

2009

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James Bolton

Palmer College of Chiropractic

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Recommended Citation

Bolton, James (2009) "Cellular Telephones and Cancer: Is There a Connection?," *International Journal of Global Health and Health Disparities*, 6(1), 102-111.

Available at: <https://scholarworks.uni.edu/ijghhd/vol6/iss1/12>

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Bolton: Cellular Telephones and Cancer: Is There a Connection?
CELLULAR TELEPHONES AND CANCER: IS THERE A CONNECTION?

James Bolton, D.C.
Palmer College of Chiropractic

INTRODUCTION

Cellular telephones have been accused of causing brain tumors for years, but none of the studies that have been published have proven there is a link. The tumors that have been researched include parotid gland tumors, acoustic neuromas, and acoustic gliomas, to name a few. Wireless cellular phone usage has been increasing over the past few years, and some European countries are said to have a penetration rate of over 100%, “which is to say there are more subscribers than inhabitants”². Wireless technology emits electromagnetic energy (AKA microwave radiation or radiofrequency radiation), and sources include not only cellular telephones, but also cordless phones in the home, Bluetooth devices, and others wireless devices.

These cancers possibly caused by an unknown dose of radiofrequency fields, or some other unknown biological mechanism, are a concern because of the huge number of cellular phone users around the world today. Children are increasingly users of cell phones and the effect of electromagnetic energy on this population is unknown, and the research on them is fraught with ethical concerns. According to one paper, and an industry research institute in Taipei, there were 2.3 billion mobile phone subscribers in 2006 worldwide². With this number increasing every year and an estimated 3.3 billion users expected by 2011, if there is any possibility the wireless phones cause tumors in the brain, the implications for public health policies would be extensive, expensive, and monumental in scale and impact. Acoustic neuroma tumors are very slow growing⁶ and one common sign, a loss of hearing in one ear, may not be recognized or diagnosed as an acoustic neuroma until years after the hearing loss is first noticed. All tumors in the brain are of course a concern to humans, so this link, or lack thereof, is important to demonstrate.

This paper focuses on several research papers that are primarily case-control or cohort studies. The papers will be reviewed for sample size, controlling for confounders, addressing biases, and the author of this paper will express his opinion about the quality of each study and answer the following research question: do cellular telephones play a role in the formation of tumors of the brain, and if they do, what can people do to limit the risk.

LITERATURE REVIEW

Literature search was conducted by hand using the Sadetzki et al references. I selected articles that were published in the last few years when possible, or chose articles based on the title mentioning brain tumor, and the availability of the entire article for review.

The first study reviewed was a case-control study conducted in Israel by Sadetzki et al¹. The methods were based on the international INTERPHONE study conducted

in 13 countries European countries, including Israel. The sample size had 531 eligible and 460 participants in the cases group. The controls group had 1920 eligible and 1266 as participants. The participants were aged 18 or older with the mean age in cases being 53.3 and in controls 59.3 years of age. Cases were identified retrospectively and all diagnoses were confirmed by a single physician. Using a single physician may lead to selection error, and was not controlled for. The authors controlled for bias by randomly selecting controls from the National Population Registry, and matched controls to cases. There is specific exclusion criteria listed, which lends to external validity, and controls for selection bias. While the parotid gland tumor may be a rare disease, there should have been some type of control to limit possible selection bias with the cases.

Participants were asked if they were “regular users” of a cellular phone, and asked to identify in a journal all of the cellular phones they had used and the usage of those phones. This allowed for some recall bias and was controlled with the cases by looking at exposures up to one year prior to their diagnosis.

The authors controlled for participant bias by conducting short telephone surveys about cellular phone use with subjects who refused to participate. They controlled for the possibility that response rates were influenced by cellular phone use. All of the cases were matched to at least one control, and 75% had two controls. The time between the interviews of cases and controls was limited to 1 year, for 98% of the sample. The interviewers were asked to rate the participants’ cooperation and recall of cellular phone use, and 95% of interviewers rated the cases and controls as “very” or “fairly good”. The bias of the interviewers was not controlled for. Bias controls were discussed in the Discussion section and they discussed what impact the different types of bias or error could have on the data.

The question most cell phone users should be asking is “what does the evidence say?” and it is reported there is an increased odds ratio in the highest categories of use. There is a dose-response relationship across all the different exposure measures. There are several studies that suggest there is an increased risk among cellular phone users who began their phone use 10 or more years in the past. One of these is a review article by Hardell et al.⁴ Most studies do not find an overall association between cellular phone use and an increased risk of tumors.

There is discussion about the amount of use over years, the total length of use in years, and the amount of energy emitted by the cellular phones in a city vs. rural setting. The authors say causality cannot be drawn from a single epidemiologic study. They explain their recommendations for further studies and give support to precautionary approaches currently used by most scientific communities and governments.

I think this study was done well. They were mostly detailed in their descriptions of patient selection, exclusions, methods, and results. The discussion brought in other studies to support their findings, and they clearly discussed bias and error in their study. They did not make wild conclusions to support any personal beliefs and even listed their funding sources.

The second study, by Lonn et al.,² discussed the same disease, i.e. parotid gland tumor, but looked at populations in Denmark and Sweden. It was a population-based case-control study in both countries with usage of cellular phones dating back to the late

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1980s. This makes the people of these countries suitable participants in a case-control study. The Denmark group had 26 cases of malignant parotid tumor to 77 controls, while the Swedish group had 34 cases of malignant parotid tumors to 604 cases and 112 benign parotid tumors to 321 controls.

Like the first study, the authors listed the potential bias and errors they encountered or expected, explained what they did to control for it, and hopefully were successful in their efforts. Some of the error or bias is discussed here. The same core study protocol was used in Denmark and Sweden allowing similar study procedures for both groups of data, controlling for systematic error. The interviews conducted with participants were structured and interviewers in both countries attended the same training workshop to minimize the risk of interviewer bias. There was an explanation given for how selection bias may have occurred, and how they controlled for it. The recall bias of participants was acknowledged. People appear to overestimate their cellular phone use and this may create misclassification error, and may have affected the results. The nonparticipation among controls may have been another source of bias. These latter two errors/bias' are likely controlled with statistics since they are random errors, vs. systematic errors.

This study did not conclude there was any association between cellular phone use and the risk for parotid gland tumors, malignant or benign. The authors specifically state their results do not associate hours of use or number of calls with disease risk. They mention all studies published as of July 2006 have relatively few long term users, i.e. over 10 years of use. They do not believe their results "support the hypothesis that exposure to radiofrequency electromagnetic fields from mobile phones increases the risk of malignant or benign parotid gland tumors."² They do acknowledge mobile phones possible carcinogenic effect can not be excluded, especially after long term use, more studies are needed.

Schoemaker et al³ performed six population-based case-control studies in four Nordic countries and the UK who were among the first countries in Western Europe to have mobile phones and widespread use of the devices. Long-term use studies are particularly suited for these countries. This study dealt with the risk of acoustic neuromas. The proximity of the acoustic nerve to a mobile phone headset should increase the risk of acoustic neuroma if the mobile phone headsets are a factor in the cause of brain tumors.

The cases were chosen from appropriate centers treating cancer patients and the controls were randomly selected from the Nordic countries, from each study area, and in the UK controls were randomly selected from general practitioners' practice lists. Controls were matched to cases as well.

Some of the bias control was done by making sure controls had never been diagnosed with a brain tumor, training interviewers who administered personal interviews in addition to having the interview be computer-assisted. To control for recall bias photographs of phones were available to subjects, and 8 cases and 16 controls were removed from the analysis because they had received radiotherapy to the skull ten or more years prior to the reference date. The exclusion of the 24 subjects did not change the results though.

The conclusion was there is no increased risk of acoustic neuroma during the 10

years since the first regular phone use but there is an increased risk of some sort after 10 or more years for tumor formation on the same side as phone use.. There was no trend in the risk with lifetime cumulative hours of phone use or cumulative number of calls. But, there was a relative risk of 1.2 (95% CI: 0.8, 2.0) for those who had cumulative hours of use 10 years or more prior to the reference date.

The significant finding for all of us who use cellular phones is that 89% of cases and 24% of controls responded positively when asked if they suffer from any loss of hearing. The cases reported the hearing loss began on average 5.5 years prior to their diagnosis. If you experience hearing loss in the ear you use for your phone, don't be alarmed, but definitely keep an eye on what is occurring. The risk of acoustic neuroma is increased for those who have hearing loss that is not explained by something else. The acoustic neuroma is a slow growing tumor as well.

The authors make similar conclusions as the previous article that there is "no significantly raised risks in relation to number of years of use, time since first use, cumulative hours of use or cumulative number of calls, or separately for analogue or digital phones."³ They do mention there is a significantly raised risk for those who reported 10 years or more of ipsilateral phone use, but they don't give the confidence interval or p-value in the text of the article. The Odds Ratio for >10 years of use was 1.8 for lifetime use, and 1.3 for >10 years since first use.

There is a sentence to take note of on page 847: "The six published studies that did not show evidence of raised risk had few long-term users."

The take home message appears to be there is no increased risk of acoustic neuroma in the first decade after beginning mobile phone usage, but there is an increased risk of tumors ipsilateral to phone usage totaling 10 or more years. The authors do mention this risk is "of uncertain interpretation."³

Lonn et al⁵ discusses the results of their study done in Sweden, where mobile phones were introduced in the late 1980s allowing the residents to be a good sample population for studying the association between use of mobile phones and the risk of glioma and meningioma, two of the most common intracranial tumors. This population-based case-control study sampled Swedish residents aged 20-69 years who were diagnosed with glioma or meningioma from September 2000 to August 2002. There were 371 cases of glioma, 273 cases of meningioma, and 674 controls randomly selected and matched on age, gender, and residential area.

The selection of cases and controls was explained in detail in this study, including ICD-10 codes for the diagnosis of the tumors. The controls were grouped in 5-year groups and were selected to cover the required number of controls to case determined by the "INTERPHONE STUDY (one per brain tumour case, two per acoustic neuroma case, and three per parotid gland tumour case)."⁵ The authors note the average time between diagnosis and identification of the tumour was shorter for glioma cases.

The attempt to control the bias and errors was mentioned first under Data collection. There was an interviewer-training workshop held for all interviewers, with regular refresher meetings held nationally. The personal interview with the computer was done to aid in recall of the type of phones used and recall of other risk factors. There is mention the interview with people took about 45 minutes, while interviews

Bolton: Cellular Telephones and Cancer: Is There a Connection? with glioma and meningioma cases took on average 2-3 minutes longer. All contacts and personal interviews were done by trained nurses and a psychologist. Recall bias was also controlled for by having pictures of different mobile phones, other key details about the phone, and date introduced. Selection bias control was detailed and primarily was attempting to get answers to several questions for all non-participants.

Additional controls were separating the analysis of analog vs. digital telephones, defining terms, categorizing usage into groups of hours, cumulative number of calls, and separating into 3 groups the number of years of usage. The analysis was also separate for mobile phone use in urban and rural areas, particularly because there are some indications of higher power levels in rural areas compared to urban areas. The confounder discussed on pg 528 was “a family history of cancer or exposure from ionization radiation during medical examinations or treatment.”

Lonn et al⁵ discuss there was “no increased risk of glioma or meningioma, related to mobile phone use, regardless of tumor histology, type of phone, and duration of use.”⁵ For all subjects using their mobile phones in rural areas, there was no statistically significant result for any tumor. Two interesting facts were that mobile phone use was higher in men, especially long-term use, and meningioma is more common in women. These two facts may account for the lower proportion of mobile phone users among meningioma cases.⁵

The authors conclude their “Swedish study, which includes a large number of long-term mobile phone users, does not support the few previously reported positive findings and does not indicate any risk increases for either short-term or long-term exposures.”⁵ So, another study does not find a link between cellular phone use and brain tumor, but they cannot rule out a carcinogenic effect that might exist after a “very long induction time”⁵ because it would remain undetected at the present time.

Most of the studies reviewed here have adults as the sample population and because children are increasingly users of mobile phones I thought it would be important and of interest to my readers to review a study of younger people. Soderqvist et al⁶ performed a population-based study on 2000 subjects, divided between age groups, with 125 males and 125 females randomly selected to be in each age category. A questionnaire was mailed to the house of the subjects and a letter was included stressing the importance of an adult working with the child while completing the form. This is a type of recall bias.

This study had more detail in the statistical methods section than many of the other studies reviewed. This is helpful to judge the accuracy of their calculations and figure reporting. Although, I am still learning how to evaluate this.

The Swedish subjects reported phone ownership by 7 year olds at 7.3% which increased to 95% in the 14 year old group, which was also the group that reported the most frequent use and girls more so than boys. This number seems very high to me, but I am not raising my children the way most are. Another amazing fact was that 44.9% of subjects, age 7-14, reported regular usage.

A key factor in this study is that regular use is defined as >2 minutes per day. This definition is never discussed so it is hard to evaluate any validity or generalizability for 2 minutes being accurate. I wonder how much this small minute definition affected the numbers that were reported. It could skew the numbers either way, for good or bad.

As we consider our mobile phone usage and may consider limiting it, we need to be cognizant of all the other sources of wireless technology and radiation. Wireless computer mouse, wireless stereo or home cinema equipment, wireless headphones, or walkie-talkies.

The authors do discuss the bias and errors possible in their study as well as the way they controlled for it in their discussion section. They do not make any conclusions about brain tumors but do mention use among children increases dramatically with age, especially among teenage girls who spoke on the devices for more minutes per day compared to boys the same age. The study was well done and I am glad I chose it for review.

Hardell et al⁷ present data showing there is an increased odds ratio for brain tumors associated with cellular telephone use, analog, digital, and cordless. This paper was an additional publication from a study they had completed and written on already, a total of four prior papers. This paper had a further analysis of their data for different age groups, i.e. 20-29, 30-39, etc. up to 80 years of age. Because teenagers were not included in the sample there are no conclusions made about this age group, but there is an acknowledged need to study the effects of cellular telephone use on children.

The overall conclusion that there is an association between cellular telephone use and brain cancers seems to be valid looking at the tables and seeing so many odds ratios (OR) over 1. Some of the ORs are even over 2.0 and one as high as 5.91. The discussion reveals there are some small n's and therefore create higher ORs, but these are "elevated, but not significant, ORs." The greatest risk is shown to be in the 20-29 and 70-80 age groups. With a first exposure during the teenage years, the younger group may confirm there is a stronger effect of radiation exposure in the young, compared to an older population. This is supported by a study of the A-bomb survivors, say the authors.

An interesting note given that I am a chiropractor who believes there is a need to x-ray my patients. Will the need outweigh the risk? Will there be a need to x-ray someone who is younger than 13? Younger than 20 with no recent trauma?

The median time of use was 7 years for analog phones, 3 years for digital, and 5 years for cordless phones. There appears to be an increased risk for analog phone users, but cordless phones with a 10 plus year latency period were based on small n's, so the conclusion here is not as strong. The digital phones have not been in use long enough to make any firm conclusions, but the authors note no users had used digital phones for more than 10 years.

The authors control for confounding in their analysis, and mention the inherent bias in case-control studies, i.e. recall and observational bias, are unlikely in this study given the prevalence of the cancers ipsilateral to phone use side. The study was done ok, but I'm not convinced of the risk given the other papers I've read.

One last note of interest to everyone who might visit a dentist. Since we take our children to the dentist and they get x-rays, I want to express my caution, in light of this quote from the authors. "For brain tumors after medical and dental x-rays to the head, the strongest effect seems to be before age 20."⁷

Johansen et al⁸ is a retrospective cohort study of cancer incidence conducted in Denmark of all cellular telephone users during the period of 1982 to 1995. The authors

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had access to the cellular providers' records and after evaluation and exclusion of certain subscribers according to pre-established criteria, the existing list of subscribers was compared to a national data base for cancer incidence. This study is the first nationwide cancer incidence study of cellular telephone use looking for support for the hypothesis that there is an association between cellular telephone use and site-specific cancer incidence.

Beginning with a total 723,421 subscribers the final cohort consisted of 420,095 cellular telephone users, 357,550 men and 62,545 women. The median male age was 37.4 years and median female age was 38.4 years.

There is very little mention of bias control or confounding control. There is a comment that because the records of cellular telephone subscribers was compiled before the cases of cancer occurred in the cohort members and because the national cancer registry information was compiled independently of any company files, the possibility of observation or recall bias should be minimal. The authors mention one strength of their study is the large number of subjects allowing more than one million person-years of follow-up. The sample consisted of about 15% of the adult Danish population. The authors also list their ability to list the cancers according to location and morphology as a strength.

Some things I found noteworthy regarding RF radiation are that the RF radiation does not have the ability to remove electrons from atoms or molecules, and is therefore not an ionization causing radiation. RF radiation is called "non-ionizing" and therefore different from x-rays and gamma rays which are known to be genotoxic and known to damage DNA through free-radical formation.⁸ There is mention of a study conducted on Motorola workers who were engaged in cellular telephone manufacturing and testing that showed no association between RF exposure and cancers of the brain and nervous system. Of all populations we might expect to see some link between cellular telephone usage and cancer in, the employees who make the phones would be high on the list.¹² Their exposure dose is potentially higher for a longer time period than consumers. The authors state that RF signals are "unlikely to cause gene mutations, the biologic process underlying a possible association between exposure to cellular telephones and the risk of cancer has been proposed to be a thermal or non-thermal mechanism that promotes tumor growth."⁸

A few conclusion comments made in the paper state there is no significant risk associated with cellular telephone usage and cancers. "The absence of an excess risk was seen not only for the rapidly growing tumors such as gliomas but also for the less aggressive tumors such as meningiomas and acoustic neuromas."⁸ Tumors of the pituitary gland and pineal gland do have a non-significant increase, and these areas are usually exposed to the RF radiation of mobile phones. There does not seem to be any difference in cancer risk between using analogue or digital systems.⁸ While there was a slightly increased risk of testicular cancer in cellular telephone users, it was not linked to cellular telephone usage, but rather to socioeconomic status and being male, obviously.

This paper was published in 2001 and did not include much discussion on heavy users of cellular telephones and therefore could not deny with confidence the possibility of a carcinogenic effect on brain tissue.⁸ Other papers in this review were published after

International Journal of Global Health and Health Disparities, Vol. 6, No. 1 [2009], Art. 12 this one, and included discussion of users of more than 10 years. This paper though does a good job of discussing the risk association and the variety of cancers experienced in the sample population. I think the study was done well, but other studies in this review are better.

Schuz et al⁹ is a follow-up to the Johansen et al study, based on the same sample population, and investigates the cancer risk among Danish cellular telephone users followed for up to 21 years. It was a not a new study, but I think worthwhile in the scope of this paper to see if there is a link between cancer and RF radiation. The comment is made that during operation, cellular telephones emit “radio frequency electromagnetic fields that can penetrate 4-6 cm into the human brain”⁹ but there is no evidence to suggest an increased risk of tumors among users of less than 10 years, and only 2 of 10 studies found a statistically significant risk among users of 10 or more years.

The mean time for cellular phone use in the sample was 8.5 years while the maximum was 21 years. Regular use was defined as one call per week over a 6 month or more period. The other demographic data remained the same because the sample did not change.

There is more discussion in this paper of trying to control for misclassification of exposure, generalizability, and the effect of attenuation of relative risk. Through all the comparison and analyzing of the data, the authors are confident they have controlled for the bias and misclassification of exposure that might have occurred in their study.

A key point to mention is the authors conclude there is still no increased risk of brain tumors of various types among cellular telephone users. Importantly, there “was also no increased risk of brain tumors and leukemias observed among the 56,648 persons whose subscription to cellular telephone service was greater than 10 years.”⁹ There was a survey done in the United States that found only 48% of cellular telephone users were the sole user of their phone.⁸ So while there was no increased risk noticed among the 56,000 plus users, I would ask how many of them were high usage users during those 10 years? Higher economic status individuals were among the first users of cellular phones, and there is a possibility they may not be the sole user of their cellular telephone.

I think this paper is on par with the first one done by 4 of the authors of this paper. There is still not enough discussion of the bias and confounders control, compared to some of the first papers reviewed, but this is a good paper to add to my overall knowledge on the subject of cellular telephone use and cancers. Having a good balance of information is important with any topic, and being informed is priceless compared to making a mistake and alarming friends or patients.

Lonn et al¹⁰ discuss the output power associated with using cellular telephones and compare the power output between urban and rural usage. The amount of power output is important to consider in the discussion of cancer related to cellular telephone usage because if there is a risk among certain usage patterns, it could help each user modify their usage to reduce their cancer risk.

A cellular telephone power output changes frequently during a conversation and is influenced by the distance to the base station, the location of the user inside or outside a building, barriers between the phone and the base, and whether the user is moving

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or not. When a user moves the signal is transferred between towers and this is called a handover. The power output of cellular phones is generally highest during a handover.¹⁰

While base towers are more densely located in cities, and sparsely located in rural areas, the output power is not always lower in the cities. Depending on the number of calls handled by one tower, the need to have phones operate at a higher output level could exceed that of the rural telephone user. In addition, work calls, primarily made in the cities, are typically longer than personal telephone calls.¹⁰

There is no clear conclusion to make from this one study that looked at one week's cellular telephone usage in 4 different areas in one country. The authors state more studies are needed which hopefully will be possible.

SUMMARY AND CONCLUSIONS

The idea of cancer being caused, or influenced, by using a cellular telephone is a concern for me, and probably for all of us. The scientific evidence is not clear, but all the negative findings can not be considered conclusive. There is still not enough evidence to rule out a possible link, especially for long term or heavy users because cancers are likely dose-dependent and several are slow-growing.

While Johansen et al and Schuz et al do not report a link between phone use and cancer, other studies appear to find an increased odds ratio for cancer^{3,4}. There is disagreement among the researchers looking at the INTERPHONE study data.

It is clear the cellular telephone emits RF radiation and it is absorbed by tissue in close proximity to the signal. This radiation differs from x-rays and gamma rays which are known to cause problems such as cancer in exposed individuals.

To err on the side of caution regarding cellular phones is a wise course especially given the huge economic impact of the cellular telephone industry and the possibility of the industry's influence on studies. Also, caution until evidence proves there is no link is a good decision for anyone with children, because of the unknown effects on the developing brains and nervous systems.

I believe people should limit their cellular telephone use while traveling because of the increased power output while in the rural areas and during handovers between cell towers. Talking on the cellular phone for work may be unavoidable, but unless absolutely impossible, I would recommend using a land-line to limit exposure to the RF radiation for long periods of time. Knowing many people have only cellular telephones makes it difficult to advise against children using the phones. If a family can only afford a cellular telephone the decision to allow children to use the cellular telephone becomes difficult because of the importance for kids to interact with family members or friends who may not live close by.

For myself, I can't make any definite statement based on the review of the articles I have done so far. An increased odds ratio of less than 2 doesn't seem too bad, but then again, any increased risk is increased. I think the larger concern personally is accumulated exposure over 10+ years for my children and me. To allow my children to use our cellular telephones has become a harder decision knowing there is an increased risk, but not allowing them to use the mobile phone has its shortcomings as well. Moderation in all things is a good maxim to live by, and a safe course that is not overreacting, but is still more cautious than not.

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