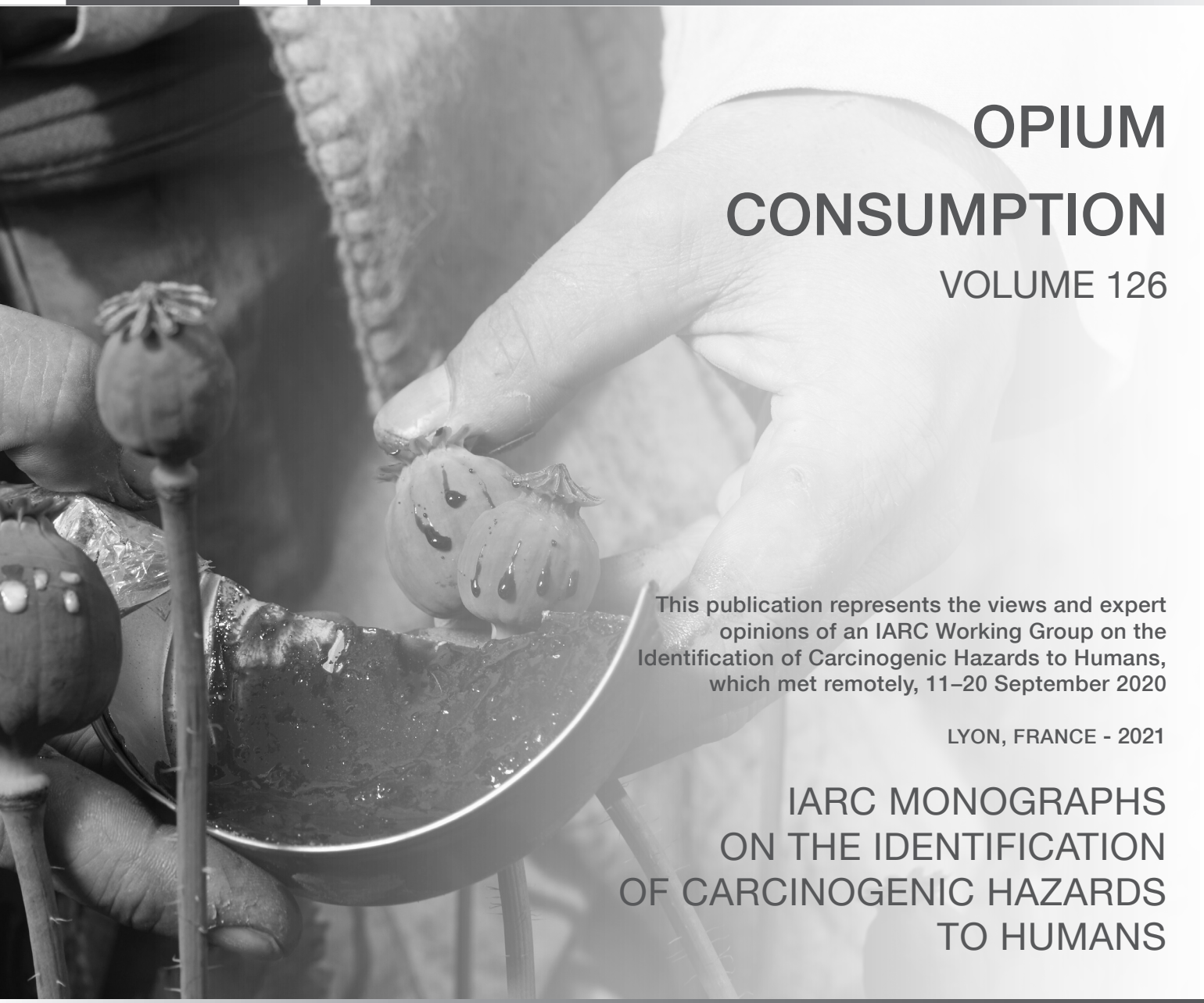
IARC MONOGRAPHS



OPIUM CONSUMPTION

VOLUME 126

This publication represents the views and expert opinions of an IARC Working Group on the Identification of Carcinogenic Hazards to Humans, which met remotely, 11–20 September 2020

LYON, FRANCE - 2021

IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

World Health Organization

ANNEX 2
METHODOLOGICAL CONSIDERATIONS FOR EPIDEMIOLOGICAL STUDIES ON OPIUM CONSUMPTION AND CANCER

The epidemiological evidence regarding associations between opium use and cancer includes two cohort studies and several case–control studies. Bias in estimates of associations between opium exposure and cancer can result from limitations in study design or execution. Potential biases in studies of opium–cancer associations discussed in the present Annex include reverse causation, protopathic bias, selection bias, information bias (for example, recall bias), and confounding. For each potential bias, we review possible threats to validity in the most informative cohort study (the Golestan cohort study, GCS) and in case–control studies of the association between opium use and cancer. We conclude with a summary regarding the extent to which these biases could explain the observed findings in these studies of opium–cancer associations.

Reverse causation

It has been suggested that individuals living in regions where opium is used who are diagnosed with cancer may take opium to relieve disease symptoms. "Reverse causation" is a term used when a defined outcome of interest causes a change in the exposure of interest (Fig. A1). A prospective cohort design, such as the GCS, in which participant entry to the study is conditional on being disease-free (not having had a cancer diagnosis), allows one to avoid reverse causation when assessing opium use and cancer in a population that is followed over time for subsequent cancer. Assessment of opium use at baseline is conditional on not having disease diagnosis and therefore disease must be ascertained after exposure assessment. In contrast, in case–control studies on opium use and cancer, if cancer diagnosis affects subsequent opium exposure then a statistical estimate of association derived from a model in which cancer was the outcome of interest and opium was the explanatory variable

Fig. A1 Reverse causation: the association between outcome (D) and exposure (T)

Subscripts indicate time on study, where 0 denotes study entry and 1 represents a subsequent time-point during follow-up.

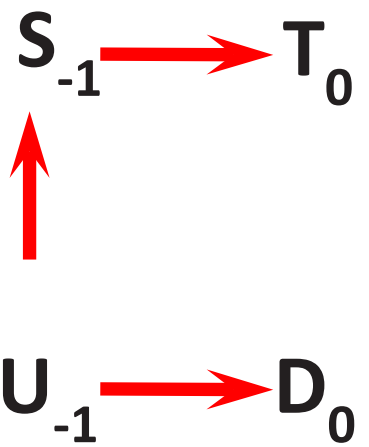
could be liable to misinterpretation about the direction of the causal association.

In a case–control study, reverse causation is not a concern if the investigator was able to reliably assess opium history before diagnosis and focus the analysis on the association between opium history before a cancer diagnosis has been made. However, when information about exposure is collected after cancer diagnosis, as in nearly all of these case–control studies of opium use and cancer, the exposure assessment for cases often fails to distinguish information regarding opium exposure before diagnosis from information about exposure after diagnosis. Aliasgari et al. (2004), Aliramaji et al. (2015), and Bakhshaee et al. (2017) provided no clear indication of the time frame relevant to history of opium use assessment (e.g. distinguishing use before an index date defined by diagnosis). In contrast, Nasrollahzadeh et al. (2008) empirically assessed the potential for this form of bias, noting that exclusion of the cases and controls who had recently started using opium from the analysis made no notable difference to the study results, and younger age at first use was a strong predictor of cancer risk. Also, in a lung cancer case–control study in which some patients started using opioids after being diagnosed with cancer, Naghibzadeh-Tahami et al. (2020) excluded both opioid consumption after cancer diagnosis, and recent opium use, defined as within 2 years of the diagnosis date for cancer cases or the enrolment date for controls.

Protopathic bias

A threat to validity that is related to reverse causation is protopathic bias (Porta et al., 2014), a form of confounding that may occur if an individual uses opium in response to a symptom of an outcome of interest that is – at the time of exposure – still undiagnosed, and if those

Fig. A2 Protopathic bias: the association between a latent factor (U), associated with a symptom (S), true exposure (T), and outcome (D)



Subscripts indicate time on study, where 0 denotes study entry and –1 represents a time-point before study entry.

with symptoms have a higher probability of the outcome. Protopathic bias refers to settings in which a symptom experienced before disease diagnosis causes a change in the exposure of interest. For example, symptoms, such as chronic cough or pain, that are associated with a particular cancer may be causes of opium use among individuals who have not yet been diagnosed with cancer. In Fig. A2, D denotes cancer status at study entry time 0 and U denotes a latent factor at time –1 (for example, a premalignant condition leading to a symptom, S, and associated with cancer, D). A cohort study design, such as the GCS, is susceptible to protopathic bias if exposure is assessed in a population that includes symptomatic individuals. If symptoms at baseline are associated with opium use at baseline and with subsequent cancer risk, then bias would occur. In the GCS, Sheikh et al. (2020) addressed the potential for such bias by conducting a sensitivity analysis that excluded events occurring in the first 24 months of follow-up.

This form of bias was also considered in some papers reporting on studies with a case–control

design. Nasrollahzadeh et al. (2008) noted that people in Golestan may start using opiates to alleviate pain before receiving a cancer diagnosis. The Working Group suggested that cough is a source of protopathic bias, noting that cough may lead to use of opium as an antitussive and cough is associated with certain cancers. Rahmati et al. (2017) noted in the GCS that, in the Islamic Republic of Iran, opium is a well-known antitussive and chronic cough is associated with laryngeal cancer. Protopathic bias could occur if people who had these symptoms used opium to suppress their cough and had a higher probability of the outcome.

Concerns about protopathic bias can be addressed by assessment of opium history in a period before the symptomatic period of disease. Unfortunately, interpretation of several of the case–control studies in the literature is complicated by potential protopathic bias. Aliasgari et al. (2004), Akbari et al. (2015), Aliramaji et al. (2015), Bakhshaee et al. (2017), and Pournaghi et al. (2019) provide no clear indication of the time frame relevant to history of opium use assessment (e.g. distinguishing use before the onset of symptoms).

Sensitivity analyses can be informative in considering the potential extent of protopathic bias under a specified scenario. For example, consider protopathic bias due to cough as an explanation for an observed opium–lung cancer association as large as a risk ratio of 3.0 (e.g. Masjedi et al., 2013). Suppose that the risk of lung cancer is higher by 20-fold among people with chronic cough, and by 2-fold in people with occasional cough, than among those who report no cough. Most people with cough do not develop lung cancer even if the majority of patients with some forms of lung cancer experience cough. Moreover, suppose that among people who never use opium the prevalence of chronic cough is 10%, occasional cough is 40%, and no cough is 50%. For a risk ratio of 3.0 to be entirely due to this type of protopathic bias, the prevalence of cough would need to be approximately reversed among people who were opium ever-users (i.e. among users of opium: a prevalence of chronic cough, 50%; occasional cough, 40%; and no cough, 10%).

Alternatively, concerns about protopathic bias can be directly addressed if the investigator solicits information specifically about opium use in the year (or years) before diagnosis. Nasrollahzadeh et al. (2008) offer a direct assessment of the potential for protopathic bias, noting that ever-use of opium was associated with oesophageal squamous cell carcinoma (SCC) (odds ratio, OR, 2.00; 95% confidence interval, CI, 1.39–2.88), as was opium use in the period more than 1 year before diagnosis (OR, 1.92; 95% CI, 1.30–2.84). Of course, this approach does not rule out protopathic bias entirely; a symptomatic period that is longer than 1 year before diagnosis is possible. However, the lack of sensitivity of results to the discounting of recent initiators of opium use reduces concern about such bias.

Finally, controlling for measured confounders in many of the published studies of opium use and cancer may also help reduce concern about protopathic bias. For example, premalignant conditions are not the only possible common causes of symptoms (such as cough) and cancer. One common reason that cough is associated with lung cancer is that smokers tend to cough and are at elevated risk of lung cancer. If the backdoor path (i.e. the presence of a common cause) from symptoms to cancer is blocked in part or entirely by conditioning on smoking, then case–control analyses that adjust for smoking will reduce the potential for protopathic bias.

In summary, it is unlikely that the results observed in the cohort and case–control studies of opium and cancer are entirely due to protopathic biases.

Selection bias

Selection bias arises when inclusion in a study sample is associated with the exposure and outcome of interest. Selection bias is not a primary concern in the GCS because entry into the study was not conditional on factors associated with opium use. However, in some case–control studies of the association between use of opium and cancer, controls were recruited from hospitals (rather than the general population) (Aliasgari et al., 2004; Masjedi et al., 2013; Aliramaji et al., 2015). Selection bias may arise if opium use is associated with being in the hospital. The controls in a case–control study are used to estimate the prevalence of opium use in the underlying study base from which the cases arose; if hospital patients are more likely than the general population to have used opium, then use of hospital-based controls may lead to a biased estimate of association. For example, in Shakeri et al. (2012), the hospital-based controls were defined as patients with injuries or illnesses that were not associated with smoking, but who may have had conditions that were affected by opium use. If the outcome defining the control series is affected by opium use, bias will occur in a case–control analysis of the opium–cancer association. As indicated in Fig. A3, conditioning on being in hospital opens a bias pathway between exposure, T, and outcome, D.

One way to assess this potential bias is to evaluate whether an estimate of the prevalence of opium use in the hospital-based control series is comparable to external information, where available, about opium use in the general population; Shakeri et al. (2012) compared the prevalence of opium use among the hospital controls in their study (28%) with that reported in the GCS and noted that opium use was higher among hospital controls than in the cohort study. Another approach is to recruit controls that are not hospital-based. Masjedi et al. (2013) recruited

Fig. A3 Selection bias: the association between true exposure (T), outcome (D), and hospital control selection

Conditioning on hospital control status opens a path between T and D
Subscripts indicate time on study, where 0 denotes study entry.

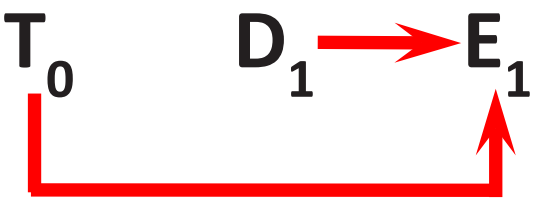
both hospital-based controls and hospital visitor controls (the latter is perhaps less susceptible to this bias), but the authors did not report analyses in which the sensitivity of the results was affected by the use of one type of control or the other. Shakeri et al. (2012) evaluated hospital versus neighbourhood controls in a case–control study on oesophageal SCC in which hospital-based controls were patients with other conditions thought to be unrelated to tobacco use, alcohol consumption, or diet. Evidence of bias to the null was reported by Shakeri et al. (2012) in study findings comparing hospital-based controls with neighbourhood controls, where opium use was associated with a significantly increased risk of oesophageal SCC (OR, 1.77; 95% CI, 1.17–2.68) in analyses using neighbourhood controls, while this was not the case (OR, 1.09; 95% CI, 0.63–1.87) in the study using hospital controls. The authors noted that, "Hospital controls may not be representative of the population because in this area opium has traditionally been used to treat pain and numerous ailments". Neighbourhood controls offer a source of information with which to address such concerns about selection bias; for example, Alizadeh et al. (2020) used neighbourhood controls in a case–control study on head and neck cancers.

In summary, selection bias in hospital-based case–control studies may have led to bias to the null in those studies.

Information bias, including recall bias

Opium consumption was assessed by asking study participants about their current and past use of opium. In studies in which the outcome (cancer diagnosis) occurred before the exposure assessment, a person's outcome status may have affected their self-reported exposure status (Masjedi et al., 2013). This is referred to as "recall bias". Fig. A4 illustrates this problem, where true exposure, T, affects the outcome of interest, D, and both T and D affect the assessed exposure, E. In the GCS, recall bias is not a major concern because exposure assessment at baseline was conducted before disease diagnosis. In contrast, recall bias may be a concern in case–control studies. However, recall bias does not necessarily affect all case–control studies; for example, in a case–control study in which exposure assessment is based on records rather than self-report, recall bias may be avoided if the information in the records is constrained to information collected before diagnosis. Several of the case–control studies on opium and cancer were based on information regarding opium use that was derived from hospital records, although it was unfortunately not always clear whether this record-based information consisted solely of information collected before diagnosis of the disease of interest (in which case, disease, D, does not affect assessed exposure, E). Concerns regarding recall bias can be addressed, in part, by assessments of the reliability of self-reported opium use in the Islamic Republic of Iran. In general, evaluations of self-reported opium use in these populations are reasonably concordant with classifications based on urinary markers of opium use (Abnet et al., 2004).

Fig. A4 Recall bias: the association between true exposure (T), outcome (D), and assessed exposure (E), in an observational study with recall bias

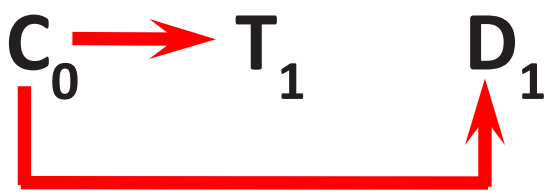


Subscripts indicate time on study, where 0 denotes study entry and 1 represents a subsequent time-point.

Confounding

Unlike in randomized experimental studies, in observational studies on cancer the investigator cannot rely upon randomization to balance between exposure groups the other factors that affect risk of cancer. In an observational study, treatment is not randomized, and factors associated with cancer risk may differ between unexposed and exposed groups. Therefore, a comparison of cancer risk between the unexposed and exposed groups may potentially be distorted by baseline differences between the groups in factors other than opium use that cause cancer. This is referred to as confounding bias. Fig A5 illustrates this problem, where the confounder, C, affects true exposure, T, and affects the outcome of interest, D. An association between T and D may be observed in the absence of any true association due to C, which is a common cause of T and D. As indicated in Fig. A5, confounding bias requires an association between the confounding factor and the exposure of interest (opium use); it also requires an association between the confounding factor and

Fig. A5 Confounding bias: the association between confounder (C), true exposure (T), and outcome (D), in an observational study with classical confounding



Subscripts indicate time on study, where 0 denotes study entry and 1 represents a subsequent time-point.

the outcome of interest (even in the absence of exposure to the agent of primary interest).

Confounding is a potential source of bias in analyses of the association between opium use and cancer in the GCS. A crude analysis of an association between opium use and cancer could be distorted by differences in characteristics between opium users and non-users, such as age and sex, which are also characteristics associated with cancer risk. The investigators measured many of the important potential confounding factors and subsequently accounted for them in the analysis of associations between opium use and cancer by regression modelling, or, in some cases, by restriction of their analysis to people in one stratum of the confounding factor (e.g. to men) (Sheikh et al., 2020).

From the outset of the GCS, which was motivated by an observed excess of oesophageal cancer (SCC) in the north-eastern region of the Islamic Republic of Iran, attention has been paid to tobacco use and alcohol consumption as risk factors of interest associated with oesophageal SCC. Therefore, the GCS participants were asked about tobacco and alcohol use, as well as duration, frequency, and consumption of each; in addition, the reliability of self-reported tobacco use was assessed and compared with urine cotinine. Analyses of associations between opium use and cancer in the GCS have employed regression model adjustment for tobacco and alcohol use, as well as restriction to never-smokers, to address potential confounding by smoking.

Confounding is also a potential source of bias in the case–control studies on opium consumption and cancer. Most case–control studies on opium use and cancer collected information for cases and controls about major risk factors, such as age, sex, and tobacco and alcohol use. Clearly there is a strong association between opium use and tobacco consumption, as described in Section 1.4.3. The major case–control analyses of associations between opium use and cancer have employed either stratification or restriction on age and sex, and regression model adjustment for tobacco and alcohol use, to account for these potential confounding factors. In some settings, matching in case–control studies can provide an effective approach to controlling for potential confounding factors that might be otherwise difficult to measure. The use of neighbourhood controls in a case–control study, as was done in the study by Naghibzadeh-Tahami et al. (2020) for example, implies a form of matching by which controls are sampled from the neighbourhood in which the case arose. A study design in which cases and controls are matched on neighbourhood of residence may help to control for the confounding effects of socioeconomic and environmental factors that are similar within-neighbourhood.

Another possible source of confounding may be occupational exposure to carcinogens. Such concerns about confounding may be greatest for cancers of the urinary bladder and lung, which have many occupational causes (Loomis et al., 2018). As noted in Section 2.6.6, many of the studies were conducted in rural populations, where exposure to industrial urinary bladder carcinogens is unlikely. There is little evidence that occupational exposures to lung carcinogens are associated with opium consumption, except perhaps for welding exposures (see Section 1.4.3). The magnitude of lung cancer risk associated

with exposure to welding fumes is relatively low (IARC, 2018), and even a strong association between work as a welder and opium use cannot explain the large magnitude of the association between opium and lung cancer observed in these studies.

Residual confounding

Although analyses of opium consumption and cancer conducted in the GCS and in most case–control studies adjust for potential confounders such as age, sex, and tobacco and alcohol use, it is possible that confounding bias remains in the adjusted analyses. This is referred to as "residual confounding".

The most plausible concern regarding residual confounding relates to tobacco use. This is because, in the populations under study, there is a strong association between opium use and tobacco use, and tobacco use is strongly associated with some types of cancer. Therefore, it is possible that residual confounding may remain.

One reason for residual confounding could be that the statistical control for confounding by the measured covariates was not sufficiently tight. For example, an analysis of the association between opium use and cancer might control for tobacco smoking by adjusting for ever versus never smoking tobacco. In such an analysis, differences in smoking histories between opium users and non-users might remain within the stratum of people classified as "ever-smokers". Consider the potential concern about residual confounding by smoking level among those who were ever-smokers: one way to address this concern is to conduct an analysis restricted to the stratum of study participants who were never-smokers. Among never-smokers, residual confounding by smoking is presumably minimal or non-existent, because the control for confounding by smoking is tight within the stratum of never-smokers.

Another reason for residual confounding could be that there are substantial errors in the classification of people with respect to confounding variables (for example, if the available information regarding tobacco consumption is not reliable or valid). One way to address concerns regarding errors in classification of study members by tobacco use is to undertake a validation study, as was done in the GCS, where the reliability and validity of tobacco use were assessed. Another way to address such concerns is to examine analyses restricted to women. Tobacco smoking is strongly associated with sex in these studies. Therefore, sex is a strong proxy for tobacco use and, while there may be errors in the classification of study members with regard to smoking, it is less plausible that there are substantial errors in the classification of study members by sex. Given the low prevalence of smoking among women in these studies, analyses that stratify by sex offer indirect assessment of potential residual confounding by smoking. In analyses that restrict to women, among whom smoking prevalence is very low, residual confounding by smoking is presumably minimal.

Finally, evidence of residual confounding by smoking can be assessed in cohort studies by examining patterns of association between opium use and cancer at different organ sites. Potential for bias due to confounding of the association between opium use and cancer by cigarette smoking depends, in part, upon the association between cigarette smoking and the cancer organ sites of interest. External information provides useful indications of the cigarette-smoking–site-specific cancer associations in the Islamic Republic of Iran. Consider for example: if the observed associations between opium consumption and cancers of the oesophagus and lung are entirely due to residual confounding by smoking; and suppose that the

association between smoking and oesophageal cancer in the Iranian population is smaller than the association between smoking and lung cancer; then an analysis of opium use and lung cancer in the same population, using the same methods of analysis, would be expected to be larger than the association between opium use and oesophageal cancer. In fact, tobacco smoking is a weaker risk factor for lung cancer in the Islamic Republic of Iran than is reported elsewhere; tobacco smoking increased the risk of oesophageal SCC less than 2-fold. Nonetheless, the approach, considering other smoking-related diseases, does provide a framework for indirect assessment of residual confounding by smoking.

Overall, in the GCS, the modelling of smoking was fairly tight, with statistical adjustment for pack-years of tobacco use. In addition, analyses restricted to non-smokers are reported in some publications. The GCS addresses errors in the classification of study participants with regard to smoking through the collection of reliable study information as well as the use of biomarkers of smoking. Indirect assessments of residual confounding by smoking find relatively weak evidence of an association between opium consumption and lung cancer, relatively strong evidence of an association between opium consumption and mortality from non-malignant respiratory diseases (such as asthma, chronic obstructive pulmonary disease, and pneumonia), and some positive associations with malignant diseases that also are smoking-related (such as laryngeal cancer).

The available literature from case–control studies on opium consumption and cancer provide less detailed information for evaluation of the potential for residual confounding by smoking. It is often unclear how smoking-adjusted estimates of associations between opium consumption and cancer were derived, leaving open the possibility for residual confounding due to inadequate modelling of smoking status; none of the case–control studies directly assessed the validity of tobacco use information, and few case–control studies examined results stratified by sex (in fact, some were restricted to men by design).

Summary

There are a range of concerns about bias in observational epidemiological studies. Some of the notable concerns in this literature relate to reverse causation, protopathic bias, selection bias, and recall bias in case–control studies. The most informative cohort study on opium consumption and cancer (the GCS) is unlikely to be substantially affected by these sources of bias: reverse causation, selection bias, and recall bias are not major concerns in the cohort study on opium consumption and cancer; it is also unlikely that the results observed in the cohort study on opium consumption and cancer are entirely due to protopathic biases. Of course, none of these studies were randomized trials and therefore confounding remains a potential concern. For example, the available evidence strongly suggests that opium users reported significantly higher levels of cigarette smoking than non-opium users (e.g. Aliasgari et al., 2004; Sheikh et al., 2020). However, the most informative cohort study, and nearly all case–control studies, addressed potential confounding by cigarette smoking through either adjustment or restriction; and, while residual confounding is a concern, the studies with the strongest exposure assessments also benefit from strong assessments of potential confounders.

References

Abnet CC, Saadatian-Elahi M, Pourshams A, Boffetta P, Feizzadeh A, Brennan P, et al. (2004). Reliability and validity of opiate use self-report in a population at high risk for esophageal cancer in Golestan, Iran. *Cancer Epidemiol Biomarkers Prev*. 13(6):1068–70. PMID:15184266

Akbari M, Naghibzadeh-Tahami A, Khanjani N, Baneshi MR, Kamali E, Hesampour M, et al. (2015). Opium as a risk factor for bladder cancer: a population-based case-control study in Iran. *Arch Iran Med*. 18(9):567–71. PMID:26317596

Aliasgari MA, Kaviani A, Gachkar L, Hosseini-Nassab SR (2004). Is bladder cancer more common among opium addicts? *Urol J*. 1(4):253–5. PMID:17914701

Aliramaji A, Kaseean A, Yousefnia Pasha YR, Shafi H, Kamali S, Safari M, et al. (2015). Age distribution types of bladder cancers and their relationship with opium consumption and smoking. *Caspian J Intern Med*. 6(2):82–6. PMID:26221505

Alizadeh H, Naghibzadeh Tahami A, Khanjani N, Yazdi-Feyzabadi V, Eslami H, Borhaninejad V, et al. (2020). Opium use and head and neck cancers: a matched case-control study in Iran. *Asian Pac J Cancer Prev*. 21(3):783–90. doi:10.31557/APJCP.2020.21.3.783 PMID:32212808

Bakhshaee M, Raziee HR, Afshari R, Amali A, Roopoosh M, Lotfizadeh A (2017). Opium addiction and risk of laryngeal and esophageal carcinoma. *Iran J Otorhinolaryngol*. 29(90):19–22. PMID:28229058

IARC (2018). Welding, molybdenum trioxide, and indium tin oxide. *IARC Monogr Eval Carcinog Risks Hum*, 118:1–310. Available from: http://publications.iarc.fr/569 PMID:31268644

Loomis D, Guha N, Hall AL, Straif K (2018). Identifying occupational carcinogens: an update from the IARC Monographs. *Occup Environ Med*. 75(8):593–603. doi:10.1136/oemed-2017-104944 PMID:29769352

Masjedi MR, Naghan PA, Taslimi S, Yousefifard M, Ebrahimi SM, Khosravi A, et al. (2013). Opium could be considered an independent risk factor for lung cancer: a case-control study. *Respiration*. 85(2):112–8. doi:10.1159/000338559 PMID:22759984

Naghibzadeh-Tahami A, Marzban M, Yazdi-Feyzabadi V, Dabiri S, Mohseni S, Abbasi Rayeni R, et al. (2020). Is opium use associated with an increased risk of lung cancer? A case-control study. *BMC Cancer*. 20(1):807. doi:10.1186/s12885-020-07296-0 PMID:32842991

Nasrollahzadeh D, Kamangar F, Aghcheli K, Sotoudeh M, Islami F, Abnet CC, et al. (2008). Opium, tobacco, and alcohol use in relation to oesophageal squamous cell carcinoma in a high-risk area of Iran. *Br J Cancer*. 98(11):1857–63. doi:10.1038/sj.bjc.6604369 PMID:18475303

Porta M, Greenland S, Hernan M, dos Santos Silva I, Last JM, editors (2014). A dictionary of epidemiology. 6th ed. New York (NY), USA: Oxford University Press. doi:10.1093/acref/9780199976720.001.0001

Pournaghi S-J, Hojjat SK, Barazandeh Noveyri F, Tavakkoli Ghouchani H, Ahmadi A, Hamedi A, et al. (2019). Tobacco consumption, opium use, alcohol drinking and the risk of esophageal cancer in North Khorasan, Iran. *J Subst Use*. 24(1):105–9. doi:10.1080/14659891.2018.1523962

Rahmati A, Shakeri R, Khademi H, Poutschi H, Pourshams A, Etemadi A, et al. (2017). Mortality from respiratory diseases associated with opium use: a population-based cohort study. *Thorax*. 72(11):1028–34. doi:10.1136/thoraxjnl-2015-208251 PMID:27885167

Shakeri R, Kamangar F, Nasrollahzadeh D, Nouraie M, Khademi H, Etemadi A, et al. (2012). Is opium a real risk factor for esophageal cancer or just a methodological artifact? Hospital and neighborhood controls in case-control studies. *PLoS One*. 7(3):e32711. doi:10.1371/journal.pone.0032711 PMID:22396792

Sheikh M, Shakeri R, Poustchi H, Pourshams A, Etemadi A, Islami F, et al. (2020). Opium use and subsequent incidence of cancer: results from the Golestan Cohort Study. *Lancet Glob Health*. 8(5):e649–60. doi:10.1016/S2214-109X(20)30059-0 PMID:32353313