

The Possible Role of Radiofrequency Radiation in the Development of Uveal Melanoma

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There are few epidemiologic studies dealing with electromagnetic radiation and uveal melanoma. The majority of these studies are exploratory and are based on job and industry titles only. We conducted a hospital-based and population-based case-control study of uveal melanoma and occupational exposures to different sources of electromagnetic radiation, including radiofrequency radiation. We then pooled these results. We interviewed a total of 118 female and male cases with uveal melanoma and 475 controls matching on sex, age, and study regions. Exposure to radiofrequency-transmitting devices was rated as (a) no radiofrequency radiation exposure, (b) possible exposure to mobile phones, or (c) probable/certain exposure to mobile phones. Exposures were rated independently by two of the authors who did not know case or control

status. We used conditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs). We found an elevated risk for exposure to radiofrequency-transmitting devices (exposure to radio sets, OR = 3.0, 95% CI = 1.4–6.3; probable/certain exposure to mobile phones, OR = 4.2, 95% CI = 1.2–14.5). Other sources of electromagnetic radiation such as high-voltage lines, electrical machines, complex electrical environments, visual display terminals, or radar units were not associated with uveal melanoma. This is the first study describing an association between radiofrequency radiation exposure and uveal melanoma. Several methodologic limitations prevent our results from providing clear evidence on the hypothesized association. (Epidemiology 2001;12:7–12)

Keywords: uveal melanoma, eye neoplasms, radio waves, electromagnetic fields, case-control studies, Germany.

Although it is a rare disease, uveal melanoma of the eye is the most common primary intraocular malignancy in adults, with an incidence rate of up to 1.0 per 100,000 person-years (age-standardized, world standard) in Europe.¹ Only a few consistent risk factors have been identified for this disease. One set of uncommon risk factors includes predisposing diseases such as dysplastic nevus syndrome, atypical ocular nevi, and ocular and oculardermal melanocytosis.^{2,3} Another set of host risk factors comprises ancestry, light skin, and iris pigmentation.^{3–6} In addition, a number of environmental factors are weakly or inconsistently associated with uveal mel-

anoma. Occupation may be also relevant and may include chemical work,^{7,8} arc welding,⁸ and agriculture and farming work.^{9,10}

Few epidemiologic studies dealing with electromagnetic radiation and uveal melanoma have been published. The majority of these studies are exploratory and are based on job and industry titles only. In a cancer registry study in England and Wales, Swerdlow¹¹ found an increased risk for eye cancer among electrical and electronics workers in particular. This finding could not be reproduced in a small case-control study conducted by Gallagher *et al.*⁴ Holly *et al.*⁸ found a twofold increased risk of uveal melanoma among subjects with occupational exposure to microwaves and radar units.

There is currently much uncertainty about the role, if any, of radiofrequency transmitted by radio sets or mobile phones in human carcinogenesis. The assessment of the potential association of radiofrequency radiation (RFR) and cancer risk is hampered by uncertainties about effective electromagnetic frequency ranges, the lack of a clear biological mechanism, and difficulties of exposure assessment. To date, no study has been published concerning intraocular melanoma in relation to occupational exposures to electromagnetic fields, including RFR as transmitted by radio sets or wireless telephones.

Electromagnetic waves with frequencies of 300 kHz to 300 GHz are called RFR. Typical occupational sources

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TABLE 1. Methodological Features of the Two Case-Control Studies on Uveal Melanoma

	Population-Based Study	Hospital-Based Study
Cases		
Diagnosis	Primary incident uveal melanoma, reviewed by a reference pathologist	Primary incident uveal melanoma treated at the University of Essen
Period of diagnosis	7/1/95–12/31/97	12/1/96–3/31/98
Age at diagnosis	35–69 years	35–74 years
Region of residence	Bremen, Essen, Hamburg, Saarbrücken, Saarland	Federal State of North-Rhine Westphalia
Case ascertainment	Active reporting system of clinical and pathological departments; in addition, cancer registry reports in Hamburg	Active reporting at the Division of Ophthalmology, University of Essen
Interviewed cases (N) and Response proportion (%) [*]	37 (84%)	81 (88%)
Main reasons for nonparticipation	Refusal 11% No contact 5%	Refusal 8% No contact 2% Too ill 2%
Controls		
Sampling frame	Mandatory lists of residence	Patients with newly diagnosed benign disease of the posterior eye segment, treated at the University of Essen, excluding occupational accidents involving the eye
Matching factors	Age (5-year age bands) Sex Region (Bremen, Essen, Hamburg, Saarbrücken, and Saarland)	Age (5-year age bands) Sex Region [Ruhrarea, non-Ruhrarea southern part (<100,000 or ≥100,000 inhabitants) and non-Ruhrarea northern part (<100,000 or ≥100,000 inhabitants)]
Interviewed controls (N) and response proportion (%) [*]	699 (48%)	148 (79%)
Main reasons for nonparticipation	Refusal 31% No contact 8% Other reasons 5%	Refusal 13% No contact 4% Other reasons 4%

* Calculation of response proportions according to Slattery *et al.*¹⁴

transmitting RFR in Germany include walkie-talkies in the military and security services and in plants; radio sets on ships, transporters, freight trains, and police cars; and wireless phones, including cellular phones [C-net, 450–465 MHz (since the 1990s); D-net, 890–960 MHz; and E-net, 1710–1800 MHz] and cordless phones (800–1900 MHz) with different modulation types.^{12,13}

Here, we report findings from a hospital-based and population-based case-control study that used the same standardized questionnaires about potential risk factors, including electromagnetic radiation, for uveal melanoma. The studies produced findings for several potential risk factors. This report concerns the association of RFR with the risk for uveal melanoma.

Subjects and Methods

Between 1994 and 1997, our research group participated in a multinational population-based case-control study on occupational risk factors for eight rare cancers including uveal melanoma, mycosis fungoides, cancer of

the small intestine and bones, cancer of the bile duct and breast in males, thymoma, and testicular cancer, the latter only in Germany. During the field phase of this study we started an additional hospital-based case-control study at the Division of Ophthalmology, University of Essen, using the same questionnaire and study personnel. The University of Essen is a referral center for tumors of the eye and treats about 250–300 patients with uveal melanoma per year. The methodologic features of the two studies are presented in Table 1.

Controls in the population-based study were selected randomly from mandatory lists of residence that cover the total population of the local districts. The lists of residence are regarded as the most complete sampling frame for population-based studies in Germany.¹⁵ For each case, about four potential controls matching on sex, age (5-year groups), and region of residence (five regions) were selected and contacted by letters, phone calls, and home visits if necessary. The number of controls was determined by the stratum-specific maximum number of any of the eight rare cancers included in the study. The matching resulted in matching ratios for the uveal melanoma study of up to ten controls per case, because other cancers were more common than uveal melanoma. Owing to the inclusion of testicular cancer in Germany, the number of matching male controls in the uveal

melanoma study exceeded that of matching female controls. We excluded 372 control interviews from the analysis of the population-based study because these controls matched to the other rare cancer cases only.

The major diagnoses among the hospital controls were retinal detachment and defects (32%), degeneration of the macula (18%), retinal vascular occlusion (14%), diabetic retinopathy (10%), and others (26%). No hospital control suffered from an occupational accident involving the eye.

EXPOSURE ASSESSMENT

Data were collected from study participants by interviewers who were trained specifically for this project and were monitored throughout the study to ensure uniform quality of the questionnaire data. They were unaware of specific study hypotheses as they administered structured questionnaires. Interviews took about 70 minutes (median).

The interview topics included medical history, phenotypic characteristics, life-style factors, details of the

TABLE 2. Characteristics of Cases and Controls Included in the Analyses

	Pooled Analysis		Population-Based Study		Hospital-Based Study	
	Controls	Cases	Controls	Cases	Controls	Cases
Interviewed subjects (N)	475	118	327	37	148	81
Interview modus (%)						
Face-to-face interview	81.6	78.8	93.6	89.2	55.4	74.1
Telephone interview	18.3	21.2	6.4	10.8	44.6	25.9
Gender (%)						
Men	65.9	50.0	72.5	54.1	51.4	48.1
Women	34.1	50.0	27.5	45.9	48.6	51.9
Age at reference date (%)						
35–44	20.6	13.6	26.0	10.8	8.8	14.8
45–54	17.3	16.1	17.4	18.9	16.9	14.8
55–64	37.1	40.7	34.6	40.5	42.6	40.7
65–74*	25.1	29.7	22.0	29.7	31.8	29.6
Years at school (%)						
≤9 years	58.1	62.7	56.9	62.2	60.8	63.0
10 years	20.8	13.6	22.0	18.9	18.2	11.1
12–13 years	18.5	21.2	18.3	18.9	18.9	22.2
Other	2.5	2.5	2.8	0.0	2.0	3.7

* Population-based study only 65–69 years.

lifetime occupational history, and occupational sources of electromagnetic radiation. These sources included working close to high-voltage electric lines, electrical machines, complex electrical environments (that is, control rooms or computer rooms), and visual terminal displays. We added questions about radar units and RFR to the electromagnetic radiation section of the international questionnaire that enabled us to estimate the risk of uveal melanoma associated with these sources within the German study part. Exposed subjects were asked about the starting and ending year of exposure and details of the electromagnetic radiation sources.

Occupational exposure to RFR devices was assessed by asking subjects, "Did you use radio sets, mobile phones, or similar devices at your workplace for at least several hours per day?" Subjects who answered "yes" were asked about the beginning and ending year of exposure and about the way the RFR source was carried with the subjects. This question often helped to identify the source of RFR, because subjects gave details on the RFR sources.

The reference date for the exposure was the date of diagnosis (cases), date of first contact letter (population controls), and date of diagnosis (hospital controls). Exposures after the reference date were not considered. All information on the RFR exposure and on corresponding occupational periods (including production processes, job tasks, etc) were reviewed for all subjects who reported being exposed to RFR devices (pooled analysis; 18 cases and 55 controls). With the case-control status masked, subjects were rated by one of the authors (A. S.) as (a) exposed only to radio receivers that do not transmit RFR and therefore unexposed, (b) exposed to walkie-talkies and radio sets, (c) possibly exposed to mobile phones, and (d) probably or certainly exposed to mobile phones.

Subsequently, all subjects were reviewed and rated under similar circumstances by another author (K. H. J.), who was not aware of the other ratings. All subjects with

discrepant ratings were evaluated and the discrepancy was resolved. The interrater agreement for the ratings (a–d), as expressed by weighted kappa, was 0.78 [95% confidence interval (95% CI) = 0.67–0.88].

STATISTICAL METHODS

We applied conditional logistic regression models to calculate odds ratios (ORs) and 95% CIs.^{16,17} If cell sizes across the strata were five or lower, we calculated exact OR estimates and exact 95% CI.¹⁸ Matching factors for the conditional analysis were age (5-year groups), sex, and geographic area [population-based study, Bremen, Essen, Hamburg, Saarbrücken, and the federal state of Saarland without Saarbrücken; hospital-based study, Ruhrarea, non-Ruhrarea

southern part (<100,000 or ≥100,000 inhabitants), and non-Ruhrarea northern part (<100,000 or ≥100,000 inhabitants)]. After we estimated the ORs for the separate studies, we pooled the two studies and ran the same conditional logistic models taking the matching into account.

First, we estimated ORs without assumptions about latency periods or exposure duration. Second, we estimated ORs on the basis of exposures that started at least 5 years before the reference year. Third, we calculated ORs on the basis of exposures with durations of at least 3 years before the reference year. We used dummy coding to control for potential confounding by social class with "9 years at school or less" as the reference category.

Results

Tumors involved the choroid (98%), iris (1%), and unknown parts of the uveal tract (1%). The proportion of face-to-face interviews in the hospital-based study was lower than in the population-based study. In addition, the proportion of male controls was larger in the population-based study because the control group was used for several rare cancers and its size was determined by the most frequent cancers in each stratum. Compared with the population-based study, cases of the hospital-based study had a slightly higher and controls a slightly lower socioeconomic status as measured by the number of years at school (Table 2).

Table 3 presents the exposure prevalences and OR estimates for the different sources of electromagnetic radiation. The highest exposure prevalences were seen for electrical machines and visual display terminals. Only the effect estimates for the exposure to radio sets or mobile phones were consistently elevated across the studies. The remaining effect estimates either were close to unity or were noninformative owing to low exposure prevalences (radar units).

TABLE 3. Lifetime Exposure to Different Sources of Electromagnetic Radiation

EMF Source*	Pooled Analysis				Population-based Study				Hospital-Based Study			
	Controls	Cases	OR†	95% CI	Controls	Cases	OR	95% CI	Controls	Cases	OR	95% CI
Overall (N)	475	118			327	37			148	81		
Working close to												
High-voltage lines	6.3	2.5	0.6	0.1–2.3	7.6	5.4	0.8	0.1–3.6	3.4	1.2	0.4	0.0–4.5
Electrical machines	26.3	17.8	1.0	0.6–1.7	29.7	21.6	0.9	0.4–2.1	18.9	16.0	1.1	0.5–2.3
Complex electrical environments	14.5	8.5	0.8	0.4–1.7	15.9	10.8	1.0	0.2–3.2	11.5	7.4	0.7	0.3–2.0
Visual display terminals	24.2	20.3	1.1	0.6–1.9	27.5	27.0	1.3	0.6–3.0	16.9	7.3	0.9	0.4–2.0
Radar units	4.0	0.8	0.4	0.0–2.6	4.6	2.7	0.8	0.0–6.5	2.7	0	0	0–3.6
Radio sets or mobile phones	9.7	13.6	3.0	1.4–6.3	11.9	18.9	3.2	1.2–9.0	4.7	11.1	2.7	0.9–8.1

* EMF = electromagnetic field.

† Matched evaluation: odds ratio estimate (OR) and 95% confidence interval (95% CI).

Table 4 presents the OR estimates for uveal melanoma based on the RFR exposure rating for both studies and the pooled analysis. Overall, 46 controls (9.7%) and 16 cases (13.6%) were rated as ever having been exposed to any kind of RFR at their jobs for at least a 6-month duration and several hours per day. The lifetime prevalences were lower for both cases and controls in the hospital-based study. Only one female case and one female control (both in the hospital-based study) reported having been exposed to any RFR at their jobs. These women were rated as “probably or certainly exposed to mobile telephone.” Occupational exposures to radio sets included walkie-talkies in the military and security services and in plants and radio sets on ships, transporters, freight trains, and police cars. The median year of start of exposure was 1975 (25% percentile, 1963; 75% percentile, 1983). Twelve subjects were rated as “possibly exposed to mobile phones” because occupational information was scant or equivocal with regard to mobile phone exposure. The median year of start of

exposure was 1992 (25% percentile, 1988; 75% percentile, 1996).

Subjects probably or certainly exposed to mobile phones typically worked in the service sector as real estate agents, tax consultants, or sales representatives. The median year of start of exposure was 1993 (25% percentile, 1990; 75% percentile, 1995) and was considerably later compared with subjects exposed to radio sets. The comparatively late onset of exposure to mobile phones may be explained by the recent widespread introduction of mobile phones to the German market.

Occupational exposure to radio sets was associated with an increased risk for uveal melanoma in both studies and under different exposure-disease assumptions. The separate analyses for the exposure categories “possibly exposed to mobile phones” and “probably or certainly exposed to mobile phones” were not informative within the studies because the exposure prevalences were too low in these categories. The combined analysis of these two exposure categories showed consistently

TABLE 4. Estimated Odds Ratios of Uveal Melanoma Associated with Radio Frequency Radiation (RFR)

RFR Exposure Condition	Pooled Analysis				Population-Based Study				Hospital-Based Study			
	Controls	Cases	OR*	95% CI	Controls	Cases	OR	95% CI	Controls	Cases	OR	95% CI
Overall (N)	475	118			327	37			148	81		
Radio set exposure (%)												
Ever exposed	4.4	7.6	3.3	1.2–9.2	5.5	13.5	4.6	1.0–19.2	2.0	4.9	1.8	0.3–14.3
≥5 years before RD†	3.8	7.6	3.3	1.2–9.2	4.6	13.5	4.5	1.0–17.5	2.0	4.9	2.0	0.3–15.8
≥3 years duration‡	3.8	5.9	2.5	0.8–7.7	4.6	10.8	3.8	0.7–16.9	2.0	3.7	1.3	0.1–11.4
Possible mobile phone exposure (%)												
Ever exposed	2.1	0.8	1.1	0.0–10.1	2.1	2.7	3.9	0.1–52.9	2.0	0	0	0–10.1
≥5 years before RD	1.3	0.8	2.9	0.0–42.9	1.5	2.7	6.8	0.1–145.9	0.7	0	0	0–130.0
≥3 years duration	1.7	0.8	1.6	0.0–19.1	1.8	2.7	5.8	0.1–129.7	1.4	0	0	0–20.5
Probable/certain mobile phone exposure (%)												
Ever exposed	3.2	5.1	4.2	1.2–14.5	4.3	2.7	1.6	0.0–16.5	0.7	6.2	10.1	1.1–484.4
≥5 years before RD	0.8	2.5	4.9	0.5–51.0	1.2	0	0	0–34.8	0	3.7	∞	0.7–∞
≥3 years duration	1.7	4.2	3.8	0.8–19.7	2.1	0	0	0–16.5	0.7	6.2	10.1	1.1–484.4
Possible/probable/certain mobile phone exposure (%)												
Ever exposed	5.3	5.9	2.8	1.0–7.9	6.4	5.4	2.3	0.2–14.2	2.7	6.2	3.2	0.6–17.0
≥5 years before RD	2.1	3.4	4.1	0.7–24.0	2.8	2.7	2.7	0.1–32.2	0.7	1.3	6.3	0.5–341.4
≥3 years duration	3.4	5.1	3.0	0.9–9.7	4.0	2.7	1.8	0.0–19.0	2.0	6.2	3.9	0.7–27.2

* Matched evaluation: odds ratio estimate (OR) and 95% confidence interval (95% CI).

† Exposure started at least 5 years before reference date (RD).

‡ Exposure for at least 3 years of occupation.

elevated OR estimates across the studies and across different exposure definitions (Table 4).

The adjustment for socioeconomic status as measured by years at school did not alter our results. Light iris color (blue, gray, green, or light brown) as compared with dark iris color (dark brown) was associated with an increased risk of uveal melanoma (pooled OR = 2.9, 95% CI = 1.5–5.6). People with light hair color (red or blonde) at age 20 years showed an increased risk for uveal melanoma (pooled OR = 1.4, 95% CI = 0.9–2.3). The control for iris and hair color did not change our results substantially (data not shown).

Discussion

We found an increased risk of uveal melanoma in relation to RFR as transmitted by radio sets and mobile phones. The association between electromagnetic fields and uveal melanoma was limited to RFR. Analyses based on different RFR exposure definitions [minimum exposure duration (3 years) and RFR exposure beginning at least 5 years before the diagnosis of the disease] changed the magnitudes of effect estimates to some extent but did not change our interpretation of the data. Furthermore, we restricted our analyses to face-to-face interviews, to interviews that were rated as reliable by the interviewers, or to both and found that the effect estimates were stable (data not shown). Adjustment for social class as measured by highest degree of schooling did not change our results.

The exposure prevalences for sources of electromagnetic radiation in the control groups were consistently higher in the population-based study as compared with the hospital-based study. After adjusting for age and gender, we found that the prevalence differences in the control group were mainly explained by differences in the sex and age distributions of the control groups (for the population-based and hospital-based study, respectively, the proportions of males were 73% and 51%, and median ages were 56 and 61 years).

The analysis of the German testicular cancer study (269 interviewed cases and 797 interviewed controls), which used the same study methodology and questionnaire as the population-based eye melanoma study, showed OR estimates close to unity for all sources of electromagnetic fields (data not shown). Thus, the RFR finding within the uveal melanoma study is specific for this tumor site.

It is still unclear whether RFR exposures too weak to increase temperature measurably could have biological effects.¹⁹ Biological interaction mechanisms are not necessarily thermal; however, many studies have suggested that RFR exposure at low levels that do not challenge thermoregulation or produce any change in cell temperature may have biological effects, but they have either not been consistently replicated or else their relevance for human health cannot be adequately assessed using information currently available. A hypothesized mode of action is that RFR might promote (that is, speed up) the development of cancer that has been caused by other agents.²⁰

How could RFR act as a promoter for uveal melanoma? Ocular melatonin is synthesized in the retina and the ciliary body and is also found in the aqueous humor.²¹ Experimental studies on cultured human uveal melanoma cells indicate that melatonin inhibits the growth of uveal melanoma cell lines in a dose-dependent manner and therefore has an antiproliferative effect.²² The following explanation is speculative: if RFR decreased the amount of ocular melatonin, it would promote the development of uveal melanoma.

The results of the present study do not provide a firm indication of an effect on uveal melanoma for several reasons. If cases tend to overreport use of radio sets in their work place relative to controls, the OR estimates would be biased upward. Study subjects, however, were unlikely to be aware of the hypothesis, because no study on the relation between radio set use and uveal melanoma has been previously reported. We selected controls in the hospital-based case-control study from the same division as the cases, with benign eye diseases of the posterior eye segment that are diagnosed in a way similar to that for uveal melanoma. This choice may have reduced recall and interviewer bias. In addition, among the different sources of occupational electromagnetic radiation that were asked, the association was limited to radio sets and mobile phones. If recall bias would explain the association between RFR and uveal melanoma, it is implausible that the relative risk estimates for visual display terminals would not be increased, because there are public concerns regarding display terminals and eye diseases.

Our questionnaire, which dealt with many potential risk factors, not only for uveal melanoma, was not originally designed for a detailed exposure history of RFR. It therefore contained few questions about RFR. We did not explicitly ask the subjects which specific kinds of RFR devices they used (including electromagnetic properties of the devices such as signal frequency, modulation type, etc) and how many hours per day they actively used the RFR devices. Also, we did not study the laterality of the tumor in relation to the hand that usually used the RFR device.

Our exposure rating is another limitation of the study. About 12 subjects (19% of all exposed subjects) were rated as only "possibly exposed to mobile phones" because the information was scanty or equivocal. The similarity of the median start year of exposure for "subjects possibly exposed" (1992) and "subjects probably or certainly exposed to mobile phones" (1993) is a rough indicator of validity of the assignment. Low exposure prevalences of mobile phone use and almost no female cases and controls exposed further limit our study. Two other methodologic aspects might have influenced our results. Nonresponse in the population-based control group might have biased our results if nonparticipation was associated with a higher prevalence of radio set or mobile phone use. In addition, the selection criteria for the hospital-based control group might have biased our results if the prevalence estimates of RFR exposure are underestimated.

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