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Cellular Telephone Use and Risk of Acoustic Neuroma

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Despite limited evidence, cellular telephones have been claimed to cause cancer, especially in the brain. In this Danish study, the authors examined the possible association between use of cellular telephones and development of acoustic neuroma. Between 2000 and 2002, they ascertained 106 incident cases and matched these persons with 212 randomly sampled, population-based controls on age and sex. The data obtained included information on use of cellular telephones from personal interviews, data from medical records, and the results of radiologic examinations. The authors obtained information on socioeconomic factors from Statistics Denmark. The overall estimated relative risk of acoustic neuroma was 0.90 (95% confidence interval: 0.51, 1.57). Use of a cell phone for 10 years or more did not increase acoustic neuroma risk over that of short-term users. Furthermore, tumors did not occur more frequently on the side of the head on which the telephone was typically used, and the size of the tumor did not correlate with the pattern of cell phone use. The results of this prospective, population-based, nationwide study, which included a large number of long-term users of cellular telephones, do not support an association between cell phone use and risk of acoustic neuroma.

case-control studies; cellular phone; ear neoplasms; neuroma, acoustic

Abbreviation: CI, confidence interval.

Acoustic neuromas are benign tumors that arise from the Schwann cells, which enfold the vestibulocochlear nerve (eighth cranial nerve). These tumors grow slowly, and the primary symptoms usually include unilateral hearing loss accompanied by tinnitus and dizziness (1). The tumor occurs mainly in people aged 50 years or more, except for rare tumors that develop during the course of neurofibromatosis type II, which are often diagnosed in younger persons (2). Women are more often affected than men, with a sex ratio close to 1.3 (3).

The incidence of acoustic neuroma has increased over the past 20 years and is currently 1–20 per million population per year in most industrialized countries (2, 3). This recorded increase in incidence may be due to better diagnostic tools and increased awareness of the disease (3); however, a number of environmental factors have been suspected to increase the risk of acoustic neuroma. The suspected factors include electromagnetic fields emitted by hand-held cellular telephones (4), since this type of tumor is located in an anatomic region where a considerable amount of the power emitted from cell phones is absorbed. The power absorption is attenuated by more than 90 percent within 4–5 cm (5).

In contrast to ionizing radiation, electromagnetic fields emitted from cellular telephones do not have enough energy to break chemical bonds or damage DNA. Electromagnetic radiation from a cell phone can penetrate the skull and deposit energy 4–6 cm into the brain. This can potentially result in a heating of the tissue of up to 0.1°C (6, 7). Therefore, it has been debated whether these fields could initiate or promote cancer (8, 9). The most provocative experimental study to date is that of Repacholi et al. (10), who reported an excess risk of lymphoma in genetically engineered mice

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exposed to a pulsed 900-MHz electromagnetic field for 1 hour per day for 18 months. However, the relevance of that finding for human health has been questioned, both by the authors and by others (11, 12). Because radio-frequency signals are unlikely to cause genetic mutations, the biologic basis for a possible association between cell phone use and cancer risk has been proposed to be a thermal mechanism, such as changes in protein phosphorylation, or a nonthermal mechanism that promotes tumor growth (11, 13).

Four epidemiologic studies have examined the association between use of cellular telephones and risk of acoustic neuroma (9, 14–17). However, only the most recent case-control study of prevalence showed a significantly increased risk of acoustic neuroma among users of analogue cellular telephones (17).

Here we report the first results from the Danish portion of the Interphone project, an international case-control study of incident glioma, meningioma, parotid gland tumors, and acoustic neuroma based on a common core protocol in 14 countries (18). In this nationwide, population-based study, we were able to obtain detailed information on patterns of cell phone use among 107 patients with incident acoustic neuroma and 214 matched population-based controls.

MATERIALS AND METHODS

Study setting and population

In Denmark, cases of acoustic neuroma (*International Classification of Diseases for Oncology* topography code 192.0 and morphology code 9560.0) are primarily verified by magnetic resonance imaging. In magnetic resonance imaging, acoustic neuroma is found in the cerebello-pontine angle, with a portion of the tumor filling the internal auditory canal, which is often enlarged. The tumor is bright (hyperintense) on images with long acquisition time (T1 weighted images) and colored like the surroundings (isointense) on images with short acquisition time (T2 weighted images). An acoustic neuroma appears inhomogeneous with possible cystic and hemorrhagic components. Contrast enhancement with gadolinium reveals the intracanalicula proportion of the tumor securing the diagnosis (19). All cases of acoustic neuroma in the study are referred to the Department of Otolaryngology–Head and Neck Surgery, Gentofte Hospital, University of Copenhagen, for verification and a treatment decision. We recently reported that the registration of cases in the Department was almost complete (3). All case patients were cancer-free prior to the diagnosis of acoustic neuroma. We identified 141 patients aged 20–69 years with incident cases of acoustic neuroma who were referred to the Department between September 1, 2000, and August 31, 2002. Case ascertainment is regarded as nearly complete, since all patients with suspected acoustic neuroma are referred to this one department, regardless of where they live or whether immediate treatment follows. The age range of the study subjects was considered to cover the population in which the prevalence of cell phone use is highest.

Of the 141 eligible case patients, we excluded eight cases because they were prevalent or occurred in persons aged 69 years or more at diagnosis, and we excluded a further three cases because the patients died before we were able to approach them. Twenty-three case patients refused to participate, leaving 107 (82 percent) patients for interview. Eighty cases (75 percent) were diagnosed on the basis of magnetic resonance scanning, and 27 cases (25 percent) were confirmed by histologic examination. One case patient and two matched controls were excluded from the study base, because the patient was found to have had neurofibromatosis type II before the diagnosis of acoustic neuroma.

We selected two controls for each case, individually matched according to age (within 5 years) and sex. The controls were randomly sampled from the Danish Central Population Register on the basis of the unique 10-digit personal identification number that has been assigned to all Danish residents since April 1, 1968; those data include information on age and sex. All controls were free of cancer prior to the date of interview. The response rate was 64 percent (n = 214). Each control was contacted by mail, and both patients and controls were asked to give written and oral informed consent before the interview was conducted.

Data collection

A computerized personal questionnaire was developed as part of the Interphone Study (18). Face-to-face interviews were conducted by either a research nurse or a specially trained medical student. Subjects were asked whether they had ever used a cellular telephone, and those who had used one were asked whether they were regular users (more than one call per week for 6 months or more) and how many different cell phones they used regularly. For each cell phone used regularly, starting and stopping dates of use were recorded. If the respondent was still using a cell phone on the day of the interview, the stopping date was set at the date of diagnosis (for cases) or the date of diagnosis of the corresponding matched case (for controls).

The questionnaire sought information on numbers of calls made or received, average duration of calls for each cell phone used by the respondent, and changes in the pattern of use over a period of more than 6 months. On the basis of this information, we calculated the lifetime number of calls made and the lifetime number of hours of cell phone use. For each cell phone, we recorded information on use of a handset with a microphone in terms of period of use and proportion of use, as well as use of a hands-free set installed in a vehicle. This information was used to modify the exposure estimate (see below). Furthermore, the interview also contained questions on hearing loss or tinnitus. Finally, information on the educational level of cases and controls and their spouses was obtained during the interview and was used as a proxy for socioeconomic status in the regression analysis.

In all cases, clinical data were used to calculate tumor size from the diameter of the portion of the tumor reaching out of the internal auditory canal (extrameatal proportion) (20) and to characterize the laterality of the tumor.

We obtained information on the socioeconomic status of all of the eligible patients (n = 129) and controls (n = 332), including educational level, marital status, employment, income in the year 2001, and wealth, defined as taxable

TABLE 1. Selected characteristics (%) of 318 participants and 143 nonparticipants in a Danish case-control study of cellular telephone use and risk of acoustic neuroma, 2000–2002*

Characteristic	Cases		Controls	
	Participants (n = 106)	Nonparticipants (n = 23)	Participants (n = 212)	Nonparticipants (n = 120)
Sex				
Male	51	25	51	36
Female	49	75	49	64
Age group (years)				
20–29	8	13	8	7
30–39	16	13	12	17
40–49	21	13	22	23
50–59	34	39	32	34
60–69	21	22	26	19
Educational level†				
Low	40	25	44	42
Intermediate	54	55	41	53
High	6	21	15	5
Marital status				
Unmarried	33	26	32	33
Married	62	74	63	63
Widowed	5	0	5	4
Occupation				
Self-employed	8	13	5	7
White-collar worker	27	26	21	18
Blue-collar worker	35	61	41	38
On social welfare	30	0	33	37
Income (thousands of $US)‡				
<31	49	52	44	48
31–62	45	39	48	41
62–93	6	9	5	8
93–124	1	0	2	1
>124	0	0	1	2
Total assets (thousands of $US)§				
<31	67	87	65	61
31–62	12	13	12	12
62–93	6	0	6	6
93–124	6	0	6	6
>124	9	0	11	15
Region				
Eastern Denmark	46	52	47	40
Fünen	11	22	10	8
Western Denmark	42	26	43	52

* Based on data from Statistics Denmark.

† Low = completion of primary school or its equivalent; intermediate = completion of 3 years of adult education or a bachelor's degree; high = master's degree or higher.

‡ Income reported to the Danish tax authorities in 2001.

§ Total assets reported to the Danish tax authorities in 2001.

assets in 2001, from the Integrated Database for Labor Market Research at Statistics Denmark (21). Since this information was provided in an anonymous form, we could not adjust for it in the conditional logistic regression models (see

TABLE 2. Odds ratios for acoustic neuroma according to level of use of hand-held cellular telephones, Denmark, 2000–2002

	Cases		Controls		OR*,†	95% CI*
	No.	%	No.	%		
Use of cellular telephones (ever/never)						
Never or rarely used	61	58	115	54	1.00	
Used regularly	45	42	97	46	0.90	0.51, 1.57
Time (years) since first regular use						
Never or rarely used/<1 year	64	60	115	54	1.00	
1–4	23	22	47	22	0.86	0.45, 1.62
≥5	19	18	50	24	0.68	0.32, 1.44
5–9	17	16	35	17	0.86	0.39, 1.93
≥10	2	2	15	7	0.22	0.04, 1.11
First telephone operating system						
Never or rarely used	61	58	115	54	1.00	
No information	5	5	8	4	1.58	0.38, 6.51
Analogue	4	4	30	14	0.26	0.08, 0.83
Digital	36	34	59	28	1.11	0.60, 2.04
Lifetime cumulative no. of calls‡						
Never or rarely used	61	58	115	54	1.00	
≤2,975	26	25	49	23	0.99	0.53, 1.83
>2,975–11,550	10	9	24	11	0.79	0.32, 1.92
>11,550	9	8	24	11	0.72	0.28, 1.87
Lifetime cumulative hours of use‡						
Never or rarely used	61	58	115	54	1.00	
≤167.5	25	24	49	23	0.93	0.49, 1.74
>167.5–654	12	11	24	11	1.01	0.43, 2.38
>654	8	8	24	11	0.66	0.25, 1.74
Cumulative use (years) before diagnosis§						
Never or rarely used	61	58	115	54	1.00	
<5	26	25	47	22	1.03	0.54, 1.95
≥5 (≤81.7 hours)	10	9	25	12	0.73	0.28, 1.89
≥5 (>81.7 hours)	9	8	25	12	0.72	0.28, 1.88

* OR, odds ratio; CI, confidence interval.

† Odds ratios and 95 percent confidence intervals were derived from conditional logistic regression analysis for 1:2-matched pairs, with results adjusted for educational level, marital status, use of hands-free devices in vehicles (ever vs. never), and region.

‡ Based on the empirical distribution among controls, modified according to use of hands-free devices (earphones, hands-free sets). Data were divided into the following categories: ≤median, >median–≤third quartile (75%), and >third quartile.

§ Cumulative use was divided into four groups: never or rarely used a cell phone, used a cell phone regularly for less than 5 years before diagnosis, and used a cell phone regularly for 5 or more years before diagnosis and had cumulative use of ≤81.7 hours or >81.7 hours (81.7 hours = median) for the period prior to the 5 years before diagnosis, respectively.

below). Nevertheless, it enabled us to compare the distributions of various socioeconomic characteristics between cases and controls eligible for the study (table 1).

Ethical considerations

Approval was obtained from the Danish Ethical Committee and the Danish Data Protection Agency. Written material was produced in accordance with the Helsinki II declaration.

Statistical analysis

Conditional logistic regression models for data sets matched 1:2 were used to estimate odds ratios and their respective 95 percent confidence intervals (PROC PHREG

TABLE 3. Handedness and cellular telephone handedness for regular users of cellular telephones among patients with acoustic neuroma and controls, Denmark, 2000–2002

Handedness and laterality of cellular telephone use	Cases		Controls	
	No.	%	No.	%
Same side	19	42	57	59
Opposite side	14	31	30	31
Ambidextrous*	3	7	4	4
No preferred side	9	20	6	6

* Two ambidextrous cases preferred the left side of the head for cellular telephone use, and one had no preferred side; among ambidextrous controls, the respective figures were one for the right side, two for the left side, and one with no preference.

in SAS, version 8; SAS Institute, Inc., Cary, North Carolina). The odds ratio was used as an estimate of the relative risk. All analyses accounted for educational level (low, intermediate, or high), region of residence (eastern part of Denmark, Fünen, or western part of Denmark), marital status (married vs. single, divorced, or widowed), and use of hands-free devices in vehicles (ever vs. never). Cumulative use of cellular telephones was modified according to the use of hands-free sets, by a factor that varied with the answers given. Thus, we reduced exposure by 100 percent, 75 percent, 50 percent, or 25 percent when respondents reported use of hands-free devices all of the time, most of the time, half of the time, or less than half of the time, respectively. Cumulative use was multiplied by the modification factor for the periods in which hands-free devices were used. The possible association between the laterality of the tumor and self-reported handedness was examined using a method described elsewhere (14). To examine the impact of prediagnostic hearing loss on our risk estimates, we also created a regression model with long-term hearing loss and long-term cell phone use included as possibly competing risk factors. Finally, the associations between the degree of participation and the baseline variables were evaluated by means of generalized logistic regression with four outcome categories: case participant, case nonparticipant, control participant, and control nonparticipant.

RESULTS

Besides sex, which differed significantly between participants and nonparticipants, we observed no significant difference when comparing cases and controls or when comparing the two case groups or the two control groups (table 1). In particular, there were only minor differences with respect to the indicators of socioeconomic status. However, among the cases, there appeared to be differences with respect to the proportions of blue-collar workers and persons on social welfare. In Denmark, social welfare covers citizens who have retired and receive a pension, students depending on public subsidies, and persons who are totally dependent on public welfare. These broad categories may explain why case participants were slightly more likely to have a lower occupational level (to be blue-collar or on social welfare) and, at the same time, were more likely to have greater assets (21 percent above $62,000 vs. 0 percent).

We did not observe increased risk of acoustic neuroma among regular cell phone users (odds ratio = 0.90, 95 percent confidence interval (CI): 0.51, 1.57) (table 2). In addition, no association was observed between risk of acoustic neuroma and cell phone use with increasing time since first regular exposure (reflecting latency), with increasing amount of use (reflecting dose), or with amount of use during the period 5 or more years before diagnosis (reflecting both latency and dose) (table 2). The risk of acoustic neuroma among regular cell phone users did not differ by sex: The odds ratio was 0.79 (95 percent CI: 0.36, 1.75) for males and 1.05 (95 percent CI: 0.45, 2.47) for females.

Similar proportions of cases and controls reported using their telephone on the side of the head opposite from the side of their handedness, but somewhat more cases than controls reported having no side preference (table 3). Thus, the relative risk of a tumor on the left or right side of the head with respect to the laterality of regular use of a hand-held cellular telephone (at least one call per week within 6 months) was 0.68 (Fisher's exact test: $p = 0.02$), according to the method of Inskip et al. (14); three left tumors and 11 right tumors were observed among patients who held their telephone in their left hand, and seven right tumors and 14 left tumors were observed among those who held their telephone in their right hand. Nevertheless, 10 of the 45 regular cell phone users among the cases were excluded from the analysis because they had no preference regarding the hand in which they held their telephone.

Since most regular cell phone users among the cases reported holding their telephone mainly on the right side of the head (47 percent) or on both sides (22 percent), the left: right ratio of the tumor localization might have differed for users and nonusers. In our sample, however, the tumors of regular cell phone users appeared as often on the right side of the head (24 out of 45 (53 percent)) as the tumors of nonusers or rare users (32 out of 60 (53 percent)).

The mean size of the tumors was 1.66 cm^3 for regular cell phone users and 1.39 cm^3 for nonusers (Wilcoxon test: $p = 0.03$). The mean size of the tumors of cases who had had a hearing problem for 5 years or more was 1.54 cm^3, whereas that of cases with a shorter history or no history of hearing problems was 1.44 cm^3 (Wilcoxon test: $p = 0.42$). The risk of developing a larger acoustic neuroma (with a volume of ≥ 1.51 cm^3) was 1.87 (95 percent CI: 0.75, 4.64) for regular users of cell phones in comparison with nonusers or rare users. Increasing duration of use did not increase the risk of larger tumors significantly (odds ratios were 1.67 for 1–4 years of regular cell phone use and 1.44 for 5 or more years of regular use; data not shown).

DISCUSSION

In this first national report from the Interphone Study, there was no significantly increased risk of development of acoustic neuroma among regular users of handheld cellular telephones. In addition, the pattern of use of a cellular telephone did not correlate with the location of the tumor or symptoms of the disease. In line with previous studies, we found no correlation between the side on which the telephone was most frequently held and the site of the tumor (14, 15). Finally, there was no increase in risk according to the telephone operating system first used (analogue or digital).

The main result of this study is in line with the majority of epidemiologic findings reported so far (9, 14, 15, 22). In two US case-control studies comprising 96 and 90 cases of acoustic neuroma, respectively, no association was observed between use of cellular telephones and risk of acoustic neuroma (14, 15). Likewise, in our previous cohort study of more than 420,000 Danish cellular telephone subscribers, only seven cases of acoustic neuroma were observed, with 11 cases having been expected (standard incidence ratio = 0.64, 95 percent CI: 0.26, 1.32) (9). In a Swedish case-control study of 159 cases of acoustic neuroma, the authors found a significant association between use of analogue cellular telephones and risk of this type of tumor (odds ratio = 3.5, 95 percent CI: 1.8, 6.6); however, there was no clear trend in the risk estimates by latency period (>1, >5, or >10 years) since first use (23). In an update of this analysis, the risk of acoustic neuroma was found to be significantly increased among persons who had used digital cellular telephones for more than 5 years and among persons who had used cordless telephones for more than 10 years (17). This study (23) has been criticized for several methodological weaknesses, including a high rate of loss of cases due to death, the use of retrospective case ascertainment, possible interviewer bias, and a lack of information on how the controls were approached (24). The other studies had low statistical power to detect moderate risk increases among long-term users (12, 13, 20).

Our study had statistical power of more than 75 percent to detect a doubling in the risk of acoustic neuroma with a latency of 5 or more years. Furthermore, it was a population-based study based on complete, high-quality registers. We used standardized face-to-face interviews, which are superior to self-administered questionnaires in terms of obtaining reliable answers to complex questions and in terms of diminishing recall bias (25, 26). In addition, we observed that cases and controls spent equal amounts of time answering the questions. The individual matched design diminished bias due to the longer exposure of controls, because their exposure was cut off at the date of diagnosis of the corresponding case.

If radio-frequency fields promote cancer, one would expect that cumulative exposure would be associated with tumor size; however, we did not observe this association. It may be argued that persons with poor hearing might have larger tumors and therefore might be discouraged from using a cellular telephone. However, tumor size is not associated with hearing loss (27).

We have no reason to believe that our overall findings are due to selection bias. The information we obtained on socioeconomic factors came from public registers and was established independently of the study hypothesis, thus excluding information bias. In particular, there were no differences in socioeconomic characteristics between participants and nonparticipants among either patients or controls. This is reassuring, because long-term use of cell phones might have been related to higher income or higher education, thus introducing selection bias.

In general, patients with acoustic neuroma do not have memory deficits, so this should not have compromised the quality of the data collected (27). The presence of hearing problems prior to diagnosis might have prevented some cases from becoming regular cell phone users and might have reduced their lifetime calling time. Hence, hearing loss might act as a negative confounder, being positively related to diagnosis of acoustic neuroma and negatively related to use of cell phones. This may partially explain why we observed some decreased odds ratios in our risk analyses and why we found a significant disagreement between tumor laterality and preferred side of cell phone use. Nevertheless, comparison of the risk of acoustic neuroma among long-term users (≥5 years) who had not developed hearing problems with that among nonusers or rare users gave a odds ratio of 0.96 (95 percent CI: 0.40, 2.26), which is somewhat higher that the overall odds ratio of 0.68 (95 percent CI: 0.32, 1.44) (table 2).

On the basis of these first data from the Interphone Study, we conclude that there is no evidence for an association between use of cellular telephones and the risk of developing acoustic neuroma.

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