of self-reported physical activity has been successfully evaluated in a number of other studies [31, 32]. In the large-scale EPIC cohort, after a validation stage with an accelerometer in a sample of subjects, those authors found that self-reported questionnaires showed acceptable measurement characteristics for ranking participants by their level of total physical activity [31]. In a cohort of pregnant women, Brantsaeter et al. [32] observed significant positive associations between self-reported exercise activity and motion sensor measurements of physical activity, indicating that the questions used for exercise assessment may be useful for ranking pregnant women by recreational exercise level. Another limitation comes from the absence of occupational or household physical activity assessments, which could be important determinants of the total energy expenditure, which may affect the thyroid cancer risk.

The last limitation came from the pool of 2 sets of heterogeneous data in which subjects came from 2 countries (France and Cuba) and did not have the same median age (28 vs. 39 years). However, these factors were taken into account in the analyses because logistic regressions were stratified for age, sex, and country.

In summary, our study found an overall significant but rather weak negative association between physical activ-

ity and DTC risk. This association is higher for a more frequent practice rather than for a longer duration of practice.

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Disclosure Statement

The authors have nothing to declare.

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