Unveiling an Association between Waterpipe Smoking and Bladder Cancer Risk: A Multicenter Case–Control Study in Iran

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ABSTRACT

Background: Limited data exist for the association between bladder cancers and waterpipe smoking, an emerging global public health concern.

Methods: We used the IROPICAN database in Iran and used multivariable logistic regression, adjusting for cigarette smoking, opium use, and other confounding factors. In addition, we studied the association between exclusive waterpipe smoking and bladder cancer.

Results: We analyzed 717 cases and 3,477 controls and a subset of 215 patients and 2,145 controls who did not use opium or cigarettes. Although the OR adjusted for opium, cigarettes, and other tobacco products was 0.92 [95% confidence interval (CI), 0.69–1.20], we observed a statistically significant elevated risk in exclusive waterpipe smokers (OR = 1.78; 95% CI, 1.16–2.72) compared with non-users of opium or any tobacco. Associations were strongest for smoking more than two heads/day (OR = 2.25; 95% CI, 1.21–4.18) and for initiating waterpipe smoking at an age less than 20 (OR = 2.73; 95% CI, 1.11–6.72). The OR for urothelial bladder cancer was higher in ex-smokers (OR = 2.35; 95% CI, 1.24–4.42) than in current smokers (OR = 1.52; 95% CI, 0.72–3.15). All observed associations were consistently higher for urothelial histology.

Conclusions: Waterpipe smoking may be associated with an increased risk of bladder cancer, notably among individuals who are not exposed to cigarette smoking and opium.

Impact: The study provides compelling evidence that waterpipe smoking is a confirmed human carcinogen, demanding action from policymakers.

See related In the Spotlight, p. 461

Introduction

Bladder cancer stands as a significant global health concern, ranking as the 10th most prevalent cancer worldwide (1). In 2020 alone, approximately 573,000 new cases and 213,000 deaths were attributed to bladder cancer globally, with a higher incidence rate among men in most populations. Although age-standardized death rates and disability-adjusted life year rates have shown a decline on a global scale, certain countries have experienced an upward trend, including in the southern and eastern parts of Europe (2). Several well-established risk factors contribute to the development of bladder cancer, including tobacco smoking, occupational exposure, and Schistosoma haematobium infection (3, 4). Notably, tobacco smoking plays a pivotal role in bladder cancer incidence, accounting for an estimated 49.4% and 39.5% of cases among men in the USA and Europe, respectively. The corresponding population attributable fractions for women were 39.1% and 22.6% in the USA and Europe, respectively (5, 6).

Waterpipe smoking, known by various names such as hubble-bubble, narghile, hookah, or shisha, is a distinct method of tobacco consumption (7). Although waterpipe smoking has been prevalent for

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centuries among men in the Eastern Mediterranean Region (EMR), including West Asia and North Africa, it has witnessed an unprecedented surge among the region's youth since the 1990s (8). Its prevalence has also increased worldwide, emerging as a global public health concern. Although the prevalence of regular waterpipe smoking among adults is higher in the EMR (7.2%) compared with Europe (3.8%) and the USA (0.4%), the prevalence of waterpipe smoking in the last 30 days is similarly high in Europe (10.6%), the USA (6.8%), and the EMR (10.6%) (9). Factors contributing to this rapid global spread include the introduction of flavored tobacco, social acceptability due to café and restaurant culture, advancements in mass communication and social media, and the lack of waterpipe-specific policies and regulations (7).

Despite the escalating global burden of waterpipe smoking, there remains a paucity of research investigating its associated health hazards (7). Given that a significant proportion of waterpipe smokers in more developed countries are young individuals, it will take several decades before the long-term impacts of waterpipe smoking manifest within these populations. Conversely, high-prevalence countries in Asia and Africa face challenges related to limited research capacity and resources. Although existing data on the health outcomes associated with waterpipe smoking are scarce, studies have suggested associations between waterpipe smoking and various conditions, including periodontal disease, chronic obstructive pulmonary disease, cancer, cardiovascular diseases, and low birth weight (7).

Although nearly 16 cancer types have been linked to cigarette smoking (1), and estimating that a 45-minute session of waterpipe smoking is equivalent to smoking about 60 cigarettes (10), few studies have explored the association between waterpipe smoking and cancer. Previous research has demonstrated similar concentrations of urinary carcinogen biomarkers in cigarette and waterpipe users (11). Moreover, a recent meta-analysis comprising 28 studies, primarily conducted in the EMR, reported significant associations between waterpipe smoking and five cancer sites, including head and neck, esophagus, stomach, lung, and bladder cancers (12). Among the five studies that reported an association between waterpipe smoking and bladder cancer risk, the summary estimate was 1.25 (95% confidence interval (CI), 1.05–1.51; refs. 13–16). However, the summary estimate for the association between waterpipe smoking and bladder cancer risk was heavily influenced by a prominent Egyptian study that did not adequately adjust for confounding variables (11). Similarly, previous studies examining the relationship between waterpipe smoking and bladder cancer risk have been hindered by methodological limitations, such as the absence of an appropriate control group, inadequate adjustment for confounders, and small sample sizes (12, 17). We conducted a large case–control study to assess the association between waterpipe smoking and bladder cancer risk in Iran, a country with a high prevalence of waterpipe smoking (18).

Materials and Methods

We utilized data from the IROPICAN study, a multicenter case–control study conducted in Iran. Detailed information and protocols regarding the IROPICAN study can be found elsewhere (19). In brief, between 2017 and 2020, the IROPICAN study recruited patients with cancers of lung, colorectum, bladder, or head and neck from hospitals in 10 provinces in Iran. A control group consisted of individuals visiting non-oncology wards of the hospital for reasons unrelated to cancer treatment and was frequency-matched to the combined gender, age group, and place of residence distribution of the lung, colorectum, bladder, or head and neck cancers. The controls were initially matched with the cases according to their respective cancer groups. However, we used a common set of controls and deviated from this matching in our analysis. During face-to-face interviews, demographic data and comprehensive information on various factors potentially associated with the risk of the target cancer types were collected in an identical manner from both cases and controls by trained interviewers who were blinded for the objective of this study as it was aimed to study several hypotheses. The nonresponse rate was 1% among patients and 11% in controls. This suggests that there were very few dropouts that could not significantly impact the results obtained from the study. The present study is based on patients with a confirmed histopathologic diagnosis of bladder cancer and all controls of the IROPICAN data.

Exposure assessment

Trained interviewers used a validated questionnaire and collected comprehensive information on confirmed and possible risk factors for bladder cancer, including cigarette smoking, waterpipe smoking, opium consumption, other tobacco types such as nass or pipe, and variables related to socioeconomic status (SES), including education, assets, and access to information technology (e.g., mobile phones, laptops, and internet access). SES was determined using a principal component analysis based on data regarding education, assets, and access to information technology (e.g., mobile phones, laptops, and internet access).

The participants provided details on the intensity and frequency of waterpipe smoking (please see Supplementary Materials and Methods). The frequency of waterpipe smoking was measured as daily or occasional (i.e., weekly or monthly) smoking, while the intensity was measured by the number of waterpipe heads smoked in each session. The intensity and frequency of waterpipe smoking were used to generate a new variable called "head-week," classifying participants as having smoked less or more than two heads per week. Additionally, as an analogy to pack-year in cigarette smoking, a new metric called "head-year" was created by multiplying the head-weeks of waterpipe smoking by the duration in years, categorized as less or more than 20 or more head-years. A head-year indicates smoking a waterpipe once a week for one year. The participants were categorized into three groups (less than 20, 21–29, and 30 years or older) according to the age they initiated waterpipe smoking. Moreover, we evaluated the association between bladder cancer and the types of tobacco use during waterpipe smoking (flavored and non-flavored varieties). Different models were utilized to investigate the correlation between various metrics and bladder cancer risk.

Outcome definition

All bladder cancer patients in this study were confirmed through histopathologic examination and were coded according to the third edition of the International Classification of Diseases for Oncology (ICD-O-3). Patients with a topography code of C67.0-C67.9 were included. Additionally, we reviewed the pathology reports and recorded the morphology of the tumors, including urothelial (ICD-O3 M8120/3, M8131/3) and other histologic types of bladder cancer. Patients with tumor histology not consistent with urothelial histology were excluded from the analysis. This detailed coding enabled us to also investigate the association of waterpipe smoking focused only on urothelial histology which is the major type of bladder cancer ($N = 687$, 95%).

Statistical analyses

We applied unconditional multiple logistic regression models to calculate odds ratios (OR) and 95% CI. In the model based on all

IROPICAN participants, we adjusted for age, gender, province, SES, cigarette smoking in pack-year categories, opium use in the frequency of use, and nass/pipe use (ever/never). To study the association between exclusive waterpipe smoking and bladder cancer, we excluded individuals who had ever used opium, cigarettes, or other forms of tobacco, such as nass and pipes. By enrolling a large number of bladder cancer patients and a 4-to-1 ratio of controls, the IROPICAN study provided sufficient power to study several hypotheses. However, after excluding opium and waterpipe users, 215 cases and 2,145 controls remained for statistical analysis. Given the 8.3% prevalence of waterpipe use in controls and considering 0.05 type 1 error, we had about 90% power to an OR of 2 for the association between exclusive waterpipe smoking and bladder cancer risk. Because about 90% of the patients were men, we did not have the power to examine the effect modification by sex and study the association in men and women, exclusively. Stata software was used for statistical analyses (version 17, Stata Corp, College Station, Texas 77845 USA, licensed to Tampere University).

Data availability

The data generated in this study are not publicly available due to restrictions such as information that could compromise patient privacy or consent. It might be available upon reasonable request from the corresponding author. Additional approval from the institutional review board is also required.

Ethics statement

The study was approved by the Ethics Committee of the National Institute for Medical Research Development (NIMAD) of Iran (Code: IR.NIMAD.REC.1394.027). All participants signed written informed consent to participate in the study.

Results

In the study, a total of 717 bladder cancer cases and 3,477 controls were included. Among them, 2,145 (62%) controls and 215 (30%) patients did not use cigarettes, nass, or opium, as shown in **Table 1**. The majority of bladder cancer cases were male (87%), over the age of 70 (37.2%), and had a low SES (40.2%). More than 50% of patients were recruited from the provinces of Fars (19.4%), Bushehr (23.2%), and Tehran (20.9%). After excluding cigarette, nass, and opium users, the proportion of female and younger age groups was higher than in the overall population. Additionally, the proportion of patients and controls from the southern provinces of Iran, including Fars, Bushehr, Hormozgan, and Sistan-Baluchistan, which have a higher prevalence of waterpipe smoking, increased. However, the distribution of socioeconomic groups remained unchanged.

Based on analysis of all data from the IROPICAN project and accounting for various confounders, no significant association was observed between bladder cancer and waterpipe smoking (OR = 0.92; 95% CI, 0.69–1.20) or nass usage (OR = 1.00; 95% CI, 0.52–1.91; **Table 2**). However, statistically significant associations were found for cigarette smoking (OR = 2.43; 95% CI, 1.97–2.98) and opium use (OR = 3.00; 95% CI, 2.42–3.73). Furthermore, when we looked at the exclusive use of cigarettes (OR = 2.39; 95% CI, 1.84–3.11) and opium use (OR = 3.41; 95% CI, 2.30–4.04), we observed associations similar to those seen in the overall analysis. Notably, exclusive waterpipe smoking showed a significant excess odds of bladder cancer (OR = 1.78; 95% CI, 1.16–2.72) higher association, with a statistically significant OR of approximately 2 for urothelial bladder cancer (OR = 2.07; 95% CI, 1.29–3.31). We also identified a stronger association between bladder cancer and the combined use of waterpipe and other products (OR = 2.55; 95% CI, 1.79–3.65) as well as poly use of other

Table 1. Distribution of bladder cancer patients and controls overall and among those who were not users of opium, cigarettes, or other tobacco, by gender, age at interview, province, and socioeconomic status. IROPICAN study 2017 to 2020.

	Total data set		Non-users of opium, cigarette, nass	
Variables	*N* Controls (%) *N* = 3,477	*N* Cases (%) *N* = 717	*N* Controls (%) *N* = 2,145	*N* Cases (%) *N* = 215
Gender				
Female	1,077 (31.0)	93 (13.0)	981 (45.7)	80 (37.2)
Male	2,400 (69.0)	624 (87.0)	1,164 (54.3)	135 (62.8)
Age (years)				
30–49	257 (7.4)	14 (2.0)	549 (25.6)	24 (11.2)
50–59	559 (16.1)	50 (7.0)	646 (30.1)	29 (13.5)
60–69	1,070 (30.8)	181 (25.2)	651 (30.4)	67 (31.2)
≥70	1,092 (31.4)	267 (37.2)	299 (13.9)	95 (44.2)
Province				
Fars	816 (23.5)	139 (19.4)	534 (24.9)	48 (22.3)
Bushehr	943 (27.1)	166 (23.2)	65 (3.0)	39 (18.4)
Tehran	525 (15.1)	150 (20.9)	546 (25.5)	36 (16.7)
Kerman	374 (10.8)	46 (6.4)	260 (12.1)	24 (11.2)
Golestan	136 (3.9)	24 (3.4)	271 (12.6)	20 (9.3)
Hormozgan	251(7.2)	52 (7.3)	58 (2.7)	14 (6.5)
Mazandaran	170 (4.9)	30 (4.2)	101 (4.7)	13 (6.1)
Kermanshah	84 (2.4)	56 (7.8)	144 (6.7)	8 (3.7)
Khorasan-Razavi	78 (2.2)	27 (3.8)	115 (5.4)	7 (3.3)
Systan-Balouchestan	100 (2.9)	27 (3.8)	51 (2.4)	6 (2.8)
Socioeconomic status				
Low	974 (28.0)	288 (40.2)	638 (29.7)	104 (48.4)
Medium	1,175 (33.8)	227 (31.7)	674 (31.4)	59 (27.4)
High	1,328 (38.2)	202 (28.2)	833 (38.8)	52 (24.2)

Table 2. OR and 95% confidence intervals in relation to waterpipe, cigarette, and opium consumption for bladder cancer overall and for urothelial histology. IROPICAN database (2017–2020).

	Number of controls	All bladder cancer patients			Urothelial histology		
Variable	*N* = 3,477	*N* cases *N* = 717	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	*N* cases *N* = 587	Crude OR (95% CI)	Adjusted OR (95% CI)
Waterpipe smoking							
Non-users	3,068	617	Reference	Reference	505	Reference	Reference
All users	409	100	1.22 (0.96–1.54)	0.92 (0.69–1.20)	82	1.22 (0.94–1.57)	0.97 (0.72–1.31)
Opium use							
Non-users	2,881	387	Reference	Reference	306	Reference	Reference
All users	596	330	4.12 (3.47–4.89)	3.00 (2.42–3.73)	281	4.44 (3.69–5.34)	2.99 (2.37–3.76)
Nass use							
Non-users	3,431	700	Reference	Reference	573	Reference	Reference
All users	46	17	1.81 (1.03–3.18)	1.00 (0.52–1.91)	14	1.82 (0.99–3.34)	0.94 (0.47–1.88)
Cigarette smoking							
Non-users	2,500	287	Reference	Reference	220	Reference	Reference
All users	977	430	3.83 (3.25–4.53)	2.43 (1.97–2.98)	362	4.27 (3.56–5.12)	2.6 (2.08–3.25)
Exclusive users							
Non-users of any products	1,965	172	Reference	Reference	125	Reference	Reference
Only waterpipe	180	43	2.72 (1.89–3.94)	1.78 (1.16–2.72)	33	2.88 (1.91–4.35)	2.07 (1.29–3.31)
Only opium	143	47	3.75 (2.61–5.41)	3.41 (2.30–4.04)	39	4.29 (2.88–6.38)	3.58 (2.34– 5.47)
Only cigarette	570	144	2.88 (2.27–3.67)	2.39 (1.84–3.11)	125	3.45 (2.65–4.49)	2.79 (2.10–3.72)
Only nass	13	0	—	—	0	—	—
Poly users							
Waterpipe/cigarette/opium/nass	229	57	2.84(2.05–3.95)	2.55 (1.79–3.65)	49	3.63 (2.35–4.81)	3.02 (2.05–4.45)
Cigarette/opium/nass	377	254	7.69 (6.16–9.61)	7.48 (5.77–9.712)	216	9.01 (7.04–11.52)	8.20 (6.17–10.90)

[a]Adjusted for age, gender, province, and socioeconomic status and mutually adjusted for other tobacco products and opium.

products, including opium, cigarettes, and/or nass (OR = 7.48; 95% CI, 5.77–9.712).

Analysis of waterpipe metrics revealed that waterpipe smokers who consumed two or more heads per week (OR = 2.25; 95% CI, 1.21–4.18) and initiated waterpipe smoking at age 20 or younger (OR = 2.73; 95% CI, 1.11–6.72; **Table 3**). The excess risk was higher among those who had smoked for less than 20 years (OR = 2.35; 95% CI, 1.20–4.64) than among those who had smoked for >20 years. We observed no significant difference in the risk of bladder cancer between current waterpipe smokers and ex-smokers overall. However, to our surprise, we found that the risk of urothelial bladder cancer was higher among ex-smokers (OR = 2.35; 95% CI, 1.24–4.42), particularly those who had quit smoking more than 10 years prior to the interview (OR = 2.81; 95% CI, 1.33–8.31). Most users (75%) reported using non-flavored tobacco and had a borderline significant association with the risk of bladder cancer (OR = 1.62; 95% CI, 0.99–2.65). The association was statistically significant with urothelial bladder cancer (OR = 1.98; 95% CI, 1.15–3.42). All the observed associations between waterpipe smoking and its metrics were higher for urothelial bladder cancer in all analyses.

Discussion

In a multicenter case–control study, we did not find an association between bladder cancer and waterpipe smoking based on all subjects involved in the IROPICAN study. However, there was an association in the data that excluded users of cigarettes, opium, and nass/pipe; this association was stronger with a higher frequency and intensity of waterpipe smoking. The ORs of waterpipe smoking tended to be higher when restricted to the urothelial type of bladder cancer.

Limited epidemiologic studies have investigated the association between waterpipe smoking and bladder cancer risk (13–15, 20, 21). To our knowledge, our study stands out as the largest of its kind, considering potential confounding variables and providing estimates of the risk associated with exclusive waterpipe smoking and bladder cancer. A systematic review and meta-analysis of five studies supported our findings, demonstrating a significant overall OR for waterpipe smoking and bladder cancer risk (9). Notably, previous studies were hindered by methodological limitations, such as small sample sizes and inadequate adjustment for confounding variables. Thus, our study contributes valuable insights to the existing literature by addressing these limitations and providing robust evidence on the association between waterpipe smoking and bladder cancer risk.

Waterpipe smoke contains 82 toxicants, including nicotine, tar, carbon monoxide (CO), polyaromatic hydrocarbons (PAH), tobacco-specific nitrosamines (TSNA), carbonylic compounds, volatile organic compounds (VOC), and various organic and inorganic compounds (11, 22). Urine analysis from the Golestan Cohort Study in Iran showed similar concentrations of biomarkers of exposure to tobacco-related carcinogens in waterpipe and cigarette smokers (11). However, certain biomarkers were higher in waterpipe smokers, including PAHs and VOCs (i.e., phenylmercapturic acid and phenylglyoxylic acid). From the list of above carcinogenic compounds, the tobacco-specific nitrosamines include 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), and primary aromatic amines are linked to bladder cancer risk. Cytochrome P450 enzymes activate NNK and PAHs and lead to the binding of these carcinogens to DNA and the formation of bulky DNA adducts. These adducts can induce gene mutations and alter the regulation of the transcription of oncogenes and tumor suppressor genes. The carcinogen–adduct level seems to be associated with bladder cancer risks based on the intensity of exposure to carcinogens. These data support a possible association between waterpipe smoking and bladder cancer.

Table 3. Waterpipe smoking metrics and bladder cancer in Iran, excluding users of opium, cigarette, and other tobacco types. IROPICAN database (2017–2020).

	Number of controls	All bladder cancer patients			Urothelial histology		
Waterpipe metrics	***N* = 2,145**	***N* cases** ***N* = 215**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)[a]**	***N* cases** ***N* = 158**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)[a]**
Waterpipe use							
Non-users	1,965	172	Reference	Reference	125	Reference	Reference
Users	180	43	2.72 (1.89–3.94)	1.78 (1.16–2.72)	33	2.88 (1.91–4.35)	2.07 (1.29–3.31)
Frequency							
Daily	80	28	3.99 (2.52–6.31)	1.70 (0.96–3.03)	21	4.12 (2.46–6.89)	1.92 (1.03–3.61)
Occasional	100	15	1.71 (0.97–3.01)	1.61 (0.85–3.05)	12	1.88 (1.00–3.52)	1.92 (0.95–3.87)
Weekly dose							
<2 head/day	127	16	1.43 (0.83–2.47)	1.29 (0.71–2.36)	13	1.60 (0.88–2.92)	1.54 (0.80–2.98)
≥2 head/day	53	27	5.81 (3.56–9.48)	2.25 (1.21–4.18)	20	5.93 (3.43–10.23)	2.51 (1.27–4.99)
Duration (years)							
<20 years	65	14	2.46 (1.35–4.47)	2.35 (1.20–4.64)	14	3.39 (1.84–6.20)	3.61 (1.80–7.22)
≥20 years	86	26	3.45 (2.17–5.50)	1.34 (0.75–2.39)	17	3.11 (1.79–5.39)	1.25 (0.64–2.46)
Unknown	29	3	—	—	2		—
Cumulative amount							
<20 head-years	76	11	1.64 (0.86–3.15)	1.58 (0.77–3.24)	10	2.07 (1.04–4.10)	2.03 (0.95–4.33)
≥20 head-years	72	27	4.26 (2.66–6.81)	1.56 (0.86–2.81)	20	4.37 (2.58–7.40)	1.77 (0.92–3.42)
Unknown	32	4	—	—	3		
Starting age							
≥30 years	72	72	1.90 (1.01–3.58)	1.22 (0.60–2.48)	20	2.40 (1.24–4.64)	1.65 (0.79–3.46)
20–29 years	59	59	3.29 (1.88–5.77)	1.75 (0.89–3.43)	5	3.20 (1.67–6.10)	1.95 (0.91–4.17)
<20 years	22	22	5.71 (2.72–11.97)	2.73 (1.11–6.72)	6	5.71 (2.49–13.10)	2.83 (1.05–7.61)
Unknown	27	27			2		
Waterpipe smoking status							
Current smokers	87	18	2.53 (1.44–4.46)	1.64 (0.85–3.18)	11	1.97 (0.96–4.02)	1.52 (0.72–3.15)
Ex-smokers	66	22	3.39 (2.09–5.48)	1.65 (0.92–2.96)	20	4.27 (2.58–7.07)	2.35 (1.24–4.42)
Stopped <10 years ago	31	7	2.58 (1.11–5.94)	1.45 (0.55–3.82)	5	2.53 (0.97–6.63)	1.51 (0.72–3.18)
Stopped ≥10 years ago	35	15	4.90 (2.62–9.14)	1.82 (0.87–3.81)	15	6.74 (3.58–12.67)	2.81 (1.33–8.31)
Unknown	27	3	—	—	2	—	—
Tobacco type							
Flavored	47	5	1.22 (0.48–3.10)	1.89 (0.68.22)	3	1.00 (0.31–3.27)	1.61 (0.45–5.76)
Non-flavored	133	38	3.26 (2.20–4.83)	1.62 (0.99.65)	30	3.54 (2.29–5.48)	1.98 (1.15–3.42)

[a]Adjusted for age, gender, province, and socioeconomic status.

Our study possesses several strengths that enhance the reliability of our findings. Firstly, all cases of bladder cancer underwent histologic confirmation, ensuring accurate diagnosis. Additionally, our control group was carefully selected from healthy visitors, with meticulous matching based on age, sex, and residential place, to minimize potential referral bias. The use of a validated questionnaire administered by trained interviewers further enhanced the quality of data collection. Moreover, we a had high response rate in both bladder cancer patients (99%) and controls (89%), strengthening the representativeness of our study population (19). The strength of our study is further reinforced by the large sample size and collected comprehensive information on waterpipe smoking and potential confounding variables, allowing us to compare the odds ratio of waterpipe smoking with other products, including opium and cigarette use, and conduct a more focused analysis on individuals who did not smoke cigarettes or use opium. Nevertheless, our study encountered certain limitations. Recall bias which may have especially affected the accuracy of reported waterpipe usage in terms of dose and duration. Nonetheless, we believe that any potential bias of this nature has a minimal impact on the overall assessment of exposure to waterpipe smoke. Despite using pack-year of cigarette smoking and frequency of opium use to make fine adjustments for these confounding variables, potential misclassification of these risk factors that are strong determinants of bladder cancer may have biased the true association between waterpipe smoking and bladder cancer. A validation study in the IROPICAN study showed that self-reporting of opium use is subject to approximately 30% under-reporting both in the cases and controls (19). Additionally, the frequency and intensity of cigarette and opium use can vary over an individual's lifetime, thereby making it challenging to make appropriate adjustments in the regression model. To mitigate the influence of residual confounding, our analysis focused on exclusive waterpipe smokers, offering more refined and accurate findings on the association between waterpipe smoking and the risk of bladder cancer. Another limitation is that in spite of using data from a large multicenter case–control study, our analyses for different categories in waterpipe smoking metrics faced power imitations after excluding cigarette and opium smokers. Larger studies to address different aspects of waterpipe smoking and cancer risk are highly warranted.

Unexpectedly, we observed that individuals with a shorter duration of waterpipe smoking seemed to have a higher risk of bladder cancer and ex-smokers exhibited a greater risk of urothelial bladder cancer compared with current smokers. Due to limited statistical power, it is important to interpret these findings with caution. A cross-tabulation of the data revealed that the intensity of waterpipe smoking was notably higher among those with a shorter duration of smoking and

among ex-smokers and ex-smokers were older (mean age 64.6 years) than current smokers (55.6 years). The effect of such factors should have been adjusted in the multivariate model, but the possibility of residual confounding remains. A larger study is required to account for the dose effect while assessing the impact of smoking duration and cessation on cancer risk.

In our study, the prevalence of non-flavored waterpipe tobacco was notably higher than that of flavored tobacco types, and we observed an elevated risk of urothelial bladder cancer, specifically among users of non-flavored tobacco. Flavored tobacco consists of a mixture of tobacco, molasses, vegetable glycerol, and various flavorings, offering distinct tastes or aromas such as spice, herbs, alcohol, candy, menthol, or vanilla (23, 24). In the flavored waterpipe tobacco type, the lit charcoal is separated from the tobacco mixture by a perforated aluminum foil. Flavored tobacco is often preferred by many waterpipe smokers, particularly younger individuals who occasionally smoke the waterpipe in cafes and restaurants. Conversely, in the traditional method, non-flavored waterpipe tobacco is directly placed in the charcoal pot. A recent study in Florida, USA, revealed higher levels of exhaled carbon monoxide in non-flavored waterpipe tobacco, while the plasma nicotine levels were similar between flavored and non-flavored waterpipe tobacco (25). In our study, the prevalence of flavored tobacco was low—only five cases used flavored tobacco—which greatly limits our ability to compare the association between flavored and non-flavored tobacco concerning bladder cancer risk (7, 25).

Our findings indicated a stronger association with waterpipe smoking among individuals presenting urothelial histology, which aligns with prior evidence (26). Urothelial histology predominates in over 90% of bladder cancers in the Western world and has been linked to tobacco smoke and occupational toxins (26, 27). Squamous cell carcinoma (SCC) represents the second most common type of bladder cancer and is highly prevalent in Africa. Bladder SCC is associated with the risk factors related to chronic irritation and inflammation of the bladder such as Schistosoma haematobium infection (28), bladder stones, urinary outflow obstruction, recurrent urinary tract infections, and irritation due to catheters (29, 30). It appears that non-urothelial histology in our data is not associated with waterpipe smoking. Consequently, focusing our analysis on urothelial histology, a more tobacco-related phenotype, strengthens the association between waterpipe smoking and bladder cancer. The limited number of non-urothelial bladder cancers in our study prevented us from exploring the association between waterpipe smoking and other bladder cancer histologic types.

Notwithstanding the strengths mentioned, our study also encountered certain limitations. Waterpipe smokers typically engage in prolonged smoking sessions during social gatherings, which could expose them to high levels of side-stream smoke, particularly in cafes or homes. Therefore, we did not have the opportunity to collect data on the extent of exposure to side-stream smoke among waterpipe users (31). Moreover, to date, no study has assessed the impact of passive waterpipe smoking on cancer or other tobacco-related health outcomes. Consequently, we strongly recommend including questions about second-hand exposure from waterpipe smoking in future research endeavors.

This study showed higher odds of bladder cancer among daily waterpipe users and individuals who were exposed to a higher dose of tobacco smoke. Although the odds were higher among individuals who started smoking when they were younger than 20, we did not observe an increasing trend in the risk by duration of smoking. In addition, the increase in cumulative exposure to waterpipe smoking did not inflate the bladder cancer risk. Larger studies with sufficient power are warranted to validate our findings and examine the dose- and duration-response and risk of bladder cancer due to waterpipe smoking. In conclusion, our study suggests that waterpipe smoking may add to the risk of bladder cancer. Given the global increase in waterpipe smoking, our findings underscore the importance of including waterpipe tobacco control measures not only in regions with traditionally high prevalence but also in other areas, including Western countries grappling with the waterpipe smoking epidemic among younger generations.

Authors' Disclosures

No disclosures were reported.

Disclaimer

Where authors are identified as personnel of the Italian Association for Research on Cancer (AIRC)/World Health Organization (WHO)/NCI, the authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policy, or views of the AIRC/WHO/NCI.

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Note

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