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European Journal of Cancer 41 (2005) 601–612

European Journal of Cancer

www.ejconline.com

European multi-centre case–control study on risk factors for rare cancers of unknown aetiology

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Received 28 October 2004; received in revised form 12 November 2004; accepted 16 December 2004
Available online 26 January 2005

Abstract

To search for occupational risk factors, we conducted a case–control study in nine European countries of cancers of the small intestine, male gall bladder, thymus, bone, male breast, melanoma of the eye, and mycosis fungoides. Recruitment was population based in Denmark, Latvia, France, Germany, Italy, and Sweden, from hospital areas in Spain and Portugal, and from one United Kingdom (UK) hospital. We recruited 1457 cases (84% interviewed). Numbers identified corresponded to those in the EUROCIM database for Denmark, but were below those observed for France, Italy and Sweden in the database. We recruited 3374 population (61% interviewed) and 1284 colon cancer controls (86% interviewed). It was possible to undertake this complicated study across Europe, but we encountered three main problems. It was difficult to ensure complete case ascertainment, for population controls, we found a clear divide in the response rate from 75% in the South to only 55% in the North, and a somewhat selective recruitment was noted for the colon cancer controls. The study showed there is a clear dose–response relationship between alcohol intake and the risk of male breast cancer, and an excess risk of mycosis fungoides among glass formers, pottery and ceramic workers. Further data are expected.

Keywords: Case–control study; Rare cancer; Occupational risk factors; Methods; Multi-centric case–control study

1. Introduction

Some rare cancers are caused by mutations in a single gene, like retinoblastoma of the eye [1]. Other rare cancers are closely associated with a specific exposure, like adenocarcinoma of the vagina in daughters of mothers using diethylstilbestrol during pregnancy [2]. Several

Abbreviation: ICD, International Classification of Diseases; ICD-O, International Classification of Diseases for Oncology; NA, Not available; NOS, Not otherwise specified; UK, United Kingdom.

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doi:10.1016/j.ejca.2004.12.016

rare cancers are known to be caused by occupational exposures, such as pleural mesothelioma in asbestos workers [3], bone sarcoma in radium dial painters [4], and liver angiosarcoma in vinyl chloride workers [5]. Historically, the term "signal cancer" has been used for rare cancers clustering in specific occupations, like nasal adenocarcinoma in furniture-makers in Buckinghamshire, in the United Kingdom (UK), in the early 1960s [6].

However, little is known about the aetiology of most rare cancers, and these cancers are difficult to study on a national basis due to the small numbers seen. We therefore conducted a case–control study in nine European countries of cancers of the small intestine, male gall bladder and bile ducts, thymus, bone, male breast, eye melanoma, and mycosis fungoides. Before initiation of the study, we conducted a literature review [7], and showed that occupational risk factors could be involved in the aetiology of these cancers. The review resulted in some specific hypotheses and data were collected to test these. However, the primary aim of the study was to undertake a systematic search for occupational risk factors. We report here on the design and organisation of the study, ascertainment of cases and controls, and participation in the interviews.

2. Patients and methods

2.1. Definition of diseases and study base

The cancers were defined by topography and morphology codes according to International Classification of Diseases for Oncology [8,9] (Table 1). Only invasive malignancies with behaviour code "3" were included. Exceptions were carcinoids with behaviour code "1" located in the gallbladder, extrahepatic bile duct and small intestine, and thymoma with code "0". Topographically, eye melanoma was restricted to the eyeball, choroid, and eye not otherwise expected (NOS). Morphologically, bone cancer was restricted to osteosarcoma and chondosarcoma, and small intestine cancer to adenocarcinoma and carcinoid.

A population-based recruitment scheme was set up in Denmark and Latvia, in ten areas in France, five in Germany, three in Italy, and four in Sweden. Recruitment was based on hospital referral areas in three places in Spain and two in Portugal. A small non-representative sample of eye melanoma patients was recruited from a UK hospital. Data collection was started, but could not be completed in Lithuania. The study base comprised 37 million. We aimed at recruiting all incident cases aged 35–69 years and diagnosed from 1 January, 1995 to 31 December, 1996. Due to the waiting time involved to obtain local funding, the period had to be adjusted locally (Table 2).

2.2. Ascertainment of cases and controls

To ensure rapid contact with newly diagnosed patients, case identification was based on regular contacts to clinical and pathology departments. A computerised identification procedure was set up in areas with registers of pathology, hospital discharges and/or cancer. Ascertainment was made elsewhere by manual search of files in the collaborating hospitals, (Table 2). The same procedures were used for recruitment of cancer controls, see below. For each of the seven cancer sites, one expert pathologist reviewed the pathology report and one representative, haematoxylin–eosin stained slide and classified the case as definite, possible or non-eligible. For melanoma of the eye, the review could be based on the ophthalmological report only. Other cancers without slides could be classified as possible based on the pathology report.

Before selection of controls, the expected number of cases was estimated from local or nearby cancer registers. The controls were frequency matched with the expected number of cases by region, gender and 5-year age group. Within each stratum, we aimed to select a number of controls that was four times the number of the most "frequent" of the seven rare cancers.

Controls were selected randomly at specific points in time during case recruitment from population registers in Denmark, Italy, and Sweden, and from electoral rolls in France. In Germany, population controls were selected from municipality registers. As this was relatively expensive, a large pool of potential controls was selected at the beginning of the study, and controls were subsequently selected from this pool. In the UK, one control per case was selected from the list of the general practitioner (GP) of the case.

Where population controls could not be selected, colon cancer patients were regarded as appropriate alternatives, as the only known occupational risk for colon cancer is sedentary work [10]. Population-based colon cancer controls were selected randomly in Latvia. Hospital-based cancer controls were selected randomly among the incident colon cancer patients in two areas in Spain, and among the colon and a few stomach cancer patients in Portugal. Patients attending the emergency ward were selected as controls in one area in Spain. To provide data for a validity study, population-based colon cancer controls were selected as a second control group in Denmark [11].

2.3. Data collection

A questionnaire was developed in English, and translated into the other eight national languages, and for quality control back-translated in part. It included demographic variables, characteristics such as eye colour, medical and X-ray history, use of drugs, to-

Table 1
Definition of cancer sites included in the European Rare Cancer Study

Site	ICD-O, 1976	ICD-O, 1990	EUROCIM	EUROCIM codes
Cases				
Gall bladder and extrahepatic bile ducts	Topography: 156.0–156.9 Morphology: behaviour code '3' in interval 80103–85703 and 82401 Gender: Men only	Topography: C23.9, C24.0–C24.9 Morphology: behaviour code '3' in interval 80103–85703 and 82401 Gender: Men only	Topography: C239, C240, C241 Morphology: 8000–8034, 8140–8550 Gender: Men only	271, 274, 275, 276, 279, 280
Small intestine (including duodenum, jejunum, ileum)	Topography: 152.0–152.9 Morphology: behaviour code '3' in interval 81403–85703 and 82401 Topography: 164.0 Morphology: 85800, 85803	Topography: C17.0–C17.9 Morphology: behaviour code '3' in interval 81403–85703 and 82401 Topography: C37.9 Morphology: 85800, 85803	Topography: C170, C171, C172, C173, C178, C179 Morphology: 8000–8034, 8140–8473, 8480–8490, 8500–8550 Topography: C379 Morphology: 8580	183, 184, 187, 188, 189, 190, 193, 194, 195, 196, 199, 200, 201, 202, 205, 206 346
Bone	Topography: 170.0–170.9 Morphology: behaviour code '3' in interval 91803–92403	Topography: C40.0–41.9 Morphology: behaviour code '3' in interval 91803–92403	Topography: C400–C403, C408, C409, C410–C414, C418–C419 Morphology: 9180–9200, 9210–9241, 9260	370, 371, 372, 377, 378, 379, 384, 385, 386, 373, 380, 387
Male breast	Topography: 175.9 Morphology: behaviour code '3' in interval 80103–85703 Gender: Men only	Topography: C50.0–C50.9 Morphology: behaviour code '3' in interval 80103–85703 Gender: Men only	Topography: C500–C506, C508, C509 Morphology: 8000–8034, 8211, 8260, 8480–8481, 8500, 8501, 8503, 8510–8512, 8520, 852 Gender: Men only	473, 474, 475, 476, 477, 478, 479, 480, 483, 484
Eye melanoma	Topography: 190.0, 190.6, 190.9, Morphology: 87203, 87223, 87303, 87703, 87713, 87723, 87733, 87743, 87753	Topography: C69.3, C69.4, C69.6 Morphology: 87203, 87223, 87303, 87703, 87713, 87723, 87733, 87743, 87753,	Topography: C698, C699 Morphology: 8720–8790	614
Mycosis fungoides	Morphology: 97003, 97013	Morphology: 97003, 97013	Not available	Not available
Cancer controls				
Colon	Topography: 153.0–153.9 Morphology: 81403, 82103, 82313	Topography: C18.0–C18.9 Morphology: 81403, 82103, 82313	Not relevant	Not relevant
Stomach	Topography: 151.0–151.9 Morphology: 81403, 82103, 82313	Topography: C16.0–C16.9 Morphology: 81403, 82103, 82313	Not relevant	Not relevant

Table 2
Study base of the European rare cancer study

Country/region	Study base	Total population of study base in million	Recruitment period	Data source for case identification	Type of control	Permission to contact	
						Cases	Population controls
Denmark	Population	5.2	Jan 95–Dec 96	Register: Pathology, hospital, cancer	Population Colon cancer	Ethics committee + treating physician	Ethics committee
France	Population	6.4		Department: Pathology + in some regions clinical departments and centres of proton-treatment	Population	Data protection agency + treating physician	Data protection agency
Bas-Rhin		0.9	Jan 95–June 97				
Calvados		0.6	Jan 95–June 97				
Cte d'Or		0.5	Jan 95–June 97				
Doubs		0.5	Jan 95–June 97				
Haut-Rhin		0.7	Apr 95–June 97				
Hrault		0.8	Jan 95–June 97				
Isre		1.0	Jan 95–June 97				
Manche		0.5	Jul 95–June 97				
Somme		0.5	Jan 95–June 97				
Tarn		0.3	Jan 95–June 97				
Germany	Population	3.8		Department: Medicine, oncology, radiology, surgery, pathology	Population	Data protection agency + treating physician	Data protection agency
Bremen		0.5	Jul 95–Dec 97				
Hamburg		1.6	Jul 95–June 97				
Essen		0.6	Jul 95–Dec 97				
Saarland		0.7	Jul 95–Dec 97				
Saarbruecken		0.4	Jul 95–Dec 97				
Italy	Population	3.0	Jan 95–June 97	Department: Medicine, oncology, radiology, surgery, pathology. Register: cancer	Population	Ethics committee + treating physician	Ethics committee
Florence		1.0					
Padua		1.1					
Torino		0.9					
Latvia	Population	2.5	Aug 95–Dec 96	Register: Cancer	Colon cancer	Ethics committee + treating physician	Not relevant
Portugal	Hospital referral area	4.3	Feb 95–Dec 96	Register: Cancer	Colon cancer	Ethics committee	Not relevant
Porto		2.3					
Lisboa		2.0					
Spain	Hospital referral area	6.5	Jan 95–Aug 97	Department: clinical + pathology	Colon cancer	Medical service chief + treating physician	Not relevant
Basque C.		2.1					
Navarra		0.5					
Valencia		3.9					
Sweden	Population	5.4	Sept 95–Aug 97	Register: Cancer, histologically confirmed cases only	Population	Ethics committee + treating physician	Ethical committee
Linköping		1.0					
Lund		1.6					
Umeå		0.9					
Örebro/Uppsala		1.9					
United Kingdom (UK)	Cancer register patients from one eye clinic	Not relevant	Jan 95–May 96	Department: Eye	Person selected from GP-list of the case	Ethics Committee + treating physician	GP
Total		37.2					

GP, General practitioner.

bacco, alcohol, and a number of specific occupational exposures, such as organic solvents, pesticides, and electromagnetic fields. A complete list was made of all jobs lasting at least six months with the start and end years of working hours, materials handled, and chemical exposures. Following the method used by Siemiatycki in Ref. [12], questionnaires were developed for 27 jobs.

All countries required approval of the study by an Ethics Committee, and contact with individual patients normally required approval from the physician. In most centres, a case was contacted by letter or telephone by the project physician. If a case agreed to participate, in most centres, he/she was sent the job list for completion. This list was used as a starting point for the interview undertaken either face-to-face or by telephone. The procedure depended on local access to telephones in homes or hospitals, clinicians' acceptance of telephone interviews, travelling distances, and ability of the cases to complete a telephone interview.

For population controls, the access granted to selection of controls from the population registers normally implied that the local study coordinator could contact the selected controls by mail or telephone. For cancer controls, procedures were the same as for the cases. Cases and cancer controls were interviewed as soon as possible after diagnosis. Population controls were interviewed in batches during the study period. Surrogate interviews, with husband/wife, child or friend, were performed if a case or control was too ill or died before contact was established [13].

Almost all interviewers were female university students, nurses, physicians or medical secretaries, except for professional interviewers in Germany. All interviewers were trained. Jobs were coded according to the European Classification of Industries from 1993 [14], and the International Classifications of Occupations from 1968 [15] on a four-digit level, and medical disorders were coded according to the International Classification of Diseases, revision 8 or 9.

Tumour tissue was collected for cases with small intestine adenocarcinoma, melanoma of the eye or osteosarcoma in Denmark, Sweden, Germany, France, and Italy. DNA was extracted from the tumour tissue. For adenocarcinoma, *p53* deactivation and *GSTM1*-null genotype were measured [16].

A data entry program in the Statistical Package of the Social Sciences (SPSS) was developed at the University of Aarhus. Data entry was done nationally and files with personal identifiers were kept locally. Files with anonymised identification numbers were sent to Aarhus, where they were checked and merged. Checking included logical checks of single and combined variables. Errors were corrected locally and sent to Aarhus. A final, merged data file was ready after 11 rounds of corrections. For each of the seven rare cancers, the analysis was conducted on the pooled European data-set using only definite and possible cases and all of the controls.

2.4. Comparison of number of identified cases with EUROCIM data

It was possible for Denmark, France, Italy and Sweden to compare the number of recruited cases in the study with the number of incident cases in the official cancer statistics available in the EUROCIM database [17].

3. Results

3.1. Case ascertainment

We identified 1457 cases, with 359 cases of melanoma of the eye, which was the largest subgroup and 123 male breast cancer cases which was the smallest. For 93% of the cases, specimens were available for pathology review. This percentage varied little for the different cancer sites, with the lowest percentages being observed for thymus and mycosis fungoides, 86% and 90%, respectively. At the review, 78% of the diagnoses were considered definite, 15% possible, and 7% not eligible. There was a considerable variation across the cancer sites, as only 1% of the cases of melanoma of the eye were not eligible compared with 13% of the mycosis fungoides cases (Table 3).

The number of cases identified varied across the countries, with a maximum of 286 cases coming from France to a minimum of 29 cases from the UK. Specimens for pathology review were available for 100% of the cases from Sweden and from between 90% and 97% of the cases from other countries, except from Latvia where only 55% were available. Ineligible cases varied from 2% and 3% of the cases in Spain and Sweden, to 16% and 17% in Italy and Latvia (Table 4).

For Latvia, Italy, Germany, Sweden and France, there is a correlation between population size in the catchment area and number of identified cases (Fig. 1). Denmark was an outlier as more cases were recruited than expected from the pattern across the other countries. Spain and Portugal were outliers as fewer cases were recruited than expected from the other countries. For all four countries where a comparison was made with the EUROCIM database, there were more cases of thymus cancer registered in the study than entered in EUROCIM, due to the inclusion in the study of thymoma with behaviour code "0". Denmark also had slightly more cases with gall bladder, small bowel and male breast cancer in the study than noted in EUROCIM. By contrast, France, Italy and Sweden had a clear deficit for both gall bladder and bone cancer. France and Italy also had a deficit for small bowel cancer, and Italy had a deficit of male breast cancer and melanoma of the eye. The lowest coverage was found for gall

Table 3
Case identification, pathology review, and interview by cancer site in the European Rare Cancer Study[a]

	Case site							Total	Control			Total
	Gall Bladder	Small intestine	Thymus	Bone	Male breast	Melanoma of the eye	Mycosis fungoides		Population	Colon cancer	Stomach cancer	
Identified	295[c]	251[d]	137	138	123	359	147	1457[f]	3374	1284[d]	13	4671
Pathology review	279	239	118	128	119	338	132	1353				
Definite	205	194	91	94	104	283	82	1053				
Possible	53	22	22	22	13	34	33	199				
Ineligible	20	22	5	12	2	16	17	94				
Missing	1	1				5		7				
% Definite + possible	258/279 = 92%	216/239 = 90%	113/118 = 96%	116/128 = 91%	117/119 = 98%	317/338 = 94%	115/132 = 87%	1252/1353 = 93%				
Interview[b]	258	216	113	116	117	317	115	1252	3357	1262[e]	10	4629
Yes, index person	122	150	97	95	95	276	97	932	2035	998[e]	10	3043
Yes, surrogate person	64	21	4	10	5	13	4	121	27	86[e]		113
No	72	45	12	11	17	28	14	199	1295	178[e]		1473
% Interviewed	186/258 = 72%	171/216 = 79%	101/113 = 89%	105/116 = 91%	100/117 = 85%	289/317 = 91%	101/115 = 88%	1053/1252 = 84%	2062/3357 = 61%	1084/1262 = 86%	10/10 =100%	3156/4629 = 68%

[a] The numbers reported here may differ slightly from those used in the individual papers reporting on this study. This is due to minor variations in the definitions of eligible age groups and eligible recruitment periods.

[b] Only relevant age groups and recruitment periods are shown, and for cases only definite + possible.

[c] Including 23 male cases originally identified as cancer of the small intestine, but at the pathology review classified as cancer of the biliary tract.

[d] Excluding 23 male cases and 12 female cases originally identified as cancer of the small intestine, but at the pathology review classified as cancer of the biliary tract.

[e] Including emergency ward controls from Spain.

[f] Including 7 cases with unspecified site.

Table 4
Case identification, pathology review, and interview by country in the European rare cancer study[a]

	Country									Total
	Denmark	France	Germany	Italy	Latvia	Portugal	Spain	Sweden	UK	
Cases										
Identified	261	286	174	173	75	80	191	188	29	1457
Pathology review	245	268	168	166	41	77	172	188	28	1353
Definite	200	211	127	108	30	56	143	169	9	1053
Possible	33	36	24	37	1	9	26	14	19	199
Ineligible	12	21	13	21	7	12	3	5	0	94
Missing	0	0	4	0	3	0	0	0	0	7
% Definite + possible	233/245 = 95%	247/268 = 92%	151/168 = 90%	145/166 = 87%	31/41 = 76%	65/77 = 84%	169/172 = 98%	183/188 = 97%	28/28 = 100%	1252/1353 = 93%
Interview of definite + possible cases	233	247	151	145	31	65	169	183	28	1252
Yes, index person	146	204	104	104	31	47	134	136	26	932
Yes, surrogate person	19	19	11	24		8	19	20	1	121
No	68	24	36	17		10	16	27	1	199
% Interviewed	165/233 = 71%	223/247 = 90%	115/151 = 76%	128/145 = 88%	31/31 = 100%	55/65 = 85%	153/169 = 91%	156/183 = 85%	27/28 = 96%	1053/1252 = 84%
Controls										
Identified	1011[b]	630	1325	405	151	138	580	407	24	4671
Interview[c]	994[b]	627	1325	405	151	121	576	407	23	4629
Yes, index person	552[b]	469	705	296	148	103	518	229	23	3043
Yes, surrogate person	14[b]	9	11	5	2	15	56	1		113
No	428	149	609	104	1	3	2	177		1473
% Interviewed	566/994 = 57%	478/627 = 76%	716/1325 = 54%	301/405 = 74%	150/151 = 99%	118/121 = 98%	574/576 = 100%	230/407 = 57%	23/23 = 100%	3156/4629 = 68%

[a] The numbers reported here may differ slightly from those used in the individual papers reporting on this study. This is due to minor variations in the definitions of eligible age groups and eligible recruitment periods.

[b] Of which 583, 570, 313 and 1, respectively, are population controls.

[c] Eligible due to age, gender, site, year of diagnosis.

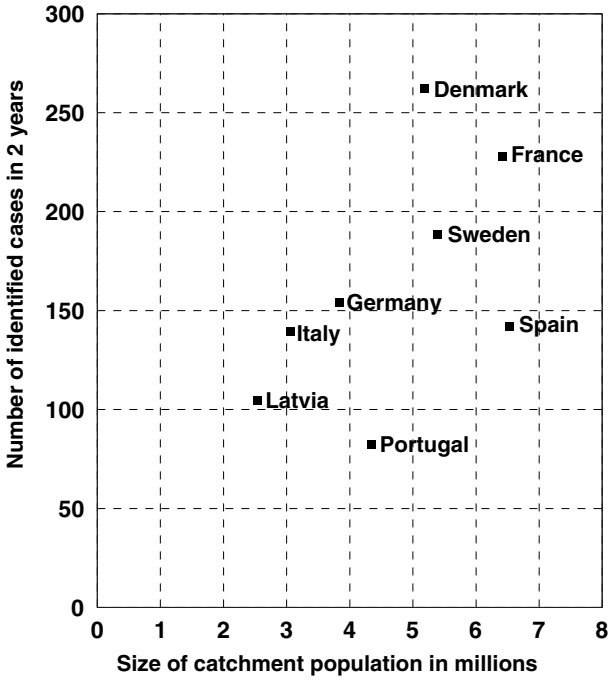

Fig. 1. European case–control study on rare cancers. Size of catchment population and number of identified cases in a two-year period. Note: The same pattern was seen for the number of cases available for pathology review, and for the number of cases considered definitive or possible at the pathology review. An exception was Latvia where only 55% of the cases were available for pathology review.

bladder cancer in Italy, where the number of cases in the study corresponded to only 32% of the cases in EUROCIM (Table 5).

3.2. Participation in the interview

Interviews were obtained for 84% of cases, for 74% with the patient her/himself, and for 10% with a surrogate person. For thymus, bone, male breast, melanoma of the eye and mycosis fungoides between 85% and 91% of the cases were interviewed, mostly involving the patient her/himself. By contrast, only 72% of the gall bladder cases were interviewed, and only 47% were conducted with the patient her/himself (Table 3). There was a considerable variation across the countries in the proportion of cases interviewed, from 100% in Latvia to 71% in Denmark. All of the interviews conducted in Latvia were with the patient her/himself whereas this rate was only 63% in Denmark.

We identified 4671 controls, divided between 3374 population controls, 1284 colon cancer controls, and 13 stomach cancer controls. The number of controls recruited per case varied across the countries from 7.6 in Germany to 1.7 in Portugal. Overall, 86% of the colon cancer controls participated in the interviews which was fairly similar to the percentage for all the cases. However, there was a considerable variation across the

Table 5
Comparison of number of cases identified and recruited to the study with the numbers reported in the EUROCIM database for the same cancer site, gender, age group, and calendar period

Cancer site	Denmark			France		Italy			Sweden		
	Study	EUROCIM	% in study	Study	EUROCIM	% in study	Study	EUROCIM	% in study	Study	EUROCIM[a]	% in study
Gall bladder, men	68	61	111%	55	102	54%	34	106	32%	37	72	51%
Small bowel	48	41	117%	57	85	67%	21	57	37%	72	95	76%
Thymus	14	5	280%	26	17	153%	26	10	260%	14	3	467%
Bone	30	37	81%	28	50	56%	17	33	52%	11	25	44%
Breast, men	12	10	120%	30	42	71%	21	36	58%	10	NA	–
Melanoma of the eye	76	81	94%	55	53	104%	20	30	67%	41	51	80%
Mycosis fungoides	13	NA	–	33	NA	–	29	NA	–	3	NA	–

NA, not available.
[a] Including 5.4/8.8 of the incident cases reported in EUROCIM.

countries, as 100% participated in Spain, 99% in Latvia, 98% in Portugal, and only 59% in Denmark. Overall 61% of the population controls participated in the interviews. For the individual countries, these rates were 76% in France, 74% in Italy, 57% in Sweden, 55% in Denmark, and 54% in Germany.

4. Discussion

Conducting a case–control study in nine European countries, using nine languages, and including seven rare cancer sites was a major undertaking. Nevertheless, we succeeded in recruiting 1457 cases and 4671 controls with interviews being obtained for 84% and 68%, respectively.

The number of recruited cases per million people in the catchment area varied widely between countries. Differences in gender and age structures between these European countries are unlikely to explain this pattern. This leaves us with differences in incidence rates and/or differences in the completeness of case ascertainment as possible explanations. Differences do exist in incidence rates. Men in Northern Europe, for instance, have twice the rate of eye malignancies, mainly melanoma of the eye, of men in Southern Europe [18]. However, differences in the incidence do not explain the observed differences in the number of recruited cases between Italy on the one hand and Spain and Portugal on the other; nor does it explain the differences observed between Denmark and Sweden. The observed pattern is therefore most likely influenced by differences across the countries in the completeness of their case ascertainment. This hypothesis was further validated by data from the comparisons with the EUROCIM database.

Recruitment seems to have worked best in Denmark, where potential cases were identified every three months from comprehensive and daily updated pathology and hospital discharge registers. Portugal and Sweden relied on cancer registers where there is often a time lag in registration. Latvia also relied on the cancer register, but in practice had to restrict interviewing to patients coming to the oncology centre in Riga. France, Germany, Italy and Spain relied primarily on clinical and pathology departments. Treating physicians may here have found some patients were too ill to be reported to the study, and some patients may erroneously have been omitted. We, in particular, had a deficit in the recruitment of gall bladder cancer cases. These patients are often terminally ill at the time of diagnosis, and a personal interview was obtained for only half of the cases we actually recruited. It is unlikely that the Danish procedure led to recruitment of more problematic cases, as the percentage of cases considered ineligible at the pathology review was 5% in Denmark, close to the overall average of 7%. We therefore conclude from data in the present study that case ascertainment works best when it is based on an updated comprehensive and computerised register. Clinicians asked to report cases may filter out patients they considered unsuitable despite strict guidelines not to do so. Where there is a lack of registers, weekly contacts must be made with all clinical and pathology departments. This procedure was followed in Germany, where most areas had no registers or did not permit use of registers for case recruitment.

It was possible in all of the countries to establish a good working relationship with the pathology departments as specimens for review were obtained for almost all cases. However, it should be noted that Sweden recruited only cases with histology. Specimens were only available for 55% of the cases from Latvia, where the study was undertaken during a period of economic hardship.

As expected, a high proportion of cases with cancers of the small intestine and male breast and with melanoma of the eye had their diagnoses confirmed at the pathology review. The percentages were lower for gall bladder cancer where the diagnosis can be hard to distinguish from bordering lesions, and for bone cancer where the primary tumours are mixed with many bone metastases from other primary sites. Given the long clinical course of mycosis fungoides, it was not surprising that only 62% of the recruited cases could be definitely confirmed at the pathology review. The results proved that a pathology review was needed to ensure similar diagnostic entities were identified in the nine countries.

For the cases, the lowest interview response rate was 71% in Denmark, which was to be expected given that these recruited cases probably included a relatively high proportion of severely ill patients. The 100% rate of completed interviews in the Latvian cases was a result of the case ascertainment procedure as described above.

In Latvia, Spain and Portugal, colon cancer controls were contacted in the hospitals and very high response rates of 100–97% were found. In Spain and Portugal, these response rates were even higher than those for the cases indicating a somewhat incomplete identification of eligible control subjects. Germany recruited many controls as other cancer sites were studied in parallel on a national basis [19,20]. For population controls, a clear south/north divide was found with the response rate being 75% in Italy and France, but only 55% in Germany, Denmark and Sweden. The Danish colon cancer controls behaved like the Northern population controls with a response rate of 59%. In order to improve the control response rate, the interviewing procedures were changed in Denmark and Germany after completion of a pilot phase. New introduction letters and telephone reminders were introduced, and a telephone or gift card was given to participants.

The study relied on recalled exposure data for it was impossible to collect blood samples as many of the cases

Table 6
Selected results from the European Multi-centre case–control study on risk factors for rare cancers of unknown aetiology

Cancer site	Exposure	Relative risk	(95% Confidence interval)	[Reference]
Male breast	Alcohol (per 10 g/day)	1.17	(1.03–1.33)	[21]
	Fertility problems	4.87	(0.78–30.40)	[21]
Mycosis fungoides	Glass formers, pottery and ceramic workers (men only)	17.9	(5.4–59.4)	[29]
	Psoriasis (5+ years before mycosis fungoides)	7.2	(3.6–14.5)	[28]
	Atopic dermatitis (5+ years before mycosis fungoides)	1.6	(0.8–3.0)	[28]
	Mumps (5+ years before mycosis fungoides)	1.8	(1.0–3.0)	[28]
Small bowel adenocarcinoma	Dry cleaning industry (women only)	6.5	(1.6–26.9)	[22]
	General farm labourers (women only)	4.6	(1.8–12.0)	[22]
	Building caretakers (men only)	5.7	(1.8–18.3)	[22]
	Crohn's disease	53.6	(6.0–477)	[24]
	Gall stone	1.4	(0.6–2.9)	[24]
Small bowel carcinoid	Structural metal preparer/erector (men only)	4.3	(1.2–15.9)	[26]
	Other construction workers (men only)	3.1	(1.1–8.6)	[26]
	Gall stone	1.9	(1.0–3.6)	[25]

and controls were interviewed by telephone. A new future recruitment strategy could include sampling of DNA using new "do-it-yourself" kits.

Our study highlights the current pitfalls in undertaking case–control studies. It is difficult to interview population controls, especially in Northern Europe, and the responders might be a selected subgroup. Cancer controls are overall easier to interview, but there is a risk of selective recruitment, and risk factors associated with the control disease might bias the results of the study. This is not only a theoretical possibility, but a real challenge that has to be addressed in a study like this, as illustrated by the fact that the Relative Risk of melanoma of the eye among the physically hard working group of male farmers was 2.64 (95% Confidence Interval (CI) 1.46–4.77) when the colon cancer controls were used for comparison, but only 0.87 (95%CI 0.52–1.45) when the population controls were used. Although this deviance would not be expected for most of the studied exposures, it illustrates the problems of getting data on the underlying distribution of exposure time in the study group from non-randomly selected members of the group.

More than 4000 Europeans contributed data to the study, and it is our hope that new aetiological leads will be identified from this common effort. Some results have now been reported [21–29], and the findings are summarised in Table 6. A key finding is a clear dose–response relationship between alcohol intake and risk of male breast cancer, with a relative risk of 1.17 (95%CI 1.03–1.33) for an increase in the alcohol intake of 10 g/day [21]. Mycosis fungoides was found to be associated with skin problems, such as psoriasis and atopic dermatitis, occurring five years or more before the diagnosis with mycosis fungoides [28]. The heavily dust exposed group of glass formers, pottery and ceramic workers was found to be at increased risk of mycosis fungoides, RR 17.9 (95%CI 5.4–59.4) [29]. The known association between Crohn's disease and subsequent excess risk of adenocarcinoma of the small bowel was also found in the present dataset, indicating the validity of the data [24]. Women working in dry cleaning and agriculture, and men working as building caretakers were found to be at an increased risk of adenocarcinoma of the small bowel [22]. Structural metal workers and other construction workers were found to be at an increased risk of carcinoid of the small bowel [26]. These selected results illustrate the strength of the European collaboration where, for instance, the dose-response analysis for alcohol intake and risk of male breast cancer was possible only with cases recruited simultaneously from several countries. Results are due soon on melanoma of the eye [30], and cancers of the bone, thymus and gall bladder.

Conflict of interest statement

None declared.

Acknowledgements

We acknowledge collaboration from the patients, the controls, the participating hospitals and data providers such as the French Cancer Registry Associated (Résion FRANCIM). The data used in this publication was taken from the EUROCIM database of the European Network of Cancer Registries. The contribution of the individual registries is gratefully acknowledged.

The study was financially supported by the European Commission, DGXII, Grants No. BMH1 CT 931630 and ERB CIPD CT 940285, and national funding agencies. Denmark: The Stategic Enviroment Programme and the Danish Science Foundation. France: Ligue Nationale contra le Cancer, Fondation de France (Grant No. 955368), Institut National de la Santé et de la Recherche Médicale (Réseau en Santé Pulique),

Programme Environment-Sante, Ministere de l'Environment. Germany: Federal Ministry for Education, Science, Reseach and Technology (BMBF), Grant No. 01-HP-684/8. Italy: MURST, Italian Association for Cancer Research, Compagnia San Paolo/FIRMS. Portugal: Junta Nacional de Investigacäo Cientifica e Tecnológica, Praxis XXI, No. 2/2.1/SAU/1178/95. Spain: Fondo de Investigación de la Sanitarie, Ministerio de Sanidad y Consumo, Unidad de Investigación Clinico-Epidemiológica, Hospital Dr. Peset. Generalitet Valenciana; Departmento de Sanidad y Consumo, Gobierno Vasco; Fondo de Investigación de la Sanitaria (FIS), Ministerio de Sanidad y Consumo, Ayuda a la Investigación del Departamento de Salud del Gobierno de Navarra. Sweden: Swedish Council for Work Life Research, Research Foundation of the Department of Oncology in Umeå, Swedish Society of Medicine, Lund University Hospital Research Foundation, Gunnar, Arvid and Elsebeth Nilsson Cancer Foundation.

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The study has been undertaken in accordance with the requirements from the Ethics Committees in each of the participating countries or regions.

References

1. Knudson AG. Hereditary cancers disclosed a class of cancer genes. *Cancer* 1989, **63**, 1888–1891.
2. Herbst AL, Scully RE. Adenocarcinoma of the vagina in adolescence. A report of 7 cases including 6 clear-cell carcinomas (so-called mesonephromas). *Cancer* 1970, 25, 745–757.
3. Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. *Br J Indus Med* 1960, **17**, 266–271.
4. Rowland RE, Stehney AF, Lucas Jr HF. Dose–response relationship for female radium dial workers. *Radiat Res* 1978, **76**, 368–383.
5. Creech JL, Johnson MN. Angiosarcoma of liver in the manufacture of polyvinyl chloride. *J Occup Med* 1974, **13**, 150–151.
6. Macbeth R. Malignant disease of the paranasal sinused. *J Laryng Otol* 1965, **79**, 592–612.
7. Kolstad H, Lynge E, Olsen J. Occupational causes of some rare cancers. A literature review. *Scand J Soc Med*(Suppl 48), 1–48.
8. World Health Organisation. International Classification of Diseases for Oncology, First edition. Geneva, World Health Organisation, 1976.
9. Percy C, van Holten V, Muir C, eds. *International classification of diseases for oncology*. 2nd ed. Geneva, World Health Organisation, 1990.
10. Oliveria SA, Christos PJ. The epidemiology of physical activity and cancer. *Ann N Y Acad Sci* 1997, **29**, 79–90.
11. Kaerlev L, Lynge E, Sabroe S, *et al*. Colon cancer controls versus population controls in case–control studies of occupational risk factors. *BMC Cancer* 2004, **4**(15), 1–6.
12. Siemiatychi J. *Risk factors for cancer in the workplace*. Boca Raton, CRC Press, 1991.
13. Kaerlev L, Lynge E, Sabroe S, *et al*. Reliability of data from next-of-kin: results from a case–control study of occupational and lifestyle risk factors for cancer. *Am J Ind Med* 2003, **44**, 298–303.
14. European Commission. Nomenclature generale des activités economiques dans les Communautes Européennes (NACE). Rec. 1, 2nd edition. Luxembourg, European Commission, 1993.
15. International Labour Organisation. International standard classification of occupation. Geneva, International Labour Organisation, 1968.
16. Norum Pedersen L, Kaerlev L, Stubbe Teglbjaerg P, *et al*. Glutathione S-transferase genotype and p53 mutations in adenocarcinoma of the small intestine. *Scand J Gastroenterol* 2003, **38**, 845–849.
17. European Network of Cancer Registries. EUROCIM DATABASE VERSION 4.0. Lyon, Interntional Agency for Research on Cancer, 2001.
18. Ferlay J, Black RJ, Whelan SL. *et al.* CI5VII: Electronic database of Cancer Incidence in Five Continents, **Vol VII**. Lyon, International Agency for Research on Cancer, 1997.
19. Baumgardt-Elms C, Ahrens W, Bromen K, *et al*. Testicular cancer and electromagnetic fields (EMF) in the workplace: results of a population-based case–control study in Germany. *Cancer Cause Control* 2002, **13**, 895–902.
20. Stang A, Jockel KH, Baumgardt-Elms C, *et al*. Firefighting and risk of testicular cancer: results from a German population-based case–control study. *Am J Ind Med* 2003, **43**, 291–294.
21. Guenel P, Cyr D, Sabroe S, *et al*. Alcohol drinking may increase risk of breast cancer in men: a European population-based case–control study. *Cancer Cause Control* 2004, **15**, 571–580.
22. Kaerlev L, Teglbjaerg PS, Sabroe S, *et al*. Occupation and small bowel adenocarcinoma: a European case–control study. *Occup Environ Med* 2000, **57**, 760–766.
23. Kaerlev L, Teglbjaerg PS, Sabroe S, *et al*. Is there an association between alcohol intake or smoking and small bowel

adenocarcinoma? Results from a European multi-center case–control study. *Cancer Cause Control* 2000, **11**, 791–797.
24. Kaerlev L, Teglbjaerg PS, Sabroe S, *et al*. Medical risk factors for small-bowel adenocarcinoma with focus on Crohn disease: a European population-based case–control study. *Scand J Gastroenterol* 2001, **36**, 641–646.
25. Kaerlev L, Teglbjaerg PS, Sabroe S, *et al*. The importance of smoking and medical history for development of small bowel carcinoid tumor: a European population-based case–control study. *Cancer Cause Control* 2002, **13**, 27–34.
26. Kaerlev L, Teglbjaerg PS, Sabroe S, *et al*. Occupational risk factors for small bowel carcinoid tumor: a European population-based case–control study. *J Occup Environ Med* 2002, **44**, 516–522.
27. Morales Suarez-Varela MM, Olsen J, Kaerlev L, *et al*. Are alcohol intake and smoking associated with mycosis fungoides? A European multicentre case–control study. *Eur J Cancer* 2001, **37**, 392–397.
28. Morales MM, Olsen J, Johansen P, *et al*. Viral infection, atopy and mycosis fungoides: a European multicentre case–control study. *Eur J Cancer* 2003, **39**, 511–516.
29. Morales-Suarez-Varela MM, Olsen J, Johansen P, *et al*. Occupational risk factors for mycosis fungoides: a European multicenter case–control study. *J Occup Environ Med* 2004, **46**, 205–211.
30. Lutz JM, Cree I, Sabroe S. *et al.* Occupational risks for uveal melanoma. Results from a case–control study in nine European countries. *Cancer Causes Control* in press.