International Journal of Epidemiology
Vol. 20, No. 4

Printed in Great Britain

Cancer and Non-Cancer Controls in Studies on the Effect of Tobacco and Alcohol Consumption

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Barra S (Epidemiology Unit, Aviano Cancer Center, Via Pedemontana Occ, 33081 Aviano (PN), Italy), Barón A E, Franceschi S, Talamini R and La Vecchia C. Cancer and non-cancer controls in studies on the effect of tobacco and alcohol consumption. *International Journal of Epidemiology* 1991; **20**: 845–851.

A comparison of risk estimates using controls with other cancers versus controls with acute diseases unrelated to tobacco and alcohol consumption in the study of the effect of these two factors has been performed using data on tumours of the oral cavity and pharynx from an ongoing case-control surveillance programme in Northeastern Italy. Similar results were obtained using either type of controls: as compared to never smokers, moderate smokers (≤14 cigarettes/day) showed age- and sex-adjusted odds ratio (OR) = 5.2 (95% confidence interval (CI): 2.9–9.2) when using cancer controls and 5.8 (95% CI: 3.3–10.1) when using non-cancer controls. Similarly, those who had smoked for 40 years or longer showed ORs of 7.4 (95% CI: 4.0–13.6) and 8.8 (95% CI: 4.9–15.6), respectively, using cancer and non-cancer controls. For moderate drinkers of alcoholic beverages (21–34 drinks/week) and heavy drinkers (≥84 drinks/week) the ORs, as compared to individuals who drank <21 drinks/week, were 1.9 (95% CI: 1.0–3.6) and 2.2 (95% CI: 1.2–4.0) and 10.6 (95% CI: 5.5–20.6) and 11.4 (95% CI: 6.0–21.4) using cancer and non-cancer controls, respectively. The same comparability of ORs for tobacco- and alcohol-related variables using either type of controls was observed when separate analyses of the two sexes were performed. The close similarity between cancer and non-cancer controls in studies on tabacco- and alcohol-related risks may be exploited when the choice of other types of controls would increase the costs and the feasibility of the study, and thus hamper its statistical power. Moreover, this investigation provides some reassurance about the validity of risk estimates using carefully selected groups of hospital controls.

Tobacco and alcohol have been well established as the most important risk factors for tumours of the upper aero-digestive tract.[1,2] The influence of these habits has been explored in several studies[1–11] using either community or hospital controls. In a few studies,[12–15] a cancer control group has been used and in one study[16] results obtained with multiple control groups including cancer and non-cancer hospital controls have been shown.

The advantages of the use of cancer controls, which have been discussed by some authors,[17,18] include the reduction of selection, recall and interviewer biases. However a potential disadvantage of their use is the inclusion of cancer types which are associated, positively or negatively, with the exposures of interest, resulting in under- or overestimation of risk estimates.

The purpose of the present investigation is to examine the comparability of risk estimates for smoking and drinking habits in tumours of the oral cavity and pharynx using two different control groups, one selected from patients admitted to hospital for a wide spectrum of acute diseases unrelated to tobacco and alcohol use, and the other control group selected from patients with cancers also believed to be unrelated to these exposures. The results are expected to be useful in demonstrating that cancer controls constitute an appropriate control group in this context. More importantly, they will provide further information about the validity of risk estimates using hospital controls for two behavioural risk factors which have been shown to be less than reliably, and therefore inaccurately, reported in

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hospital interview settings.[19] For this purpose we took advantage of the data collected in the framework of a case-control surveillance programme ongoing since 1985 in Pordenone province, Northeastern Italy.

MATERIALS AND METHODS

The study design of the present case-control surveillance has been described elsewhere.[20] Briefly, 236 male cases and 36 female cases below age 75 years (median age = 60), with histologically-confirmed cancer of the oral cavity and pharynx, diagnosed in the hospitals of the western part of the Friuli-Venezia Giulia region (Pordenone province) between January 1985 and July 1990, constituted the case group. All cases were resident in the same area in which the hospitals are located.

Similarly, criteria for inclusion as a cancer control were: (1) to be below age 75 years (median age = 57) (2) to be affected by a cancer type not consistently related to tobacco or alcohol consumption and (3) to come from the same catchment area as the cases of cancer of the oral cavity and pharynx. After a review of recent epidemiological literature and our partly published case-control study results[21-23] five tumour sites were selected for inclusion as controls: colorectal, renal cell, prostate, thyroid, and haematological (i.e., Hodgkin's disease, non-Hodgkin's lymphoma and multiple myeloma). All eligible cancer controls were included, thus making a group in which each cancer site accounted for about one-fifth of the total. Table 1 shows the distribution of 577 males and 446 females according to these cancer sites.

Eligible non-cancer controls were individuals admitted for acute illnesses to selected departments of local hospitals. These departments were chosen in order to cover the same catchment area as those from where cancer patients originated and to allow the inclusion of a wide spectrum of diseases (i.e., no category was to account for more than a quarter of the total). Specifically excluded were patients who had malignant tumours or any condition consistently related to alcohol or tobacco consumption. A total of 1122 male controls and 762 female controls chosen on the basis of age (below 75 years, median age = 58), and area of residence were interviewed. Their distribution according to hospital discharge diagnostic categories is given in Table 1. In particular, non-traumatic orthopaedic conditions included mainly low back pain and disk disorders; traumatic conditions included mainly sprains and fractures; and surgical conditions were chiefly represented by benign cysts, abdominal hernia and acute appendicitis. The 'Others' category mostly included skin illnesses.

All study patients were interviewed in hospital. Refusals were about 3% for all three study groups. Interviewers were pilot-trained to reduce variability using the same pre-coded questionnaire to obtain information on sociodemographic factors, occupation, lifestyle, including tobacco and alcohol consumption habits, dietary habits, and past history of selected medical conditions. All of the information referred to the patient's situation before the onset of the disease which led to the hospital admission.

Information on smoking habits included smoking status (never, ex, current smoker), the type of products smoked (cigarettes, pipe or cigar), the number of cigarettes (or pipe/cigars) smoked per day before the onset of the disease, duration of cigarette smoking, the age at starting smoking, and, for ex-smokers, years since they quit smoking. In the part of the questionnaire dealing with alcohol consumption, the number of glasses of alcohol-containing beverages (wine, beer, spirits) consumed per week was elicited. Taking into account the different alcohol concentration, consumption of one drink corresponded to 150 ml of wine, 330 ml of beer and 30 ml of spirits (i.e. approximately 15 ml of ethanol).

The odds ratios (ORs), together with their 95% approximate confidence interval (CI) were computed accounting simultaneously for age (in quinquennia), sex, years of education, occupation and for the reciprocal confounding effects of tobacco and alcohol. Unconditional multiple logistic regression with maximum likelihood estimation was used to obtain these estimates.[24]

RESULTS

Table 2 shows the distribution of cases and two control groups according to sex and sociodemographic characteristics. When compared to either cancer or non-cancer controls, cases of cancer of the oral cavity and pharynx appeared to be less educated. Also the distribution by occupation was different and, in particular, farmers were more frequent among male cases than among either of the control groups (27% versus 18% of cancer controls and 14% of non-cancer controls), while fewer female cases than controls reported clerical/professional occupation (6% versus 20% in both control groups).

Table 3 gives the risks of cancer of the oral cavity and pharynx for various measures of tobacco consumption. A close similarity in the ORs using the two different types of controls was evident for all smoking-related variables. Moderate smokers ($\leq$14 cigarettes/day) showed, as compared to never smokers, an OR of 5.2 (95% CI: 2.9–9.2) when contrasted to cancer controls

TABLE 1 *Distribution of cancer and non-cancer controls according to sex and diagnosis. Pordenone, Italy, 1985–1990*

	Cancer controls (No. = 577)			Non-cancer controls (No. = 1122)	
	No.	(%)		No.	(%)
Males					
Colorectal cancer	130	(22)	Orthopaedic	251	(22)
Kidney cancer	82	(14)	Trauma	291	(26)
Prostate cancer	125	(22)	Surgical conditions	303	(27)
Haematological cancer	195	(34)	Eye disorders	67	(6)
Thyroid cancer	45	(8)	Others	210	(19)
	Cancer controls (No. = 446)			Non-cancer controls (No. = 762)	
	No.	(%)		No.	(%)
Females					
Colorectal cancer	82	(18)	Orthopaedic	243	(32)
Kidney cancer	51	(11)	Trauma	151	(20)
Haematological cancer	173	(39)	Surgical conditions	131	(17)
Thyroid cancer	140	(31)	Eye disorders	53	(7)
			Others	183	(24)

and 5.8 (95% CI: 3.3–10.1) when contrasted to non-cancer controls; the ORs associated with heavy smoking (≤25 cigarettes/day) were 9.6 (95% CI: 4.9–18.9) and 12.2 (95% CI: 6.4–23.2), respectively. Those who had smoked for 40 years or more had a 7.4-fold increased risk when compared to cancer controls and 8.8-fold increased risk when compared to non-cancer controls. Such similarities in the ORs were also obtained with age at starting smoking (OR = 6.8, 95% CI: 3.8–12.2, and 6.6, 95% CI: 3.8–11.5, using cancer and non-cancer controls, respectively, for ≤16 versus ≥25 years) and, among ex-smokers, with years since quitting (OR = 3.9 using both types of controls for <10 years).

Drinking-related variables are shown in Table 4. For moderate wine drinkers (21–34 drinks/week) the ORs, as compared to individuals who drank <21 drinks/week, were 1.8 (95% CI: 1.0–3.1) and 1.7 (95% CI: 1.0–3.1) using cancer and non-cancer controls respectively. Heavy wine drinkers (≥84 drinks/week) had

TABLE 2 *Distribution of cases of cancer of the oral cavity and pharynx, and cancer and non-cancer controls according to sex and various socio-demographic characteristics.* Pordenone, Italy, 1985–1990*

	Oral cavity-pharynx cancer cases				Cancer controls				Non-cancer controls			
	Males		Females		Males		Females		Males		Females	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Age (years)												
≤49	58	(25)	7	(19)	126	(22)	164	(37)	353	(32)	313	(41)
50–59	65	(28)	15	(42)	132	(23)	110	(25)	331	(29)	177	(23)
60–69	85	(36)	11	(31)	168	(29)	95	(21)	283	(25)	152	(20)
≥70	28	(12)	3	(8)	151	(26)	77	(17)	155	(14)	120	(16)
Education (years)**												
≤4	58	(25)	15	(42)	145	(25)	142	(32)	221	(20)	241	(32)
5–7	132	(56)	16	(44)	259	(45)	178	(40)	540	(48)	333	(44)
≥8	45	(19)	5	(14)	173	(30)	126	(28)	361	(32)	187	(24)
Marital status												
Never married	34	(14)	2	(6)	61	(11)	62	(14)	133	(12)	102	(13)
Ever married	202	(86)	34	(94)	516	(89)	384	(86)	989	(88)	660	(87)
Occupation**												
Clerical/Professional	52	(22)	2	(6)	190	(33)	90	(20)	346	(31)	149	(20)
Manual worker	118	(50)	10	(27)	266	(46)	108	(24)	609	(54)	221	(29)
Farmer	64	(27)	4	(11)	104	(18)	74	(17)	158	(14)	109	(14)
Other	2	(1)	20	(56)	17	(3)	174	(39)	9	(1)	282	(37)

*Total sample size varies because of missing values.

**Difference between cases and either control group was statistically significant (P<0.01).

TABLE 3 *Odds ratios for cancer of the oral cavity and pharynx according to smoking habits.* Pordenone, Italy, 1985–1990*

	Oral cavity pharynx cancer cases		Cancer controls		Odds ratio** (95% CI)	Non-cancer controls		Odds ratio** (95% CI)
	Males	Females	Males	Females		Males	Females	
Never smoker	6	15	115	330	1	216	553	1
Cigar or pipe smoker only	5	—	7	—	5.2 (1.4–19.6)	7	—	6.4 (1.8–23.6)
Cigarette smoker (cigarettes/day)								
≤14	44	14	86	48	5.2 (2.9–9.2)	165	89	5.8 (3.3–10.1)
15–24	69	4	98	21	5.8 (3.2–10.5)	221	47	6.1 (3.5–10.9)
≥25	48	1	40	8	9.6 (4.9–18.9)	80	7	12.2 (6.4–23.2)
X^2_1 trend					42.1†			57.5†
Duration of smoking (years)								
<30	53	4	161	76	2.7 (1.5–4.9)	391	146	2.7 (1.5–4.7)
30–39	69	9	99	24	7.0 (3.9–12.6)	221	37	6.9 (3.9–12.1)
≥40	99	8	171	15	7.4 (4.0–13.6)	266	22	8.8 (4.9–15.6)
X^2_1 trend					55.3†			75.9†
Age at starting smoking (years)								
≥25	24	2	73	48	2.8 (1.4–5.4)	123	69	3.3 (1.7–6.2)
17–24	113	9	245	53	4.7 (2.7–8.1)	500	83	4.9 (2.9–8.4)
≤16	91	10	141	14	6.8 (3.8–12.2)	279	52	6.6 (3.8–11.5)
X^2_1 trend					49.0†			51.0†
Years since quitting smoking								
≥10	22	—	139	12	1.4 (0.6–3.1)	236	25	1.6 (0.8–3.5)
<10	41	2	94	26	3.9 (2.0–7.8)	201	38	3.9 (2.0–7.8)
X^2_1 trend					18.8†			19.2†

*Total sample size varies because of missing values.
**Estimates adjusted for age, sex, years of education, occupation and number of alcoholic drinks per week.
†P<0.01.

ORs of 13.7 (95% CI: 6.9–27.2) and 15.6 (95% CI: 8.2–29.7), respectively. Close similarities were observed for beer and spirits as well, although these alcoholic beverages were substantially less frequently used (Table 4). The same pattern of risk was obtained as regards the total alcohol intake (OR = 10.6, 95% CI: 5.5–20.6, and OR = 11.4, 95% CI: 6.0–21.4, using cancer and non-cancer controls, respectively).

Separate analysis of the two sexes (not shown) showed similar results, thus indicating that the close similarities in ORs based on either cancer or non-cancer controls apply to males or females.

DISCUSSION

Control selection is crucial in case-control studies, since the use of inappropriate controls can lead to both selection and information bias and, therefore, affect the validity of a study.[25] Cancer controls are commonly utilized in studies performed in clinical settings, where establishing an internal comparison between patients with different, but generally closely related, cancer sites (e.g. cancers of the upper respiratory and digestive tract, gynaecological tumours, etc.) seen by the same physician saves both time and money.[26] However, the problem is that the similarities between such cases and controls, not only as regards the anatomical site but, in most instances, the probable aetiology, result in estimation of relative risks which are biased towards the null. Other limitations of using cancer controls, which must be borne in mind, include representative-

TABLE 4 *Odds ratios for cancer of the oral cavity and pharynx according to drinking habits.* Pordenone, Italy, 1985–1990*

	Oral cavity-pharynx cancer cases		Cancer controls		Odds ratio** (95% CI)	Non-cancer controls		Odds ratio** (95% CI)
	Males	Females	Males	Females		Males	Females	
Wine (drinks/week)								
0–6	5	5	41	146	1	82	267	1
7–20	7	14	84	217		138	359	
21–34	26	9	176	68	1.8 (1.0–3.1)	329	118	1.7 (1.0–3.1)
35–55	42	4	119	10	3.5 (1.9–6.4)	272	14	3.3 (1.8–5.9)
56–83	95	4	120	4	7.6 (4.2–13.8)	240	2	6.8 (3.9–12.1)
⩾84	61	—	37	1	13.7 (6.9–27.2)	61	2	15.6 (8.2–29.7)
X_1^2 trend					89.6†			107.9†
Beer (drinks/week)								
0	141	27	325	395	1	633	643	1
1–13	27	5	144	41	0.5 (0.3–0.9)	242	107	0.7 (0.4–1.0)
⩾14	68	4	108	10	1.5 (1.0–2.2)	247	12	1.4 (1.0–1.9)
X_1^2 trend					1.8			1.5
Spirits (drinks/week)								
0	107	30	275	359	1	554	650	1
1–13	66	3	217	77	0.6 (0.4–0.8)	391	100	0.8 (0.6–1.1)
⩾14	63	3	85	10	1.4 (1.0–2.2)	177	12	1.6 (1.1–2.3)
X_1^2 trend					0.5			1.1
Total (drinks/week)								
0–6	3	4	30	140	1	62	254	1
7–20	4	13	62	200		107	347	
21–34	17	11	127	75	1.9 (1.0–3.6)	215	123	2.2 (1.2–4.0)
35–55	29	2	136	19	2.1 (1.1–4.2)	291	31	2.4 (1.2–4.7)
56–83	78	5	133	10	5.8 (3.0–11.1)	260	3	6.6 (3.5–12.5)
⩾84	105	1	89	2	10.6 (5.5–20.6)	187	4	11.4 (6.0–21.4)
X_1^2 trend					78.1†			92.8†

*Total sample size varies because of missing values.
**Estimates adjusted for age, sex, years of education, occupation and smoking habits.
†$P<0.01$.

ness of risk estimates, additional potential confounding by exposure-related factors, and potentially different catchment areas across cancer types.[18]

A potential strength of the use of cancer controls, in case-control studies, is, however, the possibility of minimizing many problems related to other hospital and population controls, namely recall, selection and information bias. These biases are often not quantifiable and may be towards or away from the null. Specifically, the choice of cancer controls has been advocated in the past to reduce recall bias, since all cancer patients should have been similarly interviewed for their past medical histories and various exposures and therefore should be more apt to recall them accu-

rately, especially in the context of their severe illness.[17,18] To this extent, cancer controls can be better than non-cancer hospital controls and greatly superior to healthy community controls by providing risk estimates which are not biased away from the null value. In light of the practical difficulties in blinding the interviewer to case-control status, a reduction in interviewer bias is also likely to be achieved by using cancer patients as a control group.[17,18]

Generally, in cancer epidemiology, hospital and population controls have been compared. The use of other cancer sites as controls has been evaluated less often. They were first utilized as far back as 1931.[12] Among case-control studies on risk factors for upper aero-digestive tract tumours, only a few studies[12,16] have used other cancer patients as controls. In one of them dealing with the importance of type of alcoholic beverages on oesophageal cancer risk, Tuyns *et al.*[16] included digestive tract cancers and other medical and surgical patients in the control group. While the analyses performed by these authors did not separate the risk estimates by cancer versus non-cancer controls, the inclusion of cancer controls were presumably done to reduce recall and interviewer bias.[27]

Special concern arises when the aetiologies of different types of cancer (or other diseases), even if not closely linked anatomically, are unknown and, thus, similarities in risk factors cannot be confidently discarded.[17,18] In this study we attempted to minimise this problem by including control patients with cancers of different sites which, to the best of present epidemiological knowledge, are not consistently or substantially associated with tobacco and/or alcohol use. If they exist, some weak associations (e.g. direct for renal cancer[28] and inverse for colorectal cancer[29]) may counterbalance each other. Similarly, nearly a fifth of non-cancer controls came from each different category of disease, thus reducing the magnitude of selection bias. The effectiveness of this strategy is still open to debate,[30-33] particularly in situations where exposure-disease associations may be population-specific.[33] However, tobacco and alcohol have been shown to be strong and consistent risk factors for oral cavity and pharynx cancer in a large variety of populations and settings.[7-9,34,35] Their specificity would not then be expected to bias the results in this study.

With regard to the specific exposures investigated in the present study, the work of Kelly *et al.*[19] suggests that the reliability of reporting alcohol consumption, and to a lesser extent tobacco use is only moderate in a hospital interview setting, thereby calling into question the validity of such self-reports. Differential misclassification of specific risk factors across diagnostic categories was not addressed in their study, but is ultimately of concern in the present study where both the cancer controls and the hospital controls are made up of several diagnostic groups. Given that the expected biases resulting from using cancer versus non-cancer controls are in opposite directions, the congruence between the risk estimates based on cancer controls and non-cancer controls in the present study suggests that the misclassification of alcohol and tobacco consumption was, in effect, non-differential.

Finally, when hospital records constitute the predominant source of identification of cancer cases, a good comparability of catchment areas of cases with malignant diseases and controls with less severe acute conditions is very difficult to achieve. While this type of selection bias is unlikely to operate in the present study area, because of the established primary care and referral network, it is also likely to be alleviated by the choice of cancer controls.[17,18]

In this study the use of population controls would have been best in methodological terms, although the similarity of ORs when either cancer or non-cancer controls were used was so close as to provide, by itself, important information, particularly since all eligible and available cancer and non-cancer controls were included in the analysis. In practical terms, the present findings of high comparability of cancer and non-cancer controls in the study of tobacco- and alcohol-related tumours are useful given that, along with the minimization of selection, recall and information bias, the choice of cancer controls would diminish the costs and the difficulty of the study, and thus make it possible to increase its statistical power.

The use of other cancer types as controls may be also useful when investigating whether a specific exposure is associated with one specific tumour or to all tumours in general; or when a specific exposure, which has received particular attention in the media for its (adverse) effects, could result in overestimation because of recall bias. This could occur particularly in cancer studies on the effect of various components of diet which are subject to continuous attention in the media. Thus, while the present results strictly apply only to the effect of smoking and drinking on the risk of cancer of the oral cavity and pharynx, and are largely reassuring, they point to the need for further research on the validity of risk estimates obtaining using selected groups of hospital and non-hospital controls.

ACKNOWLEDGEMENTS

The contribution of the Italian Association for Cancer Research, Milan and the Italian National Research Council (CNR Applied Projects 'Oncology', Contract

87.01544.44 and 'Risk Factors for Disease') are gratefully acknowledged. We also thank Mrs Tiziana Angelin, and Dr Derna Gerdol for interviewing patients and Mrs Anna Redivo and Ilaria Calderan for editorial assistance.

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(Revised version received February 1991)