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Original Contribution

Mobile Phone Use and Risk of Parotid Gland Tumor

Stefan Lönn[1], Anders Ahlbom[1], Helle C. Christensen[2], Christoffer Johansen[2], Joachim Schüz[2], Staffan Edström[3], Gert Henriksson[4], Jan Lundgren[4], Johan Wennerberg[5], and Maria Feychting[1]

[1] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.
[2] Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark.
[3] Department of Otorhinolaryngology, Sahlgrenska University Hospital, Göteborg, Sweden.
[4] Department of Otorhinolaryngology, Karolinska University Hospital, Stockholm, Sweden.
[5] Department of Otorhinolaryngology, Head and Neck Surgery, Lund University Hospital, Lund, Sweden.

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Handheld mobile phones were introduced in Denmark and Sweden during the late 1980s. This makes the Danish and Swedish populations suitable for a study aimed at testing the hypothesis that long-term mobile phone use increases the risk of parotid gland tumors. In this population-based case-control study, the authors identified all cases aged 20–69 years diagnosed with parotid gland tumor during 2000–2002 in Denmark and certain parts of Sweden. Controls were randomly selected from the study population base. Detailed information about mobile phone use was collected from 60 cases of malignant parotid gland tumors (85% response rate), 112 benign pleomorphic adenomas (88% response rate), and 681 controls (70% response rate). For regular mobile phone use, regardless of duration, the risk estimates for malignant and benign tumors were 0.7 (95% confidence interval: 0.4, 1.3) and 0.9 (95% confidence interval: 0.5, 1.5), respectively. Similar results were found for more than 10 years' duration of mobile phone use. The risk estimate did not increase, regardless of type of phone and amount of use. The authors conclude that the data do not support the hypothesis that mobile phone use is related to an increased risk of parotid gland tumors.

case-control studies; cellular phone; electromagnetic fields; neoplasms, radiation-induced; parotid gland; salivary glands

Abbreviation: UICC, International Union against Cancer.

During recent years, the prevalence of mobile phone users has increased, and concerns have been raised that the use has increased dramatically without sufficient understanding of the potential adverse health effects. Originally, the focus of epidemiologic research was the possible association between mobile phone use and risk of brain tumors, because of elevated exposure to the radiofrequency electromagnetic fields by the temporal region of the brain close to the antenna of the mobile phone. So far, the majority of published studies have not indicated an increased risk of brain tumors (1–3). Another organ of interest is the parotid gland, which is located over the jaw bone in front of the ear. This gland is likely to be exposed to radiofrequency radiation during mobile phone use if the handset is held close to the ear. Hence, if radiofrequency radiation has a carcinogenic effect, the exposure might be associated with parotid gland tumor. The few epidemiologic studies that have investigated the association between the use of mobile phones and the risk of malignant parotid gland tumors did not identify any association (4–6). However, these studies have limitations due to the small number of exposed cases (4, 5) and the short duration of phone use among study subjects (4–6).

Correspondence to Stefan Lönn, Institute of Environmental Medicine, Karolinska Institutet, Box 210, S-171 77 Stockholm, Sweden (e-mail: Stefan.Lonn@ki.se).

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Tumors in the parotid gland are very rare, and the etiology is largely unknown. In the Nordic countries, the incidence of malignant parotid gland tumor is less than 1/100,000 person-years. Benign tumors are more common than malignant tumors, but even they are very rare (7–9). The majority of the parotid gland tumors are benign pleomorphic adenomas (7, 10).

The study reported here is part of the Interphone Study (11), a collaborative study that includes cases (intracranial tumors and for some countries parotid gland tumors) and controls in 13 countries and is coordinated by the International Agency for Research on Cancer. The aim of the present study was to test the hypothesis that exposure to radiofrequency electromagnetic fields from mobile phones (450–1,800 MHz) increases the risk for malignant parotid gland tumor and benign pleomorphic adenoma in Denmark and Sweden. This is, to the best of our knowledge, the first study of the association between use of mobile phones and risk of benign pleomorphic adenomas.

MATERIALS AND METHODS

Two population-based case-control studies were conducted, one in Denmark and one in Sweden, following the same core study protocol. Both studies have been described in detail elsewhere (2, 3, 12, 13). The total study population was approximately 6.7 million people and included all persons aged 20–69 years who were residents of Denmark (approximately 3.6 million people) or Sweden (geographic area of three regional cancer registry areas: Stockholm, Göteborg, and Lund (approximately 3.1 million people)). The study period was from September 1, 2000, to August 31, 2002. Eligible malignant cases were individuals diagnosed with primary malignant parotid gland tumors during the study period. Eligible benign cases were individuals diagnosed with primary benign pleomorphic adenomas who lived in the Stockholm area and the Göteborg municipality within the Göteborg cancer registry area during the study period.

Cases with malignant and benign tumors were identified continuously during the study period in collaboration with many different clinics, including neurosurgery, oncology, neurology, and otorhinolaryngology clinics at the hospitals where these patients were treated. In order to ensure full coverage of malignant cases, we searched the regional cancer registries in Sweden and the national cancer registry in Denmark for cases not previously identified at the clinics. Benign parotid gland tumors are not reported to the cancer registries in any of the countries. To minimize the problem of identification of benign cases, we restricted the ascertainment of benign pleomorphic adenomas to Stockholm and the Göteborg municipality. Within these two areas, all public and private clinics in which these patients were treated were contacted to ensure the highest possible degree of ascertainment. Medical records for malignant and benign cases were examined to confirm the diagnosis, to establish the date of diagnosis (first medical examination leading to the diagnosis), and to determine the location of the tumor. The date of diagnosis was used for all cases as the referent date for exposure calculations. A total of 71 eligible malignant cases (33 cases in Denmark, 38 cases in Sweden) and 128 eligible benign cases were identified. Six percent ($n = 4$) of the malignant cases were identified at the cancer registry.

Controls were selected from the continuously updated national population registries. In Denmark, controls were individually matched to cases on age (in 5-year groups) and sex (three participating controls per participating case). In Sweden, the required number of controls stipulated by the common core protocol for the Interphone Study (11) was frequency matched by age (in 5-year groups), sex, and residential area as described previously (2, 13). The entire set of Swedish controls was used in the present study. The Danish controls received the date of diagnosis of the matched case as a referent date. The referent date for the Swedish controls was defined as the date when the control was identified, adjusted for the average time difference between the date of diagnosis and the date of identification of the cases within the same matching stratum to ensure a comparable length of follow-up for cases and controls. In total, 966 controls were identified (128 controls in Denmark, 838 controls in Sweden).

A rapid ascertainment procedure ensured that all individuals were approached as soon as possible after identification. The treating physician or the head of the clinic gave permission before any contact was made with the case. Each case and eligible control for the study was offered the opportunity to participate in a personal interview and a telephone interview if refusing a personal interview. If the person also refused a telephone interview, the person was invited to respond to a mailed questionnaire (only in Sweden). If a case had died, the closest family member was asked to participate (one malignant case in Sweden). Persons who were completely deaf prior to the referent date or who did not possess the intellectual and language skills necessary to complete the interview were excluded.

Information about lifestyle and environmental exposures was obtained by use of a computer program that guided the interview with questions read by the interviewer. The responses were entered directly into the computer by the interviewer. All interviewers were provided with cards displaying photographs of mobile phones and information about make, models, and year of introduction.

Individuals were unexposed if they reported never or only rarely (not regularly) using a mobile phone and exposed if they reported regular use (mobile phone use on average once per week during 6 months or more). Exposure within 1 year of the referent date was not considered. The number of years of regular mobile phone use was categorized as less than 5 years, 5–9 years, and 10 years or more. The same categorization was used for time since first regular use. Calculated cumulative number of hours of mobile phone use and cumulative number of mobile phone calls were divided into categories with cutpoints approximately at the 25th and 75th percentile for controls. Usages of analog (Nordic Mobile Telephone (NMT)) and digital (Global System Mobile (GSM)) mobile phones were analyzed separately, because it is believed that the old analog phones emitted on average higher power signals than do the later digital models. Separate analyses were also performed for persons reporting mobile

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TABLE 1. Basic characteristics of participating malignant parotid gland tumor cases, benign pleomorphic adenoma cases, and controls in Denmark and Sweden, 2000–2002

	Denmark		Sweden			
	Malignant parotid ($n = 26$)	Controls* ($n = 77$)	Malignant parotid ($n = 34$)	Controls† ($n = 604$)	Benign parotid ($n = 112$)	Controls†,‡ ($n = 321$)
Median age (years) at referent date	53	55	58	54	45	54
Sex (%)						
Female	42	42	62	52	48	52
Male	58	58	38	48	52	48
Education (%)						
Compulsory school	35	19	29	22	14	21
Vocational/secondary school	4	19	26	27	20	24
Upper secondary school	42	45	18	20	29	20
University	19	16	24	30	37	34
Unknown	0	0	3	1	0	1

* Three individually matched controls per case (except for one case that had only two matched controls).
† Frequency matched controls.
‡ Controls restricted to pleomorphic adenoma cases (included in only the Stockholm area and the Göteborg municipality).

phone use mainly in urban areas, in rural areas, and in both urban and rural areas, because higher exposure levels have been reported for phone use in rural areas (14).

The possible association between laterality of phone use and laterality of tumors was analyzed with a method described previously (2, 13). The cases were divided into a left-side and a right-side group depending on the location of the tumor. The Danish controls were assigned the same side as the matched cases. The Swedish controls were randomly assigned into the left-side or right-side group—one for cases with left-side tumors and one for cases with right-side tumors. For both cases and controls, exposure was defined as ipsilateral phone use or use of the phone on both sides, whereas contralateral use was considered unexposed. Based on this, side-specific risk estimates were calculated and then pooled into one risk estimate. To test for potential recall bias, we made similar analyses where contralateral phone use or use on both sides was considered exposed, and ipsilateral use was considered unexposed.

Associations between indicators of exposure to radiofrequency electromagnetic fields from mobile phone use and parotid gland tumors were estimated as odds ratios, using unconditional logistic regression models with 95 percent confidence intervals. All analyses were adjusted for age, gender, residential area (regional cancer registry area), country, and educational level (compulsory school, vocational or secondary school, upper secondary school, and university). The analyses were also adjusted for smoking, exposure to ionizing radiation, and history of prior cancer, but none of these factors was included in the final statistical model because they did not influence the results.

The odds ratio for the Danish data was first estimated by conditional logistic regression models but, since there were no appreciable differences in the results between the conditional and the unconditional analysis (data not shown), only unconditional logistic regression analyses are presented.

The studies were approved by the ethical committees and the Data Protection Agency in both Denmark and Sweden.

RESULTS

The overall participation rate was 70 percent for controls (60 percent in Denmark, 72 percent in Sweden), 85 percent for the malignant parotid gland tumor cases (79 percent in Denmark, 89 percent in Sweden), and 88 percent for the benign cases in Sweden. Basic characteristics for study participants are presented in table 1. Face-to-face interviews provided exposure information for the majority of participating cases (92 percent) and controls (90 percent). Results were unchanged after excluding answers through telephone interviews (7 percent for cases, 4 percent for controls) and mailed questionnaires (2 percent for cases, 6 percent for controls). We did not observe any major differences between the country-specific results (data not shown); thus, results are presented for the two countries combined and include information from both telephone interviews and mailed questionnaires.

For regular mobile phone use, the estimated odds ratio was 0.7 (95 percent confidence interval: 0.4, 1.3) for malignant parotid gland tumors and 0.9 (95 percent confidence interval: 0.5, 1.5) for benign pleomorphic adenomas. The risk estimates did not increase with amount of use (hours, calls, or years of use) (table 2). Analyses of digital and analog phone use separately did not reveal any increased

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TABLE 2. Odds ratio* of malignant parotid gland tumors and benign pleomorphic adenoma† according to mobile phone use in Denmark and Sweden, 2000–2002‡

	Malignant parotid gland tumors				Benign pleomorphic adenomas			
	No. of cases	No. of controls	Odds ratio	95% confidence interval	No. of cases	No. of controls	Odds ratio	95% confidence interval
Frequency of use								
Never or rarely§	35	280	1.0		35	119	1.0	
Regular use¶	25	401	0.7	0.4, 1.3	77	202	0.9	0.5, 1.5
Duration (years) of regular use								
<5	15	237	0.7	0.3, 1.4	48	110	1.0	0.6, 1.7
5–9	8	125	0.7	0.3, 1.8	24	72	0.9	0.5, 1.7
≥10	1	30	0.3	0.0, 2.5	5	13	1.1	0.4, 3.6
Time (years) since first regular use								
<5	14	228	0.7	0.3, 1.3	47	104	1.0	0.6, 1.8
5–9	8	128	0.7	0.3, 1.7	23	76	0.8	0.4, 1.5
≥10	2	36	0.4	0.1, 2.6	7	15	1.4	0.5, 3.9
Cumulative use (hours)								
<30	7	110	0.7	0.3, 1.6	20	45	1.1	0.6, 2.3
30–449	11	184	0.7	0.3, 1.4	34	92	0.9	0.5, 1.6
≥450	5	90	0.6	0.2, 1.8	22	52	1.0	0.5, 2.1
Cumulative no. of calls								
≤624	5	101	0.5	0.2, 1.3	13	37	0.9	0.4, 2.0
625–7,349	12	190	0.7	0.3, 1.6	40	100	0.9	0.5, 1.7
≥7,350	6	95	0.7	0.3, 2.0	21	53	1.0	0.5, 2.1

* Adjusted for age, gender, geographic region, and education.
† Included in only two regions (Stockholm area and Göteborg municipality).
‡ Totals for variables are not equal because of missing responses to several questions.
§ Referent category.
¶ "Regular use" defined as use of a mobile phone on average once per week or more, during 6 months or more.

risks, and the odds ratio did not increase for use of mobile phones mainly in rural or urban areas. Similar results were found for 5 years' duration of use (data not shown).

Table 3 shows the risk estimates of malignant and benign tumors according to self-reported laterality of phone use in relation to laterality of the tumor. The results for benign tumors displayed higher odds ratios for ipsilateral use compared with those for malignant tumors, although the confidence intervals were relatively wide and no estimates were significantly different from 1.0. The risk estimates for contralateral exposure showed decreased odds ratios for both malignant and benign tumors.

DISCUSSION

Our findings do not indicate any association between mobile phone use and the risk of malignant or benign parotid gland tumors. The results are in agreement with previous findings in studies of the association between use of mobile phones and risk of malignant parotid gland tumors (4–6). The present study is the first report to investigate benign parotid gland tumors in association with mobile phone use. Our results are based on two population-based case-control studies, including a rapid ascertainment procedure of cases through active participation by clinics involved in the treatment of the tumors included. Diagnostic information from the cancer registries was obtained as a supplement to the identification of cases at the clinics, ensuring a high quality of total ascertainment of malignant cases. Controls randomly sampled in population registries continuously throughout the study period ensured that controls did not have a longer opportunity for exposure than did cases. The age and sex differences between parotid gland cases and controls in the Swedish data are due to the frequency matching of controls to the entire case group (also including brain tumors and acoustic neurinomas) (2, 13) and not frequency matching of controls to the parotid gland cases only. The same core study protocol was used in both Denmark and Sweden, ensuring similar procedures underlying the entire data collection. The interviews were highly structured to minimize the risk of interviewer bias. Before the beginning

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TABLE 3. Odds ratio* of malignant parotid gland tumors and benign pleomorphic adenoma† according to laterality of the tumor in relation to laterality of mobile phone use in Denmark and Sweden, 2000–2002‡

	Malignant parotid gland tumors				Benign pleomorphic adenomas			
	No. of cases	No. of controls	Odds ratio	95% confidence interval	No. of cases	No. of controls	Odds ratio	95% confidence interval
Ipsilateral exposure§								
Referent	36	452	1.0		58	210	1.0	
Regular use¶	16	226	1.2	0.6, 2.6	51	111	1.4	0.9, 2.2
Duration (years) of regular use								
<5	10	128	1.2	0.6, 2.7	30	57	1.4	0.8, 2.5
5–9	5	73	1.1	0.4, 3.2	17	41	1.5	0.7, 2.8
≥10	1	19	0.9	0.1, 7.4	4	8	2.0	0.5, 7.0
Time (years) since first regular use								
<5	9	125	1.2	0.5, 2.6	29	55	1.4	0.8, 2.5
5–9	6	72	1.3	0.5, 3.6	16	42	1.3	0.6, 2.5
≥10	1	23	0.7	0.1, 5.7	6	9	2.6	0.9, 7.9
Contralateral exposure#								
Referent	45	460	1.0		74	209	1.0	
Regular use	8	218	0.5	0.2, 1.1	35	112	0.7	0.4, 1.1
Duration (years) of regular use								
<5	5	130	0.5	0.2, 1.3	24	60	0.9	0.5, 1.5
5–9	2	66	0.4	0.1, 1.8	10	40	0.6	0.3, 1.2
≥10	0	16			1	8	0.3	0.0, 2.6
Time (years) since first regular use								
<5	4	122	0.4	0.1, 1.2	24	54	1.0	0.5, 1.8
5–9	3	71	0.6	0.2, 2.0	10	45	0.5	0.2, 1.0
≥10	0	19			1	9	0.3	0.0, 2.3

* Adjusted for age, gender, geographic region, education, and country.

† Included in only two regions (Stockholm area and Göteborg municipality).

‡ Totals for variables are not equal because of missing responses to several questions. Three controls did not state on which side of the head they generally held the phone and were therefore excluded in the analysis; 11 cases were excluded because of missing information on tumor side or phone side.

§ "Exposure" defined as phone use on the same side as the tumor or on both sides and "referent category" defined as never or rare use of any type of mobile phone and use on the opposite side of the tumor.

¶ "Regular use" defined as use of a mobile phone on average once per week or more, during 6 months or more.

"Exposure" defined as phone use on the opposite side of the tumor or on both sides and "referent category" defined as never or rare use of any type of mobile phone and use on the same side as the tumor.

of the study, interviewers in Denmark and Sweden attended the same interview-training workshop based on the Interphone Study protocol.

Benign parotid gland tumors are not reported to the cancer registry, and therefore it is likely that the ascertainment of benign tumors is not as complete as that of the malignant tumors. To minimize the problem with identification of benign cases, the ascertainment was restricted to two urban areas to ensure the highest possible degree of ascertainment. Even if some cases were not ascertained, there is, however, no reason to believe that the use of mobile phones would be associated with the probability of ascertainment, thereby leading to selection bias.

Our results did not indicate any association between amount of mobile phone use in hours or number of calls and disease risk. There is, however, some evidence that people tend to overestimate their amount of use, and the correlation between subjective reports about amount of use and what was registered by the operator is low (15, 16). Thus, there is a possibility that exposure misclassification may have affected these results.

Many of the observed risk estimates were below unity, especially for malignant parotid gland tumors but to some degree also for the benign tumors. There are several plausible noncausal explanations for these findings. Nonparticipation among controls is a possible source of bias. All

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study persons were informed about the aim of the study and, if mobile phone users among controls were more willing to participate than were nonusers, the risk might be underestimated. To test this potential problem, individuals in the Swedish study that declined participation when contacted by phone were asked if they had regularly used a mobile phone. Only a limited number of persons answered the question, but the results indicated that controls who declined participation had a lower proportion of regular users compared with participants (13). This type of bias would lead to findings of risk estimates below unity. It is also possible that cases with malignant tumors might have more difficulties in remembering details about phone use than would healthy persons (or cases with benign tumors), and the exposure could therefore be underreported. Furthermore, some of the findings are based on very small numbers, especially for long-term mobile phone use, and shifting only one or two cases between exposure categories would have a large impact on the results. Thus, random variation might also contribute to the observation of reduced risk estimates.

For a slow-growing tumor such as benign parotid gland tumor (10), the latency period can be several years, whereas more rapidly developing malignant tumors are detected within a short time period after occurrence. This makes it especially difficult to predict the actual length of a latency period for benign parotid gland tumors. Among cases with short-term mobile phone use, the tumor could have been present before the start of mobile phone use.

The results for ipsilateral phone use and contralateral phone use need to be interpreted in concert, because these analyses are dependent on each other. An observed increased risk of ipsilateral phone use cannot be interpreted as evidence of a causal association if the contralateral analysis displays an equivalent decreased risk. For example, the laterality analyses for the benign parotid gland tumors indicate an increased risk for long-term (more than 10 years of use) ipsilateral use but also an equivalent decreased risk for contralateral use, which indicates possible recall bias when answering the question about on which side of the head the phone was usually held. The interpretation of the risk estimates for short-term and long-term mobile phone use in relation to malignant parotid gland tumors is limited by small numbers but does not indicate any increased risk.

The etiology of tumors in the parotid gland is largely unknown. Many etiologic factors have been suggested (e.g., smoking, ultraviolet radiation, and occupation exposures), but the only established risk factors are ionizing radiation and history of prior cancer (17–21). Adjustment for smoking, ionizing radiation, and history of prior cancer in the analyses did not change the results. However, because of this sparse knowledge on risk factors of parotid gland tumors, our variants to control for confounding were limited. Thus, it cannot be ruled out that an unknown risk factor correlated with mobile phone use explains to some extent some of the decreased risks that we observed.

Even though radiofrequency radiation is unlikely to cause gene mutations (1), it is too soon for firm conclusions regarding the health risk from mobile phones. The major reason for this is that the phones have not been present for a long time, and all studies to date have relatively few long-term users, that is, persons who have used a mobile phone for more than 10 years.

In conclusion, our results do not support the hypothesis that exposure to radiofrequency electromagnetic fields from mobile phones increases the risk of malignant or benign parotid gland tumors. However, mobile phones have not been used long enough to exclude their possible carcinogenic effect after long-term use, and more epidemiologic studies including long-term users are clearly warranted.

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Conflict of interest: none declared.

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