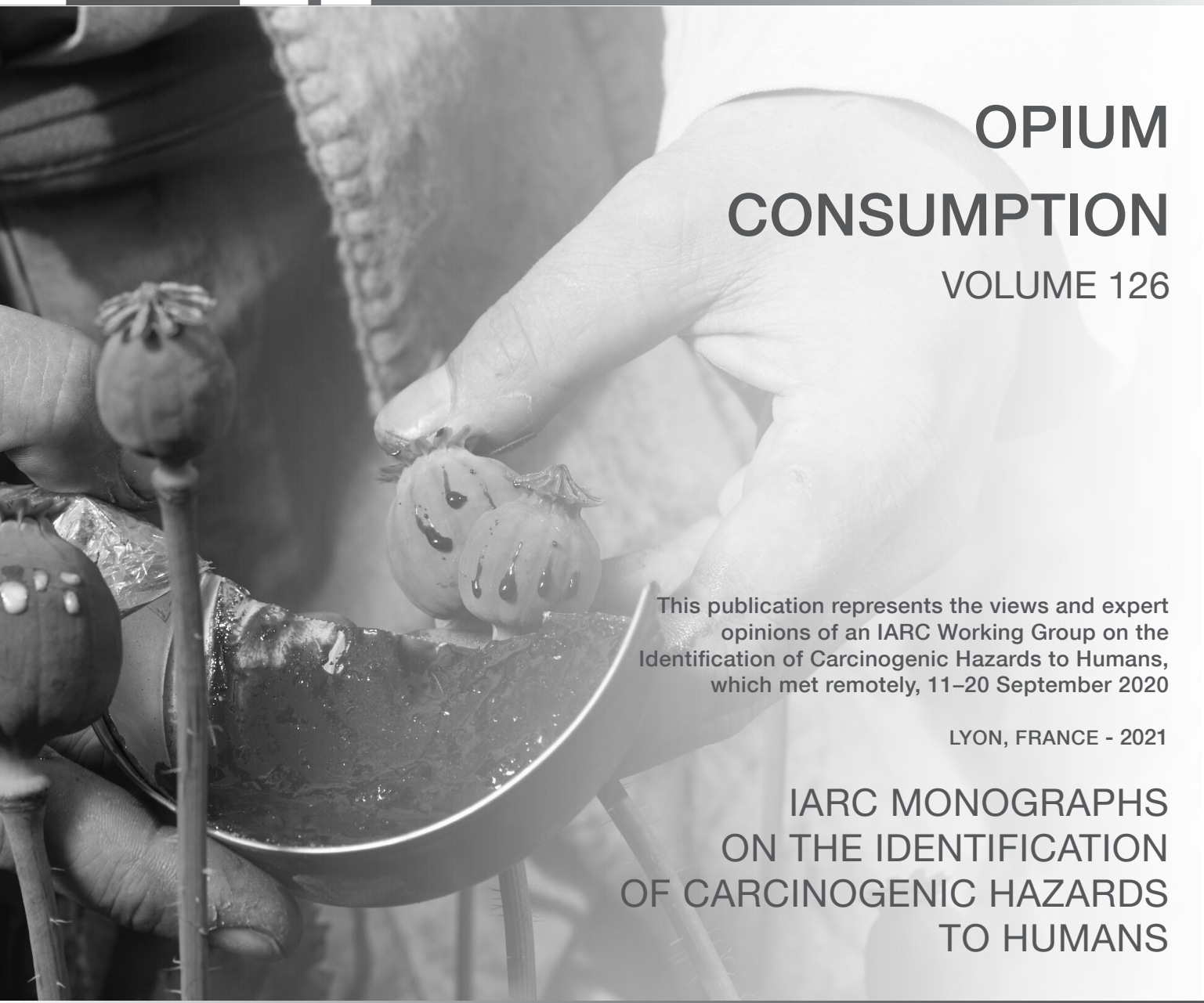
IARC MONOGRAPHS



OPIUM CONSUMPTION

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IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

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2. CANCER IN HUMANS

This section reviews studies of opium consumption in relation to cancer incidence or mortality in humans. The first documented suspicions that opium was a potential carcinogen originate from the Islamic Republic of Iran (hereafter referred to as "Iran") in the 1970s. A potential role for opium consumption in the etiology of oesophageal cancer was suggested on the basis of the results of a 2-year clinical observation study conducted in the Iranian province of Golestan (then, the eastern part of Mazandaran Province; Dowlatshahi et al., 1977; Dowlatshahi & Miller, 1985). Incidence rates of oesophageal squamous cell carcinoma (SCC) were extremely high in Golestan (up to 180 new cases per 100 000 population annually), despite low rates of alcohol consumption and cigarette smoking, the main known risk factors for this cancer. The study reported that 61% of men and 25% of women among 126 patients with documented oesophageal cancer had a 5- to 20-year history of opium addiction antecedent to the onset of their symptoms. In addition, brownish-black particles of burnt opium were noted on the oesophageal mucosa and the odour of the compound was detected during endoscopic examination of these patients (Dowlatshahi et al., 1977; Dowlatshahi & Miller, 1985). In parallel, a potential role for opium consumption in the etiology of urinary bladder cancer was proposed on the basis of observation of a male to female ratio in the Iranian province of Fars that was unusually high (9 : 1) compared with that typically seen (3 : 1) in many other areas of the world (Sadeghi & Behmard, 1978). The researchers were not able to identify any obvious reason(s) for such unusually high ratios, because there were no major factories or dye-production facilities in the area; tobacco-smoking prevalence and intensity were not unusually high among men; and schistosomiasis was virtually non-existent in the area. However, the authors noted that opium consumption was widespread in Fars, with a male to female ratio of 8 : 1 in registered addicts, and speculated that opium consumption played a role in bladder carcinogenesis (Sadeghi & Behmard, 1978).

The findings above led to several case–control or cross-sectional studies being undertaken in the 1970s and 1980s in Golestan (for oesophageal cancer) and Fars (for urinary bladder cancer), as well as in Singapore and Hong Kong Special Administrative Region, China (for laryngeal and lung cancers). They also led to the initiation of a small and limited number of mechanistic and experimental animal studies, primarily led by the International Agency for Research on Cancer (IARC).

Despite initial positive findings, published research on opium consumption ceased in the early 1980s. For studies in Iran, this was due to the sociopolitical changes that happened in 1979.

For the studies in eastern Asia, it is unclear why the research did not continue. [The Working Group considered it possible that the following factors were contributory: declining opium consumption due to changing drug preferences, including access to more potent alternatives such as heroin, and increased law enforcement.]

Epidemiological studies on opium and cancer in humans resumed in the 2000s, and have continued, exclusively in Iran, to the present day. Iran is a unique site for the investigation of opium as a potential human carcinogen because opium consumption is common and is socially tolerated despite being illegal, and there is a strong research infrastructure to support the conduct of epidemiological studies. Since research recommenced, studies have evaluated the role of opium consumption as a potential carcinogen for several organ sites, including the oesophagus, urinary bladder, lung, stomach, colon, pancreas, larynx, and other sites in the head and neck. These studies include one very large and well-conducted cohort study (the Golestan Cohort Study, GCS) undertaken in Golestan Province, and a large, multisite, multicentre case–control study (the Iranian Study of Opium and Cancer, IROPICAN), both of which have contributed evidence for several cancer sites.

An important consideration underlying the body of literature on opium consumption in relation to cancer incidence and mortality in humans is the largely illicit, and therefore unregulated, nature of opium as an agent. Natural variation in the chemical composition of opium occurs in different cultivars of the poppy flower, but may also be influenced by the growing conditions, including the increasing use of fertilizers and pesticides. Contaminants may also be introduced into the product, either intentionally or unintentionally, during the process of turning the poppy latex into a saleable and consumable product. [The Working Group recognized that "street opium" is not a standardized product; that variations in chemical composition are an innate part of the complex nature of the agent; and that the current body of evidence on cancer in humans does not allow the effects of different aspects of the mixture to be disentangled.]

Sections 2.1 to 2.5 summarize all available cohort and case–control studies on opium consumption in humans and form the majority of this section. The text presents a synthesis of the study findings with only the essential details included. More details on the analyses and results are included in the relevant tables. Specifically, for the sake of brevity, confounders are listed in full in the tables but mentioned in the text only when they have particular importance for the evaluation of study quality and informativeness, for example, if age and sex were *not* adjusted for. [The Working Group also noted that socioeconomic status was often adjusted for in the design (matching on neighbourhood of residence), rather than in the analysis, for many of these studies and is therefore often missing from the list of the confounders.] Instances where a matching design has particular importance for the evaluation of study quality and informativeness have been noted in the text.

Annex 2 describes some specific methodological considerations for the evaluation of the human cancer evidence related to opium consumption. While all observational epidemiological studies may present concerns about confounding, selection and information bias, and other sources of bias, the Working Group took the view that there were specific conditions related to consumption of opium that presented particular challenges for the evaluation of potential carcinogenicity. For example, the potential for reverse causation (the consumption of opium as a result of a cancer diagnosis) or protopathic bias (the consumption of opium as a result of prediagnostic symptoms of disease) necessitate consideration of the extent of control for, and impact of, these special sources of bias in observational studies of opium consumption

and cancer. The Working Group considered that an explicit discussion of the potential for, and impact of, these specific sources of bias would aid in the interpretation and synthesis of the evidence and would increase the transparency of the evaluations.

Other information relevant to the Working Group's consideration of bias and confounding more generally, including several directed acyclic graphs, is also outlined in Annex 2.

Finally, Section 2.6 presents the Working Group's synthesis of the body of evidence in relation to cancers at individual organ sites, including cancers of the oesophagus, urinary bladder, lung, larynx, pancreas, stomach, colon and rectum, and pharynx.

2.1 Cancer of the oesophagus

See Table 2.1.

Analyses from one cohort study and three case–control studies investigating the association between opium consumption and oesophageal cancer are presented below. Five descriptive studies, two investigating morphine metabolites in urine and three describing the prevalence of opium consumption among oesophageal cancer cases, were not considered informative by the Working Group and are not discussed further here (Joint Iran-International Agency for Research on Cancer Study Group, 1977; Ghadirian et al., 1985; Islami et al., 2004; Marjani et al., 2010; Hamrah et al., 2017). In studies discussed in this section, the large majority of the cases of oesophageal cancer were SCCs. Therefore, the results presented in this section are most applicable to oesophageal SCC.

2.1.1 Cohort study

Sheikh et al. (2020) is the most recent study arising out of the GCS. The GCS is a large-scale, population-based study that was initially established to explore possible etiological factors for the high rates of oesophageal SCC in the province of Golestan in Iran (Pourshams et al., 2005, 2010). The cohort was established in 2004 and, during 4 years of data collection, recruited 50 045 individuals aged 40–75 years from both rural and urban areas (Pourshams et al., 2010). Participation rates ranged from 50% for men in urban areas to 84% for women in rural areas (Sheikh et al., 2019). Data collection was via a structured questionnaire, the Golestan Cohort Study Questionnaire (GCSQ). Participants were asked about consumption of opium that occurred at least weekly for a minimum of 6 months, including the type of opium consumed (raw, refined, or dross), duration (years), ages started and stopped, frequency (per day), amount (in the local unit called a *nokhod*), and route of consumption (smoking or ingestion). The GCS also collected information on potential confounders including socioeconomic status, cigarette smoking, the use of water pipes to smoke tobacco, and consumption of nass (a tobacco product that is chewed), alcohol, and hot tea. Self-reported information on opium and tobacco consumption was found to be valid and reliable in this population (Abnet et al., 2004; Pourshams et al., 2005). Participants have been followed annually via telephone surveys, home visits, and regular reviews of provincial cancer and death registration data, and loss to follow-up is very low (< 1%) (Sheikh et al., 2019). GCS staff conduct follow-up on self-reports via medical record review or verbal autopsy, with around 90% of self-reported cancer diagnoses confirmed by expert physicians (Sheikh et al., 2019, 2020). Baseline data on exposure variables have not been updated during the follow-up period (Pourshams et al., 2010). [The Working Group noted that the lack of updated data on whether opium users quit during the follow-up period may be less of a concern than the lack of updated data on opium use in the referent population if they began using opium, or used opium more frequently, after baseline data had been collected.] [The Working

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) Golestan Province, Iran (Islamic Republic of) Enrolment, 2004–2008/follow-up, 531 789 person-years (through December 2018; median, 10 yr) Cohort	GCS: 50 045 individuals aged 40–75 yr from rural and urban areas of Golestan Province (50 034 after excluding 11 diagnosed with cancer before enrolment); among them 342 oesophageal cancers (309 histologically confirmed) Exposure assessment method: validated GCSQ assessing complete opium exposure history at baseline including intensity, duration, cumulative exposure, and type and method of exposure; systematic prospective data collection	Oesophagus (mainly SCC), incidence Oesophagus (mainly SCC), incidence Oesophagus (mainly SCC), incidence	Opium use (HR): Never Ever Opium use, men (HR): Never Ever Opium use, women (HR): Never Ever	 249 93 NR NR NR NR	 1 1.38 (1.06–1.80) 1 1.31 (0.94–1.82) 1 1.40 (0.87–2.23)	Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	*Exposure assessment critique*: High-quality, multimetric exposure assessment collected prospectively, with temporal aspects mostly incorporated into estimates. Considers duration, cumulative exposure, and exposure method. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: prospective study; large sample size; minimal missing data; large group of regular opium users; validation of self-reported opium consumption; low prevalence of some confounders. *Limitations*: potential errors in exposure and outcome measurements (although steps taken to minimize such errors); presence of contaminants in opium unaccounted for (may have contributed to carcinogenicity); effects of residual confounding.

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) (cont.)		Oesophagus (mainly SCC), incidence	Cumulative opium use, any route (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never used	NR	1		
			1st quartile (≤ 5 nokhod-years)	NR	1.34 (0.84–2.12)		
			2nd quartile (5.1–21 nokhod-years)	NR	1.18 (0.73–1.91)		
			3rd quartile (21.1–60 nokhod-years)	NR	1.42 (0.90–2.21)		
			4th quartile (> 60 nokhod-years)	NR	1.60 (1.06–2.42)		
			Trend-test *P* value, 0.0099				
		Oesophagus (mainly SCC), incidence	Cumulative opium use, by smoking (HR):				
			Never used	NR	1		
			1st quartile (≤ 4 nokhod-years)	NR	1.34 (0.78–2.31)		
			2nd quartile (4.1–18 nokhod-years)	NR	1.00 (0.54–1.85)		
			3rd quartile (18.1–60 nokhod-years)	NR	1.62 (1.00–2.61)		
			4th quartile (> 60 nokhod-years)	NR	1.79 (1.12–2.86)		
			Trend-test *P* value, 0.0046				

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) (cont.)		Oesophagus (mainly SCC), incidence	Cumulative opium use, by ingestion (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never used	NR	1		
			1st quartile (≤ 9 nokhod-years)	NR	1.34 (0.71–2.54)		
			2nd quartile (9.1–30 nokhod-years)	NR	1.05 (0.51–2.14)		
			3rd quartile (30.1–78 nokhod-years)	NR	1.53 (0.83–2.84)		
			4th quartile (> 78 nokhod-years)	NR	0.91 (0.44–1.87)		
			Trend-test *P* value, 0.527				
		Oesophagus (mainly SCC), incidence	Opium type (HR):				
			Never used opium	249	1		
			Raw opium (*teriak*)	83	1.43 (1.09–1.89)		
			Refined opium (*shireh*)	5	0.92 (0.37–2.26)		
			Burned opium (*sukhteh*)	0	–		
			Heroin	0	–		
			Combination of any of the above	5	1.58 (0.64–3.93)		
		Oesophagus (mainly SCC), incidence	Opium use status (HR):				
			Never used opium	249	1		
			Former user	8	1.05 (0.51–2.16)		
			Current user	85	1.44 (1.09–1.90)		

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) (cont.)		Oesophagus (mainly SCC), incidence	Route of opium use (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/ never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never used	249	1		
			Only smoking	55	1.43 (1.04–1.95)		
			Only ingestion	29	1.20 (0.79–1.82)		
			Both routes	9	1.95 (0.98–3.87)		
		Oesophagus (mainly SCC), incidence	Route of opium use, never-users of tobacco (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, regular alcohol drinking (ever/ never)	
			Never used opium	NR	1		
			Only opium smoking	NR	1.58 (1.08–2.30)		
			Only opium ingestion	NR	0.90 (0.47–1.69)		
			Both routes	NR	2.34 (0.86–6.31)		
		Oesophagus (mainly SCC), incidence	Route of opium use, ever-users of tobacco (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never used opium	NR	1		
			Only opium smoking	NR	1.19 (0.69–2.07)		
			Only opium ingestion	NR	1.57 (0.85–2.89)		
			Both routes	NR	1.69 (0.64–4.46)		

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) (cont.)		Oesophagus (mainly SCC), incidence	Individual and combined effects of opium and tobacco (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, regular alcohol drinking (ever/ never)	
			Used neither opium nor tobacco	220	1		
			Used opium but not tobacco	46	1.41 (1.02–1.96)		
			Used tobacco but not opium	29	1.07 (0.71–1.62)		
			Used both opium and tobacco	47	1.51 (1.07–[2.14][a])		
		Oesophagus (mainly SCC), incidence	Opium use, lower SES (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), cigarette smoking (ever/ never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	NR	1		
			Ever	NR	1.28 (0.93–1.76)		
		Oesophagus (mainly SCC), incidence	Opium use, higher SES (HR):				
			Never	NR	1		
			Ever	NR	1.80 (1.07–3.01)		

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) (cont.)		Oesophagus (mainly SCC), incidence	Opium use, histologically confirmed cases (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/ never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	224	1		
			Ever	85	1.43 (1.08–1.90)		
		Oesophagus (mainly SCC), incidence	Opium use, excluding first 2 yr of follow-up (HR):				
			Never	199	1		
			Ever	77	1.52 (1.13–2.04)		

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Khademi et al. (2012) Golestan Province, Iran (Islamic Republic of) Enrolment, 2004–2008/follow-up, 234 928 person-years (through May 2011; median, 4.7 yr) Cohort	GCS: 50 045 participants; prospective population-based cohort of Golestan population aged 40–75 yr Exposure assessment method: validated GCSQ assessing complete opium exposure history at baseline including intensity, duration, cumulative exposure, and type and method of exposure; systematic prospective data collection	Oesophagus, mortality Oesophagus, mortality	Opium use, men (HR) Never Ever Opium use, women (HR): Never Ever	 NR NR NR NR	 1 1.12 (0.62–2.04) 1 2.40 (1.13–5.10)	Age, ethnicity (Turkman/ non-Turkman), education (illiterate/up to 8 yr/high school/ university), marital status (married/ single/widow or widower/ divorced or other), residence (rural/ urban), cigarette smoking (ever/ never)	*Exposure assessment critique*: High-quality, multimetric exposure assessment collected prospectively, with temporal aspects mostly incorporated into estimates. Considers duration, cumulative exposure, and exposure method. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: prospective design; large sample size; extensive data collection for the exposure of interest (opium) and potential confounders; blinded evaluation of outcome. *Limitations*: small number of deaths among participants who ingested opium (vs smoking); may also be some degree of misclassification of cause of death, in spite of the validity of the verbal autopsy.

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Malekzadeh et al. (2013) Golestan Province, Iran (Islamic Republic of) Enrolment, 2004–2008/follow-up, through December 2012 (median, 6.3 yr) Cohort	GCS: 50 045 participants; prospective population-based cohort of Golestan population aged 40–75 yr Exposure assessment method: validated GCSQ assessing complete opium exposure history at baseline including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic prospective data collection	Oesophagus, mortality	Opium use (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), cigarette smoking (ever/ never), alcohol consumption (ever/never), HBV infection	*Exposure assessment critique*: High-quality, multimetric exposure assessment collected prospectively with temporal aspects mostly incorporated into estimates. Considers duration, cumulative exposure, and exposure method. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: prospective design; large sample size; extensive data collection for the exposure of interest (opium) and potential confounders; blinded evaluation of outcome. *Limitations*: small number of deaths among participants who ingested opium (vs smoking); may be also some degree of misclassification of cause of death, in spite of the validity of the verbal autopsy.
			Never	NR	1		
			Ever	NR	1.55 (1.02–2.34)		
		Oesophagus, mortality	Opium use, excluding deaths in first 12 mo (HR):				
			Never	NR	1		
			Ever	NR	1.54 (0.99–2.38)		
		Oesophagus, mortality	Opium use, excluding participants who started using opium after disease diagnosis (HR):				
			Never	NR	1		
			Ever	NR	1.69 (1.11–2.56)		

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Shakeri et al. (2012) Golestan Province, Iran (Islamic Republic of) Hospital study (March 2002 to November 2003) Case–control	Cases: 130 pathology-proven cases identified at Atrak Clinic in Khatam Hospital, Gonbad City Controls: 260 hospital-based controls; inpatients (without diseases thought to be related to tobacco use, alcohol consumption, or diet) individually matched on age and sex Exposure assessment method: validated GCSQ assessing complete opium exposure history including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic retrospective data collection	Oesophagus (SCC), incidence	Opium use (OR):			Age, sex, cigarette smoking, nass, hookah, ethnicity (Turkman/ non-Turkman), education, place of residence (urban/ rural)	*Exposure assessment critique*: Well-defined and well-characterized opium exposure, but timing of opium use relative to outcome not considered. Exposure data collection after case identification. Exposure frequency (per day), and type and method of exposure. Risk analysed by ever/never, intensity as daily frequency of use, duration in years. No exposure lagging. *Other comments*: the standardized prevalence of opium consumption was 17%, 16%, and 23%, respectively, in the GCS, neighbourhood-based controls, and hospital-based controls in this study. *Strengths*: two methods of control selection; information on potential covariates; cancer cases confirmed by biopsy; high participation rates of the controls; steps taken to minimize interviewer bias. *Limitations*: small sample size; possible biases in controls; no information on tea/fruit/vegetable consumption.
			Never	85	1		
			Ever	45	1.09 (0.63–1.87)		
		Oesophagus (SCC), incidence	Duration of opium use (OR):				
			Never	85	1		
			≤ Median duration of use among controls	27	1.48 (0.78–2.81)		
			> Median duration of use among controls	18	0.73 (0.35–1.51)		
		Oesophagus (SCC), incidence	Age started opium use (OR):				
			Never	85	1		
			> Median age started among controls	26	1.07 (0.54–2.10)		
			≤ Median age started among controls	19	1.11 (0.55–2.27)		

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Shakeri et al. (2012) Golestan Province, Iran (Islamic Republic of) Neighbourhood study (December 2004 to June 2007) Case–control	Cases: 300 pathologically confirmed cases identified at Atrak Clinic in Khatam Hospital, Gonbad City Controls: 571 neighbourhood controls individually matched on place of residence, age, and sex Exposure assessment method: validated GCSQ assessing complete opium exposure history including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic retrospective data collection	Oesophagus (SCC), incidence	Opium use (OR):			Age, sex, cigarette smoking, nass, hookah, ethnicity (Turkman/ non-Turkman), education, place of residence (urban/ rural)	*Exposure assessment critique*: Opium exposure well defined and well characterized, but timing of opium use relative to outcome not considered. Exposure data collection after case identification. Exposure frequency (per day), and type and method of exposure. Risk analysed by ever/never, intensity as daily frequency of use, duration in years. No exposure lagging. *Other comments*: the standardized prevalence of opium consumption was 17%, 16%, and 23%, respectively, in the GCS, neighbourhood-based controls, and hospital-based controls in this study. *Strengths*: two methods of control selection; information on potential covariates; cancer cases confirmed by biopsy. *Limitations*: small sample size; possible biases in controls; no information on tea/fruit/vegetable consumption.
			Never	210	1		
			Ever	90	1.77 (1.17–2.68)		
		Oesophagus (SCC), incidence	Duration of opium use (OR):				
			Never	210	1		
			≤ Median duration of use among controls	34	1.44 (0.84–2.45)		
			> Median duration of use among controls	56	2.12 (1.28–3.50)		
		Oesophagus (SCC), incidence	Age started opium use (OR):				
			Never	210	1		
			> Median age started among controls	41	1.25 (0.71–2.18)		
			≤ Median age started among controls	49	2.32 (1.40–3.82)		

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Nasrollahzadeh et al. (2008) Golestan Province, Iran (Islamic Republic of) December 2003 to June 2007 Case–control	Cases: 300; as for Shakeri et al. (2012) (neighbourhood study) above Controls: 571; as for Shakeri et al. (2012) (neighbourhood study) above Exposure assessment method: validated GCSQ assessing complete opium exposure history including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic retrospective data collection	Oesophagus (SCC), incidence	Opium and tobacco use (OR): Never opium – never tobacco Never opium – ever tobacco Ever opium – never tobacco Ever opium – ever tobacco	 166 43 30 60	 1 1.70 (1.05–2.73) 2.12 (1.21–3.74) 2.35 (1.50–3.67)	Age, sex, residence (urban/ rural), education, ethnicity (Turkman/non-Turkman), total intake of fruit and vegetables	*Exposure assessment critique*: Opium exposure well defined and well characterized, but timing of opium use relative to outcome not considered. Exposure data collection after case identification. Exposure frequency (per day), and type and method of exposure. Risk analysed by ever/never, intensity as daily frequency of use, duration in years. No exposure lagging. *Strengths*: information on potential covariates; cancer cases confirmed by biopsy. *Limitations*: small sample size; possible biases in controls; no information on tea/fruit/vegetable consumption.

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bakhshaee et al. (2017) Mashhad, Iran (Islamic Republic of) 2008–2010 Case–control	Cases: 95 biopsy-confirmed cases of oesophageal SCC from otolaryngology and radiation oncology department at Mashhad University of Medical Sciences Controls: 28 hospital-based healthy controls from otolaryngology and radiation oncology department at Mashhad University of Medical Sciences, with no evidence of head and neck or oesophageal malignancies, matched on age Exposure assessment method: questionnaire; interview collected data on opium use, defined as "snuffing"	Oesophagus (SCC), incidence	Opium dependency (OR): Never Ever	 NR NR	 1 1.44 (0.57–3.62)	Age	*Exposure assessment critique*: Opium exposure well defined but poorly characterized. Timing of opium use relative to outcome unclear. Information on intensity, duration, and type of opium exposure not collected. Only "snuffing" (presumed to be smoking) use is described. Not clear how systematic the interview was. Limited details and exposure information. Unexposed referent group could include exposed. Exposure data collection after case identification. No exposure lagging. *Other comments*: cigarette smoking was inversely associated with risk of oesophageal cancer. *Strengths*: biopsy-confirmed cases. *Limitations*: controls were selected from the otolaryngology and radiation oncology department; only opium consumption by snuffing was assessed; limited information in the methods and results to allow critical review by the Working Group.

Table 2.1 Cohort and case–control studies on opium consumption and cancer of the oesophagus (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Pournaghi et al. (2019) North Khorasan, Iran (Islamic Republic of) 2013–2015 Case–control	Cases: 96 pathologically confirmed cases from cancer registry Controls: 187 hospital-based controls matched on age and sex Exposure assessment method: questionnaire; structured interview of cases and controls	Oesophagus (SCC), incidence	Opium use (OR):			Age, sex	*Exposure assessment critique*: Opium exposure poorly defined and poorly characterized. Exposure data collection after case identification. Considers age at onset, duration, intensity, and exposure method. No exposure lagging. *Other comments*: prevalence of opium use was 45%. *Strengths*: pathologically confirmed cases. *Limitations*: high prevalence of drug use (45%) may indicate some selection bias; minimal adjustment for possible confounding.
			Never used	42	1		
			Current use	51	2.1 (1.2–3.5)		
			Previous use	3	0.6 (0.1–2.2)		
		Oesophagus (SCC), incidence	Consumption methods (OR):				
			Never used	42	1		
			Inhaler	42	2.3 (1.3–3.9)		
			Eating [ingestion]	12	1.2 (0.5–2.8)		
		Oesophagus (SCC), incidence	Age at onset of opium use (OR):				
			Never used	45	1		
			< 30 yr	9	1.3 (0.5–3.1)		
			30–50 yr	24	2.8 (1.4–5.6)		
			≥ 50 yr	18	2.5 (1.2–5.1)		
		Oesophagus (SCC), incidence	Duration of opium use (OR):				
			Never used	45	1		
			< 10 yr	27	2.2 (1.2–4.2)		
			10–20 yr	15	1.6 (0.8–3.5)		
			20–30 yr	6	7.8 (1.5–40.1)		
			≥ 30 yr	3	0.5 (0.1–2.03)		
		Oesophagus (SCC), incidence	Daily opium consumption (OR):				
			Never consumed	45	1		
			≤ 1 time per day	9	0.8 (0.3–2.01)		
			1–3 times per day	30	2.8 (1.5–5.2)		
			≥ 3 times per day	12	2.4 (1.03–5.7)		

–, risk estimate could not be calculated; CI, confidence interval; GCS, Golestan Cohort Study; GCSQ, Golestan Cohort Study Questionnaire; HBV, hepatitis B virus; HR, hazard ratio; mo, month; NR, not reported; OR, odds ratio; SCC, squamous cell carcinoma; SES, socioeconomic status; vs, versus; yr, year.

[a] This value was incorrectly reported in the original publication as 1.14, but was verified by the Secretariat with the authors (Sheikh et al., 2020).

Group noted that the strengths of the GCS include the large study size with minimal loss to follow-up; the collection of detailed information on exposure; the collection of data for multiple possible confounders, including multiple forms of tobacco use; and the use of a reliable and valid questionnaire (validated against the presence of opium metabolites in urine). A limitation of the study was that the definition of opium exposure allows some exposed individuals to be classified as never-users.]

Sheikh et al. (2020) investigated associations with regular opium use in 342 cases of oesophageal cancer, the majority of which (over 90%) were histologically confirmed as SCC. Overall, a hazard ratio (HR) of 1.38 (95% confidence interval, CI, 1.06–1.80) for ever-use of opium compared with never-use was observed for oesophageal cancer incidence, adjusting for a range of factors including cigarette smoking (status and pack-years) and regular alcohol use. Results were similar with further adjustment for chewing nass, using a water pipe, household fuel type, and diet, and similar, but less precise, when stratified by sex (HR for men, 1.31; 95% CI, 0.94–1.82; HR for women, 1.40; 95% CI, 0.87–2.23). There was also a positive trend with increasing quartiles of cumulative opium consumption by smoking (P = 0.0046; HR, 1.79; 95% CI, 1.12–2.86 in the highest consumption quartile) but not by ingestion (P = 0.527). Regarding opium type, the majority of users consumed raw opium (*teriak*), for which the hazard ratio was 1.43 (95% CI, 1.09–1.89) compared with never-users, whereas results for other opium types were based on smaller numbers of users. Results were also stronger for current (HR, 1.44; 95% CI, 1.09–1.90) than for former (HR, 1.05; 95% CI, 0.51–2.16) opium consumption (as measured at baseline). [The Working Group noted that cessation of opium use appears to reduce the risk of oesophageal cancer for former users compared with current users (as measured at baseline). No information on the length of cessation among former users at baseline was provided.] Among tobacco never-users, the adjusted hazard ratio for oesophageal cancer in opium users (compared with never-users) was higher than that for the overall study population, although the confidence intervals widened slightly (HR, 1.41; 95% CI, 1.02–1.96). The evidence for an interaction between opium use (ever or never) and either socioeconomic status (P for interaction, 0.236) or sex (P for interaction, 0.481) was not strong. Findings were similar, but somewhat stronger, upon the exclusion of cases without histological confirmation (HR, 1.43; 95% CI, 1.08–1.90) as well as exclusion of the first 2 years of follow-up (HR, 1.52; 95% CI, 1.13–2.04).

[The strengths of this study, beyond those already stated for the GCS, include the sensitivity analysis and the sex-specific analysis, given the lower prevalence of opium consumption among women than men.] Previous analyses of oesophageal cancer in the GCS have reported similar findings for both cancer incidence (Sheikh et al., 2019) and mortality (Malekzadeh et al., 2013), including among women (Khademi et al., 2012).

2.1.2 Case–control studies

Shakeri et al. (2012) reported the results of two related case–control studies conducted in Golestan Province, Iran; one included 130 cases of oesophageal SCC and 260 hospital-based controls (inpatients with diseases unrelated to tobacco, alcohol, or diet), and the other included 300 cases of oesophageal SCC and 571 neighbourhood-based controls. Case definition and selection were the same for both studies. The neighbourhood control study reported elevated adjusted odds ratios (ORs) for opium use compared with never-use (adjusted OR, 1.77; 95% CI, 1.17–2.68), as well as increasing effects with increasing duration of use and with decreasing age of start of use. However, the effect estimates for the hospital-based control study were not as large as the neighbourhood-based

study (adjusted OR, 1.09; 95% CI, 0.63–1.87), and did not show consistent increases with duration or earlier age at which consumption started. The prevalence of opium smoking was similar in cases and hospital-based controls (cases, 30–35%; hospital controls, 28%), and higher than in neighbourhood controls (18%). [The Working Group noted that the prevalence of opium consumption differed in the two control groups. The lower prevalence of opium consumption in the neighbourhood controls may be an indicator of under-reporting of opium use in this group; however, the prevalence was generally consistent with prevalence estimates from other sources in this region (Pourshams et al., 2005; Shakeri et al., 2013). The similarly elevated prevalence of consumption in both cases and hospital controls, compared with the neighbourhood controls, may have been the result of similar biases or artefacts of data collection operating in both these groups. For example, recent opium consumption as a method of pain relief for underlying health conditions could inflate the prevalence of opium consumption for cases and for hospital-based controls. In addition, recall bias could similarly affect both cases and hospital controls. Hospital controls were mainly admitted for elective surgery (73%) or trauma (21%), or by the internal medicine department (6%). These biases and artefacts would tend to bias the results from the study with hospital-based controls towards the null, and the results from the study with neighbourhood-based controls away from the null (reverse causation). Consequently, the neighbour-control results for the categories of longer duration of use (greater than the median) and younger age of start of use (less than or equal to the median) may be less likely to be biased due to the effects of reverse causation.] The study with neighbourhood controls reported an increase in risk of more than 2-fold for the categories of longer duration of use (greater than the median) and younger age of start of use (less than or equal to the median). [The Working Group noted that the median duration of use and median age started were not reported in the paper. A strength of this study was the adjustment for multiple possible confounders, including multiple forms of tobacco use.]

Two papers have presented additional analyses of the neighbourhood-based control case–control study described in Shakeri et al. (2012). Nasrollahzadeh et al. (2008) reported a 2-fold increase in risk among opium users who did not use tobacco. Abedi-Ardekani et al. (2011) reported a high ratio of *TP53* mutations among oesophageal SCC cases, with 84.2% of the mutations detected in exons 5–8, although the mutation pattern was not observed to differ with opium use.

Bakhshaee et al. (2017) reported an elevated age-adjusted odds ratio (OR, 1.44; 95% CI, 0.57–3.62) for the association between opium dependency and oesophageal cancer (SCC) in a study of 95 cases and 28 controls (as per the methodology description; however, the abstract indicated 98 cases and 27 controls) in Mashhad, Iran. Controls were described as healthy individuals selected from the otolaryngology and radiation oncology department of the same hospital as the cases. The study collected data via "comprehensive interview" but did not present the demographic characteristics of the participants, did not adequately assess opium exposure, and did not further adjust for potential confounders in the analysis. [The Working Group noted that the limited reporting of the methods and results hampered critical review. Moreover, the small sample size, the control selection, and the lack of adjustment in these results, particularly for tobacco use, may have contributed to biased estimates.]

Pournaghi et al. (2019) described a hospital-based case–control study of 96 cases and 187 controls from North Khorasan, Iran. They reported elevated age- and sex-adjusted odds ratios for association between oesophageal cancer SCC and opium consumption,

including for current use, smoking as the mode of consumption, later age at first use, and higher frequency of consumption. The results were not further adjusted for potential confounders, such as tobacco consumption. The prevalence of tobacco consumption was reported to be around 23% (and similar in cases and controls). [The Working Group noted that the lack of adjustment for potential confounding in these results, particularly for tobacco use, may have biased estimates away from the null.] Exposure assessment in this study was by structured interview. The study reported a high prevalence of opium use in the study population (overall, 45%; cases, 56%; controls, 41%). [The Working Group noted that limited details were provided in the paper to allow critical review of the assessment of exposure. Both cases and controls in a hospital-based setting may have recently consumed opium as a method of pain relief for underlying health conditions, and this may explain the high prevalence of opium use in this study.]

2.2 Cancer of the urinary bladder

See Table 2.2.

Results from a systematic review and meta-analysis (Afshari et al., 2017), one cohort study (Sheikh et al., 2020), and eight case–control studies (Sadeghi et al., 1979; Asgari et al., 2004; Hosseini et al., 2010; Shakhssalim et al., 2010; Akbari et al., 2015; Aliramaji et al., 2015; Ghadimi et al., 2015; Lotfi et al., 2016) were evaluated to draw inferences on the association between opium exposure and risk of urinary bladder cancer. A total of eight studies were excluded on the basis of the study design (cross-sectional or case series) or a lack of information on the analysis, population characteristics, and/or exposure to opium (Behmard et al., 1981; Tootoonchi et al., 2000; Ghavam-Nasiri et al., 2002; Ketabchi et al., 2005; Mohseni et al., 2005; Nourbakhsh et al., 2006; Salehi et al., 2011; Karbakhsh et al., 2013).

2.2.1 Systematic reviews

Kamangar et al. described the characteristics and outcomes of seven primary studies on the association between opium exposure and bladder cancer published between 1979 and 2010 (Kamangar et al., 2014); however, an updated systematic review and meta-analysis that included these studies summarized the evidence and estimated a meta-risk using a fixed effects model (Afshari et al., 2017). A pooled odds ratio of 3.9 (95% CI, 3.1–5.1) was reported for opium use adjusted for other potential confounders including cigarette smoking, while the pooled unadjusted odds ratio was 3.40 (95% CI, 1.60–7.21) for 34 cases exposed only to opium (Afshari et al., 2017). [The Working Group noted that these odds ratios may not be meaningful as this result was based on five studies presenting methodological limitations and because of the heterogeneity in the definition of the comparison groups between studies. Control selection, adjustment for confounding, and a clear definition of exposure were among the limitations of several of these studies. Nevertheless, the Working Group noted that all study risk estimates pointed towards an increased risk of bladder cancer associated with opium exposure.]

2.2.2 Cohort study

Sheikh et al. recently published results for the incidence of urinary bladder cancer from the GCS; see the detailed description of the GCS in Section 2.1 (Sheikh et al., 2020). Of the 47 cases of bladder cancer, 43 were histologically confirmed. Hazard ratios were estimated by Cox regression analyses, with adjustment for a range of factors including cigarette smoking (status and pack-years). The fully adjusted hazard ratio was 2.86 (95% CI, 1.47–5.55) for ever-users compared with never-users, the hazard ratio was 3.36 (95% CI, 1.74–6.50) for current users (as measured at baseline), and there was a positive trend in

Table 2.2 Cohort and case–control studies on opium consumption and cancer of the urinary bladder

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) Golestan Province, Iran (Islamic Republic of) Enrolment, 2004–2008/follow-up, 531 789 person-years (through December 2018; median, 10 yr) Cohort	GCS: 50 045 individuals aged 40–75 yr from both rural and urban areas of Golestan Province (50 034 after excluding 11 diagnosed with cancer before enrolment); among them 47 bladder cancers (43 histologically confirmed) Exposure assessment method: validated GCSQ assessing complete opium exposure history at baseline including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic prospective data collection	Urinary bladder, incidence	Opium use (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	*Exposure assessment critique*: High-quality, multimetric exposure assessment collected prospectively with temporal aspects mostly incorporated into estimates. Considers duration, cumulative exposure, and exposure method. Potential for non-differential measurement error. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: selection of the population; detailed exposure assessment and validation of exposure with urine testing; the temporality of the effect; extensive statistical and sensitivity analysis conducted. *Limitations*: relatively small sample size; unclear whether opium exposure was collected during follow-up.
			Never	24	1		
			Ever	23	2.86 (1.47–5.55)		
		Urinary bladder, incidence	Opium use status (HR):				
			Never	24	1		
			Former	0	–		
			Current	23	3.36 (1.74–6.50)		
		Urinary bladder, incidence	Cumulative opium use (HR):				
			0 (never used)	24	1		
			≤ 5 nokhod-years	NR	3.24 (1.28–8.20)		
			5.1–21 nokhod-years	NR	0.55 (0.07–4.21)		
			21.1–60 nokhod-years	NR	3.31 (1.27–8.59)		
			> 60 nokhod-years	NR	4.28 (1.81–10.15)		
			Trend-test *P* value, 0.0009				

Table 2.2 Cohort and case–control studies on opium consumption and cancer of the urinary bladder (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) (cont.)		Urinary bladder, incidence	Opium use, men (HR):			Age, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	NR	1		
			Ever	NR	2.57 (1.23–5.37)		
		Urinary bladder, incidence	Opium use, women (HR):				
			Never	NR	1		
			Ever	NR	4.10 (1.03–16.22)		
		Urinary bladder, incidence	Route of opium use (HR):				
			Never used opium	24	1		
			Only by smoking	13	2.56 (1.21–5.40)		
			Only by ingesting	9	3.79 (1.61–8.88)		
			Both routes	1	1.66 (0.21–13.02)		
		Urinary bladder, incidence	Individual and combined effects of opium and tobacco (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, regular alcohol drinking (ever/never)	
			Used neither opium nor tobacco	17	1		
			Used opium but not tobacco	9	3.74 (1.63–8.59)		
			Used tobacco but not opium	7	2.03 (0.78–5.27)		
			Used both opium and tobacco	14	4.21 (1.87–9.46)		

Table 2.2 Cohort and case–control studies on opium consumption and cancer of the urinary bladder (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sadeghi et al. (1979) Shiraz, Fars Province, Iran (Islamic Republic of) 1969–1976 Case–control	Cases: 99 histologically confirmed cases with diagnosis of bladder carcinoma Controls: 99 controls individually matched on age (± 5 yr) and sex Exposure assessment method: opium exposure data were from patient records and reported as verified for controls but no details on how this was done	Urinary bladder, incidence	Opium and cigarette use, men and women combined (OR):			Age, sex	*Exposure assessment critique*: Opium exposure poorly defined and poorly characterized, and timing of opium use relative to outcome not considered. Exposure data collection after case identification. No analyses by intensity or duration of use, or type of opium. Exposure was likely by smoking and/or ingesting. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: opium and smoking combined estimates provided. *Limitations*: small sample size; exposure assessment from clinical records. *Other comments*: almost all opium users were also cigarette smokers, consequently the OR CI for opium use among non-cigarette smokers was quite wide; ORs presented here are relative to non-users of both opium and cigarettes.
			Never opium, never cigarette	24	1		
			Never opium, ever cigarette	30	[1.6 (0.8–3.1)]		
			Ever opium, never cigarette	2	[4.3 (0.4–49.2)]		
			Ever opium, ever cigarette	43	[13.1 (5.1–33.2)]		
		Urinary bladder, incidence	Opium and cigarette use, men only (OR):			Age	
			Never opium, never cigarette	17	1		
			Never opium, ever cigarette	27	[2.1 (1.0–4.4)]		
			Ever opium, never cigarette	1	[2.7 (0.2–45.7)]		
			Ever opium, ever cigarette	43	[19.4 (7.0–53.7)]		

Table 2.2 Cohort and case–control studies on opium consumption and cancer of the urinary bladder (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Asgari et al. (2004) Tehran, Iran (Islamic Republic of) 1997–2000 Case–control	Cases: 52 hospital cases of men with pathological diagnosis of bladder cancer; undergone surgery Controls: 108 men in hospital with diagnosis of BPH; undergone surgery Exposure assessment method: data on duration of opium consumption was taken from patients' records	Urinary bladder, incidence	Opium use (OR):			Cigarette smoking	*Exposure assessment critique*: Opium exposure poorly defined and poorly characterized, and timing of opium use relative to outcome not considered. Exposure data could have been before case identification. No data on intensity, type, or method of opium exposure. Unexposed referent group could include exposed. No exposure lagging. *Other comments*: cigarette smoking-adjusted result reported in Kamangar et al. (2014). One of the first studies that reported an association between opium exposure and bladder cancer risk. *Limitations*: small sample size; poor and retrospective exposure assessment from patient's records; controls with BPH; minimally adjusted risk estimates.
			Never	39	1		
			Ever	13	2.6 (0.8–8.5)		
		Urinary bladder, incidence	Opium use, cigarette smokers (OR):			None	
			Never opium	24	[1]		
			Ever opium	12	[2.0 (0.6–6.6)]		
		Urinary bladder, incidence	Opium and cigarette use (OR):			None	
			Never opium – never cigarette	15	[1]		
			Never opium – ever cigarette	24	[6.6 (3.0–14.9)]		
			Ever opium – never cigarette	1	–		
			Ever opium – ever cigarette	12	[13.3 (4.1–43.2)]		

Table 2.2 Cohort and case–control studies on opium consumption and cancer of the urinary bladder (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hosseini et al. (2010) Tehran, Iran (Islamic Republic of) 2004–2008 Case–control	Cases: 179 consecutively recruited, histologically confirmed, incident cases of TCC of the bladder. Controls: 179 hospital-based controls recruited from those who were seeking health care and assumed to be cancer-free if urine cytology, cystoscopy, and bladder biopsy did not reveal evidence of bladder cancer; frequency-matched on sex, geographical origin, age (± 5 yr), ethnicity, and smoking history	Urinary bladder (TCC), incidence	Opiate use (OR):			Age, sex, geographical origin, ethnicity, smoking status (never/ever/former), family history of cancer	*Exposure assessment critique*: Opiate exposure well defined and moderately characterized. Timing of opium use relative to outcome not considered. Exposure data collection after case identification. No data on intensity of opium exposure. Only raw opium and opiates discussed, heroin was included in many analyses. Method of exposure to opium categorized but includes injection, which is unlikely (except for heroin). Unexposed referent group could include exposed. No exposure lagging. *Other comments*: it is unclear whether the identical CIs for men and/or women are correct.
			Never	119	1		
			Ever	60	4.60 (3.53–6.28)		
		Urinary bladder (TCC), incidence	Type of opiate (OR):				
			Never used opiates	119	1		
			Codeine	8	2.12 (1.22–3.32)		
			Raw opium	37	4.16 (2.62–6.34)		
			Heroin	15	6.16 (4.24–8.22)		
		Urinary bladder (TCC), incidence	Route of administration (OR):				
			Never used opiates	119	1		
			Smoking	20	3.80 (2.74–5.48)		
			Snorting	13	3.86 (2.57–5.36)		
			Ingestion	7	4.10 (3.22–6.22)		
			Both smoking or snorting and ingestion	6	4.88 (3.54–6.76)		
			Injection	9	5.72 (3.44–7.24)		

Table 2.2 Cohort and case–control studies on opium consumption and cancer of the urinary bladder (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hosseini et al. (2010) (cont.)	Exposure assessment method: questionnaire; retrospective data from an interview including smoking history; opiate exposure duration collected; opiate abuse and dependency categorized from DSM-IV and urine analysis	Urinary bladder (TCC), incidence	Opiate consumption, men (OR):			Age, geographical origin, ethnicity, smoking status (never/ever/former), family history of cancer	*Strengths:* validated questionnaires with urine tests; risk models adjusted for potential confounders; stratified analysis by sex, age, tobacco-smoking status and pack-years, type of opium/opiates, and routes of administration. *Limitations:* controls may suffer from selection bias (86% men with BPH and 84% women with urinary symptoms); risk estimates based on small numbers in the control group; consumption of opiates (codeine, heroin) cannot be ruled out.
			Non-addicts	95	1		
			Addicts	48	5.10 (3.54–5.88)		
		Urinary bladder (TCC), incidence	Opiate consumption, women (OR):				
			Non-addicts	24	1		
			Addicts	12	4.10 (3.54–5.88)		
		Urinary bladder (TCC), incidence	Opiate consumption, age ≥ 60 yr (OR):			Sex, geographical origin, ethnicity, smoking status (never/ever/former), family history of cancer	
			Non-addicts	97	1		
			Addicts	29	5.42 (4.12–7.28)		
		Urinary bladder (TCC), incidence	Opiate consumption, age ≤ 60 yr (OR):				
			Non-addicts	22	1		
			Addicts	31	3.8 (2.72–6.12)		
		Urinary bladder (TCC), incidence	Opiate consumption, < 28 pack-years of cigarette smoking (OR):			Age, sex, geographical origin, ethnicity, family history of cancer	
			Non-addicts	17	1		
			Addicts	21	1.8 (1.42–2.62)		
		Urinary bladder (TCC), incidence	Opiate consumption, ≥ 28 pack-years of cigarette smoking (OR):				
			Non-addicts	27	1		
			Addicts	34	6.16 (3.34–8.3)		

Table 2.2 Cohort and case–control studies on opium consumption and cancer of the urinary bladder (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Shakhssalim et al. (2010) Iran (Islamic Republic of) (Tehran, Khorasan, Khoozestan, Isfahan, and East Azarbayjan) 2006 Case–control	Cases: 692 pathologically confirmed, newly registered cases of TCC bladder cancer Controls: 692 population-based controls individually matched on age (± 5 yr), sex, and neighbourhood Exposure assessment method: questionnaire; data from questionnaire by interview; no evidence presented for its reliability or validity; 38% of cases and 23% of controls completed by proxy	Urinary bladder (TCC), incidence Urinary bladder (TCC), incidence Urinary bladder (TCC), incidence	Opium consumption (OR): Never Ever History of opium consumption (OR): Never Ever Current opium consumption (OR): No Yes	 NR NR 20 67 34 85	 1 2.57 (1.55–4.26) 1 3.50 (2.41–8.41) 1 2.88 (1.84–4.50)	Age, sex, neighbourhood, cigarette smoking Age, sex, neighbourhood	*Exposure assessment critique*: Opium exposure poorly defined and poorly characterized, and timing of opium use relative to outcome not considered. High proportion of missing exposure information. Exposure data collection after case identification. No information on intensity, method, or duration of use, or type of opium. Food and occupational exposures examined as co-exposures. Unexposed referent group could include exposed. No exposure lagging. *Other comments*: the definitions and applications of the categories for "current opium consumption" and "history of opium consumption" were unclear. *Strengths*: large population-based case–control study. *Limitations*: unclear whether newly registered cases could include prevalent cases; selection bias towards less aggressive bladder cancer; large proportion of proxy respondents.

Table 2.2 Cohort and case–control studies on opium consumption and cancer of the urinary bladder (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Akbari et al. (2015) Shiraz, Fars Province, Iran (Islamic Republic of) 2012–2013 Case–control	Cases: 198 incident cases identified from cancer registry or hospital records Controls: 396 sex- and age- (± 5 yr) matched neighbourhood controls Exposure assessment method: validated GCSQ assessing complete opium exposure history including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic retrospective data collection For cases, history of opium exposure reported to be taken before diagnosis to "minimize the impact of reverse causality". [However, this seems inconsistent with other descriptions of the exposure assessment in the paper.]	Urinary bladder, incidence	Opium use (OR):			Age, sex, neighbourhood, tobacco use (never/ever), alcohol use (never/ever), dietary variables (red meat, poultry, fish, hydrogenated oil, olive oil, butter intake, fat intake, fruits, nut consumption, and mouldy food)	*Exposure assessment critique*: Opium exposure well defined and well characterized. Systematic data collection after case identification. Opium use defined as ever used, cumulative opium dose known. Type of opium and exposure routes combined. A few heroin users included. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: population-based case–control study; relatively large sample size; detailed exposure assessment; minimized bias and variation due to the interviewer. *Limitations:* no combined opium + smoking risk estimate is provided; reverse causation cannot be ruled out.
			Never	155	1		
			Ever	43	3.9 (1.3–12.0)		
		Urinary bladder, incidence	Amount of daily opium use (OR):				
			Never	155	1		
			≤ Median amount in controls	17	4.4 (0.5–33.5)		
			> Median amount in controls	26	2.4 (0.6–9.4)		
		Urinary bladder, incidence	Duration of opium use (OR):				
			Never	155	1		
			≤ Median duration in controls	17	2.5 (0.5–11.3)		
			> Median duration in controls	26	6.0 (1.1–34.7)		
		Urinary bladder, incidence	Cumulative opium use (OR):				
			Never	155	1		
			≤ Median use in controls, nokhod-years	12	3.3 (0.5–23.1)		
			> Median use in controls, nokhod-years	31	4.9 (1.1–21.9)		

Table 2.2 Cohort and case–control studies on opium consumption and cancer of the urinary bladder (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Aliramaji et al. (2015) Babol, Iran (Islamic Republic of) 2001–2012 Case–control	Cases: 175 patients diagnosed with histologically confirmed bladder cancer who underwent surgery during 2001–2012 in Shahid Beheshti Hospital Controls: 175 controls selected among the patients who underwent ERCP for gallstones in the same hospital and had no tumours and genitourinary problems, and matched to cases by age and sex Exposure assessment method: questionnaire; details from patient records but also telephone calls; data collated with checklist	Urinary bladder, incidence Urinary bladder, incidence	Opium use (> 1 yr) (OR): Never Ever Opium and cigarette use (OR): Never opium – never cigarette Never opium – ever cigarette Ever opium – never cigarette Ever opium – ever cigarette	 117 58 67 50 14 44	 [1] [2.7 (1.6–4.6)] [1] [9.3 (4.5–19.0)] [4.1 (1.6–10.6)] [4.5 (2.5–8.2)]	Age, sex	*Exposure assessment critique*: Opium exposure defined but poorly characterized, and timing of opium use relative to outcome undefined. Opium exposure data could have been collected before case identification. No data on amount or type of opium, or method of exposure. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: relatively large sample size. *Limitations*: poor assessment of opium exposure; risk estimates not provided; minimally adjusted estimates; potential selection bias among cases; relatively low sample size.

Table 2.2 Cohort and case–control studies on opium consumption and cancer of the urinary bladder (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ghadimi et al. (2015) Kurdistan Province, Iran (Islamic Republic of) around 2012–2014 Case–control	Cases: 152 patients with histologically confirmed bladder cancer in the cancer registry system in Kurdistan Province (in the west of the Islamic Republic of Iran) during the past 3 yr Controls: 152 hospital controls; patients referred to a specialized clinic in the same city and hospital, frequency-matched for age (± 5 yr), sex, and place of residency Exposure assessment method: retrospective data from a questionnaire that asked for history of smoking and drug use; 20 yr job history; job titles translated into ISCO codes	Urinary bladder, incidence	Opium use (OR): Never Ever	 136 16	 1 4.96 (1.07–22.92)	Age, sex, place of residency (urban/ rural), smoking status	*Exposure assessment critique*: Opium exposure poorly defined and poorly characterized, and timing of opium use relative to outcome unclear. Exposure data collection after case identification. Opium use undefined, all opium use via smoking. No data on duration, amount, or type of opium exposure. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: relatively large sample size. *Limitations*: unclear from which specialist clinics the controls were recruited, with the potential for selection bias; the exposure assessment was not well described; lack of adjustment for other potential confounders.

Table 2.2 Cohort and case–control studies on opium consumption and cancer of the urinary bladder (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Lotfi et al. (2016) Yazd Province, Iran (Islamic Republic of) 2009–2013 Case–control	Cases: 200 pathologically confirmed cases of bladder cancer Controls: 200 population controls frequency-matched for age (± 2 yr), sex, and residence Exposure assessment method: researcher-designed questionnaire; no evidence presented for its reliability or validity; includes use of hookah but not clear if this is tobacco, opium, or both	Urinary bladder, incidence	Opium use (OR): Never Ever	 147 52	 1 3.01 (1.73–5.23)	Age, sex, residence	*Exposure assessment critique*: Opium exposure poorly defined and poorly characterized, and timing of opium use relative to outcome not considered. Exposure data collection after case identification. No information on intensity or duration of use, type of opium, or method of exposure. No exposure lagging. *Strengths*: population-based; relatively large sample size. *Limitations*: no adjustment for tobacco consumption; information on recent vs distant use of opium was not collected; potential for reverse causation in patients who began using opium to control pain associated with cancer.

–, risk estimate could not be calculated; BPH, benign prostatic hyperplasia; CI, confidence interval; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; ERCP, endoscopic retrograde cholangiopancreatography; GCSQ, Golestan Cohort Study Questionnaire; HR, hazard ratio; ISCO, International Standard Classification of Occupations; NR, not reported; OR, odds ratio; TCC, transitional cell carcinoma; vs, versus; yr, year.

risk of bladder cancer with cumulative exposure (P = 0.0009) with a hazard ratio of 4.28 (95% CI, 1.81–10.15) for the highest quartile of cumulative use (> 60 nokhod-years) compared with never-users. Risk estimates for ever-use of opium tended to be higher among women (HR, 4.10; 95% CI, 1.03–16.22) than men (HR, 2.57; 95% CI, 1.23–5.37), among those who ingested opium (HR, 3.79; 95% CI, 1.61–8.88), and among tobacco never-users (HR, 3.74; 95% CI, 1.63–8.59), although the test for interaction with tobacco was not significant. [The Working Group noted that despite the small number of cases observed in this cohort, there was a consistent positive association between each of the opium exposure-related variables and risk of bladder cancer, as well as a strong monotonic exposure–response relationship with respect to cumulative use of opium. The GCS represents an important improvement over previous case–control studies in terms of the selection of the population, exposure assessment and validation, rigorous study design, temporality of the effect, and the statistical and sensitivity analysis conducted, and the continuing surveillance for further cases in this cohort, which should strengthen the current body of evidence.]

2.2.3 Case–control studies

The eight case–control studies contributing evidence on opium exposure and risk of bladder cancer are described in chronological order below.

Sadeghi et al. (1979) conducted a hospital-based case–control study between 1969 and 1976 in Shiraz, southern Iran. The study included 122 patients with histologically confirmed bladder cancer (23 were excluded because of lack of tobacco information) and 99 age- and sex-matched controls. Opium exposure data were collected from patient records. [The Working Group noted that the very small number of cases and controls exposed to opium but not tobacco, missing data from patient records, and poor statistical analysis performed with inappropriate reference categories made this a less informative study.]

Asgari et al. (2004) conducted a study between 1997 and 2000 in Tehran, Iran. This study included 52 men consecutively diagnosed with pathologically confirmed bladder cancer (case group) and 108 patients with benign prostatic hyperplasia (BPH; control group) who had undergone surgery. [The Working Group noted that BPH has been suggested as a risk factor for bladder cancer. Therefore, the study may suffer from differential misclassification that could have an impact on the risk estimates in both directions.] Data on opium addiction were collected from patients' records. [The Working Group noted that the data on opium exposure were not comprehensive, potentially leading to exposure misclassification.] The unadjusted odds ratio for individuals exposed to both opium and tobacco was 6.2 (95% CI, 2.04–18.7). [The Working Group noted, however, that the results compared users of both cigarettes and opium with a combined group consisting of users of neither, users of just opium, and users of just cigarettes. Using data reported in the paper, compared with those who used neither opium nor cigarettes, the Working Group calculated that the unadjusted odds ratio for cigarette smoking alone was 6.6 (95% CI, 3.0–14.9) and that the odds ratio for both opium use and cigarette smoking was 13.3 (95% CI, 4.1–43.2); however, an odds ratio for opium use alone could not be determined because practically all opium users were also cigarette smokers.] Kamangar et al. (2014) reported an odds ratio for opium use, adjusted only for cigarette smoking, of 2.6 (95% CI, 0.8–8.5) based on data provided in Asgari et al. (2004). [The Working Group noted that although this was one of the first case–control studies published on the risk of bladder cancer associated with opium exposure, the small sample size, poor characterization of exposure to

opium, and poorly conducted statistical analyses made it less informative.]

Hosseini et al. (2010) carried out a hospital-based case–control study between 2004 and 2008 in Tehran, Iran, including 179 consecutive newly diagnosed patients with histologically confirmed transitional cell carcinoma of the bladder and 179 cancer-free controls, matched to cases by age, sex, geographical origin, ethnicity, and smoking status. Controls were recruited from patients under investigation for BPH (86% in men) or urinary symptoms (84% in women). Multivariable logistic regression analysis including smoking history indicated that opiate use was associated with an increased risk of bladder cancer (OR, 4.60; 95% CI, 3.53–6.28). [The Working Group noted that BPH has been suggested as a risk factor for bladder cancer, hence the inclusion of such patients in the control group could result in an underestimation of the risk. However, while urinary symptoms in women may relate to urinary tract infections, also suggested to be a potential risk factor for bladder cancer, it has been suggested that the risk of bladder cancer is inversed when such infections are treated. This could result in overestimation of the risk of bladder cancer associated with opium use.] Participants were also assessed for dependence on and abuse of 13 substance types using the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). Over 60% of those diagnosed as "addicts" were using raw opium, with the remainder using heroin (25%) or codeine (13%). The adjusted odds ratio for raw opium use was 4.16 (95% CI, 2.62–6.34). Results for routes of administration were similarly elevated. [The Working Group noted, however, that the different opiate types (opium, codeine, and heroin) were combined for these analyses and, as such, may be less informative for the evaluation of opium as an independent agent.] Stratified analyses showed that odds ratios for opiate use were slightly higher among men, older (aged > 60 years) participants, and heavy smokers, and were also higher for muscle-invasive bladder cancer and high-grade tumours. [However, again the Working Group noted that the different opiate types were combined for all these stratified analyses and, as such, may be less informative for the evaluation of opium.]

Shakhssalim et al. (2010) conducted a population-based case–control study in 2006 in several provinces of Iran. The study included 692 patients with histologically confirmed transitional cell carcinoma of the bladder and 692 healthy controls who were neighbours of cases, individually matched on sex and age. Cases were identified from the Iranian cancer registry and were alive at study entry [The Working Group noted that by including only patients who were alive, the study may suffer from survival bias. No information on patient survival at entry was provided.] The participation rate was 80%. Opium exposure data were collected during face-to-face interviews using a structured questionnaire. A tobacco smoking-adjusted odds ratio of 2.57 (95% CI, 1.55–4.26) for opium consumption was reported, in addition to non-adjusted odds ratios of 2.88 (95% CI, 1.84–4.50) for current opium consumption and 3.50 (95% CI, 2.41–8.41) for history of opium consumption. [The Working Group noted that the results were difficult to interpret because of the high percentage of cases (> 80%) with missing information on opium exposure compared with 4% of controls. Also, a large proportion of information was provided by proxy responders, and it is unclear whether the variable "history of opium consumption" refers to former users or ever-users.]

Akbari et al. (2015) carried out a population-based case–control study between 2012 and 2013 in Shiraz, southern Iran. The study included 198 patients with bladder cancer, identified mainly on the basis of the results of pathology assessment, and 396 healthy controls matched for age, sex, and residence setting. Opium exposure assessment was done through the structured and validated GCSQ. For analysis, exposure

was characterized in detail including intensity (nokhods per day), duration, cumulative exposure, route of exposure, and type of opium. [The Working Group noted that while the authors stated that the history of opium consumption before cancer diagnosis was obtained to minimize the chances of reverse causation, the lack of a well-defined cut-off period may still have hampered this objective being achieved because opium use to relieve cancer pain could not be excluded.] The study estimated a multivariable-adjusted (including tobacco) odds ratio in opium ever-users of 3.9 (95% CI, 1.3–12.0) for bladder cancer. An exposure–response relationship was reported with an odds ratio of 4.9 (95% CI, 1.1–21.9) for the highest (above the median) consumption category compared with non-use. The duration of consumption also showed an exposure–response relationship with an odds ratio of 6.0 (95% CI, 1.1–34.7) for the longest duration of consumption (above the median). [The Working Group noted that the medians for duration and consumption were not reported in the paper.]

Aliramaji et al. (2015) conducted a hospital-based case–control study between 2001 and 2012 in Babol, northern Iran. The study included 236 patients with histologically confirmed bladder cancer (transitional cell carcinoma, 96%) who underwent surgery; 61 cases (26%) were excluded due to incomplete data. [The Working Group noted that further information on the characteristics of the excluded cases without bladder cancer morphology was not provided.] Controls (n = 175) were sex- and age-matched participants selected from patients with gallbladder stones who sought treatment with endoscopic retrograde cholangiopancreatography in the same hospital. Opium exposure data were collected from the patients' files and telephone calls. [The Working Group noted that opium exposure was poorly defined and its assessment not comprehensive, and that timing of opium use relative to outcome occurrence was not considered. Furthermore, the timing of exposure data in relation to case identification was unclear. No data were included on the intensity, type, or method of opium exposure.] Opium exposure (consumption for > 1 year) was more prevalent among cases (33%) than controls (15%). Using data reported in the paper, compared with those who used neither opium nor cigarettes, the odds ratio for opium use alone was [4.1 (95% CI, 1.6–10.6)], the odds ratio for cigarette smoking alone was [9.3 (95% CI, 4.5–19.0)], and the odds ratio for both opium use and cigarette smoking was [4.5 (95% CI, 2.5–8.2)]. Duration of opium use was positively associated (P = 0.0001) with risk of bladder cancer. [The Working Group noted that this risk was calculated using the numbers displayed in Fig. 1 of the published study and that, on the basis of the previously mentioned limitations, this study was less informative for the evaluation.]

Ghadimi et al. (2015) conducted a hospital-based case–control study in Kurdistan Province, Iran, during 3 years. [The Working Group noted that the exact years of the study were not mentioned in the paper but inferred that the study was conducted in about 2012–2014.] The study included 152 patients with histologically confirmed bladder cancer and 152 hospital-based, cancer-free controls who were frequency-matched to cases on the basis of age, sex, and place of residency. [The Working Group noted that the lack of information on the disease categories relating to the controls did not allow assessment of the appropriateness of this group, leading to possible exposure misclassification. Selection of hospital controls is always a limitation in studies of this kind, especially if some of the conditions leading to hospitalization are indeed related to opium use and/or tobacco use, and this would bias results towards the null.] Opium exposure status was assessed retrospectively using a structured questionnaire. [The Working Group noted that opium exposure was poorly defined and characterized in this study,

and that no information had been collected regarding the duration of exposure or the amount or type of opium consumed; therefore, non-differential misclassification of exposure could result. Information on route of exposure was collected, with all participants reported to consume opium by smoking.] A tobacco smoking-adjusted logistic regression model estimated an odds ratio of 4.96 (95% CI, 1.07–22.92) for the association between opium exposure and bladder cancer. [The Working Group noted the nearly 5-times increased risk for opium exposure and bladder cancer; however, due to the large confidence interval resulting from the small numbers of exposed cases and controls, it was deemed less informative for the evaluation.]

Lotfi et al. (2016) conducted a population-based case–control study between 2009 and 2013 in Yazd Province, Iran. The study included 200 patients with pathologically confirmed bladder cancer and 200 healthy controls, matched on age and sex, who were neighbours of patients. Opium exposure data were collected during interviews using a structured questionnaire. The odds ratio for opium history (3.01; 95% CI, 1.73–5.23) was obtained using logistic regression analysis but was not adjusted for cigarette smoking. [The Working Group noted that because the results were not adjusted for tobacco smoking, residual confounding may be present, which would partly explain the reported increased risk of bladder cancer. Therefore, the results were less informative for the evaluation.]

2.3 Cancers of the respiratory tract

See Table 2.3.

2.3.1 Cancer of the larynx

A cohort study (Sheikh et al., 2020) and six case–control studies (Khoo, 1981; Mousavi et al., 2003; Bakhshaee et al., 2017; Berjis et al., 2018; Alizadeh et al., 2020; Mohebbi et al., 2020) have investigated the association between opium use and incidence of laryngeal cancer. In addition, the cohort study also investigated laryngeal cancer mortality (Rahmati et al., 2017). [The Working Group considered that the cross-sectional study by Dabirmoghaddam et al. (2016) was uninformative for the evaluation and it was not considered further.]

(a) Cohort study

Sheikh et al. (2020) investigated the incidence of cancer of the larynx in the GCS, the methods of which have been described previously. There were 38 cases of laryngeal cancer, of which almost 80% were histologically confirmed. Adjusting for a range of factors including cigarette smoking (status and pack-years), the study reported a hazard ratio of 2.53 (95% CI, 1.21–5.29) in opium ever-users compared with never-users for cancer of the larynx, with a positive exposure–response trend (P = 0.0004) for increasing quartiles of consumption (HR, 3.34; 95% CI, 1.33–8.34; in the highest consumption quartile). Sex-stratified analysis yielded evidence of increased risk associated with ever-consumption of opium in men (HR, 2.24; 95% CI, 1.03–4.86) while only 5 cases of cancer of the larynx were reported in women (HR, 6.09; 95% CI, 0.67–54.82). The majority of opium users smoked opium (HR, 2.54; 95% CI, 1.14–5.68; for ever-smoking of opium) and consumed raw opium (*teriak*) (HR, 2.38; 95% CI, 1.10–5.12; for ever-consumption of *teriak*), and strong positive associations were observed. However, elevated hazard ratios were also observed for ingesting opium (all forms combined) as well as consuming refined opium. There was also some evidence for an interaction between opium consumption and tobacco use, although the multiplicative interaction term was not significant and results were based on small numbers (n = 38) of cases of laryngeal cancer. Risks for laryngeal cancer were found to be consistently elevated when excluding the first 2 years of follow-up and in the

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) Golestan Province, Iran (Islamic Republic of) Enrolment, 2004–2008/ follow-up, 531 789 person-years (through December 2018; median, 10 yr) Cohort	GCS: 50 045 individuals aged 40–75 yr from both rural and urban areas of Golestan Province (50 034 after excluding 11 diagnosed with cancer before enrolment); among them 38 laryngeal (30 histologically confirmed) and 116 lung (76 histologically confirmed) cancers Exposure assessment method: validated GCSQ assessing complete opium exposure history at baseline including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic prospective data collection	Larynx, incidence	Opium use (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	*Exposure assessment critique*: High-quality, multimetric exposure assessment collected prospectively with temporal aspects mostly incorporated into estimates. Considers duration of exposure, cumulative exposure, and exposure method. Potential for non-differential measurement error. Unexposed referent group could include exposed. No exposure lagging. *Other comments*: respiratory tract (154 cases) included lung cancer (116 cases) and laryngeal cancer (38 cases). *Strengths*: prospective design; large sample size, extensive data collection for the exposure of interest (opium) and potential confounders, and blinded evaluation of outcome; sensitivity analyses were conducted excluding recent use of opium and deaths that occurred during the first 2 yr of follow-up.
			Never	15	1		
			Ever	23	2.53 (1.21–5.29)		
		Larynx, incidence	Opium use, men (HR):			Age, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	NR	1		
			Ever	NR	2.24 (1.03–4.86)		
		Larynx, incidence	Opium use, women (HR):				
			Never	NR	1		
			Ever	NR	6.09 (0.67–54.82)		
		Larynx, incidence	Cumulative opium use (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never used opium	15	1		
			1st quartile (≤ 5 nokhod-years)	NR	1.11 (0.24–5.01)		
			2nd quartile (5.1–21 nokhod-years)	NR	2.55 (0.87–7.42)		

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) (cont.)		Larynx, incidence (cont.)	3rd quartile (21.1–60 nokhod-years)	NR	2.98 (1.08–8.22)		*Limitations*: small number of cases; may be some degree of misclassification of cause of death, in spite of the validity of the verbal autopsy.
			4th quartile (> 60 nokhod-years)	NR	3.34 (1.33–8.34)		
			Trend-test *P* value, 0.0004				
		Larynx, incidence	Individual and combined effects of opium and tobacco (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, regular alcohol drinking (ever/never)	
			Used neither opium nor tobacco	6	1		
			Used opium but not tobacco	4	4.85 (1.33–17.62)		
			Used tobacco but not opium	9	8.65 (2.86–27.84)		
			Used both opium and tobacco	19	17.75 (6.06–51.94)		
		Larynx, incidence	Route of opium use (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never used opium	15	1		
			Only by smoking	14	2.54 (1.14–5.68)		
			Only by ingesting	7	2.48 (0.93–6.62)		
			Both routes	2	2.61 (0.55–12.41)		

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) (cont.)		Larynx, incidence	Opium type (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never used opium	15	1		
			Raw opium (*teriak*)	18	2.38 (1.10–5.12)		
			Refined opium (*shireh*)	3	3.40 (0.92–12.55)		
			Burned opium (*sukhteh*)	0	–		
			Heroin	0	–		
			Combination of the above	2	3.63 (0.77–17.15)		
		Larynx, incidence	Opium use, excluding the first 2 yr of follow-up (HR):				
			Never	15	1		
			Ever	22	2.38 (1.12–5.03)		
		Lung, incidence	Opium use (HR):				
			Never	59	1		
			Ever	57	2.21 (1.44–3.39)		
		Lung, incidence	Opium use, men (HR):			Age, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	NR	1		
			Ever	NR	2.37 (1.45–3.72)		
		Lung, incidence	Opium use, women (HR):				
			Never	NR	1		
			Ever	NR	1.60 (0.48–5.38)		

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) (cont.)		Lung, incidence	Cumulative opium use (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never used opium	59	1		
			1st quartile (≤ 5 nokhod-years)	NR	1.15 (0.49–2.73)		
			2nd quartile (5.1–21 nokhod-years)	NR	2.34 (1.23–4.43)		
			3rd quartile (21.1–60 nokhod-years)	NR	2.04 (1.05–3.95)		
			4th quartile (> 60 nokhod-years)	NR	3.19 (1.85–5.50)		
			Trend-test *P* value, < 0.0001				
		Lung, incidence	Individual and combined effects of opium and tobacco (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, regular alcohol drinking (ever/never)	
			Used neither opium nor tobacco	41	1		
			Used opium but not tobacco	8	1.50 (0.69–3.25)		
			Used tobacco but not opium	18	2.56 (1.38–4.76)		
			Used both opium and tobacco	49	7.34 (4.43–12.13)		

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) (cont.)		Lung, incidence	Route of opium use (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never used opium	59	1		
			Only by smoking	30	1.90 (1.17–3.10)		
			Only by ingesting	20	2.66 (1.51–4.68)		
			Both routes	7	3.27 (1.40–4.64)		
		Lung, incidence	Opium type (HR):				
			Never used opium	59	1		
			Raw opium (*teriak*)	48	2.19 (1.41–3.4)		
			Refined opium (*shireh*)	3	1.25 (0.38–4.12)		
			Burned opium (*sukhteh*)	0	–		
			Heroin	1	109.28 (13.98–853.93)		
			Combination of the above	5	3.05 (1.16–7.99)		
		Lung, incidence	Opium use, excluding the first 2 yr of follow-up (HR):				
			Never	52	1		
			Ever	44	1.96 (1.22–3.14)		
		Respiratory tract, incidence	Opium use (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	74	1		
			Ever	80	2.28 (1.58–3.30)		

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) (cont.)		Respiratory tract, incidence	Opium use, men (HR):			Age, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	NR	1		
			Ever	NR	2.30 (1.54–3.44)		
		Respiratory tract, incidence	Opium use, women (HR):				
			Never	NR	1		
			Ever	NR	2.08 (0.74–5.83)		
		Respiratory tract, incidence	Cumulative opium use (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	74	1		
			1st quartile (≤ 5 nokhod-years)	NR	1.14 (0.54–2.40)		
			2nd quartile (5.1–21 nokhod-years)	NR	2.38 (1.37–4.11)		
			3rd quartile (21.1–60 nokhod-years)	NR	2.26 (1.30–3.92)		
			4th quartile (> 60 nokhod-years)	NR	3.22 (2.02–5.14)		
			Trend-test *P* value, < 0.0001				

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) (cont.)		Respiratory tract, incidence	Individual and combined effects of opium and tobacco (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, regular alcohol drinking (ever/never)	
			Used neither opium nor tobacco	47	1		
			Used opium but not tobacco	12	1.94 (1.02–3.71)		
			Used tobacco but not opium	27	3.35 (1.96–5.72)		
			Used both opium and tobacco	68	8.71 (5.56–13.66)		

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Rahmati et al. (2017) Golestan Province, Iran (Islamic Republic of) Enrolment, 2004–2008/ follow-up, through June 2015 Cohort	GCS: a sample of 50 045 healthy men and women from Golestan Province of Iran aged 40–75 yr; urban dwellers were selected randomly from five areas of Gonbad City by systematic clustering, while all eligible residents of villages in the study catchment area were invited to participate Exposure assessment method: validated GCSQ assessing complete opium exposure history at baseline including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic prospective data collection	Larynx, mortality Larynx, mortality Lung, mortality Lung, mortality Respiratory tract, mortality (all were cancers of lung or larynx)	Opium use (HR): Never Ever Opium use > 10 yr (HR): Never used opium Ever Opium use (HR): Never Ever Opium use > 10 yr (HR): Never used opium Ever Opium use (HR): Never Former Current	 NR NR NR NR NR NR NR NR 42 5 38	 1 3.46 (0.99–12.07) 1 4.16 (1.10–15.74) 1 1.73 (0.99–3.03) 1 2.42 (1.32–4.46) 1 1.95 (0.73–5.16) 2.11 (1.25–3.55)	Age, sex, residence (urban/rural), education, marital status, drinking alcohol, and cumulative use of any type of tobacco (pack-years for cigarette and amount × duration of use for hookah and nass)	*Exposure assessment critique*: High-quality, multimetric exposure assessment collected prospectively, with timing of opium use relative to outcome mostly incorporated into estimates. Potential for non-differential measurement error. Unexposed referent group could include exposed. No exposure lagging. *Other comments*: respiratory tract (85 deaths) included lung cancer (70 deaths) and laryngeal cancer (15 deaths). *Strengths*: prospective design, large sample size, extensive data collection for the exposure of interest (opium) and potential confounders, and blinded evaluation of outcome; sensitivity analyses were conducted excluding deaths that occurred during the first 2 yr of follow-up and excluding subjects who had used opium for < 10 yr.

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Rahmati et al. (2017) (cont.)		Respiratory tract, mortality (all were cancers of lung or larynx)	Duration of opium use (HR):				*Limitations*: small number of deaths; may be some degree of misclassification of cause of death, in spite of the validity of the verbal autopsy.
			Never	42	1		
			Former	5	2.01 (0.75–5.31)		
			1st quintile (≤ 3 yr)	3	1.11 (0.34–3.66)		
			2nd quintile (4–7 yr)	2	0.73 (0.17–3.08)		
			3rd quintile (8–12 yr)	5	1.77 (0.67–4.66)		
			4th quintile (13–20 yr)	10	2.58 (1.22–5.44)		
			5th quintile (> 20 yr)	18	3.01 (1.55–5.81)		
			Trend-test *P* value, < 0.001				
		Respiratory tract, mortality (all were cancers of lung or larynx)	Cumulative opium use (HR):				
			Never	42	1		
			Former	5	1.99 (0.75–5.27)		
			1st quintile (≤ 1148 nokhod-days)	2	0.73 (0.17–3.09)		
			2nd quintile 1149–4383 nokhod-days)	5	1.64 (0.63–4.28)		
			3rd quintile (4384–12 054 nokhod-days)	6	1.92 (0.78–4.68)		
			4th quintile (12 055–30 681 nokhod-days)	9	2.38 (1.09–5.18)		
			5th quintile (> 30 682 nokhod-days)	16	2.95 (1.48–5.88)		
			Trend-test *P* value, < 0.001				

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Rahmati et al. (2017) (cont.)		Respiratory tract, mortality (all were cancers of lung or larynx)	Type of opium product used (HR):				
			Never used opium	42	1		
			Teriak only	37	2.01 (1.19–3.35)		
			Shireh only	2	1.06 (0.25–4.53)		
			Combinations	4	3.06 (1.02–9.18)		
		Respiratory tract, mortality (all were cancers of lung or larynx)	Route of opium use (HR):				
			Never used opium	42	1		
			Smoking	21	1.69 (0.94–3.03)		
			Ingestion	17	2.29 (1.21–4.36)		
			Both	5	2.99 (1.11–8.06)		

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
MacLennan et al. (1977) Singapore 1972–1973 Case–control	Cases: 233 patients (147 men; 86 women) with provisional hospital diagnosis of lung cancer Controls: 300 (134 men; 166 women); hospital controls from the same wards, matched on sex, age (5 yr), and dialect; patients with smoking-related diagnosis were excluded (chronic bronchitis, emphysema, myocardial infarction, oral cancer, pharyngeal cancer, laryngeal cancer, and cancers of oesophagus, pancreas, and bladder)	Lung, incidence	Opium smoking, men (OR): Never smoked Ever smoked	 84 63	 1 [2.39 (1.43–4.00)]	Age, dialect	*Exposure assessment critique*: Opium exposure poorly defined and poorly characterized. Timing of opium use relative to outcome unclear. The consistency of exposure ascertainment was assessed to some degree by comparing how questions were asked in cases and controls. Exposure ascertained after case identification. Unexposed referent group could include exposed. No exposure lagging. *Other comments*: too few opium users who were women to calculate OR.

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopa-thology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
MacLennan et al. (1977) (cont.)	Exposure assessment method: questionnaire; opium only investigated as "ever smoked" in interviews with no information on how systematic these were; no information on any metrics of exposure.						*Limitations*: provisional diagnosis of lung cancer includes any type of cancer (including adenocarcinoma and SCC); there is concern about risks of different types of lung cancers and some cases could have had tuberculosis; information on recent vs distant use of opium was not collected; potential for reverse causation in patients who began using opium to control pain associated with cancer.

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Khoo (1981) China, Hong Kong Special Administrative Region 1970–1977 Case–control	Cases: 123 patients with SCC of the larynx, who were referred to the radiotherapy division in Queen Mary Hospital for primary radiotherapy from January 1970 to December 1977 Controls: NR; those with other cancers not associated with smoking or drinking alcohol, matched for sex and age Exposure assessment method: questionnaire; unclear how information was obtained; no definition of opium exposure, opium and/or heroin addiction used	Larynx (SCC), incidence	Opium and/or heroin addiction, non-drinking cigarette smokers (OR): Never addicted to opium Ever addicted to opium	 42 27	 1 9.3 (2.1–42.3)	Sex, age	*Exposure assessment critique*: Opium exposure poorly defined and poorly characterized. Timing of opium use relative to outcome unclear. Exposure assessment unclear. Heroin addiction included as exposed. Exposure ascertained after case identification. Unexposed referent group could include exposed. No exposure lagging. *Other comments*: the OR was not calculated by the study's authors but by Kamangar et al. (2014) for their systematic review of epidemiological studies associating opium use with cancer. *Limitations*: no definition of "other cancers", which form the "control" group.

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mousavi et al. (2003) Kerman Province, Iran (Islamic Republic of) 1996–2002 Case–control	Cases: 98 pathologically confirmed laryngeal SCCs, referred by a Kerman University of Medical Sciences-affiliated hospital in Kerman Province in the south of the Islamic Republic of Iran Controls: sex- and age-matched patients (312 patients in all) who were admitted to the otolaryngology department in the same period; patients with other cancers of the head and neck were excluded because of the possible effect of opium	Larynx (SCC), incidence	Opium consumption for ≥ 5 yr (OR): Never Ever	 23 75	 1 10.74 (5.76–20.02)	Age, sex, cigarette smoking status (ever/ never)	*Exposure assessment critique*: Opium exposure well defined but poorly characterized. Timing of opium use relative to outcome unclear. Not a comprehensive approach to exposure assessment (no intensity, duration, cumulative exposure, temporality, or type of exposure). Exposure ascertained after case identification. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: pathologically confirmed cases; large number of exposed cases.

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mousavi et al. (2003) (cont.)	Exposure assessment method: questionnaire; exposure: opium-dependent based on DSM-IV opium dependency and opium consumption for ≥ 5 yr; types of consumption and route of ingestion not recorded						*Limitations*: selection bias possible with controls selected from an otolaryngology department; these patients may be less likely to use opium and cigarettes than the general population; information on recent vs distant use of opium was not collected; potential for reverse causation in patients who began using opium to control pain associated with cancer.

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Masjedi et al. (2013) Tehran, Iran (Islamic Republic of) 2002–2005 Case–control	Cases: 242 histologically and cytologically confirmed cases of primary lung cancer Controls: 484 (242 hospital controls and 242 visiting healthy controls) matched on age (± 3 yr), sex, and place of residence Exposure assessment method: questionnaire; opium addiction defined as consumption of opium at least once per day for minimum of 6 mo; study considered smoked and ingested opium via assessment of ever vs never use, frequency of use based on ≤ or > median per day, duration of use, cumulative use, age at start of use, and method of exposure	Lung, incidence	Opium smoking, men (OR): Never Ever	 145 33	 1 3.1 (1.2–8.1)	Age, residence, ethnicity (Fars/Azeri/Kurd/Lur/other), education (ordinal: nil, < 5 yr, 5–8 yr, 8–12 yr, > 12 yr), cigarette smoking pack-years	*Exposure assessment critique*: Opium exposure well defined and well characterized. Table 3 mentions smoked "opiate"; not clear if this instead means opium (therefore, not clear whether opiates also included in the exposure here). Exposure ascertained after case identification. Unexposed referent group could include exposed. No exposure lagging. *Other comments*: too few opium users who were women to calculate OR; the authors reported that a dose–response association was present, but the data provided in the tables of the article did not show such a pattern. *Strengths*: histologically and cytologically confirmed primary lung cancer; high participation rate (91%); both population and hospital controls; different metrics of exposure were investigated.
		Lung, incidence	Opium smoking, men (OR): Never Ever	 145 33	 1 7.5 (3.4–16.7)	Age, residence, ethnicity (Fars/Azeri/Kurd/Lur/other), education (ordinal: nil, < 5 yr, 5–8 yr, 8–12 yr, > 12 yr)	
		Lung, incidence	Frequency of opium smoking, men (OR): Never ≤ Median among controls (twice per day) > Median among controls Trend-test *P* value, < 0.0001	 145 30 3	 1 7.7 (3.4–17.4) 5.3 (0.8–36.8)		

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Masjedi et al. (2013) (cont.)		Lung. incidence	Cumulative opium smoking, men (OR):				*Limitations*: only one set of analyses were adjusted for cigarette smoking.
			Never	145	1		
			≤ Median among controls (36.5 nokhod-years)	18	9.6 (3.5–26.8)		
			> Median among controls	15	6.9 (2.3–20.4)		
			Trend-test *P* value, < 0.0001				
		Lung, incidence	Opium ingestion, men (OR):				
			Never	142	1		
			Ever	36	2.2 (1.3–3.8)		
		Lung, incidence	Frequency of opium ingestion, men (OR):				
			Never used	142	1		
			≤ Median (once per day)	13	1.5 (0.7–3.4)		
			> Median	14	17.5 (3.4–89.8)		
			Trend-test *P* value, < 0.0001				
		Lung, incidence	Cumulative opium ingestion, men (OR):				
			Never used	142	1		
			≤ Median among controls (23 nokhod-years)	13	3.8 (1.5–9.9)		
			> Median among controls	14	2.5 (1.01–3.2)		
			Trend-test *P* value, 0.003				

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Masjedi et al. (2013) (cont.)		Lung, incidence	Age started opium use, men (OR):				
			Never	142	1		
			≤ Median among controls (35 yr)	19	2.9 (1.3–6.5)		
			> Median among controls	16	2.4 (1.1–5.1)		
			Trend-test *P* value, 0.003				
		Lung, incidence	Route of opium use, men (OR):				
			Never used	127	1		
			Ingested only	18	1.4 (0.7–2.7)		
			Smoked only	15	5.4 (2.1–14)		
			Both	18	13.7 (4.2–44)		

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bakhshaee et al. (2017) Mashhad, Iran (Islamic Republic of) 2008–2010 Case–control	Cases: 58 cases of laryngeal cancer from otolaryngology and radiation oncology department at Mashhad University of Medical Sciences Controls: 27 healthy hospital-based controls from otolaryngology and radiation oncology department at Mashhad University of Medical Sciences, with no evidence of head and neck or oesophageal malignancies, matched for age Exposure assessment method: questionnaire; interview collected data on opium use, defined as "snuffing"	Larynx, incidence	Opium dependency (OR): Never Ever	 NR NR	 1 6.06 (1.10–33.23)	Smoking, age, sex	*Exposure assessment critique*: Opium exposure well defined but poorly characterized. Timing of opium use relative to outcome unclear. Intensity, duration, and type of opium exposure not collected. Only "snuffing" (presumed to be smoking) use is described. Not clear how systematic the interview was. Limited details, limited exposure information. Exposure ascertained after case identification. Unexposed referent group could include exposed. No exposure lagging. *Other comments:* the number of controls in abstract was 27 but in methods was 28. *Strengths*: pathologically confirmed cases.

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopa-thology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Bakhshaee et al. (2017) (cont.)							*Limitations*: matching was only on age (without defined difference number) and not on sex; small number of controls and unclear how they were selected; controls described as "healthy" but were selected from otolaryngology and radiation oncology departments; only opium consumption by snuffing was assessed; unclear whether primary exposure was opium use or opium dependency.

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Berjis et al. (2018) Isfahan, Iran (Islamic Republic of) 2015 Case–control	Cases: 180 biopsy-confirmed SCCs of the larynx Controls: 180; people aged > 40 yr referred to hospital clinics Exposure assessment method: questionnaire; no information on how opium "drug addicted" was defined; three sources of data collection but not clear how systematic	Larynx (SCC), incidence	Drug (opium) addiction (OR): Never Ever	 79 101	 1 18.6 (7.9–43.6)	Tobacco	*Exposure assessment critique*: Opium exposure poorly defined and poorly characterized. Timing of opium use relative to outcome unclear. No evidence of questionnaire validation. No information on the data collection instrument. Information regarding the intensity and duration of opium consumption not collected. No dose–response assessment. Exposure ascertained after case identification. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: large number of exposed cases; cases were pathologically confirmed. *Limitations*: details on the selection method, including the clinics from which controls were selected, were unclear, with potential for selection bias; information on recent vs distant use of opium was not collected; potential for reverse causation in patients who began using opium to control pain associated with cancer.

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Alizadeh et al. (2020) Kerman, Iran (Islamic Republic of) 2014–2017 (and earlier) Case–control	Cases: 140 patients with head and neck cancers (nasal cavity, pharynx, paranasal sinuses, oral cavity, larynx, or salivary gland) with pathological information in the cancer registry of Kerman University of Medical Sciences Controls: 280 neighbourhood-based controls; individually matched on age (± 5 yr), sex, and neighbourhood (nearest and first neighbours to the right of the case's home who met the inclusion criteria)	Larynx, incidence	Opium use (OR):			Age, sex, neighbourhood, dietary factors (meat, fruit, vegetables, hydrogenated fats, and olive oil), education (illiterate, elementary/ middle school, high school/high school diploma, or above), cigarette smoking, alcohol drinking	*Exposure assessment critique*: Opium exposure well defined and well characterized. Comprehensive exposure assessment (intensity, duration, cumulative exposure, type, and mode). Temporality not specified; opium use in the 2 yr before cancer diagnosis excluded to minimize reverse causation. Exposure data collection after case identification. Unexposed referent group could include exposed. No exposure lagging. Only raw opium and opium sap used. *Strengths*: cases confirmed pathologically; used population-based neighbour controls; showed a dose–response relationship with opium use.
			Never	23	1		
			Ever	88	11.98 (5.05–28.39)		
		Larynx, incidence	Amount of daily opium use (OR):				
			Never used	23	1		
			≤ Median (among controls)	41	11.17 (4.33–28.83)		
			> Median (among controls)	47	12.82 (4.96–33.11)		
		Larynx, incidence	Duration of opium use (OR):				
			Never used	23	1		
			≤ Median (among controls)	57	7.05 (3.17–15.67)		
			> Median (among controls)	31	13.68 (5.12–36.56)		
		Larynx, incidence	Cumulative use of opium (OR):				
			Never used	23	1		
			≤ Median (among controls)	44	9.46 (3.97–22.52)		
			> Median (among controls)	44	11.17 (4.44–28.09)		

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Alizadeh et al. (2020) (cont.)	Exposure assessment method: validated GCSQ assessing opium exposure history including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic retrospective data collection; trained interviewers; conducted at participants homes; comfortable and friendly environment; used median use in controls to define non-use, and low and high use						*Limitations*: retrospective study (sampling began by enrolling all diagnosed cases from 2017 and then enrolling cases from previous years); possible recall bias, most of the cases (60%) but fewer of the controls (30%) were illiterate or had only elementary education; the frequency of non-response was 19.5%; timing of opium use relative to outcome unclear and uncertainty about reverse causation; small sample size.

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mohebbi et al. (2020) Iran (Islamic Republic of) April 2016 to April 2019 Case–control	Cases: 663 (327 larynx) incident cases of head and neck SCC referred to cancer care centres in 10 provinces (IROPICAN study) Controls: 3065; ≥ 4 controls per case, frequency-matched on age, sex, and place of residence, selected from hospital visitors who were either relatives or friends of hospitalized patients in non-oncology wards, or persons who visited the hospital for any reason other than receiving treatment concurrently	Larynx (SCC), incidence	Regular opium use (OR):			Age, sex, place of residence (centre/non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	*Exposure assessment critique*: Opium exposure well defined and well characterized. Timing of opium use relative to outcome was considered. Multiple exposure metrics (regular/non-regular use, average intensity as daily amount of use, duration in years, type of opium used, and route of use). Exposure data collection after case identification. Unexposed referent group could include exposed. No exposure lagging.
			Non-user	96	1		
			Regular user	231	6.55 (4.69–9.13)		
			Centre-heterogeneity *P* value, < 0.0001				
		Larynx (SCC), incidence	Duration of opium use (OR):				
			1st tertile (≤ 11 yr)	35	1		
			2nd tertile (12–23 yr)	80	1.91 (1.10–3.31)		
			3rd tertile (≥ 24 yr)	116	2.71 (1.56–4.68)		
			Trend-test *P* value, < 0.0001				
			Centre-heterogeneity *P* value, < 0.0001				
		Larynx (SCC), incidence	Cumulative opium use (OR):				
			1st tertile (≤ 3.6 gram-years)	26	1		
			2nd tertile (3.7–24.4 gram-years)	77	2.32 (1.28–4.20)		
			3rd tertile (≥ 24.5 gram-years)	128	2.29 (1.26–4.16)		
			Trend-test *P* value, 0.01				
			Centre-heterogeneity *P* value, < 0.0001				

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mohebbi et al. (2020) (cont.)	Exposure assessment method: validated GCSQ assessing complete opium exposure history including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic retrospective data collection	Larynx (SCC), incidence	Frequency-years of opium use (OR):				*Strengths*: all cases confirmed pathologically (SCC); a multicentre study with large numbers of cases and controls; 4 controls for each case, frequency-matched on age, sex, and place of residence; opium use disregarded for those who started using opium in the 3 yr before cancer diagnosis to reduce reverse causation; evaluated dose–response relationship between opium use and larynx cancer; use of hospital visitor controls; to minimize interviewer bias, a comprehensive protocol of interviewer training, data collection, and monthly review of the protocols was used; confounders were strictly controlled by limiting the analyses of head and neck cancers to never tobacco smokers. *Limitations*: potential information bias; centre heterogeneity.
			1st tertile (≤ 8 frequency-years)	14	1		
			2nd tertile (8.1–22 frequency-years)	43	3.38 (1.63–6.99)		
			3rd tertile (≥ 23 frequency-years)	174	9.05 (4.62–17.71)		
			Trend-test *P* value, < 0.0001				
			Centre-heterogeneity *P* value, < 0.0001				
		Larynx (SCC), incidence	Average intensity of opium use (OR):				
			1st tertile (≤ 0.4 g/day)	44	1		
			2nd tertile (0.5–2 g/day)	83	1.27 (0.74–2.16)		
			3rd tertile (≥ 2 g/day)	104	0.92 (0.53–1.60)		
			Trend-test *P* value, 0.62				
			Centre-heterogeneity *P* value, < 0.0001				
		Larynx (SCC), incidence	Type of opium used (OR):				
			Non-user	96	1		
			Crude opium (*teriak*)	182	5.77 (4.09–8.15)		
			Opium juice (*shireh*)	49	12.69 (7.25–22.22)		
			Centre-heterogeneity *P* value, < 0.0001				
		Larynx (SCC), incidence	Route of opium use (OR):				
			Non-user	96	1		
			Only smoking	125	4.28 (2.98–6.14)		
			Only oral ingestion	25	17.17 (8.44–34.91)		
			Both routes	81	25.11 (14.55–43.33)		
			Centre-heterogeneity *P* value, < 0.0001				

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Naghibzadeh-Tahami et al. (2020) Kerman, Iran (Islamic Republic of) 2014–2017 Case–control	Cases: 140 patients with pathologically confirmed lung cancer in the Kerman University of Medical Sciences cancer registry Controls: 280; 2 healthy controls per case, individually matched on age (± 5 yr), sex, and neighbourhood Exposure assessment method: questionnaire; used the GCSQ, systematic retrospective data collection; validated questionnaire assessing complete opium exposure history including intensity, duration, cumulative exposure, and type and method of exposure	Lung, incidence	Opium use (OR): Never Ever	 57 83	 1 5.95 (1.87–18.92)	Age, sex, neighbourhood, dietary factors (meat, fruit, vegetables, hydrogenated fats, and olive oil), cigarette smoking (non-user/low user/high user), alcohol (non-user/low user/high user), education (illiterate, elementary/middle school, high school/high school diploma, or above)	*Exposure assessment critique*: Opium exposure not well defined but well characterized. Timing of opium use relative to outcome was considered. Risks by ever-/never-use, average intensity as daily amount of use, and duration in years were considered. Risks by type of opium used and by route of using opium were not considered. Exposure data collection after case identification. Unexposed referent group could include exposed. No exposure lagging *Other comments*: interaction *P* values for cigarette smoking (ever-use) with opium (and derivatives) were 0.38 and 0.14 for ever-use and cumulative dose, respectively.
		Lung, incidence	Opium use, never cigarette smokers (OR): Never Ever	 30 29	 1 6.50 (2.89–14.64)	Age, sex, neighbourhood	
		Lung, incidence	Amount of daily opium use (OR): Never used ≤ Median among controls (4.5 g/day) > Median among controls (4.5 g/day)	 57 36 47	 1 3.81 (1.13–12.77) 9.36 (2.05–42.72)	Age, sex, neighbourhood, dietary factors (meat, fruit, vegetables, hydrogenated fats, and olive oil), cigarette smoking (non-user/low user/high user), alcohol (non-user/low user/high user), education (illiterate, elementary/middle school, high school/high school diploma, or above)	

Table 2.3 Cohort and case–control studies on opium consumption and cancers of the lung, larynx, or combined respiratory tract (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Naghibzadeh-Tahami et al. (2020) (cont.)		Lung, incidence	Duration of opium use (OR):				*Strengths*: cases confirmed pathologically; use of population-based neighbourhood controls; evaluated exposure–response association between opium use and lung cancer; disregarded opium use in those who started in the 2 yr before diagnosis to address reverse causation. *Limitations*: pathological subtypes of the cases were not clear (the risk factors of adenocarcinoma, SCC, and metastatic form may be different); possible recall bias, most of the cases but about 1/4 of the controls were illiterate or had just elementary education; the frequency of non-response was 19.5%; timing of opium use relative to outcome unclear and uncertainty about reverse causation; imprecise estimates due to small sample size.
			Never used	57	1		
			≤ Median among controls (20 yr)	41	3.47 (1.13–10.62)		
			> Median among controls (20 yr)	42	5.50 (1.32–22.91)		
		Lung, incidence	Cumulative opium use (OR):				
			Never used	57	1		
			≤ Median among controls (87.5 gram-years)	46	3.95 (1.29–12.12)		
			> Median among controls (87.5 gram-years)	37	4.79 (0.88–26.08)		
		Lung, incidence	Age at start of opium use (OR):				
			Never used	57	1		
			> Median among controls (41 yr)	22	4.71 (1.38–16.08)		
			≤ Median among controls (41 yr)	61	8.64 (1.90–39.18)		

–, risk estimate could not be calculated; CI, confidence interval; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; GCS, Golestan Cohort Study; GCSQ, Golestan Cohort Study Questionnaire; HR, hazard ratio; IROPICAN, Iranian Study of Opium and Cancer; mo, month; NR, not reported; OR, odds ratio; SCC, squamous cell carcinoma; SES, socioeconomic status; vs, versus; yr, year.

subgroup of tobacco never-users (HR, 4.85; 95% CI, 1.33–17.62; 4 exposed cases). However, many of these analyses were based on small numbers of exposed cases and the estimates were imprecise.

Analyses of laryngeal cancer mortality in the GCS have reported similar findings (Rahmati et al., 2017). Opium use for at least 6 months was associated with higher risk of laryngeal cancer mortality overall (HR, 3.46; 95% CI, 0.99–12.07; based on 15 laryngeal cancer deaths), compared with never-use, and in sensitivity analyses that excluded users with less than 10 years of use (HR, 4.16; 95% CI, 1.10–15.74 based on 13 laryngeal cancer deaths) (Rahmati et al., 2017). [The Working Group noted that limitations of the study included the small numbers of deaths, and possibly also some degree of misclassification of cause of death, in spite of the validity of the verbal autopsy.]

(b) Case–control studies

Khoo (1981) conducted a hospital-based case–control study in Hong Kong Special Administrative Region, China. The cases were 123 patients with SCC of the larynx, who were referred to the radiotherapy division in Queen Mary Hospital for primary radiotherapy from January 1970 to December 1977. Controls were patients with other cancers (diagnosed in the same department, but not associated with smoking or drinking alcohol), matched on sex and age. The odds ratio of 9.3 (95% CI, 2.1–42.3) for opium and/or heroin addiction among smokers was not calculated by these authors but by Kamangar et al. (2014) in their systematic review of epidemiological studies associating opium use with cancer. [The Working Group noted several limitations of this study. Opium exposure in this study was poorly defined, its assessment was not comprehensive, and opium users included an unknown proportion of heroin users. In addition, information on recent versus distant use of opium was not collected and there was the potential for reverse causation in patients who began using opium to control pain associated with cancer. Furthermore, there was potential for control selection bias, given that the "other cancers" experienced by the controls were undefined and may have been associated with opium exposure, which would have biased results towards the null.]

In a study by Mousavi et al. (2003), 98 pathologically confirmed cases of laryngeal SCC, referred by a Kerman University of Medical Sciences-affiliated hospital in Kerman Province, southern Iran, were compared with 312 patient controls (sex- and age-matched) who were admitted to the otolaryngology department during the same period as the cases. [The Working Group noted that selection bias was possible since these controls would likely have already been experiencing functional disease to warrant admittance to the otolaryngology department and, as a result, may have been less likely to use opium and cigarettes than the general population, possibly resulting in a bias away from the null. However, bias towards the null may also have resulted if controls were protopathic opium users or if opium use induced other otolaryngological disease.] Opium dependency, as determined by the DSM-IV, Text Revision, was used as the opium exposure metric. A multivariable-adjusted odds ratio (including ever-smoking of tobacco) was calculated for ever having consumed opium for at least 5 years compared with never having done so (OR, 10.74; 95% CI, 5.76–20.02). [The Working Group considered that opium exposure was well-defined but that its assessment was not comprehensive. Information on recent versus distant use of opium was not collected, although the exposure criteria included using opium regularly for at least 5 years. The Working Group further noted that the exposure assessment approach was not comprehensive (e.g. no information on intensity, duration, cumulative exposure, temporality, type of opium, or route of exposure) and that the reference group could have included patients who used opium

for less than 5 years, possibly resulting in bias towards the null. The Working Group also noted difficulty in interpreting the odds ratio reported given a possible reporting error in the original manuscript that suggested an apparently high prevalence of opium consumption.]

In a case–control study conducted by Bakhshaee et al. (2017) in Mashhad, Iran, between 2008 and 2010, 58 cases of laryngeal cancer (pathology not mentioned) were compared with 27 or 28 controls. [The Working Group noted that the number of controls reported was different in the abstract compared with in the methods.] Matching was on age (without a defined difference number) but not on sex. [The Working Group noted that controls were described as "healthy" but were selected from otolaryngology and radiation oncology departments, which may have introduced selection bias.] Exposure information was collected by interview, with the metric being opium use (described as snuffing or inhalation) at least once per day for a minimum of 1 year. [The Working Group considered opium snuffing or inhalation, as mentioned in this paper, to be equivalent to opium smoking.] The tobacco smoking-adjusted odds ratio for opium consumption was 6.06 (95% CI, 1.10–33.23). [The Working Group noted that opium exposure was well-defined but that the assessment was not comprehensive. Timing of opium use relative to outcome was unclear, as was how systematic the interviews were.]

Berjis et al. (2018) compared 180 biopsy-confirmed cases of SCC of the larynx with 180 controls (people aged > 40 years referred to hospital clinics) in Isfahan, Iran, in 2015. Details regarding the selection method, including of the clinics from which controls were selected, how "drug addicted" was defined, and how data were collected were not provided. Information on recent versus distant use of opium was not collected. A highly elevated (yet imprecise) tobacco smoking-adjusted odds ratio of 18.6 (95% CI, 7.9–43.6) was calculated for drug (opium) addiction. [The Working Group noted that given the lack of information on study design, the potentials for selection, misclassification, and information bias were difficult to evaluate. There was potential for selection bias because the controls were selected from individuals who had been referred to the hospital and had undergone indirect laryngoscopy examination. The reason for referral may also have been related to opium use. The lack of a clear definition of "drug addicted" and the collection of non-systematic data across multiple sources (patient records, telephone interviews with patients, or telephone interview with family members), without a clear description of the collection parameters, may have contributed to misclassification and information bias. In addition, there was potential for bias if cases or controls began using opium due to disease symptoms. Other limitations included the fact that information on the intensity and duration of opium consumption was not collected, and that exposure–response associations were not provided.]

Alizadeh et al. (2020) conducted a case–control study in Kerman, Iran, in 2014–2017, that enrolled 140 patients with cancers of the head and neck (including 111 cases of cancer of the larynx) and included 280 healthy controls (matched for age, sex, and place of residence) (see also Section 2.5). Information about use of opium and its derivatives was collected using the validated GCSQ. Conditional logistic regression was used to investigate the relationships between variables. The use of opioids at least 2 years before cancer diagnosis, adjusted for a range of potential confounders including tobacco, was associated with an increased risk of cancer of the larynx (OR, 11.98; 95% CI, 5.05–28.39). The amount of daily opium use, duration of use, and cumulative use showed consistent evidence for increasing odds with increasing exposure (below- and above-median exposure in controls compared with never-users) for cancer of the larynx. [The Working Group considered the well-defined

opium exposure, pathologically confirmed cases, use of population-based neighbour controls, and evaluation of an exposure–response relationship with opium use to be strengths of the study. Limitations included the retrospective study design, potential recall bias, non-response frequency of 19.5%, uncertainty about reverse causation, and the small sample size.]

Mohebbi et al. (2020) conducted a multicentre case–control study within the IROPICAN study. They recruited 327 cases of cancer of the larynx and 3065 frequency-matched controls between 2016 and 2019. Regular opium use was associated with an increased risk of cancer of the larynx, with an odds ratio of 6.55 (95% CI, 4.69–9.13), adjusted for potential confounders including multiple forms of tobacco use. There were also strong positive trends observed with increasing tertiles of frequency, duration, and cumulative opium use. While associations between opium use and cancer of the larynx were not reported for tobacco never-smokers, the observed associations for cancers of the head and neck, nearly half of which were cancers of the larynx, were also strongly positive among tobacco never-smokers (including cigarette and water-pipe smoking). Risk estimates tended to be higher among those participants who ingested opium (HR, 17.17; 95% CI, 8.44–34.91) and those who consumed opium juice (*shireh*) (HR, 12.69; 95% CI, 7.25–22.22). However, positive hazard ratios were also observed for smoking opium as well as consuming raw opium (*teriak*). [Strengths of the study included all cases having been confirmed pathologically (as SCC), the large-scale multicentre design, opium use having been disregarded in those who started using opium 3 years before cancer diagnosis, and analysis among tobacco never-smokers. Limitations included information bias and centre heterogeneity.]

2.3.2 Cancer of the lung

One cohort study (Sheikh et al., 2020) and three case–control studies (MacLennan et al., 1977; Masjedi et al., 2013; Naghibzadeh-Tahami et al., 2020) investigated associations between opium use and lung cancer incidence. In addition, the cohort study also investigated lung cancer mortality (Khademi et al., 2012; Rahmati et al., 2017).

(a) Cohort study

Sheikh et al. (2020) investigated incidence of lung cancer in the GCS, the methods of which have been described previously (Sections 1.6 and 2.1.1). Of the 116 cases of lung cancer, 76 (65%) were histologically confirmed. Adjusting for a range of factors including cigarette smoking (status and pack-years), the study reported that ever-users of opium had an increased risk of lung cancer (HR, 2.21; 95% CI, 1.44–3.39) with an exposure–response trend ($P < 0.0001$) for increasing quartiles of cumulative consumption (HR, 3.19; 95% CI, 1.85–5.50; in the highest quartile). In sex-stratified analysis, results were stronger in men (HR, 2.37; 95% CI, 1.45–3.72) than in women (HR, 1.60; 95% CI, 0.48–5.38). Risks for lung cancer were found to be elevated in the subgroup of tobacco never-users; however, there was only a small number of exposed cases and the estimate was imprecise (HR, 1.50; 95% CI, 0.69–3.25; 8 exposed cases). The majority of opium users smoked opium (HR, 1.90; 95% CI, 1.17–3.10) and consumed raw opium (*teriak*) (HR, 2.19; 95% CI, 1.41–3.40), and strong positive associations were observed. There was also a strong positive association with ingestion of opium (HR, 2.66; 95% CI: 1.51–4.68). There was also some evidence for an association between opium and tobacco use, although the association was imprecise because of the small number of lung cancer cases. Most of the subgroup and sensitivity analyses for this site also reported elevated lung cancer risk; however, many of

these analyses were based on small numbers of exposed cases and the estimates were imprecise.

A mortality study within the GCS also reported that ever-consumption of opium (at least once a day for at least 6 months) (adjusted HR, 1.73; 95% CI, 0.99–3.03 on the basis of 70 lung cancer deaths) and long-term opium consumption (≥ 10 years) (adjusted HR, 2.42; 95% CI, 1.32–4.46 on the basis of 65 lung cancer deaths) were associated with lung cancer mortality (Rahmati et al., 2017). [The Working Group noted that a limitation of the study was that there may be some degree of misclassification of cause of death, in spite of the validity of the verbal autopsy.]

(b) Case–control studies

MacLennan et al. (1977) conducted the first case–control study that evaluated the association between opium use and lung cancer in Singapore (1972–1973). Initial selection of cases and controls for data collection was on the basis of a provisional diagnosis of lung cancer for cases and, for controls, non-smoking-related causes (as defined by the United States Public Health Service in 1964). Before analysis, all diagnoses were reviewed and several participants were reassigned, including 13 controls who, upon review, were found to have lung cancer. Only half of the cases were histologically confirmed, and the types of lung cancer (i.e. adenocarcinoma or SCC) could not be specified. The final analysis compared 233 cases (147 men, 86 women) with 300 hospital controls (134 men, 166 women) from the same wards (patients with smoking-related diagnoses were excluded: chronic bronchitis, emphysema, myocardial infarction, oral cancer, pharyngeal cancer, laryngeal cancer, and cancers of the oesophagus, pancreas, and urinary bladder), matched on sex, age (± 5 years), and dialect (MacLennan et al., 1977). Opium use was defined as "ever smoked". Information on recent versus long-ago use of opium was not collected. [The Working Group noted the potential for reverse causation in patients who began using opium to control pain associated with cancer, and also noted concern that any opium-related risks may differ for different subtypes of lung cancer.] Minimal results were reported, and no 95% confidence intervals were presented. An unadjusted odds ratio was calculated in men of 2.39 [95% CI, 1.43–4.00]. [The Working Group noted that the authors calculated the odds ratio but reported it as relative risk.]

Masjedi et al. (2013) conducted a case–control study in Tehran, Iran, in 2002–2005. Masjedi et al. (2013) is a more recent update of the study by Hosseini et al. (2009), so only the former study is discussed here. Masjedi et al. (2013) compared 242 histologically and cytologically confirmed primary lung cancers with 484 controls (hospital controls, excluding those with neoplasms and respiratory disease, 242; visiting healthy controls, 242), matched on age, sex, and place of residence. Opium addiction was defined as consumption of opium at least once per day for a minimum of 6 months. A detailed structured questionnaire, administered by a physician, was used to collect information on tobacco and opium use, including age use started and stopped, duration and frequency of use, and types of products used. Information was available on smoking, alcohol use, and other risk factors, but analyses were, in general, only adjusted for education and ethnicity. The odds ratio for opium smoking among men was reduced from 7.5 (95% CI, 3.4–16.7) to 3.1 (95% CI, 1.2–8.1) when the model was additionally adjusted for cigarette smoking (pack-years) (33 exposed cases). The study also presented results for mode of opium ingestion, duration and frequency of use, and types of products, including exposure–response trends, but these results were not adjusted for tobacco use. [The Working Group noted the potential for confounding by tobacco in studies of lung cancer and also that the data provided in the tables of the article did not always show a pattern to support a strong positive exposure–response trend.]

Naghibzadeh-Tahami et al. (2020) conducted a case–control study in Kerman, Iran, in 2014–2017. They enrolled 140 patients with lung cancer and 280 healthy controls matched on age, sex, and place of residence. Data were collected on four categories of opiates – raw opium (*teriak*), sap (*shireh*), burned opium (*sukhteh*), and heroin – using a structured questionnaire; however, no participants reported use of heroin or burned opium. The relation between the use of opium and lung cancer was evaluated using conditional logistic regression adjusted for a range of factors including tobacco smoking. Opium ever-use was associated with an increased risk of lung cancer (adjusted OR, 5.95; 95% CI, 1.87–18.92). Participants were divided into low- and high-use groups based on the median of opium use in the control group. A positive exposure–response relation was observed between the amount of opium consumed per day and lung cancer, and the relation was stronger for the high-use group (for low-use group: adjusted OR, 3.81; 95% CI, 1.13–12.77; and for high-use group: OR, 9.36; 95% CI, 2.05–42.72). The odds ratio for the association between opium consumption and lung cancer among non-smokers of tobacco was 6.50 (95% CI, 2.89–14.64). Interaction *P* values for cigarette smoking (ever-use) with opium were 0.38 and 0.14 for ever-use and cumulative exposure, respectively. [The Working Group noted that strengths of the study included well-defined opium exposure, use of pathologically confirmed cases, and the use of population-based neighbour controls. Limitations included the retrospective study design, lack of clarity regarding the pathological subtypes of cases (the risk factors for adenocarcinoma could be different from those for SCC, as well as from those for metastatic cancers), potential recall bias, non-response, and the small sample size.]

2.3.3 Combined cancers of the respiratory tract

Sheikh et al. (2020) also investigated all respiratory cancers combined in the GCS. The study reported a fully adjusted hazard ratio in opium ever-users of 2.28 (95% CI, 1.58–3.30) for all respiratory cancers combined, with similar results when men and women were analysed separately. There was a positive exposure–response trend ($P < 0.0001$) for increasing quartiles of consumption (in the highest consumption quartile: HR, 3.22; 95% CI, 2.02–5.14). Risks for respiratory cancers combined were not as strong when limited to the subgroup of tobacco never-users (HR, 1.94; 95% CI, 1.02–3.71; 12 exposed cases). Analysis of mortality from respiratory cancers combined in the GCS revealed that current opium consumption, longer-term opium use, and higher cumulative consumption were all associated with an increased risk of death from respiratory cancers of 2–3-fold (Rahmati et al., 2017). [The Working Group noted that deaths from lung and laryngeal cancers made up all the cases included in these analyses, and that those sites were reported separately (and are included in the relevant sections above).]

2.4 Cancer and preneoplastic lesions of the stomach

See Table 2.4.

Two cohort studies and two case–control studies investigated the association of opium use with cancer of the stomach, in some cases including gastric cardia and preneoplastic lesions of the stomach. There was also a case series by Islami et al. (2004), which reported opium use data for 82 cases of gastric cancer (43% used opium) and 260 patients with no lesions that were visible endoscopically (27% used opium). [The Working Group considered the study to be uninformative because it was analysed as a case

Table 2.4 Cohort and case–control studies on opium consumption and cancer and preneoplastic lesions of the stomach

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) Golestan Province, Iran (Islamic Republic of) Enrolment, 2004–2008/ follow-up, 531 789 person-years (through December 2018; median, 10 yr) Cohort	GCS: 50 045 individuals aged 40–75 yr from rural and urban areas of Golestan Province (50 034 after excluding 11 diagnosed with cancer before enrolment); among them 308 stomach cancers (243 histologically confirmed) Exposure assessment method: validated GCSQ assessing complete opium exposure history at baseline including intensity, duration, cumulative exposure, and type and method of exposure; systematic prospective data collection	Stomach, incidence	Opium use (HR): Never Ever	 218 90	 1 1.36 (1.03–1.79)	Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes, regular alcohol drinking (ever/never)	*Exposure assessment critique*: High-quality, multimetric exposure assessment collected prospectively with temporal aspects mostly incorporated into estimates. Considers duration, cumulative exposure, and exposure method. Potential for non-differential measurement error. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: prospective design; large sample size; extensive data collection for the exposure of interest (opium) and potential confounders, and blinded evaluation of outcome; sensitivity analyses were conducted excluding recent use of opium and deaths that occurred during the first 2 yr of follow-up. *Limitations*: small number of cases; may be some degree of misclassification of cause of death, in spite of the validity of the verbal autopsy.
		Stomach, incidence	Opium use, men (HR): Never Ever	 NR NR	 1 1.43 (1.05–1.93)	Age, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes, regular alcohol drinking (ever/never)	
		Stomach, incidence	Opium use, women (HR): Never Ever	 NR NR	 1 1.08 (0.51–2.24)		

Table 2.4 Cohort and case–control studies on opium consumption and cancer and preneoplastic lesions of the stomach (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) (cont.)		Stomach (cardia subtype), incidence	Opium use (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes, regular alcohol drinking (ever/never)	
			Never	133	1		
			Ever	48	1.18 (0.81–1.70)		
		Stomach (noncardia subtype), incidence	Opium use (HR):				
			Never	85	1		
			Ever	42	1.69 (1.11–2.56)		
		Stomach, incidence	Cumulative opium use (HR):				
			Never used opium	218	1		
			≤ 5 nokhod-years	NR	1.33 (0.83–2.13)		
			5.1–21 nokhod-years	NR	1.57 (1.01–2.43)		
			21.1–60 nokhod-years	NR	1.19 (0.73–1.94)		
			> 60 nokhod-years	NR	1.37 (0.88–2.11)		
			Trend-test *P* value, 0.067				
		Stomach/gastric cancer, incidence	Individual and combined effects of opium and tobacco (HR):			Age, sex, ethnicity (Turkman/non-Turkman), residence (urban/rural), wealth score quartile, regular alcohol drinking (ever/never)	
			Used neither opium nor tobacco	188	1		
			Used opium but not tobacco	37	1.22 (0.85–1.75)		
			Used tobacco but not opium	30	0.79 (0.53–1.18)		
			Used both opium and tobacco	53	1.33 (0.96–1.86)		

Table 2.4 Cohort and case–control studies on opium consumption and cancer and preneoplastic lesions of the stomach (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Malekzadeh et al. (2013) Golestan Province, Iran (Islamic Republic of) Enrolment, 2004–2008/ follow-up, through December 2012 (median, 6.3 yr) Cohort	GCS: 50 045 participants in a population-based cohort of individuals aged 40–75 yr at enrolment; cohort participants were primary rural individuals; 58% women; 123 stomach cancer deaths Exposure assessment method: validated GCSQ assessing complete opium exposure history at baseline including intensity, duration, cumulative exposure, and type and method of exposure; systematic prospective data collection	Stomach, mortality	Opium use (HR): Never Ever	 NR NR	 1 1.19 (0.78–1.83)	Age, sex, ethnicity (Turkman/non-Turkman), place of residence (urban/rural), cigarette smoking (ever/never), alcohol consumption (ever/never), and HBV infection	*Exposure assessment critique*: High-quality, multimetric exposure assessment collected prospectively, with timing of opium use relative to outcome mostly incorporated into estimates. Potential for non-differential measurement error. Risk analysed by opium type and method of exposure. Also combined in analyses to ever/never opium exposure and cumulative nokhod-days. Few heroin users. Considers current and former exposure, duration of exposure, and time since last exposure. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: prospective; large sample size; minimal loss to follow-up; adjustment for major confounders; exposure measurement validated; reverse causation sensitivity analysis. *Limitations*: reverse causation not entirely ruled out; potential for outcome misclassification for deaths with verbal autopsy only.

Table 2.4 Cohort and case–control studies on opium consumption and cancer and preneoplastic lesions of the stomach (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sadjadi et al. (2014) Ardabil Province, Iran (Islamic Republic of) Enrolment, NR/ follow-up, 9036 person-years (median, 10 yr) Cohort	928; healthy individuals aged ≥ 40 yr and infected with *Helicobacter pylori* Exposure assessment method: data collected using a questionnaire described as validated, but no details of questions or validation provided; very low prevalence of opium use	Stomach, incidence	Opium use (HR): Never Ever	 32 4	 1 4.6 (1.6–13.3)	Age	*Exposure assessment critique*: Well-defined but poorly characterized (single-metric) exposure assessment collected prospectively, with timing of opium use relative to outcome mostly incorporated into estimates. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: prospective study; low loss to follow-up; adjustment for major confounders; availability of biopsy data and reporting associations with precancerous lesions; outcome ascertainment using histology in > 90% of cases. *Limitations*: small sample size; no information on dose–response relationship; no sensitivity analyses reported.
		Stomach, incidence	Opium use (HR): Never Ever	 32 4	 1 3.24 (1.37–7.66)	Age, sex, cigarette smoking, hookah smoking, alcohol use, fruit/vegetable intake < 400 g/day, salt intake > 6 g/day, family history of gastric cancer	
		Stomach (baseline precancerous lesion: antral intestinal metaplasia), incidence	Opium use (OR): Never Ever	 NR NR	 1 3.29 (1.2–9.1)	Age, cigarette smoking, hookah smoking, fruit/ vegetable intake < 400 g/day, salt intake > 6 g/day	
		Stomach (baseline precancerous lesion: gastric body intestinal metaplasia), incidence	Opium use (OR): Never Ever	 NR NR	 1 7.34 (2.5–21.5)		

Table 2.4 Cohort and case–control studies on opium consumption and cancer and preneoplastic lesions of the stomach (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Shakeri et al. (2013) Golestan Province, Iran (Islamic Republic of) 2004–2011 Case–control	Cases: 309 cases of gastric cancer (adenocarcinoma) including 118 noncardia, 161 cardia, and 30 of mixed or unspecified site were enrolled from patients referred to Atrak Clinic, the only gastroenterology specialty clinic in the area Controls: 613 controls were selected from the GCS, a population-based cohort in the area; controls were individually matched on age, sex, and neighbourhood	Stomach (adenocarcinoma), incidence	Opium use (OR):			Age, sex, neighbourhood, ethnicity, education, wealth score, total daily fruit intake, total daily intake of vegetables, use of hookah, nass, and cigarettes, and *Helicobacter pylori* infection	*Exposure assessment critique*: Opium exposure well defined and well characterized, and timing of opium use relative to outcome considered. Opium exposure intensity, duration, cumulative use, and temporality determined. Data on type or method of consumption were not considered. Sensitivity analyses excluding exposure 1 yr before diagnosis to minimize reverse causation. Unexposed referent group could include exposed. No exposure lagging.
			Never	200	1		
			Ever	109	3.1 (1.9–5.2)		
		Stomach (adenocarcinoma), incidence	Cumulative opium use (OR):				
			Never used opium	200	1		
			≤ Median among controls (29 nokhod-years)	87	2.5 (1.4–4.3)		
			> Median among controls	22	4.5 (2.3–8.5)		
		Stomach (adenocarcinoma), incidence	Opium use, excluding cases who started within 1 yr before diagnosis (OR):				
			Never	NR	1		
			Ever	NR	2.9 (1.7–4.8)		

Table 2.4 Cohort and case–control studies on opium consumption and cancer and preneoplastic lesions of the stomach (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Shakeri et al. (2013) (cont.)	Exposure assessment method: GCSQ; reasonably detailed exposure history, although type of opium exposure and method of exposure was not defined; median opium use in controls considered cut-off point for low vs high use (to reflect intensity of use in background population)	Stomach (adenocarcinoma: cardia subtype), incidence	Opium use (OR): Never Ever	 110 51	 1 2.8 (1.4–5.7)	Age, sex, neighbourhood, ethnicity, education, wealth score, total daily fruit intake, total daily intake of vegetables, use of hookah, nass, and cigarettes, and *Helicobacter pylori* infection	*Other comments*: neither the interviewers nor the participants had a preconceived notion that opium was a risk factor for gastric cancer, which reduced the possibility of reporting bias. *Strengths*: histological diagnosis of all cases; classification of most cases as noncardia or cardia subsites; use of population-based controls previously shown to be appropriate controls for cases; use of reliable and validated questionnaires with detailed questions about opium use. *Limitations*: slight potential for reporting bias and reverse causation.
		Stomach (adenocarcinoma: noncardia subtype), incidence	Opium use (OR): Never Ever	 72 46	 1 3.9 (1.6–9.4)		

Table 2.4 Cohort and case–control studies on opium consumption and cancer and preneoplastic lesions of the stomach (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Naghibzadeh Tahami et al. (2014) Kerman Province, Iran (Islamic Republic of) 2010–2012 Case–control	Cases: 142 cases cancer of the upper GI tract (oral cavity, oesophagus, liver, pancreas, and stomach) were identified using a local cancer registry (89 stomach cancer cases) Controls: 284 neighbours of the cases, matched on sex and age (± 5 yr) (178 matched controls for stomach cancer cases); The closest neighbour to the right was selected	Stomach, incidence Stomach, incidence	Opium use (OR): Never Ever Cumulative opium use (OR): Never ≤ Median among controls, nokhod-years > Median among controls, nokhod-years	 55 34 55 8 26	 1 3.0 (1.6–5.6) 1 7.3 (1.2–43.0) 9.2 (2.5–33.7)	Age, sex, residence (urban/rural), dietary factors (meat, fruit, vegetables, and hydrogenated fats), smoking	*Exposure assessment critique*: Opium exposure well defined and well characterized. Opium use defined. Intensity, duration, cumulative use, and type of use included. No information on mode of exposure. Systematic data collection after case identification. Raw and prepared opium only, no heroin or dross users. Unexposed referent group could include exposed. No exposure lagging.

Table 2.4 Cohort and case–control studies on opium consumption and cancer and preneoplastic lesions of the stomach (continued)

Reference, location enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Naghibzadeh Tahami et al. (2014) (cont.)	Exposure assessment method: validated GCSQ assessing complete opium exposure history including intensity, duration, cumulative exposure, and type and method of exposure; systematic retrospective data collection; one interviewer (main researcher) performed most interviews; median opium use in controls considered cut-off point for low vs high use (to reflect intensity of use in background population)						*Strengths*: used structured questionnaire with detailed data on opium use and potential confounders; used trained interviewers; adjusted for potential confounders; conducted the study in an area where opium use is common and relatively free of stigma; a system for selecting controls. *Limitations*: limited sample size; small potential for interviewer bias; potential control selection bias, if the neighbourhood controls did not trust the interviewers; potential reporting bias in controls.

CI, confidence interval; GCS, Golestan Cohort Study; GCSQ, Golestan Cohort Study Questionnaire; GI, gastrointestinal; HBV, hepatitis B virus; HR, hazard ratio; NR, not reported; OR, odds ratio; vs, versus; yr, year.

series and only percentages were shown, without adjustment for potential confounders.]

Sheikh and colleagues investigated stomach cancer incidence (308 cases; 79% histologically confirmed) in the GCS; see the detailed description of the GCS in Section 2.1 (Sheikh et al., 2020). After adjusting for potential confounders, including cigarette smoking (status and pack-years), opium use was associated with increased incidence of cancer of the stomach (HR, 1.36; 95% CI, 1.03–1.79), particularly for men (HR, 1.43; 95% CI, 1.05–1.93; 225 cases) and the noncardia subtype (HR, 1.69; 95% CI, 1.11–2.56; 127 cases). Stomach cancer incidence generally increased with increasing amounts of opium used; however, the increase was not monotonic (*P* for trend, 0.067).

Two earlier analyses of the GCS investigated the association of mortality from cancer of the stomach with opium use (Khademi et al., 2012; Malekzadeh et al., 2013). Because the study by Sheikh et al. (2020) had a longer follow-up period and included a larger number of cases, these two studies are not discussed in detail here; however, the results of Malekzadeh et al. (2013) (as the more recent of the two analyses) are included in Table 2.4.

In a population-based cohort study (Sadjadi et al., 2014) in Ardabil Province, Iran, 928 healthy, *Helicobacter pylori*-infected individuals were randomly selected. During nearly 10 years of follow-up, 36 new cases of gastric cancer were identified. Opium use was associated with an increased risk of gastric cancer, with an age-adjusted hazard ratio of 4.6 (95% CI, 1.6–13.3) and a multivariable-adjusted hazard ratio of 3.24 (95% CI, 1.37–7.66). Furthermore, opium use was strongly associated with increased risk of precursor lesions for gastric cancer at baseline, including antral (OR, 3.29; 95% CI, 1.2–9.1) and gastric body (OR, 7.34; 95% CI, 2.5–21.5) intestinal metaplasia.

In a case–control study (Shakeri et al., 2013), 309 cases of gastric adenocarcinoma (noncardia, 118; cardia, 161; and mixed or unspecified adenocarcinomas, 30) and 613 matched controls were enrolled. Cases were enrolled from December 2004 to December 2011 at Atrak Clinic, a gastroenterology specialty clinic in Gonbad City, the largest city in Golestan Province, Iran. For each case, up to 2 age-, sex-, and neighbourhood-matched controls were selected from 50 045 healthy participants, aged 40–75 years, who were enrolled in the GCS. Detailed information on long-term use of opium was obtained using the structured, validated GCSQ. After adjustment for multiple potential confounders including tobacco, opium use was associated with an increased risk of gastric adenocarcinoma with an adjusted odds ratio of 3.1 (95% CI, 1.9–5.2), and this increased risk was apparent for both anatomical subsites (cardia and noncardia). When cases who started using opium 1 year or less before diagnosis were excluded from the analysis, the results did not change materially, reducing the possibility of protopathic bias and reverse causality. There was an exposure–response effect, and individuals with the highest cumulative opium use had the strongest association (OR, 4.5; 95% CI, 2.3–8.5).

Another case–control study (Naghibzadeh Tahami et al., 2014) enrolled 89 cases of gastric cancer and 178 controls from Kerman Province, Iran. The cases were identified using a cancer registry. For each case, 2 neighbourhood controls were selected, matched to cases on sex, age, and place of residence. Data were collected on the amount of daily use and duration of use, from which cumulative use was calculated. All interviews were conducted by the primary investigator. After adjusting for potential confounders (including smoking), ever-use of opium was associated with an increased risk of gastric cancer, with an odds ratio of 3.0 (95% CI, 1.6–5.6). There was some evidence of an exposure–response association, and those who had cumulative use above the median had an odds ratio of 9.2 (95% CI, 2.5–33.7). [The Working Group noted that it

was unclear why the odds ratios for these two groups, stratified on exposure below and above the median, were both higher than the summary odds ratio for all opium users combined.]

2.5 Other cancers

See Table 2.5.

2.5.1 Cancer of the pancreas

Two epidemiological studies, a cohort study and a case–control study, investigated the association between opium use and incidence of pancreatic cancer.

The cohort study (Sheikh et al., 2020) investigated the association between opium use and incidence of pancreatic cancer in the GCS, updating an earlier analysis by Moossavi et al. (2018). During a median of 10 years of follow-up, 1833 individuals were diagnosed with cancer, including 78 with pancreatic cancer (65 diagnoses were histologically confirmed). Adjusting for a range of factors including cigarette smoking (status and pack-years), only high-exposure (> 60 nokhod-years) opium users had an increased risk of pancreatic cancer (HR, 2.66; 95% CI, 1.23–5.74; *P* for trend, 0.028). Risk of pancreatic cancer was not increased for ever-use of opium overall (HR, 1.54; 95% CI, 0.87–2.72), in sex-stratified results, or in the subgroup of tobacco never-users (HR, 1.40; 95% CI, 0.65–3.00).

The case–control study (Shakeri et al., 2016) recruited 357 cases of pancreatic cancer (316 histologically confirmed) and 328 controls from among patients who were referred to four endoscopic ultrasound centres in Tehran, Iran, from 2011 to 2015. Opium consumption was ascertained using the structured GCSQ (see Section 1.6, and Table S1.6.2D, Annex 1, Supplementary material for Section 1, web only; available from: https://publications.iarc.fr/600). The unadjusted odds ratio was 2.77 (95% CI, 1.64–4.69). After adjusting for potential confounders, including tobacco use, opium consumption was associated with an increased risk of cancer of the pancreas, with an odds ratio of 1.91 (95% CI, 1.06–3.43). Reclassification of individuals who started using opium 1 year before diagnosis as non-users did not materially change the results. There was no exposure–response association with either duration of opium use or cumulative opium use.

2.5.2 Cancers of the colon and rectum

One cohort study investigated the association between opium use and cancer of the colon, and two case–control studies investigated the association between opium use and cancers of the colon and rectum.

Sheikh and colleagues investigated the incidence of colon cancer (95 cases; 80% histologically confirmed) in the GCS cited earlier (Sheikh et al., 2020). Ever-use of opium was not associated with overall incidence of colon cancer (adjusted HR, 0.90; 95% CI, 0.48–1.67) or cumulative opium use (*P* for trend, 0.379), nor for men or women separately.

In a population-based case–control study conducted in the city of Kerman in Iran (Naghibzadeh-Tahami et al., 2016), 175 patients with cancer of the colon or rectum (diagnosed between January 2012 and December 2014) and 350 healthy controls were interviewed from September to November 2014. [The Working Group noted that it was not specified when the cases diagnosed in December 2014 were interviewed.] The cases were identified using a cancer registry. For each case, 2 controls were selected and matched to cases on the basis of sex, age, and place of residence. The use of opium was assessed using the structured and validated GCSQ. Opium use was associated with an increased risk of colorectal cancer, with an adjusted odds ratio of 4.5 (95% CI, 2.4–8.7). An exposure–response relation was observed between cumulative use of opium and incidence of colorectal cancer, where the odds ratios were 3.7 (95% CI, 1.6–8.6) and

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) Golestan Province, Iran (Islamic Republic of) Enrolment, 2004–2008/ follow-up, 531 789 person-years (through December 2018; median, 10 yr) Cohort	GCS: 50 045 individuals aged 40–75 yr from rural and urban areas of Golestan Province (50 034 after excluding 11 diagnosed with cancer before enrolment); among them 78 pancreatic, 95 colon, 914 GI, 80 brain, and 73 liver cancers (65, 76, 761, 52, and 51 histologically confirmed, respectively) Exposure assessment method: validated GCSQ assessing complete opium exposure history at baseline including intensity, duration, cumulative exposure, and type and method of exposure; systematic prospective data collection	Pancreas, incidence	Opium use (HR): Never Ever	 56 22	 1 1.54 (0.87–2.72)	Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	*Exposure assessment critique*: High-quality, multimetric exposure assessment collected prospectively, with temporal aspects mostly incorporated into estimates. Considers duration of exposure, cumulative exposure, and exposure method. Potential for non-differential measurement error. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: prospective design; large sample size; extensive data collection for the exposure of interest (opium) and potential confounders, and blinded evaluation of outcome; sensitivity analyses were conducted excluding recent use of opium and cases that occurred during the first 2 yr of follow-up.
		Pancreas, incidence	Opium use, men (HR): Never Ever	 NR NR	 1 1.85 (0.91–3.72)	Age, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
		Pancreas, incidence	Opium use, women (HR): Never Ever	 NR NR	 1 1.19 (0.42–3.33)		

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) (cont.)		Pancreas, incidence	Cumulative opium use (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	*Limitations*: small number of cases; may be some degree of misclassification of cause of death, in spite of the validity of the verbal autopsy, for cases identified after death.
			Never used opium	56	1		
			1st quartile (≤ 5 nokhod-years)	NR	0.91 (0.28–2.97)		
			2nd quartile (5.1–21 nokhod-years)	NR	1.50 (0.58–3.90)		
			3rd quartile (21.1–60 nokhod-years)	NR	1.19 (0.41–3.43)		
			4th quartile (> 60 nokhod-years)	NR	2.66 (1.23–5.74)		
			Trend-test *P* value, 0.028				
		Pancreas, incidence	Individual and combined effects of opium and tobacco (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, regular alcohol drinking (ever/ never)	
			Used neither opium nor tobacco	48	1		
			Used opium but not tobacco	8	1.40 (0.65–3.00)		
			Used tobacco but not opium	8	1.44 (0.63–3.30)		
			Used both opium and tobacco	14	2.52 (1.25–5.07)		

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) (cont.)		Colon, incidence	Opium use (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	80	1		
			Ever	15	0.90 (0.48–1.67)		
		Colon, incidence	Opium use, men (HR):			Age, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	NR	1		
			Ever	NR	0.75 (0.36–1.56)		
		Colon, incidence	Opium use, women (HR):				
			Never	NR	1		
			Ever	NR	1.30 (0.43–3.88)		

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) (cont.)		Colon, incidence	Cumulative opium use (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never used opium	80	1		
			1st quartile (≤ 5 nokhod-years)	NR	1.58 (0.71–3.51)		
			2nd quartile (5.1–21 nokhod-years)	NR	0.49 (0.11–2.06)		
			3rd quartile (21.1–60 nokhod-years)	NR	0.74 (0.22–2.44)		
			4th quartile (> 60 nokhod-years)	NR	0.66 (0.19–2.25)		
			Trend-test *P* value, 0.379				
		GI cancers (oesophagus, stomach, pancreas, liver, colon, and rectum) combined, incidence	Opium use (HR):				
			Never	672	1		
			Ever	242	1.31 (1.11–1.55)		

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) (cont.)		GI cancers combined, incidence	Opium use, men (HR):			Age, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	NR	1		
			Ever	NR	1.34 (1.10–1.62)		
		GI cancers combined, incidence	Opium use, women (HR):				
			Never	NR	1		
			Ever	NR	1.18 (0.83–1.66)		
		GI cancers combined, incidence	Individual and combined effects of opium and tobacco (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, regular alcohol drinking (ever/ never)	
			Used neither opium nor tobacco	580	1		
			Used opium but not tobacco	105	1.27 (1.03–1.57)		
			Used tobacco but not opium	92	1.02 (0.80–1.29)		
			Used both opium and tobacco	137	1.46 (1.18–1.79)		

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Sheikh et al. (2020) (cont.)		Brain, incidence	Opium use (HR):			Age, sex, ethnicity (Turkman/ non-Turkman), residence (urban/ rural), wealth score quartile, cigarette smoking (ever/never), cumulative pack-years of smoked cigarettes (continuous variable), regular alcohol drinking (ever/never)	
			Never	63	1		
			Ever	17	1.13 (0.61–2.09)		
		Brain, incidence	Route of opium use (HR):				
			Never used opium	63	1		
			Only smoking	7	0.71 (0.31–1.64)		
			Only ingesting	9	2.15 (1.00–4.63)		
			Both	1	1.05 (0.14–7.90)		
		Liver, incidence	Opium use (HR):				
			Never	53	1		
			Ever	20	1.22 (0.68–2.18)		
		Liver and bile ducts, incidence	Route of opium use (HR):				
			Never used opium	53	1		
			Only smoking	8	0.78 (0.35–1.71)		
			Only ingesting	12	2.46 (1.23–4.95)		
			Both	0	–		

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Malekzadeh et al. (2013) Golestan Province, Iran (Islamic Republic of) Enrolment, 2004–2012/ follow-up, through December 2012 (median, 6.3 yr) Cohort	GCS: a population-based cohort of 50 045 individuals (women, 58%) aged 40–75 yr at enrolment; cohort participants were primarily from rural areas Exposure assessment method: validated GCSQ assessing complete opium exposure history at baseline including intensity, duration, cumulative exposure, and type and method of exposure; systematic prospective data collection	Combined cancers of pancreas, colon, and rectum, mortality	Opium use (HR): Never Ever	 NR NR	 1 1.39 (0.90–2.16)	Age, sex, ethnicity (Turkman/non-Turkman), place of residence (urban or rural), cigarette smoking (ever or never), alcohol consumption (ever or never), and hepatitis B virus (HBV) infection	*Exposure assessment critique*: High-quality, multimetric exposure assessment collected prospectively, with timing of opium use relative to outcome mostly incorporated into estimates. Potential for non-differential measurement error. Risk analysed by opium type and method of exposure. Also combined in analyses of ever/ never opium exposure and cumulative nokhod-days. Few heroin users. Cancer risk analysed by current and former exposure, duration of exposure, and time since last exposure. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: prospective study; large sample size; minimal loss to follow-up; adjusted for major confounders; validation of exposure measurement; sensitivity analysis for reverse causation. *Limitations*: reverse causation cannot be entirely ruled out; potential for outcome misclassification for deaths that only had verbal autopsy.

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Naghibzadeh Tahami et al. (2014) Kerman Province, Iran (Islamic Republic of) 2010–2012 Case–control	Cases: 142 cases of cancer of the upper GI tract (oral cavity, oesophagus, liver, pancreas, and stomach) were identified using a local cancer registry Controls: 284 neighbours of the cases, matched on sex and age (± 5 yr); the closest neighbours to the right were selected Exposure assessment method: validated GCSQ assessing complete opium exposure history including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic retrospective data collection; one interviewer (main researcher) performed most interviews; median opium use in controls considered cut-off point for low vs high use (to reflect intensity of use in background population)	Other upper GI tract (oral cavity, oesophagus, liver, and pancreas), incidence	Opium use (OR): Never Ever	 33 20	 1 9.3 (1.6–53.9)	Age, sex, residence (urban/rural), dietary factors (meat, fruit, vegetables, and hydrogenated fats), smoking	*Exposure assessment critique*: Opium exposure well defined and well characterized. Opium use defined. Intensity, duration, cumulative use, and type of use included. No information on mode of exposure. Systematic data collection after case identification. Raw and prepared opium only, no heroin or dross users. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: used structured questionnaire with detailed data on opium use and potential confounders; used trained interviewers; adjusted for potential confounders; conducted the study in an area where opium use is common and relatively free of stigma; a system for selecting controls. *Limitations*: limited sample size; small potential for interviewer bias; potential control selection bias, if the neighbourhood controls did not trust the interviewers; potential reporting bias in controls; exposure–response not considered for this end-point.

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Naghibzadeh-Tahami et al. (2016) Kerman, Iran (Islamic Republic of) 2012–2014 Case–control	Cases: 175 cases of cancer of the colon or rectum selected using a local cancer registry Controls: 350 neighbours of the cases, matched on sex and age (± 5 yr); the closest neighbour to the right was selected Exposure assessment method: validated GCSQ assessing opium exposure history including intensity, duration, cumulative exposure, and type and method of exposure; systematic retrospective data collection; median opium use in controls considered cut-off point for low vs high use (to reflect intensity of use in background population)	Colon and rectum, incidence	Opium use (OR):			Age, sex, residence, consumption of various dietary items (total daily fruit and vegetables, red meat, and hydrogenated fats), cigarette smoking	*Exposure assessment critique*: Opium exposure well defined and well characterized. Timing of opium use relative to outcome considered. Study considered ever vs never opium use, amount of daily opium use (based on median), duration of use, and cumulative use. History of opium use before diagnosis considered to neutralize the effect of reverse causation. Exposure assessed after case identification. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: reasonable sample size; structured questionnaire with detailed data on opium use and potential confounders; trained interviewers; adjusted for potential confounders; study conducted in area where opium use is common and relatively free of stigma; system for selecting controls.
			Never	130	1		
			Ever	45	4.5 (2.4–8.7)		
		Colon and rectum, incidence	Cumulative opium use (OR):				
			Never	130	1		
			≤ Median among controls (nokhod-years)	21	3.7 (1.6–8.6)		
			> Median among controls (nokhod-years)	24	8.0 (2.9–21.7)		
		Colon, incidence	Opium use (OR):				
			Never	103	1		
			Ever	39	5.7 (2.7–11.9)		
		Colon, incidence	Cumulative opium use (OR):				
			Never	103	1		
			≤ Median among controls (nokhod-years)	16	3.9 (1.5–9.9)		
			> Median among controls (nokhod-years)	21	9.4 (3.3–27.0)		

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Naghibzadeh-Tahami et al. (2016) (cont.)							*Limitations*: some potential for interviewer bias; potential control selection bias, if the neighbourhood controls did not trust the interviewers; potential reporting bias in controls.
Shakeri et al. (2016) Tehran, Iran (Islamic Republic of) 2011–2015 Case–control	Cases: 357 cases with histopathologically or clinically confirmed pancreatic carcinoma selected from patients referred for endoscopic ultrasonography to 4 endoscopic ultrasound centres in Tehran Controls: 328 controls without pancreatic adenocarcinoma selected from patients referred for ultrasonography to the same 4 endoscopic ultrasound centres Exposure assessment method: validated GCSQ assessing complete opium exposure history including intensity, duration, cumulative exposure, and type and method of exposure; systematic retrospective data collection	Pancreas, incidence	Opium use (OR):			None	*Exposure assessment critique*: Opium exposure well defined and well characterized, and timing of opium use relative to outcome considered. Comprehensive exposure assessment, just before case/control identification. Exposure included combined smoked and ingested opium, ever vs never, frequency of use based on ≤ or > the median per day, duration of use, cumulative use, and age at start of use. To address reverse causation, opium use was excluded 1, 2, and 3 yr before diagnosis. Study mentions "injected" use so could therefore incorporate heroin use, but no details are given. Unexposed referent group could include exposed. No exposure lagging.
			Never	300	1		
			Ever	57	2.77 (1.64–4.69)		
		Pancreas, incidence	Opium use (OR):			Age, sex, residence (urban/rural), alcohol use, ever-use of any type of tobacco	
			Never	300	1		
			Ever	57	1.91 (1.06–3.43)		
		Pancreas, incidence	Opium use (OR):				
			Never-use or use only within 1 yr of diagnosis	302	1		
			Ever	55	1.82 (1.01–3.29)		
		Pancreas, incidence	Duration of opium use (OR):				
			Never	305	1		
			≤ Median among controls (20 yr)	22	1.61 (0.72–3.52)		
			> Median among controls	30	1.79 (0.81–3.97)		

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Shakeri et al. (2016) (cont.)	Questionnaires administered by general practitioners when cases, controls, and interviewers were blinded to disease status (i.e. before ultrasound); route and type of opium consumed assessed but results are not included	Pancreas, incidence	Cumulative opium use (OR):			Age, sex, residence (urban/rural), alcohol use, ever-use of any type of tobacco	*Strengths*: relatively large sample size; detailed questions on opium use and potential confounders; uniform data collection; cases and controls selected from the same clinics; patients were questioned about opium use before diagnosis; strict case and control selection criteria. *Limitations*: potential for selection bias and information bias.
			Never	305	1		
			≤ Median among controls (34 nokhod-years)	26	1.85 (0.85–4.01)		
			> Median among controls	26	1.52 (0.67–3.43)		

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Iankarani et al. (2017) Fars Province, Iran (Islamic Republic of) 2014–2015 Case–control	Cases: 160 cases identified from the cancer registry centre of Shiraz University of Medical Sciences Controls: 320 controls selected from cases' neighbours, matched on age (± 5 yr) and sex Exposure assessment method: validated GCSQ assessing opium exposure history including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic retrospective data collection Trained interviewers; median opium use in controls considered cut-off point for low vs high use (likely reflective of background population)	Colon and rectum, incidence Colon and rectum, incidence	Opium use (OR): Never Ever Cumulative opium use (OR): Never used opium ≤ Median use among controls > Median use among controls	 128 32 128 16 16	 1 4.48 (2.27–8.82) 1 3.82 (1.58–9.18) 4.63 (1.78–12.05)	Age, sex, neighbourhood, special dietary factors (meat, fruit, vegetables, and hydrogenated fats), plus other main exposures (smoking)	*Exposure assessment critique*: Opium exposure well defined and well characterized, and timing of opium use relative to outcome considered. Comprehensive exposure assessment (intensity, duration, cumulative exposure, temporality, type, and mode). Exposure assessed after case identification. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: adequately large sample size; matched and/or adjusted for important potential confounders; used a structured questionnaire with detailed data on opium exposure; provided dose–response data. *Limitations*: potential for interviewer and reporting bias; potential for reverse causation.

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Tahergorabi et al. (2018) Birjand, Iran (Islamic Republic of) 2016–2017 Case–control	Cases: 68 patients referred to a hospital for colonoscopy with pathologically confirmed GI cancer (oesophagus, stomach, colon, or rectum) Controls: 100 healthy individuals referred to 3 health clinics in the same city, matched on age and sex Exposure assessment method: structured questionnaire with no further details; exposure defined only as "opium addict" with no additional information	GI cancers (oesophagus, stomach, colon, or rectum) combined, incidence	Opium use (OR): Never Ever	 48 20	 1 4.3 (1.6–11.5)	Age, sex	*Exposure assessment critique*: Opium exposure poorly defined and poorly characterized. No cumulative exposure or information on duration. Exposure data collection after case identification. Unexposed referent group could include exposed. No exposure lagging. *Limitations*: lack of detailed data on opium exposure; adjustment methods and covariates included in the model are unclear; potential for reverse causation; potential interviewer bias; potential under-reporting by cases.

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Alizadeh et al. (2020) Kerman, Iran (Islamic Republic of) 2014–2017 (and earlier) Case–control	Cases: 140 patients with head and neck cancers (nasal cavity, pharynx, paranasal sinuses, oral cavity, larynx, or salivary gland) with pathological information in the cancer registry of Kerman University of Medical Sciences Controls: 280 neighbourhood-based controls individually matched on age (± 5 yr), sex, and neighbourhood (nearest and first neighbours on the right side of the case's home who met the inclusion criteria)	Head and neck, incidence	Opium use (OR):			Age, sex, neighbourhood, dietary factors (meat, fruit, vegetables, hydrogenated fats, and olive oil), education (illiterate, elementary/middle school, high school/high school diploma, or above), cigarette smoking, alcohol drinking	*Exposure assessment critique*: Opium exposure well defined and well characterized. Comprehensive exposure assessment (intensity, duration, cumulative exposure, type, and mode). Temporality not specified; opium use in the 2 yr before cancer diagnosis excluded to minimize reverse causation. Exposure data collection after case identification. Unexposed referent group could include exposed. No exposure lagging. Only raw opium and opium sap used.
			Never	42	1		
			Ever	98	8.13 (4.08–16.21)		
		Head and neck, incidence	Amount of daily opium use (OR):				
			Never used opium	42	1		
			≤ Median (among controls)	45	7.19 (3.32–15.60)		
			> Median (among controls)	53	9.22 (4.19–20.28)		
		Head and neck, incidence	Duration of opium use (OR):				
			Never used opium	42	1		
			≤ Median (among controls)	58	5.65 (2.90–10.98)		
			> Median (among controls)	40	13.16 (5.32–32.53)		
		Head and neck, incidence	Cumulative use of opium (OR):				
			Never used opium	42	1		
			≤ Median (among controls)	48	6.52 (3.18–13.36)		
			> Median (among controls)	50	8.91 (4.03–19.65)		

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Alizadeh et al. (2020) (cont.)	Exposure assessment method: validated GCSQ assessing opium exposure history including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic retrospective data collection; trained interviewers; conducted at participants' homes; comfortable and friendly environment; used median use in controls to define non-use, and low and high use						*Strengths*: adequately large sample size; matched and/ or adjusted for important potential confounders; used a structured questionnaire with detailed data on opium exposure; provided dose–response data; disregarded opium use in those who started using opium in the 2 yr before diagnosis to address reverse causation. *Limitations*: potential for interviewer bias; potential under-reporting by controls.

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mohebbi et al. (2020) Iran (Islamic Republic of) April 2016 to April 2019 Case–control	Cases: 663 incident cases of head and neck SCC referred to cancer care centres in 10 provinces (IROPICAN study) Controls: 3065; ≥ 4 controls per case, frequency-matched on age, sex, and place of residence, selected from hospital visitors who were either relatives or friends of hospitalized patients in non-oncology wards, or persons who visited the hospital for any reason other than receiving treatment concurrently Exposure assessment method: validated GCSQ assessing complete opium exposure history including intensity, duration of exposure, cumulative exposure, and type and method of exposure; systematic retrospective data collection	Head and neck (SCC), incidence	Regular opium use (OR): Non-user Regular user Centre-heterogeneity *P* value, < 0.0001	 368 295	 1 3.76 (2.96–4.79)	Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	*Exposure assessment critique*: Opium exposure well defined and well characterized. Timing of opium use relative to outcome was considered. Multiple exposure metrics (regular/non-regular use, average intensity as daily amount of use, duration in years, type of opium used, and route of use). Exposure data collection after case identification. Unexposed referent group could include exposed. No exposure lagging. *Strengths*: large sample size; detailed data on opium exposure assessment; assessment of dose–response relationship; adjustment for important confounders, using the most reliable control group; sensitivity analysis for differential response between cases and controls; disregarded opium use in those who started using opium in the 3 yr before diagnosis to address reverse causation.
		Head and neck (SCC), incidence	Regular opium use, never-smokers of tobacco (OR): Non-user of opium Regular user Centre-heterogeneity *P* value, < 0.0001	 207 39	 1 5.17 (3.26–8.21)	Age, sex, place of residence (centre/ non-centre), alcohol drinking (regular/non-regular), SES, oral health	
		Head and neck (SCC), incidence	Duration of opium use (OR): 1st tertile (≤ 11 yr) 2nd tertile (12–23 yr) 3rd tertile (≥ 24 yr) Trend-test *P* value, < 0.0001 Centre-heterogeneity *P* value, < 0.0001	 51 101 143	 1 1.68 (1.04–2.72) 2.52 (1.55–4.11)	Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mohebbi et al. (2020) (cont.)		Head and neck (SCC), incidence	Duration of opium use, never-smokers of tobacco (OR):			Age, sex, place of residence (centre/ non-centre), alcohol drinking (regular/non-regular), SES, oral health	*Limitations*: retrospective design; potential for under-reporting by controls.
			1st tertile (≤ 11 yr)	15	1		
			2nd tertile (12–23 yr)	11	2.11 (0.68–6.49)		
			3rd tertile (≥ 24 yr)	13	2.70 (0.95–7.65)		
			Trend-test *P* value, 0.05				
			Centre-heterogeneity *P* value, < 0.0001				
		Head and neck (SCC), incidence	Cumulative opium use (OR):			Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	
			1st tertile (≤ 3.6 gram-years)	38	1		
			2nd tertile (3.7–24.5 gram-years)	104	2.27 (1.36–3.78)		
			3rd tertile (≥ 24.5 gram-years)	153	2.06 (1.22–3.47)		
			Trend-test *P* value, 0.022				
			Centre-heterogeneity *P* value, < 0.0001				

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mohebbi et al. (2020) (cont.)		Head and neck (SCC), incidence	Cumulative opium use, never-smokers of tobacco (OR):			Age, sex, place of residence (centre/ non-centre), alcohol drinking (regular/non-regular), SES, oral health	
			1st tertile (≤ 3.6 gram-years)	11	1		
			2nd tertile (3.7–24.4 gram-years)	17	2.08 (0.77–5.59)		
			3rd tertile (≥ 24.5 gram-years)	11	2.42 (0.80–7.35)		
			Trend-test *P* value, 0.10 Centre-heterogeneity *P* value, < 0.0001				
		Head and neck (SCC), incidence	Frequency-years of opium use (OR):			Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	
			1st tertile (≤ 8)	30	1		
			2nd tertile (8.1–22)	52	1.70 (0.97–2.99)		
			3rd tertile (≥ 23)	213	5.09 (3.05–8.47)		
			Trend-test *P* value, < 0.0001 Centre-heterogeneity *P* value, < 0.0001				
		Head and neck (SCC), incidence	Frequency-years of opium use, never-smokers of tobacco (OR):			Age, sex, place of residence (centre/ non-centre), alcohol drinking (regular/non-regular), SES, oral health	
			1st tertile (≤ 8)	8	1		
			2nd tertile (8.1–22)	11	1.91 (0.61–6.02)		
			3rd tertile (≥ 23)	20	6.27 (2.03–19.39)		
			Trend-test *P* value, 0.001 Centre-heterogeneity *P* value, < 0.0001				

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mohebbi et al. (2020) (cont.)		Head and neck (SCC), incidence	Average intensity of opium use (OR):			Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	
			1st tertile (≤ 0.4 g/day)	62	1		
			2nd tertile (0.5–2 g/day)	110	1.33 (0.83–2.13)		
			3rd tertile (≥ 2 g/day)	123	0.88 (0.53–1.44)		
			Trend-test *P* value, 0.46				
			Centre-heterogeneity *P* value, < 0.0001				
		Head and neck (SCC), incidence	Average intensity of opium use, never-smokers of tobacco (OR):			Age, sex, place of residence (centre/ non-centre), alcohol drinking (regular/non-regular), SES, oral health	
			1st tertile (≤ 0.4 g/day)	17	1		
			2nd tertile (0.5–2 g/day)	9	0.57 (0.16–2.01)		
			3rd tertile (≥ 2 g/day)	13	1.71 (0.50–5.80)		
			Trend-test *P* value, 0.26				
			Centre-heterogeneity *P* value, < 0.0001				
		Head and neck (SCC), incidence	Type of opium used (OR):			Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	
			Non-user	368	1		
			Crude opium (*teriak*)	238	3.40 (2.64–4.37)		
			Opium juice (*shireh*)	57	7.17 (4.44–11.58)		
			Centre-heterogeneity *P* value, < 0.0001				

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mohebbi et al. (2020) (cont.)		Head and neck (SCC), incidence	Type of opium used, never-smokers of tobacco (OR):			Age, sex, place of residence (centre/ non-centre), alcohol drinking (regular/non-regular), SES, oral health	
			Non-user	207	1		
			Crude opium (*teriak*)	35	5.11 (3.16–8.26)		
			Opium juice (*shireh*)	4	5.79 (1.71–19.57)		
			Centre-heterogeneity *P* value, < 0.0001				
		Head and neck (SCC), incidence	Route of opium use (OR):			Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	
			Non-user	368	1		
			Only smoking	168	2.66 (2.03–3.47)		
			Only ingestion	35	8.33 (4.67–14.85)		
			Both routes	92	12.96 (8.14–20.62)		
			Centre-heterogeneity *P* value, < 0.0001				
		Head and neck (SCC), incidence	Route of opium use, never-smokers of tobacco (OR):			Age, sex, place of residence (centre/ non-centre), alcohol drinking (regular/non-regular), SES, oral health	
			Non-user	207	1		
			Only smoking	20	3.39 (1.93–5.95)		
			Only ingestion	6	6.45 (2.21–18.82)		
			Both routes	13	24.78 (9.18–66.89)		
			Centre-heterogeneity *P* value, < 0.0001				

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mohebbi et al. (2020) (cont.)		Lip and oral cavity (SCC), incidence	Regular opium use (OR):			Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	
			Non-user	221	1		
			Regular user	33	1.53 (0.97–2.41)		
			Centre-heterogeneity *P* value, 0.28				
		Lip and oral cavity (SCC), incidence	Duration of opium use (OR):				
			1st tertile (≤ 11 yr)	8	1		
			2nd tertile (12–23 yr)	11	1.01 (0.37–2.76)		
			3rd tertile (≥ 24 yr)	14	2.09 (0.75–5.80)		
			Trend-test *P* value, 0.15				
			Centre-heterogeneity *P* value, 0.43				
		Lip and oral cavity (SCC), incidence	Cumulative opium use (OR):				
			1st tertile (≤ 3.6 gram-years)	7	1		
			2nd tertile (3.7–24.4 gram-years)	13	1.52 (0.56–4.13)		
			3rd tertile (≥ 24.5 gram-years)	13	1.24 (0.44–3.43)		
			Trend-test *P* value, 0.73				
			Centre-heterogeneity *P* value, 0.46				

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mohebbi et al. (2020) (cont.)		Lip and oral cavity (SCC), incidence	Frequency-years of opium use (OR):			Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	
			1st tertile (≤ 8)	11	1		
			2nd tertile (8.1–22)	5	0.41 (0.13–1.27)		
			3rd tertile (≥ 23)	17	1.24 (0.52–2.95)		
			Trend-test *P* value, 0.53				
			Centre-heterogeneity *P* value, 0.19				
		Lip and oral cavity (SCC), incidence	Average intensity of opium use (OR):				
			1st tertile (≤ 0.4 g/day)	7	1		
			2nd tertile (0.5–2 g/day)	15	2.28 (0.869–6.03)		
			3rd tertile (≥ 2 g/day)	11	1.12 (0.39–3.19)		
			Trend-test *P* value, 0.96				
			Centre-heterogeneity *P* value, 0.52				
		Lip and oral cavity (SCC), incidence	Type of opium used (OR):				
			Non-user	221	1		
			Crude opium (*teriak*)	28	1.41 (0.87–2.27)		
			Opium juice (*shireh*)	5	2.90 (1.05–7.97)		
			Centre-heterogeneity *P* value, 0.37				
		Lip and oral cavity (SCC), incidence	Route of opium use (OR):				
			Non-user	221	1		
			Only smoking	20	1.09 (0.64–1.86)		
			Only oral ingestion	6	4.25 (1.45–11.69)		
			Both routes	7	5.10 (2.41–12.89)		
			Centre-heterogeneity *P* value, 0.17				

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mohebbi et al. (2020) (cont.)		Pharynx (SCC), incidence	Regular opium use (OR):			Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	
			Non-user	37	1		
			Regular user	17	2.90 (1.40–6.02)		
			Centre-heterogeneity *P* value, < 0.0001				
		Pharynx (SCC), incidence	Duration of opium use (OR):				
			1st tertile (≥ 11 yr)	5	1		
			2nd tertile (12–23 yr)	5	0.93 (0.23–3.75)		
			3rd tertile (≥ 24 yr)	7	1.9 (0.4–8.6)		
			Trend-test *P* value, 0.40				
			Centre-heterogeneity *P* value, < 0.0001				
		Pharynx (SCC), incidence	Cumulative opium use (OR):				
			1st tertile (≥ 3.6 gram-years)	4	1		
			2nd tertile (3.7–24.4 gram-years)	6	1.35 (0.31–5.83)		
			3rd tertile (≥ 24.5 gram-years)	7	1.07 (0.22–5.08)		
			Trend-test *P* value, 0.95				
			Centre-heterogeneity *P* value, < 0.0001				

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mohebbi et al. (2020) (cont.)		Pharynx (SCC), incidence	Frequency-years of opium use (OR):			Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	
			1st tertile (≥ 8)	3	1		
			2nd tertile (8.1–22)	3	0.99 (0.17–5.54)		
			3rd tertile (≥ 23)	11	3.24 (0.76–13.71)		
			Trend-test *P* value, 0.07				
			Centre-heterogeneity *P* value, < 0.0001				
		Pharynx (SCC), incidence	Average intensity of opium use (OR):				
			1st tertile (≥ 0.4 g/day)	5	1		
			2nd tertile (0.5–2 g/day)	8	1.63 (0.48–6.51)		
			3rd tertile (≥ 2 g/day)	4	0.41 (0.07–2.26)		
			Trend-test *P* value, 0.26				
			Centre-heterogeneity *P* value, < 0.0001				
		Pharynx (SCC), incidence	Type of opium used (OR):				
			Non-user	37	1		
			Crude opium (*teriak*)	15	2.81 (1.32–5.97)		
			Opium juice (*shireh*)	2	3.77 (0.80–17.68)		
			Centre-heterogeneity *P* value, < 0.0001				
		Pharynx	Route of opium use (OR):				
			Non-user	37	1		
			Only smoking	15	3.04 (1.43–6.47)		
			Only oral ingestion	1	2.67 (0.33–21.57)		
			Both routes	1	1.74 (0.21–14.26)		
			Centre-heterogeneity *P* value, < 0.0001				

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mohebbi et al. (2020) (cont.)		Other subsites of head and neck (sinus, nasal cavity, middle ear, head and neck, and NOS) (SCC), incidence	Regular opium use (OR):			Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	
			Non-user	14	1		
			Regular user	14	5.95 (2.41–14.71)		
			Centre-heterogeneity *P* value, < 0.0001				
		Other subsites of head and neck (sinus, nasal cavity, middle ear, head and neck, and NOS) (SCC), incidence	Duration of opium use (OR):				
			1st tertile (≥ 11 yr)	3	1		
			2nd tertile (12–23 yr)	5	1.89 (0.35–10.05)		
			3rd tertile (≥ 24 yr)	6	2.96 (0.55–15.91)		
			Trend-test *P* value, 0.20				
			Centre-heterogeneity *P* value, NR				
		Other subsites of head and neck (sinus, nasal cavity, middle ear, head and neck, and NOS) (SCC), incidence	Cumulative opium use (OR):				
			1st tertile (≥ 3.6 gram-years)	1	1		
			2nd tertile (3.7–24.4 gram-years)	8	9.79 (1.06–89.78)		
			3rd tertile (≥ 24.5 gram-years)	5	6.71 (0.65–68.99)		
			Trend-test *P* value, 0.13				
			Centre-heterogeneity *P* value, < 0.0001				

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mohebbi et al. (2020) (cont.)		Other subsites of head and neck (sinus, nasal cavity, middle ear, head and neck, and NOS) (SCC), incidence	Frequency-years of opium use (OR):			Age, sex, place of residence (centre/ non-centre), pack-years of cigarette smoking, head-years of water-pipe smoking, alcohol drinking (regular/ non-regular), SES, oral health	
			1st tertile (≥ 8)	2	1		
			2nd tertile (8.1–22)	1	0.31 (0.02–4.06)		
			3rd tertile (≥ 23)	11	5.53 (1.03–29.66)		
			Trend-test *P* value, 0.02				
			Centre-heterogeneity *P* value, < 0.0001				
		Other subsites of head and neck (sinus, nasal cavity, middle ear, head and neck, and NOS) (SCC), incidence	Average intensity of opium use (OR):				
			1st tertile (≤ 0.4 g/day)	6	1		
			2nd tertile (0.5–2 g/day)	4	0.80 (0.19–3.34)		
			3rd tertile (≥ 2 g/day)	4	0.82 (0.19–3.42)		
			Trend-test *P* value, 0.77				
			Centre-heterogeneity *P* value, < 0.0001				
		Other subsites of head and neck (sinus, nasal cavity, middle ear, head and neck, and NOS) (SCC), incidence	Type of opium used (OR):				
			Non-user	14	1		
			Crude opium (*teriak*)	13	6.04 (2.43–15.05)		
			Opium juice (*shireh*)	1	4.83 (0.55–41.97)		
			Centre-heterogeneity *P* value, 0.002				
		Other subsites of head and neck (sinus, nasal cavity, middle ear, head and neck, and NOS) (SCC), incidence	Route of opium use (OR):				
			Non-user	14	1		
			Only smoking	8	3.97 (1.44–10.99)		
			Only oral ingestion	3	17.92 (4.32–74.26)		
			Both routes	3	11.96 (2.83–50.52)		
			Centre-heterogeneity *P* value, < 0.0001				

Table 2.5 Cohort and case–control studies on opium consumption and cancer at other organ sites (excluding oesophagus, stomach, urinary bladder, and respiratory tract) or organ site combinations (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vazirinejad et al. (2020) Rafsanjan, Iran (Islamic Republic of) 2016–2018 Case–control	Cases: 95 patients with cancer of the GI tract (oesophagus, stomach, pancreas, and colon or rectum) aged ≥ 18 yr referred to the oncology department of Ali ibn Abi Talib Hospital in Rafsanjan Controls: 190 relatives and neighbourhood controls individually matched on age (± 2 yr), sex, place of residence (urban/ rural), and smoking status Exposure assessment method: questionnaire; retrospective interview using checklist including intensity, duration of exposure, cumulative exposure, and type and method of exposure	GI cancers (oesophagus, stomach, pancreas, colon, and rectum) combined, incidence GI cancers combined, incidence	Opium use (OR): Never Ever Cumulative opium use (OR): Per 1 mesghal/ year increase	 70 25 25	 1 5.95 (2.37–14.99) 1.04 (1.02–1.06)	Age, sex, residence, smoking status, education, diet, family history of cancer	*Exposure assessment critique*: Opium exposure well defined and well characterized. Timing of opium use relative to the outcome was considered; did not record opium use in the 1 year before cancer diagnosis, to minimize reverse causation. Exposure data collection after case identification. No exposure lagging. Use of one trained interviewer minimized interpersonal variability and, potentially, interviewer bias. *Strengths*: adequately large sample size; matched and/ or adjusted for important confounders; excluded exposure to opium in the 1 yr before case diagnosis; detailed exposure data; reported dose–response relationship with cumulative opium exposure. *Limitations*: potential interviewer bias; potential under-reporting by controls.

–, risk estimate could not be calculated; CI, confidence interval; GCS, Golestan Cohort Study; GCSQ, Golestan Cohort Study Questionnaire; GI, gastrointestinal; HBV, hepatitis B virus; HR, hazard ratio; IROPICAN, Iranian study of Opium and Cancer; NOS, not otherwise specified; NR, not reported; OR, odds ratio; SCC, squamous cell carcinoma; SES, socioeconomic status; vs, versus; yr, year.

8.0 (95% CI, 2.9–21.7) for lower and higher than median use, respectively. Similar results were obtained when cancer of the colon alone was the outcome.

The second case–control study was similar to the one reported above, except that it was conducted in Fars Province, Iran (Iankarani et al., 2017). In this study, 160 new cases of cancer of the colon or rectum and 320 age-, sex-, and place of residence-matched healthy neighbourhood controls (2 controls to each case) were selected. The cases were identified using the cancer registry centre of Shiraz University. Opium use was assessed using the structured and validated GCSQ. The use of opium was associated with an increased risk of colorectal cancer. The multivariable-adjusted odds ratio was 4.48 (95% CI, 2.27–8.82) for the association of opium use with cancer of the colon or rectum. Furthermore, there was some evidence of an exposure–response association, with odds ratios of 3.82 (95% CI, 1.58–9.18) and 4.63 (95% CI, 1.78–12.05) for cumulative opium use below and above the median, respectively, compared with never-use.

2.5.3 Cancers of the head and neck, excluding the larynx

The carcinogenic potential of opium use regarding carcinoma of the tongue was first proposed by Lyons & Yazdi (1969). Since then, a large case series (Fahmy et al., 1983), an ecological study (Rashidian et al., 2016), and four case–control studies (Saedi et al., 2012; Razmpa et al., 2014; Alizadeh et al., 2020; Mohebbi et al., 2020) have been published on this topic. The case series (Fahmy et al., 1983) and the ecological study (Rashidian et al., 2016) were considered uninformative by the Working Group. The case–control study by Saedi et al. (2012) reported data for 557 cases of oral cancer referred to two tertiary hospitals in Tehran, Iran. Of these cases, 9% had a history of opium abuse; however, the study did not report the results of opium use in the 300 controls, so the study was not considered informative. Another case–control study by Razmpa et al. (2014), which included 80 cases of oral cancer and 80 controls, was also considered uninformative because of methodological issues and potential problems with statistical analysis. In particular, the crude odds ratios could not be confirmed; the magnitudes of adjusted odds ratios were not presented; and although the reported *P* value for opium was below 0.05, the value of the corresponding *t*-statistic did not reach 1.96. The study by Alizadeh et al. (2020) did not report results for individual subsites (other than the larynx) and their results for "other head and neck cancers combined" are included in Section 2.5.4 below.

A large-scale case–control study by Mohebbi et al. (2020) compared opium use of 663 cases with SCC of the head and neck (lip and oral cavity, 254 cases; pharynx, 54 cases; larynx, 327 cases; and other subsites, 28 cases) with 3065 controls. The cases were selected from 10 centres in various cities in Iran. For each case, at least 4 frequency-matched controls (matched on age, sex, and place of residence) were selected. Potential controls were hospital visitors who were either relatives or friends of hospitalized patients in non-oncology wards, or who visited the hospital for reasons other than receiving treatment. Pilot studies showed that this control group was more appropriate for opium use studies than other control groups (e.g. hospital or clinic patients, or neighbourhood controls). Detailed data were available on the history of opium use (e.g. frequency, duration, amount used each time, type of opium used, etc.) and for a range of potential confounders (including tobacco use). To alleviate concerns regarding protopathic bias and reverse causality, opium use was disregarded in those who started using opium up to 3 years before diagnosis. Results for cancer of the larynx are presented in Section 2.3; results for other cancers are discussed here. After adjusting

for potential confounders, including pack-years of cigarette smoking, head-years of water-pipe smoking, and regular alcohol drinking, there was an increased risk of all head and neck SCCs (OR, 3.76; 95% CI, 2.96–4.79), and cancers of the pharynx (OR, 2.90; 95% CI, 1.40–6.02), lip and oral cavity (OR, 1.53; 95% CI, 0.97–2.41), and other subsites (OR, 5.95; 95% CI, 2.41–14.71). On the basis of frequency-years of opium use, there was a clear exposure–response relation for all cancers of the head and neck combined, cancer of the pharynx, and cancers of other subsites. [The Working Group noted that this measure seemed to be the most appropriate measure of cumulative use.] The point estimate for the association of opium use with all head and neck cancers was larger among never-smokers, with an odds ratio of 5.17 (95% CI, 3.26–8.21), ruling out confounding by smoking. Associations were seen both for those who smoked and for those who ingested opium, but the strongest association was seen for those who used opium by both ingestion and smoking. After adjusting for the sensitivity of responses in cases (0.77) and controls (0.68), obtained from previous studies, the odds ratios were attenuated but the association remained strong. A positive association was observed for those participants who used crude opium (*teriak*) (OR, 2.81; 95% CI, 1.32–5.97) and cancer of the pharynx.

2.5.4 Other cancer sites or cancer combinations

Data for other cancers, as well as for other cancer combinations, were sparse.

(a) Cohort studies

Sheikh and colleagues investigated the incidence of all cancers of the gastrointestinal (GI) tract combined (914 cases; 83% histologically confirmed), cancer of the brain (80 cases; 65% histologically confirmed), and cancer of the liver (73 cases; 70% histologically confirmed) in the GCS cited earlier (Sheikh et al., 2020). Compared with never-use of opium, there was no association between ever-use of opium and incidence of cancer of the brain or liver; however, incidence was increased among opium users who only ingested opium compared with never-users for both of these sites. After adjustment for multiple potential confounders, opium users also had increased risk of incidence of all GI cancers combined (HR, 1.31; 95% CI, 1.11–1.55). Results were similar for men (HR, 1.34; 95% CI, 1.10–1.62), but not as strong for women (HR, 1.18; 95% CI, 0.83–1.66). Compared with non-users of both tobacco and opium, opium use was associated with increased incidence of all GI cancers combined both for non-tobacco users (HR, 1.27; 95% CI, 1.03–1.57) and for tobacco users (HR, 1.46; 95% CI, 1.18–1.79). Malekzadeh et al. (2013) found that the mortality of "cancers of pancreas, colon, and rectum combined in this same cohort was slightly elevated in opium users", with a hazard ratio of 1.39 (95% CI, 0.90–2.16), but did not report results for each individual cancer.

Sheikh et al. (2020) also investigated the association between opium use and all cancers combined. In total, 1833 of the study participants were diagnosed with cancer. After adjusting for multiple potential confounders, opium use was associated with an increased risk of developing all cancers combined, with a hazard ratio of 1.40 (95% CI, 1.24–1.58). The association for all cancers remained positive in a group of tobacco never-users, with a hazard ratio of 1.32 (95% CI, 1.13–1.55). There was a clear exposure–response association ($P < 0.0001$), and for the highest quartile of use the hazard ratio was 1.70 (95% CI, 1.42–2.04). Likewise, there was an increased risk of all cancers combined for those who smoked and those who ingested opium.

Two other reports presented data for all cancers combined. Nalini et al. (2020) used data from the GCS, which were the same as those used by Sheikh et al. (2020). [Given that the

paper by Sheikh and colleagues was focused on cancer outcomes and provided a substantially more detailed analysis, the Working Group considered that the data presented by Nalini et al. did not add any further information.] Another cohort study (Firouzabadi et al., 2020) reported very few (only 8) cases of cancers among opium users and the data were not adjusted for important confounders. [The Working Group considered this study uninformative because of these limitations.]

(b) Case–control studies

The case–control study by Naghibzadeh Tahami et al. (2014) (previously described for gastric cancer) reported data for a total of 53 cases of cancer of other upper GI sites (oral cavity, oesophagus, liver, and pancreas), but did not report the results for each cancer because of the small sample size. After adjusting for potential confounders, ever-use of opium was associated with increased risk of other upper GI cancers, with an odds ratio of 9.3 (95% CI, 1.6–53.9). Results for an exposure–response association were not reported. A study by Tahergorabi et al. (2018) used data from 68 patients with histologically confirmed GI cancer (cancers of the oesophagus, stomach, colon, and rectum) and 100 controls. The controls were patients referred to three centres in the same city as the cases (Birjand, Iran), matched on age and sex. It was reported that 29.4% of the cases and 8.8% of the controls used opium, leading to an odds ratio of 4.3 (95% CI, 1.6–11.5) that was not adjusted for smoking or other potential confounders.

Vazirinejad et al. (2020) investigated the incidence of GI cancers combined (cancers of the oesophagus, stomach, pancreas, colon, and rectum) in the city of Rafsanjan, Kerman Province, Iran (cases, 95; controls, 190). Cases were selected by convenience sampling and had received a pathologically confirmed diagnosis in the previous 2 years. [The Working Group noted the potential for selection bias in the use of convenience sampling of controls.] Cases were excluded if the patient consumed alcohol, nass, or other opioid drugs. Cases were individually matched to 1 family and 1 neighbourhood control on age (± 2 years), sex, residence (urban or rural), and smoking status (26% of cases and controls smoked cigarettes). After adjustment for several potential confounders, ever-use of opium was associated with an increased risk of GI cancer (OR, 5.95; 95% CI, 2.37–14.99; on the basis of 25 exposed cases). The average daily intake of opium in this study, 0.54 among cases and 0.07 among controls, was measured in *mesghals*, which is reported to be equal to 4.55 g (see Section 1.6.1). [The Working Group noted the use of the *mesghal* is unique to this study, and other studies have reported opium consumption in the much smaller unit of the *nokhod*.] Cumulative opium use was associated with an odds ratio of 1.04 (95% CI, 1.02–1.06) for an increase of 1 mesghal per year.

Alizadeh et al. (2020) conducted a case–control study of incident cancers of the head and neck (including tumours of the nasal cavity, pharynx, paranasal sinuses, oral cavity, larynx, and salivary gland) (see also Section 2.3). Cases were identified from a cancer registry both prospectively and retrospectively, and each case was matched on age (± 5 years) and sex to 2 neighbourhood controls. Information on opium consumption was collected using the validated GCSQ. Only opium use that occurred at least 2 years before cancer diagnosis was considered. Ever-use of opium was associated with increased risk of all cancers of the head and neck combined (OR, 8.13; 95% CI, 4.08–16.21) in multivariable-adjusted analyses (including adjustment for alcohol and tobacco use). Increased exposure, as measured by increased daily opium use, duration of use, and cumulative use, was associated with increased risk (below and above median exposure in controls compared with never-users) for all cancers of the head and neck combined.

2.6 Evidence synthesis for cancer in humans

This section provides a synthesis of studies of opium consumption in humans in relation to cancer of various sites. A detailed definition of opium, as the agent of investigation in the present monograph, has been provided in Section 1.1. It is important to note that the body of evidence regarding the carcinogenicity of opium and cancer in humans is derived from studies of populations exposed to the minimally processed latex of the poppy plant (*Papaver somniferum*). Processing may have included air drying, heat drying, or boiling, and included dross and (minimally) processed opium. Opium products, as consumed by the people in these epidemiological studies, comprise a complex chemical mixture that includes alkaloids (e.g. morphine and thebaine), non-alkaloids (e.g. sugars, fats, meconic acid, and water), and adulterants or contaminants (e.g. lead and chromium). Opium consumption by participants in the available studies was of raw or crude opium (*teriak*), opium dross (*sukhteh*), or refined or sap opium (*shireh*). All these forms of opium may be commonly ingested or smoked. No studies of cancer in humans were found that investigated users of opium tinctures that are produced legally and used for medicinal purposes.

Three prospective cohort studies and a large number of retrospective case–control studies investigated the association between opium use and different cancers. Cancers that were studied more extensively were those of the oesophagus, urinary bladder, larynx, lung, pancreas, stomach, colon and rectum, and oral cavity and pharynx; less evidence was available for other cancer types. With a few exceptions, the majority of the studies were conducted in Iran, where opium use is common, and a reasonably strong epidemiological research infrastructure allows for the study of the association between opium use and cancer. While the studies were conducted in a limited geographical area, the results can probably be generalized to other populations. The studies were conducted in various provinces of Iran (Table 2.6; Fig. 2.1), with substantial diversity in dietary and cultural habits, as well as different prevalence rates and average amounts of opium consumption. Their findings are unlikely to be attributable to an unnoticed fixed and strong confounding structure limited to Iran, because the reported associations between opium use and some cancers were stronger than for most other major cancer risk factors (e.g. cigarette smoking).

2.6.1 Studies evaluated

In assessing the carcinogenicity of opium use, substantial weight was given to the results from the GCS, a prospective study of over 50 000 individuals with median follow-up of 10 years (Sheikh et al., 2020). The GCS collected detailed and validated data on opium use, adjusted the results for a large number of potential confounders, and applied multiple methods to minimize the possibility of reverse causation. Although the GCS results offered high-quality data, sample sizes were only sufficiently large for a limited number of cancer sites (e.g. cancers of the oesophagus and stomach). Another limitation of the GCS was that the median amount of opium use was quite low (0.6 g/day according to Khademi et al., 2012); therefore, the results may have underestimated the associations for other populations that may consume higher amounts of opium. Another cohort in Ardabil Province offered data only for gastric cancer and had a small sample size (Sadjadi et al., 2014). The results of the third cohort study were not informative because the study had a short follow-up period and only 8 individuals had developed cancer (Firouzabadi et al., 2020). These three cohort studies used similar questionnaires.

Case–control studies were at greater risk of selection, information, and protopathic bias (more details in Annex 2 and

Table 2.6 Geographical distribution of key epidemiological studies of cancer and opium consumption in the Islamic Republic of Iran, by province

Province	Number of studies[a]	References
Kerman	7	IROPICAN (Mohebbi et al., 2020); Mousavi et al. (2003), Naghibzadeh-Tahami et al. (2014, 2016, 2020), Alizadeh et al. (2020), Vazirinejad et al. (2020)
Tehran	7	IROPICAN (Mohebbi et al., 2020); Asgari et al. (2004), Hosseini et al. (2010), Shakhssalim et al. (2010), Masjedi et al. (2013), Razmpa et al. (2014), Shakeri et al. (2016)
Golestan	5	GCS (Khademi et al., 2012, Malekzadeh et al., 2013, Rahmati et al., 2017, Sheikh et al., 2020); IROPICAN (Mohebbi et al., 2020); Nasrollahzadeh et al. (2008); Shakeri et al., (2012, 2013)
Khorasan-Rasavi	5	IROPICAN (Mohebbi et al., 2020); Shakhssalim et al. (2010), Bakhshaee et al. (2017), Tahergorabi et al. (2018), Pournaghi et al. (2019)
Fars	4	IROPICAN (Mohebbi et al., 2020); Sadeghi et al. (1979), Akbari et al. (2015), Iankarani et al. (2017)
Esfahan	2	Shakhssalim et al. (2010), Berjis et al. (2018)
Mazandaran	2	IROPICAN (Mohebbi et al., 2020); Aliramaji et al. (2015)
Ardabil	1	Sadjadi et al. (2014)
Boushehr	1	IROPICAN (Mohebbi et al., 2020)
East Azarbaijan	1	Shakhssalim et al. (2010)
Hormozgan	1	IROPICAN (Mohebbi et al., 2020)
Kermanshah	1	IROPICAN (Mohebbi et al., 2020)
Khouzestan	1	Shakhssalim et al. (2010)
Kordestan	1	Ghadimi et al. (2015)
Sistan and Baluchestan	1	IROPICAN (Mohebbi et al., 2020)
Yazd	1	Lotfi et al. (2016)

GCS, Golestan Cohort Study; IROPICAN, Iranian Study of Opium and Cancer.
[a] The GCS has multiple references.

Sections 2.6.3 and 2.6.4), but generally had larger numbers of cases and were mainly conducted in areas where average opium consumption was higher, for example, in Kerman Province, Iran. The degree to which each study was informative varied substantially. Some case–control studies, such as the IROPICAN study (Mohebbi et al., 2020), had a clear definition of exposure, were adjusted for multiple confounders, presented exposure–response analyses, provided results in tobacco never-smokers, and incorporated exposure only up to a certain period before diagnosis, avoiding reverse causality; however, other case–control studies were less informative due to a lack of information in one or more of the areas discussed above. While the IROPICAN study and some other case–control studies (e.g. Naghibzadeh-Tahami et al., 2020) were focused on opium consumption as a potential carcinogen, many of the other case–control studies were designed to study a host of risk factors and provided relatively little information on opium use.

Case series, cross-sectional studies, and ecological studies were considered, but ultimately excluded from this review because they were uninformative for the assessment of the association between opium consumption and cancer. In some earlier GCS publications, cancer mortality, rather than incidence, was the outcome; however, these publications were superseded by the paper by Sheikh et al. (2020), which presented data on

Fig. 2.1 Map of the Islamic Republic of Iran

cancer incidence. The results of the latter study were qualitatively and quantitatively similar to those of the earlier publications.

2.6.2 Exposure assessment and misclassification of exposure

The GCS collected detailed data on lifetime opium consumption at baseline, which included duration of use, ages of initiation and quitting, frequency and amount of use, and route of consumption (Section 2.1). It has been shown (Abnet et al., 2004) that the participants in the GCS provided data that were reliable and highly correlated with results from testing for metabolites of opium in the urine, and therefore that the quality of exposure assessment was high; however, there may have been a small amount of bias towards the null, because infrequent opium users (use for < 6 months) were included in the referent group of "never" opium users. The Working Group considered that the accuracy of the GCS exposure data may be close to that of studies of cigarette smoking, in which misclassification is low enough for the effect of the exposure to be studied. While some level of non-differential misclassification may still exist, which may bias the results towards the null, the positive and statistically significant associations between opium use and cancer identified by this study partially alleviate this concern.

Several of the case–control studies, such as the IROPICAN study (Mohebbi et al., 2020) and some other studies from Kerman Province (e.g. Naghibzadeh Tahami et al., 2014, 2020), also collected detailed exposure data. Some case–control studies may have suffered from differential exposure misclassification, particularly if they chose to use neighbourhood controls. Neighbourhood controls may under-report their amount of use and current use status, particularly if they were interviewed in their homes, where they may potentially have been heard by family members and friends. Such under-reporting in controls may bias the results away from the null. To avoid this problem, studies such as IROPICAN (Mohebbi et al., 2020) used healthy hospital visitors who were not family members of cancer cases and conducted sensitivity analyses for the differential sensitivities of responses between cases and controls.

Some case–control studies were even more limited, reporting the results of opium use in a dichotomous fashion and providing very little information on how opium use was assessed. For example, a case–control study by Pournaghi et al. (2019) offered almost no detail regarding exposure assessment beyond the statement that "data were collected through structured interviews".

2.6.3 Confounding and selection bias

There are at least four major confounding factors in assessing the causality of association between opium consumption and various cancers: sex, age, tobacco use, and socioeconomic status. Opium use in Iran, where the majority of the data came from, is much more common among men, older individuals, people with lower socioeconomic status, and those who use tobacco. All of these attributes are also associated with increased risk of several cancers. Many studies either adjusted for or matched on sex, age, and neighbourhood (a proxy for socioeconomic status). Likewise, many studies adjusted for tobacco smoking or stratified the results by smoking status.

The results from the GCS were meticulously adjusted for sex, age, tobacco use, and socioeconomic status. For reasons that are unclear, the association between tobacco use and oesophageal SCC and lung cancer in Iran and in some other Asian countries (Tran et al., 2005; Kamangar et al., 2007; Nasrollahzadeh et al., 2008; Zheng et al., 2014; Naghibzadeh-Tahami et al., 2020) is not as strong as that seen in countries in North America and Europe (e.g. Freedman et al., 2007, 2008). In fact, the association between opium

use and overall mortality and some tobacco-associated cancers (e.g. cancers of the larynx, pharynx and oral cavity, oesophagus, stomach, and urinary bladder) was stronger than the association between tobacco use and these outcomes; hence, any residual confounding after careful adjustment for tobacco use should have been minimal. Furthermore, the GCS and several other studies showed strong associations between certain cancers and opium use among never-smokers, which should considerably alleviate any concerns about residual confounding from tobacco use. While confounding by other exposures cannot be completely refuted, adjustments for other exposures have not been shown to materially affect relative risk estimates for opium. The GCS, due to its prospective nature and high participation rate, is not subject to selection bias.

Case–control studies varied in their adjustment for confounders. However, most had adjusted for age, sex, study location (if conducted in multiple cities), and tobacco use. Selection bias remains a concern. Case–control studies that used hospitalized patients as their sources of controls may have provided biased estimates, because opium use may be associated with various non-malignant diseases, such as chronic obstructive pulmonary disease and liver cirrhosis, leading to estimates of measures of association that would be likely to be biased towards the null. On the other hand, neighbourhood controls who were opium users may have been less likely to participate in such studies, leading to estimates of measures of association that were biased away from the null. It has been suggested that the best controls may be individuals who visit the hospital where the cases are treated, but who are neither sick nor family members of cases (Rashidian et al., 2017). Recall bias is unlikely to be a problem, because nearly all participants remembered their long-term use of opium, regardless of their case status.

2.6.4 Protopathic bias and reverse causation

The association between opium consumption and cancer may be subject to protopathic bias and reverse causation. Extensive treatment of this is provided in Annex 2. Reverse causation did not affect the GCS or the Ardabil cohort study, because the participants did not have cancer at baseline. Protopathic bias may be eliminated easily for cancers with relatively short survival periods, such as oesophageal or pancreatic cancer, by excluding cases that were diagnosed within the first year (or the first few years) of the cohort study. In these cohort studies, the exclusion of the early period of follow-up had little effect on risk estimates. Likewise, these biases may be addressed in case–control studies by excluding exposure that occurred one or several years before case enrolment. By contrast, it may be more difficult to address protopathic bias for cancers that have longer survival periods, particularly if those cancers have long-standing symptoms before diagnosis that may be alleviated by opium use (e.g. by opium's antitussive effect).

2.6.5 Cancer of the oesophagus

The results of the GCS (Sheikh et al., 2020) included an increased risk of cancer of the oesophagus in opium ever-users, with an adjusted hazard ratio of 1.38 (95% CI, 1.06–1.80). The point estimates remained similar or became even stronger among tobacco never-users (HR, 1.41; 95% CI, 1.02–1.96), and after excluding cases that were diagnosed within the first 2 years of follow-up (HR, 1.52; 95% CI, 1.13–2.04), making residual confounding and reverse causation unlikely explanations for the findings. There was a positive exposure–response relation (*P* for trend, 0.0099), with the highest quartile (> 60 nokhod-years) showing a hazard ratio of 1.60 (95% CI, 1.06–2.42). The association was stronger for those who smoked opium

than for those who ingested it. While there were at least three non-overlapping case–control studies (Shakeri et al., 2012; Bakhshaee et al., 2017; Pournaghi et al., 2019), only one (Shakeri et al., 2012) had investigated sizable numbers of cases and controls and had adequately adjusted for potential confounders. This study, which was conducted in Golestan Province (the same location as the GCS), found different results depending on which control group was considered. Compared with a neighbourhood control group, the cases were more likely to be opium ever-users (adjusted OR, 1.77; 95% CI, 1.17–2.68), whereas there was almost no increased probability of opium use compared with hospital-based controls (adjusted OR, 1.09; 95% CI, 0.63–1.87). While it is difficult to determine which control group (if either) was most appropriate, it appears that the reported prevalence of opium use in the neighbourhood controls (18%) was closer to that of the validated reports from the general population.

The Working Group concluded that a positive association between opium consumption and cancer of the oesophagus is credible; however, chance, bias, and confounding cannot be ruled out with reasonable confidence. The association observed in the GCS was not very strong, which makes it possible that it arose due to residual confounding. The results of the case–control study were subject to interpretation based on the appropriateness of the control group. These findings were applicable primarily to oesophageal SCC, which constituted the majority of the cases of oesophageal cancer in both the case–control and cohort studies.

2.6.6 Cancer of the urinary bladder

The GCS found an adjusted hazard ratio of 2.86 (95% CI, 1.47–5.55) for opium ever-users compared with never-users (Sheikh et al., 2020). There was a positive exposure–response relation (P = 0.0009), with an adjusted hazard ratio of 4.28 (95% CI, 1.81–10.15) for the highest quartile of cumulative use (> 60 nokhod-years). The point estimate for the association was stronger among tobacco never-users (HR, 3.74; 95% CI, 1.63–8.59).

Nearly all eight case–control studies, involving a total of almost 1750 cases of bladder cancer combined, found higher odds of opium use among cases than in controls (Sadeghi et al., 1979; Asgari et al., 2004; Hosseini et al., 2010; Shakhssalim et al., 2010; Akbari et al., 2015; Aliramaji et al., 2015; Ghadimi et al., 2015; Lotfi et al., 2016). The adjusted odds ratios, when calculated, typically ranged from 2 to 5. These numbers are consistent with a summary pooled point estimate odds ratio of 3.40 calculated in a meta-analysis (Afshari et al., 2017) and those from the GCS (HR, 2.86) (see above). Control selection, adjustment for confounding, and a clear definition of exposure were among the limitations of several of these studies. However, studies that collected detailed data on exposure and adjusted for multiple confounders (e.g. Hosseini et al., 2010; Akbari et al., 2015) found strong associations between opium use and urinary bladder cancer. It is notable that the results of all studies, regardless of design, point in the same direction.

While many occupational exposures have been identified as risk factors for bladder cancer (Cogliano et al., 2011), occupation is unlikely to have been a major confounder for the association of opium use with bladder cancer in Iran. In the GCS, approximately 80% of the study population came from villages, where most of participants were farmers and did not have substantial exposure to occupational risk factors for bladder cancer. Likewise, in the earlier studies in Fars Province, where a very high male to female ratio (9 : 1) was found, there were no factories in the research area at the time. Thus far, no clear pattern of association has been shown between opium use and occupational exposures. As such, the Working Group did not consider occupational

exposure to be an important confounder in associations between opium consumption and bladder cancer in Iran.

The Working Group concluded that despite a modest number of cases in the GCS, a positive association was observed. Collectively, the most informative studies rule out chance, bias, confounding, and reverse causation with reasonable confidence. This inference is based on the observation of very strong associations, positive exposure–response associations, consistency across studies, the availability of studies with large sample sizes, and various efforts to rule out bias and confounding in a key study (the GCS).

2.6.7 Cancer of the larynx

The association between opium consumption and cancer of the larynx was extensively studied in a cohort study (the GCS) and in six case–control studies that included nearly 900 cases combined.

The GCS reported a fully adjusted hazard ratio of 2.53 (95% CI, 1.21–5.29) and a positive exposure–response trend (P = 0.0004), with an adjusted hazard ratio of 3.34 (95% CI, 1.33–8.34) in the highest cumulative consumption quartile (> 60 nokhod-years) (Sheikh et al., 2020). While the numbers were small, the point estimates were higher among women and those who had never smoked cigarettes.

All six case–control studies showed substantially increased opium use among patients with laryngeal cancer compared with controls, with odds ratios ranging from 2 to 16 (Khoo, 1981; Mousavi et al., 2003; Bakhshaee et al., 2017; Berjis et al., 2018; Alizadeh et al., 2020; Mohebbi et al., 2020). Four of these studies had serious methodological limitations, including lack of adjustment for important confounders, potential selection bias, and lack of analyses for reverse causation. However, two of these studies adjusted for many confounders and analysed the data in various ways (Alizadeh et al., 2020; Mohebbi et al., 2020), and found strong associations between opium use and laryngeal cancer. Alizadeh et al. (2020) found that the prevalence of opium use was 79% among the cases of cancer of the larynx, substantially higher than the prevalence of 29% among the controls, and the adjusted odds ratio was 11.98 (95% CI, 5.05–28.39). Likewise, 71% of the 327 cases of cancer of the larynx enrolled in the IROPICAN study (Mohebbi et al., 2020) were opium users, compared with only 13% of the controls, yielding an adjusted odds ratio of 6.55 (95% CI, 4.69–9.13). Furthermore, the IROPICAN study results showed a clear positive exposure–response relation with duration of opium use, with an odds ratio of 2.7 in the third tertile of use compared with the first tertile (P for trend, < 0.0001). The associations are unlikely to be attributable to recall bias because most people (cases and controls alike) recollect opium use. The study by Mohebbi et al. (2020) classified participants as non-users if they started using opium 3 years or less before diagnosis, ruling out reverse causation and protopathic bias. They also conducted a sensitivity analysis by calculating the odds ratio (95% CI) considering the sensitivity of self-report among cases and controls, and the results remained strongly positive.

The Working Group concluded that a positive association had been established between opium consumption and cancer of the larynx. Collectively, the most informative studies permitted chance, bias, confounding, and reverse causation to be ruled out with reasonable confidence. This inference was based on the observation of very strong associations, positive exposure–response trends, consistency across studies, availability of studies with large sample sizes, and various efforts to rule out bias and confounding in at least two key studies: the GCS and the IROPICAN study.

2.6.8 Cancer of the lung

Data on the association between opium consumption and cancer of the lung were limited to one cohort study (the GCS) and three case–control studies. The cohort study by Sheikh et al. (2020) found an adjusted hazard ratio of 2.21 (95% CI, 1.44–3.39) with a positive exposure–response trend ($P < 0.0001$) for increasing quartiles of consumption (HR, 3.19; 95% CI, 1.85–5.50 in the highest consumption quartile, i.e. > 60 nokhod-years). These results were carefully adjusted for cigarette smoking; however, assessment of cigarette never-smokers was difficult, because only 8 study participants with lung cancer had used opium but never smoked cigarettes. This may represent a limitation on the interpretation of the data due to the very strong associations between opium use and both smoking and lung cancer.

One of the case–control studies was conducted in the 1970s, when statistical adjustment methods were not as readily available (MacLennan et al., 1977). While the odds ratio for opium use was above unity, the limited adjustment for confounding makes interpretation difficult. A second case–control study enrolled 242 histologically and cytologically confirmed cases of primary cancer of the lung with 484 controls (hospital controls, 242; visiting healthy controls, 242) – matched on age, sex, and place of residence – and reported an increase in the risk of lung cancer among opium users after adjusting for pack-years of cigarette smoking, with an odds ratio of 3.1 (95% CI, 1.2–8.1) (Masjedi et al., 2013). The magnitude of this association was similar to that identified in the GCS and the other case–control study; however, no obvious exposure–response pattern was observed. A third case–control study enrolled 140 patients with cancer of the lung and 280 healthy controls matched on age, sex, and place of residence, and reported an adjusted odds ratio of 5.95 (95% CI, 1.87–18.92) (Naghibzadeh-Tahami et al., 2020). There was a positive exposure–response association, with an odds ratio of 9.36 (95% CI, 2.05–42.72) for high-level users. While this study had many strengths, it was difficult to rule out the possibility of under-reporting of opium use by the neighbourhood-based controls.

Despite the limitations observed in these three studies, the Working Group concluded that a positive association had been observed between opium consumption and cancer of the lung. Given the totality of evidence and the strong association observed in the GCS, the Working Group concluded that chance, bias, and confounding were unlikely to explain these findings.

2.6.9 Cancer of the stomach

The association between opium consumption and cancer of the stomach was well studied in two cohort studies (the GCS and Ardabil cohort study) with a combined total of nearly 380 cases, and in two case–control studies with nearly 400 cases combined. All studies showed increased risk of gastric cancer. In one study, opium consumers were observed to be at increased risk of precursor lesions for gastric cancer, alleviating concerns about reverse causation.

The GCS results showed an association between opium use and the risk of gastric cancer, with a fully adjusted hazard ratio of 1.36 (95%, CI, 1.03–1.79), particularly for the noncardia subtype (HR, 1.69; 95% CI, 1.11–2.56; 127 cases) (Sheikh et al., 2020); however, the strength of the evidence for an exposure–response trend was marginal ($P = 0.067$). In the Ardabil cohort study, opium use was associated with an increased risk of cancer of the stomach, with a multivariable-adjusted hazard ratio of 3.24 (95% CI, 1.37–7.66). Opium use in this cohort was also associated with a substantially increased risk of baseline antral and body intestinal metaplasia,

which are precursor lesions for gastric cancer (Sadjadi et al., 2014).

Both case–control studies showed an increased risk of gastric cancer of nearly 3-fold in multivariable-adjusted analyses, with odds ratios of 3.1 (95% CI, 1.9–5.2) and 3.0 (95% CI, 1.6–5.6) for studies conducted by Shakeri et al. (2013) and Naghibzadeh Tahami et al. (2014), respectively. The study by Shakeri et al. (2013) had a reasonably large sample size (n = 309 cases), used the GCSQ, adjusted for the most important potential confounders, performed a sensitivity analysis to rule out reverse causation, and found some evidence of a positive exposure–response association, such that individuals with the highest cumulative opium use had the strongest association (OR, 4.5; 95% CI, 2.3–8.5). The study by Naghibzadeh Tahami et al. also adjusted for multiple confounders and found some evidence of a positive exposure–response relation, showing an odds ratio of 9.2 (95% CI; 2.5–33.7) for those whose cumulative opium use was greater than the median. One of these studies (Shakeri et al., 2013) recruited controls from the GCS, and the other (Naghibzadeh Tahami et al., 2014) from the neighbourhoods of the participants, leaving some potential for under-reporting by the controls.

The Working Group's assessment was that the body of evidence indicated that a positive association was credible. However, chance, confounding, and bias could not be ruled out with reasonable confidence because of the lack of a positive exposure–response in the GCS, lack of adjustment for important risk factors of gastric cancer (most importantly, *H. pylori* and dietary intake) in some studies, and the possibility of under-reporting in controls in case–control studies.

2.6.10 Cancer of the pancreas

In the GCS, there was no evidence of a clear association between ever-use of opium and increased risk of cancer of the pancreas (adjusted HR, 1.54; 95% CI, 0.87–2.72) (Sheikh et al., 2020). However, there was an increased risk among those who were using opium at very high cumulative rates (> 60 nokhod-years), with an adjusted hazard ratio of 2.66 (95% CI, 1.23–5.74) and a trend P value of 0.028.

The case–control study by Shakeri et al. (2016) found an odds ratio of 1.91 (95%, CI, 1.06–3.43). This study had a reasonably large sample size (n = 357 cases), used detailed data similar to those collected in the GCS, adjusted for nearly all of the important confounders, and conducted a sensitivity analysis to rule out reverse causation. The controls were from the same clinic from which the cases were recruited, therefore reducing the possibility of biased reports; however, bias from data collection on the part of the interviewers cannot be entirely ruled out. Furthermore, there was no exposure–response association with either duration of opium use or cumulative opium use.

Although a positive association between opium consumption and cancer of the pancreas was seen in two studies, the Working Group concluded that chance, bias, and confounding cannot be ruled out, partly because the number of studies was small. Although the only case–control study showed some evidence for an association, the cohort study only showed an association with very high exposures.

2.6.11 Cancers of the colon and rectum

The association between opium consumption and cancers of the colon and rectum was studied in a cohort study and two case–control studies. The GCS, with 95 cases of colon cancer, found no positive association between opium use and risk of colon cancer (HR, 0.90; 95% CI, 0.48–1.67),

nor did it find an association with cumulative opium use. However, two case–control studies with similar designs, one conducted in Kerman Province (Naghibzadeh-Tahami et al., 2016) and the other in Fars Province (Iankarani et al., 2017), Iran, both found strong positive associations, with adjusted ORs of 4.5 (95% CI, 2.4–8.7) and 4.48 (95% CI, 2.27–8.82), respectively. Both studies found some evidence of exposure–response associations and both used neighbourhood controls.

The Working Group concluded that bias cannot be ruled out for the association between opium use and cancer of the colon and rectum. While two case–control studies (which were similar in design and were conducted by the same group of investigators) found a strong association with some evidence of an exposure–response relation, the cohort study did not find evidence of a positive association, despite reasonable numbers of cases. Because of conflicting evidence, the Working Group concluded that a positive association had not been observed in the overall body of evidence.

2.6.12 Cancers of the oral cavity, pharynx, and other sites in the head and neck

Although there were six studies of opium consumption and cancers of the oral cavity and pharynx (one case series, one ecological study, and four case–control studies), only one case–control (Mohebbi et al., 2020) study was informative. This study included 254 cancers of the lip and oral cavity, 54 cancers of the pharynx, 28 cases of other subsites, and thousands of controls. Opium consumers were at substantially increased risk of cancers of the pharynx (OR, 2.90; 95% CI, 1.40–6.02) and other subsites of the oral cavity (OR, 5.95; 95% CI, 2.41–14.71) compared with controls. The results were properly adjusted for all important confounders, and showed an exposure–response pattern that remained in tobacco never-smokers, and in sensitivity analysis adjusting for the sensitivity of response among combined cases of head and neck cancer and controls. Furthermore, the study disregarded all opium use that was initiated 3 years or less before case diagnosis.

The Working Group concluded that a positive association between opium consumption and cancer of the pharynx was credible; however, chance, bias, and confounding could not be excluded with reasonable confidence because there was only one well-conducted study.

For all other cancer sites there were too few studies, and the available studies were not considered suitably informative.

2.6.13 Results by route and type of opium consumed

Opium products are typically smoked or ingested. Where results showed an overall positive association between opium use and cancer risk, and were then stratified by route of exposure, increased risk of cancer was seen for both smoking and ingestion. Those who used opium via both routes typically had the highest relative risk compared with never-users. For example, in the GCS, increased risk and a positive exposure–response association ($P < 0.0001$) were seen for all cancers combined (Sheikh et al., 2020). In this study, for all cancers combined and the highest quartile of cumulative opium use (> 60 nokhod-years), the hazard ratios were 1.49 (95% CI, 1.14–1.95), 1.64 (95% CI, 1.33–2.02), and 1.70 (95% CI, 1.42–2.04) for ingestion, smoking, and any route, respectively. In the GCS, the results varied by cancer type. For example, smoking opium was more strongly associated with oesophageal cancer than was ingesting opium. Conversely, ingesting opium was more strongly associated with liver cancer than was smoking opium. However, because of the modest numbers of each cancer, the confidence intervals were wide and overlapping. In a case–control study, Masjedi et al. (2013) found that opium

smoking was a much stronger risk factor for lung cancer than opium ingestion. By contrast, in the IROPICAN case–control study (Mohebbi et al., 2020), ingesting opium was a stronger risk factor for all head and neck cancers combined, as well as for cancers of the lip and oral cavity (excluding the pharynx) and laryngeal cancers, than was smoking opium. Several other examples are summarized in a review article (Kamangar et al., 2014). In summary, the current evidence points to both smoking and ingesting opium as being carcinogenic.

Opium products studied in this monograph included raw opium (*teriak*), opium dross (*sukhteh*), and refined opium (*shireh*). A subset of studies examined risks according to the type of opium used. In these studies, where a positive association was found overall, all opium types were typically associated with an increased risk of cancer. In the GCS (Sheikh et al., 2020), 86% of the participants used raw opium only, 9% used refined opium only, and 5% used opium dross, heroin, or a combination of the above; therefore, it was difficult to adequately study each type of opium used. However, in the GCS, consumption of raw opium, refined opium, and a combination of all forms were positively associated with increased risk of all cancers combined, with hazard ratios of 1.40 (95% CI, 1.23–1.58), 1.18 (95% CI, 0.84–1.66), and 1.67 (95% CI, 1.14–2.44), respectively. In the IROPICAN case–control study (Mohebbi et al., 2020), consumption of raw and refined opium were each associated with increased risk of all head and neck cancers combined, with odds ratios of 3.40 (95% CI, 2.64–4.37) and 7.17 (95% CI, 4.44–11.58), respectively. When stratified by cancer type, refined opium was more strongly associated than raw opium with an increased risk of cancers of the lip and oral cavity, pharynx, and larynx. In summary, the current evidence suggests that all commonly consumed types of opium are associated with higher risk of cancer.

2.6.14 Results stratified by sex and other attributes of the study participants

Where data were provided, positive associations between opium consumption and cancer risk were seen for both men and women. For example, in the GCS (Sheikh et al., 2020), the adjusted hazard ratios for the association between opium use and all cancers combined were 1.43 (95% CI, 1.24–1.65) and 1.26 (95% CI, 1.00–1.59) for men and women, respectively. Increased risks of cancers of the oesophagus, urinary bladder, and lung were observed for both men and women who consumed opium compared with those who did not (Table 2.1, Table 2.2, and Table 2.3).

Similarly, when stratified by tobacco smoking or socioeconomic status, opium consumption was associated with increased risk of cancer in nearly all subgroups (Sheikh et al., 2020).

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