



Original Contribution

Long-Term Mobile Phone Use and the Risk of Vestibular Schwannoma: A Danish Nationwide Cohort Study

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Vestibular schwannomas grow in the region within the brain where most of the energy by radiofrequency electromagnetic fields from using mobile phones is absorbed. The authors used 2 Danish nationwide cohort studies, one a study of all adult Danes subscribing for a mobile phone in 1995 or earlier and one on sociodemographic factors and cancer risk, and followed subjects included in both cohorts for occurrence of vestibular schwannoma up to 2006 inclusively. In this study including 2.9 million subjects, a long-term mobile phone subscription of ≥ 11 years was not related to an increased vestibular schwannoma risk in men (relative risk estimate = 0.87, 95% confidence interval: 0.52, 1.46), and no vestibular schwannoma cases among long-term subscribers occurred in women versus 1.6 expected. Vestibular schwannomas did not occur more often on the right side of the head, although the majority of Danes reported holding their mobile phone to the right ear. Vestibular schwannomas in long-term male subscribers were not of larger size than expected. Overall, no evidence was found that mobile phone use is related to the risk of vestibular schwannoma. Because of the usually slow growth of vestibular schwannoma and possible diagnostic delay, further surveillance is indicated.

brain neoplasms; cellular phone; cohort studies; Denmark; electromagnetic fields; neuroma, acoustic

Abbreviations: CI, confidence interval; RF-EMF, radiofrequency electromagnetic field.

Vestibular schwannoma, also termed acoustic neuroma, is a tumor that arises on the eighth cranial nerve leading from the brainstem to the inner ear and accounts for about 5%–6% of all intracranial tumors (1). Vestibular schwannomas occur in a sporadic, mostly unilateral form and a hereditary, mostly bilateral form, accounting for about 5%–10% of vestibular schwannoma cases (2, 3). Recent research has focused on the use of mobile phones as a putative risk factor (4). Mobile phones emit radiofrequency electromagnetic fields (RF-EMFs) and, when the handset is held to the ear, RF-EMFs penetrate into the brain, decreasing rapidly with increasing depth (5, 6). Thus, in principle, vestibular schwannomas occur where the most energy from RF-EMF exposure is absorbed in the tissue. Mobile phones comply with protection guidelines defined to protect users from adverse health effects and, according to the current scientific

evidence, tumorigenic effects below these guidelines appear to be unlikely (7). However, with the number of mobile phone users approaching 5 billion worldwide, even small risks would have a large public health impact, justifying continued research (8). As vestibular schwannomas grow slowly and the first symptoms often occur years before clinical diagnosis (9–11), longer term use of mobile phones is of particular importance for vestibular schwannomas to be more certain that exposure preceded disease.

The possible association between mobile phone use and the risk of vestibular schwannoma has been investigated in interview-based case-control studies, but most were limited by too small numbers of mobile phone users of more than 10 years. A recent review showed an overall 40% risk increase with mobile phone use of ≥ 10 years, although the pooled studies showed marked heterogeneity, with individual

relative risk estimates ranging from 0.2 to 3.5 (4). The largest and most comprehensive study on this topic (Interphone) showed a statistically significant risk increase when restricting the analyses of long-term users to subjects who used the mobile phone mainly on the side of the head on which the vestibular schwannoma occurred subsequently, when pooling data sets from the United Kingdom and Nordic countries (12). In addition, the Danish component of the Interphone study showed that mobile phone users had slightly larger vestibular schwannoma than did nonusers (13). Firm conclusions are difficult to draw as a number of major biases and errors have been identified in the case-control studies. In particular, it was difficult to recruit control groups representative with respect to mobile phone use (14) and, furthermore, recall of past mobile phone use was not accurate (15, 16), providing potential for both upward and downward bias in the risk estimation (17).

Here, we report results from linkage of 2 Danish nationwide cohort studies followed up for occurrence of vestibular schwannoma until 2006 using complete case ascertainment based on the oldest nationwide cancer registry in the world, established in 1942, and a population-based, nationwide clinical database, which also includes laterality, spread, and size of the tumor. The 3 objectives were as follows: 1) to estimate the risk of vestibular schwannomas among long-term mobile phone subscribers of 11 years or more compared with short-term and nonsubscribers; 2) to investigate laterality of vestibular schwannomas in long-term mobile phone subscribers compared with short-term and nonsubscribers; and 3) to investigate the size of vestibular schwannomas in long-term mobile phone subscribers compared with short-term and nonsubscribers.

MATERIALS AND METHODS

Cohort definitions

The composition of the cohort of mobile phone subscribers has been reported previously (18, 19). In brief, we received customer records of all 723,421 mobile phone subscriptions in Denmark during the period 1982–1995. From these, 200,507 corporate subscriptions were deleted as the individual users could not be identified. A further 102,819 records were excluded because of duplicate addresses (one of them removed), errors in name or address, a nonresidential address, the subscriber under 18 years of age at first subscription, the subscriber's being a permanent resident of Greenland or the Faroe Islands, or the subscriber's request to be excluded from the study ($n = 53$). The final study cohort comprised 420,095 private cellular telephone subscribers. Unlike in some previous analyses, we left censored exposure of all mobile phone subscribers starting before 1987, as mobile phones held directly to the head only became available during this year in Denmark, and exposure from car phones with the antenna farther away from the head is magnitudes lower. In previous studies using this cohort, we observed that mobile phone users during the early time period of their introduction had lower incidence rates of lifestyle-related cancers, particularly tobacco-related cancers, and it was therefore a limitation that we

did not have any information to adjust for socioeconomic status (19).

To compensate for this shortcoming, we now linked the subscriber cohort with data from a Danish nationwide cohort study on social inequality and cancer, the CANULI study (20). All residents born between 1925 and 1976 who resided in Denmark between 1998 and 2006 were enrolled for this study. Entry into the cohort was at age 30 years, because younger persons might still be in the educational system. Those who immigrated to Denmark and their descendants were excluded because they composed an ethnically very heterogeneous group, and data on their education, if acquired abroad, were not available. In total, after exclusions, we had 2.88 million Danes for follow-up. Information on the socioeconomic status of the study cohort was obtained from the population-based Integrated Database for Labour Market Research at Statistics Denmark, which contains yearly data since 1980. The level of highest attained education was grouped into basic school/high school (primary, secondary, and grammar school education), middle (vocational education), and higher education (postgraduate education). Disposable income was calculated on the basis of household income after taxation and interest per person, adjusted for the number of persons in the household and deflated according to the year 2000 value of the Danish crown, following a formula from the Danish Ministry of Finance. Disposable income was grouped into low (first quartile), middle (second and third quartiles), and high (fourth quartile), by separated distributions for men and women in the cohort for each study year (20). Cohabiting status was grouped as married versus not married.

By linkage of the 2 cohorts, each of the 2.88 million subjects of the nationwide cohort was classified as either a long-term mobile phone user (by having the first subscription 11 years ago or longer) or other, with the latter to be included in the comparison group. We used 11 years as a cutoff so that no person in the comparison group had a mobile phone subscription for as many years as persons in the exposed group and, as outlined above, we were interested only in longer term exposure because of the assumed slow development of vestibular schwannoma.

Case ascertainment

Since April 1, 1968, all Danish residents have been assigned a unique 10-digit personal identification number, which includes information on date of birth and gender. Information on vital statistics is continuously updated. The personal identification number enables linkage of databases containing information on social, economic, educational, health, and disease-specific characteristics for each individual living in the population of approximately 5.5 million people. In this study, record linkage of cohort members by the personal identification number enabled perfect linkage of databases without any loss to follow-up, data on vital status, date of death, or date of emigration—all obtained from the central population registry. Information on all cases of vestibular schwannoma was obtained from 2 sources, again using the personal identification number for the record linkage. First, in Denmark, vestibular schwannoma

patients are treated mainly in one clinical center at Gentofte University Hospital, Copenhagen, and this clinical database contains detailed information on each person referred for a diagnosis of vestibular schwannoma, including diagnostic work-up to establish a confirmed diagnosis, treatment information, and pathology report (21). We included information on the size of the tumor given as the extrameatal diameter in mm, measured at diagnosis, and spread of the vestibular schwannoma discriminated into intrameatal spread only or intra- and extrameatal spread.

Second, the cohort was linked with the nationwide population-based cancer registry to identify patients not registered in the clinical registry and vice versa (22). This register has almost complete coverage of the population since 1942 and, since 1978, contains detailed information about topography and morphology of all tumors following the *International Classification of Diseases for Oncology* (ICD-O). All persons were followed up for the occurrence of vestibular schwannoma from age 30 years or January 1, 1998, whichever came last and ended on the date of diagnosis of vestibular schwannoma, date of a cancer diagnosis except nonmelanoma skin cancer, date of death, date of emigration, or December 31, 2006, whichever came first.

Statistical analyses

Incidence rates by 5-year age groups were calculated for long-term mobile phone subscribers versus others. Log-linear Poisson regression models were used to estimate incidence rate ratios, with 95% confidence intervals, always adjusted for period (1998–2001, 2002–2006) and age (modeled as age and age² in years). Further variables for adjustment included the highest attained educational level, disposable income, and marital status. We used the status of the socioeconomic status indicator 2 years before the year of observation in order to allow some lag time before changes may modulate disease risk. Persons who had a cancer diagnosis before being diagnosed with vestibular schwannoma were censored at the date of diagnosis of their cancer and from then on excluded from the follow-up.

The proportion of vestibular schwannomas occurring on the right side of the head was estimated in the long-term mobile phone subscribers and compared with the proportion in short-term and nonsubscribers. Logistic regression analysis was used to additionally adjust for age (using age and age²).

Among patients with intra- and extrameatal vestibular schwannoma, the size of tumor was examined with univariate characteristics (mean, median, and first and third quartiles) in long-term mobile phone subscribers compared with short-term or nonsubscribers, and the difference was explored by using the Kruskal-Wallis test. Multiple linear regression analysis was used to additionally adjust for age (using age and age² in the model) and year of diagnosis when investigating the association between vestibular schwannoma size and mobile phone subscription. We checked whether the inclusion of highest attained educational level, disposable income, or marital status changed the overall results. As this was not the case, we report only the results with a few adjustment variables in this paper.

RESULTS

The study was based on 2,883,665 persons and 22,884,931 person-years of follow-up for vestibular schwannoma after linkage of the 2 cohorts. A total of 404 cases in men and 402 cases in women were diagnosed in the cohort as having vestibular schwannoma without any previous cancer diagnosis. Only a few women were long-term mobile phone users ($n = 44,025$) of 11 years or more. In women, no cases of vestibular schwannoma were observed among long-term mobile phone subscribers versus 1.6 cases expected; hence, most of the following analyses are based only on men.

The age-adjusted incidence rate of vestibular schwannoma among long-term male subscribers of mobile phones (≥ 11 years) was similar to that of short-term and nonsubscribers (Figure 1). This was confirmed by an incidence rate ratio close to 1.0 (Table 1). The effect estimate changed only marginally when adjustment to educational level, disposable income, and marital status was applied.

The recent launch of a prospective cohort study (Cosmos) showed that, among Danish mobile phone users, 53% preferred the right, 35% preferred the left, and 13% had no preferred ear when making or receiving phone calls with their mobile phone; there was only minor variation between men and women (23). Hence, one would expect that, among mobile phone users also, more vestibular schwannomas would occur on the right side. In the subscriber cohort overall, 48% (95% confidence interval (CI): 43–53; $n = 384$) of vestibular schwannomas were on the right side in men and also 48% (95% CI: 43–53; $n = 386$) were on the right side in women. Splitting men into long-term subscribers and others showed right-side vestibular schwannomas in 47% (95% CI: 21–72; $n = 15$) compared with 48% (95% CI: 43–53; $n = 369$). There was no evidence that vestibular schwannomas tended to become more common on the right side of the head over time (Figure 2).

Among 383 male vestibular schwannoma cases with available information on size and spread (95%), 122 were only of intrameatal spread. The size of the remaining vestibular schwannomas of intra- and extrameatal spread did not differ between long-term mobile phone subscribers and others; however, there were only 8 male vestibular schwannoma cases in the long-term subscriber category (Table 2).

DISCUSSION

In this nationwide, record linkage-based cohort study in Denmark, we did not find any evidence of an increased risk of vestibular schwannomas in long-term mobile phone subscribers. Comparing long-term mobile phone subscribers of 11 years or more with short-term and nonsubscribers, we found that the 2 groups did not differ in regard to vestibular schwannoma incidence rates, vestibular schwannoma size, and laterality of vestibular schwannoma.

Little is known about environmental risk factors for vestibular schwannoma, with ionizing radiation and noise being suspected but not established (24–27). Hence, it is speculative if and, if yes, which other factors may play a role in the association between mobile phone use and vestibular schwannoma. Vestibular schwannoma is more common in

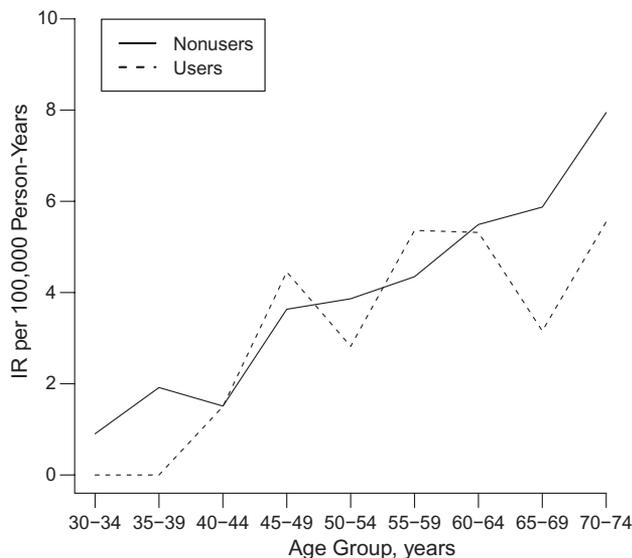


Figure 1. Age-specific incidence rates (IRs) per 100,000 persons of vestibular schwannoma in the period 1998–2006 among Danish men with (“users” curve) or without (“nonusers” curve) a long-term mobile phone subscription (first subscription 11 years ago or longer).

affluent persons (28), and our data confirmed a distinct social gradient and association with marital status, with the incidence rate of vestibular schwannoma being 3 times higher in married men of high education compared with nonmarried men of low education (29). We had previously reported the higher income of men in the mobile phone subscriber cohort compared with the general population (19). Consequently, adjustment for education, income, and marital status appeared to be essential but at the end did not matter with the effect estimate after adjustment being almost identical to the unadjusted one. Vestibular schwannoma cases among mobile phone users might be diagnosed

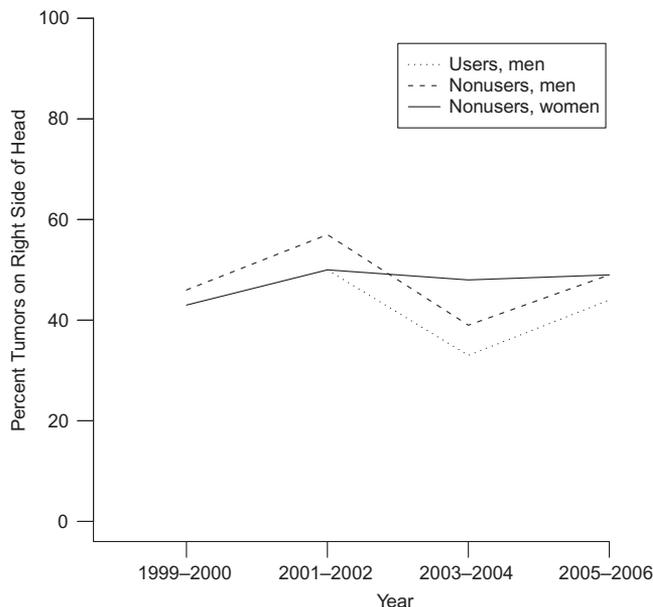


Figure 2. Proportion of vestibular schwannoma on the right side of the head among Danish long-term mobile phone subscribers (first subscription 11 years ago or longer; “users” curve) compared with short-term and nonsubscribers in men and overall proportion in women (“nonusers” curve), by years of diagnosis; because of small numbers of users, 2-year periods were combined, and the curve for users starts in 2001–2002.

earlier because of increased awareness of early symptoms such as hearing problems when using a mobile phone, but we found no evidence for this hypothesis. Patients with an undiagnosed vestibular schwannoma but early symptoms might, for this reason, refrain from becoming mobile phone users, which would lead to an inverse association, but our time lag between early symptoms and diagnosis was at least 11 years, and we did not observe an inverse association.

Table 1. Risk of Vestibular Schwannoma in Relation to a Long-Term Mobile Phone Subscription,^a Denmark, 1982–2006

	Men ^b			
	No. of Cases	Person-Years at Risk	IRR	95% CI
Mobile phone subscription ≥ 11 years				
No	389	11,019,107	1.00	Referent
Yes	15	462,430	0.88	0.52, 1.48
Mobile phone subscription ≥ 11 years, adjusted for educational level, disposable income, and marital status				
No	389	11,019,107	1.00	Referent
Yes	15	462,430	0.87	0.52, 1.46

Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

^a First subscription 11 years ago or longer.

^b Only for men as no vestibular schwannoma cases occurred in long-term female mobile phone subscribers.

Table 2. Size of Vestibular Schwannoma With Intra- and Extrameatal Spread in Relation to a Long-Term Mobile Phone Subscription,^a Men Only, Denmark, 1982–2006

	No.	Size by Diameter, mm				P_{uni}	P_{mult}
		Mean	Median	First Quartile	Third Quartile		
All	261						
Long-term mobile phone subscription							
No	253	15.92	13	10	21		
Yes	8	14.63	8	6	22	0.32	0.95

Abbreviations: P_{uni} , P value by Kruskal-Wallis test; P_{mult} , P value by multiple linear regression analysis additionally adjusted for age (age and age²) and year of diagnosis.

^a First subscription 11 years ago or longer.

Early symptoms might affect the preferred side of the head during mobile phone use as the hearing loss is unilateral (30), but we did not observe an excess of left-sided vestibular schwannoma in mobile phone subscribers either. It has been discussed that RF-EMFs might not initiate but rather lead a promotion of the growth of vestibular schwannoma (13, 31), but the size of vestibular schwannoma in mobile phone subscribers was not larger than expected.

We have eliminated a number of limitations raised when we previously used this cohort (32). By linking the subscriber cohort and nationwide cohort on social inequality and cancer, we were able to adjust for all relevant demographic and sociodemographic characteristics. We removed all exposure due to subscriptions before 1987 to exclude the time period of sole use of car phones with lower exposures as the antenna is farther away from the head (33). We had access to a unique national clinical vestibular schwannoma tumor registry whereby we obtained complete data about a benign disease (vestibular schwannoma) that is possibly underreported in the nationwide cancer registries, including the Danish Cancer Register. We were also able to obtain valuable information on tumor characteristics such as the size and laterality of the incident vestibular schwannoma tumor. These improvements in methodology and data quality strengthened the weight of the results. In addition, we noted that the data used for this study were obtained in registries established for administrative reasons independently of the study hypothesis, thereby excluding information bias. We have previously demonstrated that a mobile phone subscription was a good predictor of regular mobile phone use (34).

Our main limitation continues to be the fact that we do not have any information on the amount of use of the mobile phone; thus, we were unable to investigate the risk restricted to the group of heavy users of mobile phones. Corporate subscriptions could not be included in the cohort when the subscription was in the name of the company but not in the name of an individual. Short-term mobile phone users were included in the nonexposed comparison group, which might dilute an association if short-term use was associated with an increased vestibular schwannoma risk; however, there is evidence from other studies that such an association is unlikely (4, 12, 18, 19) and, given the high proportion of short-term mobile phone users in Denmark, the observa-

tion that vestibular schwannoma incidence rates remained stable in recent years provides a strong argument against such an assumption (21). We have no information on the use of cordless phones, which is another source of RF-EMF exposure to the head, but perhaps a minor issue in our group of mobile phone users of 11 years or more, using either analog technology with much higher output power than cordless phones (35) or early users of digital technology when the average output power reduction due to power adaptation was not substantial (36).

A current general limitation to study the relation between long-term mobile phone use and vestibular schwannoma risk in epidemiologic studies is the combination of a rare exposure and rare disease, which is why in our study including the entire population of Denmark numbers of exposed are still small and confidence intervals are wide. However, today the number of never users of mobile phones is very small, and the proportion of long-term users is increasing steadily to the extent that any mobile phone use-related vestibular schwannoma risk would lead to a marked increase in the incidence rates of vestibular schwannoma.

Another general limitation of our study and other studies on this topic is the still-short time duration under risk of 10–15 years even among long-term mobile phone users in relation to the usually slow growth of vestibular schwannoma (11). Given the assumed diagnostic delay of up to several years, the “true” induction period for all studies would even be substantially shorter (37). Therefore, our finding of no association is not unexpected. However, it is unclear why the case-control studies by Hardell et al. (38) observed increased risks already in the group of short-term mobile phone users of only a few years, a group including patients starting to use a mobile phone only after the “true” onset of disease, and this would most likely be explained by bias; without any efforts to estimate the magnitude of bias, these studies are relatively difficult to include in an overall risk assessment. In addition, the finding of up to 3–4-fold increased vestibular schwannoma risks in analog mobile phone users of ≥ 10 years is in sharp contrast to the nationwide incidence rates in mobile phone subscribers in our study (38). On the other hand, our results are not incompatible with the suggestion of a possibly modestly increased risk restricted to subgroups of mobile phone users as

observed in the Nordic/United Kingdom component of the Interphone study (12), although, with a relative risk estimate just below 1 but not above 1, there is also no further support for such a modest risk increase based on the results of our cohort study. For risk assessment, our study becomes valuable because, even when being conservative and not designed to address the risk in subgroups of mobile phone users, it defines unambiguous limits of what magnitude of risk can be ruled out.

In conclusion, the results from this comprehensive study do not support the hypothesis that use of a mobile phone increases the risk of vestibular schwannoma. However, as vestibular schwannomas grow slowly and there is the possibility of some diagnostic delay, the observation period of 10–15 years after the widespread introduction of mobile phones may still be too short to observe an effect, and thus further surveillance of vestibular schwannoma is indicated, preferably by monitoring incidence rates in high-quality cancer registers combined with access to clinical databases, or by conducting prospective cohort studies. Across studies published so far, we find little evidence that mobile phone use increases the risk of vestibular schwannomas.

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