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Association of Marijuana Use and the Incidence of Testicular Germ Cell Tumors

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Abstract

Background—The incidence of testicular germ cell tumors (TGCT) has been increasing the past 4–6 decades, but exposures accounting for this rise have not been identified. Marijuana use has also grown over this time period, and chronic marijuana use produces adverse effects on the human endocrine and reproductive systems. We tested the hypothesis that marijuana use is a risk factor for TGCT.

Methods—A population-based case-control study of 369 men age 18–44 years diagnosed with a TGCT from January 1999– January 2006 was conducted in King, Pierce and Snohomish Counties in Washington State. Their responses to questions on lifetime marijuana use were compared to those of 979 age-matched controls residing in the same three counties during the case diagnosis period.

Results—Men with a TGCT were more likely to be current marijuana smokers at reference date compared to controls, OR (odds ratio) =1.7, 95% CI (Confidence Interval) =1.1–2.5. When we conducted analyses according to histologic type, most of the association between current marijuana use and TGCT was in nonseminomas-mixed histology tumors, OR current use=2.3, 95% CI=1.3–4.0. Age at first use among current users appeared to modify risk (age<18 OR=2.8 vs. age≥18 OR=1.3) as did frequency of use (daily or weekly OR=3.0 vs. <once per week OR=1.8).

Conclusions—We observed an association between marijuana use and occurrence of nonseminoma germ cell tumors of the testis. Additional studies of TGCTs are needed to test this hypothesis, including molecular analyses of cannabinoid receptors and endocannabinoid signaling that may provide clues to biologic mechanisms.

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Keywords

Marijuana Use; testicular tumors

INTRODUCTION

Testicular germ cell tumors (TGCTs) are the most common type of malignancy in American men between 15–34 years of age (1). These cancers are traditionally classified into two broad groups: pure seminoma (60% of TGCTs) and nonseminoma (40% of TGCTs). Nonseminomas include tumors that have purely nonseminomatous elements (e.g., embyronal carcinomas) as well as tumors that have both seminomatous and non-seminomatous elements (2). The age-specific incidence of nonseminomas peaks ten years earlier (20–35 years) compared to seminomas (30–45 years) (3). During the last half of the 20th century the incidence of TGCT increased by 3–6% per annum in the United States as well as in Europe, Australia, New Zealand, and Canada (2;4–6). The rising rates have been evident for both seminoma and nonseminoma. There are few established risk factors for TGCT beyond cryptorchidism, gonadal dysgenesis, age, race and family history of TGCT (6–8); most but not all studies indicate that risk factors do not vary between the two histologic groups (8;9). The current prevailing paradigm is that the disease is initiated in early fetal life when some primordial germ cells fail to differentiate, remain susceptible to malignant transformation, and develop into carcinoma in situ. It is thought that this neoplasm progresses to invasive cancer under the influence of adult steroid hormones and/or gonadotropins (10;11).

The increasing incidence of TGCT over time strongly suggests that young men have been exposed to one or more increasingly prevalent causal factors. One exposure that has been increasing in the US and in Europe over the same time period as the rise in the incidence of TGCTs is the use of marijuana (12) (13;14). Chronic marijuana use has multiple adverse effects on the endocrine and reproductive systems. For example, chronic marijuana use is associated with reduced hypothalamic release of GnRH, decreased plasma levels of gonadotropins (FSH, LH and prolactin) and testosterone, reduced spermatogenesis and impotency in men (15–17). In mice, cannabis-like compounds target cannabinoid receptors in Leydig and Sertoli cells, influencing testosterone secretion and serttoli cell survival. (18–22) Male infertility and poor semen quality are also associated with risk of TGCT (6). We therefore tested the hypothesis that marijuana use is a risk factor for TGCT using data from the Adult Testicular Cancer Lifestyle and Blood Specimen (ATLAS) Study, a population-based case-control study conducted in the Seattle/Puget Sound region of Washington State.

METHODS

Study Subjects

Cases—Cases eligible for participation in the ATLAS Study were all 18–44 year-old male residents of King, Pierce and Snohomish Counties, Washington State, diagnosed with an invasive TGCC between January 1, 1999 and January 31, 2006, who had a landline residential telephone at diagnosis (because controls were ascertained through random-digit dialing (RDD) of landline residential telephone numbers) and were capable of communicating in English. Potentially eligible cases were identified from the files of the population-based Cancer Surveillance System (CSS), a part of the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute, (23) based on the following International Classifications of Diseases – Oncology (ICD-O) topography and histology codes: topography C62.0 – C62.9, histology 9060 – 9091 (24).

To contact each case in order to determine his final eligibility and recruitment, we asked his follow-up physician to determine whether there was any reason why the man should not be approached for the study. If no such reason was given, we sent the man an introductory letter and followed up with a telephone call from a study interviewer who assessed final eligibility and attempted to recruit him into the study protocol.

Of the 550 total cases identified with eligible diagnosis dates, we interviewed 371 (67.5%). The rest of the cases fell into the following categories: subject refusal (n=112, 62.6% of non-interviewed); lost to follow-up (n=50, 27.9%); doctor refusal (n=11, 6.1%); deceased (n=6, 3.4%). Of the 371 cases we have successfully interviewed, we excluded from our analyses two whose tumors were classified as choriocarcinoma, based on the uniqueness of this histology.

Controls—Mitofsky-Waksberg random digit dialing with a clustering factor ("k") of five was used to recruit controls (25–27). Controls were men without a history of TGCT, who resided in the same three counties as the cases during the case diagnosis period, and were frequency-matched to the cases on five-year age groups using one-step recruitment (28). Each telephone number was called at least nine times over two or more weeks, including weekday, weekend, and evening calls. When a call was answered, the interviewer sought to determine whether the phone rang in a residence and was a landline telephone, the county of the residence, and whether a man 18–44 years of age lived in the residence. If the household census identified a man 18–44 years of age and he was eligible after age stratification criteria were applied, the interviewer attempted to obtain the name and address of the man so that a letter of introduction to the study could be sent to him. Following the mailing of the letter, an interviewer called the man to conduct a final eligibility assessment and attempted to recruit him into the study protocol.

Of the 1875 eligible controls identified, we interviewed 979 (52.2%). Screening proportion was calculated as the number of screened households divided by the number of all confirmed households plus the number presumed households (answering machine on every call, immediate hang-up and refusal to answer screening questions). The screening response was 82.9%, which when combined with interview proportion yields an overall response proportion of 43.3%.

Interviews

After providing written informed consent, cases and controls were interviewed in person by trained interviewers in a place of the respondent's choosing (including home, office, or research institution office), using a structured questionnaire. All questions referred to the time period prior to each man's assigned reference date. For each case, the reference date was the month and year of his TGCT diagnosis. Each control was assigned a reference date selected at random from among all possible dates given the distribution of diagnosis years of cases identified as of the time of selection of the control via RDD. Information collected during the interview included: 1) demographic characteristics; 2) cigarette smoking and alcohol consumption; 3) recreational drug use; and 4) other known or suspected risk factors for TGCT. Prior to the in-person interview, each participant was asked to complete a self-administered questionnaire regarding his family history of cancer and ethnic heritage.

Each man was asked whether he had ever used marijuana, hashish or both. Each man who reported having used marijuana was asked to recall different periods in his life when he used this drug, defined by the ages in which he first and last used it at a given frequency (times per day, week, month, or year), and form (marijuana, hashish or both).

STATISTICAL ANALYSIS

Analyses were conducted for all cases combined as well as classified by histologic subtype: seminomas included those with ICD-O histologies 9060–9064; nonseminomas included embryonal (9070), yolk sac (9071), teratoma (9080, 9082–9084), non-seminoma NOS (9065), and mixed germ cell tumors with (9085) and without (9081, 9101) seminomatous features. Using the data collected on episodes of marijuana use, we created analytic variables for ever use, former vs. current use, age at first use, lifetime duration of use, and frequency of use. Frequency of use was calculated in two forms, one averaged over each man's lifetime and one for the current episode of use, if applicable.

Odds ratios (OR) and 95% confidence intervals (CI) were calculated as estimates of relative risk using unconditional logistic regression. Polytomous logistic models were used to compare controls with each of the case groups defined by histologic type. P-values comparing OR by histology were obtained using likelihood-ratio tests, and p-values for trend were evaluated among ever-users of marijuana by fitting a grouped linear version of the variable of interest in that group. To assess the extent of confounding, we included in the logistic regression models terms for age and reference year (since the controls were frequency matched to the cases on these characteristics), history of cryptorchidism, first-degree family history of TGCC, race, and income. We also examined confounding by two additional habits that might be expected to be correlated with marijuana use, smoking and alcohol drinking, and found alcohol drinking (frequency of use in the 5 years before reference date) and current smoking to be confounders. Final models were adjusted for age, reference year, alcohol use, current smoking, and history of cryptorchidism. Subgroup analyses were performed by age group, excluding men with a history of cryptorchidism, and excluding men with a first-degree family history of TGCC. All analyses were performed in Stata/SE (Stata Statistical Software, version 9.2; StataCorp, College Station, TX).

To evaluate the extent to which the reporting of marijuana use among our controls was consistent with other population-based data, we analyzed publicly-available data for 18–34 year-old men from the National Survey on Drug Use and Health (NSDUH); formerly known as the National Household Survey on Drug Abuse conducted between 1999 through 2006. We did not include data on men 35–44 years old because the NSDUH data aggregated them with 45–49 year-old men (who were not included in our study). We compared the observed number of controls who reported ever using marijuana, being a current vs. former marijuana users, and using marijuana currently one or more days per week to the expected number based on the age- and race-specific proportions in the NSDUH data. We calculated observed-to-expected ratios (O/E), and corresponding 95% CI's using the Poisson process and logarithmic transformation (29).

RESULTS

Cases were more likely to be white men, whether Hispanic or non-Hispanic white, and none of the cases were African-American (Table 1). Cases tended to be from somewhat lower income households and to be slightly less likely to have more than a college education compared to controls.

Men with TGCT were more likely than controls to have a history of cryptorchidism, 9.9% versus 2.5% (age adjusted OR = 4.4, 95% CI = 2.6–7.5) and to have a first degree family history of TGCT, 2.8% versus 1.0% (age adjusted OR = 2.9, 95% CI = 1.1–7.3) (Table1).

Men with TGCT were slightly more likely to have ever smoked marijuana than controls (72.6% vs. 68.0%); OR = 1.3, 95% CI = 1.0–1.8 (Table 2). Twenty-six percent of cases reported being current marijuana smokers at reference date compared to 20% of controls

(OR = 1.7, 95% CI = 1.1–2.5). The ORs for first use at age less than 18 years among current users was somewhat higher than for first use at age 18 years or older (OR=1.8 vs. 1.4). The ORs did not differ appreciably by total years of use, but the risk associated with daily or weekly use among current users was somewhat higher than less frequent use (OR 2.0 vs. 1.4).

When we conducted similar analyses according to histologic type, the association between current marijuana use and TGCT was primarily limited to the nonseminomas (OR = 2.3, 95% CI = 1.3–4.0) as compared to the pure seminomas (OR=1.3, 95% CI=0.8–2.1); p=0.08 for difference between the two histologic groups (Table 3). For nonseminomas, the risk was higher only for current users who started using marijuana at less than 18 years of age (2.8, 95% CI =1.6–5.1) compared to 18 years or older, (OR = 1.3, 95% CI = 0.6–3.2), p = 0.08 for the test for difference in OR. There appeared to be increasing risk with years of use (i.e., 1.8 <10 years vs. 2.7 ≥ 10 years). However, the difference in those estimates was not statistically significant (p= 0.32). Risk did not vary according to whether use was daily or weekly, so we combined these frequencies (OR = 3.0, 95%CI = 1.5–5.6); the OR associated with use on a less than weekly basis was 1.8 (95% CI=0.9–3.5). Sub-analyses by age or after excluding men who have a family history or who have undescended testes did not substantially change the results.

In the 1953 episodes of marijuana use reported in our study population (268 cases and 666 controls who “ever” used), 20 (1%) were hashish users. An additional 247 (12.7%) were both hashish and marijuana users, and the remaining 1683 (86.3%) were marijuana only users. In the episodes where both were used, there is no way to know how much of each, When we eliminated those respondents who had used hashish, the results did not change.

Among 493 18–34 year-old controls in our study, 295 were ever marijuana users compared to 276.1 expected based on NSDUH data (O/E=1.1, 95% CI=0.90–1.26). Among the 102 current marijuana users (compared to 103 expected; O/E=1.0; 95% CI=0.75–1.32), 56 reported using this drug weekly compared to 76.5 expected; O/E=0.7, 95% CI=0.51–1.05.

DISCUSSION

We found a 70% increased risk of TGCT associated with current marijuana use, and the risk was particularly elevated for current use that was at least weekly or that began in adolescence. These associations were independent of known TGCT risk factors. In addition, all of the associations we observed appeared to be limited to nonseminoma/mixed histologies.

Our results must be interpreted in light of several limitations of our study. First, we only interviewed 67.5% and 52.2% of apparently eligible cases and controls, respectively. Our results may be biased if, among the cases and controls we were unable to interview, the association between marijuana use and TGCT was different than among those men that we did interview. In order to have produced a spurious positive association, there would need to be an inverse association among the non-participating subjects. Second, we had to rely on self-report of marijuana use, an illicit drug. Cancer cases might be expected to more accurately admit to the use of an illegal substance than controls. However, our finding of an increased risk of TGCT associated with marijuana use that was confined to nonseminoma or mixed histologies indicates that it is unlikely that over-reporting occurred, since there would be no reason to expect that recall bias would occur preferentially according to tumor type. Furthermore, after adjusting for age and race, the marijuana use characteristics (ever, current and frequency of use) of our controls were essentially the same as would be predicted from national data. Finally, we did not conduct centralized pathologic review but relied on the

histologic description provided by community pathologists and coded by the CSS. Any resulting misclassification, however, would be expected to obscure differences in associations between pure seminomas and non-seminomas/mixed seminomas.

Our original hypothesis sought an increasing exposure that would be associated with the risk of all histologic types of TGCT, since the incidence of seminomas, non-seminomas and mixed histologies has been increasing. We found, however, that the excess risk of TGCT associated with marijuana use was essentially confined to the nonseminomas and mixed histology tumors. In fact, the increase in the incidence of seminoma from 1973 to 1998 in the United States was 64% compared to an increase of only 24% for nonseminoma (2). However, the opposite is true in the Netherlands and Norway with the largest increase occurring in the non-seminoma histologic groups (30). If the increase in nonseminomas is in part due to an increase in the use of marijuana, some other increasing exposures must account for the higher incidence of seminomas over time. Akre et al. (8) suggest that increased maternal age, increased placental weight, and decreased parity are factors that are more closely associated with seminoma compared with nonseminoma. These exposures have also been increasing over the past decades (31–33) and thus could explain differential increases in incidence according to histology.

We can only speculate whereby marijuana use may be associated with TGCT. Moller (34) showed a significant association between male subfertility and subsequent risk of TGCT, and it has been suggested that both TGCT and male subfertility may be caused by one or more common exposures. Could one of these common exposures be the use of marijuana? Marijuana use is known to adversely affect male fertility including sperm output, motility and fertilizing capacity in various species including humans (17;35). In addition, chronic marijuana exposure adversely affects both the endocrine and reproductive systems in humans (17;36). It has been suggested that puberty is a “window of vulnerability” during which environmental factors increase the risk of TGCT (37). This is consistent with our finding that the elevated risk of nonseminomatous TGCTs was particularly associated with the use of marijuana starting prior to the age of 18 years. It is also speculated that primitive germ cells persisting into the pubertal period multiply under the stimulation of gonadotropins and other hormones (38). It is then possible that altered levels of gonadotropins and other hormones during this “window of vulnerability” due to exposure of marijuana increase the risk of TGCTs. However, none of these explanations would likely be specific to nonseminomas. If indeed the association is true, new avenues of research will be needed to address the specificity of the association to nonseminomas.

The mechanism by which marijuana exerts its effects on various biological processes remained unknown until cannabinoid receptors were identified in the 1990s. Cannabinoid receptors are part of the G-protein coupled receptor family and comprise two major subtypes, brain-type receptors (CB1) and spleen-type receptors (CB2) (20;21;39). They are G-protein coupled seven transmembrane spanning receptors and influence a variety of biological responses. CB1 and CB2 are expressed in the testes and sperm as well as in the brain, heart, uterus, embryo, spleen and immune cells (17).

There are two major endogenous cannabinoid-like (endocannabinoid) lipid mediators, N-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG) that are produced from arachidonic acid. They mimic many of the effects of THC and activate both CB1 and CB2 (18;40–43). The endocannabinoid system is operative in the male reproductive organs (14). Endocannabinoid signaling is associated with anti-tumor effects on a variety of human tumor cells in vitro and in xenograft models in vivo (44;45), findings that would appear to be inconsistent with our observation of an association between marijuana use and TGCTs. Endocannabinoids are rapidly degraded by fatty acid amid

hydrolase and monoacylglycerol lipase, whereas marijuana derivatives are mainly metabolized by cytochrome P_{450} enzymes with a half life of about 4 days in chronic marijuana users (46). Thus, relatively prolonged activation of CB1 and CB2 in marijuana users may disrupt normal anti-tumorigenic endocannabinoid signaling. Alternatively, the effects of cannabinoid/endocannabinoid signaling on tumorigenesis may be organ specific and age dependent. Although both the main psychoactive component of marijuana, THC, and anandamide have higher affinity for CB1, cannabinol, an oxidation product of THC, has 10- fold higher affinity for CB2 compared to CB1(21). Therefore, the activation of CB receptors coupled to different effectors may lead to distinct biological functions. In addition, other biologically active components of marijuana may function through pathways other than endocannabinoid system. Future epidemiologic and model system studies are needed to confirm or refute our findings. Such studies should include assessment of the role of CB receptors and endocannabinoid signaling in TGCTs.

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Table 1

Characteristics of testicular cancer cases and population controls. Western Washington State, January 1999 – January 2006

Characteristic	Controls (N =979)		Cases (N = 369)	
	N	%	N	%
Age at reference date (years)				
18–24	121	12.3	55	14.9
25–29	127	13.0	60	16.3
30–34	245	25.0	94	25.5
35–39	247	25.2	83	22.5
40–44	239	24.4	77	20.9
Reference year				
1999–2002	630	64.4	217	58.8
2003–2006	349	35.6	152	41.2
Race and Hispanic ethnicity				
White non-Hispanic	783	80.0	324	87.8
African-American (Hispanic or non-Hispanic)	28	2.9	0	0.0
White Hispanic	15	1.5	10	2.7
Other non-Hispanic	117	12.0	28	7.6
Other Hispanic	36	3.7	7	1.9
Household income at reference date				
<$25,000	110	11.3	55	14.9
$25,000 – 50,000	236	24.2	108	29.3
$50,000 – 90,000	400	41.0	126	34.2
$90,000 +	229	23.5	79	21.5
Refused	4		1	
Highest level of education				
High school or less	229	23.4	96	26.0
Trade school	124	12.7	49	13.3
College	473	48.3	183	49.6
> College	153	15.6	41	11.1
History of cryptorchidism				
No	955	97.5	329	90.1
Yes	24	2.5	36	9.9
Don’t know	0		4	
First degree family history of testicular cancer				
No	863	99.0	315	97.2
Yes	9	1.0	9	2.8
Don’t know	107		45	

Table 2

Risk of testicular cancer associated with marijuana use - all histologies. Western Washington State, January 1999 – January 2006

	Controls (N=979)		Cases (N=369)			
Characteristic	**N**	**%**	**N**	**%**	**OR[1]**	**95% CI**
Ever used marijuana						
No	313	32.0	101	27.4	1.0	(ref)
Yes	666	68.0	268	72.6	1.3	1.0–1.8
Marijuana use as of reference date						
Never	313	32.0	101	27.4	1.0	(ref)
Former	474	48.4	171	46.3	1.2	0.9–1.7
Current	192	19.6	97	26.3	1.7	1.1–2.5
Age at first use among current users						
<18	143	14.6	76	20.6	1.8	1.2–2.8
18+	49	5.0	21	5.7	1.4	0.8–2.5
Years of use among current marijuana users						
<10 years	44	4.5	27	7.3	1.8	1.0–3.3[2]
10+ years	148	15.1	70	19.0	1.6	1.1–2.5
Frequency of current marijuana use						
Daily or >=1 day a week	101	10.3	57	15.4	2.0	1.3–3.2
Less than once a week	91	9.3	40	10.8	1.4	0.9–2.3

[1] Adjusted for age at reference date, reference year, alcohol use, current smoking, and history of cryptorchidism.

[2] Confidence interval excludes 1.0

Table 3

Risk of testicular cancer associated with marijuana use according to histology. Western Washington State, January 1999 – January 2006

	Controls (N=979)		Pure Seminoma (N = 230)				Nonseminoma/Mixed (N = 139)			
	N	%	N	%	OR[1]	95% CI	N	%	OR[1]	95% CI
Ever used marijuana										
No	313	32.0	65	28.3	1.00	(ref)	36	25.9	1.00	(ref)
Yes	666	68.0	165	71.7	1.2	0.9–1.8	103	74.1	1.5	0.9–2.4
Marijuana use as of reference date										
Never	313	32.0	65	28.3	1.0	(ref)	36	25.9	1.00	(ref)
Former	474	48.4	121	52.6	1.2	0.8–1.8	50	36.0	1.2	0.7–2.0
Current	192	19.6	44	19.1	1.3	0.8–2.1	53	38.1	2.3	1.3–4.0
Age at first use among current users										
<18 years	143	14.6	31	13.5	1.2	0.7–2.0	45	32.4	2.8	1.6–5.1
18+ years	49	5.0	13	5.7	1.5	0.7–2.9	8	5.8	1.3	0.6–3.2
Years of use among current users										
<10 years	44	4.5	9	3.9	1.5	0.7–3.5	18	12.9	1.8	0.8–3.8
10+ years	148	15.1	35	15.2	1.2	0.7–2.1	35	25.2	2.7	1.5–5.0
Frequency of current marijuana use										
Daily or >=1 day a week	101	10.3	23	10.0	1.3	0.7–2.4	34	24.5	3.0	1.5–5.6
Less than once a week	91	9.3	21	9.1	1.2	0.7–2.2	19	13.7	1.8	0.9–3.5

[1] Adjusted for age at reference, reference year, alcohol use, current smoking, and history of cryptorchidism.