Incident cancers attributable to using opium and smoking cigarettes in the Golestan cohort study

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Summary

Background Opium consumption has recently been identified as a carcinogen, but the impact of opium use on cancer burden is unknown. We aimed to evaluate the fraction of cancers that could be attributed to opium use alone and in combination with cigarette smoking in a region where opium is widely used.

Methods 50,045 Iranian adults were recruited to this prospective cohort study between 2004 and 2008 and were followed through January 2022. We assessed the association between using opium and/or cigarette smoking and various cancers using proportional hazards regression models. We then calculated population attributable fractions (PAFs) for all cancers and for groups of cancers causally linked to opium and cigarette smoking.

Findings Of the total participants, 8% only used opium, 8.3% only smoked cigarettes, and 9% used both substances. During a median 14 years of follow-up, 2195 individuals were diagnosed with cancer, including 215 opium-related cancers (lung, larynx, and bladder) and 1609 tobacco-related cancers (20 types). Opium use alone was estimated to cause 35% (95% CI: 26%–45%) of opium-related cancers, while smoking cigarettes alone was estimated to cause 9% (6%–12%) of tobacco-related cancers in this population. Using opium and/or cigarettes was estimated to cause 13% (9%–16%) of all cancers, 58% (49%–66%) of opium-related cancers, and 15% (11%–18%) of tobacco-related cancers. Moreover, joint exposure to opium and cigarettes had the greatest impact on cancers of the larynx, pharynx, lung, and bladder, with PAFs ranging from 50% to 77%.

Interpretation Using opium and smoking cigarettes account for a large proportion of cancers in this population. To reduce the cancer burden, prevention policies should aim to decrease the use of both substances through public awareness campaigns and interventional efforts.

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Research in context

Evidence before this study

Opium consumption was recently classified as "carcinogenic to humans" by the International Agency for Research on Cancer (IARC) based on sufficient evidence for cancers of the lung, larynx, and bladder. While opium is used for recreational and pain-relieving purposes by millions of people in central and western Asia, its impact on the burden of cancers in these regions remains unknown. Few studies assessed the population attributable fraction (PAF) of cancers in relation to using opium, which was reported at 6% for overall cancer deaths, and 5%–8% for esophageal and stomach cancers. However, no study has assessed the impact of using opium on cancer types that were identified by IARC to be causally related to opium consumption. Further, while around half of individuals who use opium also smoke cigarettes, no study has estimated the proportion of cancers that could be prevented if either opium or cigarettes or both were controlled at the safest level.

Added value of this study

This study provides the first comprehensive assessment of the impact of opium consumption on all cancer types, including cancers of the lung, larynx, and bladder which were classified as causally related to opium use. This is also the first study that provides detailed estimates of the impact of opium consumption among different population subgroups including among males and females and among ever and never cigarette smokers. This study highlights the significant, but underestimated, contribution of opium consumption to the incidence of cancers in populations where opium use is prevalent, particularly in the Middle East and south-eastern Asia. By estimating the proportion of cancers that could have been prevented if either or both opium consumption and cigarette smoking were controlled at the safest level, the study provides valuable information for developing cancer prevention policies in regions where both opium and cigarette smoking are common. The study's findings have significant public health implications for these regions and underscore the need for targeted interventions to reduce opium consumption and cigarette smoking to prevent cancer.

Implications of all the available evidence

Available evidence indicates the impact of using opium on cancer incidence in regions where opium is commonly used has been largely underestimated. Using opium and smoking cigarettes account for a large proportion of some cancer types such as lung, larynx, and bladder cancers in these populations. Given the long-standing historical acceptance of opium use as a traditional medicine among certain populations in the Middle East and south-eastern Asia, to decrease cancer burden in these regions, it becomes crucial to implement prevention policies that target decreasing the use of opium and cigarettes through raising public awareness and interventional efforts.

Introduction

Opium is the raw extract of the poppy plant that is widely used in some societies for recreational and pain-relieving purposes.[1] Minimally processed opium can be ingested or smoked after heating with special devices.[1] In 2020, the International Agency for Research on Cancer (IARC) classified opium consumption (through smoking or ingesting) as "carcinogenic to humans",[2] adding it to the list of other known carcinogens such as tobacco and alcohol consumption.[3,4] Around 25% of cancer-related deaths worldwide are attributable to smoking tobacco, with significant variations across countries and between males and females (35% vs. 10%, respectively).[5] Also, around 4% of incident cancers worldwide are attributable to drinking alcohol.[6] Although opium and its natural derivatives are used by more than 30 million people worldwide,[7] little is known about the fraction of cancers that could be attributable to this exposure in the corresponding populations.

Opium use is most prevalent in the Middle East and south-eastern Asia, where it has been cultivated and used as a traditional medicine since Mesopotamia (3400 BCE).[8,9] Due to its high prevalence, opium use may be a major contributor to the cancer burden in these regions,[2] where its impact might surpass other known but less prevalent carcinogens, such as alcohol consumption.[6,8] Only three studies assessed the population attributable fraction (PAF) of cancers in relation to using opium which was reported at 6% for overall cancer deaths,[10] and 5%–8% for esophageal and stomach cancers.[11,12] However, no study has assessed the impact of using opium on the cancer types that have been identified to be causally related to opium consumption by IARC monographs (i.e. lung, larynx, bladder).[2] Further, up to half of those who use opium also smoke cigarettes.[1] To develop appropriate cancer prevention policies in regions where using opium and cigarettes are both prevalent, it is critical to estimate the proportion of cancers that would have been prevented if each or both carcinogens had been controlled at the safest level.

Due to the inherent challenges associated with studying opium, such as acquiring accurate

consumption data and concerns surrounding stigma and prosecution, there is a notable lack of prospective studies examining opium use over the long term. The Golestan Cohort Study is the only population-based prospective study that includes a large group of opium users with validated opium use data,[13] who have been followed for over a decade with a minimum (around 1%) loss to follow-up. We used data from the GCS to evaluate the proportions of incident cancers that are attributable to individual and joint exposure to opium consumption and cigarette smoking in northeast Iran, where one fourth of the population regularly use opium or smoke cigarettes.

Methods

Study design and population

The design of the Golestan Cohort Study (GCS) have been previously described in detail.[14] Briefly, GCS is a prospective study of 50,045 adults, aged 40–75 years, who were enrolled between 2004 and 2008, from 329 rural and urban areas of the Golestan province in northeast Iran. We employed a systematic clustering method to randomly select urban participants based on household numbers. Trained healthcare workers reached out to these individuals and invited them to visit the GCS center for study participation. In rural areas, all eligible individuals residing in the villages within the study area were contacted and invited to take part in the study. This outreach was facilitated through the network of health houses, which constitute the smallest units of the primary healthcare system and are present in each group of villages. For this specific analysis, we excluded participants who reported a history of cancer diagnosis at enrollment.

Ethics statement

All participants provided informed written consent before enrollment. The GCS was approved by the institutional review boards of the Digestive Disease Research Institute of the Tehran University of Medical Sciences, the International Agency for Research on Cancer, and the US National Cancer Institute.

Exposure assessments

At enrollment, participants were interviewed by trained personnel to collect data on baseline demographics, lifestyle, diet, habits, and various exposures via validated structured questionnaires.[15] Data on opium use was collected using a questionnaire that showed ≥90% sensitivity and specificity for self-reported opium use when compared to urinary opium metabolites.[13] Participants were asked whether they ever used opium regularly, defined as using opium at least once a week for at least 6 months. If applicable, participants were also asked about the frequency, and amount of opium use in nokhods (local unit ≈ 0.2 g), and the starting and stopping ages for opium use. Data on smoking cigarettes was collected using a questionnaire that was validated against urinary cotinine levels.[15] If applicable, participants were also asked about the frequency, and amount of smoking cigarettes, and the starting and stopping ages for smoking. The amounts of cumulative opium used (in nokhod-years) and cigarettes smoked (in pack-years) were calculated by multiplying the number of units (nokhods/or packs) used per day by the consumption years. Alcohol consumption is rare in this region (ever drinking reported by 3%) and therefore we categorized this exposure as never/ever drinking alcohol.

To determine the socio-economic status, we used quartiles of a composite wealth score, that was created previously based on the size and structure of individuals' residence, and their ownership of property, vehicle, and specific home appliances.[16]

Follow-up process and outcome ascertainments

The participants were followed-up annually by telephone surveys. When an incident cancer or death was reported, a team was sent to interview the patient or the relatives of the deceased to fill a structured questionnaire collecting information related to the reported cancer diagnosis or death. Then, a team visited the corresponding medical centers to collect all relevant medical records, which were then reviewed by at least 2–3 expert physicians to verify the diagnosis of cancer or cause of death. To minimize possible misclassifications, the cohort records were further matched to the Golestan population-based cancer registry to confirm the type and date of cancer diagnosis. Cancer diagnosis and death causes were recorded based on the International Classification of Diseases 10th Revision (ICD-10) codes.

For this analysis, we focused on three groups of incident cancers as the outcomes of interest. The first group included all incident cancers (ICD-10 C00–C97); the second group included incident cancers that were classified by IARC to be causally related to opium consumption (cancers of the larynx (C32), lung (C34), and bladder (C67))[2]; and the third group included incident cancers that were classified by IARC to be causally related to smoking tobacco (cancers of the oral cavity (C00–C09), nasopharynx/oropharynx/hypopharynx (C10–C14), esophagus (C15), stomach (C16), colorectum (C18 to C21), liver (C22), pancreas (C25), nasal cavity and sinuses (C30–C31), larynx (C32), lung (C34), breast (C50), uterine cervix (C53), ovary (C56), kidney (C64–C65), ureter (C66), urinary bladder (C67) and myeloid leukemia (C92)).[3]

Statistical analyses

We estimated the hazard ratios (HRs) and corresponding 95% of confidence intervals (95% CIs) using Cox proportional hazards regression models. The entry time was defined as the enrollment date and end of follow-up

time was set at the date of first cancer diagnosis for participants who developed cancer, death date for those who died from other causes, and date of last contact for the remaining participants (through 8 January 2022). We adjusted the models for baseline confounders that were selected *a priori* based on our previous analysis on the risk of different cancers in relation to using opium in this population.[1] The models were adjusted for age at recruitment, sex, ethnicity (Turkman/Non-Turkman), residence (Urban/Rural), wealth score quartiles, alcohol drinking status, and education. The estimates remained consistent after further adjustments were made to the models, including variables such as family history of cancer, history of chewing tobacco, predominant household fuel (gas/kerosene/biomass/mixed), and diet (tertiles of the Healthy Eating Index score). Consequently, these factors were not included in the final models. None of the included participants had missing data on the exposures of interest (i.e. opium consumption, cigarette smoking) and other covariates that were included in the model.

Baseline status of opium consumption and cigarette smoking were strongly correlated (chi test: P < 2.2e–16, Supplementary Table S1). Therefore, to avoid multicollinearity and to maximize adjustments, we used separate models when assessing the effects of opium consumption by adjusting for cigarette packyears and for cumulative nokhod-years of opium used when assessing the effects of smoking cigarettes. We checked the proportional hazards assumptions for each model using the Schoenfeld's test. None of the opium use and tobacco smoking variables violated the proportional hazards assumption. We used the Formula 1 to calculate the PAFs of cancers related to individual exposure to opium consumption and smoking cigarettes[17–19]:

Formula 1. Calculating attributable fractions related to individual exposures in time-to-event studies.

$$PAF = 1 - \frac{1 - S_0(t)}{1 - S(t)}$$

With $S_0(t)$ as the counterfactual survival function for the event if the exposure has been eliminated from the population at baseline, and $S(t)$ as the factual survival function. The PAFs showed similar estimates from 1 to 10 years. Consequently, we used $t = 5$ for the analyses.

To calculate the PAFs of cancers related to combined exposure to opium consumption and cigarette smoking, we used estimates from the same model without further adjustments for cumulative opium used or cigarettes smoked, as the joint PAF formula already considers the overlap between the two exposures. Using the obtained hazard ratios, we calculated the PAFs of cancers related to joint opium consumption and cigarette smoking using Formula 2:[20,21]

Formula 2. Calculating attributable fractions for joint exposures.

$$PAF = 1 - \sum_{i=0}^{k} \frac{pd_i}{RR_i}$$

With I as the number of exposure levels, pd_i as the proportion of cases falling into the ith exposure level and RR_i as the relative risk comparing the ith level of exposure to the reference. As cancers are rare events, we used hazard ratios to approximate relative risks.

We used bootstrap (500 resampling) to estimate the 95% CIs for the joint PAF; we calculated the PAF at each iteration and kept the values at 2.5% and 97.5% of this distribution to obtain the 95% CI. The point estimate was obtained in the cohort without resampling. Sensitivity analyses were performed by excluding cancer cases that did not have histological confirmation, by dropping the first 2 years of follow-up to address reverse causation, by adding the cumulative pack-years of smoked cigarettes and nokhod-years of consumed opium to the model that was used to calculate the PAF for joint exposure to opium and tobacco, and by modelling the main continuous variables (age, pack-years of cigarettes smoked and nokhod-yeas of opium used) in quintiles.[22] Type 1 error was set as 5% and all analyses were two-sided and were performed with R, version 4.1.2 software (used packages: survival for Cox proportional hazards models,[23] version 3.3.1; package AF for population attributable fraction,[24] version 0.1.5 and package ggplot2 for figures,[25] version 3.3.6).

Role of funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Descriptive statistics

Of the total 50,045 participants, we excluded 97 who were diagnosed with cancer before enrollment. Among the remaining 49,948 participants, 2195 developed cancers during the follow-up. The most common cancer sites were esophagus (n = 393), stomach (n = 384), colorectal (n = 161), lung (n = 119), and breast (n = 111). Detailed information on the diagnosed cancer sites in the full cohort and across the male and female subgroups is provided in Supplementary Table S2.

The participants were followed for a median of 14 years. At enrollment, participants' median age was 50.2 years (Interquartile range = 44.8–57.8). Of the enrolled participants, 42% were males, 3997 (8%) only used opium, 4176 (8.3%) only smoked cigarettes, and 4467

(9%) used both opium and cigarettes. Most participants (80%) lived in rural areas and 74% were Turkman (Table 1). Participants who developed cancer tended to be older, male, have less education, lower SES, and lower BMI, and more commonly had a positive history for using opium, smoking cigarettes, and drinking alcohol (P < 0.05 for all) (Table 1).

Fraction of cancers related to opium consumption

Opium was more commonly used by males than females (29% vs. 8%). Participants who used opium tended to be older and more educated, live in rural areas, have lower SES and BMI, and more commonly reported smoking cigarettes and drinking alcohol (P < 0.001 for all, Supplementary Table S3). Opium consumption was associated with increased risk for developing all cancers combined [HR: 1.25 (95%CI: 1.12–1.40)], opium-related cancers [HR: 2.92 (2.17–3.94)], and smoking-related cancers [1.30 (1.14–1.47)]. Detailed effect estimates for different cancer sites in relation to opium consumption are provided in Supplementary Table S4. Of the total incident cancers, 5% (95%CI: 3%–8%) were attributable to opium consumption, while this proportion was 6% (3%–10%) for smoking-related cancers (Table 2). More

	Cases (*n* = 2195)	Non-Cases (*n* = 47,753)	Full cohort (*n* = 49,948)
Follow-up (person-years)	15,116	653,166	668,282
Sex[b]			
Female	1006 (45.8%)	27,748 (58.1%)	28,754 (57.6%)
Males	1189 (54.2%)	20,005 (41.9%)	21,194 (42.4%)
Age[b]			
Median (IQR[a])	56.6 (14.8)	50.0 (12.8)	50.2 (13)
Residence			
Rural	1738 (79.2%)	38,196 (80.0%)	39,934 (80.0%)
Urban	457 (20.8%)	9557 (20.0%)	10,014 (20.0%)
Ethnicity			
Non-Turkman	523 (23.8%)	12,244 (25.6%)	12,767 (25.6%)
Turkman	1672 (76.2%)	35,509 (74.4%)	37,181 (74.4%)
Education[b]			
No	1634 (74.4%)	33,412 (70.0%)	35,046 (70.2%)
Yes	561 (25.6%)	14,341 (30.0%)	14,902 (29.8%)
Socio Economic Status[b]			
Q1[a] (lowest)	632 (28.8%)	11,856 (24.8%)	12,488 (25.0%)
Q2	545 (24.8%)	11,945 (25.0%)	12,490 (25.0%)
Q3	554 (25.2%)	11,939 (25.0%)	12,493 (25.0%)
Q4 (highest)	464 (21.1%)	12,013 (25.2%)	12,477 (25.0%)
BMI [ab]			
≤25	1070 (48.8%)	19,272 (40.4%)	20,342 (40.7%)
>25–≤30	659 (30.0%)	16,250 (34.0%)	16,909 (33.9%)
>30–≤35	331 (15.1%)	8827 (18.5%)	9158 (18.3%)
>35	134 (6.1%)	3397 (7.1%)	3531 (7.1%)
Using opium[b]			
Never	1676 (76.4%)	39,808 (83.4%)	41,484 (83.1%)
Ever	519 (23.6%)	7945 (16.6%)	8464 (16.9%)
Opium nokhod-years[b]			
Median (IQR[a])	35 (9.00–91.0)	21 (5.00–60.0)	22 (5.14–60.0)
Smoking cigarettes[b]			
Never	1626 (74.1%)	39,679 (83.1%)	41,305 (82.7%)
Ever	569 (25.9%)	8074 (16.9%)	8643 (17.3%)
Cigarettes pack years			
Median (IQR[a])	18 (27.3)	11.25 (21.4)	11.8 (21.5)
Drinking alcohol[b]			
Never	2082 (94.9%)	46,163 (96.7%)	48,245 (96.6%)
Ever	113 (5.1%)	1590 (3.3%)	1703 (3.4%)

[a]BMI: body mass index, Q1, Q2, Q3, Q4: quartiles, IQR=Interquartile range. [b]Statistically significant difference between cases and non-cases, assessed by t-test for continuous variables and chi-square test for categorical variables (P-value < 0.001).

Table 1: **Baseline characteristics of the study population.**

than one third [35% (26%–45%)] of opium-related cancers were attributable to using opium (Table 2). Detailed estimates for the PAF of opium consumption for each cancer site are provided in Supplementary Table S5.

The estimated PAFs for opium consumption were higher among males than females (all cancers: 8% vs. 2%, opium-related cancers: 43% vs. 8%, and smoking-related cancers: 9% vs. 2%) (Table 2). Also, compared to never smokers, ever smokers had higher PAFs for opium consumption (all cancers: 12% vs. 2%, opium-related cancers: 39% vs. 14%, and smoking-related cancers: 12% vs. 2%) (Table 3). Similar estimates were observed when we excluded cancer cases that did not have histological confirmation (Supplementary Table S6), and after dropping the first 2 years of follow-up (Supplementary Table S7).

Fraction of cancers related to cigarette smoking

Cigarette smoking was frequent among males and rare among females (39% vs. 2%). Participants who smoked cigarettes tended to be more educated, have lower BMI, and more commonly reported using opium and drinking alcohol ($P < 0.001$ for all, Supplementary Table S8). Cigarette smoking was associated with increased risk of developing all cancers combined [HR: 1.49 (1.21–1.83)], opium-related cancers [HR: 2.71 (1.59–4.62)], and smoking-related cancers [HR: 1.53 (1.21–1.94)]. Detailed estimates for the effect of cigarette smoking for each cancer site are provided in Supplementary Table S4. Of the total incident cancers, 8% (95% CI: 5%–11%) were attributable to cigarette smoking, while this proportion was 45% (35%–54%) for opium-related cancers, and 9% (6%–12%) for smoking-related cancers (Table 2). Detailed estimates for the PAF of cigarette smoking for each cancer site are provided in Supplementary Table S5.

The estimated PAFs for cigarette smoking were higher among males than females (all cancers: 12% vs. 2%, opium-related cancers: 54% vs. 8%, and smoking-related cancers: 14% vs. 2%) (Table 2). Also, compared to never opium users, ever opium users had higher PAFs for cigarette smoking (all cancers: 21% vs. 3%, opium-related cancers: 51% vs. 25%, and smoking-related cancers: 22% vs. 4%) (Table 3). Similar estimates were observed when we excluded cancer cases that did not have histological confirmation (Supplementary Table S6), and after dropping the first 2 years of follow-up (Supplementary Table S7).

Fraction of cancers related to joint exposure to opium consumption and cigarette smoking

Of all participants who used opium, 53% reported to also smoke cigarettes, while of all participants who smoked cigarettes, 52% reported to use opium simultaneously (using both opium and cigarettes: n = 4,467, 9% of the full cohort). Effect estimates for the interaction between using opium and smoking cigarettes for different cancer sites are provided in Supplementary Table S9. Given the limited sample size, it was not possible to evaluate the potential interaction between opium use and smoking cigarettes in relation to an increased risk of various cancers. Consequently, instead of calculating the PAFs for each exposure category of opium use and smoking cigarettes interaction, we computed the joint PAFs considering exposure to either opium consumption, or cigarette smoking, or both. PAFs for using opium and/or smoking cigarettes were estimated as 13% (95% CI = 9%–16%) for all cancers combined, 58% (49%–66%) for opium-related cancers, and 15% (11%–18%) for smoking-related cancers (Fig. 1a). Highest joint PAFs belonged to cancers of the larynx [combined PAF = 77% (59%–90%)], pharynx [combined PAF = 76% (47%–100%)], lung [combined PAF = 55% (43%–64%)], and bladder (combined PAF = 50% (28%–67%)] (Fig. 1a).

When we restricted the analyses to the male participants (due to limited number of female smokers), we found exposure to either cigarette smoking or opium consumption or both to contribute to 21% (95% CI: 15%–26%) of all-cancers combined, 72% (62%–80%) of opium-related cancers, and 23% (17%–30%) of smoking-related cancers (Fig. 1b).

The observed estimates for the combined PAFs in the full cohort were comparable after excluding cancer cases without histological confirmation, after dropping the first 2 years of follow-up, and after adding the cumulative pack-years of smoked cigarettes and nokhod-years of consumed opium to the model that was used to calculate the PAF for joint exposure to opium consumption and cigarette smoking (Supplementary Fig. S1). Finally, modelling the main continuous variables in quintiles gave estimates that were comparable to the analyses where these variables were modelled as continuous.

Discussion

Analyzing data from almost 50,000 participants of the Golestan Cohort Study who were followed for an average median of 14 years, showed that 5% of all cancers and 35% of opium-related cancers are attributable to using opium, while 8% of all cancers, and 9% of smoking-related cancers were attributable to smoking cigarettes. We also found that 13% of all cancers, 58% of opium-related cancers, and 15% of smoking-related cancers in this population are attributable to using either opium or smoking cigarettes or both. In this population, among all cancer sites, cancers of the larynx (77%), pharynx (76%), lung (55%), and bladder (50%) had the highest PAFs related to consuming opium and smoking cigarettes. The fraction of cancers that were attributable to using opium were higher among males than females (8% vs. 2%) and among ever cigarette smokers than never smokers (12% vs. 2%). Similarly,

	Males (n = 21,194)		Females (n = 28,754)		Full cohort (n = 49,948)	
	Cases (N)	Opium consumption PAF [95% CI]	Cases (N)	Opium consumption PAF [95% CI]	Cases (N)	Opium consumption PAF [95% CI]
All cancers combined	1189	8% [4%–12%]	1006	2% [0%–4%]	2195	5% [3%–8%]
Opium related cancers [a]	167	43% [32%–54%]	48	8% [−5 to 20%]	215	35% [26%–45%]
Tobacco related cancers [b]	879	9% [4%–15%]	730	2% [0%–5%]	1609	6% [3%–9%]
	Cases (N)	**Cigarettes smoking PAF [95% CI]**	**Cases (N)**	**Cigarettes smoking PAF [95% CI]**	**Cases (N)**	**Cigarettes smoking PAF [95% CI]**
All cancers combined	1189	12% [8%–17%]	1006	2% [1%–4%]	2195	8% [5%–11%]
Opium related cancers [a]	167	54% [43%–66%]	48	8% [0%–17%]	215	45% [35%–54%]
Tobacco related cancers [b]	879	14% [9%–20%]	730	2% [1%–4%]	1609	9% [6%–12%]

N: number, PAF: population attributable fraction. [a]Opium related cancers include cancers of lung, larynx and bladder. [b]Tobacco related cancers include cancers of lung, oral cavity, naso-, oro- and hypopharynx, nasal cavity and sinuses, larynx, esophagus, stomach, pancreas, colorectum, liver, kidney, ureter, urinary bladder, breast, uterine cervix and ovary (mucinous), and myeloid leukemia.

Table 2: **The proportion of all cancers, opium-related cancers, and smoking-related cancers, that are attributable to opium consumption and cigarettes smoking.**

Cancer sites	Opium consumption PAF [95% CI]		Tobacco smoking PAF [95% CI]	
	Ever tobacco smokers (N = 4467)	Never tobacco smokers (N = 3997)	Ever opium users (N = 4467)	Never opium users (N = 4176)
All cancers combined	12% [3%–21%]	2% [−0.4 to 4%]	21% [10%–31%]	3% [1%–5%]
Opium related cancers [a]	39% [22%–56%]	14% [3%–25%]	51% [30%–72%]	25% [14%–36%]
Tobacco related cancers [b]	12% [2%–23%]	2% [−0.3 to 4%]	22% [10%–34%]	4% [1%–6%]

N: number, PAF: population attributable fraction. [a]Opium related cancers include cancers of lung, larynx and bladder. [b]Tobacco related cancers include cancers of lung, oral cavity, naso-, oro- and hypopharynx, nasal cavity and sinuses, larynx, esophagus, stomach, pancreas, colorectum, liver, kidney, ureter, urinary bladder, breast, uterine cervix and ovary (mucinous), and myeloid leukemia.

Table 3: **The proportion of all cancers that are attributable to opium consumption and tobacco smoking, stratified by ever/never tobacco smoking and ever/never opium consumption.**

the fraction of cancers that were attributable to smoking cigarettes were higher among males than females (12% vs. 2%) and among ever opium users than never opium users (21% vs. 3%).

Opium is a highly addictive narcotic drug that is consumed by millions of people, especially among populations concentrated in the Middle East and south-eastern Asia.[2] Common routes for consuming opium include smoking (≈70%) and ingestion (≈30%), and both were identified as carcinogenic to humans by IARC.[2] While in our previous analysis we found opium consumption to be related to a wide range of cancer types,[1] an IARC working group reviewed all evidence and concluded that there is sufficient evidence for the carcinogenicity of opium consumption for cancers of the lung, larynx, and bladder, while there is limited evidence for cancers of the esophagus, stomach, pancreas, and pharynx.[2] Importantly, in populations where opium use is widespread, the epidemiology of cancers appears to differ, with a higher prevalence of opium-related cancers compared to populations where opium use is absent.[26,27] In three separate analyses that used data from two prospective cohorts, Nalini et al. assessed the fraction of all cancer deaths,[10] Mohammadi et al. assessed the fraction of stomach and esophageal cancer deaths,[11] and Sadjadi et al. assessed the fraction of incident stomach cancers, that could be attributable to using opium.[12] The reported PAFs for opium consumption from these 3 studies are similar to our estimated PAF for all cancers (5%–8%). However, our study is the first to assess the contribution of using opium to all cancer types that were classified as causally related to opium. We found that opium consumption plays a major role in the incidence of opium-related cancers in this population, as one third of the incident lung and bladder cancer cases and half of the incident laryngeal cancer cases were attributable to using opium.

Smoking tobacco has been classified as carcinogenic for 20 cancer sites,[3] and continues to be the major driver of the cancer burden worldwide.[5] An estimated 25% of global cancer deaths in 2019 were attributable to tobacco smoking, with large variations across different cancer sites (ranging from 6% for prostate cancer to 64% for lung cancer), and across males and females (35% vs. 10%).[5] Smoking tobacco is less prevalent in low- and middle-income countries (LMICs) than high income countries (HICs).[28] Consequently, a smaller proportion of cancers might be attributed to smoking tobacco in LMICs. Using population-level data, we previously found that smoking tobacco contributes to 14% of incident cancers in the eastern Mediterranean region (26% in males, 3% in females).[29] In the current analysis, 8% of incident cancers were attributable to smoking cigarettes (12% in males, 2% in females). While the lower prevalence of smoking tobacco (particularly among females) in this region may explain the lower tobacco related PAFs in our study, using individual-level data that allowed obtaining PAFs that are adjusted for

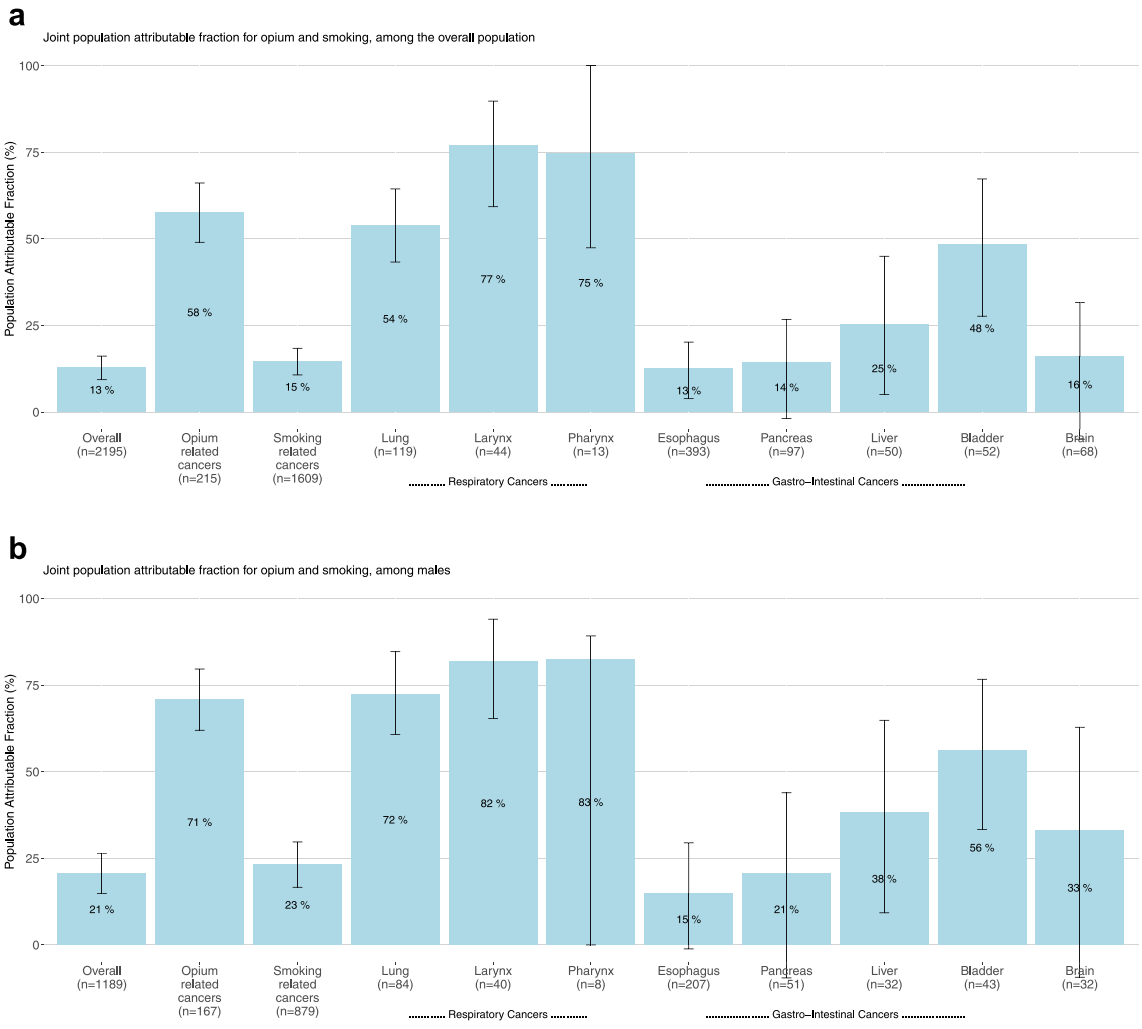

Fig. 1: Joint population attributable fraction of Opium consumption and Tobacco smoking on different cancer site a) in the full cohort b) in the male subgroup.

other confounders and risk factors may have also contributed to having lower estimates than other studies that used population-level data.[29]

Dual use of opium and cigarettes is common in regions where opium is prevalent. The prevalence of ever cigarette smoking among individuals who use opium has been reported to be as high as 50%–70% in most studies.[2] Our study shows that 50%–70% of incident cancers in the lung, larynx, pharynx, and bladder in this population could be attributed to joint use of opium and cigarettes, while 14% of these cancers could be attributed to only using opium and 25% to only smoking cigarettes. Therefore, to decrease the burden of cancers in regions where using opium and cigarette smoking is prevalent, efforts should target decreasing the prevalence of both exposures, rather than focusing on only one agent. Further, while 45% of tobacco related cancers and 22% of opium related cancers in this study occurred among females, only 2%–8% of these cancers were attributable to smoking cigarettes and using opium. Consequently, studies are needed to identify other possible exposures that may drive the burden of cancer among females in this population.

The strengths of this study include its large sample size, long follow-up time with minimum loss, validation of self-reported data on opium consumption and cigarette smoking using urinary biomarkers and being the first study to provide insight on the impact of using opium individually and in combination with smoking cigarettes on the incidence of different cancers. However, this study also has some limitations. The small number of female participants who smoked cigarettes and the small number of participants who developed smoking-related cancer types in this study, may have

resulted in underestimating the impact of smoking cigarettes, particularly among females and never opium users. Thus, these results should be interpreted with caution as they may not be generalized to populations where opium use is rare and smoking tobacco is prevalent among females. In addition, due to the high prevalence of smoking among the male participants, passive smoking may potentially contribute to the burden of smoking-related cancers. However, it's important to note that passive smoking data were not collected in this cohort, which may lead to an underestimation of the smoking-related cancer burden, particularly among the female participants in this study. Due to the few numbers of cases in the tobacco-related cancer types, we could not accurately estimate the PAFs of cigarette smoking for several individual tobacco-related cancer types and larger studies are needed to estimate the burden of cigarette smoking in this population. Finally, the analysis of opium- and tobacco-related cancer sites in this study was conducted based on the latest classifications provided by IARC monographs. Nevertheless, as we previously showed, using opium is associated with increased risks for developing other cancer types such as esophageal and gastric cancers, in this population. Consequently, it is possible that this analysis may have underestimated the impact of opium use on opium-related cancers that have not yet been officially recognized as causally associated with opium by IARC monographs.

In conclusion, using opium and smoking cigarettes account for a large proportion of cancers in this population. To effectively reduce the cancer burden in this region, it is crucial to implement prevention policies that focus on education, enhancing public awareness, and implementing intervention measures to decrease the consumption of both substances. Notably, there has been a long-standing historical acceptance of opium use as a traditional medicine for pain relief and recreational purposes, among certain populations in the Middle East and south-eastern Asia.[9] Therefore, it becomes particularly important to educate the public and raise awareness about the detrimental effects of opium use within these communities.

Contributors

AP, SMD, CCA, PBr, PBo, FK, and RM designed and implemented the Golestan Cohort Study. HP, AP, AS, MK, AG, GR, and MH contributed significantly to data gathering and the follow up process. MS conceptualized this project. KA, VV, FI, SN, KZ, and MS contributed to the methodology and analytical plans. KA conducted the analysis. KA and MS drafted the manuscript. All authors contributed to the interpretation of the study results and critical revision of the manuscript. All authors reviewed the manuscript and approved the final version to be published. MS and RM are guarantors and had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

Data described in the manuscript, data dictionary, and analytic codes will be made available upon request (pending filling an application to access the database of the Golestan Cohort Study (https://dceg2.cancer.gov/gemshare), review and approval by the study principal investigators).

Declaration of interests

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, 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 International Agency for Research on Cancer/World Health Organization.

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102229.

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