Opium Use Reporting Error in Case-Control Studies: Neighborhood Controls vs. Hospital Visitor Controls

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Abstract

Background There are relatively scant data to determine whether hospital visitors could serve as a proper source of controls in substance abuse case-control studies. The aim of this study was to evaluate using neighborhood versus hospital visitor controls in reporting opium use.

Methods We conducted two independent case-control studies of cancer in Iran. In the first study, we selected controls from neighborhoods of the patients. For the second one, we selected controls among hospital visitors. In the latter study, hospital visitors could be companions of the patients or others visiting the hospital for any reasons except disease treatment from non-oncology wards of referral hospitals. Opium use and cigarette smoking information were self-reported in both studies.

Results A total of 616 of neighborhood controls and 414 of hospital visitor controls were analyzed. Regular opium use among men was significantly higher in hospital visitors than neighborhood controls (43.3% vs. 32.2%, P=0.03) while the prevalence of regular cigarette smokers was very similar in both control groups (46.3 vs. 47.2, P=0.87). After adjusting for potential confounders using logistic regression, the differences of opium use between the two control groups became more pronounced (Adjusted OR=0.26, 95% CI: 0.10-0.69).

Conclusions Because of the similarity of reporting cigarette smoking among neighborhood controls but substantially lower reporting of opium use among them, we concluded that neighborhood controls underreported opium use-a sensitive question- and that their use biases the findings in case-control studies. Hospital visitor controls may be more appropriate than neighborhood controls for studies of banned substances.

Introduction

Case-control studies are designed to be more efficient versions of prospective cohort studies, particularly when the disease is relatively rare. The most appropriate controls are those that accurately represent exposure rates in the base cohort from which the cases come. Despite many years of research, however, selection of appropriate controls remains a challenge [1–6], particularly when the exposure of interest is a sensitive question such as using a banned substance (e.g. Opium) [7–10].

Researchers may choose to select controls from patients with other diseases in the same clinic or hospital to which the cases are referred (disease controls), friends of family members accompanying patients to the clinic or hospital (hospital visitor controls), or a random sample of the source population from which the cases come (population controls). Each of these methods has its own limitations. Disease controls are relatively accessible, often motivated to participate, and more likely to provide accurate information, but they are also more likely to be exposed a host of risky behaviors than the source population from which the case come [1], potentially leading to underestimate the associations with the risk factor under study [11]. Population controls, on the other hand, are more likely to have exposure levels similar to the source population, but they are less cooperative and may underreport

exposure, particularly for banned substances. There is also a high cost to identifying and interviewing such controls in the population specially when they will be requested to donate biological sample, and their lack of cooperation may lead to selection bias [1].

Hospital visitors (visitor controls) are often reasonably motivated to answer questions relatively accurately because of their interest in their treatment process, relatively easy to recruit, and are less likely to be over-exposed to risky behaviors, as disease controls are. To reduce the potential for over-matching, visitor controls are preferably not selected from friends or family members of cases; rather they are selected from friends or family members of patients of diseases deemed to be unrelated to the exposure of interest.

Opium use is quite common in several areas of Iran, and some studies have suggested that opium use may be associated with higher risk of several adverse health outcomes, such as cancer, cardiovascular diseases, diabetes, and metabolic syndrome [12–20]. Therefore, finding the most appropriate type of control focusing on opium is case of interest. The aim of this study is to compare two control types, neighborhood controls vs. visitor controls, with regards to their responses to opium use. To assess and compare the validity of responses, we asked detailed questions about both opium and cigarette use. Cigarette smoking is not banned, nor is its use stigmatized for men. By contrast, opium use is banned and is associated with some level of stigmatization.

Methods

Study design

The two controls groups came from two independent case-control studies that were conducted in Kerman Province, in southeastern of Iran. It is noteworthy that the prevalence of cigarette smoking and opium use have been stable for the last decade, since, difference of the period of study is not affect out results [7, 21]. The methods for each study are briefly discussed below.

Neighborhood-based case-control study

From 2013 to 2015, a population-based case-control study (study I) was designed to determine the association of opium use and risk of bladder cancer. All bladder cancer cases who were residence of Kerman province, were able to speak Persian, had a histological diagnosis of cancer within one year prior to interview (incident cases), and were able to undergo an 80-minute interviewing, were eligible. Nursing and pregnant women were excluded. Data from two sources were used to identify and recruit the large majority of the bladder cancer cases: the Kerman Province cancer registry and records from a provincial-level referral hospital for treatment of cancer patients, resulting in enrollment of 308 bladder cancer cases. A total of 616 eligible controls (2:1 control-case ratio) were selected from residents of Kerman Province. Controls were cancer free and were individually matched to cases for gender, age (± 2 years), and residential place.

Matching by residential place was done by municipality district, using a predefined plan. Six houses were selected from the main street where the house of cases was located. The interviewers planned the order of approaching the houses. If no eligible controls were found in the first selected house, or the eligible controls refused to participate, the interviewers approached the second designated household, and so forth. This strategy was followed until two eligible controls were found for each case. In all, 62 (10%) invited potential controls refused to participate.

All interviews were done face-to-face in an environment that allowed for uninterrupted privacy. Data were collected using a structured questionnaire that included detailed questions on tobacco, opium use, demographic information, and other relevant data.

Hospital-based case-control study

From 2016 to 2018, a multicenter case-control study-Iran Opium and Cancer study (IROPICAN)- was designed and conducted to assess the association of the lung, colorectal, head and neck, and bladder cancers in ten provinces of Iran (study II), including Kerman Province. We used data from controls selected in Kerman Province. Cases were cancer patients admitted to one of three referral cancer care centers in Kerman. Eligibility criteria were the same as the previous study, i.e., being Iranian, having received a histological diagnosis of cancer within one year prior to the study, ability to speak Persian, and ability to interview for 80 minutes. Women who were nursing or pregnant were not eligible.

Potential controls were hospital visitors who were relatives or friends of hospitalized patients in non-oncology wards, or those who visited the hospital for any reasons other than receiving treatment. Further eligibility criteria were the same as those set for cases, except that the controls had to be absolutely free of any history of cancer. A total of 414 hospital visitors were asked to participate as controls, of whom 25 (6%) refused to participate. The controls were frequency-matched to cases by age (five-year intervals; 30 to 75 + groups), gender, and residential place (Kerman city residence and non-Kerman residence). Trained interviewers gathered tobacco and opium use data at the hospital, in face-to-face interviews using structured questionnaires.

Opium Use Data

Opium use was self-reported in both studies. In a previous validation study, we found a high level of sensitivity (77%) for self-reported opium use among visitor controls, using thin layer chromatography (TLC) as the gold standard [9]. Regular opium users defined as consuming opium at least once a week for at least a six-month consecutive period during the subjects' lifetime. A similar definition was used for regular cigarette smoking.

Statistical Analysis

The two primary exposures of interest were opium use and cigarette smoking in neighborhood and visitor controls. Data were categorized and presented by gender, age, socio-economic status (SES). An overall

SES score was determined by combining years of education (continuous variable) and some assets (dichotomous variables; washing machine, freezer, personal computer, sofa, vacuum cleaner, dishwasher, split air conditioner, owned house, owned car, sponsored by charitable /supporting organizations, complementary insurance), using principal components analysis. We used chi-square test to compare proportions between groups.

Analyses were done for all subjects together, by subgroups, and for only men. An analysis for men only was useful because: 1) rates of cigarette smoking and opium use were substantially lower in women, leading to random error; 2) the use of cigarette smoking may be associated with stigma among women but not in men.

We estimated a logistic regression that included type of controls (neighborhoods/visitors) as the dependent variable and gender, education, age, SES, the area of residence, opium regular use (yes/no), and cigarette smoking for adjustment.

A P-value of less than 0.05 was considered statistically significant. All analyses were performed using STATA (version 12; Stata Corp, College Station, TX, USA).

Results

Data from a total of 616 of neighborhood controls and 414 of visitor controls were analyzed. Table 1 compares some basic demographic factors. The majority of the controls in both studies were men, 87.7% of study I and 74.1% of study II. Visitor controls were more likely to be younger, have some education, and reside outside Kerman City. Marriage rates were similar across both control groups (P = 0.97).

Demographic characteristics.

Table 1
Characteristics of neighborhood and visitor controls in Kerman province, Southern Iran.

Characteristics	Neighborhood Controls (N = 616)	Visitor Controls (N = 414)	P
Gender			< 0.0001
Men	540 (87.7)	307 (74.1)	
Women	76 (12.3)	107 (25.9)	
Age			< 0.0001
≤ 50	66 (10.7)	99 (24)	
51–60	143 (23.2)	151 (36.4)	
61–70	244 (39.6)	109 (26.3)	
≥ 71	163 (26.5)	55 (13.3)	
Place of residence			< 0.0001
Kerman city	372 (60.4)	172 (41.5)	
Non-Kerman city	244 (39.6)	242 (58.5)	
Education			0.001
Illiterate	171 (27.8)	76 (18.4)	
Literate	445 (72.2)	337 (81.6)	
Marital Status			0.97
Married	551 (89.4)	370 (89.4)	
Non-married	65 (10.6)	44 (10.6)	

Table 2

illustrates the frequency of regular use of opium and cigarettes among both control groups. Thirty-five percent of visitor controls were regular opium users, compared to 29.4% in the neighborhood controls (P = 0.171). Age, the area of residence and SES were inconsistently changed by control type while men were always more regular opium users. In contrast to regular opium use, regular cigarette use was more frequent among neighborhood controls (41.1% vs. 37.0%; P = 0.79) (Table 2).

Characteristics	**Neighborhood controls**			**Visitor controls**		
	Total	**Regular Opium Users (%)**	**Regular Cigarette Smokers (%)**	**Total**	**Regular Opium Users (%)**	**Regular Cigarette Smokers (%)**
Total	616	181 (29.4)	253 (41.1)	414	145 (35.0)	153 (37.0)
Gender						
Men	540	174 (32.2)	250 (46.3)	307	133 (43.3)	145 (47.2)
Women	76	7 (9.2)	3 (4.0)	107	12 (11.2)	8 (8.4)
Age						
≤ 60	209	69 (33.0)	101 (48.3)	248	87 (35.1)	102 2.9)
> 60	407	112 (27.5)	152 (37.4)	166	58 (34.9)	51 (31.1)
Place of residence						
Kerman city	372	100 (26.9)	155 (41.7)	172	56 (32.6)	64 (38.6)
Non-Kerman city	244	81 (33.2)	98 (40.2)	242	89 (36.8)	89 (37.7)
Socioeconomic status						
Low	309	87 (28.2)	117 (37.9)	213	85 (39.9)	78 (37.1)
High	307	94 (30.6)	136 (44.3)	201	60 (29.9)	75 (39.1)
Characteristics of opium users and cigarette smokers.						

Table 2- Characteristics of regular opium users and regular cigarette smokers by type of controls.

Because of the relatively low prevalence of opium and cigarette use among women, we repeated all analyses once for men only (Table 3). Regular opium use was higher among men visitor controls (43.3% vs. 32.2%; P = 0.03), while the distribution of regular cigarette users was similar between neighborhood and visitor controls (46.3% vs. 47.2%, P = 0.87). A similar pattern was seen when stratified by other characteristics; while reported regular cigarette smoking quite comparable across all strata between

visitor and neighborhood controls, reported regular opium use was substantially lower among neighborhood controls (Table 3).

Characteristics of opium users and cigarette smokers among men by controltype.

Table 3
Characteristics of regular opium users and regular cigarette smokers by type of controls among men.

Characteristics	Neighborhood controls			Visitor controls		
	Total	Regular Opium Users (%)	Regular Cigarette Smokers (%)	Total	Regular Opium Users (%)	Regular Cigarette Smokers (%)
Total	540	174 (32.2)	250 (46.3)	307	133 (43.3)	145 (47.2)
Age						
≤ 60	183	67 (36.6)	101 (55.2)	185	83 (44.9)	99 (53.5)
> 60	357	107 (29.9)	149 (41.7)	122	50 (41.0)	46 (37.7)
Place of residence						
Kerman city	338	96 (28.4)	154 (45.6)	124	51 (41.1)	58 (46.8)
Non-Kerman city	202	78 (38.6)	96 (47.5)	183	82 (44.8)	87 (47.5)
Socioeconomic status						
Low	270	83 (30.5)	116 (43.0)	153	35 (48.6)	71 (46.4)
High	270	91 (33.7)	134 (49.6)	154	41 (50.6)	74 (48.1)

When control type, gender, age, area of residence, SES, and regular cigarette smoking were mutually adjusted for each other in a logistic regression model, neighborhood controls had a statistically significant lower odds ratio (OR) of reported regular opium use compared to visitor controls (Table 4). In fact, after adjustment, the differences between the two control groups became more pronounced. Those men who lived outside the city of Kerman (OR:1.40; 95%CI: 1.03 to 1.91), people with higher SES (OR:0.54; 95%CI: 0.33 to 0.88), and regular smokers were also more likely to report regular opium use (OR:5.49; 95%CI: 4.04 to 7.47) (Table 4).

Adjusted odds ratios of regular opium use associated with selected characteristics.

Characteristics	Crude† OR (95% CI)	P	Adjusted OR‡ (95% CI)	P
Control type				
Visitor controls	Referent	0.06	Referent	0.007
Neighborhood controls	0.77 (0.59, 1.00)		0.26 (0.10, 0.69)	
Gender				
Men	Referent	< 0.0001	Referent	< 0.0001
Women	0.20 (0.12, 0.33)		0.35 (0.20, 0.61)	
Age (Years)				
≤ 60	Referent	0.13	Referent	0.85
> 60	0.81 (0.62, 1.05)		1.03 (0.75, 1.41)	
Place of residence				
Kerman city	Referent	0.03	Referent	0.03
Non-Kerman city	1.33 (1.02, 1.74)		1.40 (1.03, 1.91)	
Education				
Illiterate	Referent	0.70	Referent	0.80
Literate	0.94 (0.69, 1.27)		0.95 (0.65, 1.37)	
Socioeconomic status				
Low	Referent	0.36	Referent	0.02
High	0.88 (0.68, 1.15)		0.54 (0.33, 0.88)	
Regular cigarette smoking				
Non-smoker	Referent	< 0.0001	Referent	< 0.0001
Smoker	6.15 (4.60, 8.21)		5.49 (4.04, 7.47)	
†Crude estimates are unadjusted for covariates.				
‡ Adjusted OR was adjusted for gender, age, area of residence, socioeconomic status, and cigarette smoking				

Table 4- Crude and adjusted odds ratios of regular opium use associated with selected characteristics

Discussion

In this study, the self-reported rates of cigarette smoking were similar between neighborhood and visitor control groups but the self-reported rates of opium use were lower among neighborhood controls. When restricting the analysis to men, we saw a similar pattern: nearly 47% of both groups reported cigarette smoking while there was a substantial difference in reporting opium use: 32% in neighborhood controls compared to 43% in visitor controls. Adjusting for various characteristics in the logistic regression model explicit these differences. These results possibly indicated a substantial information bias when selecting controls from the neighborhoods in regard to sensitive questions like opium use.

The current study showed that the prevalence of regular cigarette smoking was approximately the same between visitor and neighborhood controls. The approximation of cigarette smoking as a social norm has been demonstrated among some types of controls [19, 22, 23]. Accordingly, reporting of cigarette smoking could be used as the gold standard of reporting banned substances.

The observed differences of opium use and cigarette smoking among two series of controls are likely because opium is an illicit substance while cigarettes are not legally banned in Iran. Neighborhood controls are often approached by interviewers who are strangers and aware of the subjects home address. Therefore, they may be suspicious of the interviewers, hence may be less likely to respond truthfully to questions about opium use. Also, because visitor controls are often seeking medical care for themselves or a patient they accompany, they are more likely to have thought about potential causes of disease (e.g. opium use), which could lead to recall bias. Therefore, we concluded that based on these differences, a higher rate of participation in visitor controls was observed than in neighborhood controls.

According to the current study, visitor controls are recommended specially for case-control studies collecting biological samples, as they are more likely to provide biological samples, particularly urine samples, in the hospital setting-urine rapid test can be used to check opioid use during last 72 hours. Because of legal concerns, neighborhood controls might well refuse to donate urine or even blood samples. Although, in Iran, opium use itself is not a crime, a person convicted of possessing 5-kilograms of opium and its derivatives would receive the death penalty [24]. Misunderstanding of the law and the history of arresting the opium users before 1979 revolution provoke the public to refuse to participate and consequently reporting opium use precisely.

Hospital controls can be selected among hospital visitors or hospitalized patients; the prevalence of opium use among the visitor controls is closer to the estimated prevalence of general population while prevalence of opium use is higher among disease controls [9, 19, 25]. Hence, using disease controls lead to non-differential misclassification (OR will be diluted towards the null value). The higher prevalence of opium use among disease controls could be due to traditionally opioid use as a pain killer and various ailments, or, in fact, is because of long-term exposure to as the main risk factor for the reason of hospitalization [9].

Our finding was consistent with other study result as in a case-control study of alcohol drinking and breast cancer, however, the investigators recruited hospital visitor and community-based controls, all analyses were performed on only community-based controls. They justified that disease controls was a

powerful source of bias because of cigarette smoking and alcohol drinking might mask the association of the risk factors and breast cancer [26]. In another study, Frisch and colleague assessed the association of sexually transmitted infection and anal cancer using disease controls and population controls [27]. Population controls reported less high-risk sexual behavior while cigarette smoking was not statistically different, this is because of the strong taboo of some aspects of sexual behaviors (like visiting female sex workers, number of partners, and relationships out of family frame) in most societies.

In the literature, few studies have used hospital visitors as a source of controls. In the Philippines, companions of the patients and neighborhood controls mentioned as the control group for female breast cancer patients. As we expected, cigarette smoking was very close to each other between two series of controls while alcohol drinking was less reported by neighborhood controls (18% vs. 12%, respectively), however, the underreporting was not statistically significant [23]. The other study on organochloride compounds and risk of breast cancer was also used visitor as the control group but no other type of control recruited for comparison [28].

Altogether, underreporting of opium use among neighborhood controls and high prevalence of opium use among disease controls, visitor controls may be more appropriate than neighborhood controls for studying of other banned substances, as well as other stigmatized or banned behaviors, such as certain sexual relationships. However, this needs to be studied and confirmed in other studies. In addition, apart from the exposure, control selection is pragmatic and depends on the research question [29–31].

This study has some strength. To the best of our knowledge, this is the first study that has investigated the reporting error of opium use in control selection for case-control studies using hospital visitor controls. Notable strength was the high participation rate of both controls. Besides, the same researchers involved in both studies which increased quality of data collection. The study also has limitation. Sample size of hospital visitor controls was modest but it could show the substantial difference of opium use, by increasing the sample size the difference may even be more outstanding.

Conclusion

In summary, for studying opium use in case-control studies, hospital visitor controls could serve more accurate answers. These findings should be verified in future studies and be considered for studies of illicit substances or other stigmatized behaviors.

Abbreviations

CRC
Cancer Reaserch Center
IROPICAN
Iran Opium and Cancer study
TLC

Thin Layer Chromatography
SES
Socio-economic Status
OR
Odds Ratio

Declarations

Ethics approval and consent to participate

The designing and implementation of both studies were approved by the Kerman University of Medical Sciences Ethics Committee (KMU.9421). Because of its multi-center nature, study II received additional approval from the Institutional Review Board of the National Institute for Medical Research Development (IR.NIMAD.REC.1394.027). A written informed consent was obtained from all study participants. After explaining the study, a written consent was obtained from all participants.

Consent for publication

Not Applicable

Availability of data and materials

The dataset used in this study is held securely in coded format at Cancer Reaserch Center (CRC) of Iran. Although data sharing agreements prohibit CRC from making the dataset publicly available, access may be granted to those who meet the conditions for confidential access and on reasonable request via the corresponding author's email (*kzendeh@sina.tums.ac.ir*).

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

EM analyzed, interpreted, and was a major contributor in writing paper. HR, ANT, MH, MM,MGh and MSS collected data. AAH, ARM,AR,AM, KZ, and FF designed the current study and interpreted the result. FF and KZ were major contributors in preparing the paper. All authors read and approved the final manuscript

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