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Occupational risks for uveal melanoma results from a case-control study in nine European countries

Jean-Michel Lutz[1], Ian Cree[2], Svend Sabroe[3], Tine Kajsa Kvist[4], Lene Bjørk Clausen[4], Noemia Afonso[5], Wolfgang Ahrens[6], Terri J. Ballard[7], Janine Bell[8], Diane Cyr[9], Mikael Eriksson[10], Joëlle Févotte[11], Pascal Guénel[12], Lennart Hardell[13], Karl-Heinz Jöckel[14], Ana Miranda[15], Franco Merletti[16], Maria M. Morales-Suarez-Varela[17], Aivars Stengrevics[18] & Elsebeth Lynge[4]

[1]*Registre Genevois des Tumeurs, Geneva, Switzerland;* [2]*Translational Oncology Research Centre, Queen Alexandra Hospital, Portsmouth, UK;* [3]*Department of Epidemiology and Social Medicine, University of Aarhus, Denmark;* [4]*Institute of Public Health, University of Copenhagen, Denmark;* [5]*Serviço de Bioestatística e Informática Médica, Al. Hernani Monteiro, Porto, Portugal;* [6]*Bremen Institute for Prevention Research and Social Medicine, Bremen, Germany;* [7]*The Venetian Tumour Registry, Padua, Italy;* [8]*Thames Cancer Registry, London, UK;* [9]*INSERM Unité 88, Saint Maurice, France;* [10]*Department of Oncology, University Hospital, Lund, Sweden;* [11]*Institut Universitaire de Médecine du Travail, Université Claude Bernard, Lyon, France;* [12]*INSERM Unité 170, Villejuif, France;* [13]*Department of Oncology, University Hospital, Örebro, Sweden;* [14]*Institute for Medical Informatics, Biometry and Epidemiology, University Clinics of Essen, Germany;* [15]*Instituto Portuquès de Oncologia de Francisco Gentil, Lisboa, Portugal;* [16]*Unit of Cancer Epidemiology, University of Turin, CERMS and CPO - Piemonte, Italy;* [17]*Unit of Public Health, Valencia University, Dr. Peset University Hospital, Spain;* [18]*Latvia Cancer Register, Latvia Oncology Centre, Riga, Latvia*

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Abstract

Objective: Uveal melanoma is a rare disease with poor prognosis and largely unknown etiology. We studied potential occupational risk factors.
Methods: A population based case-control study was undertaken during 1995–1997 in nine European countries using population and colon cancer controls with personal interviews. Occupational exposure to sunlight and artificial UV radiation was assessed with a job exposure matrix. In total, 320 uveal melanoma cases were eligible at pathology review, and 292 cases were interviewed, participation 91%. Out of 3357 population controls, 2062 were interviewed, 61%, and out of 1272 cancer controls 1094 were interviewed, 86%.
Results: Using population controls, occupational exposure to sunlight was not associated with an increased risk (RR = 1.24, 95% CI = 0.88–1.74), while an excess risk found with use of colon cancer controls was attributed to confounding factors. An excess risk in welders was restricted to the French part of the data. Cooks, RR = 2.40; cleaners, RR 2.15; and laundry workers, RR = 3.14, were at increased risk of uveal melanoma.
Conclusion: Our study does overall not support an association between occupational sunlight exposure and risk of uveal melanoma. The finding of an excess risk of eye melanoma in cooks in several European countries is intriguing.

Abbreviations: CI – Confidence interval; ICD-O – International classification of diseases for oncology; ISCO – International Standard Classification of Occupation; JEM – Job exposure matrix; NOS – Not otherwise specified; NR – Not relevant; Obs – Observed number of cases; RR – Relative risk; UK – United Kingdom; US – United States

* Address correspondence to: Elsebeth Lynge, Institute of Public Health, University of Copenhagen, Blegdamsvej 3, DK 2200 København N, Denmark. Ph.: 453-532-7635; Fax: 453-535-1181; E-mail: elsebeth@pubhealth.ku.dk

Introduction

Malignant neoplasm of the eye is rare but carries a fairly high mortality with only half of the patients alive after

ten years [1]. In high-risk areas, the age standardized incidence is around 1 per 100,000 in the World Standard Population, and almost consistently higher in men than in women. High risks are found in the Nordic countries, Scotland, Switzerland, parts of Australia, and in the US in Iowa and among whites in New Orleans and Los Angeles. Low risks are found in Japan, China and India, and among West Coast Americans of Asian origin [2]. In the US, whites have almost ten times the risk of blacks [3]. In Europe, uveal melanoma accounts for 84% of eye cancer in adults [4].

Both cutaneous and uveal melanomas derive from melanocytes, but there are considerable differences between the two tumors in terms of molecular biology [5], pathology and clinical behavior [6]. Nevertheless, it is intriguing that the incidence of uveal melanoma remained fairly stable over the past 50 years: while the incidence of cutaneous melanoma has increased many fold [7].

Having blue eyes carries two to three times the uveal melanoma risk of having brown eyes [8–12], and people with blond hair and light skin tend to be at increased risk [8–11]. Presence of naevi is a risk factor [10–13], particularly atypical or iris naevi [13, 14]. An excess risk of uveal melanoma has been reported for a variety of jobs, for instance farmers [15–18], sailors [19], and teachers [20]. Some, but not all, of these jobs entail occupational exposure to visible light and ultraviolet radiation, either from sunlight as for farmers, or from artificial UV radiation as for welders. Risk of occupational sunlight exposure has, however, been assessed thoroughly in only three studies with inconsistent results [15, 21, 22], and only one study assessed occupational exposure to artificial UV radiation [21].

To investigate further occupational risks of uveal melanoma we undertook a case control study, where cases were recruited over a two-year period among 37 million people from nine European countries.

Material and methods

The study base was the national populations in Denmark and Latvia, administrative regions in France, Germany, Italy and Sweden, hospital recruitment areas in Portugal and Spain, and an eye hospital in the UK (Table 1).

Cases

We aimed at including all incident cases of uveal melanoma in patients aged 35–69 within a period of normally two years, mostly 1 January 1995 to 31 December 1996, Table 1. Eligible cases were defined by topography codes 199.0 eyeball, 190.6 choroid, or 190.9 eye not otherwise specified, combined with morphology codes 8720/3, 8722/3, 8730/3, 8771/3, 8772/3, 8773/3, 8774/3 or 8775/3 in the International Classification of Diseases on Oncology (ICD-O), version 1 [23]. Patients were identified via personal contacts to ophthalmology and pathology departments, or via manual or computerized hospital records or cancer registries. The diagnoses were reviewed centrally, for enucleated patients based on a haematoxylin-eosin stained slide, or otherwise on the ophthalmological report. Cases with definite or possible diagnosis were considered eligible.

Controls

Controls were selected for use in the present and six other rare cancers studies [24, 25]. Controls were frequency matched with cases by region, sex, and five-year birth cohorts. Within each stratum we aimed at selecting a number of controls four times the number of cases of the most 'frequent' of the seven rare cancers. Population controls were selected randomly at specified points in time during recruitment of cases from population registers in Denmark, Germany, Italy, and Sweden, and from electoral rolls in France. In the UK, one control per case was selected from the list of the general practitioner of the case. Population based cancer controls were selected randomly from incident colon cancer cases in Denmark and Latvia. Hospital based controls were selected randomly from the colon cancer patients in Valencia and the Basque Country of Spain, and colon and stomach cancer patients in Portugal. Patients attending the emergency ward were selected as controls in Navarra, Spain.

Questionnaire

Based on a literature review [26], a common questionnaire was developed in English and translated into the eight other languages, and for quality control in part back-translated into English. Questions covered demography, personal characteristics as eye color, medical history, tobacco and alcohol use, and a number of occupational exposures such as pesticides and solvents. A complete occupational history was obtained including each job lasting at least six months.

Interviews

All countries required approval of the study by the Ethics Committees, and contact to patients normally required approval also from the treating physician. In

Table 1. Study base of the European rare cancer study

Country region	Study base	Total population of region in million	Recruitment period	Data source for case identification	Type of control
Denmark	Population	5.2	January 95–December 96	Register: Pathology, hospital, cancer	Population colon cancer
France	Population	6.4		Department:	Population
Bas-Rhin		0.9	January 95–June 97	Pathology + in some	
Calvados		0.6	January 95–June 97	regions clinical	
Côte d'Or		0.5	January 95–June 97	departments and centres	
Doubs		0.5	January 95–June 97	of proton-treatment	
Haut-Rhin		0.7	April 95–June 97		
Hérault		0.8	January 95–June 97		
Isére		1.0	January 95–June 97		
Manche		0.5	January 95–June 97		
Somme		0.5	January 95–June 97		
Tarn		0.3	January 95–June 97		
Germany	Population	3.8	July 95–June 97	Department: Medicine,	Population
Bremen		0.5		oncology, radiology,	
Hamburg		1.6		surgery, pathology	
Essen		0.6			
Saarland		0.7			
Saarbruecken		0.4			
Italy	Population	3.0	January 95–June 97	Department: Medicine,	Population
Florence		1.0		oncology, radiology,	
Padua		1.1		surgery, pathology,	
Torino		0.9		cancer register	
Latvia	Population	2.5	August 95–December 96	Register: Cancer	Colon cancer
Portugal	Hospital referral area	4.3	February 95–December 96	Register: Cancer	Colon and stomach cancer
Porto		2.3			
Lisboa		2.0			
Spain	Hospital referral area	6.5	January 95–August 97	Department: Clinical + pathology	Colon cancer and emergency ward patients
Basque Country		2.1			
Navarra		0.5			
Valencia		3.9			
Sweden	Population	5.4	September 95–August 97	Register: Cancer	Population
Linköping		1.0			
Lund		1.6			
Umeå		0.9			
Örebro/ Uppsala		1.9			
United Kingdom	Cancer register	Not relevant	January 95–May 96	Department: Eye	Person selected from
London	patients from one eye clinic				GP-list of the case
Total		37.2			

most centers, cases were contacted by letter or telephone by the project physician. When a case agreed to participate, the interview was undertaken either face-to-face or by telephone. For population controls, the granted access to selection of controls from population registers implied also permission to contact controls by letter or telephone. For cancer controls, contact procedures were as for the cases. Cases and cancer controls were interviewed as soon as possible after diagnosis. Population controls were interviewed concurrently with the cases. Surrogate interviews, in the order husband/wife, child or friend, were performed if a case or control was too ill or died before contact was established.

A total of 359 potential cases were identified, of which 342 underwent pathology review, 320 were considered eligible cases, and 292 were interviewed, giving a participation rate of 91%. Out of the 3357 identified population controls, 2062 were interviewed, with a

participation rate of 61%, and out of the 1272 identified cancer controls, 1094 were interviewed, with a participation rate of 86%. Only 13 cases, 27 population controls, and 86 cancer controls had surrogate interviews (Table 2).

Coding and data entry

The national study coordinator coded the jobs following the International Classification of Occupations (ISCO), from 1968 [27]. Data were entered locally using a common data entry program in SPSS [28], and the files were merged and checked at the University of Aarhus, Denmark.

Analysis

Occupational exposure to sunlight and artificial UV radiation was assessed from a Job Exposure Matrix (JEM) [21]. For each job, defined by the ISCO code, probabilities were assigned for proportion of workers exposed, frequency of exposure, and intensity of exposure. An exposure index, called the 'dose', was calculated as the product of these probabilities. For each person, a cumulative dose was calculated as the product of dose and length of employment for a given job, and summarized across jobs held. Three cumulative dose levels were used in the analysis: zero, $<$ median, and $\geq$ median. People were defined as belonging to a certain occupation if they ever held one of the jobs defined by the ISCO codes for more than six months. This implied that one person could contribute data to more than one occupation.

The relative risks, RR, of developing uveal melanoma in exposed persons compared with unexposed persons were estimated by unconditional logistic regression controlling for country, sex, and five-year birth cohort using SAS version 8.2 [29]. The small UK data set was merged with the German data. Sedentary work is a known risk factor for colon cancer [30], and sedentary work could be expected to be negatively associated with sunlight exposure. We therefore made separate analyses with population and colon cancer controls. The analysis was repeated also with control for eye color, which gave similar results [data not shown]. RRs are presented with 95% confidence intervals (95% CI).

Results

When the colon cancer controls were used in the analysis, sunlight exposure was associated with a significantly increased risk of uveal melanoma, 51 obs (RR = 1.91, 95% CI = 1.22–2.98), but with no trend by cumulated dose (Table 3). However, exposure to sun-

Table 2. Eligible, interviewed uveal melanoma cases, population controls and colon cancer controls by country and sex

Country	Uveal melanoma cases			Population controls			Colon cancer controls[a]			All controls		
	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total
Denmark	34	24	58	192	122	314	151	101	252	343	223	566
France	29	21	50	321	157	478	NR	NR	NR	321	157	478
Germany	19	20	39[b]	561	155	716	NR	NR	NR	561	155	716
Italy	8	10	18	209	92	301	NR	NR	NR	209	92	301
Latvia	11	13	24	NR	NR	NR	68	82	150	68	82	150
Portugal	13	6	19	NR	NR	NR	68[c]	50[d]	118[d]	68	50	118
Spain	12	8	20	NR	NR	NR	362	212	574[a]	362	212	574
Sweden	21	16	37	140	90	230	NR	NR	NR	140	90	230
UK	17	10	27	17	6	23	NR	NR	NR	17	6	23
Total	164	128	292	1440	622	2062	649[c]	445[d]	1094[a,e]	2089	1067	3156

NR Not relevant.
[a] include 114 controls from emergency wards.
[b] Monárrez-Espino *et al.* [31] reported 37 cases. Difference due to inclusion here of one case with a surrogate interview and one case with possible eligibility according to histology review.
[c] of whom two stomach cancer controls.
[d] of whom eight stomach cancer controls.
[e] of whom 10 stomach cancer controls.

light was not associated with an increased risk of eye melanoma when the population controls were used in the analysis, 63 obs (RR = 1.24, 95% CI = 0.88–1.74). With these differences, confounding by sedentary work could not be excluded when the colon cancer controls were used in the analysis. Further analysis was therefore restricted to data from the countries with population controls. Exposure to artificial UV radiation was associated with an increased risk of eye melanoma not reaching statistical significance, 19 obs (RR = 1.56, 95% CI = 0.91–2.66). The association was found in France, as reported previously [21], but not in the other countries 12 obs (RR = 1.08, 95% CI = 0.56–2.07).

Previous studies observed excessive risk of uveal melanoma for a number of occupations. We tested these associations in our data set with a negative outcome for most occupations (Table 4). Cooks, however, had an excess risk, 18 obs (RR = 2.40, 95% CI = 1.35–4.28). As part of the previous reports on cooks came from national subsets of our data [21, 31, 32], we tested also the association excluding data from France, Germany, and UK. Fourteen exposed cases remained, giving a RR = 3.24, 95% CI = 1.58–6.62. Service workers not otherwise specified had an excess risk of uveal melanoma (RR = 1.43, 95% CI = 1.02–2.00). Among the 66 exposed cases, 26 were cleaning workers (RR = 2.15, 95% CI = 1.30–3.54); 16 were housemaids (RR = 1.77, 95% CI = 0.94–3.31); and 12 were waiters (RR = 1.61, 95% CI = 0.84–3.09). The association remained when France, where the association was first found [21], was excluded, 45 obs (RR = 2.06, 95% CI = 1.30–3.27). Male welders had an excess risk, 15 obs (RR = 2.18, 95% CI = 1.18–4.04), which, however, disappeared when data from France, where the association was found previously [21], were excluded, 8 obs (RR = 1.22, 95% CI = 0.54–2.73). Thirty subjects had reported in the questionnaire that they had worked with welding, giving a RR = 0.94, 95% CI = 0.62–1.46. Increased risks close to statistical significance, were seen for seamen and fishermen (RR = 2.46, 95% CI = 0.94–6.41), and for female farmers (RR = 1.84, 95% CI = 0.91–3.74).

A search was made for possible associations between the remaining occupational groups and risk of uveal melanoma (Table 5). Laundry and dry cleaning workers had an excess risk, 10 obs (RR = 3.14, 95% CI = 1.44–6.86), observed for both men and women. Five of the cases also reported previous work in dry cleaning in the questionnaire, 5 obs (RR = 5.08, 95%CI = 1.58–16.33). However, none of the 10 cases had an ISCO code specific for dry cleaning. An increased risk at the borderline of statistical significance was found for women in material handling and related occupations (RR = 2.13, 95% CI = 0.99–4.60). The small group of glass formers had an increased risk, 3 obs RR = 3.36, which was not statistical significant (95% CI = 0.83–13.59).

We tabulated the relative risks for uveal melanoma in relation to the specific exposures recorded in the questionnaire, but none of these were significantly elevated (data not shown).

Discussion

Our study assessed the occupational risks of uveal melanoma in 292 cases coming from nine European countries. Using population controls, occupational exposure to sunlight was overall not associated with an increased risk. An excess risk for sunlight exposure found with the colon cancer controls was attributed to confounding factors. Risks associated with artificial UV radiation and welding were found only in the French part of the data. Previously reported excess risks for cooks and service workers were confirmed in our study, and the study furthermore pointed to an excess risk in laundry workers.

It is a strength of the present study that all diagnoses of cases were reviewed centrally. Out of the 342 cases included in the analysis, 286 had a definite diagnosis of uveal melanoma according to the reference pathologist. The participation rate was high among the eligible cases being 91%. The overall participation rate in population controls was 61% varying from 54 to 57% in the Northern part of Europe, Denmark, Sweden, and Germany, from 74 to 76% in the Southern part of Europe, Italy, and France. While almost all colon cancer controls participated in Latvia, Spain, and Portugal, where the interviews took place in hospitals, only 59% of the Danish colon cancer controls participated.

In an Australian study, occupational sun exposure was assessed from the number of hours per day spent outside on weekdays at ages 10, 20, 30, and 40, respectively. It was assessed also from the number of hours worked outside throughout life. For men, both measures showed a dose dependent risk of uveal melanoma increasing to RRs of 2.6 and 2.3, respectively, in the highest category. The risk was not increased for similarly measured recreational sun exposure neither was it increased for women [15].

Occupational sun exposure was assessed also in a cohort of Swedish male construction workers. Work predominantly outside was associated with an increased risk of eye cancer (RR = 3.4, 95% CI = 1.1–10.5) [22].

A three fold risk of uveal melanoma was found in sailors and fishermen in 11 western US states [19]. This association has not been reported in other studies,

Table 3. Occupational exposure to sunlight light and artificial UV radiation as assessed by a Job Exposure Matrix and relative risks of uveal melanoma

Exposure	Population controls				Colon cancer controls			
	Exposed cases	Exposed controls	RR[a]	95% CI	Exposed cases	Exposed controls	RR[a]	95% CI
Sunlight								
No	163	1531	1		68	705	1	
Yes	63	518	1.24	0.88, 1.74	51	375	1.91	1.22, 2.98
Yes by dose								
< median	40	307	1.34	0.90, 1.99	26	147	1.95	1.14, 3.36
≥ median	23	211	1.10	0.68, 1.79	25	228	1.86	1.06, 3.25
Yes by sex								
Men	49	468	1.09	0.74, 1.62	38	302	1.71	1.00, 2.94
Women	14	50	1.83	0.94, 3.54	13	73	2.36	1.11, 5.02
Yes by country								
Denmark	21	89	1.96	0.97, 3.94	21	66	2.15	1.07, 4.31
France	14	136	1.11	0.56, 2.20	–	–	–	–
Germany and UK	14	153	1.28	0.64, 2.56	–	–	–	–
Italy	4	67	1.16	0.35, 3.83	–	–	–	–
Latvia	–	–	–	–	13	47	3.05	1.11, 8.43
Portugal	–	–	–	–	10	49	1.55	0.57, 4.20
Spain	–	–	–	–	7	213	1.13	0.41, 3.16
Sweden	10	73	0.78	0.35, 1.77	–	–	–	–
Artificial uv Radiation								
No	207	1897	1		113	1011	1	
Yes	19	152	1.56	0.91, 2.66	6	69	0.60	0.22, 1.63
Yes by dose								
< median	10	82	1.52	0.74, 3.12	3	30	0.46	0.10, 2.09
≥ median	9	70	1.60	0.76, 3.38	3	39	0.76	0.21, 2.73
Yes by sex								
Men	17	149	1.47	0.84, 2.58	5	68	0.47	0.16, 1.41
Women	2	3	3.09	0.50, 19.02	1	1	8.11	0.49, 134
Yes by country								
Denmark	5	14	1.88	0.62, 5.63	5	18	1.20	0.40, 3.62
France	7	24	4.45	1.17, 11.58	–	–	–	–
Germany and UK	3	67	0.62	0.18, 2.10	–	–	–	–
Italy	0	29	–	–	–	–	–	–
Latvia	–	–	–	–	1	5	–	–
Portugal	–	–	–	–	0	9	–	–
Spain	–	–	–	–	0	37	–	–
Sweden	4	18	1.71	0.49, 5.92				

[a] RR adjusted for country, sex, and 5-year age group.

neither was it seen in the two large proportional mortality data sets from Washington State for 1950–1979 [33], and from England and Wales for 1979–1980 and 1982–1990 [34]. In our study seamen and fishermen had an increased risk at the borderline of statistical significance. Excess risks of uveal melanoma have previously been reported for farmers from Wisconsin [16], British Columbia [17], Illinois [18], and Australia in men but not in women [15]. We found an excess risk in women, although statistically non-significant, but not in men. Only one study previously reported no increase in the risk for farmers [19]. Farmers had an excess risk of eye cancer in the Washington State proportional mortality data based on eight observed cases [33], but not in the England and Wales proportional mortality data [34]. Railway workers had an excess risk of eye melanoma in Montreal, Canada [35], and an excess risk of eye cancer in both proportional mortality data sets [33, 34], observations not supported by our data.

The findings on sunlight exposure and risk of uveal melanoma are thus inconsistent. However, exposure measurement errors are probable given the uncertainties with both JEM-assessments and self-reported data of hours spent outside back to the age of ten. For specific occupational groups, a reporting bias in the literature favoring positive findings is furthermore probable. Taking these

Table 4. Relative risk of uveal melanoma in occupational groups with previously reported associations

Reference	Occupation	ISCO-code	Men				Women				Total	
			Cases	Controls	RR[a]	95% CI	Cases	Controls	RR[b]	95% CI	RR[b]	95% CI
19	Seamen and fishermen	0-42, 0-43, 6-41, 9-81, 9-82	6	25	2.46	0.94, 6.41					2.46	0.94, 6.41
19, 31	Health workers	0-6, 0-7	6	40	1.67	0.66, 4.20	13	68	1.19	0.61, 2.32	1.33	0.77, 2.28
20	Teachers	1-3	5	104	0.48	0.19, 1.22	12	89	0.86	0.44, 1.67	0.69	0.41, 1.17
20	Athletes	1-8	0	4			0	2				
20	Clerical workers	3, except 3-51	29	377	0.90	0.58, 1.41	36	222	0.94	0.60, 1.47	0.92	0.67, 1.26
20, 21, 31, 32	Cooks	5-31	5	30	2.10	0.77, 5.74	13	32	**2.57**	**1.26, 5.25**	**2.40**	**1.35, 4.28**
21	Service workers NOS	5-0, 5-1, 5-2, 5-32, 5-4, 5-5, 5-7, 5-8, 5-9	22	171	1.61	0.97, 2.69	44	224	1.31	0.84, 2.03	**1.43**	**1.02, 2.00**
15–18	Farmers	6-0, 6-1, 6-2	21	220	0.87	0.52, 1.45	12	41	1.84	0.91, 3.74	1.09	0.72, 1.66
31	Miners, etc, stone cutters, etc	7-1, 8-2	4	38	1.16	0.39, 3.46	0	2			1.05	0.36, 3.10
19, 31	Chemical processers and related workers	7-4	3	25	2.03	0.56, 7.32	0	1			2.03	0.56, 7.32
31	Food and beverage processers	7-7	5	70	0.65	0.25, 1.67	4	10	2.43	0.73, 8.12	0.97	0.47,1.99
21	Blacksmiths, toolmakers, and machine toolmakers	8-3	11	169	0.66	0.35, 1.27	3	8	2.85	0.71, 11.45	0.80	0.45, 1.44
12, 20, 41	Electrical fitters, broadcasting station workers, etc	8-5, 8-6	15	149	1.19	0.67, 2.13	3	10	1.76	0.44, 6.99	1.26	0.74, 2.15
9, 19, 21	Welders and sheet metal workers	8-72, 8-73	15	79	**2.18**	**1.18, 4.04**	1	7	0.75	0.09, 6.33	**1.95**	**1.08, 3.52**
35	Bricklayers, and other construction workers	9-51, 9-52, 9-53, 9-55, 9-56, 9-57, 9-59	13	126	1.32	0.71, 2.47	0	2			1.29	0.69, 2.41
35	Railway workers	3-51, 9-83, 9-84	2	27	0.74	0.17, 3.19	0	1			0.66	0.15, 2.84

[a]RR adjusted for country, and 5-year age group.
[b]RR adjusted for country, sex, and 5-year age group.
Population control only.

Table 5. Relative risk of uveal melanoma in occupational groups without previously reported associations

Occupation	ISCO-code	Men				Women				Total	
		Cases	Controls	RR[a]	95% CI	Cases	Controls	RR[b]	95% CI	RR[b]	95% CI
Professional, technical and related workers NOS, administrative and managerial workers NOS	0-1, 0-2, 0-3, 0-5, 0-8, 0-9, 1-1, 1-2, 1-4, 1-5, 1-9, 2-0, 2-1	31	337	0.99	0.64, 1.53	10	54	1.12	0.54, 2.33	1.02	0.70, 1.49
Sales workers	4	19	256	0.74	0.44, 1.24	25	166	0.92	0.56, 1.51	0.83	0.58, 1.18
Launderers, dry-cleaners and pressers	5-6	3	4	**5.66**	**1.21, 26.59**	7	19	**2.60**	**1.05, 6.49**	**3.14**	**1.44, 6.86**
Forestry workers, hunters and related workers NOS	6-3, 6-49	4	32	1.25	0.41, 3.76	1	3	1.46	0.15, 14.33	1.28	0.47, 3.47
Production supervisors	7-0	9	104	0.95	0.46, 1.96	1	3	1.82	0.19, 17.64	1.00	0.51, 1.99
Metal processers	7-2	3	63	0.67	0.20, 2.24	0	3			0.60	0.18,1.99
Wood preparation, etc, cabinet makers, etc, paper makers, etc, carpenters, etc	7-3, 8-1, 9-1, 9-54	16	109	1.47	0.82, 2.66	2	8	1.91	0.37,9.81	1.52	0.87, 2.64
Spinners, etc, tanners, etc, tailors, etc, shoemakers, etc..	7-5, 7-6, 7-9, 8-0	7	66	1.28	0.56, 2.93	12	87	0.80	0.41, 1.55	0.95	0.56, 1.60
Machine fitters, etc.	8-4	19	216	1.05	0.62, 1.78	1	6	1.04	0.13, 8.71	1.05	0.63, 1.75
Plumbers and pipe fitters	8-71	2	42	0.55	0.13, 2.33					0.55	0.13, 2.33
Glass formers	8-91	2	10	3.16	0.57, 17.60	1	2	3.80	0.34, 42.03	3.36	0.83, 13.59
Rubber and plastic workers	9-0	3	27	1.16	0.33, 4.06	1	9	0.75	0.09, 6.01	1.02	0.35, 2.96
Printers and related workers	9-2	4	27	1.35	0.45, 4.09	0	16			0.70	0.25, 2.02
Painters	9-3	5	46	1.42	0.53, 3.75	0	4			1.18	0.45, 3.08
Structural metal preparers, jewelers, potters, etc, production NOS	8-74, 8-8, 8-92, 8-93, 8-94, 8-95, 8-99, 9-4	5	90	0.65	0.25, 1.67	4	24	1.20	0.40, 3.60	0.82	0.40, 1.67
Stationary engine operators	9-6	2	12	2.33	0.47, 11.48					2.33	0.47, 11.48
Material handling and related operators	9-7	9	162	0.52	0.25, 1.05	10	28	2.13	0.99, 4.60	0.87	0.52, 1.45
Motor vehicle drivers	9-85	17	180	0.99	0.58, 1.72	1	7	0.76	0.09, 6.24	0.98	0.58, 1.66
Other transport, labourers NOS	9-86, 9-89, 9-9	11	136	0.71	0.37, 1.38	1	25	0.23	0.03, 1.70	0.60	0.32, 1.11

NOS Not otherwise specified.
[a]RR adjusted for country, and 5-year age group.
[b]RR adjusted for country, sex, and 5-year age group.
Population control only.

reservations into account, the data on sun light exposure and risk of uveal melanoma are at present equivocal.

Occupational exposure to artificial light had not been assessed in previous studies and no association was found in our study, except in the French part [21]. Welding turned out to be a risk factor in two of the large US case-control studies [9, 19], but not in the third one [11]. Arc welding fumes, metallic dust, iron compounds, and mild steel dust were risks factor for eye melanoma in Montreal, Canada [35]. An excess risk was seen for welders in our study entirely explained by the French cases [21]. Welders were not at an increased risk of eye cancer in the two proportional mortality studies [33, 34]. There is overall some, but not consistent, evidence for welding as a risk factor for uveal melanoma. Different coding procedures may account for the inconsistencies, as a worker practicing welding may be coded as a welder in some settings, but may elsewhere be given another job title, *e.g.,* ship yard worker. Data have not been reported on the small group of glass formers in earlier case-control studies on uveal melanoma [8–11, 15, 35], nor have data on eye cancer been reported in cohort studies on glass workers [36–39], and glass workers did not show up with excess risks of eye cancer in the proportional mortality data [33, 34]. It is noteworthy, however, that glass formers are exposed to intensive light.

Female kitchen hands from England and Wales have previously been reported to have an excess risk of uveal melanoma [20], and cooks had an excess risk in our data, both in France [21], Germany [31, 32], and in the other countries. Cooks did not come out as a risk group in the proportional mortality data sets [33, 34].

Service workers had an excess risk of uveal melanoma in our data. Waiters are included in this group. Cooks and waiters are known to be at an excess risk of cancer mostly due to alcohol and tobacco related diseases [40]. Alcohol was, however, not a risk factor for uveal melanoma in our study; intake of beers gave 137 obs (RR = 0.86, 95% CI = 0.63–1.18), and intake of wine gave 164 obs (RR = 0.67, 95% CI = 0.48–0.93). Tobacco was not a risk factor either, as current smokers had the same risk as non-smokers, 77 obs (RR = 1.26, 95% CI = 0.88–1.80). It is therefore unlikely that the excess risk of uveal melanoma for cooks and service workers was due to excess alcohol and tobacco consumption. Among the service workers, cleaning workers were the subgroup with the highest excess risk. Janitors had an excess risk of eye cancer in the Washington State data based on three observed cases [33], but not in the England and Wales data [34].

An excess risk in laundry and dry-cleaning workers in our study was most likely associated with laundry work as none of the workers had specific dry-cleaning codes. However, exposure to carbon tetrachloride and other cleaning fluids was a risk factor for uveal melanoma in 11 western US states [19], and exposure to solvents was a risk factor in Montreal, Canada [35]. Laundry and dry-cleaning workers did not show up with excess risks in the proportional mortality data [33, 34].

The finding of an excess risk of uveal melanoma in cooks, first in France [21], then in Germany [31, 32], and here in the remaining population control countries Denmark, Italy and Sweden makes this an important observation. It should be noted though, that no exposed case occurred in Latvia, Portugal and Spain. The work tasks of cooks, cleaners, and laundry workers include elements of traditional female housework activities. One could therefore expect women to have a higher incidence of uveal melanoma than men, but the opposite is almost universally true [2]. Carcinogenic agents explaining the risks in cooks, cleaners and laundry workers should therefore most likely be searched for outside the domain of housework activities. It should be noted that cleaning products for professional use contain more alkalis and caustics than products for domestic use.

Associations between occupation and risk of uveal melanoma have now been reported from several large case-control studies [8–11, 15] and the present study, each including between 200 and 400 cases. It is nevertheless apparent that the rarity of the disease implies that only a few cases will be identified from the same occupation in a given study, and it is therefore not surprising that there has so far been limited consistency in the findings across studies. However, the studies together now comprise more than 1500 cases, and much could be learned about the possibly occupational etiology of uveal melanoma from a joint analysis of these already collected data. We are in particular interested in further elucidation of the excess risks among cooks, cleaners, and laundry workers found in the present study.

In conclusion, we found no association between occupational sunlight exposure and risk of uveal melanoma. The fact that this association was positive with use of colon cancer controls underlines the need for cautions in selection of controls. We observed excess risks of uveal melanoma in cooks, cleaners, and laundry workers. A comprehensive elucidation of occupational risks for uveal melanoma requires a large data set, and this could be obtained by merging existing studies.

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References

1. Raivio I (1977) Uveal melanoma in Finland. an epidemiological, clinical, histological and prognostic study. *Acta Ophtalmol* **133**: (Suppl) 1–64.
2. Ferlay J, Black RJ, Whelan SL, Parkin DM (1997) *CI5VII: Electronic database of Cancer Incidence in Five Continents,* Vol VII. Lyon: International Agency for Research on Cancer.
3. Inskip PD, Devesa SS, Fraumeni JF Jr (2003) Trends in the incidence of ocular melanoma in the Unites States, 1974–1998. *Cancer Causes Control* **14**: 251–257.
4. European Network of Cancer Registries (1995) *EUROCIM User Manual*. 2nd Edn. Lyon: International Agency for Research on Cancer.
5. Cree IA (2002) Cell cycle and melanoma – two different tumours from the same cell type. *J Pathol* **191**: 120–126.
6. Shields JA, Shields CL (1993) Current management of posterior uveal melanoma. *Mayo Clin Proc* **68**: 1193–1200.
7. Isager P (2004) *Ocular malignant melanoma. Epidemiology and clinical aspects*. PhD Thesis. Århus: University of Aarhus.
8. Gallagher RP, Elwood JM, Rootman J, *et al*. (1985) Risk factors for ocular melanoma: Western Canada melanoma study. *J Natl Cancer Inst* **74**: 775–778.
9. Tucker MA, Shields JA, Hartge P, Augsburger J, Hoover RN, Fraumeni JF Jr (1985) Sunlight exposure as risk factor for intraocular malignant melanoma. *N Engl J Med* **3131**: 789–792.
10. Holly EA, Aston DA, Char DH, Kristiansen JJ, Ahn DK (1990) Uveal melanoma in relation to ultraviolet light exposure and host factors. *Cancer Res* **50**: 5773–5777.
11. Seddon JM, Gragoudas ES, Glynn RJ, Egan KM, Albert DM, Blitzer PH (1990) Host factors, UV radiation, and risk of uveal melanoma. *Arch Ophthalmol* **108**: 1274–1280.
12. Stang A, Anastassiou G, Ahrens W, Bromen K, Bornfeld N, Jöckel K-H (2001) The possible role of radiofrequency radiation in development of uveal melanoma. *Epidemiol* **12**: 7-12.
13. Bataille V, Sasieni P, Cuzick J, Hunderford JL, Swerdlow A (1995) Risk of ocular melanoma in relation to cutaneous and iris naevi. *Int J Cancer* **60**: 622–626.

14. Hees CLM van, Boer A de, Jager MJ, *et al*. (1994) Are atypical naevi a risk factor for uveal melanoma? A case-control study. *J Invest Dermatol* **103**: 202–205.
15. Vajdic CM, Kricker A, Giblin M, *et al*. (2002) Sun exposure predicts risk of ocular melanoma in Australia. *Int J Cancer* **101**: 175–182.
16. Saftlas AF, Blair A, Cantor KP, Hanrahan L, Anderson HA (1987) Cancer and other causes of death among Wisconsin farmers. *Am J Ind Med* **11**: 119–129.
17. Gallagher RP (1998) Ocular melanoma in farmers. *Am J Ind Med* **13**: 523–525.
18. Keller JE, Howe HL (1994) Case-control studies of cancer in Illinois farmers using data from the Illinois State Cancer Registry and the US Census of Agriculture. *Eur J Cancer* **30A**: 469–473.
19. Holly EA, Aston DA, Ahn DK, Smith AH (1996) Intraocular melanoma linked to occupational and chemical exposure. *Epidemiology* **7**: 55–61.
20. Vågerö D, Swerdlow AJ, Beral V (1990) Occupation and malignant melenoma: a study based on cancer registration data in England and Wales and in Sweden. *Br J Ind Med* **47**: 317–324.
21. Guénel P, Laforest L, Cyr D, *et al*. (2001) Occupational risk factors, ultraviolet radiation and ocular melanoma: a case-control study in France. *Cancer Causes Control* **12**: 451–459.
22. Håkansson N, Floderus B, Gustavsson P, Feychting M, Hallin N (2001) Occupational sunlight exposure and cancer incidence among Swedish construction workers. *Epidemiololy* **12**: 552–557.
23. World Health Organisation (1976) *International Classification of Diseases for Oncology*. 1st Edn. Geneva: World Health Organisation.
24. Kaerlev L, Teglbjerg PS, Sabroe S, *et al*. (2000) Occupation and small bowel adenocarcinoma: a European case-control study. *Occup Environ Med* **57**: 760–766.
25. Suarez-Varela MM, Olsen J, Kaerlev L, *et al*. (2001) Are alcohol intake and smoking associated with mycosis fungoides? a European multicentre case-control study. *Eur J Cancer* **37**: 392–397.
26. Kolstad H, Lynge E, Olsen J, Sabroe S (1992) Occupational causes of some rare cancers: a literature review. *Scand J Soc Med* **48**: (Suppl) 1–48.
27. International Labour Organisation (1968) *International standard classification of occupations*. Geneva: International Labour Organisation.
28. SPSS Inc (1998) *SPSS Data Entry Builder 1.0*. Chicago: SPSS Inc.
29. SAS Institute Inc (1999–2001) *Release 8.2*. Cary, NC: SAS Institute.
30. Oliveria SA, Christos PJ (1997) The epidemiology of physical activity and cancer. *Ann N Y Acad Sci* **29**: 79–90.
31. Monárrez-Espino J, Stang A, Bromen K, Merzenich H, Anastassiou G, Jöckel KH (2002) Occupation as a risk factor for uveal melanoma in Germany. *Scand J Work Environ Health* **28**: 270–277.
32. Stang A, Ahrens W, Baumgardt-Elms C, *et al*. (2003) Cooking and uveal melanoma: results from two german case-control studies. *Cancer Causes Control* **14**: 377–380.
33. Milham S (1983) *Occupational mortality in Washington State 1950–1979*. Cincinnati: US Dept Health Human Services.
34. Drever F, ed. (1995) *Occupational Health Decennial Supplement*. London: Office of Population Censuses and Surveys, Health and Safety Executive. Series DS no. 10, HMSO.
35. Siemiatycki J (1991) *Risk Factors for Cancer in Workplace*. Boca Raton, FL: CRC Press.
36. Cordioli G, Cuoghi L, Solari PL, Berrino F, Crosignani P, Riboli E (1987) Tumor mortality in a cohort of glass industry workers. *Epidemiol Prev* **30**: 16–18. (in Italian).
37. Wingren G, Englander V (1990) Mortality and cancer morbidity in a cohort of Swedish glassworkers. *Int Arch Occup Environ Health* **62**: 253–257.
38. Sankila R, Karjalainen S, Pukkala E, *et al*. (1990) Cancer risk among glass factory workers: an excess of lung cancer? *Scand J Work Environ Health* **47**: 815–818.
39. Pirastu R, Bartoli D, Battista G, *et al*. (1998) Cancer mortality of art glass workers in Tuscany, Italy. *Scand J Work Environ Health* **24**: 386–391.
40. Andersen A, Barlow L, Engeland A, Kjærheim K, Lynge E, Pukkala E (1999) Work-related cancer in the Nordic countries. *Scand J Work Environ Health* **25** (Suppl 2).
41. Richter ED, Berman T, Ben.Michael E, Laster R, Westin JB (2000) Cancer in radar technicians exposed to radiofrequency/microwave radiation: sentinel episodes. *Int J Occup Environ Health* **6**: 187–193.