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Permalink

Journal

ISSN

Authors

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et al.

Publication Date

DOI

Peer reviewed

Opium, phencyclidine, and crack cocaine smoking associations with lung and upper aerodigestive tract cancers: preliminary findings from a case-control study in Los Angeles County

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Abstract

Background: Illicit drug use has become a global epidemic, yet it is unclear if drug smoking increases the risk of tobacco-related cancers.

Objectives: We aimed to evaluate hypothesized associations between smoking three drugs – opium, phencyclidine (PCP) and crack cocaine and lung and upper aerodigestive tract (UADT) cancers.

Methods: A population-based case-control study with 611 lung cancer cases (50% male), 601 UADT cancers cases (76% male), and 1,040 controls (60% male) was conducted in Los Angeles County (1999 – 2004). Epidemiologic data including drug smoking histories were collected in face-to-face interviews. Associations were estimated with logistic regressions.

Results: Adjusting for potential confounders, ever vs. never crack smoking was positively associated with UADT cancers (aOR = 1.56, 95% CI: 1.05, 2.33), and a dose-response relationship was observed for lifetime smoking frequency (p for trend = 0.024). Heavy (> median) vs. never

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crack smoking was associated with UADT cancers (aOR = 1.81, 95% CI: 1.07, 3.08) and lung cancer (aOR = 1.58, 95% CI: 0.88, 2.83). A positive association was also observed between heavy PCP smoking and UADT cancers (aOR = 2.29, 95% CI: 0.91, 5.79). Little or no associations were found between opium smoking and lung cancer or UADT cancers.

Conclusion: The positive associations between illicit drug use and lung and/or UADT cancers suggest that smoking these drugs may increase the risk of tobacco-related cancers. Despite the low frequency of drug smoking and possible residual confounding, our findings may provide additional insights on the development of lung and UADT cancers.

Introduction

Lung cancer and upper aerodigestive tract (UADT) cancers (i.e., cancers of the oral cavity, pharynx, larynx and esophagus) were estimated to be the 2nd and 3rd most common cancers, respectively, worldwide in 2020 (1). Lung cancer and UADT cancers are considered tobacco-related cancers as tobacco smoking is one of the established risk factors (2). In the past few decades, illicit drug use has gradually become a global epidemic. In 2020, an estimated 284 million people aged 15–64 (5.6% of the global population in this age group) had used illicit drugs in the previous year (3). In 2019, about 494,000 people are estimated to have died as a result of illicit drug use; about 30.9 million years of healthy life are estimated to have been lost due to illicit drug use (4). Despite the considerable numbers on disease burden associated with drug use (including drug smoking), cancers of the lung and upper aerodigestive tract had not been considered as a confirmed consequence of illicit drug use before 2020 (5, 6).

Findings from previous epidemiologic studies suggested positive associations between opium use and UADT cancers (7–14). Similarly, with respect to lung cancer, an increased risk was also reported associated with opium use (12, 15, 16). In 2020, the International Agency for Research on Cancer (IARC) finalized its evaluation of the carcinogenicity of opium consumption: opium consumption was classified as a Group 1 carcinogen to humans (17). According to the IARC, both smoking and ingestion of any forms of minimally processed opium may cause cancers of the larynx, lung, and urinary bladder. Nonetheless, it would still be of great importance to assess the extent to which consumption of opium increases cancer risks in other populations, as the IARC evaluation was primarily based on studies conducted in Iran, the country with the highest per capita opium consumption worldwide (17).

Phencyclidine (PCP) was originally developed as an anesthetic in the 1950s and then widely used as a hallucinogen due to its psychoactive effects (18). Crack cocaine (or crack), the freebase form derived from powdered cocaine, is used globally as a recreational drug (3, 19). Both PCP and crack cocaine can be administered through the airway (e.g., smoking, sniffing, and snorting). Due to the same route of administration, crack cocaine and PCP smoking share similarities with tobacco smoking and can potentially lead to airway lesions as well as complications (20–23). However, no epidemiologic studies have been conducted to investigate their associations with lung cancer and UADT cancers; crack cocaine and PCP use and cancer development remain largely unexplored.

The increasing trend of drug use raises concerns about whether such behaviors increase cancer risk. In this study, we aimed to investigate opium, PCP, and crack cocaine smoking in relation to the development of lung cancer and UADT cancers in a population-based case-control study conducted in Los Angeles County.

Methods

Study design and population

The UCLA Los Angeles Cancer Case-control Study (the UCLA cancer study hereinafter) is a population-based case-control study of lung and UADT cancers conducted within Los Angeles County from 1999 to 2004. The UCLA cancer study was initially designed and conducted to examine the association between cannabis use and lung and UADT cancers, and no clear harmful association was reported (24).

Eligible cases and controls met the following criteria: (1) residence in Los Angeles County at the time of diagnosis (cancer cases) or recruitment (controls); (2) were 18 – 65 years old when diagnosed or recruited; (3) spoke either English or Spanish or had a translator available during the interview. Histologically confirmed new cancer patients were identified from the Los Angeles Cancer Surveillance Program (LACSP) administered by the University of Southern California. Controls were recruited from LA County residents aged 18 – 65 and did not have a history of lung cancer or UADT cancers at the time of study. Identified by an algorithm based on the matching variables (sex, age decade, and residential neighborhood), eligible controls were approached (paying a visit in person or leaving an invitation letter with clear descriptions if no one answered) by trained investigators. The first eligible match willing to participate was then recruited and interviewed. Further descriptions of the original study have been described elsewhere in previous publications (24, 25).

Among all eligible cancer cases identified by study personnel, 611 (39%) of 1,556 lung cancer cases and 601 (46%) of 1,301 UADT cancer cases were able and willing to participate; many of the non-participants had already died or were too sick to be interviewed. Cancer diagnoses were classified by the International Classification of Diseases for Oncology, Second Edition (ICD-O-2) at the time of study recruitment. Of the 1,321 eligible controls identified by study personnel, 1,040 (79%) were willing to participate and were matched to cases.

This study was approved by the Institutional Review Boards of the University of California, Los Angeles and the University of Southern California, and all participants provided their written informed consent.

Data collection and exposure estimation

Enrolled subjects were interviewed by trained research staff using a standardized questionnaire. During the in-person interview, information on sociodemographic factors and detailed histories of tobacco use, alcohol consumption, and drug use were collected. All participants were assured that the confidentiality of any information they provided, including drug use, would be protected by the investigators.

For opium, PCP, and crack cocaine, cases and controls were first asked whether they ever smoked these drugs. If they answered yes to any of these three drugs, they were further asked questions about their drug smoking behaviors. Lifetime smoking frequency was collected as a categorical variable for each drug (0, 1–10 times, 11–30 times, 31–70 times, 71–150 times, and more than 150 times for opium and PCP; 0, 1–10 times, 11–30 times, 31–100 times, and more than 100 times for crack cocaine). Based on the distribution of smoking categories (represented by the midpoint of the corresponding category), the median levels among controls were used to classify the cumulative smoking status as more than median or no more than median, which referred to above or below the median level of drug smoking in the source population. In the following paragraphs, we use "heavy" to denote more than the population median level.

Participants who had used tobacco reported detailed lifetime use history, including age or year at starting and quitting (defining periods of use), route of administration (i.e., smoking and chewing), types of tobacco smoked (e.g., cigarette, cigar, and pipe), and frequency for each type of tobacco during each period of use (e.g., number of cigars smoked per day/week/ month/year). Cumulative lifetime tobacco use was expressed in pack-years. The lifetime history of alcohol consumption, including beer, wine, and liquor, was estimated in a similar manner, where one drink of each beverage type contains approximately the same amount of ethanol. Cumulative alcohol consumption was expressed in drink-years.

Statistical analysis

Not all cases were matched with a control subject during the recruitment; therefore, to preserve all enrolled cases, matched pairs were broken in the analysis. Unconditional logistic regression was then used to estimate the associations (odds ratios [ORs] and 95% confidence intervals [CIs]) of drug smoking with the odds of lung and UADT cancers. As lung cancer and UADT cancers were rare diseases in Los Angeles County residents aged 18 – 65, the odds ratios estimated from logistic regression models were used as approximations of risk ratios (26, 27). In addition to the crude (unadjusted) model for each drug, we fit two adjusted models to control for potential confounders. In Model 1, we adjusted for age, gender, race/ ethnicity (non-Hispanic Caucasian, Hispanic/Latino, non-Hispanic Black, and other races), and education (some high school or less, high school graduate, some college or more). In Model 2, we also adjusted for binary (i.e., never/ever) tobacco smoking and alcohol drinking status. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

We examined the association between smoking each kind of drug and lung and UADT cancers separately. For each drug, we fit models for binary smoking status and cumulative smoking status. Interval variables (coded 0, 1, 2,…) were assigned to categorical lifetime smoking frequencies of opium/PCP/crack cocaine to test the dose-response association for these three drugs.

Histologically, UADT cancer cases can be grouped into squamous cell carcinomas (SCC) of the esophagus and head and neck sites, and adenocarcinomas of the esophagus. Since adenocarcinomas of the esophagus are essentially different in terms of risk factors and etiology (28, 29), we repeated the main analyses by histology among the UADT patients. We

focused on squamous cell carcinomas due to their close association with tobacco smoking and the limited sample size of adenocarcinoma.

A non-user of one drug could be a user of other drugs. To address the issue that different drugs' effects may confound each other, when examining the association for each drug, those who had never smoked any of the three drugs were selected as the fixed reference group. We further verified the results by adjusting for the use of other drugs (i.e., drug variables were mutually adjusted) while keeping all subjects in the analysis.

Results

Of all 1212 cancer patients and 1040 controls, the distribution of selected social-demographic and potential confounding factors is shown in Table 1. Compared to controls, both lung cancer cases and UADT cancers cases were older and less educated. There were about 50% males and 50% females among lung cancer cases, while the proportion of male subjects was higher than that of female subjects among both UADT cancers cases (76%) and controls (60%). As expected, there were more never tobacco-smokers in the control group (45.7%) than in lung cancer cases (17.8%) and UADT cancers cases (29.0%). In addition, 32.6% of lung cancer cases tended to be heavy tobacco users (>40 pack-years), whereas the proportions were 21.8% and 5.9% in UADT cancers cases and controls, respectively. We also observed more alcohol drinkers among UADT cancers cases (80.2%) than among lung cancer cases (72.0%) and controls (74.3%). The distribution of drug smoking status is also summarized in Table 1. Drug smoking was infrequent in the study population: among controls, the proportion of ever-smokers of these drugs varied between 5.8% to 7.0%; the proportion ranged between 6.7% to 8.2% among lung cancer cases and between 10.5% to 11.8% among UADT cancers cases.

Distributions of the primary drug-smoking variables and their adjusted associations with each type of cancer are shown in Tables 2 and 3 (lung) and Tables 4 and 5 (UADT). In Tables 2 and 4, when assessing the association of each kind of drug, the reference group was selected as those who had never used any drug, and therefore the numbers of never smokers differ from Table 1.

Crude and adjusted odds ratios for lung cancer are presented in Tables 2 and 3. When using never users of crack cocaine as the reference group (Table 2), we found elevated odds of lung cancer in the crude model (OR = 1.58, 95% CI: 1.07, 2.33) and minimally adjusted model (aOR = 1.65, 95% CI: 1.07, 2.55), with a dose-response relationship for lifetime drug smoking frequency (p for trend = 0.001 and 0.003, respectively). Nevertheless, this association attenuated after controlling for tobacco smoking and alcohol drinking (aOR = 1.23, 95% CI: 0.79, 1.91; p for trend = 0.086). As compared to non-users, heavy use (6 times) of crack cocaine was associated with lung cancer with an adjusted OR of 1.58 (95% CI: 0.88, 2.83). Such patterns for crack did not change appreciably after taking into account other drug smoking behaviors (Table 3). In addition, little associations were observed between ever or any levels of opium or PCP smoking and lung cancer.

Tables 4 and 5 show the crude and adjusted associations between drug smoking and UADT cancers. In Table 4, ever PCP smoking was positively associated with the development of UADT cancers in the crude (OR = 1.77, 95% CI: 1.24, 2.51; p for trend = 0.002) and minimally adjusted (aOR = 1.48, 95% CI: 1.01, 2.15; p for trend = 0.026) models. However, the positive association weakened in Model 2 with the adjustment for tobacco smoking and alcohol drinking (aOR = 1.30, 95% CI: 0.89, 1.90; p for trend = 0.077). The adjusted OR (95% CI) for heavy PCP use (6 times) was also attenuated in the fully adjusted model (aOR = 2.29, 95% CI: 0.91, 5.79). Such patterns seemed further diminished in Table 5, where other drug smoking behaviors were accounted for. Compared to never-drug smokers (Table 4), ever crack smoking was positively associated with UADT cancers in the crude model (OR = 2.26, 95% CI: 1.57, 3.26; p for trend < 0.001) and Model 1 (aOR = 1.82, 95% CI: 1.23, 2.69; p for trend = 0.003) with a dose-response relationship for lifetime smoking frequency. Smoking crack more than 6 times was found to be positively associated with UADT cancers in the crude model (OR = 2.91, 95% CI: 1.77, 4.78) and Model 1 (aOR = 2.11, 95% CI: 1.25, 3.57). As opposed to the other two drugs, the positive associations persisted in the full model: the adjusted ORs for ever and heavy crack smoking were 1.56 (95% CI: 1.05, 2.33) and 1.81 (95% CI: 1.07, 3.08), respectively; a dose-response relationship for lifetime smoking frequency was found (p for trend = 0.024). The associations for crack smoking somewhat attenuated when being evaluated using mutually adjusted models (Table 5).

We also limited the UADT cancers cases to UADT SCC (by excluding esophageal adenocarcinomas) and head and neck SCC (by excluding all esophageal cancer cases), and the results are summarized in Supplemental Tables 1–4. No discernible difference was found as compared to the main analyses for all UADT cancer cases.

Discussion

In this case-control study, we examined the potential effect of drug smoking on lung and UADT cancers among Los Angeles County residents. With necessary adjustment for main confounding factors, our data suggested a positive association between crack cocaine smoking and UADT cancers. We also observed weak positive associations between 1) heavy crack smoking and lung cancer, and 2) heavy PCP smoking and UADT cancers.

The potential connection between cancer and crack cocaine smoking has been suggested by clinical and biological studies: the use of crack cocaine may result in airway injuries, histopathological abnormalities, increased oxidative stress, and immune function changes (20–23, 30, 31). Due to the lack of filtration and prolonged breath-holding time, infrequent crack smoking could also impose a considerable amount of exposure on human airways. While little was known about the carcinogenic effect, we found three epidemiologic studies on crack cocaine use and cancer (32–34): a positive association between parental cocaine use and childhood rhabdomyosarcoma was reported in a case-control study; a dose-response association between cocaine use and non-Hodgkin's lymphoma was observed with limited adjustment; and parental exposure to mind-altering drugs, including cocaine, appeared to be associated with K-ras and N-ras among acute lymphoblastic leukemia cases.

Our report is the first epidemiologic study on the effect of crack smoking on lung cancer and UADT cancers. In our study, crack smoking was positively associated with UADT cancers with a dose-response relationship over the lifetime crack smoking frequency, controlling for important confounders. Similar and even possibly stronger associations were observed when we limited our analyses to squamous cell carcinomas (summarized in Supplement Tables 1–4). These results were in line with the findings that crack cocaine smoking may lead to molecular and cellular abnormalities in oral cavities (35–37). In addition, a weak positive association with lung cancer was also detected for crack smoking. Nonetheless, crack's carcinogenic mechanism remained unclear, and our findings could be due to the residual confounding from alcohol drinking and tobacco use. To make causal inferences from these observed associations, more details on the biological pathways and better adjustments for alcohol drinking and tobacco use will be needed in the future.

We found a possible linear dose-response relationship between crack smoking and UADT cancers, where higher cumulative lifetime use was associated with a greater susceptibility of cancer. Considering the similarities between tobacco and drug smoking and crack's carcinogenic potentials, it would not be unreasonable to infer that the linear pattern provides additional evidence for a possible causal relationship, given no other bias was presented. However, as mentioned above, this pattern could also result from the residual confounding by tobacco/alcohol use, since these behaviors are correlated. In addition, we were only able to assess the association using categorical drug smoking variables and might not be able to detect other patterns of association.

No clear association was identified between opium smoking and lung cancer and UADT cancers in our analysis. This was not consistent with the IARC's recent evaluation of opium consumption and previously proposed theories of the carcinogenic effects of opium (17, 38–40). Notably, the smoking pattern among our study participants was not comparable with that of Iranian studies, in which opium smokers tended to be long-term regular users, and the median duration of regular use could be as long as 20 years (8, 10–13). Assuming that opium's carcinogenic potency in any one hit of smoking is identical across all studies, subjects with the highest exposure to opium in our study can easily fall into the lowest exposure categories in Iranian studies. With such low exposures and limited subjects in the exposed group, it would be hard to detect any effect, especially when strong confounders (e.g., tobacco smoking and alcohol drinking) for the underlying cancer sites are present.

We did not detect any substantial changes in the development of lung cancer due to PCP smoking. Although pulmonary manifestations of PCP smoking were discussed previously (21), there has not been any report on the potential connection between PCP use and carcinogenesis. If PCP smoking does impose no or negligible carcinogenic effects on humans, it is not surprising to see a null association after controlling for main confounders. Further studies are merited to explore the potential carcinogenic effect of PCP use. We did find a weak positive association between PCP smoking and UADT cancers. However, given the relatively small sample size (especially the heavy users) in our study and that PCP is usually smoked with tobacco or cannabis, we could not rule out the possibility of a chance finding or residual confounding. Fine adjustments for the use of tobacco and cannabis are required in future epidemiologic analyses.

The major limitation of this study is confounding. Investigators have found that appreciable proportions of lung cancer and UADT cancers are attributable to tobacco smoking and alcohol drinking (primarily UADT cancers) (2, 41–43). A common way to handle such residual confounding is to assess the effect among non-tobacco smokers and/or non-drinkers. However, due to the correlations between tobacco use/alcohol consumption and drug smoking, subgroup analyses within the above-mentioned groups would result in small numbers or even zeros in the exposed group, especially the heavy drug smoking categories, thus not feasible. Moreover, the numbers of ever and heavy opium/PCP/crack smokers were already small to begin with in our study – such limited numbers did not warrant analyses with fine adjustments for continuous pack-years and drink-years to be informative. The binary tobacco use and alcohol consumption status we used in the analysis may be considered insufficient, and therefore, the findings could be due to residual confounding. Additionally, there could be other uncontrolled confounding (e.g., diet, physical activity and infection of human papillomavirus for certain cancers at UADT sites) in our analysis. Lastly, the two methods we used to account for different kinds of drug use were not perfect. When using the "clean group" (i.e., never-drug smokers) as the reference, the ever smokers for each kind of drug could be smokers of other drugs as well, and we could not completely rule out the effect, if any, due to smoking other drugs. The second method, in which we mutually adjusted for other drug use, could also result in residual confounding if the adjustments were insufficient. Nevertheless, comparisons between these two methods showed no strong indication of confounding due to smoking other drugs.

This study could be biased by some other limitations. The first limitation was the potential selection bias. As mentioned earlier, about 30% of lung cancer cases and 15% of UADT cancers cases did not participate due to ill health or death. However, as we were unable to evaluate whether there was any difference in drug use status between participants and non-participants among cases and controls, it wouldn't be possible to predict the direction or magnitude of the potential bias. Another limitation was the information bias regarding subjects' exposure status. Despite researchers' efforts to assure confidentiality, illicit drug use history could still have been too sensitive so that certain participants were unwilling to disclose the real information. Meanwhile, the way we categorized drug smoking as above or below the population median is not ideal, as the lifetime use was only recorded in different ranges. Even if subjects did report drug use without holding back, the estimated population median might not be accurate. However, we wanted to emphasize the distribution in general rather than the exact value when using this method. Due to the same reason, we were unable to explore other possibilities of the association (e.g., nonlinearity) between drug smoking and cancer. At last, treating all UADT cancers collectively in the analysis could be misleading. While cancers at the UADT sites are referred to as UADT cancers, they do have their own etiology and can be heterogeneous groups histologically. Therefore, our findings do not preclude other possibilities for specific cancer or histological subtypes. It is possible that not all these cancers are associated with drug use; even if they are, these specific cancers may have different associations with the usage of a given illicit drug. This could also apply to different histological subtypes of lung cancer. Larger studies are needed in the future to evaluate each individual association.

Given the methodologic limitations, we would like to emphasize that our results should be interpreted with caution for making causal inferences. The observed null associations, should not be interpreted as a lack of effect on cancer susceptibility. Illicit drug use is not safe, not by any means. As discussed in earlier sections, drug smoking is indeed associated with other pulmonary complications. In addition, all these analyzed drugs have psychological effects and are addictive – regular use may lead to severe drug use disorders (3, 19). Notably, in the United States, the median age at diagnosis for lung cancer is 71 and 65 for UADT cancers (44). The average age of participants in the UCLA Cancer Study was about 50 years. Our sample is insufficient to show the whole picture of the disease development, which usually takes a long time; thus, we cannot generalize our results to persons over 65.

To the best of our knowledge, this is the first epidemiologic study to explore the association between multiple illicit drug usage and lung and UADT cancers. In conclusion, we found an increased susceptibility of UADT cancers among crack cocaine users; a somewhat increased odds of lung cancer was observed among crack users who had used more than 6 times, and a somewhat increased odds of UADT cancers was observed among PCP users who had used more than 6 times. We did not detect any association between opium smoking with lung cancer or UADT cancers in our study population. While the estimated median usage in the population did not appear to be accurate and the results might be subject to a few limitations of the study, our early findings could provide preliminary grounds for the concern that drug smoking is positively associated with lung and UADT cancers. Given the current drug use epidemic, there remains an urgent need for future work to further explore and understand the associations between drug use and cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1.

Sociodemographic characteristics and drug smoking status of cancer cases and controls in the UCLA Los Angeles cancer case-control study

	Lung cancer cases, n (%)[*] n=611	UADT cancer cases, n (%)[*] n=601	Controls, n (%)[*] n=1040
Age (years)			
<45	61 (10.0)	109 (18.1)	222 (21.3)
45 – 54	301 (49.3)	267 (44.4)	499 (48.0)
55	249 (40.7)	225 (37.4)	319 (30.7)
Sex			
Male	303 (49.6)	454 (75.5)	623 (59.9)
Female	308 (50.4)	147 (24.5)	417 (40.1)
Race/Ethnicity			
Non-Hispanic Caucasian	359 (58.8)	341 (56.7)	634 (61.0)
Hispanic/Latino	70 (11.5)	109 (18.1)	204 (19.6)
Black	96 (15.7)	69 (11.5)	102 (9.8)
Others	85 (13.9)	80 (13.3)	99 (9.5)
Missing	1 (0.2)	2 (0.3)	1 (0.1)
Education			
Some high school or less	107 (17.5)	126 (21.0)	116 (11.2)
High school graduate	158 (25.9)	147 (24.5)	184 (17.7)
Some college and more	346 (56.6)	328 (54.6)	739 (71.1)
Missing	0 (0)	0 (0)	1 (0.1)
Tobacco smoking pack-years			
Never-smokers	109 (17.8)	174 (29.0)	475 (45.7)
>0 to 20	102 (16.7)	154 (25.6)	364 (35.0)
>20 to 40	201 (32.9)	142 (23.6)	140 (13.5)
>40	199 (32.6)	131 (21.8)	61 (5.9)
Alcohol consumption drink-years			
Never-drinkers	171 (28.0)	119 (19.8)	267 (25.7)
>0 to 40	257 (42.1)	230 (38.3)	576 (55.4)
>40	183 (30.0)	252 (41.9)	196 (18.9)
Opium smoking frequency			
Never-smokers	570 (93.3)	538 (89.5)	968 (93.1)
1 – 10 times	35 (5.7)	46 (7.7)	59 (5.7)
11 – 30 times	2 (0.3)	5 (0.8)	4 (0.4)
31 – 70 times	2 (0.3)	4 (0.7)	5 (0.5)
71 – 150 times	0 (0)	1 (0.2)	1 (0.1)
>150 times	2 (0.3)	4 (0.7)	1 (0.1)
Missing	0 (0)	3 (0.5)	2 (0.2)
PCP smoking frequency			
Never-smokers	561 (91.8)	533 (88.7)	967 (93.0)

	Lung cancer cases, n (%)* n=611	UADT cancer cases, n (%)* n=601	Controls, n (%)* n=1040
1 – 10 times	40 (6.5)	53 (8.8)	63 (6.1)
11 – 30 times	3 (0.5)	5 (0.8)	3 (0.3)
31 – 70 times	1 (0.2)	3 (0.5)	1 (0.1)
71 – 150 times	1 (0.2)	1 (0.2)	1 (0.1)
>150 times	3 (0.5)	5 (0.8)	3 (0.3)
Missing	2 (0.3)	1 (0.2)	2 (0.2)
Crack cocaine smoking frequency			
Never-smokers	559 (91.5)	530 (88.2)	980 (94.2)
1 – 10 times	19 (3.1)	28 (4.7)	31 (3.0)
11 – 30 times	3 (0.5)	10 (1.7)	7 (0.7)
31 – 100 times	6 (1.0)	12 (2.0)	7 (0.7)
>100 times	24 (3.9)	20 (3.3)	13 (1.3)
Missing	0 (0)	1 (0.2)	2 (0.2)

*
Percentages may not add up to 1 due to rounding

Table 2.

The association (estimated OR and 95% CI) between drug smoking and the risk of lung cancer using non-drug-smokers as the reference group

	Controls n (%)[*]	Cases n (%)[*]	Crude OR (95% CI)	Adjusted OR (95% CI)	
				Model 1[a]	Model 2[b]
Opium smoking					
Never [†]	901 (92.8)	512 (92.6)	1 (Reference)	1 (Reference)	1 (Reference)
Ever	70 (7.2)	41 (7.4)	1.03 (0.69, 1.54)	1.25 (0.82, 1.91)	0.92 (0.60, 1.42)
median (6 times)	59 (6.1)	35 (6.3)	1.04 (0.68, 1.61)	1.30 (0.82, 2.05)	0.96 (0.60, 1.52)
> median	11 (1.1)	6 (1.1)	0.96 (0.35, 2.61)	0.99 (0.34, 2.87)	0.75 (0.26, 2.15)
P_{trend}[‡]			0.79	0.45	0.72
PCP smoking					
Never [†]	901 (92.7)	512 (91.4)	1 (Reference)	1 (Reference)	1 (Reference)
Ever	71 (7.3)	48 (8.6)	1.19 (0.81, 1.74)	1.45 (0.96, 2.20)	1.11 (0.72, 1.69)
median (6 times)	63 (6.5)	40 (7.1)	1.12 (0.74, 1.69)	1.41 (0.90, 2.20)	1.07 (0.68, 1.69)
> median	8 (0.8)	8 (1.4)	1.76 (0.66, 4.72)	1.72 (0.62, 4.80)	1.34 (0.46, 3.90)
P_{trend}[‡]			0.25	0.16	0.65
Crack cocaine smoking					
Never [†]	901 (94.0)	512 (90.8)	1 (Reference)	1 (Reference)	1 (Reference)
Ever	58 (6.0)	52 (9.2)	1.58 (1.07, 2.33)	1.65 (1.07, 2.55)	1.23 (0.79, 1.91)
median (6 times)	31 (3.2)	19 (3.4)	1.08 (0.60, 1.93)	1.18 (0.63, 2.20)	0.92 (0.49, 1.71)
> median	27 (2.8)	33 (5.8)	2.15 (1.28, 3.62)	2.20 (1.24, 3.92)	1.58 (0.88, 2.83)
P_{trend}[‡]			0.001	0.003	0.086

[*] Percentages may not add up to 1 due to rounding

[†] Participants who never used any of the three drugs

[‡] Treating the categories of lifetime smoking frequency as a continuous variable

[a] Adjusted for age (continuous), sex, race/ethnicity (4 categories: non-Hispanic Caucasian, Hispanic/Latino, Black, and others), and education levels (3 categories: some high school or less, high school graduate, some college or more)

[b] Also adjusted for binary tobacco smoking and alcohol drinking status

Table 3.

The association (estimated OR and 95% CI) between drug smoking and the risk of lung cancer (drugs are mutually adjusted)

	Controls n (%)[*]	Cases n (%)[*]	Crude OR (95% CI)	Adjusted OR (95% CI)	
				Model 1[a]	Model 2[b]
Opium smoking					
Never	963 (93.2)	567 (93.3)	1 (Reference)	1 (Reference)	1 (Reference)
Ever	70 (6.8)	41 (6.7)	0.86 (0.56, 1.34)	1.00 (0.63, 1.58)	0.83 (0.52, 1.31)
median (6 times)	59 (5.7)	35 (5.8)	0.88 (0.55, 1.40)	1.04 (0.64, 1.70)	0.86 (0.52, 1.40)
> median	11 (1.1)	6 (1.0)	0.80 (0.28, 2.23)	0.76 (0.25, 2.32)	0.65 (0.22, 1.93)
P_{trend}[‡]			0.52	0.85	0.40
PCP smoking					
Never	962 (93.1)	560 (92.1)	1 (Reference)	1 (Reference)	1 (Reference)
Ever	71 (6.9)	48 (7.9)	1.00 (0.64, 1.55)	1.20 (0.76, 1.91)	1.07 (0.67, 1.71)
median (6 times)	63 (6.1)	40 (6.6)	0.96 (0.60, 1.52)	1.19 (0.73, 1.94)	1.05 (0.64, 1.72)
> median	8 (0.8)	8 (1.3)	1.32 (0.46, 3.76)	1.32 (0.44, 3.94)	1.26 (0.41, 3.92)
P_{trend}[‡]			0.95	0.65	0.93
Crack cocaine smoking					
Never	975 (94.4)	556 (91.4)	1 (Reference)	1 (Reference)	1 (Reference)
Ever	58 (5.6)	52 (8.6)	1.64 (1.06, 2.53)	1.50 (0.94, 2.40)	1.25 (0.77, 2.00)
median (6 times)	31 (3.0)	19 (3.1)	1.13 (0.61, 2.08)	1.07 (0.56, 2.03)	0.93 (0.49, 1.77)
> median	27 (2.6)	33 (5.4)	2.20 (1.26, 3.84)	1.99 (1.09, 3.64)	1.60 (0.87, 2.94)
P_{trend}[‡]			0.002	0.009	0.078

[*] Percentages may not add up to 1 due to rounding

[‡] Treating the categories of lifetime smoking frequency as a continuous variable

[a] Adjusted for age (continuous), sex, race/ethnicity (4 categories: non-Hispanic Caucasian, Hispanic/Latino, Black, and others), and education levels (3 categories: some high school or less, high school graduate, some college or more)

[b] Also adjusted for binary tobacco smoking and alcohol drinking status

Table 4.

The association (estimated OR and 95% CI) between drug smoking and the risk of UADT cancers using non-drug-smokers as the reference group

	Controls n (%)[*]	Cases n (%)[*]	Crude OR (95% CI)	Adjusted OR (95% CI)	
				Model 1[a]	Model 2[b]
Opium smoking					
Never[†]	901 (92.8)	481 (89.1)	1 (Reference)	1 (Reference)	1 (Reference)
Ever	70 (7.2)	59 (10.9)	1.61 (1.12, 2.31)	1.29 (0.88, 1.90)	1.14 (0.77, 1.69)
median (6 times)	59 (6.1)	45 (8.3)	1.46 (0.98, 2.18)	1.16 (0.76, 1.78)	1.04 (0.67, 1.59)
> median	11 (1.1)	14 (2.6)	2.38 (1.07, 5.29)	2.00 (0.86, 4.62)	1.72 (0.74, 3.99)
P_{trend}[‡]			0.005	0.067	0.19
PCP smoking					
Never[†]	901 (92.7)	481 (87.8)	1 (Reference)	1 (Reference)	1 (Reference)
Ever	71 (7.3)	67 (12.2)	1.77 (1.24, 2.51)	1.48 (1.01, 2.15)	1.30 (0.89, 1.90)
median (6 times)	63 (8.5)	53 (9.7)	1.58 (1.08, 2.31)	1.34 (0.89, 2.00)	1.17 (0.78, 1.76)
> median	8 (0.8)	14 (2.6)	3.28 (1.37, 7.87)	2.56 (1.02, 6.41)	2.29 (0.91, 5.79)
P_{trend}[‡]			0.002	0.026	0.077
Crack cocaine smoking					
Never[†]	901 (94.0)	481 (87.3)	1 (Reference)	1 (Reference)	1 (Reference)
Ever	58 (6.0)	70 (12.7)	2.26 (1.57, 3.26)	1.82 (1.23, 2.69)	1.56 (1.05, 2.33)
median (6 times)	31 (3.2)	28 (5.1)	1.69 (1.00, 2.85)	1.54 (0.89, 2.66)	1.33 (0.77, 2.31)
> median	27 (2.8)	42 (7.6)	2.91 (1.77, 4.78)	2.11 (1.25, 3.57)	1.81 (1.07, 3.08)
P_{trend}[‡]			<0.001	0.003	0.024

[*] Percentages may not add up to 1 due to rounding

[†] Participants who never used any of the three drugs

[‡] Treating the categories of lifetime smoking frequency as a continuous variable

[a] Adjusted for age (continuous), sex, race/ethnicity (4 categories: non-Hispanic Caucasian, Hispanic/Latino, Black, and others), and education levels (3 categories: some high school or less, high school graduate, some college or more)

[b] Also adjusted for binary tobacco smoking and alcohol drinking status

Table 5.

The association (estimated OR and 95% CI) between drug smoking and the risk of UADT cancers (drugs are mutually adjusted)

	Controls n (%)[*]	Cases n (%)[*]	Crude OR (95% CI)	Adjusted OR (95% CI)	
				Model 1[a]	Model 2[b]
Opium smoking					
Never	963 (93.2)	536 (90.2)	1 (Reference)	1 (Reference)	1 (Reference)
Ever	70 (6.8)	58 (9.8)	1.13 (0.74, 1.71)	1.00 (0.64, 1.55)	0.95 (0.61, 1.47)
median (6 times)	59 (5.7)	45 (7.6)	1.08 (0.69, 1.69)	0.94 (0.59, 1.51)	0.89 (0.56, 1.43)
> median	11 (1.1)	13 (2.2)	1.42 (0.59, 3.41)	1.32 (0.53, 3.26)	1.23 (0.50, 3.04)
P_{trend}[‡]			0.39	0.67	0.88
PCP smoking					
Never	962 (93.1)	528 (88.9)	1 (Reference)	1 (Reference)	1 (Reference)
Ever	71 (6.9)	66 (11.1)	1.22 (0.80, 1.88)	1.18 (0.75, 1.84)	1.12 (0.72, 1.75)
median (6 times)	63 (6.1)	52 (8.8)	1.09 (0.70, 1.72)	1.07 (0.67, 1.71)	1.01 (0.63, 1.62)
> median	8 (0.8)	14 (2.4)	1.86 (0.71, 4.83)	1.79 (0.67, 4.82)	1.79 (0.66, 4.82)
P_{trend}[‡]			0.23	0.33	0.37
Crack cocaine smoking					
Never	975 (94.4)	527 (88.7)	1 (Reference)	1 (Reference)	1 (Reference)
Ever	58 (5.6)	67 (11.3)	1.87 (1.23, 2.83)	1.61 (1.04, 2.50)	1.47 (0.94, 2.28)
median (6 times)	31 (3.0)	26 (4.4)	1.41 (0.81, 2.48)	1.38 (0.77, 2.49)	1.26 (0.70, 2.27)
> median	27 (2.6)	41 (6.9)	2.34 (1.35, 4.06)	1.79 (1.01, 3.19)	1.62 (0.91, 2.90)
P_{trend}[‡]			0.002	0.042	0.11

[*] Percentages may not add up to 1 due to rounding

[‡] Treating the categories of lifetime smoking frequency as a continuous variable

[a] Adjusted for age (continuous), sex, race/ethnicity (4 categories: non-Hispanic Caucasian, Hispanic/Latino, Black, and others), and education levels (3 categories: some high school or less, high school graduate, some college or more)

[b] Also adjusted for binary tobacco smoking and alcohol drinking status