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## Occupation and small bowel adenocarcinoma: a European case-control study

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### Abstract

**Objectives**—Because of the rarity of small bowel adenocarcinoma (SBA), little is known about the aetiology of this disease. This study aimed to identify occupational clustering of cases SBA as a systematic approach to new hypotheses on the aetiology of this disease.

**Methods**—A European multicentre case-control study was conducted in 1995–7, inclusive. Incident cases aged 35–69 years with SBA (n=168) were recruited before acceptance by a pathologist. Altogether 107 cases and 3915 controls were accepted, of which 79 cases, 579 colon cancer controls, and 2070 population controls were interviewed.

**Results**—The strongest industrial risk factors for SBA taking account of 10 years' exposure lag were dry cleaning, manufacture of workwear, mixed farming (women), and manufacture of motor vehicles (men). A significantly increased risk of SBA (odds ratio (OR) and 95% confidence interval (95% CI)) was found among men employed as building caretakers, OR 6.7 (1.7 to 26.0) and women employed as housekeepers, OR 2.2 (1.1 to 4.9); general farm labourers, OR 4.7 (1.8 to 12.2); dockers, OR 2.9 (1.0 to 8.2); dry cleaners or launderers, OR 4.1 (1.2 to 13.6); and textile workers (sewers or embroiders), OR 2.6 (1.0 to 6.8). For the last four groups, together with welders OR 2.7 (1.1 to 6.6) (men) an exposure-response pattern was found when calculating the ORs for jobs held 1–5 years and >5 years, with never having held the job as reference. The ORs (95% CIs) for 1–5 years and >5 years were 4.3 (0.4 to 44.0) and 3.5 (0.9 to 13.7), 3.0 (0.3 to 26.2) and 4.3 (0.9 to 21.2), 4.6 (0.4 to 48.1) and 11.0 (2.0 to 60.4), 1.3 (0.2 to 11.0) and 5.8 (2.0 to 17.2), and 2.8 (0.3 to 23.8) and 4.6 (1.3 to 16.6), respectively, for each of these occupations. Among welders, people performing semi-automatic arc welding (MIG/MAG) were identified as a high risk group (OR 5.0 (1.3 to 19.6)).

**Conclusions**—This explorative study suggests an increased occurrence of SBA in certain occupations, which needs further evaluation.

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Keywords: small intestine; adenocarcinoma; occupational risk factors

Primary small bowel adenocarcinoma (SBA) is a rare cancer of unknown aetiology. The annual incidence in Europe is less than 1/100 000.<sup>1</sup> Crohn's disease,<sup>2</sup> familial adenomatous polyposis,<sup>3</sup> dietary factors, tobacco smoking, alcohol consumption,<sup>4</sup> and social status<sup>5</sup> have all been suggested as risk factors for SBA, but the evidence is sparse and the results inconsistent. A worldwide relatively high male:female ratio in Europe of about 1.5–2.0:1 may point towards a potential occupational aetiology.<sup>1</sup> Occupations such as stoker, cashier, waiter, and worker at spinning mills,<sup>6</sup> white collar worker,<sup>7</sup> forestry worker,<sup>8</sup> as well as exposure to cooking fumes,<sup>9</sup> pesticides,<sup>10</sup> asbestos, halogenated aromatic compounds, solvents, and cutting oils<sup>11 12</sup> have been associated with SBA, but only based on single studies or case reports.

The rarity of SBA indicates that it is caused by infrequent exposures. Lifestyle factors are not expected to play a major part, unless they operate in combination with rare factors. Most occupational carcinogenic exposures, on the other hand, are rare and potential causal candidates. The history of cancer epidemiology has described several examples of rare cancers caused by rare occupational exposures, the so called "signal cancers". Well known examples are mesothelioma in asbestos workers, hepatic haemangiosarcoma in vinyl chloride workers, and osteosarcoma in watch dial painters exposed to radium.<sup>13–15</sup> The causes of these rare cancers were all identified because they clustered in well recognised occupational groups with a common rare exposure. The present study was designed to be a systematic search for industrial and occupational clustering of small bowel adenocarcinoma based on lifetime job history as an approach to generate new hypotheses on the aetiology of this disease. High odds ratios (ORs) were to be expected if occupations or industries with a causal exposure were detected due to the low background disease rate.

### Material and methods

An international multicentre case-control study was conducted in 10 European countries in 1995–7. The project used the same data collection instruments to investigate occupational, medical, and lifestyle risk factors for seven rare cancers (small bowel, thymus, bone, gall bladder, male breast, skin (mycosis fungoides), and eye (malignant melanoma)). Cases of SBA and frequency matched controls were identified in six of these countries. The control groups for

all cancer types in these countries were pooled for analyses.

The following national regions participated: Denmark (the whole country), Sweden (Umeå, Örebro/Uppsala, Linköping, and Lund), France (Calvados, Côte d'Or, Doubs, Hérault, Isère, Bas-Rhin, Somme, Manche, Haut-Rhin, and Tarn), Germany (Hamburg/Bremen, and Essen/Saarland), Italy (Turin, Florence, and Eastern Veneto), and Spain (Valencia, Navarra, and Pais Vasco). The populations of each of these areas are about 5 million, 4 million, 6 million, 4 million, 3 million, and 6.5 million, respectively. Incident cases aged 35–69 years were recruited in the well defined geographical regions. Case identification was based on repeated requests to hospital and pathology departments, and by frequent screening of regional or national cancer and pathology registers.

Histologically and clinically verified cases of SBA with topography codes 152.0–152.9 (ICD-O, 1976) or C17.0–C17.9 (ICD-O, 1990) and morphology codes 80103–82313 and 82503–85703, both intervals with behaviour code 3 as the last digit, were enrolled.<sup>16 17</sup> Cases of small bowel carcinoid tumour were also ascertained, but they were not included in the present analysis because the pathology of this tumour is different from that of SBA, and there is no reason to think that these two diseases share the same aetiology. One pathologist (PST), blinded to exposure, reviewed a representative HE stained histological slide together with the local pathology report.

Of the 168 patients with a locally made histological diagnosis of SBA, 61 (36%) were not accepted by our pathologist. Thirty four of these were reclassified as biliary tract adenocarcinomas originating from the ductal epithelium of the papilla of Vater, 11 were other subtypes (stromal tumours, adenomas, melanomas), and the primary origin of the remaining 16 tumours could not be established definitely.

The expected number of cases was calculated based on data from EUROCIM,<sup>18</sup> except for Sweden where cancer registry data were used. The expected, identified, and accepted number of cases after pathology review were, for each country, Denmark (26/49/24), Sweden (51/32/27) (sarcomas included in expected), France (27/38/31) and Spain (12/26/

12), Germany (8/14/7) (expected number only reported for Hamburg) and Italy (11/9/6). In nearly all countries the expected number of cases for the study regions were too high, because tumours of the periampullary region are often misclassified as duodenal cancers. Case identification was judged as nearly complete in Denmark, Sweden, France, and Spain, whereas in the centres in Germany and Italy too little diagnostic information was available to identify as many as expected. In Denmark we further evaluated the number of identified cases 1 year after the end of the study by comparing our data based on regional pathology and patient registries with cancer registry data, and no further cases were identified.

The study was population based except in Spain where the controls were hospital patients with cancer of the colon. Population controls were randomly selected from the study base at each centre, and they were frequency matched with cases in 5 year age bands by sex and region (Denmark, Sweden, Germany, France, Italy). The goal was to get at least four controls per case for the most frequent of the seven rare cancer types within each stratum. As the control groups for all seven cancer types were pooled for the analyses of each cancer type to obtain the best possible precision, a control-case ratio much higher than four was obtained in the SBA study. This was particularly true for men as two of the other rare cancers studied (gall bladder and breast cancer) were restricted to men. For the same reasons the control group included a larger proportion of younger subjects reflecting the pooling of controls selected for seven different rare cancers of which some occurred more often among the younger population than was the case for SBA. For practical reasons the controls were selected every 3–6 months during the study period, in Germany from a pool of subjects representing the population at the start of the study. In Spain, hospital controls with a diagnosis of adenocarcinoma of the colon were selected from the same hospitals as the cases, and matched for age and sex. If the index person was dead or too ill to participate, the next of kin was interviewed if possible.

Of the 107 cases of SBA, 580 colon cancer controls (Spain), and 3335 population controls

Table 1 Recruitment of cases with small bowel adenocarcinoma and controls by country

	Denmark n	Sweden n	France n	Germany n	Italy n	Spain n	Total n
Cases:							
Eligible	24	27	31	7	6	12	107
Dead or too ill to participate	3	1	4	—	—	2	10
No contact established	—	—	1	—	—	—	1
Refused to participate or no response	8	5	2	1	—	1	17
All cases interviewed	13	21	24	6	6	9	79
Index case subjects interviewed	10	16	22	4	5	8	65
Surrogate case subjects interviewed	3	5	2	2	1	1	14
Controls:							
Population (P) or cancer (C) controls	P	P	P	P	P	C	—
Eligible	583	407	630	1325	390	580	3915
Dead or too ill to participate	1	—	4	46	4	—	55
No contact established	—	—	20	70	27	—	117
Refused to participate or no response	262	177	121	477	56	1	1094
All controls interviewed	320	230	485	732	303	579	2649
Index control subjects interviewed	318	229	477	724	298	523	2569
Surrogate control subjects interviewed	2	1	8	8	5	56	80

Table 2 Odds ratio (OR) of small bowel adenocarcinoma, by industry\*

NACE Code	Industry	Ever worked in this industry											
		No exposure lag			Exposure lag 10 y			Exposure lag 25 y					
		Cases n	Controls n	Adjusted† OR	95% CI	Cases n	Controls n	Adjusted† OR	95% CI	Cases n	Controls n	Adjusted† OR	95% CI
Women (35 cases, 837 controls):													
013	Mixed farming	7	42	3.2	1.3 to 8.3	7	41	3.3	1.3 to 8.4	7	39	3.5	1.4 to 9.1
182	Manufacture of workwear or clothes	8	68	3.5	1.5 to 8.3	8	67	3.5	1.5 to 8.4	7	61	3.2	1.3 to 7.8
553	Restaurants	6	46	2.8	1.1 to 7.6	5	41	2.3	0.8 to 6.6	2	29	0.9	0.2 to 4.3
853	Social institutions or kindergartens	9	96	2.0	0.8 to 4.8	8	83	1.9	0.7 to 4.6	4	52	1.1	0.4 to 3.5
930	Dry cleaning and laundry	3	33	2.5	0.7 to 9.1	3	30	2.7	0.8 to 9.9	2	28	1.8	0.4 to 8.4
Men (44 cases, 1812 controls):													
287	Manufacture of metal products	3	53	2.6	0.8 to 8.9	3	50	2.6	0.8 to 8.9	1	37	1.0	0.1 to 7.4
291	Manufacture or repair of engines	3	50	2.5	0.7 to 8.7	3	45	2.5	0.7 to 8.8	3	32	3.3	0.9 to 11.7
341	Manufacture of motor vehicles	4	57	5.9	1.3 to 11.9	4	55	4.1	1.3 to 12.6	3	46	3.1	0.9 to 11.0
502	General repair shops	4	84	2.1	0.7 to 6.2	4	82	2.2	0.8 to 6.5	4	60	2.6	0.9 to 7.6

\*Industry classified by the NACE revision 1 (Nomenclature générale des activités économiques dans les Communautés Européennes) 1994 according to products, activities, and production processes involving the subject. Only industries for which at least three cases had ever been employed for at least 6 months are tabulated.

†OR adjusted for sex, country, and year of birth.

accepted for study, 79 cases (44 male, 35 female) and 2649 controls (1812 male, 837 female; 579 colon cancer controls and 2070 population controls) were interviewed (table 1). The interviews were conducted by trained interviewers face to face (65.9%), by telephone (33.6%), or both (0.5%). The mean time from diagnosis to interview for cases was 7.9 months. The response rate for cases was 74% (range 54% in Denmark to 100% in Italy), and for controls 64% (range 55% in Denmark to 99.8% in Spain). The age distribution (35–49 years, 50–59 years, and 60–69 years of age) for cases and controls was 19%, 32%, and 49%, and 37%, 29%, and 34%, respectively.

#### EXPOSURE ASSESSMENT

A standard questionnaire was developed cooperatively between all the centres; it concerned occupational exposure and lifestyle factors. The original version was written in English and translated into the six national languages (Danish, Swedish, German, French, Italian, Spanish). Back translation to English was performed to ensure uniformity. A complete list was collected of all employment periods since leaving primary school of 6 months or more. All major job changes within a company were included as separate jobs—that is, when the products, activities, tasks, job title, materials, or chemicals involving the interviewee had changed significantly. For each job, the starting and ending year were reported, together with working hours/week, materials handled, chemical exposure, and occupations held by nearby workers. Industry and occupation were coded separately for each occupational period and all jobs were given one main code and up to two subcodes according to the national industrial classification of all economic activities (NACE) classification of industry (4 digits)<sup>19</sup> and the international standard classification of occupations (ISCO) classification of occupation (5 digits),<sup>20</sup> based on the aggregated available information.

Work specific questionnaires were used for in depth interviews on 27 specific work tasks with possible chemical, physical, or biological exposures assumed to carry a carcinogenic potential, when the subjects had ever been engaged in these occupational activities.

Information was also collected on socioeconomic and demographic status, lifestyle factors, reproductive factors, and medical history, including exposure to radiation and long standing medical treatment.

#### STRATEGY OF ANALYSIS

The NACE codes and the ISCO codes were scrutinised at a three digit level. Industries and occupations with at least three exposed cases among women or men separately in each category were selected for further evaluation. This strategy was determined before data analysis.

Subjects were classified according to whether they had ever been engaged in the specified industries or occupation. Account was taken for a possible latency time by disregarding jobs held during the 10 years or the 25

Table 3 Odds ratio (OR) of small bowel adenocarcinoma, by occupation\*

ISCO Code	Occupation	Ever had this occupation						Exposure lag 25 y							
		No exposure lag			Exposure lag 10 y			Cases n			Controls n			Adjusted† OR	95% CI
		Cases n	Controls n	Adjusted† OR	95% CI	Cases n	Controls n	Adjusted† OR	95% CI	Cases n	Controls n	Adjusted† OR	95% CI		
Women (35 cases, 837 controls):															
134	Preschool education teachers	4	40	2.0	0.6 to 6.2	4	55	2.2	0.7 to 7.0	1	24	0.7	0.1 to 5.3		
540	Maids and housekeeping service workers	12	160	2.1	1.0 to 4.5	12	146	2.2	1.1 to 4.9	10	124	1.9	0.8 to 4.4		
560	Dry cleaners, laundresses	4	31	3.8	1.2 to 12.6	4	27	4.1	1.2 to 13.6	2	25	1.9	0.4 to 8.9		
621	General farm labourers	7	35	4.6	1.8 to 12.0	7	34	4.7	1.8 to 12.2	7	32	5.1	1.9 to 13.4		
795	Textile workers (sewers and embroiders)	6	60	2.6	1.0 to 6.8	6	60	2.6	1.0 to 6.8	6	53	2.9	1.1 to 7.6		
971	Dockers and freight handlers	5	55	2.7	1.0 to 7.6	5	50	2.9	1.0 to 8.2	3	40	1.9	0.5 to 6.7		
Men (44 cases, 1812 controls):															
551	Building caretakers	4	28	5.7	1.8 to 18.3	3	15	6.7	1.7 to 26.0	2	9	9.1	1.7 to 48.3		
700	Production supervisors and foremen	7	127	2.4	1.0 to 5.8	6	104	2.4	0.9 to 6.0	3	71	1.5	0.4 to 5.2		
872	Welders and flame cutters	6	87	2.6	1.0 to 6.4	6	81	2.7	1.1 to 6.6	5	64	2.6	1.0 to 6.9		
873	Sheet metal workers	3	43	3.2	0.9 to 11.3	3	42	3.2	0.9 to 11.3	2	30	2.9	0.6 to 13.0		
979	Material handling equipment operators	3	50	2.6	0.7 to 9.3	3	44	2.9	0.8 to 10.5	3	23	4.9	1.3 to 18.4		

\*Occupation classified on a three digit level by the ISCO (international standard classification of occupations) 1968 according to job tasks performed for at least 6 months by the subject. Only occupations for which at least three cases had ever been employed are tabulated.

†OR adjusted for sex, country, and year of birth.

years before interview (10 and 25 year exposure lag, respectively). Data were analysed for men and women separately because the two sexes may perform different tasks even if they share occupation or industry. However, specific exposures were evaluated for both sexes combined. Further details about the study have been described elsewhere.<sup>21</sup>

The study was made in accordance with the requirements of the ethics committees in each of the participating countries or regions.

#### STATISTICAL METHODS

Crude and adjusted ORs were obtained by unconditional logistic regression with 95% confidence intervals (95% CIs). All adjusted estimates were obtained from a model that included country, year of birth, and sex, as controls were matched on these variables.

Year of birth was used as a continuous variable.<sup>22</sup> A more detailed adjustment for region did not improve the model. Smoking, alcohol consumption, and a previous diagnosis of Crohn's disease did not influence the ORs obtained from this model by 10% or more, and were not included in any of the final models.<sup>23</sup> For analyses of trend we introduced continuous exposure variables into the models.

Due to the small numbers we repeated the analyses with an exact test for stratified analyses (StatXact). This method only allowed for stratification by country (six levels), year of birth (three levels), and sex. These additional analyses did not change the results significantly and thus, we have only presented the results from the unconditional logistic regression models.

#### Results

For 20 industries (nine among women, 11 among men) and 24 occupations (11 among women, 13 among men), at least three SBA cases had ever been employed for at least 6 months. Five industries among women and four among men were identified with at least a twofold increased OR for SBA (table 2). Only manufacture of workwear and other clothes and mixed farming among women, and manufacture of motor vehicles among men were significantly increased, when lagged by 10 years. The ORs remained stable when lagged for 25 years.

We conducted an additional analysis based on the NACE codes on a four digit level to separate the dry cleaning and the laundry industries. This separation showed an OR of 6.5 (1.6 to 26.9) for the dry cleaning industry based on three cases and 10 controls, whereas a low risk was found in the laundry industry. For dry cleaning the OR was 7.5 (1.7 to 32.4) and 5.0 (0.9 to 27.7) when disregarding jobs held for the last 10 years and 25 years, respectively. A similar separation on a four digit level was not possible for the other industries or occupations identified with increased ORs.

Table 3 shows comparable data for occupation. Among the women six occupations showed ORs above two, of which five were significantly increased when lagged by 10 years: general farmers, dry cleaners and launderers,

Table 4 Odds ratio (OR) calculated for selected industries and occupations by duration of employment\*

NACE code	Duration of employment						$\chi^2$ p value test for trend
	0 y		1-5 y		>5 y		
	Case n/ control n	OR	Case n/ control n	OR	Case n/ control n	OR	
Industry:							
Women (35 cases, 837 controls):							
013 Mixed farming	31/810	1.0	1/5	4.7	3/17	2.6	(0.7 to 9.6)
182 Manufacture of workwear and other clothes (textiles)	28/782	1.0	3/20	3.7	4/30	4.7	(1.5 to 15.1)
9301 Dry cleaning	33/828	1.0	1/3	5.5	1/1	46.9	(2.5 to 863)
Men (44 cases, 1812 controls):							
341 Manufacture of motor vehicles	41/1769	1.0	0/7	—	3/35	3.7	(1.0 to 13.5)
ISCO Code							
Women (35 cases, 837 controls):							
540 Housekeeping service workers	26/720	1.0	6/61	2.5	3/51	1.9	(0.5 to 6.8)
560 Dry cleaners and laundrers	32/821	1.0	1/4	4.6	2/7	11.0	(2.0 to 60.4)
621 General farm labourers	31/810	1.0	1/5	4.3	3/17	3.5	(0.9 to 13.7)
795 Textile workers (sewers and embroiders)	29/789	1.0	1/16	1.3	5/27	5.8	(2.0 to 17.2)
971 Dockers and freight handlers	32/805	1.0	1/11	3.0	2/16	4.3	(0.9 to 21.2)
Men (44 cases, 1812 controls):							
551 Building caretakers	41/1795	1.0	1/4	13.5	2/12	6.7	(1.3 to 34.6)
872 Welders and flame cutters	40/1773	1.0	1/11	2.8	3/27	4.6	(1.3 to 16.6)

\*Industry classified by the NACE, occupation classified by the ISCO.

†OR adjusted for sex, country, and year of birth.

textile workers, dockers, and housekeeping service workers (table 3). Among the men five occupations showed ORs above 2.0, of which building caretakers and welders were significantly increased. These findings were still present when lagged for 25 years.

Table 4 presents the ORs by duration of employment for the industries and occupations with suggested increased occurrence of SBA (OR above two and significantly increased). Among women increasing duration of employment in the dry cleaning industry, and with an occupation as a dry cleaner or launderer were associated with increasing occurrence of SBA. This pattern was also found for women in the workwear and clothing industry, among female textile workers, dockers or freight handlers, general farm labourers, and male welders.

In depth exposure data were available for welding based on supplementary task specific questionnaires (table 5). Among workers who had ever performed welding, we found an association with semiautomatic arc welding (metal inert gas welding (MIG) or gas metal arc welding (MAG); OR 5.0 (1.3 to 19.6) based on six exposed cases and 94 exposed controls). Use of a cellulosic electrode in arc welding was also associated with increased risk. We did not find any association between SBA and the use of pesticides or herbicides in any job.

Rerunning all the analyses with the exclusion of the colon cancer controls together with the Spanish cases did not change these estimates by 10% or more (data not shown).

## Discussion

This study suggests that female dry cleaners, textile workers, dockers or freight handlers, general farm labourers, and male welders have an increased occurrence of small bowel adenocarcinoma. Among welders, exposures related to semiautomatic arc welding were suggested as a possible risk factor.

The quality of exposure information is crucial when studying occupational causes of cancer. We recorded lifetime job histories including main task, subtasks, and materials and chemicals handled, which were classified according to standard industrial and occupational classification schemes, whereas earlier studies on SBA and occupation have been based on register information about job title at one time or on case reports. Information about occupation and industry is to be regarded as a proxy of occupational exposures. In well defined occupational groups with only few exposures in common, occupation can reflect specific exposures.<sup>13</sup> The validity of occupational histories, compared with register information and specific exposure information is in general judged to be valid.<sup>24-26</sup> We also identified relevant time windows of exposure, disregarding jobs held for the past 10 years and 25 years, respectively, and so taking into account the expected latency time for solid malignancies.

Another strength of this study is the high number of histologically verified incident cases of SBA. Because cases were enrolled from

Table 5 Odds ratio for small bowel adenocarcinoma according to selected occupational exposures related to welding and pesticide use

Exposure	Cases n	Controls n	Crude OR	Adjusted OR	95% CI
Welding (12 cases, 384 controls):					
Welding in mild steel	9	243	1.7	1.6	0.3 to 7.3
Welding in stainless steel	5	172	0.9	0.9	0.3 to 3.0
Clean up the metal with trichloroethylene*	3	92	1.1	0.6	0.2 to 2.6
Gas welding with oxyacetylene torch*	7	222	1	1.5	0.4 to 5.5
Flame cutting*	7	212	1.1	1.0	0.3 to 3.6
Electric resistance welding*	4	135	0.9	1.0	0.3 to 3.5
Manual metal arc welding (MMA)*	8	226	1.4	1.9	0.4 to 8.3
Arc welding with tungsten electrode (TIG)*	4	50	3.3	2.7	0.6 to 11.7
Semi-automatic arc welding (MIG/MAG)*	6	94	3.1	5.0	1.3 to 19.6
Plasma arc welding*	2	25	3.1	3.0	0.5 to 17.9
Type of electrode in arc welding:	—	—	—	—	—
Rutile	3	63	1.7	2.6	0.6 to 11.6
Basic	2	85	0.7	0.7	0.1 to 3.3
Cellulosic	2	21	3.5	22.6†	2.4 to 213
Place where the welding was performed:	—	—	—	—	—
In close probing quarters	2	168	0.3	0.3	0.1 to 1.7
In open air (outdoors)	5	139	1.3	1.2	0.4 to 4.3
In small room (workshop)	4	184	0.5	0.5	0.1 to 1.8
In factory hall	9	182	3.3	3.7	0.9 to 15.3
Use of asbestos made protective equipment	5	109	1.8	2.3	0.6 to 8.5
Performance of x ray tests	1	9	3.8	4.0	0.4 to 42.6
Use of pesticides (79 cases, 2649 controls):					
Pesticides, all kinds of*	8	240	1.1	1.0	0.5 to 2.2
Herbicides*	6	141	1.2	0.9	0.1 to 6.3

\*Estimate did not change significantly after adjustment for duration of exposure.

†Adjustment for country increases the estimate from 3.5 to 22.6 (few cases were exposed).

different countries and regions, one might expect a high degree of diagnostic heterogeneity. By having one expert pathologist to review the histological slides and pathology reports from all the cases without knowledge of exposure, we could overcome this, and all cases were diagnosed according to identical criteria.

Several methodological issues should be considered when interpreting these data. In studies based on self reported data, findings may always be flawed by recall bias.<sup>27</sup> Hospital controls may overcome this (as well as increasing the participation rate), but they must be selected among patients with diseases not associated with occupation. We therefore selected patients with colon cancer as controls because there is no strong indication of occupational risk factors for this disease. Some similarities in risk factors for SBA and colon cancer outside the work environment have, however, been suggested—for example, dietary factors (high intake of bread, alcohol, and salt cured or smoked food items)—but the evidence is weak and inconsistent.<sup>4 28</sup> If we restricted the control group to population controls (excluding Spain), the risk estimates were comparable with the results presented; we therefore decided to keep the complete study population.

Because SBA is often rapidly fatal, we interviewed next of kin when the index person was dead or too ill to participate. If exposures are related to prognosis, this has probably reduced the potential for selection bias as well as increasing the statistical power, but the number of proxy responders was small.

As competing causes of SBA are expected to be rare, the risk for confounding was expected to be small, but it cannot be ruled out as the cause of this disease is unknown.

The main problem in interpreting our findings is the many associations examined. Some were likely to be spurious by chance alone. However, we found indications of increased risk in more occupations and indus-

tries than would be expected from the 20 industries and 24 occupations examined.

We found an increased occurrence of SBA among textile workers. Similar findings were presented in a follow up of the 1970 census in Denmark.<sup>6</sup> Exposures characterising this occupation are textile and dye dust, and waterproof and fireproof agents.<sup>29</sup> Our finding of an association between dry cleaning and SBA has not been reported earlier. Possible carcinogenic exposures of dry cleaning are perchlorethylene, fluorocarbons, and benzene. Exposure to perchlorethylene or working within the dry cleaning industry has been associated with leukaemia, oesophageal cancer, and bladder cancer.<sup>30</sup> Welders and people working with manufacture of motor vehicles showed an increased risk of SBA and may be exposed to various substances, including welding fumes, asbestos, trichloroethylene, or other organic solvents. Numerous earlier studies of welders have not shown an increased occurrence of SBA—but this may well be due to chance because of the rarity of this disease.

An increased occurrence of SBA among farmers, an occupational group with a low overall risk of cancer, may be due to exposure to pesticides,<sup>8 10</sup> but we found no association with this exposure. The increased occurrence among dockers, freight handlers, and building caretakers has not been described before, and there is no obvious carcinogenic exposure in these occupations.

In conclusion, the increased occurrence of SBA in dry cleaners, textile workers, general farm labourers, dockers or freight handlers, and welders may suggest that exposures in these occupations are related to SBA. However, this study was purely explorative, and all findings should be regarded as tentative and needing further investigation. Overall, the excess occurrences found were small. If an increased risk of SBA is associated with these occupations and industries, the causal factors

would be expected to affect only a limited subset of the workers involved. Thus, further studies of occupation and small bowel adenocarcinoma should focus on specific exposures in the identified occupations.

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#### Appendix: The European Study Group on Occupational Causes of Rare Cancers

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## Occupation and small bowel adenocarcinoma: a European case-control study

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