Christensen et al. (1) recently presented results on the use of cellular telephones and the risk for acoustic neuroma. However, in our opinion, several issues need to be clarified in the paper. Our main concern is that the study did not take into account exposures from cordless phones, and associations specific for ever use of analog or digital phones were not addressed. Furthermore, a truly nonexposed group was not used for comparison.

Of 130 eligible cases, 107 (82 percent) were interviewed. Two individually matched controls were used for each case. The response rate for controls was 64 percent or 214 controls. Thus, 334 controls must have initially been selected, a number that does not correspond to 2:1 matching.

Conditional logistic regression analysis was based on 106 cases and 212 controls, but it is not clear whether these numbers represented complete matched triplets. Use of cordless telephones was not assessed in contrast to our study (2–5). The output power of cordless phones is of the same order as that of digital mobile phones, and the calling times on the cordless phones are much longer, so it is an important exposure that is neglected in the study. Furthermore, the investigators did not have a clean group of “no exposure,” since subjects reporting less than two calls per week and less than 6 months’ use were included among the unexposed. This low-exposure group should be reported.

Only first use of the telephone operating system was reported (1, table 2). Certainly the results should have been given for subjects using both analog and digital telephones. In fact, in our large study (2–5), only 54.3 percent of the cases and 50.9 percent of the controls had used analog phones only, that is, no digital phones. The corresponding results for digital telephones were 73.3 percent and 75.3 percent for cases and controls, respectively.

Of the cases, 45 reported use of cellular telephones, but only four (8.9 percent) of them had used the analog type. This is a low number; for comparison, refer to the Danish cohort study of mobile telephone users (6). Of the 154 brain and nervous system tumor cases, 84 (54.5 percent) used analog phones, 20 (13.0 percent) used analog and digital, and 50 (32.5 percent) used digital phones; 104 (67.5 percent) had ever used an analog telephone. This number is considerably higher than that reported now, even if subjects with use of hands-free devices were excluded (numbers not reported). In the present study, 36 (80 percent) used digital phones, a much higher percentage than that in the cohort study. Furthermore, only two (4.4 percent) cases had used a cellular telephone for 10 or more years.

Among cellular telephone users, it was more common that the tumor appeared on the contralateral side of the head than that of the ear used during phone calls: for left-handed users, three ipsilateral and 11 contralateral tumors; for right-handed users, seven ipsilateral and 14 contralateral tumors. These numbers indicate misclassification of exposure. One early sign of acoustic neuroma is hearing loss and certainly deafness after operation. Cases tend to report the current use of ear, and therefore it is necessary to carefully assess such information over the years. In our study (2–5), supplementary information was obtained during phone calls by trained interviewers. Moreover, all cases and controls were sent an additional letter asking to clarify this issue with information on the ear used over the years. Assessment of exposure was not blinded as to case or control status in the Danish study because of face-to-face interviews.

A table with information is needed on, for example, those who never used and rarely used a cellular telephone and on the unexposed. Information is needed on the numbers excluded because of use of hands-free devices.

REFERENCES


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In their recent article reporting results of a Danish case-control study of acoustic neuroma, Christensen et al. concluded “that there is no evidence for an association between use of cellular telephones and the risk of developing acoustic neuroma” (1, p. 282). This conclusion is not in line
with the study hypothesis. The authors stated that the biologic basis for an association between cell phone use and cancer could be a thermal or nonthermal mechanism that promotes tumor growth. This, of course, extends to benign tumors such as acoustic neuroma. Indeed, there is up to now no solid basis for the assumption of a tumor-initiating capacity of microwaves and, in particular, of mobile phone use. Concerning acoustic neuroma, long induction periods and latencies have been indicated (2, 3). There are diverse patterns of schwannoma growth (4), the reason for which is largely unknown. Average volume doubling times of about 2 years were found (5). Considering this evidence, what can be expected as the result of a case-control study of a factor possibly promoting tumor growth? First of all, as the authors correctly stated, exposure to microwaves from mobile phone use is restricted to the side of the head where the telephone is held during telephoning. Hence, only in subjects that used the telephone on the same side of the head as the tumor is located can an effect on tumor growth be expected. However, unilateral hearing loss and tinnitus are likely to interfere with this habit if the tumor happens to be located on the side of predominant use. There are several indications in the data presented that such symptoms changed usage pattern: 20 percent of cellular telephone users among cases compared with 6 percent in controls had no preferred side of telephone use, ipsilateral use was significantly less frequent, compared with 6 percent in controls had no preferred side of telephone use, ipsilateral use was significantly less frequent, and there was a decrease of odds ratios by the time since first use and cumulative number of calls. These data suggest that the growing tumor led to a reduction in or even cessation of phone use and to switching side of the head in response to hearing loss. Similar results have been obtained previously (6). On the other hand, the mean size of the tumors in mobile phone users was significantly greater (1.66 cm$^3$) than in nonusers (1.39 cm$^3$). Considering an average annual tumor growth of 0.1 cm$^3$ and an average duration of mobile phone use of about 3.5 years, this difference is consistent with a substantial increase of growth rate. Combining these lines of evidence, the data presented so far are insufficient to decide the influence of symptoms on mobile phone use and laterality. However, it seems that there are too few cases of long-term use to make such an analysis meaningful.

Furthermore, it must be stressed that odds ratios considerably underestimate the effects on tumor growth. The predominant effect of a promoter is a shift of the distribution of age at diagnosis by a fraction of exposure duration. If exposure duration is short relative to the natural history of the disease and the age-incidence function has a flat slope, the odds ratios from age-matched case-control studies are generally too low to indicate an effect even if the agent under study does substantially increase the tumor growth rate. Future publications of results obtained within the framework of the Interphone Study of the World Health Organization should probably avoid presenting analyses that are based on the assumption of a tumor-inducing capacity of emissions from mobile phones, because 1) the vast majority of brain tumors have induction periods and latencies that typically exceed exposure duration that could have been accumulated up to now, and 2) promoting effects will be obscured.

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THE AUTHORS AND DR. CARDIS REPLY

We thank Dr. Hardell and Professor Hansson Mild (1) and also Dr. Kundi (2) for their observations on our recently published study on cellular telephone use and acoustic neuroma (3). Hardell and Hansson Mild raise a number of issues regarding our study. In the Interphone Study, no information was collected concerning the use of cordless telephones (other than digital enhanced cordless telecommunications (DECT)), because they emit in a different frequency band than mobile phones and because the time-averaged power emitted by such telephones is much smaller than that emitted by cellular telephones.

It is true that 82 percent of eligible cases were interviewed and, for each case, a corresponding pair of controls were ascertained. If a control denied participation, another control was sampled from the pool of randomly selected potential controls. This process was repeated until we had established a case-control study base consisting of 106 cases and 212 controls, all included in the conditional logistic regression analyses representing 106 complete matched triplets.

We do not agree with Hardell and Hansson Mild (1) that persons reporting less than two calls per week and less than 6 months of use should be reported in this context. To separate the data into two groups—analog users and digital users—will not give meaningful results because all regular users of cellular telephones in our study either started with a digital telephone or switched over from an analog telephone to a digital telephone within a few years after the introduction of the digital system.

Our paper (3) reports the results of a population-based study of use of cellular telephones and risk of acoustic neuroma, with cases diagnosed between 2000 and 2002. Contrary to this, our previously published cohort study (4) reported on a cohort of subscribers from 1982 to 1995 with an explanation of the change in proportions of analog and digital users and the high prevalence of mobile phone use.

REFERENCES