Mobile Phone Use and Risk of Uveal Melanoma: Results of the Risk Factors for Uveal Melanoma Case-Control Study

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We recently reported an increased risk of uveal melanoma among mobile phone users. Here, we present the results of a case–control study that assessed the association between mobile phone use and risk of uveal melanoma. We recruited 459 uveal melanoma case patients at the University of Duisburg-Essen and matched 455 case patients with 827 population control subjects, 133 with 180 ophthalmologist control subjects, and 187 with 187 sibling control subjects. We used a questionnaire to assess mobile phone use and estimated odds ratios (ORs) and 95% confidence intervals (95% CIs) of risk for uveal melanoma using conditional logistic regression. Risk of uveal melanoma was not associated with regular mobile phone use (OR = 0.7, 95% CI = 0.5 to 1.0 vs population control subjects; OR = 1.1, 95% CI = 0.6 to 2.3 vs ophthalmologist control subjects; and OR = 1.2, 95% CI = 0.5 to 2.6 vs sibling control subjects), and we observed no trend for cumulative measures of exposure. We did not corroborate our previous results that showed an increased risk of uveal melanoma among regular mobile phone users.

We recently reported an increased risk of uveal melanoma for subjects who reported frequent use of mobile phones at work (1). However, this study suffered from incomplete exposure assessment and relatively low statistical power due to low exposure prevalence, which triggered some discussion about the validity of these findings (2–4). Uncertainty exists about the role, if any, of radio waves transmitted by radio sets or mobile phones in human carcinogenesis (5,6). Radio waves at levels below those that cause detectable harmful heating do not have sufficient energy to destabilize electron configurations within DNA molecules. Thus, there is no direct link between exposure to radio waves and genotoxic mechanisms, such as DNA mutations, DNA strand breaks, or other genetic lesions (6). The assessment of the potential association of radio frequency radiation and cancer risk is hampered by uncertainties about effective electromagnetic frequency ranges and by difficulties of exposure assessment. We conducted a case-control study that included three control groups, the Risk Factors for Uveal Melanoma Study, between September 25, 2002, and September 24, 2004, at the University of Duisburg-Essen's referral center for eye cancers. Details of the study protocol and uveal melanoma incidence rates have been published elsewhere (7–9). Subjects were eligible when they were first diagnosed with uveal melanoma if they were aged 20–74 years, lived in Germany, and were proficient in the German language. Of 486 eligible patients, 459 (94%) participated in the study. Population-based control subjects were selected from the census of the local districts and were matched to case patients by age (5-year age groups), sex, and region of residence. Sibling control subjects who were within 10 years of the age of the case patient were recruited after the case patient interviews. Ophthalmology control subjects were recruited from practices of the same opthalmologists who had referred the uveal melanoma case patients and had to have a newly diagnosed benign disease of the eye. However, recruitment of ophthalmology control subjects became difficult because of lack of support by the ophthalmologists. We therefore stopped recruiting ophthalmologists' control subjects for incident case patients during the second half of the recruitment period. Response proportions were 94% for the case patients, 57% for the population and sibling control subjects, and 52% for the ophthalmologists' control subjects. Further details of the study characteristics are presented in Supplementary Table 1 (available online). Overall, 282 of 683 population control subjects (41%) who refused to participate completed a short questionnaire allowing the comparison of mobile phone use between participating and these 282 nonparticipating population control subjects. Trained study personnel conducted standardized computer-assisted telephone interviews with the participants. For the detailed assessment of mobile phone use, we used the questionnaire of the Interphone study (10–12). The study was approved by the ethical review board of the University of Duisburg-Essen. We classified subjects as never users, sporadic users (subjects who had used a mobile phone at least once, but did not use one on a regular basis), or regular users. Among regular users, we estimated the lifetime cumulative number of incoming and outgoing phone calls and the duration of phone calls. We used the same categories of the cumulative exposure measures as the German part of the Interphone study (10). We used conditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) accounting for the matched factors. Interval estimates did not account for the overlapping case patient membership. Detailed methods of the study are presented in the Supplementary Methods (available online).

We recruited 459 incident uveal melanoma case patients (mean age ± SD, 58 ± 11

years). As expected, the majority of case patients resided in North Rhine–Westphalia, the most populous federal state in Germany. The number of case patients declined in proportion to the distance between the region where they resided and the city of Essen (North Rhine–Westphalia), where the referral center for eye tumors was located (Table 1). Although the population-based analysis of persons who regularly used mobile phones revealed odds ratios that suggested a decreased risk of uveal melanoma with increasing use, risk estimates that were based on ophthalmologist and sibling control analyses did not show any association (OR = 0.7, 95% CI = 0.5 to 1.0 vs population control subjects; OR = 1.1, 95% CI = 0.6 to 2.3 vs ophthalmologist control subjects; and OR = 1.2, 95% CI = 0.5 to 2.6 vs sibling control subjects). Surrogate measures of cumulative dose, including cumulative years of regular use, cumulative number of phone calls, and cumulative duration of phone calls, did not show a clear association with risk of uveal melanoma (Table 2).

Odds ratios that were estimated with varying lag times that ignored mobile phone exposure 3–10 years before the reference date showed no association between mobile phone use and risk of uveal melanoma. Also, stratification of the analyses by eye color, social status, or age did not substantially modify the odds ratios (data not shown). The use of radio sets overall or the use of subtypes of radio sets (eg, walkie talkies, citizen's band radios, or other devices) was not associated with the risk of uveal melanoma (Supplementary Table 2, available online). Duration–response analyses showed no association between radio set use and risk of uveal melanoma (data not shown).

The null result of this study is inconsistent with the result of our initial study (1), which reported an increased risk of uveal melanoma among subjects who were exposed in the workplace to either mobile phones or radio sets. This earlier study had only 118 case patients and used only a crude exposure assessment. In particular, exposure assessment was restricted to the workplace and to intensive regular exposure at a time when mobile phone technology was not very common. It may be that case patients differed from control subjects in ways that were not controlled in the analysis, given that they had this unusual high-intensity exposure to mobile phones and radio sets in an era when such exposures were rare. This study included 459 case patients and used a very detailed exposure assessment, which included measurement

CONTEXT AND CAVEATS

Prior knowledge
Although there is no direct link between exposure to radio waves and the genotoxic mechanisms that lead to cancer, studies to address the association between use of cellular telephones and cancer risk have been performed.

Study design
Case-control study of uveal melanoma patients in Germany using three groups of control subjects: population-based, siblings of patients, and ophthalmology control subjects.

Contributions
No association between cellular telephone use and uveal melanoma risk was observed.

Implications
Using cellular telephones is not associated with increased risk of uveal melanoma.

Limitations
Subjects who agreed to participate in the study were more likely to regularly use cellular telephones than subjects who did not agree to participate.

From the Editors

Table 1. Characteristics of the interviewed uveal melanoma case patients and control subjects of the Risk Factors for Uveal Melanoma Case-Control Study, Germany, 2002–2004*

Characteristic	Population control subjects		Ophthalmologist control subjects†		Sibling control subjects‡	
	Control subjects, % (n = 827)	Case patients, % (n = 455)	Control subjects, % (n = 180)	Case patients, % (n = 133)	Control subjects, % (n = 187)	Case patients, % (n = 187)
Sex						
Male	55	53	57	59	43	51
Female	45	47	43	41	57	49
Age, y						
20–34	4	4	2	3	4	7
35–44	9	9	8	8	15	12
45–54	17	17	14	16	20	22
55–64	37	35	34	32	39	32
65–74	33	35	41	41	22	27
Place of residence						
North Rhine region	16	16	21	19	17	19
North Rhine- Westphalia	44	41	41	43	38	40
Midwestern region	20	20	20	21	18	19
Southern region	18	19	17	17	18	19
Eastern region	3	3	1	1	7	3
Region missing	0	0	0	0	2	0

* Risk Factors for Uveal Melanoma. Percentages may not add to 100 due to rounding error.

† Ophthalmologists' control subjects were recruited only for case patients who were diagnosed the first year of case patient recruitment (until September 24, 2003).

‡ Case patients without eligible siblings could not contribute control subjects to the study.

Table 2. Estimated odds ratios of uveal melanoma associated with mobile phone use*

Use	Population control subjects			Ophthalmologists control subjects			Sibling control subjects		
	Control subjects, % (n = 827)	Case patients, % (n = 455)	OR (95% CI)	Control subjects, % (n = 180)	Case patients, % (n = 133)	OR (95% CI)	Control subjects, % (n = 187)	Case patients, % (n = 187)	OR† (95% CI)
Mobile phone use									
Never	20	24	1.0 (Referent)	24	23	1.0 (Referent)	17	14	1.0 (Referent)
Sporadic	44	47	0.9 (0.7 to 1.3)	46	47	1.2 (0.6 to 2.1)	48	49	1.3 (0.7 to 2.6)
Regular‡	36	30	0.7 (0.5 to 1.0)	30	31	1.1 (0.6 to 2.3)	35	37	1.2 (0.5 to 2.6)
Missing	0	0		0	0		1	0	
Cumulative years of use									
Never	20	24	1.0 (Referent)	24	23	1.0 (Referent)	17	14	1.0 (Referent)
Sporadic	44	47	0.9 (0.7 to 1.3)	46	47	1.2 (0.7 to 2.2)	48	49	1.3 (0.6 to 2.5)
Regular ≤4 y	19	17	0.8 (0.5 to 1.2)	19	17	1.0 (0.5 to 2.2)	18	21	1.4 (0.6 to 3.3)
Regular 5–9 y	14	11	0.6 (0.4 to 1.0)	8	10	1.3 (0.5 to 3.2)	13	13	1.1 (0.4 to 2.8)
Regular ≥10 y	3	2	0.6 (0.3 to 1.4)	3	4	1.5 (0.3 to 6.6)	3	2	0.7 (0.2 to 3.0)
Regular, missing	1	0		1	0		1	0	
Cumulative calls									
Never	20	24	1.0 (Referent)	24	23	1.0 (Referent)	17	14	1.0 (Referent)
Sporadic	44	47	0.9 (0.7 to 1.3)	46	47	1.2 (0.6 to 2.1)	48	49	1.3 (0.7 to 2.6)
Regular ≤1176	14	13	0.8 (0.5 to 1.2)	14	16	1.2 (0.5 to 2.8)	14	15	1.3 (0.5 to 3.2)
Regular >1176 to ≤4350	10	6	0.6 (0.3 to 1.0)	8	4	0.5 (0.2 to 1.5)	9	9	1.2 (0.5 to 3.2)
Regular >4350	11	10	0.8 (0.5 to 1.3)	7	11	2.1 (0.7 to 6.4)	12	12	1.1 (0.4 to 3.1)
Missing	2	0.4	0	1	0		1	0	
Cumulative duration									
Never	20	24	1.0 (Referent)	24	23	1.0 (Referent)	17	14	1.0 (Referent)
Sporadic	44	47	0.9 (0.7 to 1.3)	46	47	1.1 (0.6 to 2.1)	48	49	1.3 (0.7 to 2.6)
Regular ≤44 h	15	11	0.6 (0.4 to 1.0)	13	14	1.2 (0.6 to 2.8)	16	12	0.8 (0.3 to 2.1)
Regular >44 to ≤195 h	8	9	0.9 (0.5 to 1.5)	8	7	0.9 (0.3 to 2.4)	8	11	1.7 (0.7 to 4.5)
Regular >195 h	12	10	0.8 (0.5 to 1.3)	8	10	1.2 (0.4 to 3.6)	11	13	1.5 (0.5 to 4.3)
Missing	2	0.4		1	0		1	0	
Regular use ≥5 y before reference date									
No	81	86	1.0 (Referent)	87	85	1.0 (Referent)	82	83	1.0 (Referent)
Yes	18	14	0.7 (0.5 to 1.0)	13	15	1.1 (0.5 to 2.3)	17	17	0.8 (0.4 to 1.5)
Missing	1	0		1	0		1	0	
Regular use ≥10 y before reference date									
No	96	97	1.0 (Referent)	97	96	1.0 (Referent)	96	97	1.0 (Referent)
Yes	3	3	0.8 (0.4 to 1.7)	3	4	1.7 (0.5 to 6.5)	3	3	1.6 (1.0 to 2.5)
Missing	1	0		1	0		1	0	

* Odds ratios were based on conditional logistic regression accounting for matching variables age, sex, and residence (population controls only); all mobile phone exposures up to the reference date; no distinction between analog or digital technique. Percentages may not add to 100 due to rounding error. CI = confidence interval; OR = odds ratio.

† Also adjusted for sex.

‡ For at least 6 months and more than once per week.

of total exposure to mobile phones and radio sets in an era when such exposures were more common. Systematic uncontrolled differences between case patients and control subjects therefore seem far less likely to occur.

A potential limitation of this study is selection bias. We used information from the questionnaires of a subgroup of the nonparticipants to evaluate the potential of selection bias among the population control subjects. Regular mobile phone use was more prevalent among participating population control subjects (45% in men and 25% in women) than nonparticipating population control subjects (37% in men and 16% in women) (Supplementary Table 3, available online). Similar potential biases have been observed in other recent case-control studies of mobile phone use (13). To quantify this potential influence we used probabilistic bias with an error model for the selection bias among population control subjects (14). We found that selection bias could not account entirely for the null results of the population-based analysis (Supplementary Table 4, available online), at least given our error model. Further results of these bias analyses will be presented in a separate report (15). We believe, therefore, that the case-control analysis using population control subjects provides the most informative results because this analysis included nearly all of the case patients, and the bias analysis indicates that selection bias does not fully explain the null association.

In conclusion, we observed no overall increased risk of uveal melanoma among regular mobile phone users or users of radio sets in Germany, where digital mobile phone technology was introduced in the early 1990s. These null results are restricted to short lag or latency periods (approximately ≤10 years).

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