A Case–Case Study of Mobile Phone Use and Acoustic Neuroma Risk in Japan

Yasuto Sato,[1] Suminori Akiba,[2] Osami Kubo,[3] and Naohito Yamaguchi[1]*

[1]Department of Public Health, School of Medicine, Tokyo Women's Medical University, Shinjuku-ku, Tokyo, Japan
[2]Department of Epidemiology and Preventive Medicine, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima City, Kagoshima, Japan
[3]Department of Neurosurgery, School of Medicine, Tokyo Women's Medical University, Shinjuku-ku, Tokyo, Japan

Results of case–control studies of mobile phone use and acoustic neuroma have been inconsistent. We conducted a case–case study of mobile phone use and acoustic neuroma using a self-administered postal questionnaire. A total of 1589 cases identified in 22 hospitals throughout Japan were invited to participate, and 787 cases (51%) actually participated. Associations between laterality of mobile phone use prior to the reference dates (1 and 5 years before diagnosis) and tumor location were analyzed. The overall risk ratio was 1.08 (95% confidence interval (CI), 0.93–1.28) for regular mobile phone use until 1 year before diagnosis and 1.14 (95% CI, 0.96–1.40) for regular mobile phone use until 5 years before diagnosis. A significantly increased risk was identified for mobile phone use for >20 min/day on average, with risk ratios of 2.74 at 1 year before diagnosis, and 3.08 at 5 years before diagnosis. Cases with ipsilateral combination of tumor location and more frequently used ear were found to have tumors with smaller diameters, suggesting an effect of detection bias. Furthermore, analysis of the distribution of left and right tumors suggested an effect of tumor-side-related recall bias for recall of mobile phone use at 5 years before diagnosis. The increased risk identified for mobile phone users with average call duration >20 min/day should be interpreted with caution, taking into account the possibilities of detection and recall biases. However, we could not conclude that the increased risk was entirely explicable by these biases, leaving open the possibility that mobile phone use increased the risk of acoustic neuroma. Bioelectromagnetics

Key words: epidemiology; detection bias; recall bias

INTRODUCTION

Since the 1990s, public concern about the safety of mobile phone use has surged along with the rapid increase in mobile phone users worldwide. Although the electromagnetic field emitted by mobile phones is extremely low, the effect of energy absorption at tissue sites close to the mobile phone needs to be clarified [Inskip et al., 2001; Johansen et al., 2001]. Particularly worthy of concern is the risk of acoustic neuroma associated with mobile phone use because acoustic nerve tissue—from which such tumors originate—is located very close to the mobile phone during use.

Epidemiological studies have been conducted to examine the risk of acoustic neuromas associated with mobile phone use [Ahlbom et al., 2009]. Of particular importance is the INTERPHONE study [Cardis and Kilkenny, 1999], an international collaborative case–control study coordinated by the International Agency for Research on Cancer of the World Health Organization. Fourteen study groups from 13 countries, including Japan, participated in the study. Although the study is still underway, some results regarding risk of acoustic neuroma have been published. Studies in Denmark [Christensen et al., 2004] and Japan [Takebayashi et al., 2006] have found no increase in the risk of acoustic neuroma associated with mobile phone use. A study in Sweden, however, identified an increased risk in the more frequently used ear among subjects who

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*Correspondence to: Naohito Yamaguchi, Department of Public Health, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan.
E-mail: nyamaguc@vega.ocn.ne.jp

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had used mobile phones continuously for ≥10 years, with an odds ratio of 3.9 (95% confidence interval (CI), 1.6–9.5) [Lönn et al., 2004]. Analysis of pooled data from six study bases (Sweden, Norway, Denmark, Finland and two sites in the United Kingdom) reported similar findings, with an odds ratio for the more frequently used ear of 1.8 (95% CI, 1.1–3.1) for long-term users with ≥10 years of cumulative mobile phone use [Schoemaker et al., 2005]. An increased risk in the more frequently used ear is thus considered important in interpreting the risk of acoustic neuroma associated with mobile phone use.

The case–control design is widely accepted as one of the most useful methods to analyze relationships between mobile phone use and acoustic neuroma. However, case–control studies are known to be vulnerable to selection and recall biases. Selection bias distorts estimates of risk when participation of cases and controls is affected differentially by the status of mobile phone use. Recall bias distorts estimates of risk when the recall of past mobile phone use is differentially biased among cases and controls. Recall bias for the ear more frequently used for mobile phone use in the past is of particular concern [Ahlbom et al., 2009; Schüz et al., 2009], as laterality of mobile phone use coinciding with acoustic neuroma is often presented as evidence for causality.

The case–case design, a less popular epidemiological method, provides a unique opportunity to analyze the risk of brain tumors [Hartikka et al., 2009]. This method can also be applied to acoustic neuroma because the disease is unilateral in most cases. The affected ear is regarded as the case side, while the opposite ear is regarded as the control side. This special situation allows a matched case–control analysis to be conducted based only on the case series. The case–case study is also vulnerable to selection and recall biases, but the situation is less complicated than in case–control studies because the same patient plays the role of both case and control. The effect of selection and recall biases may thus be evaluated more clearly using a case–case study than a case–control study.

A case–case analysis was used for the present study based on the following three assumptions identified by Inskip et al. [2001]: (1) there was no risk from mobile phones to the contralateral side; (2) risk to the ipsilateral side was the same for left- and right-sided users; and (3) for non-users, incidence of left- and right-sided tumors was the same. Given these assumptions, cross-tabulation of the side of exposure and side of disease yields an odds ratio O, and the relative risk (incidence of disease in phone users compared to non-users) is given by $(O^{0.5} + 1)/2$ [Inskip et al., 2001].

The aim of the present study was to examine, using a case–case design, the association between various parameters of mobile phone use and the risk of acoustic neuroma, taking into account the more frequently used ear and the location of acoustic neuroma.

MATERIALS AND METHODS

Sixty-eight hospitals throughout the country were selected from hospitals with neurosurgery departments participating in the nationwide registration of brain tumors, and were invited to participate in the present study. Of these, 22 hospitals (32.4%) agreed to participate. These 22 hospitals were located in various parts of Japan, and showed no indication of biased sampling.

Inclusion criteria were all cases diagnosed with acoustic neuroma between January 2000 and December 2006 in participating hospitals. Only patients alive at the time of invitation were included. Diagnosis was based on pathological examination or imaging. The protocol was approved by the Ethical Committee of Tokyo Women's Medical University.

Between January and December 2006, all patients with acoustic neuroma in participating hospitals were asked by mail to participate in the study. Questionnaires were then mailed to all patients who returned written informed consent. The questionnaire included: past history of mobile phone use; the year of starting mobile phone use; average daily number of outgoing and incoming calls; average call duration; proportion of calls using the left and right ears; and frequency of hands-free device use. Questions about disease included: date of diagnosis; subjective symptoms at diagnosis; and subjective symptoms around 1 and 5 years before diagnosis. Sex, birth date, and dominant hand were obtained as basic background information. Clinical information collected from neurosurgeons included chief complaint at first visit, past medical history, tumor location (left/right), tumor size, diagnostic method (pathology/imaging), and treatment method.

Reference dates were set at 1 and 5 years before diagnosis, and two datasets were constructed for these two reference dates. Cases with any tumor-related symptoms at the reference date were excluded from the corresponding dataset. Mobile phone use before the reference date was analyzed. A regular mobile phone user was defined as someone using a mobile phone at least once a week for ≥6 months. Average daily call duration was calculated by multiplying the average number of calls per day by the average duration of one call. These three indices were further weighted by the proportion of calls made using each ear to calculate

weighted average number of calls per day, weighted average duration of one call, and weighted average daily call duration. These three weighted indices were specified in advance as the primary indicators for intensity of use. *P* values were obtained using Fisher's exact test and *P* values for trend were Monte Carlo estimates obtained using the exact Cochrane–Armitage trend test. All *P* values were two-sided. The risk ratio of acoustic neuroma for mobile phone use compared to non-use was estimated using the methods described by Inskip et al. [2001]. StatXact-4 software (Cytel Software, Cambridge, MA) was used for analysis.

RESULTS

A total of 1589 cases met the inclusion criteria. Of these, 816 cases (51%) agreed to participate by returning written informed consent, and 804 (51%) returned the self-administered questionnaire. Four cases were found to be double-enrolled via two hospitals. Of the remaining 800 participants, 395 (49.4%) had a tumor on the left side and 392 (49.0%) had a tumor on the right side. Thirteen cases (1.6%), comprising 9 cases with tumors on both sides and 4 cases in which tumor location was missing, were excluded from analysis. A total of 787 participants were thus included for further analysis. The number of acoustic neuroma cases newly diagnosed in Japan during the period from 2000 to 2006 was estimated as approximately 11200, based on the annual incidence of 1600 cases per year [Kaneko et al., 2002]. Therefore, the 787 cases in the current study represented approximately 7% of all cases in Japan.

The proportion of cases with histological diagnosis was 44.7%. Most cases were treated surgically or by gamma knife irradiation, but cases without any therapeutic intervention were also included. The longest delay from the date of diagnosis to the date of questionnaire survey was 6 years, since all cases diagnosed between 2000 and 2006 were asked to answer the questionnaire. Age and sex distributions of study participants are shown in Table 1. With regard to dominant hand, 737 cases (94%) were right-handed, 22 (3%) were left-handed, and 27 (3%) were ambidextrous; data on handedness were missing for 1 case (0.1%).

TABLE 1. Age and Sex Distributions of Study Participants

	Male		Female	
Age (years)	*n*	%	*n*	%
≤29	4	1	17	4
30–39	37	11	36	8
40–49	48	14	66	15
50–59	105	30	121	27
60–69	85	25	128	29
≥70	66	19	74	17
Total	345	100	442	100

The dataset for analysis at 1 year before diagnosis consisted of 362 cases, and none of them experienced any tumor-related symptoms at the reference date. Among these 362 cases, 199 cases (55.0%) were mobile phone users at the time. Of the 199 mobile phone users, 18 cases (9%) answered that they used both left and right ears almost equally, and 1 case lacked information on preferred ear for mobile phone use. Excluding these 19 cases, 180 cases were used for risk analysis. Left-ear-dominant users ($n = 101$, 56%) outnumbered right-ear-dominant users ($n = 79$, 44%), but the difference was not significant ($P = 0.118$). The difference between left- and right-ear-dominant users was unrelated to mobile phone use patterns, weighted average number of calls per day ($P = 0.886$ for trend), weighted average duration of one call ($P = 0.999$ for trend) or weighted average daily call duration ($P = 0.833$ for trend).

The dataset for analysis at 5 years before diagnosis consisted of 593 cases who did not present any tumor-related symptoms at the reference date. Among these 593 cases, 167 cases (28.2%) were mobile phone users at that time. Of these 167 mobile phone users, 17 (10%) used both left and right ears equally during mobile phone use. Excluding these 17 cases, 150 cases were used for risk analysis. Left-ear-dominant users ($n = 91$, 61%) significantly outnumbered right-ear-dominant users ($n = 59$, 39%; $P = 0.011$). The difference between left- and right-ear-dominant users was unrelated to mobile phone use patterns, weighted average number of calls per day ($P = 0.312$ for trend), weighted average duration of one call ($P = 0.489$ for trend), or weighted average daily call duration ($P = 0.467$ for trend).

The risk of acoustic neuroma for mobile phone use was estimated for various subgroups (Table 2). The overall risk ratio was 1.08 (95% CI, 0.93–1.28) for regular mobile phone use until 1 year before diagnosis and 1.14 (95% CI, 0.96–1.40) for regular mobile phone use until 5 years before diagnosis. No significant increase in risk was found for different categories of sex, age, and year at start of mobile phone use. Likewise, there was no significant heterogeneity in risk estimates for different categories of sex, age at diagnosis, and year at start of mobile phone use (test of heterogeneity in Table 2). At 1 year before diagnosis, risks were slightly higher among those who started mobile phone use further in the past (1.21 for ≤1996, 1.19 for 1997–1999, and 0.94 for ≥2000), but this trend was not similar to the results at 5 years before diagnosis. A slightly higher risk of 1.62 was found for patients with >10 years since starting mobile phone use at 1 year

TABLE 2. Associations Between Laterality of Mobile Phone Use and Laterality of Acoustic Neuroma

	1 year before diagnosis								5 years before diagnosis							
	l/l[a]	l/r	r/l	r/r	Total	Risk ratio	95% CI	*P*	l/l	l/r	r/l	r/r	Total	Risk ratio	95% CI	*P*
Overall	55	37	46	42	180	1.08	0.93–1.28		56	29	35	30	150	1.14	0.96–1.40	
Sex																
Male	34	17	26	18	95	1.09	0.89–1.39	0.220[b]	39	17	23	15	94	1.11	0.90–1.44	0.313[b]
Female	21	20	20	24	85	1.06	0.87–1.36		17	12	12	15	56	1.17	0.89–1.63	
Age at diagnosis (years)																
<40	16	6	14	10	46	1.19	0.87–1.78	0.229[b]	18	3	10	10	41	1.72	1.08–3.10	0.106[b]
40–60	34	25	21	27	107	1.16	0.95–1.47		32	17	15	14	78	1.16	0.91–1.56	
≥60	5	6	11	5	27	0.81	0.64–1.18		6	9	10	6	31	0.82	0.65–1.15	
Year at start of mobile phone use																
After 2000	17	17	19	15	68	0.94	0.78–1.22	0.657[b]	5	5	3	4	17	1.08	0.72–2.03	0.920[b]
1997–1999	18	12	11	14	55	1.19	0.90–1.68		22	9	13	10	54	1.19	0.89–1.71	
Before 1996	20	8	16	13	57	1.21	0.91–1.73		29	15	19	16	79	1.14	0.90–1.51	
Years since start of mobile phone use																
≤5	30	25	28	29	112	1.06	0.88–1.31	0.240[c]	45	25	29	24	123	1.11	0.92–1.38	0.300[c]
5–10	20	11	15	10	56	1.05	0.82–1.45		9	2	5	5	21	1.56	0.90–3.34	
>10	5	1	3	3	12	1.62	0.79–4.77		2	2	1	1	6	1.00	0.59–3.23	
Weighted average number of calls per day																
≤1 call	21	8	19	16	64	1.24	0.94–1.76	0.470[c]	11	9	9	9	38	1.05	0.79–1.55	0.043[c]
1–3	16	20	16	17	69	0.96	0.79–1.24		20	11	17	13	61	1.09	0.85–1.49	
3–5	9	3	6	4	22	1.21	0.78–2.26		11	2	4	3	20	1.52	0.85–3.44	
>5	9	6	5	5	25	1.11	0.77–1.87		14	7	5	5	31	1.21	0.83–2.02	
Weighted average duration of one call																
≤1 min	22	14	16	16	68	1.13	0.89–1.51	0.230[c]	19	10	14	8	51	1.02	0.79–1.43	0.017[c]
1–3	15	15	19	13	62	0.91	0.75–1.18		16	10	15	11	52	1.04	0.81–1.44	
3–5	9	4	6	4	23	1.11	0.76–1.95		9	4	3	4	20	1.37	0.83–2.74	
>5	9	4	5	9	27	1.51	0.95–2.75		12	5	3	7	27	1.68	1.00–3.28	
Weighted average daily call duration																
≤3 min	23	13	21	22	79	1.18	0.93–1.57	0.230[c]	16	10	14	13	53	1.11	0.85–1.55	0.004[c]
3–10	16	15	12	7	50	0.89	0.72–1.21		17	12	14	6	49	0.89	0.71–1.21	
10–20	6	8	9	5	28	0.82	0.65–1.19		3	4	5	3	15	0.84	0.62–1.44	
>20	10	1	4	8	23	2.74	1.18–7.85		20	3	2	8	33	3.08	1.47–7.41	
Corded fixed phone (mobile phone non-users)																
	39	27	41	31	138	1.02	0.87–1.23		101	64	96	83	344	1.08	0.97–1.22	
Cordless fixed phone (mobile phone non-users)																
	25	23	30	20	98	0.93	0.79–1.14		68	49	72	57	246	1.02	0.91–1.17	

l, left; r, right.

[a]Tumor location/phone use side.

[b]By test of heterogeneity.

[c]By trend test.

before diagnosis, but again, this was not accompanied by a similar increase at 5 years before diagnosis (estimated risk, 1.00). Risk of acoustic neuroma did not increase with the use of corded or cordless fixed phones among mobile phone non-users. When cases were divided into three groups according to age at diagnosis (<40 years, 40–60 years, and ≥60 years), increased risk of acoustic neuroma was observed only in the <40-year-old group. Mobile phone users <40 years old at diagnosis were found to include more heavy users; 15 of 41 cases (36.6%) <40 years old at diagnosis showed a weighted average daily call duration of >20 min, compared to 12 of 78 cases (15.4%) aged 40–60 years at diagnosis, and 6 of 31 cases (19.4%) aged ≥60 years at diagnosis. Heavy mobile phone use among cases <40 years old at diagnosis thus appears likely to manifest as increased risk of acoustic neuroma, as discussed later.

The risk of acoustic neuroma among mobile phone users was further evaluated for three indices of mobile phone use: weighted average number of calls per day; weighted average duration of one call; and weighted average daily call duration.

Risk estimates did not reach statistical significance in all categories of weighted average number of calls per day for either 1 or 5 years before diagnosis. When the trend test was conducted, however, a significant tendency toward increased risk was observed for 5 years before diagnosis ($P = 0.043$). No such increasing tendency was observed for 1 year before diagnosis ($P = 0.470$).

A significant increasing tendency was observed for risk in association with increasing weighted average duration of one call for 5 years before diagnosis ($P = 0.017$). A similar increasing tendency was observed for 1 year before diagnosis as well, although the trend test did not reach statistical significance ($P = 0.230$). The highest risks were observed for >5 min per call, at 1.51 for 1 year before diagnosis and 1.68 for 5 years before diagnosis.

A significant increasing tendency was observed for risk in association with increasing weighted daily call duration for 5 years before diagnosis ($P = 0.004$). A similar increasing tendency was observed for 1 year before diagnosis, but the trend test did not reach statistical significance ($P = 0.230$). A significantly increased risk was identified for weighted average daily call duration >20 min. Risk ratio was 2.74 (95% CI, 1.18–7.85) at 1 year before diagnosis, based on 23 cases, and 3.08 (95% CI, 1.47–7.41) at 5 years before diagnosis, based on 33 cases. No increased risk was found for users with weighted average daily call duration ≤20 min. The term ''heavy use'' was applied for mobile phone use with weighted average daily call duration >20 min.

Among heavy users at 1 or 5 years before diagnosis, 16 cases were classified as heavy users at both 1 and 5 years before diagnosis, 7 cases only at 1 year before diagnosis, and 17 cases only at 5 years before diagnosis (Table 3). Sixteen cases reporting heavy mobile phone use at both 1 and 5 years before diagnosis were considered as ''persistent heavy users.'' Among these 16 persistent heavy users, 15 cases (93.8%) reported more frequent use of the affected ear (9 of 9 left tumor cases and 6 of 7 right tumor cases). The estimated risk ratio based on these 16 cases was 5.0 (95% CI, 1.3–24.8). When these 16 cases were excluded, no increased risk was observed for 1 year before diagnosis (risk ratio, 0.9; 95% CI, 0.6–2.6) and a non-significant tendency toward increased risk was observed for 5 years before diagnosis (risk ratio, 1.9; 95% CI, 0.9–5.8). Interestingly, 14 (88%) of 17 cases classified in the >20 min/day category only at 5 years before diagnosis showed left tumors and 11 (79%) of 14 left tumor cases were reported in left-ear-dominant users.

Since heavy mobile phone use on the affected ear could enhance the chance of the patient noticing slight changes in hearing ability due to disease, cases with ipsilateral mobile phone use might be more likely to be

TABLE 3. Risk of Acoustic Neuroma Among Heavy Mobile Phones Users With >20 min/day Use at 1 or 5 Years Before Diagnosis (Dx)

	l/l[a]	l/r	r/l	r/r	Total	Risk ratio	95% CI
Reference date							
1 year before Dx	10	1	4	8	23	2.7	1.2–7.9
5 years before Dx	20	3	2	8	33	3.1	1.5–7.4
Both 1 and 5 years before Dx	9	0	1	6	16	5.0[b]	1.4–24.8
Only 1 year before Dx	1	1	3	2	7	0.9	0.6–2.6
Only 5 years before Dx	11	3	1	2	17	1.9	0.9–5.8

l, left; r, right.
[a]Tumor location/phone use side.
[b]Based on odds ratio calculated by $(l/l + 0.5)/(l/r + 0.5)/(r/l + 0.5)/(r/r + 0.5)$.

TABLE 4. Distribution of Tumor Diameter (mm) at Diagnosis (Dx) in Relation to Heavy Mobile Phone (MP) Use (>20 min/day) at 1 and 5 Years Before Dx, and the Laterality of Tumor Location and MP Use Side

Reference date with MP use >20 min/day	Combination of laterality[a]	*n*	Mean	SD	Max	Min	p^b
Heavy use at 1 year before Dx	l/l	10	16.3	4.7	25	9	0.033
	l/r + r/l	5	26.6	12.6	45	12	
	r/r	8	17.7	9.6	30	6	
Heavy use at 5 years before Dx	l/l	20	22.8	10.7	50	9	0.394
	l/r + r/l	5	26.0	6.7	32	15	
	r/r	8	19.9	8.2	30	6	
Heavy use at both 1 and 5 years before Dx	l/l	9	16.4	5.0	25	9	0.167
	l/r + r/l	1	28.0	—	28	28	
	r/r	6	19.3	9.4	30	6	
No MP use at 1 and 5 years before Dx	l/l	23	20.4	8.7	40	10	0.607
	l/r + r/l	37	20.2	11.4	55	5	
	r/r	13	23.2	9.2	40	13	

l, left; r, right.
[a]Tumor location/phone use side.
[b]Comparison between ipsilateral (l/l + r/r) and contralateral (l/r + r/l) combinations.

diagnosed with the disease in the earlier stages than cases with contralateral use. If this were the case, more cases with ipsilateral use would likely be included in the study than cases with contralateral use, leading to spuriously increased risk, representing detection bias. To examine the effect of detection bias, tumor diameter was evaluated in relation to the combination of tumor location and side of mobile phone use (Table 4). Tumor diameter tended to be smaller in cases with ipsilateral use than in cases with contralateral use, although the difference was significant only among heavy users at 1 year before diagnosis. Interestingly, no difference was found between ipsi- and contralateral users with weighted average call duration $\leq$20 min. Mean tumor size among non-users was 21.3 mm with a standard deviation of 9.5 mm for left tumors, and 22.5 mm with a standard deviation of 11.4 mm for right tumors.

Since left-ear-dominant mobile phone users outnumbered right-ear-dominant mobile phone users, left tumors could be expected to be more prevalent than right tumors, if mobile phone use actually increased the tumor risk. Overall, there was no substantial deviance in tumor location, with 171 left tumors (49.9%) versus 172 right tumors (50.1%) at 1 year before diagnosis, and 289 left tumors (50.3%) and 286 right tumors (49.7%) at 5 years before diagnosis. When the distribution of tumor location was further analyzed for different categories of mobile phone use, no deviance of tumor location was observed among 180 mobile phone users at 1 year before diagnosis, with 92 left tumors (51.1%) versus 88 right tumors (48.9%; Table 5). On the other hand, left tumors outnumbered right tumors, with 85 left tumors (56.7%) versus 65 right tumors (43.3%) among 150 mobile phone users at 5 years before diagnosis. However, this deviance was accompanied by more right tumors among non-users, with 204 left tumors versus 221 right tumors. Furthermore, among mobile phone users at 5 years before diagnosis, deviance toward left tumors appeared to become larger with increasing weighted average daily call duration, although the trend test did not reach statistical significance ($P = 0.107$ for trend). This might suggest that cases with left tumors showed a tendency to recall past mobile phone use differently than those with right tumors.

DISCUSSION

Overall, no significantly increased risk was identified for regular mobile phone use compared to non-use, with risks of 1.08 (95% CI, 0.93–1.28) for use until 1 year before diagnosis and 1.14 (95% CI, 0.96–1.40) for use until 5 years before diagnosis. Increased risk of acoustic neuroma was observed in cases who reported having used mobile phones on the affected ear for >20 min/day on average. Risk ratio was 2.74 (95% CI, 1.18–7.85) for use until 1 year before diagnosis and 3.08 (95% CI, 1.47–7.41) for use until 5 years before diagnosis. Finding the most reasonable and plausible explanation of this apparently increased risk is thus of particular importance.

One possible interpretation is, of course, that the increased risk was caused by exposure to the electromagnetic field from the mobile phone. Other possible interpretations are that the apparent increase in risk was caused by selection bias and/or recall bias. Selection bias might distort the results, if heavy users with ipsilateral mobile phone use were more likely to participate in the study because of earlier detection of tumors. Recall bias might distort the result if heavy

TABLE 5. Tumor Location in Relation to Mobile Phone (MP) Use Status at 1 and 5 Years Before Diagnosis (Dx)

	Tumor location		% of left
	Left	Right	Tumor
Mobile phone status at 1 year before Dx			
Never used MP	58	58	50.0
Not yet started using MP	21	26	44.7
Subtotal	79	84	48.5
Using MP (min/day)			
≤3	36	43	45.6
3–10	31	19	62.0
10–20	14	14	50.0
>20	11	12	47.8
Subtotal	92	88	51.1
Total	171	172	49.9
Mobile phone status at 5 years before Dx			
Never used MP	96	101	48.7
Not yet started using MP	108	120	47.4
Subtotal	204	221	48.0
Using MP (min/day)			
≤3	26	27	49.1
3–10	29	20	59.2
10–20	7	8	46.7
>20	23	10	69.7
Subtotal	85	65	56.7
Total	289	286	50.3

users had a tendency to mentally associate their disease with mobile phone use, and hence misremembered using mobile phones more frequently on the ear affected by the disease.

One clue was obtained by examining tumor diameter in cases with ipsilateral mobile phone use versus cases with contralateral mobile phone use (Table 4). The smaller diameter of tumors in cases with ipsilateral use might indicate that cases with ipsilateral use were more likely to be diagnosed at an earlier stage than cases with contralateral use. Of course, the smaller diameter can also potentially be explained by slower growth rate in tumors with ipsilateral use, but this is not a particularly plausible explanation since it would mean that exposure to the electromagnetic field slowed tumor growth among ipsilateral mobile phone users. A Danish case–control study, on the other hand, reported results opposite to the current study. Mean size of the acoustic neuroma was found to be significantly larger in regular mobile phone users compared to non-users, at 1.66 cm^3 in users and 1.39 cm^3 in non-users [Christensen et al., 2004]. One difference between the Danish study and our study was that tumor size was compared between ipsilateral and contralateral mobile phone users in our study, whereas tumor size was compared between regular users and non-users in the Danish study. Non-users might have had different detection factors that were related to the smaller tumor size.

Another clue was provided by the distribution of left versus right tumors in association with mobile phone use status (Table 5). While no deviance was observed among mobile phone users or non-users at 1 year before diagnosis, a deviance toward left tumors was observed among mobile phone users at 5 years before diagnosis. This could have resulted from increased risk from mobile phone use because there were more left-ear-dominant users than right-ear-dominant users. If this was the case, however, no deviance should have been observed among non-users, whereas deviance toward right tumors was actually observed among non-users. Therefore, a more plausible explanation is that cases with left tumors were more likely to mentally associate their tumors with mobile phone use than cases with right tumors because of recall bias. This bias can be called tumor-side-related recall bias. The fact that right tumors were dominant even among those that never used a mobile phone might indicate that recall bias affected not only the memory regarding year when mobile phone use began, but also the memory of how frequently the individual had used mobile phones at 5 years before diagnosis. Interestingly, deviance toward left tumors was observed among non-heavy users and became more prominent as the weighted average daily call duration increased. This suggests that tumor-side-related recall bias might also affect the memory among non-heavy mobile phone users and the magnitude of

bias was stronger among heavy users. This possibility of tumor-side-related recall bias was solely based on observed data, and should be further explored using independent studies.

Increased risk among heavy users at 1 and 5 years before diagnosis was found to be attributable to increased risk among 16 cases with persistent heavy use. No increased risk was observed for those reporting heavy use only at 1 year before diagnosis, if these 16 cases were excluded. A non-significant increase in risk of 1.9 was observed for 17 cases reporting heavy use only at 5 years before diagnosis, after excluding the 16 cases. Of note, however, is the finding that 14 (82.4%) of 17 cases had left tumors, whereas only 3 cases (17.6%) had right tumors; this extreme deviance toward left tumors apparently reflected the effect of tumor-side-related recall bias.

The interpretation of increased risk among the 16 persistent heavy users seems to be the central issue. Detection bias could increase the number of cases with ipsilateral use, but the observed extreme distribution, in 15 of 16 cases, seems unlikely to be caused solely by detection bias. Since the recall of mobile phone use around 5 years before diagnosis was shown to be less reliable than that around 1 year before diagnosis, the effect of recall bias on these persistent heavy users should be considered. It seems reasonable to assume that recall of mobile phone use around 1 year before diagnosis would interact with recall of mobile phone use around 5 years before diagnosis. One possible explanation is that these 16 persistent heavy users had a tendency to mentally associate mobile phone use with their diseases more strongly than others, leading to the observed extreme distribution of ipsilateral users. Another possible explanation is, of course, that the observed increase in risk among these 16 cases was caused by persistent long exposure to electromagnetic fields. If this is the case, the 16 cases accounted for a rather small fraction of symptom-free mobile phone users; 8.9% of 180 cases at 1 year before diagnosis, and 10.7% of 150 cases at 5 years before diagnosis were symptom-free. Notably, only heavy mobile phone users showed an increased risk, with no increased risk observed among those who used mobile phones $\leq$20 min/day, and no dose-gradient increase in risk was observed in association with increasing daily call duration (Table 2). A biologically plausible explanation should be sought for reasons why exposure to electromagnetic fields exerted adverse effects only on a small fraction of heavy users.

Although the results of the INTERPHONE study as a whole have yet to be published, parts of the INTERPHONE study have been reported both nationally and regionally [Christensen et al., 2004; Lönn et al., 2004; Schoemaker et al., 2005; Takebayashi et al., 2006; Hours et al., 2007; Klaeboe et al., 2007; Schlehofer et al., 2007]. When analysis was restricted to long-term mobile phone users with a duration of $\geq$10 years since the start of use, the estimated odds ratio, compared to non-users, ranged from 0.22 (Denmark) to 1.9 (Sweden), none of which reached statistical significance (5% level). When analysis further took into account the ear used during mobile phone use, the odds ratio for the more frequently used ear was significantly higher among long-term users in Sweden, at 3.9 (95% CI, 1.6–9.5) [Lönn et al., 2004]. In the pooled analysis of Nordic countries and the United Kingdom, the odds ratio for the more frequently used ear reached statistical significance for those with a cumulative duration of mobile phone use $\geq$10 years (1.8; 95% CI, 1.1–3.1) [Schoemaker et al., 2005]. Such increased risk for long-term exposure is generally regarded as an observation supporting a causal relationship. In the case of mobile phone epidemiology, however, the effect of recall bias should also be taken into consideration for long-term users because memory regarding the more frequently used ear is more vulnerable to recall bias when long-term users are asked about the ear a long time before diagnosis.

One of the weaknesses of this study is that the results are dependent on data collected by a self-administered postal questionnaire, usually regarded as one of the least reliable methods of data collection. Attempts were made to make the questions in the questionnaire as reliable as possible, with nine questions on mobile phone use selected from questions in the INTERPHONE questionnaire (Japanese version).

The low response rate is another weakness of this study, as only 816 (51%) of 1589 cases approached by mail agreed to participate. However, low response rate does not seem to lower the internal validity in studies using a case–case design, unlike in the situation of case–control studies. In case–control studies, the representativeness of cases and controls in the study population is usually regarded as the most important factor to ensure internal validity. In case–case studies, however, the representativeness of cases in the study population seems less important, as the same individual plays the role of both cases and controls, and thus the study population can be defined after the cases are sampled.

In conclusion, we found an increased risk of acoustic neuroma in the more frequently used ear for heavy mobile phone users with an average daily call duration $>$20 min. This increased risk should be interpreted with caution, as detection and recall biases could distort the results away from the null hypothesis. However, we could not identify any convincing

evidence for biases that would entirely explain the observed increase of tumors, leaving open the possibility that mobile phone use increased the risk of acoustic neuroma. Further analysis is warranted to confirm our findings and to explore mechanisms underlying the observed association.

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