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Occupation as a risk factor for uveal melanoma in Germany

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Objective This study explored occupational risks linked to uveal melanoma.

Methods The analysis pooled data from two case-referent studies (hospital- and population-based) conducted in Germany between 1995 and 1998, with incident cases matched with several referents by age, gender, and region of residence. The subjects were contacted through personal or telephone interviews. Their exposure status was based on their occupational history. Dichotomous coding for the main task and categorization into different occupational classification systems was performed. Altogether of 118 cases and 475 referents were included. Adjusted odds ratios were calculated by conditional logistic regression.

Results Relevant occupations included food, beverage, and tobacco processors [odds ratio (OR) 4.7, 95% confidence interval (95% CI) 0.99–22.0] and miners (OR 2.3, 95% CI 0.92–5.99) among the men and station, engine and heavy equipment operators and freight handlers (OR 2.5, 95% CI 0.94–6.58) and medical, dental, pharmaceutical and veterinary workers (OR 2.1, 95% CI 0.71–6.02) among the women according to the International Standard Classification of Occupations, whereas, according to the European Industrial Classification, the relevant occupations were the food industry (OR 3.4, 95% CI 1.08–10.5) and the chemical and pharmaceutical industry (OR 2.8, 95% CI 1.01–7.78) among the men and machine production (OR 3.2, 95% CI 0.96–10.7) and health and veterinary sector (OR 2.4, 95% CI 0.97–5.71) among the women.

Conclusions These analyses support the potential role of occupational exposure as a risk factor for uveal melanoma. The findings must be interpreted carefully since the exposure was assessed indirectly.

Key terms case-control studies, case-referent studies, epidemiology, eye neoplasms, hospital-based, occupational exposure, population-based.

Uveal melanoma is a rare malignant tumor that occurs almost exclusively during adulthood (1–3). Although difficulties in diagnosing and classifying ocular melanomas have been reduced (4–7), the rates of metastasis and mortality remain unchanged, and survival has not improved substantially (8–11). Accordingly, identifying the risk factors has been a research priority for primary prevention.

Potential risk factors have been explored, ranging from demographic and host factors to environmental and occupational factors. Occupational exposure has been sought, as various rare cancers are caused by exposures occurring in the workplace (12). Occupations involving welding (13–17), farming (13, 14, 18–24), and exposure to chemicals (13, 25, 26) have been the most frequently mentioned. However, no causative agent has been established, and contradictory evidence is common.

Recently, Stang et al (27) reported a positive link between exposure to radio frequency radiation and uveal melanoma based on the same case-referent studies presented in our present report, and Guenel et al (17) found an elevated risk among male welders in the French data

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of the same European study on occupational causes of rare cancers from which the German part was extracted to be included in this analysis.

This paper presents a pooled analysis from two similarly designed case-referent studies conducted in Germany from 1995 to 1998 and aimed at exploring work-related risks potentially linked to uveal melanoma. All ethical, legal, and medical confidentiality aspects were considered. The involved participants provided informed consent, and the data collected were held strictly in confidence.

Subjects and methods

Between 1995 and 1997, Germany and other European countries participated in a multinational population-based case-referent study on occupational risk factors for eight rare cancers, including uveal melanoma. The German study area comprised five geographic regions covering a population of nearly 4 million inhabitants at risk.

During the fieldwork for the European study, an additional hospital-based case-referent study, limited to the German federal state of North Rhine-Westphalia, was carried out at the Eye Clinic, University of Essen, using the same questionnaires and personnel. This hospital is a referral center for eye tumors, and 250–300 uveal melanoma patients are treated there every year.

Selection of cases

For the population study, potentially eligible cases were patients with primary incident uveal melanoma located in the choroid or ciliary body. Other eligibility criteria included patient's age (35–69 years), place of residency, and date at diagnosis (1 July 1995 – 31 December 1997). An active reporting system from clinical and pathological departments within the study regions was set up to retrieve cases. Personal interviews (exceptionally by telephone) were conducted. A reference pathologist reviewed all the clinical and pathological reports, as well as specimens when available, to confirm the diagnosis. From the 47 observed cases, 44 were eligible for the study, and interviews were conducted with 37 patients, resulting in a response proportion of 84% (28). The reasons for nonparticipation were refusals and inability to contact cases, 11% and 5% of the eligible cases, respectively.

In the hospital study, patients with incident primary uveal melanoma diagnosed between 1 December1996 and 31 March1998, aged 35–74 years, who were residents of North Rhine-Westphalia were eligible. Diagnoses were confirmed histologically for those who underwent surgery. Mostly personal, but also telephone, interviews were conducted. From the 99 cases diagnosed during the 16-month recruitment period, 92 patients were eligible for the study, and 81 were actually interviewed (response proportion of 88%). Refusals were the main reason for nonparticipation, accounting for 8% of the eligible cases.

Since the city of Essen was covered by both studies, the cases from the Eye Clinic with residence in Essen were included in the population study during the 13–month overlapping period (1 December 1996 – 31 December 1997).

Selection of referents

In the population study, referents were matched by age (5-year intervals), gender, and region of residency (Hamburg, Bremen, Essen, Saarbrücken, and Saarland). The referents were randomly selected from mandatory lists of residence, which cover the total population of the local districts and are regarded as the most complete sampling frame for population-based studies in Germany (29). The number of referents was determined by the stratum-specific maximum number of any of the rare cancers included in the study. Although a minimum of four referents per case in each stratum was foreseen, the matching resulted in ratios for the uveal melanoma study of up to 10 referents per case, as other cancers were more common than uveal melanoma. Of the eligible referents who were invited to participate, 699 agreed to do so, resulting in a response proportion of 48%. The main reasons for nonparticipation were refusal and inability to contact persons, 31% and 8% of the eligible referents, respectively. Most of the participating referents were interviewed personally. Altogether 372 interviewed referents matched to cancers other than uveal melanoma were excluded from the analysis.

In the hospital study referents were also matched by age (5-year intervals), gender, and region of residency (Ruhr Area, south North Rhine-Westphalia <100 000, south North Rhine-Westphalia ≥100 000, north North Rhine-Westphalia <100 000, and north North Rhine-Westphalia ≥100 000 inhabitants). The selection of potential referents was based on the active reporting system established at the Eye Clinic. Eligible referents were patients with newly diagnosed benign disease of the posterior eye segment visiting the clinic during the same period as the cases. The major diagnoses of the referents were retinal detachment and defects (32%), degeneration of the macula (18%), retinal vascular occlusion (14%), diabetic retinopathy (10%), and others (26%). No referent had suffered from occupational accidents involving the eye. Of the 248 potential referents, 187 were eligible for the study, and 148 were interviewed, the result being a response proportion of 79%. Refusals

and inability to contact were the most frequent reasons for nonparticipation, accounting for 13% and 4% of the eligible referents, respectively. Both personal and telephone interviews were carried out with the referents. Additional details of the case and referent selection have been published elsewhere (27).

Exposure assessment and coding

The evaluation of the exposure was based on the lifetime occupational history. A work biography was constructed for each participant of the study. All the jobs with a duration of at least 6 months were chronologically recorded. Within each job period, the duty consuming most of the person's worktime was defined as the "main task", and all others as classified were "secondary tasks".

The recorded jobs were classified into 34 "job groups" according to the International Standard Classification of Occupations (ISCO) (30) and also into 36 "industrial branches" according to the General Industrial Classification of Economic Activities within the European Communities (NACE) (31). In addition, at the end of the standard interview, a checklist with 30 different occupational groups was filled out. If the respondent ever worked in one or more of these groups, a job-specific questionnaire, which has proved useful in classifying occupations in previous epidemiologic studies (32, 33), was applied. All the occupational categories utilized by these classification systems consisted of predetermined and fixed categories that were not modified or adjusted for the purpose of this study.

The interviewers were unaware of the study hypotheses as they administered the structured questionnaires. Each interview took approximately 70 minutes (median). The status of the cases and referents was unknown during the coding process. A different person conducted a second coding to assure the quality of the data. Comparisons between the first and second coding were made, and, if inconsistencies were found, a definitive coding was assigned based on a consensus.

Statistical analyses

Conditional logistic regression analyses were utilized to estimate the adjusted odds ratios (OR) and 95% confidence intervals (95% CI) (34). Dichotomous categorization for being exposed to the occupational category in question for the "main task" according to ISCO, NACE, and the checklist of the job-specific questionnaire was used to determine the exposure status. Estimates are presented only for the occupational categories with ≥5 cases. Both descriptive analyses and conditional logistic regression analyses were performed with SAS® (35).

Results

Most of the tumors involved the choroid (98%). Table 1 presents the characteristics of the cases and referents stratified by study design. The pooled analysis included 118 cases and 475 referents. The proportion of face-to-face interviews was higher in the population study than in the hospital study. There was a skewed gender distribution among the population reference responders (72.5% men, 27.5% women). The educational background, measured as the number of school years, and smoking status were similar for the cases and referents in both studies.

Table 2 presents the risks by occupational groups according to the ISCO. For the men, food, beverage and tobacco processors (OR 4.7, 95% CI 0.99–22.0) and miners (OR 2.3, 95% CI 0.92–5.99) showed the highest risks. For the women, the risks were highest for station, engine and heavy equipment operators and freight handlers (OR 2.5, 95% CI 0.94–6.58) and medical, dental, pharmaceutical and veterinary workers (OR 2.1, 95% CI 0.71–6.02).

The risks are presented by industrial branches in table 3 according to the NACE. The odds ratios were the highest for the men working in the food industry (OR 3.4, 95% CI 1.08–10.5) and chemical and pharmaceutical industry (OR 2.8, 95% CI 1.01–7.78), and for women in machine production (OR 3.2, 95% CI 0.96–10.7) and the health and veterinary sector (OR 2.4, 95% CI 0.97–5.71).

Table 4 shows the odds ratios by occupational category according to the job-specific questionnaire. The most relevant associations were found for cooking (OR 5.6, 95% CI 1.66–19.19) among the men and health care (OR 2.1, 95% CI 0.71–6.02) among the women.

No relevant negative associations were found for either classification system. Table 5 shows the consistency between the hospital and population studies for five selected occupational categories for the men and women together. Although some occupational categories had very few observations, the estimates pointed towards the same direction in both studies for chemical, farming, food, and mining.

Discussion

The lack of clear answers from prior studies indicated that a strong association with any work-related exposure was unlikely. Nevertheless, some occupational categories appeared to be positively linked to uveal melanoma.

Men working with food showed the highest risks in the three classifications. The study by Guenel et al (17)

Table 1. Comparison of the cases and referents with respect to selected characteristics, with stratification by study design. [a]

	Population-based study				Hospital-based study				Pooled analysis			
	Cases		Referents		Cases		Referents		Cases		Referents	
Characteristic	N	%	N	%	N	%	N	%	N	%	N	%
Type of interview												
Face-to-face	33	89.2	302	92.4	57	70.4	82	55.4	90	76.3	384	80.9
Telephonic	4	10.8	21	6.4	21	25.9	66	44.6	25	21.2	87	18.3
Other	0	0	4	1.2	3	3.7	0	0	3	2.5	4	0.8
Gender												
Male	20	54.1	237	72.5	39	48.1	76	51.4	59	50.0	313	65.9
Female	17	45.9	90	27.5	42	51.9	72	48.6	59	50.0	162	34.1
Age distribution												
35–44 years	4	10.8	85	26.0	12	14.8	13	8.8	16	13.6	98	20.6
45–54 years	7	18.9	57	17.4	13	16.1	25	16.9	20	16.9	82	17.2
55–64 years	15	40.5	113	34.6	32	39.5	63	42.6	47	39.8	176	37.1
65–74 years [b]	11	29.8	72	22.0	24	29.7	47	31.8	35	29.6	119	25.0
Schooling												
<10 years	23	62.2	186	56.9	51	63.0	90	60.8	74	62.7	276	58.1
10–11 years	7	18.9	72	22.0	9	11.1	27	18.2	16	13.6	99	20.8
12–13 years	7	18.9	60	18.3	18	22.2	28	18.9	25	21.2	88	18.5
Other	0	0	9	2.8	3	3.7	3	2.0	3	2.5	12	2.5
Smoking status												
None	15	40.6	129	39.5	32	39.6	77	52.0	47	39.8	206	43.4
Mild	7	18.9	57	17.4	17	21.0	32	21.6	24	20.4	89	18.8
Moderate	5	13.5	73	22.3	16	19.7	17	11.5	21	17.8	90	18.9
Heavy	10	27.0	68	20.8	16	19.7	22	14.9	26	22.0	90	18.9

[a] Number of interviewed subjects: 37 cases and 327 referents in the population-based study, 81 cases and 148 referents in the hospital-based study, and 118 cases and 475 referents in the pooled analysis.
[b] For the population-based study only 65-69 years.

Table 2. Subject distribution, odds ratios (OR) and 95% confidence intervals (95% CI) for uveal melanoma by occupational groups according to the International Standard Classification of Occupations (ISCO) in the pooled analyses and the gender of the subjects.

	Cases		Referents		Unadjusted		Adjusted [b]	
Gender [a]	N	%	N	%	OR	95% CI	OR	95% CI
Male								
Architect, engineers, air-ship craft workers, production supervisors	10	16.9	61	19.5	0.8	0.40–1.76	0.8	0.36–1.73
Jurists, teachers, scientists, other professional specialists	6	10.2	26	8.3	1.2	0.49–3.18	1.1	0.39–3.23
Managers, managerial employees	16	27.1	86	27.5	1.0	0.53–1.83	1.1	0.56–2.23
Clerical workers	17	28.8	57	18.2	1.8	0.97–3.41	1.8	0.86–3.78
Sales workers	8	13.6	40	12.8	1.1	0.47–2.42	1.0	0.40–2.43
Service workers	8	13.6	34	10.9	1.3	0.56–2.93	1.4	0.57–3.45
General farmers	7	11.9	15	4.8	2.7	1.04–6.84	1.7	0.60–4.95
Miners	10	16.9	21	6.7	2.8	1.26–6.35	2.3	0.92–5.99
Food, beverage, tobacco processors	5	8.5	5	1.6	4.5	1.16–17.0	4.7	0.99–22.0
Woodworkers	5	8.5	26	8.3	1.0	0.38–2.78	0.9	0.29–2.55
Machinery fitters-assemblers, precision-instrument workers	7	11.9	49	15.7	0.7	0.31–1.69	0.8	0.34–2.07
Plumbers, welders, sheet-structural metal workers	6	10.2	45	14.4	0.7	0.27–1.66	0.7	0.27–1.85
Bricklayers, roofers, other construction workers	12	20.3	42	13.4	1.6	0.81–3.35	1.3	0.57–2.98
Transport equipment operators	11	18.6	42	13.4	1.5	0.71–3.07	1.5	0.66–3.23
Female								
Medical, dental, pharmaceutical, veterinary workers	8	13.6	10	6.2	2.4	0.89–6.32	2.1	0.71–6.02
Jurists, teachers, scientists, other professional specialists	6	10.2	15	9.3	1.1	0.41–3.00	1.1	0.40–3.30
Managers, managerial employees	11	18.6	32	19.8	0.9	0.44–1.99	0.8	0.36–1.81
Clerical workers	19	32.2	53	32.7	1.0	0.52–1.84	0.9	0.42–1.80
Sales workers	16	27.1	53	32.7	0.8	0.40–1.48	0.7	0.34–1.44
Service workers	27	45.8	61	37.7	1.4	0.76–2.55	1.8	0.86–3.80
General farmers	5	8.5	9	5.6	1.6	0.51–4.88	1.4	0.41–4.78
Spinners, weavers, textile workers, upholsterers	9	15.3	24	14.8	1.0	0.45–2.37	1.1	0.46–2.66
Jewelers, musical instrument and other production workers	6	10.2	6	3.7	2.9	0.91–9.43	2.3	0.68–7.99
Station, engine, heavy equipment operators, freight handlers	9	15.3	12	7.4	2.2	0.89–5.62	2.5	0.94–6.58

[a] Only occupational categories with ≥5 cases were included for each gender.
[b] The conditional logistic regression model included age and region of residence.

Table 3. Subject distribution, odds ratios (OR), and 95% confidence intervals (95% CI) for uveal melanoma by industrial branches according to the European Industrial Classification of Occupations (NACE) in the pooled analyses and the gender of the subjects.

	Cases		Referents		Unadjusted		Adjusted [b]	
Gender [a]	N	%	N	%	OR	95% CI	OR	95% CI
Male								
Agriculture, forestry, hunting, fishing	7	11.9	23	7.3	1.7	0.69–4.14	1.4	0.51–3.60
Mining	11	18.6	31	9.9	2.1	0.98–4.41	1.9	0.81–4.66
Food industry	7	11.9	12	3.8	3.4	1.27–8.91	3.4	1.08–10.5
Chemical and pharmaceutical industry	9	15.3	15	4.8	3.6	1.48–8.55	2.8	1.01–7.78
Office goods manufacturing, electro and precision working	6	10.2	24	7.7	1.4	0.53–3.49	1.9	0.62–5.96
Wholesale trading and intermediates	6	10.2	32	10.2	1.0	0.40–2.49	1.3	0.49–3.54
Retail trading	6	10.2	33	10.5	1.0	0.38–2.40	0.8	0.27–2.26
Transport	9	15.3	43	13.7	1.1	0.52–2.46	1.4	0.58–3.22
Landed property services, business services	8	13.6	39	12.5	1.1	0.49–2.49	0.8	0.34–2.08
Female								
Agriculture, forestry, hunting, fishing	6	10.2	14	8.6	1.2	0.44–3.26	1.1	0.39–3.25
Textile production, manufacturing	10	16.9	21	13.0	1.4	0.60–3.10	1.6	0.66–3.93
Paper, editorial and printing industry	5	8.5	11	6.8	1.3	0.42–3.81	1.8	0.55–5.71
Machine production	6	10.2	8	4.9	2.2	0.72–6.52	3.2	0.96–10.7
Office goods manufacturing, electro and precision working	5	8.5	13	8.0	1.1	0.36–3.11	1.3	0.40–3.89
Wholesale trading and intermediates	10	16.9	17	10.5	1.7	0.75–4.03	1.7	0.68–4.31
Retail tradings	18	30.5	55	34.0	0.9	0.45–1.62	0.8	0.41–1.64
Catering trade	8	13.6	12	7.4	2.0	0.76–5.04	2.3	0.85–6.19
Landed property services, business services	11	18.6	17	10.5	1.9	0.86–4.44	2.1	0.83–5.40
Health and veterinary sector	12	20.3	16	9.9	2.3	1.03–5.24	2.4	0.97–5.71
House making	12	20.3	26	16.0	1.3	0.62–2.85	1.3	0.64–3.50

[a] Only occupational categories with ≥5 cases were included for each gender.
[b] The conditional logistic regression model included age and region of residence.

Table 4. Subject distribution, odds ratios (OR), and 95% confidence intervals (95% CI) for uveal melanoma by occupational category according to the job-specific questionnaire classification in the pooled analyses and the gender of the subjects.

	Cases		Referents		Unadjusted		Adjusted [b]	
Gender [a]	N	%	N	%	OR	95% CI	OR	95% CI
Male								
Cooking	6	10.2	8	2.6	4.3	1.44–12.8	5.6	1.66–19.1
Farming	7	11.9	21	6.7	1.9	0.76–4.61	1.4	0.50–3.77
Working with farm animals	6	10.2	14	4.5	2.4	0.89–6.54	1.5	0.47–4.54
Welding, brazing, soldering	13	11.9	101	32.3	0.6	0.31–1.15	0.9	0.43–1.76
Builder, stonemason, plasterer	14	16.9	46	14.7	1.8	0.92–3.54	1.4	0.64–2.99
Chemical industry	5	8.5	15	4.8	1.8	0.64–5.25	1.9	0.57–6.34
Metal working	11	18.6	101	32.3	0.5	0.24–0.97	0.6	0.30–1.29
Female								
Health care	9	15.2	16	9.9	1.6	0.68–3.93	2.1	0.71–6.02
Cooking	11	18.6	29	17.9	1.1	0.49–2.26	1.1	0.40–3.30
Farming	6	10.2	15	9.3	1.1	0.41–3.00	0.8	0.36–1.81
Working with farm animals	5	8.5	13	8.0	1.1	0.36–3.11	0.9	0.42–1.80

[a] Only categories with ≥5 cases were included for each gender.
[b] The conditional logistic regression model included age and region of residence.

also showed a high risk for uveal melanoma among male cooks, and Vågerö et al (36) reported an increased proportional registration ratio for ocular melanoma for female "kitchen hands" (36). Cooking fumes may be responsible for the higher risk, or, alternatively, exposure to radiation from microwaves, strong light from incandescent ovens, or infrared radiation as has been postulated by Guenel et al (17).

Various studies have found increased risks for farmers (14, 18–21) and chemical workers (13, 25, 26). Yet

Table 5. Consistency of the adjusted odds ratios between the population (P) and hospital (H) case-referent studies for the International Standard Classification of Occupations (ISCO), the European Industrial Classification of Occupations (NACE), and the job-specific questionnaire classification (JSQ) for both genders. (Adj OR = adjusted odds ratio, Ref = referents)

Occupational category	ISCO						NACE						JSQ					
	Population			Hospital			Population			Hospital			Population			Hospital		
	Cases	Ref	Adj OR [a]	Cases	Ref	Adj OR [a]	Cases	Ref	Adj OR [a]	Cases	Ref	Adj OR [a]	Cases	Ref	Adj OR [a]	Cases	Ref	Adj OR [a]
Chemical [b]	No cases			3	2	3.0	4	12	2.8	8	11	1.6	No cases			5	4	4.0
Farming [c]	2	14	1.1	10	10	1.8	3	20	1.4	10	17	1.2	2	20	0.8	11	16	1.3
Food [d]	1	5	2.5	3	3	2.8	4	26	1.1	7	9	1.5	5	21	2.0	12	16	2.2
Mining [e]	4	13	2.9	6	10	1.5	5	19	3.1	7	15	1.2	.	.	.	.	.	.
Health [f]	4	14	2.7	5	9	0.8	2	18	0.7	10	16	1.2	4	18	1.8	6	11	0.9

[a] The conditional logistic regression model included age and region of residence.
[b] Chemical, rubber and plastic workers (ISCO); chemical and pharmaceutical industry (NACE); chemical industry (JSQ).
[c] General farmers (ISCO); agriculture, forestry, hunting and fishing (NACE); farming (JSQ).
[d] Food, beverage and tobacco processors (ISCO); food industry (NACE); cooking (JSQ).
[e] Miners (ISCO); mining (NACE); no mining category (JSQ).
[f] Medical, dental, pharmaceutical and veterinary workers (ISCO); health and veterinary sector (NACE); health care (JSQ).

these analyses showed nonsignificantly elevated risks for workers in the chemical industry and farmers consistently across classifications.

Miners or mining also had increased risks. However, one study made reference to "miners, quarrymen" and found no elevated risks whatsoever (36).

In our study, the occupational categories that included welders did not show positive associations, as mentioned before (13, 15–17). Given that the proportion of welders in the study base was too small for an independent analysis, welders were dichotomized as having ever welded, but still no association was found (OR 1.3, 95% CI 0.6–2.5).

The highest risks for women were found for "station, engine, and heavy equipment operators and freight handlers" (ISCO) and "machine production" (NACE). Elevated risks for women working in "bus and truck services" and "fabricated metal products manufacturing" have been documented for eye cancer in a study from the United States among women in the workplace (37). Guenel et al (17) also showed increased risks among female "metal workers" and "material handling operators".

Women working in health care presented consistently high risks across the three classifications employed. This finding has also been previously reported (13, 38) and has been thought to be the result of referral bias (13).

The low response rate of the referents in the population study, a problem frequently faced in Germany (29), limited the interpretation of the results. Biased estimates could have occurred if nonparticipation were associated with a higher prevalence of exposure to occupations. Selection bias cannot be ruled out since meaningful comparisons between participating and nonparticipating referents could not be made because very few nonparticipating referents filled out the short questionnaire designed for this purpose.

The skewed gender distribution of the population reference responders was the result of the matching effect rather than a selection bias. The proportion of male referents was larger in the population study because the reference group was used for several rare cancers and its size was determined by the most frequent cancer in each stratum (eg, testicular cancer).

Another limitation relates to the exposure assessment, as it relied on an indirect source with which to infer the exposure status for individual persons. Occupational title was utilized as a surrogate for exposure. We used the ISCO and NACE classifications, as they allow a more-or-less precise identification of the work done by the workers, and by inference of the risks involved, and because they are major references for international comparisons. The degree to which the misclassification of recalled job periods and occupations could have occurred was largely related to the complexity of the individual persons' occupational histories. To reduce this complexity, we attempted to conduct personal interviews. The overall proportion of face-to-face interviews in the pooled analyses was 76.3% and 80.9% for the cases and referents, respectively.

Although misdiagnosis may have occurred for the nonhistologically confirmed cases, the rate of false-positive diagnoses has been reported to be as low as 0.5% when done in experienced centers (5, 39), such as in those involved on this study.

The analyses were able to replicate findings from earlier investigations. For instance, the risk of uveal melanoma was significantly higher for persons with light-color eyes than it was for those with dark-color

eyes (OR 2.9, 95% CI 1.5–5.6), as previously reported (10, 36, 40). This finding supports the trustworthiness of the presented results.

The consistency between studies was assessed by comparing the odds ratios for five relevant occupational groups according to the revised literature. Except for health, most of the estimates pointed in the same direction. Although it was not possible to stratify the results by gender due to sample size constraints, these findings also enhanced the validity of the results.

The relatively small number of cases and the dilution of the effect by pooling jobs in an occupational category could have been responsible for the lack of statistical significance. In addition, with a nondifferential misclassification of the exposure status in a dichotomous variable, a bias towards the null is expected to occur and lead to lack of significant results. Conversely, multiple testing might have induced a bias raising the likelihood that some associations could have appeared by chance.

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