

# **CEFALO: International Case-Control Study on the risk of brain tumors in children and adolescents**

## ***Background***

Mobile phone use by children and adolescents has increased considerably during the last 15 years. This has resulted in public concerns about possible adverse effects of radiofrequency electromagnetic fields generated by these devices. So far, the risk of brain tumors due to mobile phone use has not been addressed in this age group.

CEFALO is an international case-control study examining the association between mobile phone use and the risk of brain tumors in children and adolescents. The study was conducted in Switzerland, Denmark, Norway and Sweden and the main results have been published in the Journal of the National Cancer Institute in July 2011 (Aydin et al., JNCI, 2011).

## ***Methods***

All children and adolescents aged 7 to 19 years and diagnosed with a brain tumor between 2004 and 2008 were eligible for the study. For each patient, two controls of the same age, gender and region of residence were randomly selected from population registries.

The data were obtained by personal interviews with the study participants and their parents. All participants having used a mobile phone for at least 20 calls were asked about their usage pattern prior to diagnosis. The frequency and duration of mobile phone use was inquired for various time periods as well as the preferred side of the head and the use of hands-free kits. Furthermore, we asked for permission to obtain connection data from mobile phone operators.

We collected also data on other possible risk factors for brain tumors such as diagnostic x-ray radiation, infectious diseases and head injuries during childhood.

The association between mobile phone use and brain tumor risks was evaluated by comparing the duration and intensity of mobile phone use between patients and controls in conditional regression analyses. In addition, several sensitivity analyses were conducted. For instance, the brain tumor incidence rates in Swedish children and adolescents between 1990 and 2008 as registered in the nationwide cancer registry were compared with the number of mobile phone users assuming various scenarios for a hypothetical association.

## ***Results***

Overall, 352 patients and 646 controls took part in the study. The participation rates were 83% for cases and 71% for controls. Fifty-five percent of patients and 51% of controls reported regular mobile phone use (at least one call per week during at least 6 months). In the primary analysis, brain tumor risk was not significantly associated with regular mobile phone use (Odds ratio [OR] = 1.36, 95% Confidence interval [CI]: 0.92–2.02). Other exposure metrics, such as time since first mobile phone use or cumulative number and duration of calls, were also not significantly associated with brain tumors and no consistent exposure-response relationship was observed. For instance, we observed similar risks for participants who had used a mobile phone since five years or longer and short term users ( $\leq 3.3$  years) (OR=1.26 [95%CI: 0.7–2.28] vs. OR=1.35 [95%CI: 0.89–2.04]). The risk of tumors in the brain regions most highly exposed by mobile phones (temporal lobe, frontal

lobe and cerebellum) was not associated with regular mobile phone use (OR=1.00, 95%CI: 0.58–1.72). Regarding preferred side of the head for using the mobile phone, tumors did not occur more often on the ipsilateral compared to the contralateral side. Objective operator data were available for a third of the study participants. In this subset, brain tumor risk was elevated for participants with the longest period since first subscription (>2.8 years) (OR=2.15 [95%CI: 1.07–4.29]). Calculations demonstrated that such a risk, if true, would have resulted in an increase of brain tumor incidence by approximately 50% in the last few years. Such an increase was not observed in Swedish children and adolescents (Figure 1).

## ***Discussion and Conclusions***

CEFALO is the first case-control study addressing possible associations between mobile phone use and brain tumors in children and adolescents. The regression analyses revealed various risk estimates that were somewhat elevated but not statistically significant. Thus, these results do not indicate an increase in brain tumor risk related to mobile phone use. The various odds ratios above unity might be considered as weak evidence for an association because we found no indication that results were biased due to selective participation of controls or more pronounced overestimation of mobile phone use among patients compared to controls (Aydin et al., *BioEM*, 2011). However, the pattern of the risk results does not suggest a causal association. First, in most analyses there was no consistent exposure-response association observed. Second, the brain tumor risk was not elevated in brain regions that are most exposed when using a mobile phone. Third, the brain tumor incidence in children and adolescents in Sweden, where the most recent data were available, has rather decreased than increased between 2000 and 2008.

The most striking result of CEFALO is a statistically significant association between the duration of mobile phone use and brain tumor risk in the small subset of the study sample with operator data. Objective data are presumed to be more reliable than self-reported data. However, the absent increase of the brain tumor incidence based on high quality registry data strongly contradicts the observed associations.

One alternative explanation might be that patients more often succeeded in making operator data for more distant time periods available than controls. Also, cases may have changed subscriptions or phone numbers less often than controls. Thus, mobile phone operator data would cover more distant time periods in cases than controls. This would lead to an erroneous notion that cases started to use mobile phones earlier than controls. Another possibility is the presence of prodromal symptoms before diagnosis in some case patients. To provide frail children with better protection, their parents may have given them a mobile phone subscription for use in case of emergency.

Overall, CEFALO demonstrated that considerable uncertainty is related to data on long term mobile phone use (Aydin et al, *Bio EM*, 2011). It is difficult to obtain the typical usage pattern of study participants because of the high temporal variability of mobile phone use. When the CEFALO study started, the extent of the error rate for data on long term mobile phone use was unknown. Since that time, however, considerable uncertainty was also observed in other studies (e.g. INTERPHONE).

A strength of the CEFALO study is the use of objective exposure data which was rarely available in previous studies. However, it turned out that retrospectively collected operator records are as well prone to error and cannot be regarded as gold standard for several reasons. Not all operators do store traffic data long enough or data are not traceable anymore. Moreover the identification of the actual user of a mobile phone may be erroneous and study participants may not remember their previous phone numbers.

In summary, the results of the CEFALO study do not suggest a causal association between mobile phone use among children or adolescents and the brain tumor risk. However, since the duration and intensity of use was relatively low in our sample we were not able to evaluate the brain tumor risk regarding intensive long term mobile phone use. Given the substantial amount of mobile phone use among today's adolescents and the methodological limitations of case-control studies in this research area, incidence trends of brain tumors should be carefully monitored in the next years using high quality registry data.

## References

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## Figure

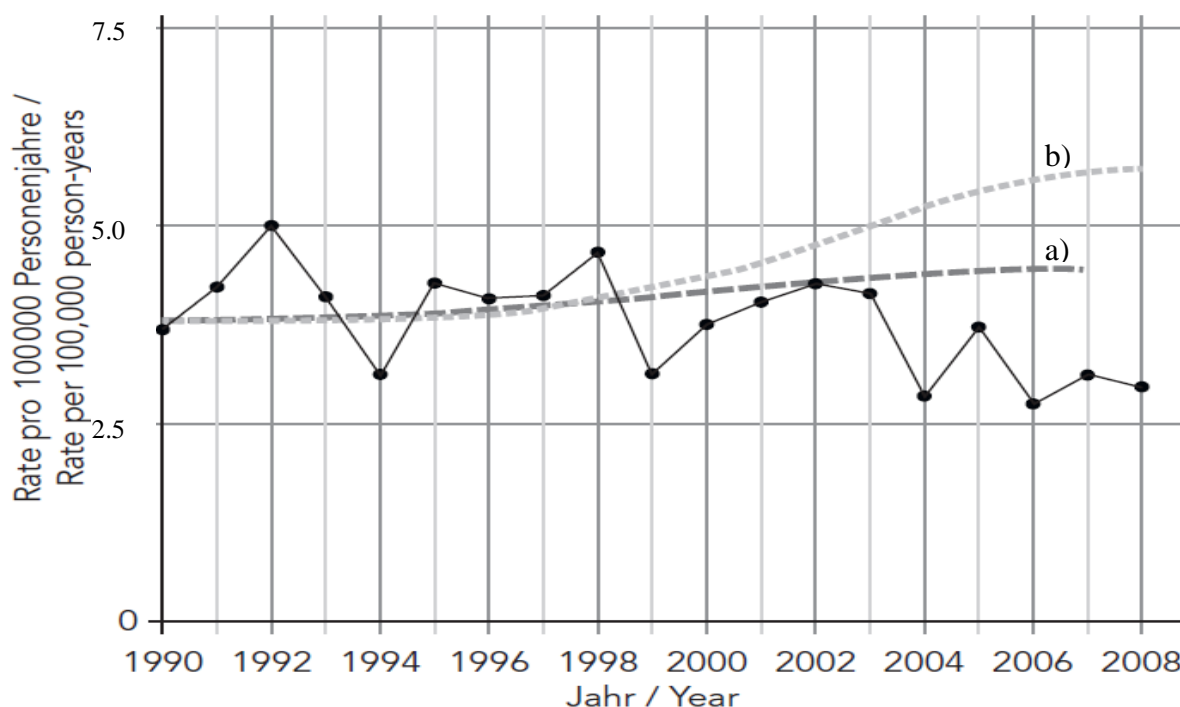


Fig 1: Gender-age-standardized incidence rate among Swedish children and adolescents aged 5 to 19 years between 1990 and 2008 (solid black line). The dotted lines are based on the results of the CEFALO study and denote the hypothetical incidence rate trends a) under the assumption that regular use of mobile phones increases the brain tumor risk by 36% (odds ratio [OR] = 1.36) (without considering any latency period) and b) under the assumption that the risk increases by 115% (OR = 2.15) after 3 years of regular mobile phone use.

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