Association between mobile phone use and pleomorphic adenoma of parotid gland

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OBJECTIVES : When a person talks on a mobile telephone, the salivary glands, and the parotid gland in particular, are among the areas of the body with most exposure to the phone, as they are located in front of the ear. We examined the association of parotid gland tumors with mobile phone use. This study included patients who had undergone surgical parotid gland tumor removal and whose pathology was designated as pleomorphic adenoma. The objective of this case–case study was to assess whether the use of wireless phones is associated with an increased risk or growth rate of tumors at this site.

METHODS : 220 patients with parotid gland pleomorphic adenoma were included. The location and volume of the tumors were determined by enhanced neck CT scan. Patients were divided according to the amount of mobile phone use in terms of duration, daily amount, and cumulative hours. We compared the volume of tumors to the above mobile phone use parameters. Associations between the laterality of phone use and tumor location were analyzed.

RESULTS : In the case–case study of all included patients, no significant difference in volume between heavy mobile phone users and light mobile phone users was observed. However, there was a strong correlation between the side of the head on which tumors were located and the side of mobile phone use (which was limited to ipsilateral users). Tumor volume and estimated cumulative hours were also strongly correlated, while tumor volume was notably larger in heavy phone users than light users (p=0.012).

CONCLUSION : We found that tumor incidence might coincide with the more frequently used ear of mobile phone users and also found that tumor volume was strongly correlated with the amount of mobile phone use. Therefore, it is possible that mobile phone use may affect tumor growth.

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INTRODUCTION

Pleomorphic adenoma is a common benign salivary gland neoplasm characterized by neoplastic proliferation of parenchymatous glandular cells along with myoepithelial components, with the potential for malignant transformation. It is the most common type of salivary gland tumor and the most common tumor of the parotid gland.

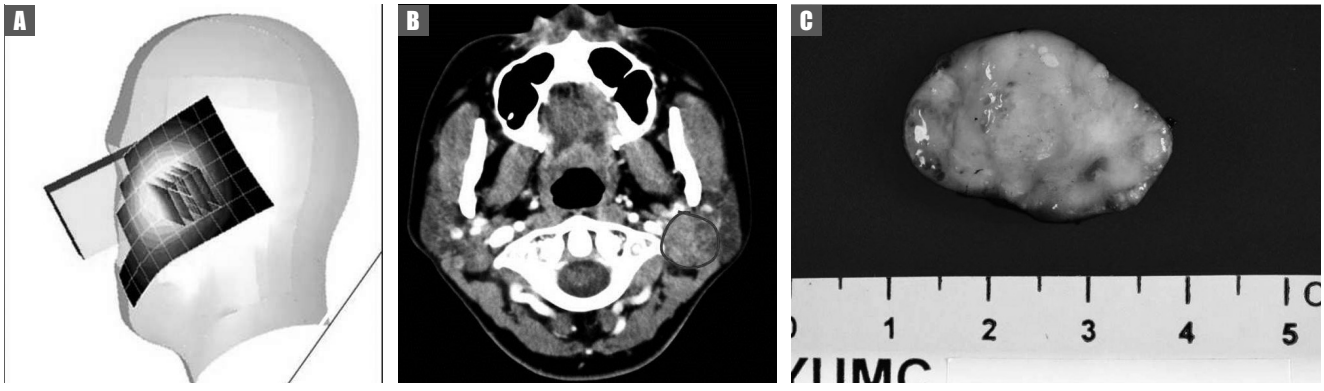
Awareness of pleomorphic adenoma of the parotid gland has increased over the past few decades. Improved diagnostic tools are likely to be responsible for a higher rate of diagnosis, but a number of potential risk factors are suspected to be responsible as well, including electromagnetic fields (EMFs) emitted by mobile phones. The rapid increase in mobile phone use during the last decade has raised some safety concerns. In particular, a risk of parotid gland tumor development is suspected to be associated with mobile phone use because the parotid gland is located close to where people hold their phones during use. This makes the parotid gland especially vulnerable to changes, if any, resulting from mobile phone heat and radiation. Mobile phones are known to generate heat and emit radio frequency radiation in the form of nonionizing electromagnetic radiation; this radiation is emitted in the range of 800–2,200MHz, similar to many home appliances. This heat can potentially increase the temperature of adjacent tissue by up to 0.1° C. This thermal effect could consequently influence protein phosphorylation.[12–14] Some studies have identified an increased risk of tumors on the side of the more frequently used ear. Potential mechanisms of carcinogenicity have been reviewed in many studies, with possibilities including oxidative stress, apoptosis, and effects on immune function.[15–18]

Contradicting literature exists regarding the potential of mobile phone emissions (thermal and radiation effects) to cause notable physiological, structural, functional, or even carcinogenic effects in the human body.

We undertook a study to evaluate any changes occurring in the incidence or growth rate of parotid gland pleomophic adenoma resulting from mobile phone use, with the aim of assessing whether any adverse health effects are associated with heavy use of mobile phones. To our knowledge, this is the first report on the association of mobile phone use and specific pathology of parotid gland tumors, such as pleomorphic adenoma.

The case–control study design is widely accepted as one of the most useful methods to analyze the relationship between mobile phone use and parotid gland tumors. However, these studies are known to be vulnerable to selection and recall biases.[5, 19] The case–case study design is also vulnerable to selection and recall biases, but the situation is less complicated than in case–control studies.[20] Therefore, we primarily conducted a case–case study for this investigation.

Fig. 1



Anatomical association of parotid gland and handheld mobile phone.

A. Location of parotid gland

B. The heating diagram of face when the mobile phone was in use.

C. The computed thomography shows 3x2.5cm sized mass in left parotid gland deep lobe. (D) Surgical specimen of pleomorphic adenoma.

In previous case-case studies, the laterality of mobile phone use coinciding with the occurrence of a parotid gland tumor is often presented as evidence for association.[21, 22] Inskip et al[21] proposed the following three assumptions: there is no risk from using a mobile phone on the contralateral side, risk to the ipsilateral side is the same for left- and right-sided tumors, and the incidence of left- and right-sided tumors is the same for non-users of mobile phones.

Most previous reports have diagnosed parotid gland tumors through imaging, but even though pleomorphic adenoma has characteristic features upon imaging, a bias may arise since its pathology cannot be confirmed.

If the main mechanism involves protein phosphorylation changes due to a heating effect rather than actual degeneration of DNA, then EMF might have the potential to increase/decrease the growth of an existing tumor or to change its shape, even though it may not actually induce tumor development. Thus, an analysis of the effects of mobile phone use on tumor growth, in addition to simply analyzing tumor incidence, is required.

For this study, we recruited patients confirmed to have pleomorphic adenoma after surgery, and the coincidence between the laterality of mobile phone use and tumor side was analyzed. Finally, based on the hypothesis that "mobile phone use may affect the physiognomy of pleomorphic adenoma," we examined the associations between pleomorphic adenoma and mobile phone use, to evaluate any differences in the growth or characteristics of tumors.

Table 1. Questions selected and modified from the INTERPHONE questionnaire.

1. Do you smoke? If a smoker, describe smoking in detail (Total pack years, whether you quit smoking before your diagnosis or not).
2. Do you drink? If a drinker, describe alcohol consumption in detail (Average drinking capacity, number of drinks per week, type of alcohol, etc.).
3. How many hours do you sleep each day on average?
4. Do you participate in regular exercise?
5. What is your occupation (especially type of working environment, exposure to harmful conditions)?
6. Where do you live (especially in regards to urban or rural areas)?
7. How are your eating habits (regular or excessive)?
8. Describe your relevant family medical history.
9. Describe your relevant past medical history.
10. Do you use illicit drugs?
11. Describe your symptoms before your diagnosis in detail (hearing impairment, facial palsy, etc.).
12. Have you used or are you currently using mobile phones?
    a. Yes → Proceed to Question 13.
    b. No → End of survey.
13. Do you use mobile phones on a regular basis? (Regular is considered to be at least once a week)
14. Which ear do you typically use for phone calls?
    a. Almost always on the tumor site (%)
    b. Almost always on the opposite of tumor site (%)
    c. Usually on the tumor site (%)
    d. Usually on the opposite of tumor site (%)
    e. Both sites used similarly
15. Do you use hands-free sets (Bluetooth ear phones or headsets) during mobile phone calls?
    a. Almost always
    b. Occasionally
    c. Infrequently
    d. Do not use
    e. Not used before, but started using recently
16. How long have you used mobile phones? (since which year and month; be as precise as possible.)
17. How much is your daily average mobile phone usage? (Check the frequency of phone calls and how long each call takes on average. The amount before the diagnosis of the tumor is more significant. The best method is to request monthly call volumes from cell phone service providers)
18. Which cell phone service provider have you used? List time periods for each provider. (Since when and till when did the patient used SK/KTF/LG?)
19. Which mobile phone device have you used? (It is best to know the model, but if it is difficult to remember, provide roughly what year and from which company the product was obtained.)
20. Where do you usually keep the mobile phone (front pocket/back pocket/purses)?
21. How often do you use other wireless devices? (wireless handsets of telephones, walkie-talkies, etc.)
    a. Never
    b. Wireless handsets of telephones → How often is the usage?
    c. Walkie-talkies or others → How often is the usage?
22. What is your frequency of usage of microwave ovens, computers or any other kind of exposure to electromagnetic fields?

METHODS

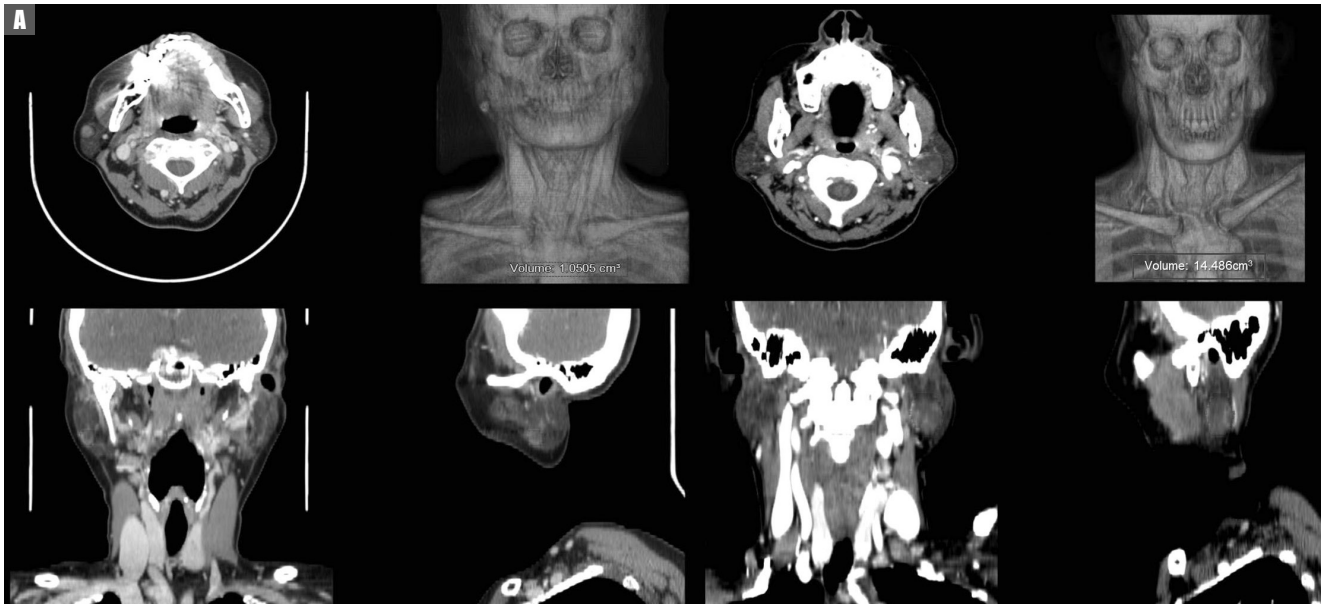
A case-case approach was used in this study.

We recruited 267 patients who had undergone surgery and were pathologically confirmed to have pleomorphic adenoma of the parotid gland by the Department of Otorhinolaryngology at Severance Hospital, Seoul, South Korea, between January 2011 and December 2013. We were able to reach 234 of the 267 patients, and 220 of them agreed to reply to a questionnaire (a 94.0% participation rate) and were included. All patients were interviewed by telephone using the same questions. The questions were modified by authors based on INTERPHONE guidelines; each participant was interviewed by one interviewer from January to March 2014. The reference dates were set around the diagnosis date and the questionnaire included the following: subject's history of mobile phone use, the year they began using a mobile phone, average daily number of outgoing and incoming calls, average call duration, dominant hand, proportion of calls using the left and right ears, and frequency of hands-free device usage. Age, gender, chief complaint at the first visit, past medical history, date of diagnosis (used as the reference date), tumor location (left or right), tumor volume, preoperative hearing threshold, and operative method were obtained from medical records as basic background information. A regular mobile phone user was defined as someone who had used a mobile phone at least once a week for the past six months. The average daily amount of mobile phone use was calculated by multiplying the average number of calls per day by the average talk time of a single call. Cumulative hours of mobile phone use were calculated by multiplying the average daily amount of mobile phone use by the duration of mobile phone use.

The location and volume of tumors were analyzed using imaging and a three dimensional volume calculation program (Aquaria INtuitionTM, TeraRecon, Foster City, CA) (Fig.2).

Duration, daily amount, and total cumulative hours were taken into account in determining mobile phone usage. Subjects who had used a mobile phone for more than 10 years were classified as long-term users, those who used a mobile phone for more than 20 min per day were deemed heavy daily users, and cumulative heavy users were those who had used a mobile phone for more than 2,000 cumulative hours in their lifetimes. The cut-off points were set based on references from previous

Fig. 2



Tumor volume was calculated using a 3D volume calculation program (Aquaria Intuition). Serial images of axial, coronal, and sagittal cuts of enhanced Neck CT were input into the program; the tumor was reconstructed three dimensionally, and the tumor volume was automatically calculated

reports. For each case, the volume of the tumor was compared according to each criterion.

The correlation between the laterality of mobile phone use and tumor location (side) was also analyzed. The most frequently used ear was defined as the side used for more than three-quarters of the time spent on the phone. Subjects who did not meet this criterion were classified as having no dominant ear. If the tumor and the most frequently used ear were on the same side, the relationship was classified as ipsilateral; when the tumor and the most frequently used ear were on opposite sides, the relationship was classified as contralateral. The risk ratio of pleomorphic adenoma for mobile phone use was analyzed using multi-nominal logistic regression.

The study protocol was approved by the Ethical Committee of Yonsei University College of Medicine (No. 4-2012-0080) and consent was obtained from all participants.

RESULTS

Characteristics

In the patient group, the longest delay from the date of diagnosis to the date of interview was two years. Among these 220 cases, all (100.0%) were mobile phone users at the reference date. With regard to dominant hand preference, 211 cases (95.9%) were right-handed and 6 (2.7%) were left-handed, while 3 (1.4%) were ambidextrous (Table 1).

Case-case analysis

The average tumor volume (n = 220) was 24.98 ± 39.79 cm3. When we limited our analysis to regular users, there was no significant difference (p = 0.255) in tumor size between long-term users (27.47 ± 43.41 cm3, n = 132) and short-term users (21.26 ± 33.53 cm3, n = 88), and no significant difference was observed between heavy users (21.93 ± 30.28 cm3, n = 102) and light users (27.62 ± 46.44 cm3, n = 118) based on the amount of daily mobile phone use (p = 0.291). In terms of cumulative hours, there were no differences in tumor volume between heavy users (26.35 ± 44.86 cm3, n = 92) and light users (23.07 ± 31.53 cm3, n = 128) (p = 0.548) (Table 2).

According to Inskip's assumption, a possible risk was associated with mobile phone use only when the ear used most frequently for speaking on mobile phones and the tumor location were ipsilateral. Of the 220 regular mobile phone users, 22 cases (10%) indicated that they used both their left and right ears almost equally, while the others favored one side. Excluding these 22 cases, 198 cases were used for our risk analysis. Right-ear dominant users (109/198, 55.1%) outnumbered left-ear dominant users (89/198, 44.9%), but the difference was not significant (p = 0.592). 131 cases were ipsilateral, and 67 were contralateral (Odds ratio = 3.073) (Table 3)

When considering only ipsilateral users, the results were very different from the overall results. For the 131 patients who used a mobile phone with the same hand as the side of their tumor, the average tumor volume (n = 131) was 25.75 ± 47.24 cm3. A significant difference (p = 0.042) was observed in tumor size between long-term users (32.23 ± 58.04 cm3, n = 82) and short-term users (14.90 ± 12.87 cm3, n = 49), but no significant difference was observed between heavy users (20.53

Table 2. Basic characteristics of patients at reference date

	All Patients (n=220)	Ipsilateal user (n=131)
Age (years)	41.66±12.91	49.21±14.59
Gender (male:female)	64:156	40:91
Side of tumor (right:left)	102:118	69:62
Residential area (urban:rural)	211:9	126:5
% of systemic disease*	14.5	13.1
% of smoking	19.4	12.2

* Systemic disease means chronic debilitation disease which can affect patients immunity such as uncontrolled DM, ESRD, and etcs.
† Chi-square test or ‡ Fischer's exact test for calculation of p-value.

± 28.79 cm3, n = 68) and light users (31.38 ± 60.99 cm3, n = 63) based on the daily amount of mobile phone use (p = 0.190). In terms of cumulative hours, no differences in tumor volume were observed between heavy users (37.73 ± 68.09 cm3, n = 80) and light users (16.80 ± 16.84 cm3, n = 51) (p = 0.012) (Table 4).

DISCUSSION

In this study, a case-case design was used to gather data from a group of patients only. From all included patients, there was no significant volume difference between heavy and light mobile phone users. However, the laterality of mobile phone use showed a strong correlation with tumor side and was limited to ipsilateral users; in addition, the tumor volume was significantly larger in both the duration and cumulative heavy user groups compared with the light user group.

Two possible explanations were suggested for these results. One was that the increased risk was caused by exposure to EMFs from mobile phones, and the other was that the apparent higher risk was due to 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 due to earlier detection of tumors than those in the general population.

According to Inskip's assumption, the possible risk from mobile phone use occurred only when the ear used most frequently for speaking on mobile phones and the tumor location were ipsilateral. In previous studies, the odds ratio for the more

Table 3. Case-only analysis: comparison of tumor volume according to duration, daily usage time and cumulative hours of mobile phone use (n=220)

	Tumor volume (cm^3)		p-value
Duration (≤ or 〉10 years)	Long-term user (n=132)	Short-term user (n=88)	0.255
	27.47±43.41	21.26±33.53	
Time (≤ or 〉20 min/day)	Heavy user (n=102)	Light user (n=118)	0.291
	21.93±30.28	27.62±46.44	
Cumulative hours (≤ or 〉2000 hrs)	Heavy user (n=92)	Light user (n=128)	0.548
	26.35±44.86	23.07±31.53	

Table 4. Analysis of tumor occurrence side and mobile phone use laterality

Tumor side	Regular side for phone use			Total	Odds ratio (95% CI)	p-value
	Right	Left	Both			
Right	68	26	8	102	3.073 (0.585-34.608)	0.005
Left	41	63	14	118		
Total	109	89	22	220		

Table 5. Case-only analysis limited to ipsilateral users: A comparison of tumor volume according to duration, daily usage time and cumulative hours of mobile phone use (n=131)

	Tumor volume (cm^3)		p-value
Duration (≤ or 〉10 years)	Long-term user (n=82)	Short-term user (n=49)	0.042
	32.23±58.04	14.90±12.87	
Time (≤ or 〉20 min/day)	Heavy user (n=68)	Light user (n=63)	0.190
	20.53±28.79	31.38±60.99	
Cumulative hours (≤ or 〉2000 hrs)	Heavy user (n=80)	Light user (n=51)	0.012
	37.73±68.09	16.80±16.84	

frequently used ear was significantly higher among long-term users (1.8 – 3.9 odds ratio) when analyses took into account the ear used during mobile phone use and the side on which the tumor developed. On the other hand, other studies have reported that the odds ratio for the more frequently used ear was not significantly higher (0.82 – 1.08).

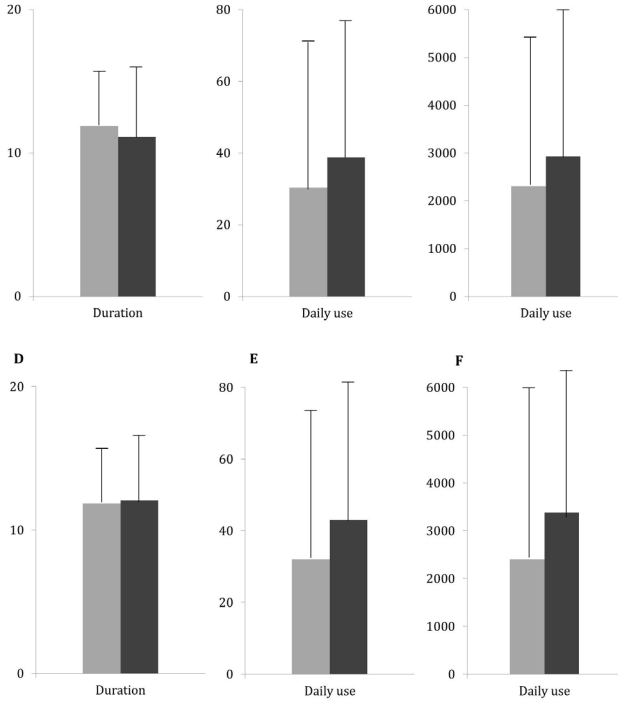
Takebayashi et al.[6] examined the tumor diameter in cases with ipsilateral mobile phone use versus cases with contralateral mobile phone use and reported that the diameter of ipsilateral-side tumors was smaller. One explanation proposed for this was that earlier diagnosis was more likely in cases with ipsilateral use than cases with contralateral use. At the same time, it is possible that ipsilateral tumors grow more slowly. However, no significant difference in tumor volume was observed between ipsilateral and contralateral users in our study.

We conclude that there was a consistent association between tumors and mobile phone use, with a greater relationship to tumor growth than incidence. We suggest that local heating caused by mobile phone use may result in a thermal effect, which may promote growth of an already existing tumor, but the effect of energy absorption at tissue sites close to the mobile phone needs to be clarified.[11,15] If energy from mobile phone use can cause tissue degeneration at the protein level, then it is also possible that these waves can induces changes in tumor growth and characteristics.

Our study had some limitations because of the previously mentioned biases, but considering that a prospective study of this particular association would be very difficult to conduct, we believe that these biases are within an acceptable range. Many efforts were taken to reduce bias in the design of our study. There are differences in absorption rates of electromagnetic waves in the brains of adults and children, but these differences were not evaluated in our study. However, pleomorphic adenoma occurs mainly in people aged 20 years or older. In this study, all patients except one were adults.

Another limitation of this study is that recall bias, residency, age, EMF according to cell phone type, and use of other electronic devices were not considered. In order to obtain accurate statistical data, other factors, such as residency, duration of use of each electronic device, use of microwave ovens, computers, televisions, amateur radios, Bluetooth devices, and cordless phones in the home need to be thoroughly evaluated. Realistically, however, it is difficult for participants to remember this information accurately and it is nearly impossible for researchers to control for all these factors. In addition, a recall bias may develop if questions are asked repeatedly in order to gather more information. As all other factors were equal, we predicted that there would be no statistical differences between the two groups. Under this supposition, there was no significant relationship between mobile phone use and tumor incidence, whereas mobile phone use was associated with a significant change in tumor volume in our study. Therefore, we predict that mobile phone use and tumor growth are mutually correlated;

Fig. 7



Amount of mobile phone use were compared by tumor location: deep lobe vs. superficial lobe. (A–C) Amount of mobile phone use between two groups were compared by each parameters; duration, daily amount, and cumulative hours. There were no significant differences between the patients with tumor in deep lobe and patients with tumor in superficial lobe in all parameters. (D–E) Amount of mobile phone use between two groups were compared by each parameters limited in ipslateral users. There were also no significant differences in all parameters.

consequently, patients diagnosed with pleomorphic adenoma should be advised to refrain from mobile phone use.

CONCLUSION

Our results showed that tumors tended to coincide on the same side as the more frequently used ear when talking on mobile phones, and tumor volume was strongly correlated with the amount of mobile phone use, thus demonstrating a possibility that mobile phone use may affect growth of existing tumors.

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