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Colon cancer controls versus population controls in case-control studies of occupational risk factors

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Abstract

Background: Since updated population registers do not exist in many countries it is often difficult to sample valid population controls from the study base to a case-control study. Use of patient controls is an alternative option if the exposure experience under study for these patients are interchangeable with the experience for population controls. Patient controls may even be preferable from population controls under certain conditions. In this study we examine if colon cancer patients can serve as surrogates for proper population controls in case-control studies of occupational risk factors.

Methods: The study was conducted from 1995 to 1997. Incident colon cancer controls (N = 428) aged 35–69 years with a histological verified diagnosis and population controls (N = 583) were selected. Altogether 254 (59%) of the colon cancer controls and 320 (55%) of the population controls were interviewed about occupational, medical and life style conditions.

Results: No statistical significant difference for educational level, medical history or smoking status was seen between the two control groups. There was evidence of a higher alcohol intake, less frequent work as a farmer and less exposure to pesticides among colon cancer controls.

Conclusions: Use of colon cancer controls may provide valid exposure estimates in studies of many occupational risk factors for cancer, but not for studies on exposure related to farming.

Background

Since good quality population registries do not exist in many countries, patient controls are often used to provide exposure data from the study base in case-control studies [1,2]. Even where good population registries exist, low response rates for population controls may make patient controls an attractive alternative. The aim of obtaining

better symmetry in recall between cases and controls may be another reason for using patient controls.

A case-control study is a design that attempts to capture the relative effect measures in the underlying population over time by using selective sampling from the same population that gave rise to the cases. Sampling of population

controls requires some kind of register to define the sampling frame. In many countries no such valid registers exist.

The condition for using patient controls to replace population controls is that the exposure experience of interest (including time, duration and intensity) should be interchangeable with the experience for proper population controls, sampled at random from the entire study base. Patients with a disease that is neither caused nor prevented by the exposure under study may sometimes fulfill this criterion.

Hospital controls have been used as controls in several studies [2-4]. Patients with colon cancer have been used as controls in occupational studies of cancer under the assumption that colon cancer has an etiology mainly related to genetic and to dietary factors [3]. High-fat, low-fiber diary, red meat, alcohol, sedentary life style, and presence of first-degree relatives with colorectal cancer, aspirin and non-steroid anti-inflammatory drugs (NSAIDs) have been associated with colon cancer [5]. It is a frequent cancer and the disease will lead to hospitalisation at some point in time for almost all with the disease in many parts of the world [6].

As part of the European multi-centre case-control study of seven rare cancers 'Occupational risk factors for rare cancers of unknown etiology', colon cancer was used as the only control group in Spain, Portugal and Latvia and as a supplementary control group for population controls in Denmark [3,7,8].

This study aimed to investigate whether a bias is introduced by using colon cancer controls instead of population controls in occupational studies of cancer. We used the Danish data of the rare cancer study to see if the colon cancer controls had an exposure experience similar to that of the population controls. We did this for a number of indicators taken from the domains of occupational, medical, social and life style factors. All these exposures were selected before data analyses started.

Methods

An international multi-centre case-control study was conducted in ten European countries from 1995 to 1997 involving persons aged 35 to 69 years using common data collection instruments [3,4,7,8].

In Denmark, both colon cancer controls and population controls were recruited in order to evaluate the potential selection bias in the use of cancer controls. Four population controls and three to four colon cancer controls were recruited for each case. Both population and colon cancer controls were frequency matched with cases in 5 year age

groups by sex and, if possible, geographical region (county) to obtain a balanced data set. The control closest in age to the case was selected. As selected colon cancer controls were removed from the study base if they at review of the histology report did not fulfill the diagnostic and histological criteria, the number of colon cancer controls was slightly less than the number of population controls.

Population controls were sampled at four occasions after the start of case enrolment, the first time in October 1995 and the last time in August 1997. Each cluster included controls for the cases identified during the preceding six months.

The colon cancer controls were defined as histologically verified incident colon cancer patients with topography codes 153.0-153.9 (ICD-O, 1976) or C18.0-C18.9 (ICD-O, 1990) and morphology codes 81403, 82103 or 82313. They were enrolled based on repeated requests to local pathology departments every four months [9,10]. Frequent screening of regional and national cancer and pathology registers were also done.

Data collection

The colon cancer patients and population controls received a short introduction letter stating that they were selected as controls for a study of rare diseases and a self-administered questionnaire asking for a chronological description of all jobs held for more than 6 months since leaving primary school. The persons who accepted to participate filled in and returned the questionnaire together with their consent. If a person did not respond, a reminder was sent by mail after 2 weeks. The interviews were performed by trained interviewers according to a highly structured questionnaire used in all centres. Most of the interviews were done by telephone, but 5% of the interviews were performed face-to-face due to impaired hearing, severe health problems or if they had no telephone at home.

Information was obtained on socio-economic and demographic factors, educational level, adult height and weight, previous medical conditions and occupational factors. A complete occupational history was recorded for all respondents as well as smoking habits and alcohol consumption up to 5 years before the interview. Questions on alcohol consumption addressed the average daily intake of specific types of alcohol. Total daily alcohol intake was computed from the average alcohol content per liter of each beverage: beer, 40 g; wine, 94 g; aperitif, 145 g; liquor, 317 g. In Denmark a drink (one beer, a glass of wine or spirit) contains approximately 12 grams of alcohol. The study was made in accordance with the

Table 1: Selected characteristics of colon cancer controls and population controls

	Colon cancer controls				Population controls			
	N	(%)	n	(%)	N	(%)	n	(%)
Responders	254	(59)			320	(55)		
Men			153	(60)			195	(61)
Women			101	(40)			125	(39)
Age at interview (years)								
35–59			125	(49)			180	(56)
60–69			129	(51)			140	(44)
Mean age, years			58.1	-			56.7	-
Non-responders	174	(41)			263	(45)		
Men			93	(53)			168	(64)
Women			81	(47)			95	(36)
Age at contact (years)								
35–59			68	(39)			114	(43)
60–69			106	(61)			149	(57)
Mean age, years			60.1	-			59.9	-
Total	428	(100)			583	(100)		

requirements of the Danish central and regional ethics committees.

Statistical analysis

We selected prior to data analysis a number of exposures to represent different aspects of interest: educational, life style, medical and occupational conditions. Three to four exposures were selected within each category including the only suggested protective occupational factor for colon cancer (physical demanding work).

To characterise the differences between colon cancer controls and population controls adjusted odds ratios (ORs) were obtained by unconditional logistic regression with 95 % confidence intervals (CIs) for the following variables: level of education, marital status, smoking status, high versus low alcohol intake, obesity, ever had certain diseases (asthma or dermatitis), ever employed in certain occupations (health care, farmer, working with farm animals), and ever having worked in high temperatures or with certain chemicals (chemicals with hormonal effects or pesticides) [11,12]. All adjusted estimates were obtained from a model that included year of birth and sex, since controls were frequency matched on these variables. Occupational data were analyzed by gender because men and women often perform different tasks within the same occupation or industry. Year of birth was used as a continuous variable [13]. A more detailed adjustment for region did not improve the model. If expected cell counts were less than 5 we performed the analyses using Fishers exact test for stratified analyses included in the software package StatXact with stratification by year of birth (2 levels) and sex [14].

Results

Of the 428 colon cancer controls and the 583 population controls recruited to the Danish study, 254 colon cancer controls (153 men, 101 women) and 320 population controls (195 men, 125 women) were interviewed (Table 1). The response rate for colon cancer controls was 59.3 % (62.2 % for men; 55.5 % for women), and for population controls 54.9 % (53.7 % for men; 56.8 % for women).

Table 2 shows a comparison between the two control groups regarding social, life style and medical factors presented as ORs for colon cancer controls. No statistically significant differences in educational level or smoking status were seen. More colon cancer patients than population controls were married or lived together with a partner. The proportion of heavy alcohol drinkers was higher for colon cancer controls than for population controls. Stratified analyses showed, however, that the tendency was seen only among older women and men. No statistical significant difference was seen between the two control groups for diseases such as asthma, dermatitis, and obesity (maximum body mass index ever being ≥ 30), although the estimated OR for obesity was above unity (1.4, 95% CI (0.9–2.2)).

Table 3 outlines occupational work tasks and occupational exposures in the two groups. The only significant difference was a lower proportion of male colon cancer controls ever having worked as a general farmer and as a farmer with animals. No significant differences were seen for working in high temperatures or for occupational use of chemicals with hormonal effects, whereas the occupational use of pesticides was higher in male population

Table 2: Odds ratios for demographic, life style and medical characteristics in colon cancer controls compared with population controls

	Colon cancer controls (N = 254)		Population controls (N = 320)		Crude OR	Adjusted OR ²	95% CI ²
	No.	%	No.	%			
Educational status, low ³	59	23	89	28	0.8	0.7	0.5–1.0
Living alone	43	17	77	24	0.7	0.6	0.4–0.9
Ever smokers	180	71	228	71	1.0	1.0	0.7–1.4
Heavy smokers ⁴	70	28	88	28	1.0	0.9	0.7–1.3
Alcohol, high ⁵	108	43	98	31	1.7	1.8	1.2–2.5
-Age 35–59	48		59		1.3	1.3	0.8–2.2
-Age 60–69	60		39		2.3	2.3	1.4–3.9
Obesity ⁶	51	20	53	17	1.4	1.4	0.9–2.2
Asthma	15	6	28	9	0.7	0.6	0.3–1.2
Dermatitis	47	19	62	19	0.9	0.9	0.6–1.4

¹ Crude odds ratio (OR). ² OR with 95 % confidence interval (CI), adjusted for sex and age. If expected values were less than 5, Fishers exact test was used with stratification by year of birth (2 levels) and sex. ³ Left school at 15 y no further education. ⁴ More than 20 pack-years ('pack-years' = number of years as a smoker * number of cigarettes per day/20). ⁵ Total alcohol intake > 24 grams alcohol per day. ⁶ Obesity defined as maximum body mass index ever being ≥ 30 .

Table 3: Odds ratios for occupational characteristics in colon cancer controls compared with population controls

Occupation	Colon cancer controls (N = 254)		Population controls (N = 320)		Crude OR ¹	Adjusted OR ²	95% CI ²	
	No.	%	No.	%				
Health care ³								
-Men ⁴	4		3	3	2	1.8	1.9	0.4–8.8
-Women ⁴	18		18	21	17	1.1	1.1	0.5–2.1
-Both sexes	22		9	24	8	1.2	1.2	0.6–2.3
Farming ³								
-Men ⁴	23		15	48	25	0.6	0.5	0.3–0.9
-Women ⁴	7		7	4	3	2.3	2.1	0.6–7.6
-Both sexes	30		12	52	16	0.7	0.7	0.4–1.1
Farming animals ³								
-Men ⁴	20		13	48	25	0.5	0.4	0.2–0.8
-Women ⁴	5		5	3	2	2.1	2.0	0.5–8.9
-Both sexes	25		10	51	16	0.6	0.5	0.3–0.9
High temperatures ⁵								
-Men ⁴	17		11	29	15	0.7	0.7	0.4–1.4
-Women ⁴	5		5	7	6	0.9	0.9	0.3–3.0
-Both sexes	22		9	36	11	0.8	0.8	0.4–1.3
Chemicals hormonal effects ⁶								
-Men ⁴	6		4	15	8	0.5	0.5	0.2–1.3
-Women ⁴	6		6	6	5	1.3	1.3	0.4–4.1
-Both sexes	12		5	21	7	0.7	0.7	0.3–1.5
Pesticides ⁷								
-Men ⁴	12		8	33	17	0.4	0.4	0.2–0.8
-Women ⁴	3		3	3	2	1.3	1.3	0.3–6.5
-Both sexes	15		6	36	11	0.5	0.5	0.3–0.9
-Adjusted for farm work	-		-	-	-	-	0.6	0.3–1.2

¹ Crude odds ratio (OR). ² OR with 95 % confidence interval (CI), adjusted for year of birth and age. If expected values were less than 5, Fishers exact test was used with stratification by year of birth (2 levels) and sex. ³ Ever working in these occupations. ⁴ OR with 95 % confidence interval (CI) adjusted for year of birth. If expected values were less than 5, Fishers exact test was used with stratification by year of birth (2 levels). ⁵ Ever working in high temperatures. ⁶ Ever working with chemicals with hormonal effects. ⁷ Ever working with pesticides.

controls. When this analysis was adjusted for farm work no statistical significant difference was seen, although the estimated OR remained below unity (0.6, 95% CI (0.3–1.2)).

Discussion

Colon cancer controls had rather similar characteristics as population controls for most of the occupational exposures under study except for work with farm animals, use of pesticides, and for certain life style related factors such as high alcohol intake. The difference in the frequency of farming between the two sets of controls may be caused by a possible protective effect of physical activity for colon cancer. The study does not prove that colon cancer patients are valid surrogates for population controls in some situations. Small to moderate true differences in the exposure experience between colon cancer controls and population controls cannot be ruled out as indicated by the confidence limits of the ORs. The study only documents that the bias associated with using colon cancer controls rather than population controls in studies of occupational risk factors for cancer in some cases is small or non-existing except for studies on exposures related to farming. An acceptable level of difference between the exposure experience of interest depends not only on the aim of the study but also of the effect of the exposure under study.

The proportion of non-responders was rather high but similar in the two groups (41% in the colon cancer controls and 45% in population controls), which is in contrast to the expectations that the response rate should be higher among patient controls. The reason could be that both groups were contacted at home by telephone.

Colon cancer controls were patients whereas most population controls were non-patients which may create an asymmetry in recall of exposure [15]. We only expect this problem to be of relevance for sensitive questions such as alcohol intake and for questions that require recall over longer time periods.

The statistically significant difference for alcohol may indicate that this is a risk factor for colon cancer. The difference for work as a farmer and work with farm animals may indicate that these job tasks protect against colon cancer. Both findings are in line with the existing literature [16]. A negative association between use of pesticides and colon cancer was seen but the significant association disappeared when the analysis was adjusted for farm work, although the OR was still low. This may be due to residual confounding, chance or that pesticides prevent colon cancer. The association between farm work and colon cancer in many studies call for caution when using colon cancer patients as controls in studies related to farm work, since

we do not know what elements of farm work prevents colon cancer [17]. The assumption is that it is physical activity but that is still just a hypothesis. If the exposures under study cause or prevent the disease in question, patients with this disease constitute an unsuitable control group for producing valid quantitative effect measures for these specific exposures [18].

Other studies have outlined benefits and limitations of using different kinds of control groups in different situations [19–23]. The perfect control group is easy to define but difficult to get. Population controls should in most cases be the first choice, if possible, since only they provide the sample from the study base we want.

Conclusions

The present study shows, that colon cancer patients have many similar characteristics as a population sample and may be used as controls in certain case-control studies of occupational risk factors for cancer, at least in countries with a similar industrial structure and similar life style as in Denmark. Our study aimed to investigate the use of colon cancer controls in *occupational* studies of cancer. In these studies it is advisable to control for factors we found to correlate with colon cancer risk (such as obesity) whether our associations were statistically significant or not. If these factors change the effect measures under study they should be adjusted for. Cancer studies on exposures that are suggested to prevent colon cancer e.g. farming or cause colon cancer e.g. alcohol intake should not use colon cancer controls. Use of colon cancer controls in these cases may lead to biased effect measures.

Competing interests

None declared.

Authors' contributions

All authors (LK, EL, SS, JO) participated in the design and coordination of the study.

LK performed the statistical analysis and drafted the manuscript.

All authors read, commented and approved the manuscript.

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