An Ecological Study of the Association between Opiate Use and Incidence of Cancers

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Original Article

Abstract

Background: Cancer is the second leading cause of death after cardiovascular disease. In recent years it has been hypothesized that opiate use could be a risk factor for cancer. This study aimed to evaluate a possible association between opiate use and common cancers using ecological statistics from around the world.

Methods: To investigate the association we used ordinary linear regression models. The $\log_{10}$-transformed age-standardized incidence rate (ASR) of cancers was used as dependent variables in the models. We adjusted for smoking, alcohol use per capita, human development index (HDI), and body mass index (BMI) as confounding variables. We extracted these variables from different data sources including the GLOBOCAN 2012, the United Nations Office on Drugs and Crime (UNODC) annual reports, World Health Organization database, the United Nations Development Program (UNDP) report 2012, and published literature. We estimated two separate models for each cancer, one for males and the other for both sexes.

Findings: Opiate prevalence ranged from 0.01% to 2.65% and its median was 0.20%. In the multiple regression models for both sexes, opiate use was significantly associated with bladder ($\beta = 0.59$), kidney ($\beta = 0.16$), oral cavity ($\beta = 0.27$), esophagus ($\beta = 0.33$), larynx ($\beta = 0.17$) and other pharynx ($\beta = 0.36$) cancers. In the models based on the male data, the coefficient and the significances were approximately the same for the above cancers but larynx cancer was no longer significantly associated with opiate use.

Conclusion: There was a significant association between opiate use and risk of cancers. We suggest that more studies should be conducted, especially in high-risk areas of the world.

Keywords: Cancer; Ecological study; Opium; Risk factors

Citation: Rashidian H, Zendehdel K, Kamangar F, Malekzadeh R, Haghdoost AA. **An Ecological Study of the Association between Opiate Use and Incidence of Cancers.** Addict Health 2016; 8(4): 252-60.

Received: 11.05.2016 **Accepted:** 28.07.2016

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Introduction

The United Nations Office on Drugs and Crime (UNODC) surveyed drugs used at least once in the year 2009 among the population aged 15-64 years, and found that opiates are the third most commonly used illicit drugs.[1] Opiates are alkaloids derived from the opium poppy. According to statistics, opiate use is increasing and remains the most problematic form of drug use globally.[1] Moreover, use of opioids has increased in the pain management of chronic disease patients.[2] In western and central Asia, lay people and some older generations of physicians believe that low doses of opium can prevent chronic diseases such as cancer, cardiovascular disease and diabetes mellitus, and increase survival.[3]

Cancer is the second leading cause of death after cardiovascular disease and caused over eight million deaths worldwide in 2013. There has been impressive progress with regard to prevention and treatment options for certain cancers in recent years. However, the growing and aging global population and risk factors like smoking, obesity, and dietary patterns have resulted in an increase in the cancer burden. Studies suggest that opiates are one of the risk factors for lung, bladder, oral cavity, larynx, stomach and esophageal cancers and its relative risk (RR) varies from 1.6 to 9.5.[3] About eighteen studies have been done to investigate the association between these cancers and opiate use.

Two major mechanisms have been suggested for carcinogenic effects of opium use, including exposure to opium smoke and the alkaloid component of opium. First, in smoking, opium users heat the opium to a high temperature and inhale the smoke through a particular tube (pipe), wherein the opium content is vaporized. The opium smoke contains polycyclic aromatic hydrocarbons which are known carcinogens. In addition, the residual component in the pipe can be eaten, without any treatment or refinement. Studies have shown that this residual substance has a mutagenic effect. Its main carcinogenic component consists of nitrogen containing heterocyclic components derived from pyrolysis of morphine.[4,5] In the second mechanism, opium contains alkaloid compounds that are absorbed in the body and can lead to cancer.[6] However, evidence on the association of opium use and cancer risk is still limited. In this study we aimed to evaluate the association between opium use and cancer incidence from a global point of view.

Methods

We extracted data on opiate use from the UNODC annual world drug report 2011 for 126 countries. UNODC uses the best available data and research on several aspects of drugs and crime to provide a complete annual review of progress in the world production of, trafficking in and consumption of the main illicit drug types and their related health conditions.[1]

We obtained the age-standardized incidence rate (ASR) of common cancers including bladder, colorectal, Hodgkin's lymphoma, kidney, larynx, leukemia, oral cavity, liver, lung, nasopharynx, non-Hodgkin's lymphoma, esophagus, other pharynx, pancreas, prostate and stomach cancers from GLOBOCAN 2012. The GLOBOCAN database provide the latest estimates of the incidence, mortality and prevalence for major types of cancer, at the national level, for 184 countries. It is published by the International Agency for Research on Cancer (IARC) and uses the best available data in each country and several methods of estimation.[7]

We obtained data on some cofounding variables including smoking, alcohol use, body mass index (BMI) and human development index (HDI) from different sources. Age-standardized prevalence of daily smoking (age 15 years or older) was obtained from a study published in the Journal of the American Medical Association (JAMA) in 2014 that reported the prevalence of daily smoking by age and sex and the number of cigarettes per smoker per day for 187 countries between 1980 and 2012. The definition of daily smoker in this study was someone who smokes any type of tobacco product at least once per day.[8]

The Global Health Observatory (GHO) database provided data on total alcohol consumption per capita (APC) in a population aged 15 years or higher[9] as well as the prevalence of high BMI (25 kg/m^2 or higher) in a population aged more than 18 years.[9] The GHO is the World Health Organization's main health statistics repository. The aim of this dataset is to provide relevant, timely, and high-quality evidence and

information to support national governments and international bodies in improving policy, practice, and management of health; it encompasses more than 50 different datasets and covers all 198 WHO member countries. Total APC was defined as the sum of the recorded APC three-year average and unrecorded APC per adult (15+ years) over a calendar year, in liters of pure alcohol.[9]

We obtained statistics about HDI from the United Nations Development Program (UNDP) report, 2012. HDI is a summary measure of human development, which is a composite index of education, life expectancy and national income.[10]

To verify the normal distribution of variables, we used Kolmogorov-Smirnov test and variable distribution graphs. ASRs of cancers were not normally distributed, so we used $\log_{10}$-transformed ASRs in our analyses. Associations between ASRs of cancers and the frequency of opiate use were explored using ordinary linear regression. We made univariate regression analyses to test the associations between opiate use and $\log_{10}$-transformed ASRs of cancers. Then we estimated multiple regression models for cancers that were significantly associated with opiate use at the 0.1 level of significance in our univariate analyses. In multiple regression analyses we adjusted the association using smoking, HDI, APC and BMI as potential confounders in the models.

Opiate use is more prevalent among males globally, for example in Iran opiate use in males is ten times that in females.[11,12] Therefore, we estimated two models for each cancer. In one model, we used data of both sexes and in another model we used male data only. Since we could not access opiate use statistics based on sex, we used opiate prevalence for both sexes in the male only model.

We graphed added-variable plots to detect outliers and influential observations in our multiple regression analyses. According to added-variable plots and the DFBETA measure, the opiate statistics for three countries: Iran (2.26%), Afghanistan (2.65%) and Russia (1.64%) were outliers and had a great influence on the estimated coefficients. Consequently, we did not use these three countries in our regression models.

We used Ramsey's RESET test to detect if there were any neglected nonlinearities in the model. In all models we used the Breusch-Pagan test method to evaluate the consistency of variances. We re-estimated the models with heteroscedasticity, using ordinary linear regression with robust standard deviations (SD). In addition, we used a variance inflation factor statistic to test multicollinearity in multiple regression models. We considered 0.05 as the level of significance in our multiple regression analyses.

Results

We used statistics for 126 countries. Opiate prevalence for both sexes ranged from 0.01% to 2.65% and its median was 0.20%. The mean of alcohol use per capita in litters was 6.76 (SD = 4.2) for both sexes and 10.4 (SD = 6.3) for males. On average smoking prevalence was 19.20 (SD = 8.4) in both sexes and 28.5 (SD = 11.6) in males. The mean prevalence of overweight and obesity was about 46% for both sexes and males. HDI for both sexes and men was about 0.7 on average (Table 1).

There were no significant associations between opiate use and log-transformed ASR for liver, nasopharynx, prostate cancers and non-Hodgkin lymphoma in univariate analyses, so we did not use their data in multiple regression models. In univariate analyses for both sexes, the highest R-squared values were found for oral cavity (0.13) and other pharynx (0.10) cancers. In multiple regression models for both sexes, opiate use was significantly associated with bladder (β = 0.59), kidney (β = 0.16), larynx (β = 0.17), oral cavity (β = 0.27), esophagus (β = 0.33), and other pharynx cancers (β = 0.36). We found the highest coefficient for the association between opiate use and bladder cancer. Also the highest adjusted R-squared value was observed for kidney (0.81) and bladder cancers (0.68) (Table 2).

In the multiple regression models for males, opiate use was significantly associated with bladder (β = 0.60), kidney (β = 0.19), oral cavity (β = 0.22), esophagus (β = 0.32) and other pharynx cancers (β = 0.38), and the highest adjusted R-squared values were found for kidney (0.79) and bladder cancers (0.71) (Table 3). Moreover, the variance inflation factor statistic for all variables was below five and there was no multicollinearity between variables in multiple regression analyses.

Table 1. Descriptive analyses of variables (n = 126)

Variable	Male			Both sex		
	Min	Max	Mean ± SD	Min	Max	Mean ± SD
Outcome variables						
Bladder cancer (ASR)**	0.3	29.1	9.92 ± 7.68	0.50	16.6	5.81 ± 4.22
Colorectal cancer (ASR)	3.1	61.6	20.60 ± 15.00	2.30	42.7	17.20 ± 11.50
Hodgkin lymphoma (ASR)	0	4.2	1.46 ± 0.91	0	3.7	1.30 ± 0.83
Kidney cancer (ASR)	0	24.1	5.81 ± 5.29	0	16.7	4.21 ± 3.68
Larynx cancer (ASR)	0	13.2	4.48 ± 2.81	0	6.3	2.36 ± 1.35
Leukemia (ASR)	0	12.5	5.92 ± 2.83	0	12.0	5.02 ± 2.28
Oral cavity cancer (ASR)	0.4	15.7	5.09 ± 3.23	0.30	11.0	3.60 ± 2.03
Liver cancer (ASR)	1.2	78.7	9.13 ± 9.67	0.90	52.6	6.51 ± 6.41
Lung cancer (ASR)	0.4	76.6	26.30 ± 19.10	0.20	51.6	17.10 ± 12.00
Nasopharynx cancer (ASR)	0	10.6	1.21 ± 1.73	0	7.2	0.82 ± 1.18
Non-Hodgkin lymphoma (ASR)	0.9	18.1	6.42 ± 3.54	0.70	16.2	5.42 ± 3.06
Esophagus cancer (ASR)	0.3	24.8	5.21 ± 4.70	0.10	19.7	3.53 ± 3.59
Other pharynx cancer (ASR)	0	14.9	2.89 ± 2.68	0	8.9	1.70 ± 1.49
Pancreas cancer (ASR)	0	11.9	4.90 ± 3.16	0	9.7	4.13 ± 2.51
Prostate cancer (ASR)	1.5	129.7	41.20 ± 33.90	1.50	129.7	41.20 ± 33.90
Stomach cancer (ASR)	2.0	35.7	11.30 ± 7.50	0.90	41.8	7.78 ± 6.12
Exposure variables						
Opiate prevalence* (%)				0.01	2.7	0.35 ± 0.40
Alcohol use per capita (litters)	0.1	27.5	10.40 ± 6.31	0.10	17.5	6.76 ± 4.25
Smoking prevalence (%)	8.0	54.4	28.50 ± 1.59	4.70	42.3	19.20 ± 8.39
BMI ≥ 25 (%)	10.6	72.8	45.60 ± 19.40	14.40	79.4	46.80 ± 16.60
HDI	0.4	0.9	0.73 ± 0.13	0.33	0.9	0.71 ± 0.14

*We could not access opiate use statistics based on sex distribution; **Age-standardize incidence rate of cancers per 100000
ASR: Age-standardized incidence rate; BMI: Body mass index; HDI: Human development index; SD: Standard deviation

Discussion

In this study we investigated the association between opiate use and the incidence of common cancers worldwide. After adjustment for confounding variables, there was a significant association between opiate use and ASR of bladder, kidney, oral cavity, esophagus, and other pharynx cancers in males and in both sexes. Larynx cancer was associated with opiate use only in the models specified for both sexes.

Table 2. Univariate and multiple regression analysis of the association between prevalence of opiate use and log10-transformed age-standardized incidence rate (ASR) of common cancers per 100000, (n = 123) for both sex

Cancer name*	Univariate regression			Multiple regression		
	Regression coefficient (opiate)	P	Adj R-squared	Regression coefficient (opiate)	P	Adj R-squared
Bladder	0.33	0.01	0.05	0.59	0.03	0.68
Colorectal	0.29	0.01	0.05	0.04	0.48	0.79
Hodgkin lymphoma	0.29	0.01	0.04	0.07	0.47	0.52
Kidney	0.44	< 0.01	0.07	0.16	0.03	0.81
Larynx	0.24	0.01	0.05	0.17	0.05	0.34
Leukemia	0.17	0.04	0.03	-0.27	0.14	0.67
Oral cavity	0.37	< 0.01	0.13	0.27	< 0.01	0.28
Lung	0.37	0.02	0.04	0.00	0.94	0.81
Esophagus	0.37	< 0.01	0.05	0.33	0.02	0.11
Other pharynx	0.48	< 0.01	0.10	0.36	0.01	0.25
Pancreas	0.23	0.03	0.03	0.09	0.16	0.75
Stomach	0.16	0.07	0.02	0.14	0.14	0.08

*Log_{10}-transformed age standardize incidence rate of cancers per 100000
ASR: Age-standardized incidence rate

Table 3. Univariate and multiple regression analysis of the association between prevalence of opiate use and log10-transformed age-standardized incidence rate (ASR) of common cancers per 100000, (n = 123) for male

Cancer name*	Univariate regression			Multiple regression		
	Regression coefficient (opiate)	P	Adj R-squared	Regression coefficient (opiate)	P	Adj R-squared
Bladder	0.42	< 0.01	0.06	0.60	0.03	0.71
Colorectal	0.34	< 0.01	0.06	0.03	0.67	0.77
Hodgkin lymphoma	0.26	0.02	0.04	0.08	0.40	0.46
Kidney	0.49	< 0.01	0.07	0.19	0.02	0.79
Larynx	0.26	< 0.01	0.05	0.09	0.30	0.42
Leukemia	0.20	0.02	0.04	0.00	0.93	0.68
Oral cavity	0.42	< 0.01	0.13	0.22	0.02	0.36
Lung	0.39	0.02	0.04	-0.04	0.59	0.81
Esophagus	0.38	< 0.01	0.06	0.32	0.02	0.19
Other pharynx	0.56	< 0.01	0.11	0.38	0.01	0.37
Pancreas	0.27	0.01	0.04	0.08	0.23	0.75
Stomach	0.20	0.04	0.03	0.10	0.30	0.19

*Log 10-transformed age standardize incidence rate of cancers per 100000
ASR: Age-standardized incidence rate

In this study we adjusted for HDI, smoking, alcohol and BMI as confounding factors. HDI is a summary measure of three basic dimensions of human development, namely, health (based on life expectancy at birth), education (based on a combination of adult literacy rate and primary to tertiary education enrolment rates) and standard of living (based on GDP per capita adjusted for purchasing power parity in US$).[10] HDI could be an indicator of socioeconomic status and state of development.[13] Recently studies have shown that HDI is associated with the incidence of cancers.[14-16] Bray et al. showed that lung, breast, colorectal and prostate cancers comprised almost half the total cancer burden in high and very high HDI regions. However, several types of cancer were more common in lower HDI regions, including liver, stomach, cervix and esophagus cancers. HDI can explain a major part of cancer incidence variation all over the world.[14] In our study there was a significant association between HDI and the incidence of cancers.

Smoking, alcohol and BMI are established risk factors for most cancers. Cigarette smoke contains over 60 well-established carcinogens and is a well-known risk factor for several cancer types.[17-19] Previous studies have confirmed the association between high BMI and risk of several cancers including, esophageal adenocarcinoma, colon, rectal, kidney, thyroid, pancreas, gallbladder (women only), postmenopausal breast, ovarian, and endometrial cancers.[20-22] Likewise, studies have shown that consumption of alcohol increases the risk of developing several cancers including oral cavity and pharynx, esophagus, stomach, larynx, colorectal, central nervous system, pancreas, breast and prostate cancers.[19,23] In our study there was a significant association between these variables and the incidence of cancers.

We found a significant association between opiate use and the incidence of bladder cancer. This is consistent with case control studies that show RRs of 2.6 to 8.0 between bladder cancer incidence and opium use.[24,25] Moreover, Khademi et al. in a large prospective cohort study showed an increased risk of death for all cancers associated with opium use [HR 1.6, 95% confidence interval (CI): 1.3–2.0].[26] In this study, we found a significant and direct association between opiate use and bladder cancer incidence in multiple regression analyses. Studies have shown that opiates can cause urinary retention[27] and increase movement and invasiveness of bladder cancer cells.[28] This mechanism could be responsible for increasing the risk of bladder cancer and the incidence of progressed bladder cancer.

There was a significant association between opiate use and the incidence of kidney cancer in the current study. Although a large cohort study showed an increased risk of death due to cancer in opium users, to the best of our knowledge, the association has not been so far investigated separately in any epidemiological studies. Experimental studies on rats have shown that chronic use of opiates increases the risk of renal damage.[29]

We found a significant association between opiate use and the risk of oral cavity and other pharynx cancers. Although a case-control study showed an association between opium use and a combination of cancers of the oral cavity, esophagus, liver, and pancreas[30] (RR: 3, 95% CI: 1.6–5.6), no study has exclusively investigated the association between opiate use and oral cavity cancer. To the best of our knowledge there is no study investigating the association between opium use and other pharynx cancers. Chronic use of opiates can weaken the immune system, effecting both adaptive and innate immunity.[31,32] Drug users have poor oral health[33,34] and heroin use[11] has degenerative effects on oral tissues. The risk of oral cancer is higher in immunosuppressed people compared with the general population[35,36] and poor oral health and severe oral lesions could be risk factors for oral cancer.[37]

Esophagus cancer and opiate use had the highest coefficient in our study. One case-control and one cohort study have shown a RR of about two between esophageal cancer and opiate use.[38,39] Esophageal reflux is a symptom of opioid use for chronic pain.[40,41] Esophageal adenocarcinoma risk is 4.9 times higher in people who have gastro-esophageal reflux disease (GERD) symptoms at least weekly, versus people who have GERD symptoms less frequently or never.[42]

Larynx cancer was not significantly associated with opiate use in the model based on male data, but the association was significant in the model for both sexes. The RR estimates for the association between opium use and squamous-cell carcinoma of the larynx was about ten in case-control studies.[43,44] GERD[45,46] and a suppressed immune system[31,32] are two risk factors for laryngeal cancer, and the consequence of chronic opioid use according to previous studies. An investigation into the association between opiate use and larynx cancer in future studies could be noteworthy.

We could not find significant association between opiate use and stomach, pancreas or lung cancer in our multiple regression analyses, but the association was significant in univariate analyses. Two case-control[30,38] and one cohort[47] study showed a RR of three for associations between opium use and stomach cancer. For pancreatic cancer a case-control study found an odds ratio (OR) of 1.91 between opium use and incidence of this cancer.[48] Moreover, two case-control studies[49,50] found a significant association between the risk of lung cancer and opium use and one cohort study[26] found a significant association between opium use and death due to lung cancer. The contrast between our study results and the above studies could be due to residual confounding, ecological fallacy or other ecological biases. In addition, variables like HDI can explain a large variation of cancer incidence. In other words, HDI can be a positive confounder in the association between opiate use and risk of cancers.

In the current study we investigated the association between global opiate use and cancer for the first time. This study was an ecological study and we could not adjust for confounding at the individual level. Like other cross-sectional studies, we could not adjust the results for temporal bias. In this study we did not have access to opiate use data from some countries and selection bias could violate our study results.

Conclusion

In summary, according to our results, opiate use could present a global cancer risk. Chronic use of opioids can cause multiple conditions such as GERD, immunosuppression and renal damage as well as carcinogenic effects, which are associated with the incidence of cancers. The association between opiate use and cancer incidence has been studied in some case-control studies. Opiates are globally used for the management of pain and there is an alarming increase in prescriptions of opiates for chronic pain. To make appropriate clinical decisions in pain management we need more strong evidence for the association between opiate use and cancer. We suggest that other countries should conduct more studies investigating this association, adjusting for potential confounders.

Conflict of Interests

The Authors have no conflict of interest.

Acknowledgements

None.

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مطالعه اکولوژیک بررسی رابطه مصرف تریاک و بروز سرطان

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مقاله پژوهشی

چکیده

مقدمه: سرطان دومین علت مرگ و میر بعد از بیماری‌های قلبی- عروقی است. در سال‌های اخیر این فرضیه مطرح شده است که مصرف تریاک و فرآورده‌های آن می‌تواند عامل خطری برای بروز این بیماری باشد. هدف از انجام مطالعه حاضر، بررسی رابطه احتمالی بین مصرف تریاک و فرآورده‌های آن با سرطان‌های شایع در جهان با استفاده از داده‌های اکولوژیک بود.

روش‌ها: در این مطالعه جهت بررسی رابطه سرطان و مصرف تریاک و فرآورده‌های آن، از مدل رگرسیون خطی استفاده گردید. لگاریتم بر مبنای ۱۰ میزان بروز استاندارد شده سرطان‌ها به عنوان متغیر وابسته در مدل‌ها در نظر گرفته شد. همچنین، متغیرهای مصرف سیگار، سرانه مصرف الکل، شاخص توسعه انسانی (Human development index یا HDI) و شاخص توده بدنی (Body mass index یا BMI) به عنوان متغیرهای مخدوش کننده وارد مدل گردید. داده‌های مربوط به این متغیرها از منابع اطلاعاتی معتبر شامل GLOBOCAN ۲۰۱۲، گزارش‌های سالانه دفتر مقابله با مواد مخدر و جرم سازمان ملل متحد (United Nations Office on Drugs and Crime یا UNODC)، پایگاه داده سازمان جهانی بهداشت، گزارش ۲۰۱۲ برنامه توسعه سازمان ملل متحد (United Nations Development Program یا UNDP) و متون چاپ شده استخراج شد. برای هر سرطان دو مدل جداگانه (یکی برای جنس مرد و دیگری برای هر دو جنس) تخمین زده شد.

یافته‌ها: شیوع مصرف تریاک و فرآورده‌های آن از ۰/۰۱ تا ۲/۶۵ درصد متغیر بود و میانه مصرف آن ۰/۲۰ درصد گزارش گردید. در رگرسیون خطی چند متغیره برآورد شده برای دو جنس، رابطه بین سرطان‌های مثانه (ضریب رگرسیون = ۰/۵۹) کلیه (ضریب رگرسیون = ۰/۱۶)، حفره دهان (ضریب رگرسیون = ۰/۲۷)، مری (ضریب رگرسیون = ۰/۳۳)، حنجره (ضریب رگرسیون = ۰/۱۷) و حلق (ضریب رگرسیون = ۰/۳۶) معنی‌دار شد. در مدل تخمین زده شده برای مردان نیز ضرایب و سطح معنی‌داری تا حدودی مشابه مدل برآورد شده برای هر دو جنس بود، به جز سرطان حنجره که در این مدل معنی‌دار نبود.

نتیجه‌گیری: بین مصرف تریاک و فرآورده‌های آن با بروز سرطان‌ها رابطه معنی‌داری در سطح جهانی وجود دارد. پیشنهاد می‌شود جهت بررسی این رابطه، مطالعات بیشتری به ویژه در مناطق پرخطر جهان صورت گیرد.

واژگان کلیدی: سرطان، مطالعه اکولوژیک، تریاک، عوامل خطر

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تاریخ دریافت: ۹۵/۲/۲۲ **تاریخ پذیرش:** ۹۵/۵/۷

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