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Marijuana use and testicular germ cell tumors

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Abstract

Background—Since the early 1970's the incidence of testicular germ cell tumors (TGCT) in the U.S. has been increasing, however, potential environmental exposures accounting for this rise have not been identified. A prior study reported a significant association among frequent and long-term current users of marijuana and TGCT risk. We aimed to evaluate the relationship of marijuana use and TGCT in a hospital-based case-control study conducted at The University of Texas M. D. Anderson Cancer Center.

Methods—TGCT cases diagnosed between January 1990 and October 1996 (n=187) and male friend controls (n=148) were enrolled in the study. All participants were between the ages of 18 and 50 at the time of cases' diagnosis and resided in Texas, Louisiana, Arkansas, or Oklahoma. Associations of marijuana use and TGCT were estimated using unconditional logistic regression, adjusting for age, race, prior cryptorchidism, cigarette smoking and alcohol intake.

Results—Overall, TGCT cases were more likely to be frequent marijuana users (daily or greater) than were controls [OR: 2.2, 95% CI: 1.0, 5.1]. In the histologic-specific analyses nonseminoma cases were significantly more likely than controls to be frequent users [OR: 3.1, 95% CI: 1.2, 8.2] and long-term users (10+ years) [OR: 2.4, 95% CI: 1.0, 6.1].

Discussion—Our finding of an association between frequent marijuana use and TGCT, particularly among men with nonseminoma, is consistent with the findings of a previous report. Additional studies of marijuana use and TGCT are warranted, especially studies evaluating the role of endocannabinoid signaling and cannabinoid receptors in TGCT.

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Keywords

marijuana use; seminomas; nonseminomas; testicular germ cell tumors; hospital-based case-control

Testicular germ cell tumors (TGCT) are relatively rare malignancies, accounting for less than 2% of male cancers; however, they are the most common malignant neoplasm occurring in young men, ages 15-44, in many countries including the United States (U.S.).[1] Based on data from 2002-2006, TGCT incidence rates among young, white men in the U.S. were 6.3 per 100,000 men.[2] In contrast, the incidence rates among black and Asian men range from 1-2 per 100,000.[2] The highest incidence rates in the world occur in populations of northern European ancestry, regardless of their country of residence.[3] In the U.S., the incidence of TGCT increased in white American men by 70.2% between 1975 and 2005.[2] Similar increases in TGCT incidence have been observed among men of European heritage in Canada, many European countries, New Zealand and Australia.[3-7] Such an increase in incidence over a relatively short time interval suggests the influence of environmental rather than genetic factors. TGCT is hypothesized to develop as a result of the neoplastic transformation of germ cells into testicular carcinoma in situ. It is believed that these neoplasms arise early in fetal life and progress to invasive cancer under the influence of adult gonadotropic and androgenic hormones.[8;9]

There are few established risk factors for TGCT beyond age, race, history of cryptorchidism, and family history of TGCT. Recently, marijuana use has been evaluated as a risk factor.[10] Daling and colleagues reported increased risk of TGCT with current marijuana use, specifically among frequent (once per week or greater) and long-term users (10+ years).[10] The exact mechanism of how heavy marijuana use might increase the risk of TGCT is unknown, however chronic marijuana exposure has multiple adverse effects on the endocrine and reproductive systems such as gynecomastia, impotence, reduced sperm counts, and suppressed testosterone.[7;11-13] We explored the relationship of marijuana use and TGCT in an existing hospital-based case-control study conducted at The University of Texas M. D. Anderson Cancer Center (UTMDACC). Specifically, we evaluated whether TGCT risk increased with increasing frequency and duration of marijuana use. We also assessed whether risk estimates for marijuana use varied by TGCT histology.

Material and Methods

TGCT cases and friend controls were enrolled into a hospital-based case-control study conducted at UTMDACC. Full details of the study design have been previously reported.[14-16] Briefly, cases were men with incident primary TGCT registered at UTMDACC between January 1990 and October 1996 through the Genitourinary Oncology clinic or had been previously treated and were recruited from The University of Texas M. D. Anderson Tumor Registry (January 1990 – August 1994). To assemble a control population, cases were asked to provide the name of at least one adult male friend of similar age and race. All participants were between the ages of 18 and 50 at the time of the cases' diagnosis and resided in Texas, Louisiana, Arkansas, or Oklahoma.

All men diagnosed with TGCT during the given time period were eligible for inclusion regardless of ethnicity, tumor stage, or tumor histology. Because it is not clear that gonadal and extragonadal germ cell tumors share common etiologies we excluded men diagnosed with extragonadal germ cell tumors to avoid introducing heterogeneity into the case group. Pathology reports were reviewed for all cases and tumors were grouped as pure seminomas,

nonseminomas (teratoma, embryonal carcinoma, and choriocarcinoma) and mixed germ cell tumors (both seminomatous and nonseminomatous elements).

Cases and controls completed a self-administered questionnaire ascertaining information on demographics, lifestyle habits, medical history and diet. Information on drug use, including use of marijuana, was also collected. The questions pertaining to drug use utilized a detachable throw-away coversheet to protect the participant's privacy. Participants were asked if they had ever used marijuana, the number of times used per week and the calendar years during which they used marijuana.

Statistical Analysis

Analyses were conducted for all cases combined and for cases classified by histologic type: seminomas, nonseminomas and mixed germ cell tumors. Using the data collected on number of times per week and years of marijuana use, we created three analytic variables: ever used marijuana, frequency of marijuana use per week and duration, number of years, of marijuana use. Study participants who self-reported never smoking marijuana served as the reference category for the marijuana use variables. Ever use was defined as self-report of smoking marijuana regardless of frequency or duration of use. The ever users were then stratified by frequency of marijuana use and duration of marijuana use. Frequency of use was categorized into marijuana use less than once per day or at least once per day or greater (daily or > 1 per day). Duration was categorized as less than 10 years of lifetime marijuana use or 10 or more years of lifetime marijuana use.

A number of cases did not have a matched control because a name was not provided or the individual named was unwilling to participate. To avoid the loss of information by excluding unmatched cases, we evaluated the results using a matched analysis (conditional logistic regression) and an unmatched analysis (unconditional logistic regression adjusting for age and race). The point estimates for the two models were not substantially different (data not shown) and did not change the interpretation of the results, thus we present the results from the unmatched analysis. Odds ratios (OR) and 95% confidence intervals (CI) were calculated as estimates of relative risk using unconditional logistic regression. Polytomous logistic regression models were used to compare controls with each of the case groups defined by histologic type. All analyses were adjusted for participants' age at diagnosis for cases and at time of interview for controls, race, and history of cryptorchidism. We also included two additional behaviors that may be correlated with marijuana use, cigarette smoking and alcohol consumption. Other covariates considered were education and income. However, the addition of these variables to a model controlling for age, history of cryptorchidism, alcohol consumption and cigarette smoking did not substantially change the ORs (less than 10% change in the risk estimate); thus, education and income were not included in the final analysis. To evaluate the robustness of our results, we conducted sensitivity analyses excluding the 60 study participants who reported very infrequent marijuana use (less than once per week). All analyses were performed in Stata/SE (Stata Statistical Software, version 10.1; StataCorp, College Station, TX).

Results

The distribution of selected demographic and health characteristics for the TGCT cases and controls are provided in Table 1. The median age for friend controls and all cases combined was similar; the median age for nonseminoma cases was approximately 10 years younger than seminoma cases. Compared to controls, cases tended to report somewhat lower annual incomes and were less likely to have more than a high school education. Cases were more likely than controls to have a history of cryptorchidism (13.4% all cases vs. 2.0 % controls; age- and race-adjusted odds ratio (OR), 7.8; 95% confidence interval (CI), 2.3-26.5).

Overall, the frequency of ever having used marijuana was similar between cases and controls (OR, 0.7; 95% CI, 0.4, 1.1) (Table 2). TGCT cases were more likely to be frequent marijuana users (daily or >1 per day) than controls (OR, 2.2; 95% CI, 1.0, 5.1) and cases were less likely than controls to report infrequent marijuana use (< 1 per day: OR, 0.5, 95% CI, 0.3, 0.9), and short-term marijuana use (< 10 years: OR, 0.6, 95% CI, 0.3, 1.0). Approximately three-quarters (75.5%) of the individuals who reported ever using marijuana initiated use at age 18 or younger (results not shown). Furthermore, we evaluated the intensity of marijuana use (frequency and duration) with TGCT risk and found that the results were consistent with a doubling of risk with high intensity use (very frequent and long-term) but was not statistically significant due to the small numbers within these categories (results not shown).

In the analyses by histologic type, nonseminoma cases were significantly more likely than controls to be frequent users (daily or > 1 per day: OR, 3.1; 95% CI, 1.2, 8.2) and long-term users (10 + years: OR, 2.4, 95% CI, 1.0, 6.1). In contrast, in the analysis limited to seminomas, cases were significantly less likely than controls to be infrequent users [OR: 0.4, 95% CI: 0.2, 0.9] and there was no significant association with duration of use.

The results of sensitivity analyses, excluding study participants reporting very infrequent marijuana use, supported the relationship between frequent marijuana use and all TGCT (results not shown). Sensitivity analyses also supported the associations between frequent and long-term use among men with nonseminoma (results not shown).

Discussion

We observed a two-fold increased risk of TGCT associated with frequent marijuana use. In histologic specific analyses, the associations were limited to nonseminomas. These associations were independent of known risk factors for TGCT, age, race and prior cryptorchidism, as well as cigarette smoking and alcohol consumption. We also reported reduced risk of TGCT associated with infrequent and short-term use; however, these findings were not robust to sensitivity analyses and require further evaluation.

There is limited evidence that marijuana use may modulate TGCT risk. The only other published study to date examined the association of marijuana use and TGCT in a population-based case-control study in Western Washington State.[10] Daling and colleagues reported that men with TGCT were significantly more likely than controls to be current marijuana users. The association was particularly strong among men who were frequent current users (at least weekly) or current users of long duration (ten years or more).[10] In addition, the associations appeared to be limited to cases with nonseminoma or mixed germ cell tumors.[10] Unlike the study in Western Washington State the results of our study are not supportive of an association between weekly marijuana use and TGCT; instead, our results are supportive of a substantially increased risk of TGCT with very frequent marijuana use, daily or greater. In addition, although we were not able to evaluate current use with our data (< 10% of our study population reported current marijuana use), our findings are supportive of the association between frequent and long-term marijuana use and nonseminoma.

Puberty may be a period of development during which environmental factors increase the risk of TGCT.[17] Exposures during this time may be more relevant to nonseminoma TGCT risk, given that the peak occurrence of nonseminoma TGCT occurs ten-years earlier than seminoma TGCT, and within a biologically relevant time period after puberty. It is plausible that the use of marijuana during puberty perturbs the hypothalamic-pituitary-gonadal axis leading to altered levels of pituitary gonadotropins (follicle-stimulating hormone (FSH) and

luteinizing hormone (LH)) and sex-steroid hormones and potentially increased risk of nonseminoma TGCT.

Studies have demonstrated that acute or chronic treatment of cannabis-extract in male mice and tetrahydrocannabinol (THC), the active ingredient in marijuana, in male rats can act centrally to affect circulating levels of testosterone, FSH, and LH.[13;18-20] Two cannabinoid receptors exist in humans, the brain-type receptors (CB1) and the spleen-type receptors (CB2).[21-23] These two major sub-types of cannabinoid receptors are part of the G-protein-coupled receptor family and influence a variety of biologic responses. CB1 and CB2 are expressed in the testes and sperm as well as in the brain, heart, uterus, embryo, spleen and immune cells.[19] Laboratory evidence demonstrates that cannabis and cannabis-like compounds target cannabinoid receptors in Leydig and Sertoli cells and influence testosterone and pituitary gonadotropin release as well as Sertoli cell survival. Studies have shown that endogenous cannabinoid-like (endocannabinoid) lipid mediators (anandamide specifically) suppressed LH and testosterone levels in wild-type but not CB1 knockout mice, providing evidence that the endocannabinoid system acts to alter testosterone and pituitary gonadotropin concentrations.[24] Further, there is evidence that cannabinoids can inhibit testosterone activity by impairing androgen binding to receptors.[25]

Although our results support the findings by Daling et al., there are several limitations to our study. The study relied on self-report of marijuana use, which is an illicit drug. Persons with a serious disease, such as cancer, may more accurately report the use of an illegal substance than individuals without a serious medical condition. To address this concern, we compared the marijuana use in the controls with publicly available national data and found no significant difference. The specificity of our finding, that the association between marijuana use and TGCT was primarily limited to nonseminoma, may be due to the limited numbers of seminoma and mixed germ cell tumors.

Use of friend controls as the referent group in any study raises the concern that controls are too similar to cases. If the controls, in fact, were too similar to cases in terms of their marijuana use patterns, then it is likely that our estimates of risk would have underestimated the true relationship between marijuana use and TGCT. In our study, however, the controls were older and reported higher incomes than cases, suggesting that over-matching was not present, at least for these factors. While we attempted to match on age, the cases tended to nominate friend controls who were generally older than they were, so we adjusted for age in all of our analyses. We also evaluated income as a potential confounding factor and found that it had no effect in a model adjusting for age, race, history of cryptorchidism, cigarette smoking and alcohol consumption. Thus, income was not included in the final models.

As the use of friend controls can bias the results of retrospective studies, we evaluated the extent to which reporting of marijuana use among the controls was consistent with data from the 1996 population-based National Survey on Drug Use and Health (NSDUH; known as the National Household Survey on Drug Abuse prior to 1999). We compared the observed number of controls who reported ever using marijuana with the expected number based on age- and race-specific proportions in the survey data[26]; we did not find a significant difference, suggesting selection or reporting bias was not an explanation for the observed associations [among 128 white men of all ages in the control group, 68 reported any marijuana use compared with 70.9 expected based on NSDUH data (O/E ratio, 0.96; 95% CI, 0.74, 1.22)]. The NSDUH did not capture information on lifetime frequency of use; however, it did collect information on current frequency of use. Using the NSDUH variable on current frequency of use, we did not find a significant observed-to-expected difference when we compared the observed number of controls who reported daily marijuana use with the expected number based on age- and race- specific proportions of current daily use

[among 123 white men of all ages in the control group, 32 reported any marijuana use compared with 32.5 expected based on NSDUH data (O/E ratio, 0.98; 95% CI, 0.67, 1.3)].

Our finding of an association between frequent marijuana use and TGCT, particularly among men with nonseminoma is consistent with the findings of a previous report.[10] The biologically active components of marijuana may directly affect TGCT risk by altering gonadotropin and hormone levels during puberty; however, these components may function through pathways other than the endocannabinoid system. Additional studies of marijuana use and TGCT are warranted, especially studies evaluating the role of endocannabinoid signaling and cannabinoid receptors in TGCT.

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Table 1

Selected characteristics of controls and testicular germ cell tumor cases by histology: The University of Texas M. D. Anderson Cancer Center January 1990 - October 1996.

					Tumor Type					
Characteristic	**Controls (n = 148)**		**All Cases (n = 187)**		**Seminoma (n = 50)**		**Nonseminoma (n = 95)**		**Mixed Germ Cell (n = 42)**	
Age in 1996										
median (min, max)	34	(18, 63)	33	(18, 57)	38.5	(24, 57)	29	(18, 51)	33.5	(20, 51)
Race	n*	%	n*	%	n*	%	n*	%	n*	%
White	130	87.8	151	80.8	41	82.0	75	79.0	35	83.3
Hispanic	14	9.5	28	15.0	7	14.0	13	13.7	7	16.7
Other	4	2.7	8	4.2	2	4.0	7	7.4	0	0.0
Cigarette smoking										
Never	88	59.5	99	52.9	25	50.0	49	51.6	25	59.5
Former (quit > 6 mos)	37	25.0	59	31.6	16	32.0	32	33.7	11	26.2
Current	23	15.5	29	15.5	9	18.0	14	14.7	6	14.3
Alcohol consumption										
Never	14	9.5	23	12.3	6	12.0	10	10.5	7	16.7
Former (quit > 6 mos)	37	25.0	53	28.3	15	30.0	29	30.5	9	21.4
Current	97	65.5	111	59.4	29	58.0	56	59.0	26	61.9
History of cryptorchidism†										
Yes	3	2.0	25	13.4	7	14.0	12	12.6	6	14.3
No	145	98.0	162	86.6	43	86.0	83	87.4	36	85.7
Income†										
<$25,000	20	14.3	55	31.6	11	23.4	30	34.1	14	35.9
$25,000 - $54,999	43	30.7	52	29.9	12	25.5	34	38.6	6	15.4
$55,000 - $74,999	36	25.7	29	16.7	8	17.0	13	14.8	8	20.5
$75,000 +	41	29.3	38	21.8	16	34.0	11	12.5	11	28.2
Years of education†										
≤ 12	31	21.0	58	31.0	12	24.0	30	31.6	16	38.1
> 12	117	79.1	129	69.0	38	76.0	65	68.4	26	61.9

*Columns may not sum to total because of missing data.

† Chi-square p-value < 0.05 comparing frequency of all cases to controls.

Table 2

Associations of testicular germ cell tumors and marijuana use according to histology: The University of Texas M. D. Anderson Cancer Center, January 1990 - October 1996.

Characteristic	Controls (N = 148)		All Cases (N = 187)				Seminoma (N = 50)				Nonseminoma (N = 95)				Mixed Germ Cell Tumors (N = 42)			
Ever used marijuana	n	%	n	%	OR*	(95% CI)	n	%	OR*	(95% CI)	n	%	OR*	(95% CI)	n	%	OR*	(95% CI)
No	66	45.2	96	51.3	1.0	Referent	30	60.0	1.0	Referent	44	46.3	1.0	Referent	22	52.4	1.0	Referent
Yes	80	54.8	91	48.7	0.7	(0.4, 1.1)	20	40.0	0.5	(0.3, 1.1)	51	53.7	0.8	(0.4, 1.4)	20	47.6	0.8	(0.3, 1.6)
Frequency of marijuana use																		
Never	66	46.8	96	52.2	1.0	Referent	30	61.2	1.0	Referent	44	46.8	1.0	Referent	22	53.7	1.0	Referent
Less than once per day	65	46.1	54	29.4	0.5	(0.3, 0.9)	12	24.5	0.4	(0.2, 0.9)	29	30.9	0.6	(0.3, 1.1)	13	31.7	0.6	(0.3, 1.4)
Daily or > 1 time per day	10	7.1	34	18.5	2.2	(1.0, 5.1)	7	14.3	1.4	(0.4, 4.6)	21	22.3	3.1	(1.2, 8.2)	6	14.6	2.0	(0.6, 7.0)
Duration of marijuana use																		
Never	66	46.8	96	52.8	1.0	Referent	30	61.2	1.0	Referent	44	47.3	1.0	Referent	22	55.0	1.0	Referent
< 10 years	59	41.8	57	31.3	0.6	(0.3, 1.0)	14	28.6	0.5	(0.2, 1.2)	29	31.2	0.6	(0.3, 1.1)	14	35.0	0.7	(0.3, 1.6)
≥ 10 years	16	11.4	29	15.9	1.2	(0.6, 2.8)	5	10.2	0.6	(0.2, 1.9)	20	21.5	2.4	(1.0, 6.1)	4	10.0	0.9	(0.2, 3.5)

OR indicates odds ratio; 95% CI, 95% confidence interval.

*Adjusted for age in 1996, race, alcohol use, cigarette smoking, and history of cryptorchidism.

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