



of epidemiological studies CE research

Epidemiology – a definition

Epidemiology deals with the spatial and temporal distribution of diseases in the population and the factors that have a causal influence on it. It thus comprises both the description of disease incidence (descriptive epidemiology) and the search for causes (analytic epidemiology), mainly in the framework of observational studies. The aim is to identify risk factors and contribute to the prevention of diseases.

The strength of epidemiological studies is that they capture real situations, i.e. the exposure is investigated under the conditions of everyday life in persons who actually are exposed. Some human experiments cannot be performed in laboratory studies and the extrapolation of observations in cells or animals to humans is not always possible. Moreover epidemiological research has the advantage that the relevance of an effect can be assessed on the level of the whole population. The observational character of epidemiological studies, however, has also disadvantages insofar that the researcher cannot control the study conditions. Therefore spurious associations can appear in epidemiological studies, e.g. by false correlations via third factors (confounders) or inappropriate group comparisons.

The evaluation of epidemiological evidence is performed under different aspects: the strength of the observed association, the consistency of results within a study and across different studies, the occurrence of a dose-response relationship as well as the biological plausibility of results (criteria as given by Hill, 1965). A special problem in the interpretation of observed associations arises when epidemiological findings are not supported by experimental studies. One

reason could be that epidemiology is an early indicator for an association, which is uncovered in laboratory studies because the underlying mechanism is unknown, or was not modelled correctly. Another reason could be that the empirically observed association is not causal. Epidemiological and experimental studies supplement each other and should always be discussed together.

Studies on mobile phones and brain tumours

There are now more than 30 original publications on the question whether mobile phone usage increases the risk of brain tumours, even after leaving out numerous letters and reviews regarding the topic. These publications can be subdivided into four groups (table 1). The **first group** comprises the studies published around the turn of the century, which were independent case-control studies from the USA and Scandinavia, performed in patients ascertained already in the nineties, i.e. the percentage of persons with mobile phone usage of more than five years was low. In summary, these studies provided no evidence that short-term mobile phone use is associated with the brain tumour risk. The **second group** is a series of case-control studies performed in parts of Sweden (three subsequent studies using the same methodology), which were published several times under partially different aspects. In a review paper by the research group who conducted these studies, a strong association between both mobile phone use and the use of cordless phones with the brain tumour risk was reported, which was most pronounced for high-grade gliomas and acoustic neuromas, but was also

found for low-grade gliomas and meningiomas. In these studies an increased risk was observed with long-term and more frequent phone use, but statistically significantly increased risks were also seen at rather moderate use patterns, i.e. already at life-time cumulative mobile phone usage between 1 and 43 hours. The **third group** is the so-called “Interphone study”, an international case-control study involving 16 centres in 13 countries. Beside Germany, the participating countries were Australia, Canada, Denmark, Finland, France, Great Britain, Israel, Italy, Japan, New Zealand, Norway and Sweden; approximately 1-hour interviews with 2765 glioma patients, 2425 meningioma patients, 1121 acoustic neuroma patients and 109 patients with malignant salivary gland tumours as well as 7658 control persons were conducted. All centres worked in accordance with an international study protocol, which allows joint analyses when the study will be completed. This pooled analyses and the large study size also allow to gain insight into possible risks among subgroups of patients, e.g. according to the type of the tumour and its localization; the latter is important because, due to the low penetration depth of radio frequency electromagnetic fields emitted by the phone, it is conceivable that an increase in risk can only be found in tumours located in the lateral area of the side of the head where the phone was held. In the meantime, more than one half of the data from the Interphone study have been published, including the studies from four Scandinavian countries, from Great Britain, from Japan and Germany. They confirm the results of the first group of no association with short-term use and contradict the second group, which has found that even short-term mobile phone use increases the risk. The results for the group of long-term users (ten years or longer) are still unclear. There is evidence of an increased risk of acoustic neuroma from Sweden, of an increased risk of glioma from Germany, keeping in mind that combining all published Interphone components weakened these single findings. The results of the joint analyses need to be awaited before drawing further conclusions. The **fourth group** is formed by a study of different design (cohort study). In a Danish study the entire adult population was divided in two

groups, into those who had their first mobile phone contract in their own name between 1982 and 1995, and into all others. Cancer incidence rates were calculated for these two population groups using the Danish Cancer Registry. The incidence rates for brain tumours, leukemias, eye and salivary gland tumours were not increased in the early mobile phone owners. Due to the rather rough division into exposed and unexposed persons, a moderately increased risk cannot be excluded in this type of study, but having missed a substantial risk increase is very unlikely. Hence, the results do contradict the observed increase in risk of the second group. For a discussion of these studies and their evaluation please refer to a recent opinion statement of the European Union (download is for free from the internet [1]). A short review in German was recently published by the Deutsches Ärzteblatt [2]. In the following, the methodological challenges of these studies will be examined in more detail.

Case-control studies – advantages and disadvantages

Case-control studies are based on the comparison of two groups of persons (fig. 1). The group of cases are the persons who have the target disease of the study and they are retrospectively examined for the occurrence of the possible risk factors of interest. A control group of persons without the disease is examined likewise. The direction of the investigation is always retrospective (the starting point is the disease), regardless of the fact whether the case identification was retrospective as well (the diagnosis was made prior to the beginning of the study; prevalent cases) or prospective (after the beginning of the study over a defined time period newly diagnosed cases are included in the study; incident cases). A prospective recruiting of patients is necessary for outcomes with poor prognosis. Case-control studies are based on one or few diseases, but a great number of potential risk factors are examined. Despite some disadvantages, case-control studies are very common in the epidemiology of chronic diseases, especially for rare outcomes. The conduct of case-control studies is usually shorter than that of cohort studies and

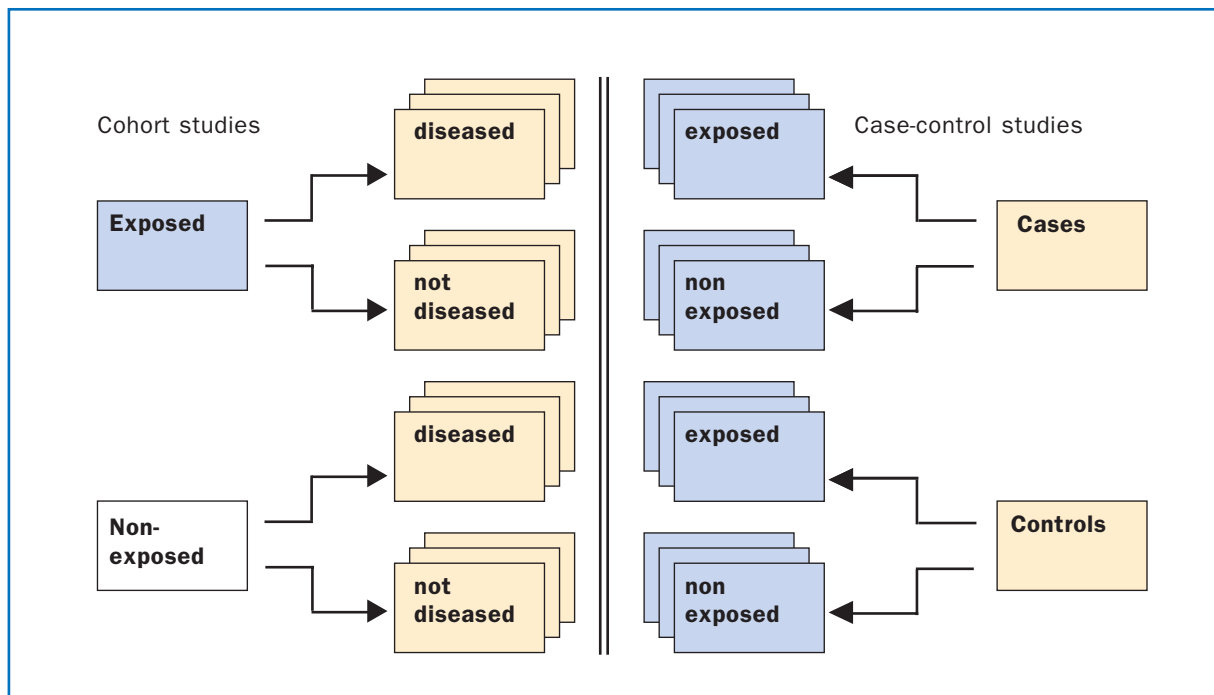


Figure 1: Overview of the designs of cohort studies and case-control studies

their sample size is smaller (see “The Danish cohort study – advantages and disadvantages”). Difficulties of case-control studies are the recruiting of representative samples and the quality of the retrospective exposure assessment.

For exposure assessments based on questionnaires the contact with the participants is necessary and prior to the interview participants need to sign informed consent. While the willingness to participate is usually high in the “case” group, many refusals will appear in the “control” group, despite of intensive persuasive efforts. An example for this is the Interphone study component in Germany, where, despite several invitation letters, the provision of comprehensive information material and manifold personal contacts, a participation rate of 62 % was reached; this was a convenient response rate for a case-control study, but still means that each third potential volunteer randomly selected from population files, could not be persuaded to cooperate [3]. The low willingness to participate becomes a problem if it is systematic, and there is often an education gradient regarding the willingness to participate. This education gradient again correlates with life style factors

and occupational exposures, which can result in distortions regarding these factors in risk estimation. A short questionnaire with non-participants used for Interphone (answered by about half of this group) showed a deficit of participants without mobile phone [3] that may have resulted in a bias towards a spurious protective effect.

Epidemiological studies often aim at exposures that happened years in the past, and the assessment of such exposures via questionnaire is another crucial disadvantage of case-control studies. First, because it is generally difficult to recall past events; e.g., the first question on mobile phone use in Interphone was when (year and month) regular mobile phone use began, defined as at least one call per week over a period of at least half a year. Second, because the disease itself affects the memory abilities. A validation study within Interphone [4], where network traffic data were compared to self-reported data of volunteers, showed great deviations even regarding current usage. On average, participants overestimated the length of phone calls by 40 %. When such reporting errors are equal in cases and controls, it is expected to lead to an underestimation of risk. A spuri-

ous risk is produced when patients tend to overestimate more strongly than the control persons; a bias often observed in case-control studies.

Already in the first case-control studies on mobile phone use, the questions regarding the side of the head to which the mobile phone was usually held where identified as problematic. The association observed in many studies with ipsilateral use (preferred side of the head during usage is the side of the head with the tumour) was balanced by a protective effect on the contralateral effect [e.g. 5 and 6]. In the joint evaluation of Interphone this will be taken one step further. The affected side of the head will be subdivided into smaller areas according to exposure intensity: if the ipsilateral effect is equally strong for all areas (like frontal, temporal and occipital), this rather indicates evidence of an interview artefact, but if it is stronger for areas with higher exposure (temporal and/or parietal), it may indicate a causal association.

The Danish cohort study – advantages and disadvantages

The basis of a cohort study is a population of non-diseased persons, which is divided into two or more groups according to the exposure of interest (figure 1). After a defined follow up period, the disease inci-

dence rates are compared across these groups. Often also a cohort of exposed persons is created, whose disease incidence rate is then compared with that of the general population. The direction of the investigation is always prospective (the starting point is the exposure), regardless of the fact whether the entire study was planned prospectively, i.e. the cohort is set up at the beginning of the study, or whether it is a historical cohort study. A historical cohort study is possible when data from the past are available, which retrospectively allows the reconstruction of cohorts. Cohort studies comprise few risk factors, but allow the examination of a great number of diseases potentially associated with these risk factors. The etiologically adequate direction of cohort studies makes them the type of study with the greatest power. As exposure is obtained prior to the disease, the assumption of a causal relation is stronger than in case-control studies. In spite of that, prospective cohort studies are an exception in the epidemiology of chronic diseases. The reason for that is the great expenditure. A very large cohort has to be formed for rare diseases and the follow up has to be done for a very long time period.

This aspect is an advantage of the Danish concept [7]. Based on customer data of all Danish network

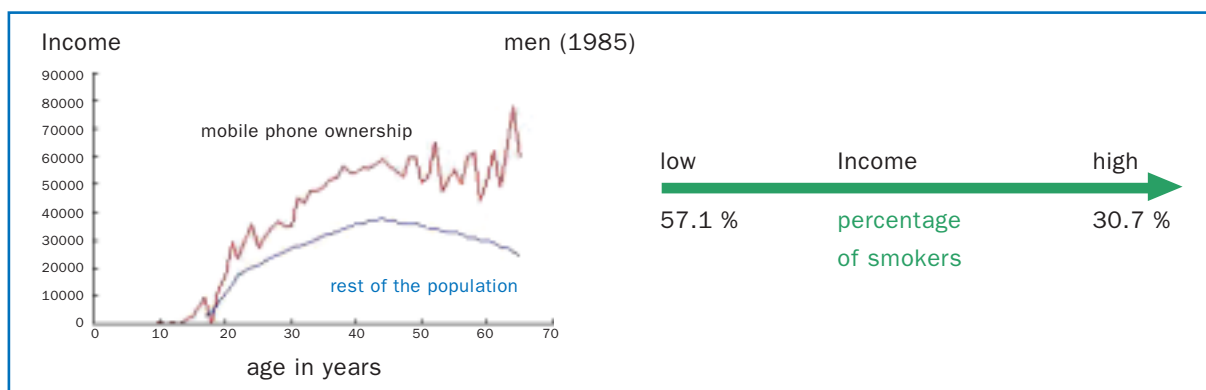



Figure 2: Spurious associations produced by a third factor: due to the correlations between early mobile phone ownership (1985) and income and between income and smoking behaviour, the proportion of smokers was lower in the cohort of mobile phone owners than in the rest of the population; hence, mobile phone ownership displayed a false protective effect on the risks of diseases associated with smoking.



operators, a cohort of 420,000 adult Danes was set up comprising mobile phone owners between 1982 and 1995. This cohort was followed up to 2002 and the cancer incidence rates of the cohort were compared with the rates of rest of the Danish population. Thus, the study is maximally representative for Denmark (the whole country was included) and has a maximal length with respect to the study period (up to 21 years), even when the average usage was only 8.5 years and the percentage of mobile phone owners of ten and more years was just 56,000 persons. A disadvantage is the rough categorization of exposure. The person with the mobile phone contract is not necessarily the mobile phone user, on the other hand there are users who have no contract in their own name (family members or contracts in the name of the company). The Danish study has no information on prepaid phones and whether car phones or handsfree kits or speakerphones were used. Moreover the exposure cannot be divided according to the frequency of use, therefore rare users and intense users are in the same exposure category. All these disadvantages can lead to an underestimation of risk, if any. If an association would have been observed in this study, it could not be explained by these restrictions. But an inconspicuous finding could mean that there was no association or that a moderate increase in risk has been missed. An evaluation of the quality of the exposure measure [8] shows that, with the Danish concept, a hypothetical increase in risk by 50 % would have been measured as a 20 % increase.

If the correlation of exposure proxies (here: purchase of a mobile phone contract) and the exposure of interest (here: mobile phone field exposure) is only moderate, the possible role of confounders, which are factors that correlate with the exposure and the disease risk as well, becomes important. The Danish cohort study can, via the purchase of a mobile phone contract, with a certain validity make a prognosis on smoking behaviour, because the cohort of contract owners had a high income and among Danish men high income correlates with smoking behaviour (fig. 2). Cancer types associated with smoking were observed less than expected in the cohort, falsely sug-

gesting a protective effect of mobile phones on e.g. lung cancer. In women, smoking is not associated with high income and the lung cancer rate in the cohort is therefore not lower than expected. Methodologically, these observations support the strength of the design. But an evaluation of the brain tumour risk associated with mobile radio is only possible since smoking and other life style factors are no confounders in this context.

The solution to the problem

A number of outlined problems could be solved with the help of prospective cohort studies. An interview of participants prior to the occurrence of the disease avoids the disease affecting responses in an interview. This would be crucial especially regarding the question for the side of the head preferred during mobile phone usage. In addition, also data of network operators could be collected prospectively, which would objectify the frequency of use. In the interview also data on competing risks could be collected, so that diseases can be examined, where life style is known to have a great influence on the risk profile. For the investigation of rare diseases a large cohort is required. Estimates suggest about 250,000 persons, so such studies would have to be conducted in a multinational approach to share the burden. This concept of prospective cohorts was piloted in some countries and the design was optimized. Under the heading Cosmos (COhort Study on MOBILE phone userS) the project starts this year in Denmark and next year in Sweden and England. While participation is still considered in Finland and the Netherlands, the project was cancelled in Germany after the end of the feasibility study. Whereas the feasibility of the concept was also successfully demonstrated in Germany, the willingness to participate in a pilot study was very low (piloted with 5000 volunteers). The resulting costs for establishing a cohort in Germany have persuaded the Federal Government to withdraw from the project.

The Cosmos study can also be seen as a tool of surveillance. Emerging questions can be answered faster and more efficient than when each issue would require an own new study. Other diseases than can-

Author + Journal	country	# exposed cases#	RR (KI)	definition	longterm exposure t	R (KI) cases R
brain tumors						
group 1 (early case-control studies)						
Hardell [6] ^a	Sweden (part)	78	1,0 (0,7-1,4)	> 5 years	34	0,8 (0,5-1,4)
Muscat, JAMA, 2000	USA (part)	66	0,8 (0,6-1,2)	≥ 4 years	17	0,7 (0,4-1,4)
Inskip, N Engl J Med, 2001	USA (part)	139	0,8 (0,6-1,1)	≥ 5 years	22	0,7 (0,4-1,4)
Auvinen, Epidemiology, 2002	Finland	40 NMT, 16 GSM	1,3 (0,9-1,8)	> 2 years	17 NMT, 1 GSM	1,5 (0,9-2,5)
group 2 (case-control study series from Sweden)						
Hardell [6] ^a	Sweden (part)	-	-	> 10 years	16	1,2 (0,6-2,6)
Hardell [9] ^b	Sweden (part)	NMT Gliom	1,5 (1,1-1,9)	> 10 years	NMT Gliom	2,4 (1,7-3,5)
		GSM Gliom	1,3 (1,1-1,6)		GSM Gliom	3,4 (1,6-7,3)
		NMT Mening.	1,3 (1,0-1,7)		NMT Meningeom	1,1 (0,9-1,3)
		GSM Mening.	1,6 (1,0-2,6)		GSM Meningeom	1,8 (0,7-4,6)
group 3 (Interphone case-control study)						
Lönn, Am J Epidemiol, 2005 ^c	Sweden	214 Gliom	0,8 (0,6-1,0)	≥ 10 years	25 Gliom	0,9 (0,5-1,5)
		118 Meningeom	0,7 (0,5-0,9)		12 Meningeom	0,9 (0,4-1,9)
Christensen, Neurology, 2005 ^c	Denmark	59 Gliom (high)	0,6 (0,4-0,9)	≥ 10 years	8 Gliom (high)	0,5 (0,2-1,3)
		47 Gliom (low)	1,1 (0,6-2,0)		6 Gliom (low)	1,6 (0,4-6,1)
		67 Meningeom	0,8 (0,5-1,3)		6 Meningeom	1,0 (0,3-3,2)
Hepworth, BMJ, 2006 ^c	Great Britain (part)	508 Gliom	0,9 (0,8-1,1)	≥ 10 years	66 Gliom	0,9 (0,6-1,3)
Klaeboe, Eur J Cancer Prev, 2007 ^c	Norway	161 Gliom	0,6 (0,4-0,9)	≥ 6 years	55 Gliom	0,7 (0,4-1,2)
		96 Meningeom	0,8 (0,5-1,1)		28 Meningeom	1,2 (0,6-2,2)
Lahkola [5] ^c	Denmark, Finland, Norway, Sweden, Great Britain (part)	867 Gliom	0,8 (0,7-0,9)	≥ 10 years	88 Gliom	0,9 (0,7-1,3)
Schüz [3]	Germany	138 Gliom	0,8 (0,6-1,1)	≥ 10 years	12 Gliom	2,2 (0,9-5,1)
		104 Meningeom	1,0 (0,7-1,3)	≥ 10 years	5 Meningeom	1,1 (0,4-3,4)
group 4 (Danish retrospective cohort study)						
Johansen, J Natl Cancer Inst, 2001 ^d	Denmark	154	1,0 (0,8-1,1)	> 5 years	24	1,0 (0,7-1,6)
Schüz [7] ^d	Denmark	580	1,0 (0,9-1,1)	≥ 10 years	28	0,7 (0,4-1,0)
acoustic neuromas						
group 1 (early case-control studies)						
Hardell [6] ^a	Sweden (part)	5	0,8 (0,1-4,2)	-	-	-
Muscat, Neurology, 2002	USA (part)	-	-	≥ 3 years	11	1,7 (0,5-5,1)
Inskip, N Engl J Med, 2001	USA (part)	22	1,0 (0,5-1,9)	≥ 5 years	5	1,9 (0,6-5,9)
group 2 (case-control study series from Sweden)						
Hardell [9] ^b	Scheden (part)	NMT	2,9 (2,0-4,3)	> 10 years	NMT	3,2 (1,7-6,1)
		GSM	1,5 (1,1-2,1)		GSM	0,8 (0,1-6,6)
group 3 (Interphone case-control study)						
Christensen, Am J Epidemiol, 2004 ^e	Denmark	45	0,9 (0,5-1,6)	≥ 10 years	2	0,2 (0,0-1,1)
Lönn, Epidemiology, 2004 ^e	Sweden	89	1,0 (0,6-1,5)	≥ 10 years	14	1,9 (0,9-4,1)
Klaeboe, Eur J Cancer Prev, 2007 ^e	Norway	22	0,5 (0,2-1,0)	≥ 6 years	7	0,5 (0,2-1,5)
Schoemaker [10] ^e	Denmark, Finland, Norway, Sweden, Great Britain (part)	360	0,9 (0,7-1,1)	≥ 10 years	47	1,0 (0,7-1,5)
Schlehofer [11]	Germany	29	0,7 (0,4-1,2)	≥ 5 years	8	0,5 (0,2-1,3)
Takebayashi, Occup Environ Med, 2006	Japan	51	0,7 (0,4-1,2)	> 8 years	4	0,8 (0,2-2,7)
group 4 (Danish retrospective cohort study)						
Johansen, J Natl Cancer Inst, 2001 ^d	Denmark	7	0,6 (0,3-1,3)	-	-	-
Schüz [7] ^d	Denmark	32	0,7 (0,5-1,0)	-	-	-

^a identical with the first study from group 1, therefore only > 10 years result taken for group 2

^b taken from a review of the working group in 2006; the original results are presented in more than a dozen publications of Hardell et al., partially with the same study population; according to the authors, three subsequently performed case-control studies

^c the glioma results of Lönn, Christensen, Hepworth and Klaeboe are pooled in Lahkola [5] (together with Finland that has not published separately)

^d Schüz [7] is the publication on the expanded follow-up of the Danish cohort of Johansen (2001)

^e the acoustic neuroma results of Lönn, Christensen and Klaeboe are pooled in Schoemaker [10] (together with Finland and Great Britain that have not published separately)

Table 1. Overview of epidemiological studies on mobile phone usage and the risk to get brain tumours (adapted and expanded from [1]); shown are groups according to the text, the references, the country, where the study was performed, the number of exposed cases with the estimated relative risk (incl. 95 % confidence interval) for overall mobile phone use and the number of exposed cases with the estimated risk (incl. 95% confidence interval) for long-term users as well as the corresponding definition of longterm use.

cer were not examined in mobile phone studies so far. The biggest challenge for the Cosmos study is the constantly changing technology and the question how to measure relevant differences of exposure across the population in the future.

Outlook

The rapid spreading of mobile phones at the end of the nineties and the development towards cheaper prices for making calls resulted in a high popularity of mobile phones. Innovative concepts like “flat rates“, “home zones“, multifunctional mobile phones and the replacement of traditional phones at home by cordless phones contribute to the development that mobile phone users use the phone more frequently, that they have begun to use phones at an earlier age and that they have phoned more than the typical users of epidemiological studies performed today. “Flat rates“, which almost allow mobile phone usage without limits, stand in contrast with the observation that e.g. in the German component of the Interphone study a user with a life-time cumulative 195 hours of usage belongs to the intensive mobile phone user group [3]. Another noteworthy trend however is that the microwave exposure from the phone became much lower over time and will most likely again be lower with the expansion of UMTS networks.

When considering all epidemiological studies completed until now, which all speak against an at least substantial cancer risk, together with the numerous experimental studies primarily speaking against adverse health effects, it seems unlikely that new national small epidemiological studies will provide new insights. Multicenter studies with a common protocol and a sufficient size of study, as e.g. the Cosmos study, have all the advantages to verify the available knowledge and to respond flexibly to new hypothesis. The popularity of the mobile telecommunication technology and its constant development require a continuous scientific monitoring of adverse health consequences, which is where epidemiology can play a key role.

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