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Original Contribution

Cellular Phone Use and Risk of Benign and Malignant Parotid Gland Tumors—A Nationwide Case-Control Study

Siegal Sadetzki[1,2], Angela Chetrit[1], Avital Jarus-Hakak[1], Elisabeth Cardis[3], Yonit Deutch[1], Shay Duvdevani[4], Ahuva Zultan[1], Ilya Novikov[5], Laurence Freedman[5], and Michael Wolf[2,4]

[1] Cancer and Radiation Epidemiology Unit, Gertner Institute, Chaim Sheba Medical Center, Tel Hashomer, Israel.
[2] Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel.
[3] Radiation Group, International Agency for Research on Cancer, Lyon, France.
[4] Department of Otolaryngology–Head and Neck Surgery, Chaim Sheba Medical Center, Tel Hashomer, Israel.
[5] Biostatistics Unit, Gertner Institute, Chaim Sheba Medical Center, Tel Hashomer, Israel.

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The objective of this nationwide study was to assess the association between cellular phone use and development of parotid gland tumors (PGTs). The methods were based on the international INTERPHONE study that aimed to evaluate possible adverse effects of cellular phone use. The study included 402 benign and 58 malignant incident cases of PGTs diagnosed in Israel at age 18 years or more, in 2001–2003, and 1,266 population individually matched controls. For the entire group, no increased risk of PGTs was observed for ever having been a regular cellular phone user (odds ratio = 0.87; $p = 0.3$) or for any other measure of exposure investigated. However, analysis restricted to regular users or to conditions that may yield higher levels of exposure (e.g., heavy use in rural areas) showed consistently elevated risks. For ipsilateral use, the odds ratios in the highest category of cumulative number of calls and call time without use of hands-free devices were 1.58 (95% confidence interval: 1.11, 2.24) and 1.49 (95% confidence interval: 1.05, 2.13), respectively. The risk for contralateral use was not significantly different from 1. A positive dose-response trend was found for these measurements. Based on the largest number of benign PGT patients reported to date, our results suggest an association between cellular phone use and PGTs.

case-control studies; cellular phone; head and neck neoplasms; Israel; parotid gland

Abbreviations: CI, confidence interval; OR, odds ratio; PGT, parotid gland tumor; UICC, Union Internationale Contre le Cancer.

Since the mid-1990s when cellular phones became widespread in most Western countries, there has been concern about the possible carcinogenic effects of the electromagnetic radiofrequency fields thereby emitted (1, 2). Numerous studies addressing this issue have been published recently (3–14). Most focused on brain tumors that occur in an anatomic location where a substantial amount of the power is absorbed. The vast majority did not show an association between cellular phone use and the development of such tumors. Most studies, however, included few long-term users, reducing the chance of finding any association if one exists because of an assumed long latency time.

In accordance with the recommendations of several expert committees, an international series of case-control studies (known as the INTERPHONE study) on the relation between cellular phone use and several types of head tumors was conducted in 13 countries, including Israel (15). Several individual reports from this collaboration have been published, each reporting on part of the collaborative study population (8–14).

Correspondence to Dr. Siegal Sadetzki, Cancer and Radiation Epidemiology Unit, Gertner Institute, Chaim Sheba Medical Center, Tel Hashomer 52621, Israel (e-mail: siegals@gertner.health.gov.il).

The Israeli study included meningioma, glioma, acoustic neuroma, and benign and malignant parotid gland tumors (PGTs).

The Israeli population is characterized by high levels of use as expressed by prevalence of phone use and cumulative number and duration of calls (16) (unpublished data).

The absorption of radiofrequency energy emitted by cellular phones is attenuated by more than 90 percent within 40–50 mm from the exposure source (3). The anatomic location of the parotid gland (at the anterior border of the external ear and between the mandibular ramus and the sternocleidomastoid muscle, 4–10 mm deep in the skin surface) makes these tumors plausible candidates for being influenced by exposure to cellular phones, on the side of the head where the cellular phone is held. This tumor occurs in the relatively young (mean age at diagnosis: 43 years for benign and 55 years for malignant tumors) (17), an age group likely to include a substantial number of long-term cellular phone users (15).

This report, from a nationwide population-based study, presents results of analyses of risk of benign and malignant PGTs in relation to cellular phone use.

MATERIALS AND METHODS

The Israeli study followed the core protocol of the INTERPHONE study. Additional national funding was allocated to extend the age range in the Israeli component from 30 to 59 years to include all persons aged 18 years or more. All 22 otolaryngology departments throughout the country participated in the study. Eligible cases were adult Jewish individuals with histologically or cytologically confirmed benign or malignant PGT, diagnosed between January 2001 and December 2003. Cases were identified through a periodic review of pathology/cytology reports of all relevant institutions. All diagnoses were validated by a single physician (S. D.).

Controls for the entire Israeli INTERPHONE study were randomly selected from the National Population Registry and were individually matched to the original case (meningioma/glioma/acoustic neuroma/PGT). Controls were not eligible if they had left the country or were mentally disabled. To increase the statistical power of the PGT comparison, we tried to include all the participating controls in the analysis by a post hoc matching. We individually assigned up to seven controls to each case, using a hierarchical algorithm that included the matching variables in the following order: gender, interview date (preferably within 1 year), age (preferably within 1 year and up to 5 years), and continent of birth.

Data were obtained by a personal interview including information on demographic variables, cellular phone use, and other possible risk factors. Participants were asked whether they were ''regular users'' of a cellular phone, defined as making or receiving more than one call per week for at least 6 months. Regular users were asked to identify in an album all of the cellular phones they had ever used and to recall their history of use of each phone, namely, dates of starting and stopping use, number of calls made or received, average duration of calls, changes in the pattern of use over a period of more than 6 months, use of headsets and hands-free devices in vehicles, the side of the head on which the phone was predominantly held, handedness, and main area of use (urban/rural/both). Exposures were considered up to 1 year prior to the reference date, which was defined as the date of diagnosis for cases and as the same date as their matched case for controls.

To investigate the possibility that response rates were influenced by cellular phone use, we conducted a short telephone interview of cellular phone use with subjects refusing to participate in the study.

Medical records were used to define the clinical characteristics of the tumor. The study was approved by the ethics committees of all hospitals and by the Clinical Trial Unit, Pharmaceutical Department, Ministry of Health. Informed consent was obtained from all participants.

For descriptive purposes pertaining to statistical analysis, distributions among controls were weighted by the inverse number of controls in matched sets, because the number of controls per case varied with some of the risk factors, particularly age. Such weighting effectively produces the distribution among controls that would have been seen if each case had the same number of controls. Case-control comparisons were performed by use of the weighted chi-square test.

The main analyses were based on conditional logistic regression; adjustment for smoking was also performed. Because of the possibility of a consistent downward bias in odds ratios caused by selective participation on the basis of cellular phone use, we repeated the analyses among regular users using the low-exposure level as reference.

Cumulative use was analyzed with modification for reported use of hands-free devices as follows: It was reduced by 100, 75, 50, and 25 percent when participants reported use of such devices all of, most of, half of, or less than half of the time, respectively.

''Ipsilateral'' exposure was defined as phone use on the same side as the tumor, ''contralateral'' as phone use on the opposite side, and ''both'' as no preferred side of phone use or presence of tumor on both sides. The association between laterality of tumor and side of cellular phone use was assessed by two approaches:

- A case-only analysis (Inskip et al. (4)), including only cases who were regular users reporting on a single dominant side of use. The relative risk was estimated as (1 + the square root of the odds ratio)/2.
- Case-control analysis stratified to ipsilateral and contralateral use in which laterality for controls was defined as the anatomic side of the tumor of their matched case. Exposure was defined as ''ipsilateral'' or ''both'' for the ipsilateral analysis and as ''contralateral'' only for the contralateral analysis; ''nonregular users'' were considered as the reference category.

To avoid exclusion of large numbers of matched sets, we based laterality analyses on unconditional logistic regression adjusted for age, gender, and year of interview. Results with conditional and unconditional logistic regression were similar.

For trend tests, categorical variables were assigned scores of 0 and 1–4 (nonregular users and quartiles) according to their ordered categories and were treated in the model as continuous variables.

TABLE 1. Comparison of selected variables between participants and nonparticipants by study group and reason for nonparticipation, Israel, 2001–2003

	Cases					Controls				
	No. eligible ($n = 531$)	Participants ($n = 460$)	Refused ($n = 60$)	Unable to be traced* ($n = 11$)	p value†	No. eligible ($n = 1,920$)	Participants ($n = 1,266$)	Refused ($n = 454$)	Unable to be traced ($n = 200$)	p value†
Total (%)		86.6	11.3	2.1			65.9	23.7	10.4	
Gender (%)										
Males	288	88.2	10.1	1.7	0.3	806	68.4	20.7	10.9	0.06
Females	243	84.8	12.8	2.5		1,114	64.2	25.8	10.1	
Mean age (years) at recruitment		53.3 (16.6)‡	59.8 (18.0)	58.7 (13.9)	<0.01		59.3 (14.9)	59.0 (14.1)	60.8 (15.5)	0.7
Place of birth (%)										
Asia	71	85.9	14.1		0.2	260	63.1	30.0	6.9	0.03
North Africa	64	93.8	6.3			252	67.1	24.6	8.3	
Europe-United States	178	83.2	13.5	3.4		877	63.5	21.0	15.5	
Israel	218	87.6	10.1	2.3		531	70.8	24.5	4.7	
Time from immigration to first contact (%)§										
<10 years	43	79.1	11.6	9.3¶	0.3	56	51.8	19.6	28.6	<0.01
≥10 years	270	87.0	12.2	0.7		1,326	64.9	23.2	11.9	
Born in Israel	218	87.6	10.1	2.3		531	70.8	24.5	4.7	
Tumor classification (%)										
Benign	462	87.0	11.0	1.9	0.6					
Malignant	69	84.1	13.0	2.9						

* Including one case who was not interviewed because of language difficulties.
† p value for comparison of participants and nonparticipants.
‡ Numbers in parentheses, standard deviation.
§ Seven controls with missing data.
¶ Untraced versus traced: $p = 0.001$.

RESULTS

Study population

During the study period, 531 eligible cases were identified. Of them, 87 percent agreed to participate, 11 percent refused, and 2 percent could not be traced (table 1). Response rates did not differ significantly by gender; by place of birth; among recent (<10 years) immigrants, earlier (≥10 years) immigrants, and the Israeli born; or by tumor classification. Participants tended to be younger than nonparticipants ($p = 0.003$), and a larger proportion of the recent immigrants could not be traced ($p = 0.001$).

In total, 1,920 eligible controls were identified; 66 percent were interviewed, 24 percent refused, and 10 percent could not be traced. Age at recruitment was similar in participants and nonparticipants, the response rate was influenced by time since immigration, and it was higher in males than females ($p = 0.06$) and in the Israeli born compared with the non-Israeli born ($p = 0.01$) (table 1).

All cases had at least one matched control; 75 percent and 42 percent had at least two and three controls, respectively; 87 percent of the controls were matched to cases within 2 years of age. The time difference between the interviews of cases and controls was within 1 year for 98 percent. Proxy interviews (spouse or offspring) were conducted for 18 cases and eight controls, and telephone interviews were conducted for 19 cases and 49 controls.

The participants' cooperation and apparent recall of cellular phone use were classified by their interviewers as very or fairly good for 95 percent of the interviewees, with no difference between cases and controls.

A short telephone interview was completed by 78 percent of the refusal controls. A significantly lower rate of regular cellular phone use was reported by the refusal control group compared with the participant group ($p < 0.001$). Among regular users, 57 percent of the refusal controls reported starting cellular phone use before 2001, compared with 80 percent in the participant controls ($p < 0.001$). No significant differences in regular cellular phone use were observed between the cases who participated in the study and those who refused but participated in the refusal questionnaire (66 percent of the 60 refusal cases).

Our analysis included 460 cases (58 malignant, 264 pleomorphic adenoma, 117 Warthin's tumor, and 21 others) and 1,266 controls (table 2). The male/female ratio among cases was 1.2, and their mean age at diagnosis was about 52 (range: 18–98) years. About 40 percent of the cases were Israeli born, more than 70 percent were married, 14 percent had only a primary school level of education, and 30 percent

TABLE 2. Distribution of demographic characteristics by study group, Israel, 2001–2003

	Cases ($n = 460$)		Controls ($n = 1,266$)		Weighted* controls (%)	p value†
	No.	%	No.	%		
Gender						
Males	254	55.2	551	43.5	55.2	1.0
Females	206	44.8	715	56.5	44.8	
Age (years) at reference date						
<30	56	12.2	69	5.5	12.6	1.0
30–39	60	13.0	88	7.0	12.0	
40–49	88	19.1	201	15.9	19.1	
50–59	113	24.6	350	27.6	24.8	
60–69	67	14.6	256	20.2	14.8	
≥70	76	16.5	302	23.8	16.7	
Origin						
Asia	60	13.0	164	13.0	12.8	0.9
North Africa	60	13.0	169	13.4	13.0	
Europe-United States	149	32.4	557	44.0	32.7	
Israel	191	41.5	376	29.7	41.5	
Marital status						
Married	332	72.2	912	72.0	73.4	0.8
Single	52	11.3	63	5.0	9.3	
Divorced/separated	35	7.6	100	7.9	7.8	
Widowed	40	8.7	184	14.5	8.7	
Unknown	1	0.2	7	0.6	0.8	
Education						
Primary school	66	14.4	177	14.0	11.5	0.4
Secondary/high school	164	35.7	425	33.6	33.6	
Medium-level school‡	87	18.9	249	19.6	20.4	
University/high-level technical school	140	30.4	408	32.2	33.8	
Unknown	3	0.6	7	0.6	0.8	
Cigarette smoking						
No	183	39.8	680	53.7	50.6	0.001
Yes	286	60.0	586	46.3	49.4	
Unknown	1	0.2				

* Weighted (inversely) to the number of controls for each case.
† Cases versus weighted controls.
‡ Technical/professional/"Yeshiva" graduate school.

were university or technical school graduates. There were no significant differences in the distribution of these variables between cases and controls. Smoking was significantly more prevalent among cases compared with controls ($p = 0.001$).

Cellular phone analysis

The weighted proportions of regular users among controls were 64 percent, 30 percent, and 3 percent at 1, 5, and 10 years before the reference date, respectively (table 3). No increased risk of PGT was seen for any of the exposure measures tested (regular use, time since start, duration of use, cumulative number of calls, and cumulative call time) for the total group, the malignant group, and the benign group. These results were substantially unchanged after controlling for smoking.

When analyses were restricted to regular users only, increased odds ratios were seen for start of use 5 years or more in the past, as well as for cumulative number of calls and cumulative call time (Appendix table 1).

Among the 284 cases who were regular users, 155 (54.6 percent) reported ipsilateral use, 101 (35.6 percent) contralateral use, and 27 (9.5 percent) use on both sides (table 4). Based on Inskip's method, the relative risk for ipsilateral compared with contralateral use was 1.32 ($p = 0.001$).

The proportions of cases and controls whose handedness corresponded to their side of phone use were similar (69 percent and 70 percent, respectively) ($p = 0.86$) (table 5).

Laterality analyses are presented in table 6. Elevated odds ratios were found for ipsilateral use 5 years (odds ratio (OR) = 1.34; $p = 0.06$) and 10 years (OR = 1.69; $p = 0.2$) in the past.

For all exposure measures studied, the odds ratios for above-median ipsilateral use were elevated and statistically significant: 1.58 (95 percent confidence interval (CI): 1.11, 2.24) for cumulative number of calls and 1.49 (95 percent CI: 1.05, 2.13) for cumulative call time. Significant trends were seen for ipsilateral use for cumulative number of calls ($p = 0.02$) and for cumulative call time ($p = 0.03$). For contralateral use, odds ratios were less than 1.0 but were not statistically significant. Both the ipsilateral group and the "both side users" group showed elevated odds ratios for most cellular phone use parameters in the highest categories of use (Appendix table 2). The odds ratios for the ipsilateral analysis remained elevated after stratifying for malignant and benign tumors, as well as when stratifying for pleomorphic adenoma and Warthin's tumor. However, statistical significance was reached only for the largest group, that is, all benign tumors. In this group, the odds ratios for above-median ipsilateral use for cumulative number of calls and cumulative call time were 1.52 (95 percent CI: 1.05, 2.20) and 1.44 (95 percent CI: 0.99, 2.09), respectively (not shown).

Among the 690 regular users' controls, 505 (73 percent) reported their use mainly in urban areas, 43 (6 percent) mainly in rural areas, and 142 (21 percent) in both (table 7). No statistical differences were noted in the distribution of areas of use between cases and controls after weighting ($p = 0.7$). For cellular phone use in rural and both areas, increased odds ratios were found for most measures of exposure. The odds ratios for the highest quartile of cumulative number of calls and cumulative call time were 1.81 (95 percent CI: 1.04, 3.14) and 1.96 (95 percent CI: 1.11, 3.44) ($p_{trend} = 0.06$ and 0.04), respectively. This pattern was not seen for mainly urban cellular phone use.

DISCUSSION

Our results suggest a relation between long-term and heavy cellular phone use and PGTs. This association was

TABLE 3. Levels of cellular phone use and risk of parotid gland tumors by tumor type, Israel, 2001–2003

	Total				Benign				Malignant			
	Cases (no.)	Controls (no.)	Odds ratio*	95% confidence interval	Cases (no.)	Controls (no.)	Odds ratio*	95% confidence interval	Cases (no.)	Controls (no.)	Odds ratio*	95% confidence interval
Regular user												
No, <1 year	175	575	1.0†		150	469	1.0†		25	106	1.0†	
Yes	285	691	0.87	0.68, 1.13	252	603	0.85	0.64, 1.12	33	88	1.06	0.54, 2.10
Regular user 5 years in the past												
No	319	969	1.0†		273	808	1.0†		46	161	1.0†	
Yes	141	297	1.01	0.77, 1.32	129	264	1.04	0.78, 1.38	12	33	0.79	0.36, 1.76
Regular user 10 years in the past												
No	447	1,240	1.0†		390	1,050	1.0†		57	190	1.0†	
Yes	13	26	0.93	0.47, 1.86	12	22	1.02	0.49, 2.12	1	4	0.45	0.05, 4.28
Time since start use (years)												
Never, <1 year	175	575	1.0†		150	469	1.0†		25	106	1.0†	
1–4.9	138	389	0.82	0.61, 1.10	117	335	0.77	0.56, 1.06	21	54	1.25	0.58, 2.68
5–9.9	134	276	0.95	0.70, 1.30	123	246	0.95	0.68, 1.32	11	30	0.92	0.37, 2.27
≥10	13	26	0.86	0.42, 1.77	12	22	0.93	0.44, 1.98	1	4	0.47	0.05, 4.51
Duration of use (years)												
Never, <1 year	175	575	1.0†		150	469	1.0†		25	106	1.0†	
1–4.9	148	405	0.84	0.63, 1.12	127	351	0.79	0.54, 1.08	21	54	1.25	0.58, 2.68
5–9.9	124	264	0.92	0.67, 1.27	113	234	0.92	0.65, 1.29	11	30	0.92	0.37, 2.27
≥10	13	22	1.0	0.48, 2.09	12	18	1.11	0.50, 2.44	1	4	0.47	0.05, 4.51
Cumulative no. of calls (with no hands-free devices)‡												
Nonusers, <1 year	176	587	1.0†		151	480	1.0†		25	107	1.0†	
≤5,479	117	382	0.79	0.59, 1.05	99	328	0.74	0.54, 1.02	18	54	1.12	0.53, 2.35
5,480–18,996	86	157	1.13	0.79, 1.61	77	141	1.10	0.76, 1.61	9	16	1.33	0.48, 3.71
≥18,997	81	140	1.06	0.73, 1.54	75	123	1.09	0.74, 1.62	6	17	0.72	0.22, 2.39
Cumulative call time (hours) (with no hands-free devices)‡												
Nonusers, <1 year	176	587	1.0†		151	480	1.0†		25	107	1.0†	
≤266.3	121	390	0.82	0.62, 1.09	103	336	0.78	0.57, 1.06	18	54	1.21	0.58, 2.53
266.4–1,034.9	80	155	1.03	0.72, 1.47	75	139	1.05	0.72, 1.53	5	16	0.67	0.19, 2.38
≥1,035	83	134	1.09	0.75, 1.60	73	117	1.08	0.72, 1.62	10	17	1.22	0.43, 3.48
Cumulative call time (hours) (with no hands-free devices)‡ by time since start use (years)												
Nonusers, <1 year	176	587	1.0†		151	480	1.0†		25	107	1.0†	
<5 years												
≤266.3	91	294	0.82	0.60, 1.12	76	248	0.77	0.55, 1.09	15	46	1.17	0.53, 2.56
>266.3	47	88	1.03	0.66, 1.62	41	81	0.96	0.60, 1.54	6	7	2.03	0.47, 8.80
≥5 years												
≤266.3	30	96	0.83	0.52, 1.31	27	88	0.79	0.48, 1.27	3	8	1.36	0.31, 5.92
>266.3	116	201	1.07	0.76, 1.50	107	175	1.11	0.77, 1.59	10	26	0.77	0.29, 2.06
Cumulative no. of calls (with no hands-free devices)‡ by time since start use (years)												
Nonusers, <1 year	176	587	1.0†		151	480	1.0†		25	107	1.0†	
<5 years												
≤5,479	91	300	0.79	0.57, 1.08	75	252	0.73	0.52, 1.03	16	48	1.19	0.54, 2.60
>5,479	47	82	1.16	0.74, 1.82	42	77	1.09	0.68, 1.74	5	5	2.26	0.49, 10.40
≥5 years												
≤5,479	26	82	0.79	0.48, 1.31	24	76	0.77	0.45, 1.30	2	6	1.06	0.20, 5.57
>5,479	120	215	1.08	0.77, 1.50	110	187	1.10	0.78, 1.57	10	28	0.85	0.33, 2.22

* The odds ratios were substantially unchanged after controlling for cigarette smoking; therefore, the unadjusted odds ratios are presented here.

† Referent.

‡ Based on the distribution of users' controls (weighted) and divided into the following categories: ≤median, >median–≤third quartile, and >third quartile.

TABLE 4. Side of cellular phone use and side of the tumor for regular users among the study cases, Israel, 2001–2003*

Side of tumor	Side of regular cellular phone use†		
	Left	Right	Both
Left	44	78	10
Right	23	111	16
Left and right	0	1	1
Total	67	190	27

* Inskip test: odds ratio (OR) = 2.72, 95% confidence interval: 1.47, 5.08; relative risk = 1.32; $p = 0.001$. Note: the relative risk was calculated as $(1 + \sqrt{OR})/2$.

† One user with missing data.

TABLE 5. Handedness and side of cellular phone use among regular users by study group, Israel, 2001–2003*

	Cases		Controls	
	No.	%	No.	% (weighted)
Same side	197	69.4	470	69.7
Opposite side	57	20.0	132	18.4
No preferred side	27	9.5	64	10.2
Ambidextrous	3	1.0	13	1.8

* $p = 0.86$ for comparison of cases and weighted controls.

seen in analyses restricted to regular users, analyses of laterality of phone use, and analyses of area of main use.

Increased risk estimates were found for ipsilateral regular use 5 and 10 years in the past, although the latter was based on small numbers. Significantly elevated odds ratios were observed consistently in the highest category of each of the measures of cellular phone use on the ipsilateral side, supporting a dose-response association. This association between side of use and PGTs was also seen by a case-only analysis. In addition, a positive association was seen for cellular phone use in rural areas, which was not shown for use mainly in urban areas.

The association between cellular phone use and PGTs has been studied in Finland, Sweden, and Denmark. One case-control study (6) and one cohort study (5) used cellular phone subscription as a measure of exposure. No association was found for salivary gland cancers in either study. Apart from the small sample size (34 cases) and a short latent period in the case-control study, major limitations of these studies were the misclassification between subscribers and users and the limited information about exposure. A case-control study conducted in several areas of Sweden during 1994–2000, comprising 267 cases (199 PGTs) and 1,053 controls, yielded odds ratios close to 1 (18). No association was found with tumor side or latent period. As only six cases had a latency of more than 10 years, no conclusion about long-term use could be drawn.

Recently, a combined analysis of PGTs from the Swedish and Danish components of the INTERPHONE study, including 60 malignant and 112 benign PGTs, was published (14). The estimated odds ratios for any regular use were 0.7 and 0.9, respectively. No association was seen with time since first use, duration of use, cumulative number of calls, or call time. Only two persons with malignant and seven individuals with benign PGTs had used cellular phones for 10 years or more. For benign tumors and ipsilateral exposure, however, the odds ratio for regular use was 1.4 (95 percent CI: 0.9, 2.2) and, for time since first use more than 10 years ago, it was 2.6 (95 percent CI: 0.9, 7.9). The odds ratio for regular use on the contralateral side was 0.7 (95 percent CI: 0.4, 1.1).

An advantage of studying patients with PGTs is that, unlike those with brain tumors, they generally do not suffer from cognitive dysfunction that would compromise the quality of the reported data. Indeed, nearly all (95 percent) cases were classified by their interviewers as very or fairly cooperative, and proxy interviews were needed for only 18 cases. Furthermore, unlike with acoustic neuroma, hearing loss, which could induce switching use of the phone to the opposite side, is not a symptom of this disease.

Our active procedure for ascertaining cases allowed us to assemble a population-based group of patients with incident malignant and benign PGTs. Moreover, our study is the first to investigate a group of benign Warthin's tumors.

The controls in our study were population based; however, while compliance among cases was rather high (87 percent), only 65 percent of the eligible controls were interviewed.

A bias that controls who were users preferentially self-select themselves as participants is an important possibility given that the study was presented as a ''cellular phone study.'' Indeed, nonparticipants who responded to the short telephone questionnaire (78 percent of refusals) reported a significantly lower rate of regular use than did control participants and, among regular users, a later start of use. This phenomenon was also seen in other components of the INTERPHONE study (9, 13). In the presence of a real association, such a differential bias would tend to diminish the odds ratio, possibly resulting in risk estimates below unity (particularly for low-to-moderate exposure level); it would not, however, create spuriously increased odds ratios when no risk exists (19, 20).

Sensitivity analyses restricted to regular users and to cases only (which are less affected by such bias) were conducted by use of the assumption that the overall decreased risks may be related to such a selection bias; both suggest an association with cellular phone use.

Another issue of concern when interpreting the results is the possibility of differential recall bias, with cases being more likely to overestimate their past use of cellular phones and to overreport their predominant side of use as the side of the head where their tumor occurred. A recent simulation paper within the INTERPHONE study (20) considered a number of scenarios of recall error. In the presence of the large random errors in recall such as those found in validation studies (16), differential errors in reporting were found to have very little additional impact. Laterality recall bias, however, would be expected to yield elevated risks for ipsilateral use and reduced risk for contralateral use. Such a reduction, although not statistically significant, was observed and may indicate the existence of such a bias. The observation of a similar relation in cases and controls between reported side of cellular phone use and handedness (a variable not expected

TABLE 6. Risk of parotid tumor for different levels of cellular phone use by ipsilateral and contralateral use, Israel, 2001–2003*

	Ipsilateral and both				Contralateral			
	Cases (no.)	Controls (no.)	Odds ratio†	95% confidence interval	Cases (no.)	Controls (no.)	Odds ratio†	95% confidence interval
Regular user								
No, <1 year	175	575	1.0‡		175	575	1.0‡	
Yes	183	390	1.01	0.75, 1.35	101	294	0.87	0.63, 1.20
Regular user 5 years in the past								
No	319	969	1.0‡		319	969	1.0‡	
Yes	96	166	1.34	0.99, 1.83	45	128	0.89	0.61, 1.30
Regular user 10 years in the past								
No	447	1,240	1.0‡		447	1,240	1.0‡	
Yes	10	16	1.69	0.74, 3.83	3	10	0.59	0.15, 2.26
Time since start use (years)								
Never, <1 year	175	575	1.0‡		175	575	1.0‡	
1–4.9	84	220	0.88	0.63, 1.24	53	166	0.82	0.56, 1.21
5–9.9	89	154	1.14	0.79, 1.65	45	118	0.96	0.63, 1.46
≥10	10	16	1.60	0.68, 3.72	3	10	0.58	0.15, 2.32
Duration of use (years)								
Never, <1 year	175	575	1.0‡		175	575	1.0‡	
1–4.9	90	229	0.88	0.64, 1.24	57	171	0.86	0.59, 1.26
5–9.9	83	148	1.13	0.78, 1.64	41	114	0.91	0.59, 1.40
≥10	10	13	1.89	0.79, 4.57	3	9	0.61	0.15, 2.47
Cumulative no. of calls (with no hands-free devices)§								
Nonusers, <1 year	176	583	1.0‡		175	578	1.0‡	
≤5,479	61	223	0.72	0.51, 1.03	55	156	0.98	0.67, 1.43
>5,479	121	159	1.58	1.11, 2.24	46	135	0.78	0.51, 1.19
Cumulative call time (hours) (with no hands-free devices)§								
Nonusers, <1 year	176	583	1.0‡		175	578	1.0‡	
≤266.3	67	224	0.79	0.56, 1.11	53	162	0.92	0.63, 1.34
>266.3	115	158	1.49	1.05, 2.13	48	129	0.84	0.55, 1.28
Cumulative call time (hours) (with no hands-free devices)§ by time since start use (years)								
Nonusers, <1 year	176	583	1.0‡		175	578	1.0‡	
<5 years								
≤266.3	50	171	0.77	0.52, 1.13	40	121	0.91	0.59, 1.39
>266.3	34	45	1.56	0.91, 2.67	13	42	0.67	0.33, 1.35
≥5 years								
≤266.3	17	53	0.84	0.46, 1.53	13	41	0.95	0.49, 1.85
>266.3	81	113	1.47	0.99, 2.17	35	87	0.92	0.57, 1.47
Cumulative no. of calls (with no hands-free devices)§ by time since start use (years)								
Nonusers, <1 year	176	583	1.0‡		175	578	1.0‡	
<5 years								
≤5,479	49	176	0.73	0.50, 1.08	41	122	0.91	0.60, 1.40
>5,479	35	40	1.80	1.05, 3.10	12	41	0.63	0.31, 1.30
≥5 years								
≤5,479	12	47	0.69	0.35, 1.36	14	34	1.19	0.61, 2.32
>5,479	86	119	1.50	1.03, 2.20	34	94	0.84	0.52, 1.34

* Unconditional logistic regression.

† Adjusted for age, sex, and year of interview; adjustment for ethnic origin did not influence the results and was not included in the final statistical model.

‡ Referent.

§ Based on the distribution of users' controls (weighted) and divided into ≤median and >median.

TABLE 7. Risk of parotid tumor for different levels of cellular phone use by main area of use, Israel, 2001–2003*

	Mainly rural or mixed rural/urban				Mainly urban			
	Cases (no.)	Controls (no.)	Odds ratio†	95% confidence interval	Cases (no.)	Controls (no.)	Odds ratio†	95% confidence interval
Regular user								
No, <1 year	175	575	1.0‡		175	575	1.0‡	
Yes	88	185	1.12	0.79, 1.61	197	505	0.90	0.68, 1.18
Regular user 5 years in the past								
No	319	969	1.0‡		319	969	1.0‡	
Yes	52	90	1.43	0.97, 2.11	89	206	1.01	0.75, 1.37
Regular user 10 years in the past								
No	447	1,240	1.0‡		447	1,240	1.0‡	
Yes	4	8	1.37	0.40, 4.68	9	18	1.16	0.50, 2.67
Time since start use (years)								
Never, <1 year	175	575	1.0‡		175	575	1.0‡	
1–4.9	34	95	0.84	0.53, 1.35	104	294	0.86	0.63, 1.18
5–9.9	50	82	1.44	0.92, 2.25	84	193	0.93	0.66, 1.32
≥10	4	8	1.39	0.40, 4.84	9	18	1.14	0.48, 2.70
Duration of use (years)								
Never, <1 year	175	575	1.0‡		175	575	1.0‡	
1–4.9	37	100	0.87	0.55, 1.38	111	305	0.87	0.64, 1.19
5–9.9	47	78	1.43	0.91, 2.26	77	185	0.91	0.63, 1.30
≥10	4	7	1.52	0.42, 5.44	9	15	1.31	0.54, 3.18
Cumulative no. of calls (with no hands-free devices)§								
Nonusers, <1 year	176	579	1.0‡		175	583	1.0‡	
≤5,479	33	94	0.89	0.56, 1.42	84	288	0.81	0.59, 1.11
5,480–18,996	22	46	1.16	0.64, 2.08	64	110	1.24	0.83, 1.85
≥18,997	32	41	1.81	1.04, 3.14	49	99	1.0	0.65, 1.55
Cumulative call time (hours) (with no hands-free devices)§								
Nonusers, <1 year	176	579	1.0‡		175	583	1.0‡	
≤266.3	28	100	0.72	0.44, 1.17	93	289	0.88	0.65, 1.21
266.4–1,034.9	27	43	1.57	0.90, 2.74	53	112	1.0	0.66, 1.51
≥1,035	32	38	1.96	1.11, 3.44	51	96	1.02	0.67, 1.58

* Unconditional logistic regression.

† Adjusted for age, sex, and year of interview; adjustment for ethnic origin did not influence the results and was not included in the final statistical model.

‡ Referent.

§ Based on the distribution of users' controls (weighted) and divided into the following categories: ≤median, >median–≤third quartile, and >third quartile.

to be affected by recall bias), however, argues against differential laterality bias. Because radiofrequency energy absorption is very localized, if radiofrequency exposure increases the risk of PGTs, any increase will be seen on the side of the head where the phone is usually held, and no effect will be observed on the opposite side. Our finding of an association in analyses restricted to ipsilateral tumors is consistent with similar findings in studies of cellular phone use and acoustic neuromas (9, 12), gliomas (7, 21, 22), and benign PGTs (14). Nevertheless, a reporting bias regarding laterality of use cannot be ruled out.

Israeli cellular phone users are exceptionally heavy users (16). Among our controls, the 75th percentiles for cumulative call time and cumulative number of calls were 1,348 hours and 26,100 calls, respectively, compared with 450 hours and 7,350 calls in a Swedish and Danish report (14) and 534 hours and 8,000 calls in a pooled analysis of north European INTERPHONE study countries (12). Thus, the exposures to cellular phone use considered in this study were higher than those in previous studies. In the ipsilateral, urban/rural, and regular-user analyses, our data showed increased odds ratios in the highest categories of use

consistently over the different exposure measures supporting a dose-response relation.

Although most studies of cellular phone use have failed to find an overall association with risk of tumors, several suggest an increased risk among those who started use 10 years or more in the past, particularly for ipsilateral use. A Swedish study reported a significantly increased risk for acoustic neuroma for 10 years or more of ipsilateral use (OR = 3.9, 95 percent CI: 1.6, 9.5) (9) and nonsignificantly increased risks for glioma and meningioma (10), on the basis of small numbers of exposed cases (14, 15, and five, respectively). A pooled analysis of acoustic neuromas found an odds ratio of 1.8 (95 percent CI: 1.1, 3.1) based on 23 cases for 10 years or more of ipsilateral use (12). Our study also included a limited number of long-term users (13 cases with >10-year latency and 10 users on the ipsilateral side). Significant increases were found in relation to heavy use of cellular phones, even among shorter-term use in analyses of ipsilateral and rural use and in analyses restricted to regular users only.

The electromagnetic fields emitted from cellular phones do not have enough energy to break chemical bonds or damage DNA and, hence, are unlikely to act in the initiation of a tumor (5). If radiofrequency radiation acts as a tumor promoter, a clinical effect could be expected more rapidly. The high level of cellular phone use in the Israeli population may explain why we found an association between ipsilateral use and PGTs despite the relatively short latency period studied.

An important determinant of output power is distance from base stations. Lönn et al. (23) have shown that, in rural areas where base stations are located far apart, the average output power of phones tends to be higher than that in urban areas. Thus, classification of cellular phone use by area (urban/rural) may be another indicator of exposure. Our results showed that the increased risk from cellular phone use was confined mostly to use involving rural areas. Although this urban-rural difference was not seen in the study of Lönn et al. on brain tumors, it is compatible with that seen in another Swedish study (24).

In conclusion, based on the largest group of benign PGT patients reported to date, a number of complementary analyses suggest a positive association between cellular phone use and PGTs. Results from a single epidemiologic study do not, however, form a strong-enough basis to assume causality, and additional investigations of this association, with longer latency periods and large numbers of heavy users, are needed to confirm our findings. Until more evidence becomes available, we believe that the precautionary approach currently adopted by most scientific committees and applied by many governments should continue to be used.

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REFERENCES

1. Repacholi MH. Low level exposure to radiofrequency electromagnetic fields: health effects and research needs. Bioelectromagnetics 1998;19:1–9.
2. McKinlay A. Possible health effects related to the use of radiotelephones. Radiol Prot Bull 1997;187:9–16.
3. Rothman KJ, Loughlin JE, Funch DP, et al. Overall mortality of cellular telephone customers. Epidemiology 1996;7:303–5.
4. Inskip PD, Tarone RE, Hatch EE, et al. Cellular-telephone use and brain tumors. N Engl J Med 2001;344:79–86.
5. Schuz J, Jacobsen R, Olsen JH, et al. Cellular telephone use and cancer risk: update of a nationwide Danish cohort. J Natl Cancer Inst 2006;98:1707–13.
6. Auvinen A, Hietanen M, Luukkonen R, et al. Brain tumors and salivary gland cancers among cellular telephone users. Epidemiology 2002;13:356–9.
7. Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of two case-control studies on use of cellular and cordless telephones and the risk for malignant brain tumours diagnosed in 1997–2003. Int Arch Occup Environ Health 2006;79:630–9.
8. Christensen HC, Schüz J, Kosteljanetz M, et al. Cellular telephone use and risk of acoustic neuroma. Am J Epidemiol 2004;159:277–83.
9. Lönn S, Ahlbom A, Hall P, et al. Mobile phone use and the risk of acoustic neuroma. Epidemiology 2004;15:653–9.

10. Lönn S, Ahlbom A, Hall P, et al. Long-term mobile phone use and brain tumor risk. Am J Epidemiol 2005;161:526–35.
11. Christensen HC, Schüz J, Kosteljanetz M, et al. Cellular telephones and risk for brain tumors. Neurology 2005;64:1189–95.
12. Schoemaker MJ, Swerdlow AZ, Ahlbom A, et al. Mobile phone use and risk of acoustic neuroma: results of the Interphone case-control study in five North European countries. Br J Cancer 2005;93:842–8.
13. Schuz J, Bohler E, Berg G, et al. Cellular phones, cordless phones, and the risks of glioma and meningioma (Interphone Study Group, Germany). Am J Epidemiol 2006;163:512–20.
14. Lönn S, Ahlbom A, Christensen HC, et al. Mobile phone use and risk of parotid gland tumor. Am J Epidemiol 2006;164:637–43.
15. Cardis E, Kilkenny M. International case-control study of adult brain, head and neck tumors: results of the feasibility study. Radiat Prot Dosimetry 1999;83:179–83.
16. Vrijheid M, Cardis E, Armstrong BK, et al. Validation of short term recall of mobile phone use for the Interphone study. Occup Environ Med 2006;63:237–43.
17. Nagler RM, Laufer D. Tumors of the major and minor salivary glands: review of 25 years of experience. Anticancer Res 1997;17:701–8.
18. Hardell L, Hallquist A, Hansson Mild K, et al. No association between the use of cellular or cordless telephone and salivary gland tumors. Occup Environ Med 2004;61:675–9.
19. Lahkola A, Salminen T, Auvinen A. Selection bias due to differential participation in a case-control study of mobile phone use and brain tumors. Ann Epidemiol 2005;15:321–5.
20. Vrijheid M, Deltour I, Krewski D, et al. The effects of recall errors and of selection bias in epidemiologic studies of mobile phone use and cancer risk. J Expo Sci Environ Epidemiol 2006;16:371–84.
21. Lahkola A, Auvinen A, Raitanen J, et al. Mobile phone use and risk of glioma in 5 North European countries. Int J Cancer 2007;120:1769–75.
22. Hardell L, Mild KH, Carlberg M. Further aspects on cellular and cordless telephones and brain tumours. Int J Oncol 2003;22:399–407.
23. Lönn S, Forssen U, Vecchia P, et al. Output power levels from mobile phones in different geographical areas; implications for exposure assessment. Occup Environ Med 2004;61:769–72.
24. Hardell L, Carlberg M, Mild KH. Case-control study of the association between the use of cellular and cordless telephones and malignant brain tumors diagnosed during 2000–2003. Environ Res 2006;100:232–41.

APPENDIX

APPENDIX TABLE 1. Risk of parotid gland tumors in relation to cellular phone use, with analyses restricted to regular users only, Israel, 2001–2003*

	Cases (no.)	Controls (no.)	Odds ratio†	95% confidence interval
Time since start use (years)				
1–4.9	138	389	1.0‡	
5–9.9	134	276	1.40	1.03, 1.90
≥10	13	26	1.45	0.82, 2.57
Duration of use (years)				
1–4.9	148	405	1.0‡	
5–9.9	124	264	1.19	0.88, 1.59
≥10	13	22	1.65	0.78, 3.45
Cumulative no. of calls (with no hands-free devices)§				
≤5,479	117	382	1.0‡	
5,480–18,996	86	157	1.48	1.05, 2.10
≥18,997	81	140	1.51	1.05, 2.17
Cumulative call time (hours) (with no hands-free devices)§				
≤266.3	121	390	1.0‡	
266.4–1,034.9	80	155	1.37	0.97, 1.95
≥1,035	83	134	1.50	1.04, 2.16

* Unconditional logistic regression.
† Adjusted for age, sex, and year of interview.
‡ Referent.
§ Based on the distribution of users' controls (weighted) and divided into the following categories: ≤median, >median–≤third quartile, and >third quartile.

(**Appendix continues**)

APPENDIX TABLE 2. Risk of benign parotid tumor for different levels of cellular phone use by ipsilateral and both sides use, Israel, 2001–2003*

	Ipsilateral				Both			
	Cases (no.)	Controls (no.)	Odds ratio†	95% confidence interval	Cases (no.)	Controls (no.)	Odds ratio†	95% confidence interval
Regular user								
No	175	575	1.0‡		175	575	1.0‡	
Yes	155	322	1.0	0.74, 1.35	28	68	1.23	0.71, 2.11
Regular user 5 years in the past								
No	319	969	1.0‡		319	969	1.0‡	
Yes	82	139	1.31	0.95, 1.82	14	27	1.56	0.78, 3.14
Regular user 10 years in the past								
No	447	1,240	1.0‡		447	1,240		
Yes	10	12	2.17	0.91, 5.18	0	4		
Time since start use (years)								
Never, <1 year	175	575	1.0‡		175	575	1.0‡	
1–4.9	71	180	0.89	0.62, 1.28	13	40	0.87	0.43, 1.77
5–9.9	74	130	1.06	0.72, 1.56	15	24	1.90	0.91, 3.98
≥10	10	12	1.97	0.81, 4.85	0	4		
Duration of use (years)								
Never, <1 year	175	575	1.0‡		175	575	1.0‡	
1–4.9	74	187	0.89	0.62, 1.27	16	42	1.0	0.51, 1.94
5–9.9	71	126	1.06	0.72, 1.57	12	22	1.72	0.78, 3.78
≥10	10	9	2.53	0.97, 6.58	0	4		
Cumulative no. of calls (with no hands-free devices)§								
Nonusers, <1 year	176	580	1.0‡		175	578	1.0‡	
≤5,479	50	181	0.71	0.48, 1.04	11	42	0.79	0.38, 1.65
>5,479	104	136	1.49	1.03, 2.14	17	23	2.42	1.14, 5.11
Cumulative call time (hours) (with no hands-free devices)§								
Nonusers, <1 year	176	580	1.0‡		175	578	1.0‡	
≤266.3	56	186	0.76	0.52, 1.10	11	38	0.94	0.45, 1.96
>266.3	98	131	1.45	1.0, 2.10	17	27	1.88	0.90, 3.92
Cumulative call time (hours) (with no hands-free devices)§ by time since start use (years)								
Nonusers, <1 year	176	580	1.0‡		175	578	1.0‡	
<5 years								
≤266.3	43	140	0.78	0.52, 1.17	7	31	0.69	0.29, 1.66
>266.3	28	38	1.51	0.85, 2.69	6	7	1.87	0.54, 6.52
≥5 years								
≤266.3	13	46	0.72	0.37, 1.40	4	7	2.37	0.63, 8.93
>266.3	70	93	1.42	0.94, 2.15	11	20	1.96	0.84, 4.58
Cumulative no. of calls (with no hands-free devices)§ by time since start use (years)								
Nonusers, <1 year	176	580	1.0‡		175	578	1.0‡	
<5 years								
≤5,479	43	142	0.78	0.52, 1.18	6	34	0.48	0.19, 1.23
>5,479	28	36	1.51	0.84, 2.71	7	4	5.0	1.31, 19.05
≥5 years								
≤5,479	7	39	0.46	0.20, 1.08	5	8	2.67	0.79, 8.99
>5,479	76	100	1.48	0.99, 2.20	10	19	1.90	0.79, 4.57

* Unconditional logistic regression.
† Adjusted for age, sex, and year of interview.
‡ Referent.
§ Based on the distribution of users' controls (weighted) and divided into ≤median and >median.