Original article

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Occupational exposure to endocrine-disrupting compounds and biliary tract cancer among men

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Objectives This study investigated the association between cancer of the extrahepatic biliary tract and exposure to endocrine-disrupting compounds.

Methods Altogether 183 men with histologically confirmed carcinoma of the extrahepatic biliary tract and 1938 matched controls were interviewed between 1995 and 1997 in the frame of an international multicenter case–control study in six European countries (Denmark, France, Germany, Italy, Spain, and Sweden). Self-reported job descriptions were converted to semiquantitative variables (intensity, probability, and duration of exposure) for 14 endocrine-disrupting compounds. The cases were compared with 1421 population controls and 517 colon adenocarcinoma patients. Odds ratios (OR) and 95% confidence intervals (95% CI) were obtained with unconditional logistic regression and adjusted for age, country, and gallstones.

Results Occupational exposure to endocrine-disrupting compounds resulted in an OR of 1.4 (95% CI 1.0–2.1) with no dose–effect relationship for cumulative exposure (low: OR 1.3, 95% CI 0.6–3.0; medium: OR 1.5, 95% CI 0.8–2.7; high: OR 1.4, 95% CI 0.9–2.4) (only index participants). The elevated risk was restricted to extrahepatic bile ducts and ampulla Vateri (OR 1.7, 95% CI 1.0–2.6). The adjusted OR for cancer of the extrahepatic biliary tract after exposure to polychlorinated biphenyls was 2.8 (95% CI 1.3–5.9, only index participants).

Conclusions The data show some associations between exposure to endocrine-disrupting compounds in the workplace and the risk for cancer of the extrahepatic biliary tract among men, particularly for the extrahepatic bile duct and ampulla of Vater. Polychlorinated biphenyls could possibly be a strong risk factor.

Key terms epidemiology; carcinoma of the extrahepatic bile duct; case–control study; gallbladder carcinoma; xenoestrogen.

Cancer of the extrahepatic biliary tract consists of gallbladder carcinoma, carcinoma of the extrahepatic bile duct, and cancer of the ampulla of Vater. These cancers occur the most often in the elderly and are often fatal (1–3). They greatly differ as to their gender distribution (1, 2, 4). Gallbladder carcinoma is more common in women

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than in men, with an overall gender ratio between 1.2 and 1.8 for most European countries (5), whereas a higher frequency among males is often found for cancers of the extrahepatic bile duct and the ampulla of Vater, the female-to-male ratio ranging from 0.6 to 1.1 (2). A history of gallstones, the most important risk factor for extrahepatic biliary tract cancer (1, 2, 6), was observed in about 60% to 80% of patients with gallbladder carcinoma (7) and in 13–40% of patients with cancer of the extrahepatic bile duct or the ampulla of Vater (8, 9). The preponderance of gallbladder carcinoma among women may be promoted by female sex hormones directly or indirectly through cholelithiasis (10). Gallbladder contractility is reduced during the second half of the menstrual cycle; residual volume and biliary stasis during the last trimester of pregnancy are increased (11). Endogenous (12) and exogenous (13) estrogens and pregnancy (14) increase the saturation of bile with cholesterol and impair biliary motility. Parity (15, 16), first birth before the age of 25 years (17), breast feeding of more than one infant (18), and hormone replacement therapy (19) may increase the risk of gallbladder carcinoma, as may the use of oral contraceptives (9, 20). However, the latter findings remain controversial (20).

Some occupational exposures with possible hormonal effect, such as exposure to pesticides and polychlorinated biphenyls (PCB), have been reported to increase the risk of hepatobiliary cancer among men (21–23). None of these studies, however, has been able to examine the risks for cancer of the extrahepatic and intrahepatic biliary tracts separately. Several xenobiotics disrupt normal functioning of the endocrine system through interference with hormones and the way hormones control growth, metabolism, and body functions. These agents are termed endocrine-disrupting compounds. As part of the European multicenter case–control study on rare cancers (24, 25), this report explores the influence of occupational exposure to endocrine-disrupting compounds on the risk of extrahepatic biliary tract cancer among men.

Table 1. Number and percentage of index participants who completed job-specific questionnaires.

Number of job-specific questionnaires per person	Cases		Controls	
	N	%	N	%
0	60	48.78	964	51.52
1	31	25.20	540	28.86
2	22	17.89	254	13.58
3	4	3.25	87	4.65
4	4	3.25	21	1.12
5	1	0.81	5	0.27
6	1	0.81	–	0
Total	123	100.00	1871	100.00
Mean	0.93		0.76	

Study population and methods

Histologically confirmed cases of carcinoma of the extrahepatic biliary tract in men 35 to 75 years of age, including gallbladder carcinoma, cancer of the extrahepatic bile duct, and cancer of the ampulla of Vater (International Classification of Diseases, 9th revision, codes 156.0, 156.1, 156.2, 156.8, 156.9), were diagnosed, and the men were interviewed face-to-face between January 1995 and June 1997 in the frame of an international multicenter case–control study in six European countries (25). The controls were randomly drawn from the general population in France, Denmark, Germany, Italy, and Sweden and were matched by age and study center. Hospital controls (patients with colon adenocarcinoma) were selected as the only control group in Spain and as an additional control group in Denmark.

About 33% (60 of 183) of the case interviews and less than 4% (67 of 1938) of the control interviews were conducted with a next-of-kin or other surrogate person, since the index participant had died or was too ill for an interview. Since occupational information on past contact with agents and the use of personal protective equipment would presumably be poorly reported by proxies, the risk estimation was restricted to the index interviews.

The core questionnaire included structured sections for sociodemographic factors (education), occupational history, physical characteristics (constitution), exposures (smoking, alcohol, pesticides, hormones, and oils with PCB, light, heat, X-rays, etc), and a medical history (including the history of gallbladder diseases). It ended with a checklist of occupations, industries, and job tasks to trigger the application of job-specific questionnaires, of which 20 addressed exposure to endocrine-disrupting compounds (table 1). Answers were entered into a common database by each study center, where editing and error checking was performed.

Data from the three job-specific questionnaires—concerning dentistry, tanneries, and railway working—contained no positive answers to questions related to endocrine-disrupting compounds. The numbers and percentages of the participants who answered the job-specific questionnaires are listed in table 1.

Qualitative exposure assessment

The agents under investigation were selected as representing the most important potential occupational endocrine-disrupting compounds (26–28). They were estrogens, alkylphenols, phthalates, oils with PCB, bisphenol pA, chlorophenols or pentachlorophenol, phenylphenol, pesticides, and other endocrine-disrupting compounds (furannic and phenolic resins, moth- or rot-proofing agents, impregnation agents, and hardeners).

A specific section in the core questionnaire addressed past contact with pesticides, its duration, and applied techniques. The section on chemicals with an estrogenic effect addressed the handling of hormonal agents and the handling of transformer oils with PCB. The use of PCB was restricted to closed environments like transformers and cooling systems in Europe since the beginning of the 1980s. Only the participants who reported past exposure to estrogenic hormones or oils with PCB and who recalled the type of agent were actually classified as exposed to endocrine-disrupting compounds.

On the basis of answers to specific questions in the job-specific questionnaires about particular chemicals or related job activities, the participants were classified as exposed if they had positively reported the past use or application of an agent. The percentage of the participants who were classified as unexposed because they did not answer the particular questions in the job-specific questionnaires (missing values) varied from 0% to 32%. The job-specific questionnaires were not mutually exclusive for a given exposure when the agent could be used in different circumstances.

Quantitative exposure assessment

Exposure records for each agent were converted into semiquantitative variables (probability, intensity, duration). Each of the 14 chemicals received a numerical code (estrogens, alkylphenols, phthalates, oils with PCB, bisphenol A, chlorophenols, phenylphenol, herbicides, insecticides, fungicides, furannic or phenolic resins, moth- or rot-proofing agents, impregnation agents, and hardeners). The exposure assessment was blinded with respect to the case–control status, and it followed an a priori strategy starting with the job-specific questionnaires.

The probability of exposure was graded according to the use of protective equipment with 0 = no exposure, 1 = use of effective protective equipment (filter mask and overall, cabin, etc), 2 = use of less protective equipment (only gloves or only mask without filter, etc), and 3 = no use of protective equipment. In health care, the exposure probability for those who injected estrogenic drugs was presumed to be very low and was graded as 1, while oral administration or the application of plasters was set to 0.

The exposure intensity was classified according to the type of process as 0 = no exposure, 1 = no personal application of the chemicals, 2 = personal application, but automatically (distant operation or distribution by machines with good protection), 3 = manual application with or without machines.

Job-specific questionnaires for all of the workers except those in farming, animal husbandry, and forestry did not contain questions on the method of application; therefore, the exposure intensity was graded according to the frequency of the corresponding activity: 1 (low)—when a work process was seldom carried out, 2 (medium)—when a work process was carried out several days a week or several days a month, 3 (high)—when a work process was carried out daily.

For the exposures to hormones, PCB, and pesticides, which were identified through the core questionnaire, but not through job-specific questionnaires, it was not possible to assess the intensity and probability of the exposure directly. This was the case for one participant (16.7%) exposed to hormones, for 17 respondents (22.4%) exposed to PCB, and for 55 respondents (18.4%) exposed to pesticides. In these cases, when the participants reported the use of hormones, PCB, or pesticides in the core questionnaire but did not fill out any of the corresponding job-specific questionnaires, the intensity and probability were estimated individually by evaluating the task description in the core questionnaire. If the task description was missing in the core questionnaire, the averaged values of the corresponding variables were obtained from the data in relevant job-specific questionnaires of all of the other exposed participants [seven job-specific questionnaires addressing exposure to pesticides and two job-specific questionnaires addressing exposure to PCB (see the appendix available on the homepage of the *Scandinavian Journal of Work, Environment & Health*)] to derive values for probability and intensity.

In a second step, the semiquantitative exposure variables for each exposure were multiplied by the duration in years and summed up for each participant. An exposure index was calculated for each person as the product of the probability, intensity, and duration for each endocrine-disrupting compound as follows:

$$Index_{\exp} = \sum_{k=1}^{K} P_k I_k D_k ,$$

where $Index_{exp}$ is the cumulative exposure index with P_k (probability), I_k (intensity), and D_k (duration, in years) in job period k of K job periods.

The exposed participants were categorized in tertiles of the joint distribution of the cases and controls according to the exposure index as low, medium, and high. For the presentation of the exposure intensity, the maximum intensity reached during a worker's entire worklife was used.

Statistical methods

The study population was stratified according to age (9 groups with an age range from 32 to 72 years) and country.

The first step of the exposure assessment was made manually using Microsoft Excel, and the second step was performed implementing an SAS program (SAS Inc, Cary, NC, USA). The reference group for the combined analysis of all of the endocrine-disrupting compounds was formed by all of the participants who were unexposed to any of them, while the reference group for agent-specific risk estimation comprised those who were unexposed to the endocrine-disrupting compound of interest.

The SAS statistical software package (8th release) was used for the statistical analyses. The odds ratios (OR), based on unconditional multiple logistic regression models, and their 95% confidence intervals (95% CI) were calculated for each exposure agent as the measure of the association between the specific exposure and extrahepatic biliary tract cancer. The following confounders were considered in the adjusted analysis: OR_1 was adjusted for age (continuous) and country. OR_2 was adjusted for age (continuous), country (one dummy variable per country), and gallstones (ever confirmed by a physician, dummy variable). The final analyses were conducted with the exclusion of the control interviews with a next-of-kin or other surrogate person, as we assumed that the detailed information on which the exposure assessment was based could only be provided by the index participants.

Results

The response proportion was 72% for the cases, providing a total of 183 interviews. The response proportion for the controls varied by country, being high in France (78%) and Italy (73%) but lower in Denmark, Germany, and Sweden (54–57%). Overall, 1421 of 2343 eligible population controls and 517 of 612 hospital controls participated. Next-of-kin interviews were obtained for 60 cases and 70 controls. Details of the responses have been given earlier (25). Altogether 59 cases were coded as gallbladder carcinoma, 55 as cancer of the extrahepatic bile duct, 58 as cancer of the ampulla of Vater, and 11 as cases with overlapping sites. The mean age of the patients in these four groups was almost the same (60.9 years, 57.3 years, 59.4 years, and 59.5 years, respectively). The mean age and the distribution of the participants by country are given in table 2.

The distribution of cases and controls by number of job-specific questionnaires is shown in table 1. Among all of the index participants, 1420 (71.2%) were unexposed. Altogether 574 (28.8%) index participants were classified as exposed, 56 (2.8%) of them only on the basis of the core questionnaire [4 cases (3.3%), 52 controls (2.8%)]. Of all the index participants, 16 (0.80%) reported exposure periods in the core questionnaire in addition to doing so on the job-specific questionnaires. There were 1235 exposed job periods overall, 1156 of which were only based on the job-specific questionnaires. Altogether 444 (22.26%) study participants were exposed to just one endocrine-disrupting compound, while 83 (4.16%), 38 (1.91%); 6 (0.30%), and 3 (0.15%) were exposed to two, three, four, or five or more endocrine-disrupting compounds, respectively. A summary of the key questions according to the job-specific questionnaire on which the exposure assessment was based and the number of index participants classified as exposed to the corresponding endocrine-disrupting compounds can

Table 2. Number of interviewed participants.[a]

	Cases					Population controls					Hospital controls					All controls				
	N	%	Mean	SD	Range	N	%	Mean	SD	Range	N	%	Mean	SD	Range	N	%	Mean	SD	Range
All interviews	183	100	·	·	··	1421	100	·	·	··	517	100	·	·	··	1938	100	·	·	··
Denmark	40	22	·	·	··	194	14	·	·	··	152	29	·	·	··	346	·	·	·	··
Sweden	29	16	·	·	··	140	10	·	·	··	–	·	·	·	··	140	·	·	·	··
France	42	23	·	·	··	320	23	·	·	··	–	·	·	·	··	320	·	·	·	··
Germany	22	12	·	·	··	560	39	·	·	··	–	·	·	·	··	560	·	·	·	··
Italy	20	11	·	·	··	207	14	·	·	··	–	·	·	·	··	207	·	·	·	··
Spain	30	16	·	·	··	–	·	·	·	··	365	71	·	·	··	365	·	·	·	··
Age (years)	–		59.3	7.48	35–70	–		52.6	11.11	33–70		·	57.2	9.66	33–70	–	·	53.8	10.9	33–70
Index interviews [a]	123	100	·	·	··	1401	100	·	·	··	470	100	·	·	··	1871	100	·	·	··
Denmark	29	24	·	·	··	192	14	·	·	··	145	31	·	·	··	337	·	·	·	··
Sweden	17	14	·	·	··	139	10	·	·	··	–	·	·	·	··	139	·	·	·	··
France	32	26	·	·	··	313	22	·	·	··	–	·	·	·	··	313	·	·	·	··
Germany	16	13	·	·	··	554	39	·	·	··	–	·	·	·	··	554	·	·	·	··
Italy	10	8	·	·	··	203	15	·	·	··	–	·	·	·	··	203	·	·	·	··
Spain	19	15	·	·	··	–	·	·	·	··	325	69	·	·	··	325	·	·	·	··
Age (years)	–	·	59.0	7.64	35–70	–	·	52.6	11.08	33–70	–	·	56.8	9.84	33–70	–	·	53.7	10.9	33–70

[a] Only interviews with index participants.

Table 3. Risk of cancer of the extrahepatic biliary tract among the men reporting activities entailing exposure to endocrine-disrupting compounds in job-specific questionnaires (only index participants). (OR = odds ratio, 95% CI = 95% confidence interval)

Job-specific questionnaire	Exposed		OR_1[a]	95% CI[b]	OR_2[c]	95% CI[d]
	Cases (N)	Controls (N)				
Health care	–	5444	..	..	..	..
Cooking and food preparation	2	32	1.5	0.3–6.5	1.7	0.4–7.3
Farming	19	172	1.4	0.9–2.4	1.6	0.9–2.8
Animal husbandry	7	102	0.8	0.3–1.5	0.7	0.3–1.5
Forestry	–	12	..	..	..	..
Foundries	1	7	2.3	0.3–20.6	2.8	0.3–25.5
Wood production	–	9	..	..	..	..
Paper production	2	14	1.3	0.3–6.1	1.1	0.2–5.2
Textile industry	2	9	3.1	0.6–15.2	3.1	0.6–15.7
Meat processing	2	11	3.2	0.7–15.6	3.8	0.8–18.4
Shoe or leather production	–	7	..	..	..	..
Electrical work	12	118	2.2	1.2–4.3	2.3	1.2–4.5
Rubber industry	1	18	1.0	0.1–7.7	1.2	0.1–9.2
Plastic production	2	26	1.6	0.4–7.2	1.9	0.4–8.6
Painting	3	36	1.2	0.4–4.2	1.3	0.4–4.4
Paint manufacturing industry	–	6	..	..	..	..
Chemical industry	–	10	..	..	..	..

[a] OR_1 adjusted for country and age.
[b] 95% CI for OR_1.
[c] OR_2 adjusted for age, country and gallstones; the reference group for each OR was formed by all of the participants not belonging to the respective category.
[d] 95% CI for OR_2.

be found in an appendix that is available on the homepage of the *Scandinavian Journal of Work Environment & Health*.

Occupation-specific analysis

For the 17 specific job-specific questionnaires with available reports on endocrine-disrupting compounds, adjusted risk estimates were increased for the index participants about twice or more as often for those working in foundries, the textile industry, meat processing, electrical work, and plastic production (table 3).

Analysis according to exposure to endocrine-disrupting compounds

Exposure to endocrine-disrupting compounds among the index participants resulted in an adjusted OR (adjusted for age, country, and gallstones) of 1.4 (95% CI 0.9–2.0). The highest OR values were observed for exposure to oils with PCB (adjusted OR 2.8, 95% CI 1.3–5.9), bisphenol A (adjusted OR 2.1, 95% CI 1.0–4.3), phthalates (adjusted OR 2.0, 95% CI 0.6–6.7), and alkylphenols (adjusted OR 2.0, 95% CI 0.9–4.8) (table 4). The odds ratios were, in general, lower in the analysis for all of the study participants (data not shown), while restriction to the specific data from the job-specific questionnaires resulted in higher odds ratios (adjusted OR for all endocrine-disrupting compounds combined 1.7, 95% CI 1.1–2.8) (table 4).

Table 4. Adjusted odds ratios (OR) for exposure to specific endocrine-disrupting compounds (only index participants). (95% CI = 95% confidence interval)

Endocrine-disrupting compounds	Unexposed		Exposed		OR_1[a]	95% CI[b]	OR_2[c]	95% CI[d]
	Cases (N)	Controls (N)	Cases (N)	Controls (N)				
Hormones	123	1866	..	5	..	..	..	..
Phthalates	120	1834	3	37	1.9	0.5–6.4	2.0	0.6–6.7
Alkylphenols	116	1811	7	60	2.0	0.9–4.6	2.0	0.9–4.8
Pesticides (job-specific questionnaires only)	101	1649	22	222	1.2	0.7–2.0	1.4	0.8–2.2
Pesticides[e]	98	1597	25	274	1.1	0.7–1.8	1.2	0.8–2.0
Oils with polychlorinated biphenyls (job-specific questionnaires only)	115	1820	8	51	2.9	1.3–6.6	3.2	1.4–7.4
Oils with polychlorinated biphenyls[e]	113	1805	10	66	2.7	1.3–5.6	2.8	1.3–5.9
Bisphenol A	114	1784	9	87	2.0	0.9–4.1	2.1	1.0–4.3
Chlorophenols	122	1847	1	24	0.5	0.1–4.0	0.4	0.0–2.9
Phenylphenols	116	1749	7	122	1.2	0.5–2.6	1.2	0.5–2.7
Other endocrine-disrupting compounds	121	1845	2	26	1.2	0.3–5.2	1.3	0.3–5.8
All endocrine-disrupting compounds[e]	78	1342	45	529	1.3	0.9–1.9	1.4	0.9–2.0
All endocrine-disrupting compounds (job-specific questionnaires only)	37	716	41	477	1.6	1.0–2.6	1.7	1.1–2.8

[a] OR_1 adjusted for country and age.
[b] 95% CI for OR_1.
[c] OR_2 adjusted for age, country and gallstones.
[d] 95% CI for OR_2.
[e] Estimation of the risk of cancer of the extrahepatic biliary tract due to exposure to endocrine-disrupting compounds, evaluated on the basis of the core questionnaire and the job-specific questionnaires; the reference group for each OR was formed by all of the participants not belonging to the respective category.

When classified by maximum exposure intensity, endocrine-disrupting compounds showed no consistent pattern (table 5). The adjusted risk estimates for pesticides were reduced for low exposure intensity (OR 0.6) and slightly elevated in the medium and high categories (OR 1.6 and 1.3, respectively). For "endocrine-disrupting compounds other than pesticides" the adjusted estimates decreased with intensity, with odds ratios of 2.8, 1.4, and 1.3 for low, medium and high intensity, respectively. The adjusted odds ratios for PCB exposure varied between 5.2 for low intensity and 1.3 for medium intensity. All of the endocrine-disrupting compounds combined showed adjusted odds ratios of 1.3, 1.5, and 1.4 for low, medium, and high intensity, respectively.

Analysis by cumulative exposure index

The range of the cumulative exposure index was divided into tertiles of the distribution for the exposed index participants (45 cases and 529 controls), the unexposed group serving as the reference group. Due to the small number of participants exposed to single endocrine-disrupting compounds, a grouped analysis was made for those exposed to pesticides, endocrine-disrupting compounds other than pesticides, and PCB, as well as for the whole group of exposed participants. No obvious increasing trends by cumulative exposure were observed for endocrine-disrupting compounds other than pesticides (phthalates, PCB, phenylphenol, pentachlorophenol, bisphenol A, alkylphenols, and other endocrine-disrupting compounds), PCB, or all endocrine-disrupting compounds (table 6). Cumulative exposure to pesticides showed a reduced risk in the low exposure category and elevated odds ratios in the medium and high category (table 6). Since gallbladder carcinoma is more frequent in women and cancer of the extrahepatic bile duct and the ampulla of Vater are more frequent in men, we stratified the analysis for all endocrine-disrupting compounds by tumor site. Gallbladder carcinoma was not associated with any risk, while cancer of the extrahepatic bile duct and the ampulla of Vater showed increased odds ratios for medium and high cumulative exposure. But these estimates were unstable due to the small numbers (table 7).

Discussion

Our exploratory analysis showed some associations between exposure to endocrine-disrupting compounds in

Table 5. Odds ratios (OR) for low, medium, and high intensity of the exposure for selected groups of endocrine-disrupting compounds (maximum intensity in lifetime, only index participants). (95% CI = 95% confidence interval)

Endocrine-disruptting compounds	Unexposed		Exposed		OR_1 [a]	95% CI [b]	OR_2 [c]	95% CI [d]
	Cases (N)	Controls (N)	Cases (N)	Controls (N)				
Pesticides [e]								
Low	·	·	2	45	0.5	0.1–2.1	0.6	0.1–2.5
Medium	·	·	7	60	1.4	0.7–2.8	1.6	0.7–3.8
High	·	·	16	169	1.2	0.6–2.2	1.3	0.7–2.3
Total	98	1597	25	274	1.1	0.7–1.8	1.2	0.8–2.0
All endocrine-disrupting compounds other than pesticides [e]								
Low	·	·	7	54	2.5	1.1–5.7	2.8	1.2–6.5
Medium	·	·	10	129	1.5	0.8–3.0	1.4	0.7–2.8
High	·	·	7	103	1.2	0.5–2.7	1.3	0.6–3.0
Total	99	1585	24	286	1.6	1.0–2.5	1.6	1.0–2.6
Polychlorinated biphenyls [e]								
Low	·	·	6	27	4.8	1.8–12.5	5.2	1.9–13.9
Medium	·	·	2	22	1.6	0.4–7.4	1.3	0.3–6.4
High	·	·	2	17	1.6	0.3–7.3	2.0	0.4–9.0
Total	113	1805	10	66	2.7	1.3–5.6	2.8	1.3–5.9
All endocrine-disrupting compounds [e]								
Low	·	·	7	93	1.2	0.5–2.7	1.3	0.6–3.0
Medium	·	·	15	171	1.5	0.8–2.8	1.5	0.8–2.7
High	·	·	23	265	1.3	0.8–2.1	1.4	0.9–2.4
Total	78	1342	45	529	1.3	0.9–2.0	1.4	1.0–2.1

[a] OR_1 adjusted for country and age.
[b] 95% CI for OR_1.
[c] OR_2 adjusted for age, country, and gallstones.
[d] 95% CI for OR_2.
[e] Estimation of the risk of extrahepatic biliary tract cancer due to exposure to endocrine-disrupting compounds, evaluated on the basis of the core questionnaire and the job-specific questionnaires; the reference group for each OR was formed by all of the participants not belonging to the respective category.

Table 6. Odds ratios (OR) for a low, medium, and high exposure index (product of duration, probability and intensity) (only index participants).

Endocrine-disrupting compounds	Unexposed		Exposed		OR_1 [a]	95% CI [b]	OR_2 [c]	95% CI [d]
	Cases (N)	Controls (N)	Cases (N)	Controls (N)				
Cancer of the extrahepatic biliary tract								
Pesticides [e]								
Low	·	·	4	94	0.6	0.2–1.5	0.6	0.2–1.7
Medium	·	·	8	92	1.1	0.5–2.4	1.3	0.6–2.8
High	·	·	12	85	1.6	0.8–3.0	1.7	0.9–3.3
Total	98	1597	24	271	1.1	0.7–1.7	1.2	0.7–1.9
Missing exposure index			1	3				
All endocrine-disrupting compounds other than pesticides								
Low	·	·	9	94	1.6	0.8–3.4	1.6	0.8–3.4
Medium	·	·	6	98	1.4	0.6–3.3	1.4	0.6–3.5
High	·	·	9	94	1.6	0.8–3.4	1.8	0.8–3.7
Total	99	1585	24	286	1.6	1.0–2.5	1.6	1.0–2.6
Polychlorinated biphenyls [e]								
Low	·	·	3	22	2.3	0.6–8.2	2.1	0.5–7.8
Medium	·	·	4	22	4.0	1.3–12.4	4.3	1.4–13.7
High	·	·	3	22	2.1	0.6–7.5	2.4	0.7–8.6
Total	113	1805	10	66	2.7	1.3–5.6	2.8	1.3–5.9
All endocrine-disrupting compounds [e]								
Low	·	·	12	182	1.0	0.5–2.0	1.1	0.6–2.0
Medium	·	·	15	172	1.6	0.9–2.9	1.8	1.0–3.3
High	·	·	18	172	1.4	0.8–2.4	1.5	0.9–2.7
Total	78	1342	45	526	1.3	0.9–2.0	1.4	1.0–2.1
Missing exposure index				3				
Only gallbladder carcinoma [f]								
All endocrine-disrupting compounds [e]								
Low	·	·	3	182	0.7	0.2–2.4	0.7	0.2–2.6
Medium	·	·	3	172	0.9	0.3–2.9	1.1	0.3–3.9
High	·	·	3	172	0.7	0.2–2.4	0.9	0.2–2.9
Total	28	1330	9	526	0.8	0.3–1.6	0.9	0.4–1.9
Missing exposure index				3				
Only carcinomas of the extrahepatic bile duct and the ampulla of Vater [f]								
All endocrine-disrupting compounds [e]								
Low	·	·	8	182	1.0	0.4–2.2	1.0	0.4–2.3
Medium	·	·	10	172	1.8	0.9–3.6	1.9	0.9–3.9
High	·	·	15	172	1.9	1.0–3.5	2.0	1.1–3.7
Total	47	1330	33	526	1.6	1.0–2.5	1.7	1.0–2.6
Missing exposure index				3				

[a] OR_1 adjusted for country and age.
[b] 95% CI for OR_1.
[c] OR_2 adjusted for age, country, and gallstones.
[e] Estimation of risk of cancer of the extrahepatic biliary tract due to exposure to endocrine-disrupting compounds, evaluated on the basis of the core questionnaire and the job-specific questionnaires; the reference group for each OR was formed by all of the participants not belonging to the respective category.
[f] Six cases in which the tumor overlapped more than one site had to be excluded from the site-specific analysis (gallbladder carcinoma, extrahepatic bile duct and ampulla of Vater).

the workplace and the risk of cancer of the extrahepatic biliary tract for men, particularly for cancer of the extrahepatic bile duct and the ampulla of Vater. Although many occupational exposures have been reported to be associated with gallbladder carcinoma and other biliary tract tumors in the past, it was often not possible to disentangle the risk of biliary tract and liver cancer in different occupations due to the limited data. Previous epidemiologic studies on cancer of the extrahepatic biliary tract have mentioned the small size of populations studied and problems with quantitatively assessing exposure to xenobiotics, particularly endocrine-disrupting compounds.

The estimation of occupational exposure to endocrine-disrupting compounds was based on reported contact with the agents during each participant's worklife and was therefore prone to misclassification and reporting bias. For this reason we excluded the control interviews with a next-of-kin or other surrogate person from the analysis assuming that these persons were unable to report the job activities of index participants with sufficient detail and reliability. The application of

job-specific questionnaires should have further improved the quality of the job task descriptions and the specificity of the exposure assessment. Based on answers to the job-specific questionnaires, the intensity and probability of the exposure to a particular compound were assessed on a relative scale. Therefore, the absolute values of intensity for a given agent may not have been perfectly comparable between different job tasks. This possibility would have resulted in some misclassification of the degree of exposure when exposures were summed up over various job tasks to estimate cumulative exposure. We assume that the misclassification of exposure was nondifferential because the exposure assessment was blinded with respect to the case–control status.

According to the exploratory design, multiple comparisons were made that entailed the problem of mass significance. The reader should take this into account when the results are interpreted. Confidence intervals have to be considered mainly as indicators of the stability of the presented risk estimates and not as formal tests of statistical significance.

Our observations are consistent with those of other investigations. Associations between female hormones and biliary tract cancer were derived from observations that parity (15) and a high number of pregnancies (16), as well as age before 25 years at first birth (17), breast feeding of more than one baby (18), and female hormone replacement therapy (19) among women increase the risk of gallbladder carcinoma. In our study, the risk of extrahepatic biliary tract cancer was increased among the participants ever exposed to endocrine-disrupting compounds with a known estrogenic effect (alkylphenols, PCB, bisphenol A), and exposure to PCB was statistically significant (table 4).

Not all of the subtypes of cancer of the extrahepatic biliary tract may be equally associated with endocrine-disrupting compounds. Gallbladder carcinoma occurs at higher rates in women than in men, the opposite is true for cancer of the extrahepatic bile duct and the ampulla of Vater. This situation would seem to suggest that gallbladder carcinoma may be associated with hormones but that cancer of the extrahepatic bile duct and the ampulla of Vater might not be. It should be noted, however, that the excess risk for all endocrine-disrupting compounds combined was restricted to the sites extrahepatic bile duct and ampulla of Vater, not the gallbladder. This observation may contradict our hypothesis although it is based on relatively small numbers. Our finding may also point towards a different etiology for cancer of the extrahepatic biliary tract among men and women, as the preponderance of gallbladder carcinoma among females could be mediated through their higher risk of developing gallstones.

The inconsistent association between pesticide exposure and cancer of the biliary tract should be interpreted with caution in relation to endocrine activity. We have grouped together all pesticide exposures even though not all of them have endocrine activity. As it is not possible to obtain valid answers to questions on brand names or chemical properties of pesticides in a retrospective study such as this one, we accepted a substantial degree of uncertainty in this exploratory analysis.

The cancer incidence and mortality of workers in transformer manufacturing plants with extensive use of transformer fluid containing mineral oil revealed an excess of biliary tract cancer, particularly of gallbladder carcinoma (23, 29). From these two large cohort studies, Yassi et al reported a standardized incidence ratio (SIR) for gallbladder carcinoma of 5.1 (95% CI 1.4–13.0) for male employees of a transformer manufacturing plant, and Gustavsson et al found a standardized incidence ratio of 2.6 (95% CI 0.3–9.3) for liver and biliary tract cancer among Swedish male capacitor manufacturing workers. Our study revealed a high risk for extrahepatic biliary tract cancer among participants exposed to PCB. The estimates became stronger when restricted to the index participants and to the more specific data obtained by job-specific questionnaires.

Although we did not observe a dose–effect relationship with increasing exposure, our findings may corroborate the assessment of PCB as a hazardous occupational exposure among electricians. It should be noted that, in our study, the participants exposed to endocrine-disrupting compounds in electrical work formed a large subgroup, not only in the whole study population, but also among those employed in occupations with possible PCB exposure (electrical work and the rubber industry). Approximately 70% of the electrical workers were classified as exposed to any of the endocrine-disrupting compounds, including PCB. Given the large number of reported simultaneous agent exposures of electrical workers, it can be assumed that electrical workers were exposed to endocrine-disrupting compounds to a greater degree than the other workers were. The coincidence of an elevated risk for PCB exposure and an excess risk among electricians may be due to frequent contact with PCB in this job group.

The exposure assessment in this study was mainly based on the detailed answers in the job-specific questionnaires. As stated previously, the advantage of such records is the possibility to assess the exposure determinants semiquantitatively. However, the amount of detail about specific agents that can be obtained by job-specific questionnaires is limited. Nondifferential misclassification of exposure that would result in a bias of odds ratios towards unity has probably occurred. In addition, occupational information based on job-specific questionnaires is not free of recall bias relative to the outcome of disease. Another bias could have been caused by the use of patients with colon adenocarcinoma as controls.

If the risk for colon cancer is influenced by exposure, risk estimates would be attenuated. Because of the small number of exposed cases, we were unable to evaluate whether country modified the effect of endocrine-disrupting compounds. Although a common questionnaire was used, it is possible that the exposure index means something different in different countries, in particular if the exposure assessment were only based on job title and industry. The specific exposure questions that we used and the use of job-specific questionnaires should, however, avert this problem to a large degree.

The results of this study partially confirm those from previous studies, and they suggest that occupational exposure to endocrine-disrupting compounds, and to PCB in particular, may be associated with an increased risk of cancers of the extrahepatic biliary tract. The appraisal of this conclusion, however, has to take into account the difficulties in retrospectively assessing the agents of interest in a population-based study such as this one. Furthermore, the endocrine-disrupting mechanism of the agents considered in this study is not yet fully understood for all of them. The estrogenic effect of alkylphenols (octyl or nonylphenole ethoxylates), PCB, pesticides [dichlorodiphenyltrichloroethane (DDT), hexachlorocyclohexane (HCH)], and bisphenol A has been shown in many studies, whereas pentachlorophenol seems to exhibit both estrogenic and anti-estrogenic effects and phthalates exhibit anti-androgenic effects and a weak affinity to the estrogen receptor. For this reason the risk estimates for each agent need to be considered separately in addition to the combined exposure index. Future studies should try to confirm or refute our observations.

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