Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

Marijuana Use is Not Associated with Cervical Human Papillomavirus Natural History or Cervical Neoplasia in HIV-Seropositive or HIV-Seronegative Women

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Abstract

Marijuana use was recently reported to have a positive cross-sectional association with human papillomavirus (HPV)–related head and neck cancer. Laboratory data suggest that marijuana could have an immunomodulatory effect. Little is known, however, regarding the effects of marijuana use on cervical HPV or neoplasia. Therefore, we studied the natural history (i.e., prevalence, incident detection, clearance/persistence) of cervical HPV and cervical neoplasia (i.e., squamous intraepithelial lesions; SIL) in a large prospective cohort of 2,584 HIV-seropositive and 915 HIV-seronegative women. Marijuana use was classified as ever/never, current/not current, and by frequency and duration of use. No positive associations were observed between use of marijuana, and either cervical HPV infection or SIL. The findings were similar among HIV-seropositive and HIV-seronegative women, and in tobacco smokers and nonsmokers. These data suggest that marijuana use does not increase the burden of cervical HPV infection or SIL. *Cancer Epidemiol Biomarkers Prev; 19(3); 869–72. ©2010 AACR.*

Introduction

A recent cross-sectional case-control investigation reported that marijuana use may be associated with increased odds of human papillomavirus (HPV)–positive, but not HPV-negative head and neck squamous cell cancer (1-3). Although carcinogens in marijuana have been shown to induce molecular (4) and cellular (5) abnormalities, carcinogenic agents might be expected to affect both HPV-positive and HPV-negative cancers. Therefore, attention has been drawn to laboratory studies showing that cannabinoids might be immunosuppressive (6), which if correct, would raise the possibility that marijuana might increase the risk of HPV-associated cancer by increasing susceptibility to infection when exposed and/or increasing the likelihood of HPV persistence. A systemic effect of marijuana use on host immune status might also be expected to affect risk of cervical HPV infection and neoplasia but this question has not been well explored. A cross-sectional study found a relation of cervical HPV prevalence with "marijuana and/or (unspecified) related substances" (7), and a longitudinal study found that recent marijuana use was associated with risk of incident cervical HPV infection among 73 HIV-seronegative but not in 146 HIV-seropositive subjects (8). Another study, however, found no association following adjustment for other risk factors (9). To build on these prior data, we examined the effects of marijuana use on the natural history of cervical HPV and neoplasia in a large, long-term cohort of HIV-seropositive and HIV-seronegative women.

Materials and Methods

Specimens and data were obtained from the Women's Interagency HIV Study, a cohort of 2,793 HIV-seropositive and 959 HIV-seronegative women (10, 11). Participants underwent semiannual clinical visits that included an interviewer-administered questionnaire, physical and gynecologic examinations that included Pap smears, and cervicovaginal lavage for HPV DNA testing (12). History of past and recent marijuana and other drug use was assessed at each semiannual visit. Data from 209 HIV positive and 44 HIV negative women with no cervix at baseline were excluded from the analysis and 121 women with hysterectomy during follow-up were censored at the visit prior to hysterectomy. HPV DNA was detected utilizing a well established L1 consensus primer MY09/MY11/HMB01 PCR assay that can identify >40 individual HPV types including HPV6/11/13/16/18/26/31/32/33/34/

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Table 1. Multivariate associations of marijuana use with the prevalent and incident detection, and persistence/clearance, of cervical HPV and SIL

(A) HPV

	Person-visits*	Prevalent HPV		Incident HPV		Clearance of HPV	
		OR	95% CI	HR	95% CI	HR	95% CI
Marijuana use							
Never	9,824	Referent	–	Referent	–	Referent	–
Ever	27,724	1.00	(0.90-1.11)	0.99	(0.88-1.11)	0.98	(0.90-1.06)
Current marijuana use							
No	30,178	Referent	–	Referent	–	Referent	–
Yes	7,428	0.98	(0.90-1.07)	0.97	(0.88-1.07)	1.00	(0.92-1.09)
Frequency of current use							
None	30,178	Referent	–	Referent	–	Referent	–
≤1/wk	3,972	1.02	(0.93-1.12)	1.02	(0.90-1.15)	0.98	(0.89-1.08)
2-6 times/wk	1,619	0.96	(0.84-1.10)	0.89	(0.73-1.08)	1.08	(0.91-1.28)
≥1/d	1,817	0.91	(0.77-1.07)	0.92	(0.76-1.10)	1.00	(0.86-1.18)
Duration of use							
Never	9,824	Referent	–	Referent		Referent	
6-12 mo	3,190	1.01	(0.89-1.15)	0.93	(0.80-1.08)	0.97	(0.87-1.08)
13-36 mo	4,102	0.92	(0.79-1.08)	1.00	(0.85-1.19)	0.98	(0.86-1.12)
>3 y	6,419	0.97	(0.81-1.17)	1.02	(0.81-1.29)	1.03	(0.88-1.20)
Duration of more than once/wk use							
Never	9,824	Referent	–	Referent	–	Referent	–
6-12 mo	1,287	0.95	(0.81-1.11)	0.91	(0.76-1.09)	1.01	(0.89-1.15)
13-36 mo	1,972	0.90	(0.73-1.10)	0.91	(0.72-1.15)	1.00	(0.82-1.21)
>3 y	3,689	0.91	(0.70-1.18)	0.87	(0.64-1.19)	1.47	(1.09-1.98)

(*Continued on the following page*)

35/39/40/42/45/51/52/53/54/55/56/57/58/59/61/62/64/66/67/68/69/70/71/72/73/74/81/82/83/84/85/89 (13).

HPV and squamous intraepithelial lesion (SIL) prevalence were studied using multivariate logistic regression models that incorporated generalized estimating equations with an exchangeable correlation structure to analyze these outcome data across HPV types and visits. Time to incident HPV detection and clearance were each analyzed using Cox proportion models that used the Wei-Lin-Weissfeld marginal model approach to adjust the results for possible correlations between multiple HPV infections. As recently reported, statistical power is substantially increased in studies of HPV and SIL when repeated observations are considered in the analysis, even after appropriately adjusting for the correlation between serial test results (14). Had we instead used standard logistic regression and/or Cox models to incorporate these repeated observations over time, the effect estimates would have been similar, but the *P* values and confidence intervals would have been incorrect (14). Incidence/clearance of SIL was studied using standard Cox models because the development and clearance of SIL are each an individual event (we did not study recurrence). In our generalized estimating equations, Wei-Lin-Weissfeld, and standard Cox models, we used time-dependent covariates including recent marijuana use, CD4+ T-cell count, age, number of sexual partners in the past 6 months, tobacco use, and cervical treatment. Race/ethnicity was a time-independent covariate.

Results

The final data set included 2,584 HIV-seropositive (93%) and 915 HIV-seronegative (95%) women, of whom 66% and 75%, respectively, reported a history of ever using marijuana when interviewed at the baseline visit. Recent marijuana use (in the past 6 months) was reported at baseline by 22% of HIV-seropositive and 33% of HIV-seronegative participants, with 13% and 17%, respectively, reporting marijuana use an average one or fewer times a week, 5% and 8% reporting use two to six times a week, and 4% and 8% reporting marijuana use one or more times a day. The pattern of marijuana use was analyzed as a time-dependent covariate in our multivariate models (i.e., updated at each visit).

Table 1 shows the associations of marijuana use with detection of cervical HPV and SIL. All models were adjusted for age, race, HIV status, CD4+ T-cell count, number of sexual partners in the past 6 months, tobacco use,

Table 1. Multivariate associations of marijuana use with the prevalent and incident detection, and persistence/clearance, of cervical HPV and SIL (Cont'd)

(B) SIL

	Person-visits	Prevalent SIL		Incident SIL		Clearance of SIL	
		OR	95% CI	HR	95% CI	HR	95% CI
Marijuana use							
Never	9,824	Referent	–	Referent	–	Referent	–
Ever	27,724	0.96	(0.77-1.20)	0.94	(0.76-1.17)	1.10	(0.90-1.33)
Current marijuana use							
No	30,178	Referent	–	Referent	–	Referent	–
Yes	7,428	0.97	(0.82-1.16)	1.09	(0.87-1.35)	1.09	(0.90-1.32)
Frequency of current use							
None	30,178	Referent	–	Referent	–	Referent	–
≤1/wk	3,972	1.04	(0.86-1.26)	1.05	(0.79-1.38)	1.02	(0.80-1.30)
2-6 times/wk	1,619	1.01	(0.75-1.37)	1.35	(0.94-1.95)	1.42	(1.01-1.99)
≥1/d	1,817	0.79	(0.56-1.12)	0.93	(0.61-1.42)	0.98	(0.67-1.43)
Duration of use							
Never	9,824	Referent	–	Referent		Referent	
6-12 mo	3,190	0.90	(0.69-1.19)	0.92	(0.69-1.23)	1.27	(0.98-1.64)
13-36 mo	4,102	0.84	(0.62-1.14)	1.06	(0.77-1.45)	1.21	(0.90-1.63)
>3 y	6,419	0.93	(0.64-1.36)	0.88	(0.54-1.42)	1.44	(0.95-2.17)
Duration of more than once/wk use							
Never	9,824	Referent	–	Referent	–	Referent	–
6-12 mo	1,287	0.91	(0.65-1.26)	0.94	(0.67-1.32)	1.27	(0.91-1.77)
13-36 mo	1,972	0.79	(0.53-1.18)	1.10	(0.74-1.65)	1.18	(0.77-1.82)
>3 y	3,689	0.66	(0.35-1.22)	0.39	(0.15-0.98)	1.88	(1.02-3.47)

NOTE: Models were adjusted for age, race, HIV status, CD4 cell count, number of sexual partners in the past 6 mo, tobacco use, and cervical treatment.

Abbreviation: HR, hazard ratio.

*Person-visits are used to express the amount of exposure in the population, and are analogous to person-years of exposure (a measure that is widely reported in the cancer literature). In contrast, the number of women in each category cannot be expressed because time-dependent covariates were used, and women may change exposure categories over time. Note: the number of person-visits is greater for current than for never/ever used marijuana because current use reflected only the past 6 mo, whereas women were censored from the analysis of never/ever used marijuana once data were missing from any visit.

and cervical treatment. We observed no relationship between marijuana use and prevalent HPV, including ever use [odds ratio (OR), 1.00; 95% confidence interval (CI), 0.90-1.11], current use (OR, 0.98; 95% CI, 0.90-1.07), current daily use (OR, 0.91; 95% CI, 0.77-1.07), or long-term frequent use (defined as marijuana use of more than once a week for >3 years: OR, 0.91; 95% CI, 0.7-1.18). Likewise, there were no associations between marijuana use and the incident detection of HPV or SIL (Table 1). The only significant association was the higher (not lower) rate of HPV clearance in long-term frequent marijuana users (hazard ratio, 1.47; 95% CI, 1.09-1.98) relative to never-users. Results were similar when examined only among HIV-seronegative or HIV-seropositive women, when limited to those who never smoked tobacco, when only oncogenic or nononcogenic HPV were considered, or following adjustment for recent cocaine use (a factor associated with increased HPV infection in an earlier Women's Interagency HIV Study; ref. 15; data not shown).

Discussion

We conducted a large prospective study of marijuana use and the natural history of HPV and cervical neoplasia, but no positive associations were detected, even when frequent, long-term marijuana use was considered. These results were similar among both HIV-seropositive and HIV-seronegative women, and independent of smoking status. Our findings, therefore, do not support recent hypotheses that marijuana might have a systemic immunomodulating effect that increases the burden of cervical HPV or disease (8).

There have been few studies of marijuana use and cervical HPV detection, and these have had inconsistent results. A Kaiser Permanente cohort study found

marginally increased risk of cervical cancer in ever marijuana users with no history of tobacco use (relative risk (RR), 1.4; 95% CI, 1.0-2.1; ref. 16), but that study did not control for certain relevant (e.g., sexual) cofactors. A large cross-sectional study of HPV found a strong relationship of cervical HPV prevalence with "marijuana and/or (unspecified) related substance use" (7). However, the inability to distinguish the type of drug was an important limitation because our group (15) and others (8) have reported that crack/cocaine use is associated with HPV and cervical neoplasia. A cross-sectional study of adolescent women found no association of marijuana with cervical HPV prevalence following adjustment for other risk factors (9).

In the only prior investigation to include HIV-seropositive women, marijuana use was not associated with cervical HPV among 146 HIV-seropositive drug users but a strong positive association was observed among 73 HIV-seronegative drug users (8). Although the reason for the differences in findings between this prior study and the current one is unknown, the current investigation was considerably larger, and differences in study design or population might also be relevant.

In summary, our investigation found no positive associations between marijuana use and cervical HPV or SIL. These findings are comforting given the high prevalence of marijuana use in HIV-seropositive and other populations, but we caution that we could not directly investigate the relationship between marijuana use and invasive cervical cancer.

Disclosure of Potential Conflicts of Interest

G. D'Souza: Commercial research grant, Merck; consultant/advisory board, Merck. M. Moxley: Consultant/advisory board, Delphi HealthCare; other, Goodman Allen & Filetti, PLLC. H. Strickler: Consultant/advisory board, Merck and GSK.

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