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January 2009
2008

Comments on the Interphone Study

Summary

The Interphone Study is an international study on the possible link between mobile phone use and the risk of developing a head tumour. Funded by the EU, the mobile phone industry and national health agencies in the 13 participating countries and coordinated by the World Health Organisation (WHO), the study is the largest-scale research programme on this issue to date.

In all, some 6,500 patients with one of the following four tumour types were investigated: tumours of the meninges, tumours of the brain tissue, tumours of the acoustic nerve, and tumours of the parotid gland. Patients' use of mobile phones in the past was compared with that of roughly the same number of members of the control group, who did not have tumours, were of the same age and sex as the tumour patients and shared other characteristics with the tumour sufferers. The aim was to establish whether the tumour patients had used mobile phones more intensively than the control group. If so, mobile phone use could be regarded as indicating a higher risk of tumour development.

To date, only the results of national studies have been published, rather than a pooled analysis of all data. The provisional main findings are as follows: (i) An overall analysis, covering all cases (not pooled), indicates that mobile phone use does not increase the risk of tumours. (ii) Mobile phone use for less than 10 years does not increase the risk of tumours. (iii) There are indications that long-term mobile phone use (more than 10 years) may increase the risk of tumours of the acoustic nerve or brain tissue. However, the comparatively small numbers of long-term users make these results statistically inconclusive. Indeed, valid conclusions can only be drawn once a pooled analysis, entailing considerably more cases, is published. (iv) The same applies to the findings for analyses broken down per side of the head. These analyses compared the position of tumours and the side of the head where the phone was normally used. National studies indicate that the risk on the side normally used for phone calls is higher than on the other side, but most results are not statistically significant. A conclusion may well only emerge once the results of the pooled analysis become available. (v) The small number of long-term users with (malignant) parotid-gland tumours precludes any interpretation of national data on this group.

1. Study Design

1.1 Subject

The Interphone Study addresses the general question of whether there is a statistical link between mobile phone use and the occurrence of cancer in the head region. As no biological mechanisms are known, no concrete causal hypotheses can be made or implemented in the study design.

To answer this general question, the investigation was limited to two types of brain tumour (meninges and brain tissue) plus tumours of the acoustic nerve and the parotid gland. The participants in the study were asked in detail about their mobile phone use to establish whether intensity of use or duration of use impacts on the risk of a tumour. The reliability of this subjective information was evaluated in control studies using objective data (measurements, data provided by network operators).

1.2 Research consortium

The Interphone Study is being run and coordinated by the WHO's International Agency for Research on Cancer (IARC) in Lyon. Research teams from 13 countries took part in the project, with each team carrying out its own national study. No pooled analysis of the individual studies has yet been published.

The table below lists the participating countries and the national studies published so far (name of lead author and year of publication) as well as the tumour types covered by the results: G = glioma (tumour of the brain tissue), M = meningioma (tumour of the meninges), AN = acoustic neuroma (tumour of the acoustic nerve), PT = parotid-gland

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tumour.

Country	Publications	Types of cancer
Australia	-	
Denmark	Christensen 04, 05	G, M, AN
Germany	Schüz 06; Schlehofer 07	G, M, AN
Finland	pooled	
France	Hours 07	G, M, AN
United Kingdom	Hepworth 06	G
Israel	Sadetzki 07	PT
Italy	-	
Japan	Takebayashi 06, 08	AN, G, M
Canada	-	
New Zealand	-	
Norway	Klaeboe 07	G, M, AN
Sweden	Lönn 04, 05	G, M, AN

Some countries only published their results in conjunction with other countries, while others published their results both separately and together with other countries:

Countries	Publication	Types of cancer
Denmark, Finland, United Kingdom, Norway, Sweden	Schoemaker 05	AN
Denmark, Finland, United Kingdom, Norway, Sweden	Lahkola 07	G
Denmark, Finland, United Kingdom,	Lahkola 08	M
Denmark, Sweden	Lönn 06	PT

1.3 Funding

The research budget totalled over €7 million. As part of the Fifth Framework Programme (FP5) the EU contributed €3.85 million to the project. The remaining funds were provided by the industry (€3.5 million) and the national health agencies in the participating countries. The funds from the industry were passed on to the researchers via the International Union against Cancer (UICC) with its headquarters in Geneva. In this way it acted as a 'firewall' vis-à-vis the backers the Mobile Manufacturers Forum (MMF) and the GSM Association (GSMA). The contracts with the UICC guaranteed the Interphone teams complete research autonomy. The UICC's contribution to the budget varied from 25 to 50%, depending on the country.

1.4 Study design

A broad-based epidemiological approach was adopted. In epidemiology, statistical instruments are used to look for associations between illnesses and presumed causes. Epidemiological studies require large numbers of cases because small samples often preclude robust statistical statements about minor increases in risks. Consequently, the adoption of an international approach involving a number of countries was the IARC's only option.

The major methodological questions for determining the definitive study design were investigated in a feasibility study (1998-1999). Based on the findings of that study, the decision was made to adopt a case-control design (protocol: http://www.iarc.fr/ENG/Units/INTERPHONEStudyProtocol.pdf). In case-control studies, researchers specifically look for people suffering from a certain disorder (in the Interphone Study, people with head tumours), ask these patients questions about the factors of interest (here mobile phone use) and then compare the responses with those given by members of a control group, who if possible share the same characteristics (especially regarding age and sex) as the patients (cases), but are not suffering from the respective disorder. The questions that interested the Interphone researchers were these: Had people with tumours used their mobile phones more frequently in the past than people without tumours? If so, was that an indication that there was a possible link between the risk of a brain tumour and mobile phone use?

People suffering from one of the aforementioned tumour types were chosen as cases, though other selection criteria were also applied to ensure that their number included as many mobile phone users as possible: They should come from urban areas (where the infrastructure has been in use for the longest period of time), be working and aged between 30 and 60 (this being the population group most likely to have been intensive mobile phone users – especially

10 years ago or more). The cases were found using national cancer registries. The individuals were then contacted and asked to take part in the study. The study included cases diagnosed for the first time between 2000 and 2004 inclusive (the periods varied slightly from country to country). In seven countries the specified criteria were implemented, whilst in the other six countries rural areas were also incorporated or cases were selected to reflect the population of the country as a whole. The number of cases was specifically calculated to ensure that it would remain possible to establish an increase in the relative risk from 1 to 1.5. A 1.5-fold increase would mean that the probability of a mobile phone user developing a tumour would be 50% higher than for a non-user. A factor of 1.5 is a relatively low value compared to the risk increases usual in epidemiology: For instance, heavy smokers face 20 times the risk of developing lung cancer as non-smokers.

For the control group the study looked for people of the same age and sex as the cases and who had lived in the same region. Ages did not have to match exactly (an overlap of five years was deemed sufficient). One, two or three control persons were investigated for each case depending on the type of cancer. However, these requirements were not strictly applied by all the countries.

1.5 People and interviews

Based on these requirements, the study managed to enlist as cases about 2,800 patients with a glioma (tumour of the brain tissue), 2,400 patients with a meningioma (tumour of the meninges), 1,100 patients with an acoustic neuroma (tumour of the acoustic nerve) and about 100 patients with a malignant parotid-gland tumour. Then, for each type of tumour, a group of about the same size and with the same characteristics (age, sex, region) as the cases was selected from the 8,000 or so members of the control group. With a total of 5,200 cases for brain tumours, the target number of cases (about 7,500) for those tumours was not reached. For parotid-gland tumours the analyses concentrated on the malignant form that is considerably less common than the benign tumour (which accounts for about 70-80% of cases).

Cases and control persons were questioned in interviews lasting about an hour. The cases were generally included shortly after their initial diagnosis by the doctor and in some cases were still in hospital. The questionnaire used asked for demographic information, details about mobile phone use, details of any occupational exposure to electromagnetic fields and other possible risk factors (ionising radiation, smoking and any family predispositions). Most of the national studies also asked questions about the use of other wireless services, including DECT phones. For cases with tumours of the acoustic nerve and the corresponding control persons, questions were also asked about noise and damage to their hearing.

A range of questions was asked to assess mobile phone use. The interviewees were shown photos of mobile phones so that they could identify all the models they had used in the past. Then they were asked how they had used their mobile phone: On average how often and for how long did they speak on the phone now and in the past? Did they tend to use their phone in urban or rural areas? Were they stationary or on the move? Was a headset used or not? And did they generally use the phone on the left or right side of their head? They were also asked whether, when and how they had changed the way in which they used their mobile phone.

The responses were used to categorise people on the basis of their mobile phone use. The label ‘regular users’ was applied to people who used their phone at least once a week over a period of at least half a year. A number of key figures on mobile phone use was derived from the answers provided, e.g. concerning the total time they had spent on the phone, average call time and the total number of conversations. The definition of a regular user is relatively unrestrictive, which has advantages and disadvantages (see section 3.1). The label ‘long-term users’ was applied to regular users who had been using a mobile phone for at least 10 years.

1.6 Analyses

The main focus of attention was the possible link between the occurrence of the selected cancer types and mobile phone use. In individual countries, laterality (i.e. a risk assessment taking account of the side of the head where tumours occur and usual mobile use) was also investigated. Only a few results relating to other radiation sources covered by the questions, such as cordless phones, have been published to date.

The studies in the participating countries were analysed individually and most, but not all, were published as national studies. A pooled analysis is also being conducted on the data from individual countries. The large number of cases in that analysis will provide statistically more robust results than any single national study. Some meta-analyses have already been carried out for groups of countries participating in the study.

2. Key results

The following charts reflect the most important results of the Interphone Study that have been made available so far. The results of the pooled data will be incorporated into these comments as soon as they are published. The charts are set out as follows: first the results for the individual types of tumour for regular users are presented, followed by partial results covering only long-term users, and finally the laterality findings for long-term users. Where laterality is concerned, the position of tumours is compared with the usual position of the phone during use.

The charts indicate odds ratios (ORs; see section 4.3). An OR indicates the probability of falling ill if the risk factor in question applies compared with the probability of falling ill in the absence of the respective risk factor. If the OR is greater than 1, this is an indication of an increased risk; if it is less than 1 this indicates a protective effect. However, not only the OR as such is important, but also the uncertainty of this number. If a study was only carried out with a few subjects, then the calculated OR will be less reliable than if a very large number of people had been examined. The uncertainty is shown by the confidence interval, which is represented in the figures by coloured bars to the left and right of the OR (left: risk underestimated; right: risk overestimated).

The bar indicates a 95% confidence interval, meaning there is a 95% probability that the values outside the bar are not random. Therefore, a result is statistically significant if the whole of a bar is to the left or right of 1. In that case the probability of the OR deviating from 1 is 95% (in other words the chances of a mistake being made in only one in 20). This means that the result is statistically very reliable. Accordingly, the basic principle applying is that the longer a bar is, the more uncertain the OR will be, whereas the shorter a bar, the more reliable the result. The bars' length is directly affected by the number of people analysed in the studies. The higher the number of studied cases and control persons, the shorter the bar (i.e. the confidence interval) will be, and the greater the likelihood of recognising even a small shift in the OR by statistical means.

The names of the lead authors of the relevant studies are indicated to the left of each chart, together with the year of publication. The OR is presented in a logarithmic scale, with ascending values from 1 to 10 left to right (representing an increase in risk), and with descending values from 1 to 0.1 right to left (decrease in risk or protective effect). The 95% confidence interval is represented as described above. Full colours mean that a statistical analysis was made of over 20 cases, slightly shaded colours indicate 10-19 cases, and the palest colours stand for fewer than 10 analysed cases.

2.1 Pooled analysis

The pooled analysis is not available yet.
As soon as the results are published, they will be presented in this section.

2.2 National analyses

2.2.1 Regular users

The following charts show the national results for regular users for individual types of tumours. The label 'regular user' was used for people who used their mobile phone for calls at least once a week over a period of at least half a year. Looking at all the results, no significant increase in risk is evident in any individual national study or for any specific type of tumour. Four studies indicate significant protective effects, these being particularly prominent in gliomas. These results are difficult to understand from a biological perspective. The Interphone authors suspect that there are methodological reasons behind this (see section 3.2): when more mobile phone users (in other words, more people exposed) are included amongst the control persons than amongst the cases, the OR may fall below 1. Adjusting for this effect would imply that the values of the reported ORs will rise.

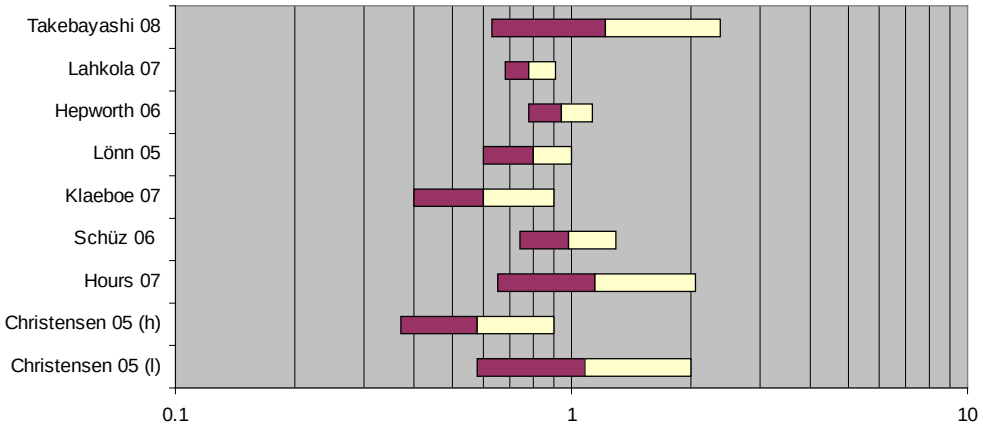

Fig. 1: Results for gliomas; (h) = high (malignant), (l) = low (still benign)

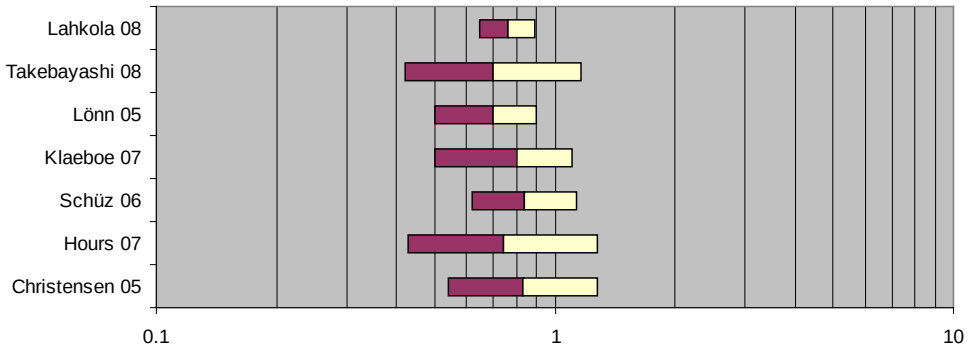

Fig. 2: Results for meningiomas

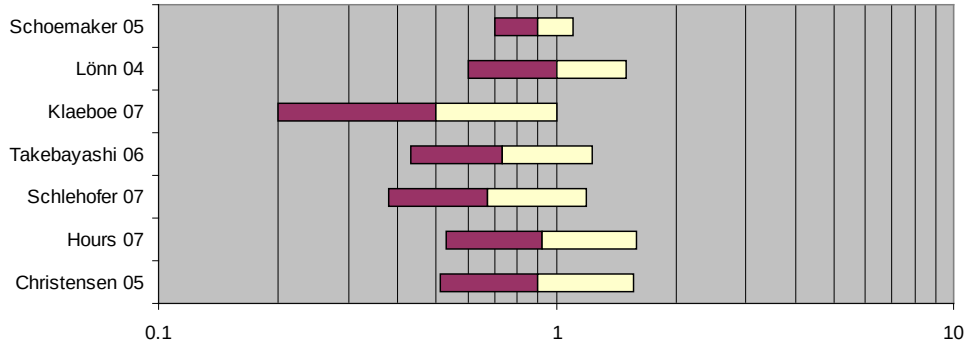

Fig. 3: Results for acoustic neuromas

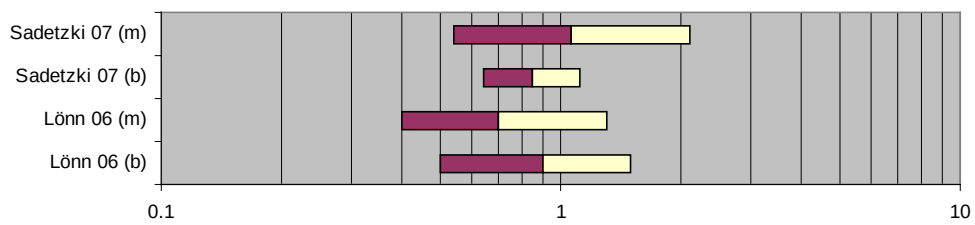

Fig. 4: Results for parotid-gland tumours; (m) = malignant, (b) = benign

2.2.2 Long-term users

The following charts present the results for long-term users. The label 'long-term user' was applied to people who had been using a mobile phone regularly for more than 10 years. The definition of 'regular users' was as above. It emerged that there were relatively few long-term users. In many national studies, depending on the type of cancer, the numbers of cases were under 20, or even fewer than 10. This helps to understand why no statistically significant results were found in the national analyses regarding long-term use. Unlike the results covering all regular users, for more than one tumour type (gliomas and acoustic neuromas) the results for regular long-term users in a number of national studies indicated an increased risk, though this was not statistically significant. Conversely there were various ORs of under 1, pointing to greater numbers of exposed people amongst the control group than amongst the cases in the relevant national studies.

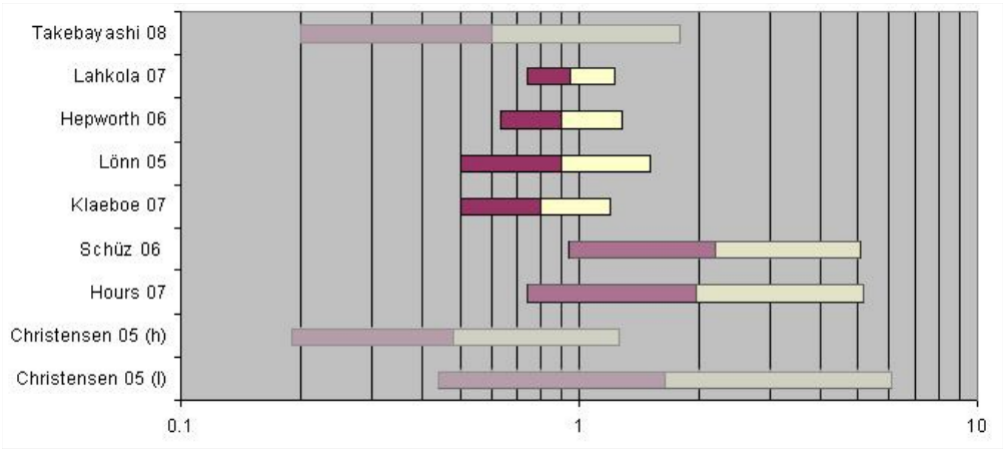

Fig. 5: Results for gliomas; (h) = high (malignant), (l) = low (still benign); Takebayashi 08: >6.5 years

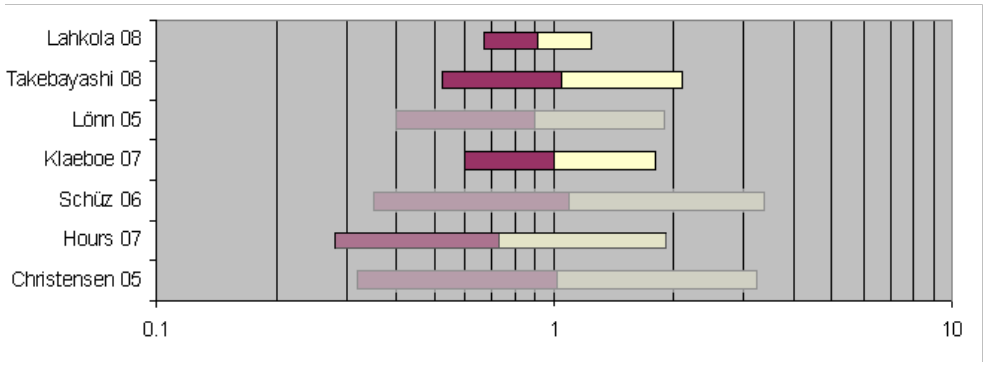

Fig. 6: Results for meningiomas; Takebayashi 08: >5.2 years

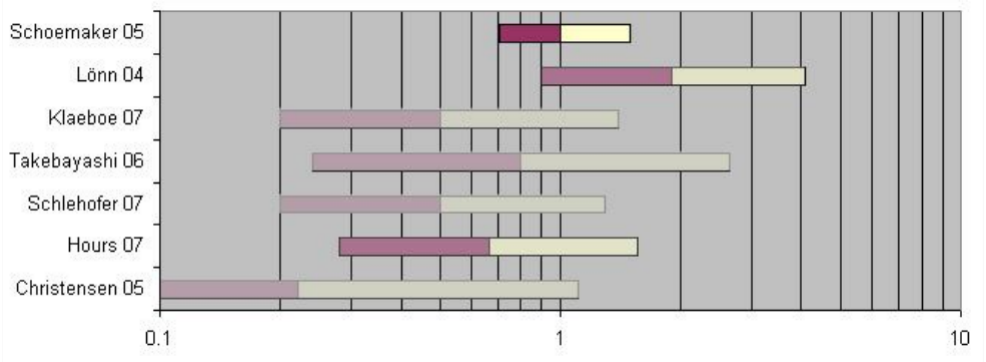

Fig. 7: Results for acoustic neuromas

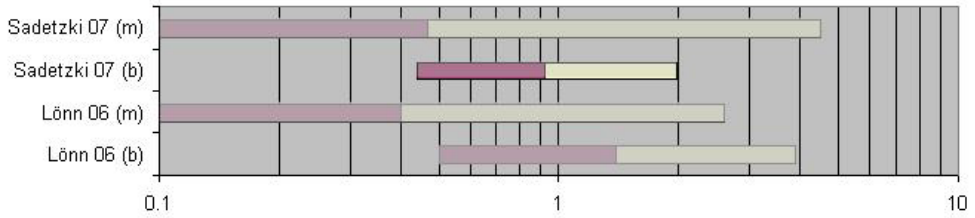

Fig. 8: Results for parotid-gland tumours; (m) = malignant, (b) = benign

2.2.3 Laterality

The charts below show the results of data on long-term users broken down in terms of their laterality. 'Ipsilateral' means the tumour occurred on the same side of the head as the phone was held, whilst 'contralateral' stands for a tumour on the opposite side of the head. Two studies showed significant effects (for gliomas and for acoustic neuromas). The data – apart from one study – reveal an overall trend for the OR in conjunction with ipsilateral tumours to be higher than for contralateral tumours and to be greater than 1. In the data a protective effect can be seen for most of the contralateral tumours. The Interphone authors do not offer any clear explanation of this result, but suspect that it may be due to both methodological reasons (see section 3.2) and an actual causal link.

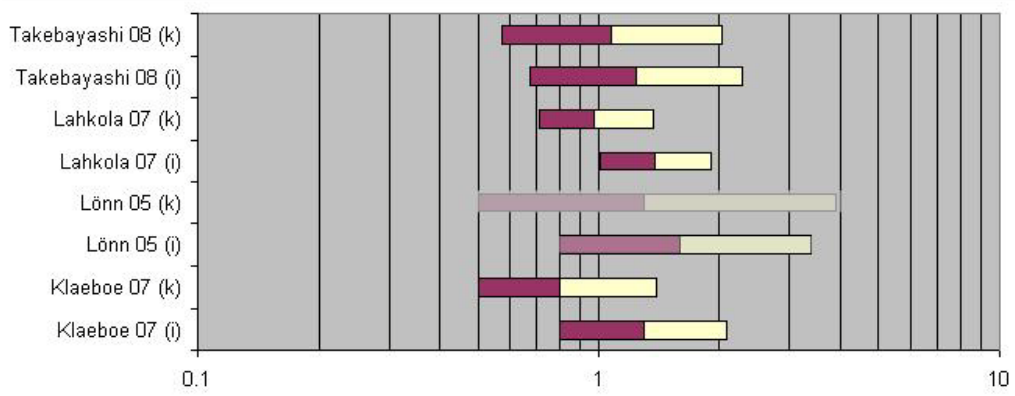

Fig. 9: Results for gliomas; (i) = ipsilateral; (k) = contralateral; Takebayashi 08: all regular users

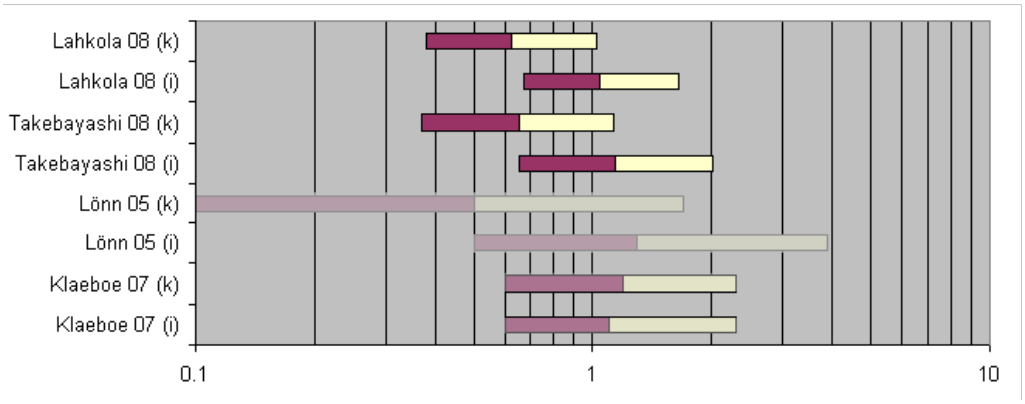

Fig. 10: Results for meningiomas; (i) = ipsilateral; (k) = contralateral; Takebayashi 08: all regular users

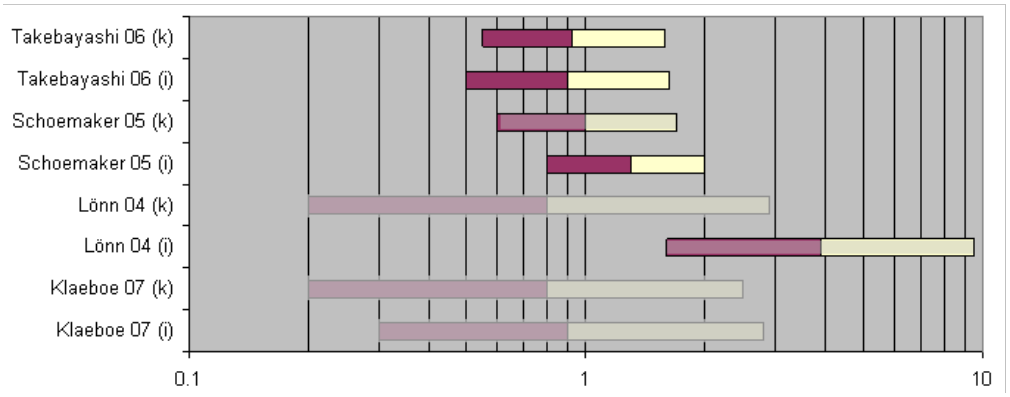

Fig. 11: Results for acoustic neuromas; (i) = ipsilateral, (k) = contralateral

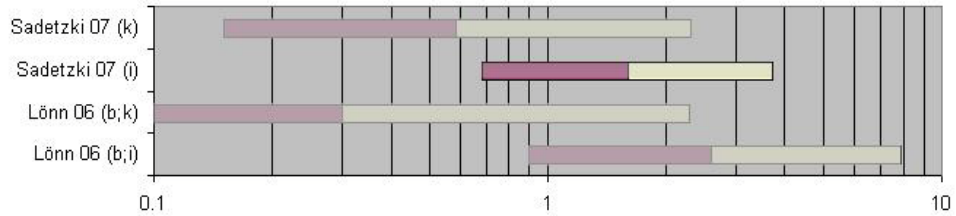

Fig. 12: Results for parotid-gland tumours; (i) = ipsilateral, (k) = contralateral; (b) = benign

3. Evaluation

3.1 General remarks

The Interphone Study is the most comprehensive study undertaken to date on the relationship between head tumours and mobile phone use. The methodological approach, involving case-control studies being carried out in a number of countries in line with a series of basic specifications (stated in a common protocol), is sound. Pooled analyses (findings not yet available) will make the results more statistically compelling. Many previous studies were unable to produce any conclusive results because of the small numbers of cases involved, particularly for long-term users.

The following points need to be borne in mind when interpreting the results:

(i) It is not yet known how non-ionising radiation (NIR) impacts on brain tumours. Laboratory investigations have indicated that not all cell types are sensitive to NIR. There may be differences in the sensitivity of tumour cells too. If more details were known, it would be possible to specifically investigate possibly critical tumour entities. However, as this is not the case, the Interphone Study was forced to investigate a comparatively large number of different tumour types. This decreased the average number of cases per tumour type (for a given total number of cases), making it more difficult to prove a small increase in risk.

(ii) For anyone assuming that radiation intensity plays an important role in the occurrence of cancer, taking account of laterality is especially useful, because tumours occurring on the side of the head used for making phone calls receive substantially higher doses of radiation and are probably associated with more of any actual effect than those occurring on the other side of the head. Therefore a possible risk will be underestimated in statistical analyses covering bilateral studies. In fact, assuming the risk is doubled, the degree of underestimation will be about 30% (OR only 1.5 instead of 2).

(iii) Little is known about latency periods of brain tumours, but they are generally estimated to be long (10 years or more). The Interphone Study includes comparatively few long-term users (10 years or more), and especially few with GSM phones. Therefore the study enables only limited statements about the long-term effects of GSM mobile phones in relation to head tumours.

(iv) For the analyses, users were divided up into exposure categories. People who were on the phone at least once a week over a period of at least half a year were classified as 'regular users'. By today's standards that is a low intensity of use, but the Interphone Study is an investigation into past use. It emerged that the criterion was relatively strict and about half of all the cases did not fall into the 'regular user' category. Had a stricter criterion been adopted, the number of cases for regular use would have been even lower, with the corresponding impact on statistical power. However, more intensive users and long-term users are classified into and analysed as subcategories of regular users, though the small numbers of cases involved make these analyses extremely unreliable. This raises the problem of multiple tests: if tests are carried out using a range of exposure values, the significance level has to be adjusted. From a purely statistical viewpoint, if 20 (independent) tests are carried out one significant result can be expected. Consequently, in multiple tests one has to adjust (increase) the significance level. However, up to now insufficient account has been taken of this adjustment.

In addition to these general points, some 'technical' aspects are important for interpreting the findings (in particular with regard to robustness). These are discussed in the next section.

3.2 Robustness of the results

Validation studies were carried out to assess the robustness of the results. Three areas were of particular interest: (i) How robust was the allocation of people to different exposure categories? To what extent do the subjective assessments of mobile phone use correlate with objective data from the operators? And are data on using mobile phones accurate indicators at all of actual exposure to radiation? (ii) Are the participants indeed representative of how people actually use mobile phones in the two population groups investigated? If not, does that have an effect on the generalisability or conclusiveness of the results? (iii) What other factors coincidentally having a similar distribution among the population to that of mobile phone use (so-called confounders) might affect the results?

(i) How accurately do people remember details of their earlier mobile phone use? To find out, the *self-reported (subjective) data on mobile phone use* for a total of about 700 people were compared with network operators' objective data. When these people were divided up into five usage groups based on the subjective data and the same procedure was adopted for the objective data, 40% of subjects were allocated to the same usage group in both cases (i.e. the questionnaires led to a 'correct' classification). These figures match the results of other validation studies. An analysis of the data from special software-modified mobile phones which recorded transmitting power produced similar results. These data too, in some cases, deviated markedly from the details people gave about their use of these phones three months after using them. The *considerable variability* in both cases' and control persons' estimation accuracy indicates that it is difficult to statistically detect small risks.

In addition to random errors in their estimations, there were systematic effects in the two groups (cases and control persons): the frequency of calls tended to be underestimated and their duration overestimated, while infrequent users tended to underestimate and intensive users tended to overestimate their personal mobile use. However, these effects were less significant than the random estimation errors mentioned above. The *recall errors* mentioned had the overall effect that people were allocated to the wrong exposure groups. The result was that the possible risk was 'diluted', i.e. statistically underestimated, with the OR being pushed downwards towards 1. In simulations, the Interphone authors established that underestimates of up to 30% are possible.

Where incorrect categorisations made on the basis of recall errors only concern the cases or the control group and not (as in the above discussion) all the respondents in equal measure, the risk is pushed in one direction or the other, depending on the type of recall error. This phenomenon is referred to as *recall bias*. In this respect, the Interphone authors were troubled by the fact that if someone with a brain tumour believes that a mobile phone might have caused their tumour – at least in part – it is quite possible that this will prompt them to overestimate their phone use, resulting in an increase in the OR. Observations backed this up. However, simulations revealed that this is only a minor effect compared to the general uncertainty of estimation discussed above.

Another form of recall bias that was investigated involves the cases' tendency to associate the side of the head they normally use for phone calls with the side where the tumour was diagnosed. This results in a higher risk for ipsilaterality and a lower risk for contralaterality. The Interphone authors attribute the high ORs for ipsilaterality and the lower ORs for contralaterality to this methodological effect. However, they also mention the possibility of a causal relationship being involved, and explain the low ORs of under 1 for contralaterality as resulting from 'selection bias' (see below).

Let's consider the issue of causality versus recall-bias. Due to the long latency of brain tumors, the Interphone-data cannot reflect cancer initiation effects, if such effects exist. Thus, the results may be interpreted either in terms of cancer promotion or in terms of biases. Actually, the ipsilaterality data shows a tendency towards higher ORs with increasing exposure (years since first use; Fig. 13-15).

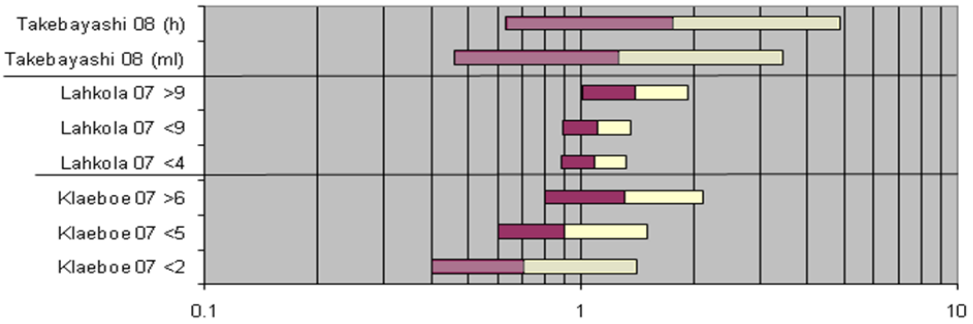

Fig. 13: Results for ipsilateral gliomas by years since first use (Takebayashi: SAR-based years of use; h=high, ml=middle to low)

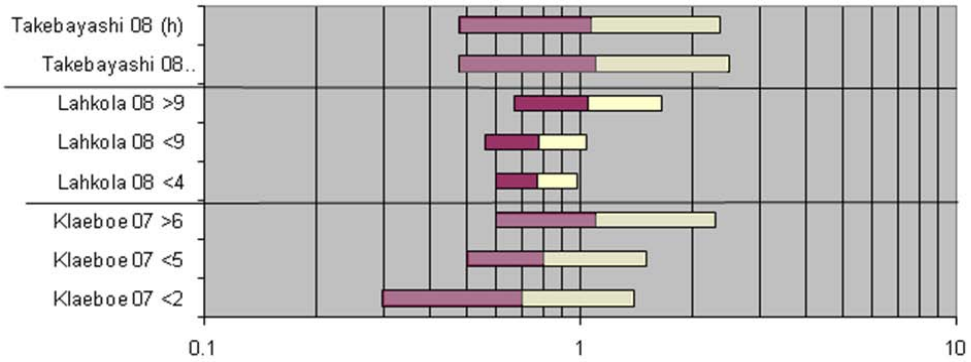

Fig. 14: Results for ipsilateral meningiomas by years since first use (Takebayashi: SAR-based years of use; h=high, ml=middle to low)

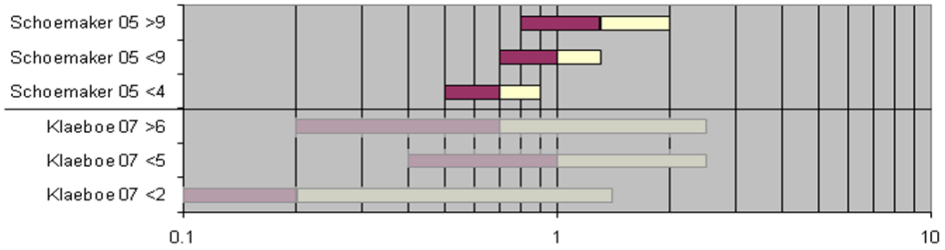

Fig. 15: Results for ipsilateral neuromas by years since first use

If this data represents a causal (promotional) effect of EMF on tumor growth, the effect should be reflected in recent brain tumor statistics. In case of a 6 years latency and a doubling of the risk, incidence in 2005 should be 15% above the 1996 level. If the latency period is reduced and/or the risk rate raised, incidence will further increase. Taking the Hardell (2005) data (RR=3.2; 5 years latency), for instance, the number of newly identified cases in 2005 should have been 30% above the 1996 level. In fact, however, incidence rates for brain tumors have been fairly stable during the last 10 years. In case latency periods are expanded and/or risk levels decreased, no effects will be seen due to the fact, that changes below 10% can be hardly detected in the statistics due to annual variations. In case of a latency-period of 8 years and a doubling of the risk, incidence in 2005 will be about 8% above the 1996 level only.

The relationship between mobile phone use and exposure to radiation was also investigated. The greater the transmitting power of a mobile phone, the more radiation will be absorbed by the person using it. Therefore a brief call on a phone with a high transmitting power can deposit more energy in the person's body than a longer call on a phone with a lower transmitting power. In validation studies, complex relationships of this type were studied to check whether the indicators under investigation, namely the number of calls and the average call duration, are a fair reflection of the *radiation actually absorbed*. The underlying assumption here is that the radiation absorbed is the factor that is relevant for assessing the biological and health effects of mobile phone radiation. In a study, 45 people were asked to use phones that recorded transmitting power (see above) for one month instead of their normal mobile phones. These data were compared with the objective data from network operators (number and duration of calls) and the subjective information given by users. The results showed that the number of calls is a feasible indicator for the mobile phone's total transmitting power. Dividing the users into two categories (intensive users, and the rest), it emerged that there was a 70% match between the subjective information provided and the total power recorded.

(ii) If mobile phone users' willingness to take part in a study differs between cases and the control group, this will lead to exposed people being under- or over-represented in one of the two groups and consequently to errors in the OR. A *selection bias* of this type was noted in the validation studies, with callers over-represented in the control group when compared with the overall population, leading to an underestimation of a possible risk. The Interphone authors explain that people without a handset were less willing than mobile phone users to take part in the study because people without mobile phones tend to rush to the conclusion that a mobile phone study will not concern them. In about half of the countries involved in the study, ethics committees required the researchers to make clear to the people interested in taking part that the study was about mobile telephony, which is likely to have had an effect on the willingness of non-users to participate. Follow-up questions put to people who declined to take part in the research confirmed this suspicion. Simulations regarding this effect showed that the OR may fall below 1 as a result. The validation studies also showed that selection bias might result in a small risk being overlooked for the group of long-term users. Correcting the results for selection bias woud raise the reported ORs by a factor of 1.1.

Another selection bias that the authors mentioned was that people with serious disorders (advanced state of illness) tended not to participate in the study or could not take part for health reasons. If a relationship exists between mobile phone use and tumours, then such selective participation by tumour-sufferers will lead to a reduction in the OR. No figures are available yet on the significance of the effect caused by this.

(iii) Another aspect concerns the so-called '*confounders*'. Confounders are known causes of an illness that are linked by chance to what are deemed possible causes. For example, developing cancer is highly age-dependent: the older someone is, the higher their risk of developing cancer. If this age-dependence is not taken into account, any factor correlating with age will appear in the statistical analysis to be a 'cause' of cancer. In the Interphone Study, care was taken to ensure that cases and control persons corresponded exactly, to rule out the effects of age, sex and place of residence (region). Since socioeconomic status (income and education) is connected both with the risk of cancer and – at least before the mobile phone boom – with mobile phone use (people with higher incomes were the first buyers of mobile phones), this factor too was included in the analyses (mostly by taking account of people's level of education).

Other factors influencing the risk of tumours (such as genetic predispositions, smoking and occupational risks) were also tested, but were found to be of limited significance. Whenever these confounders were considered, there was only an insignificant change in ORs (in percentage terms) and all the qualitative conclusions remained unaltered.

(iv) A final comment concerns statistical power. In the published Interphone papers, power does not seem to have been adequately considered. The power of a statistical test is the probability that the test will not overlook a potential risk. As a convention, power should be 80% or more, i.e. the probability to make an erroneous conclusion should not be higher than 20%. It is important to note here that in the case of statistically significant findings power tests are of minor importance. However, in case of non-significant results, power-analysis is important. If the power is 80% or more, a non-significant test-result is statistically robust, i.e. the conclusion that the test has not identified a risk is valid. If the power is below 80%, such conclusion is not justified because the probability that the test overlooked a risk is higher than 20%. Non-significant findings with insufficiant statistical power have to be interpreted very carefully.

With regard to the published Interphone results: The power of the tests with long-term users is generally below 50%.

4. Background information

4.1 Head tumours

A brain tumour is caused by the proliferation of cells in the brain. Brain tumours make up about 2-3% of all occurrences of cancer in adults. For children and adolescents, tumours originating in the brain account for up to a quarter of all tumours. On average about 1 in 10,000 adults and 1 in 50,000 children develop a brain tumour. About one in ten brain tumour patients is a child.

There are two basic types of tumours: primary tumours, which originate in the brain or head, and metastatic (or secondary) tumours, which originate from cancers primarily located in other organs, in particular the lungs. Primary tumours account for up to two-thirds of all head tumours. The most common primary tumours are in neural-supporting tissue (gliomas, such as astrocytomas; about 50% of all primary tumours), meningeal tumours (meningiomas; about 25%) and pituitary tumours (pituitary adenomas; about 15%). Another common head tumour affects the acoustic nerve (acoustic neuroma; about 5%). Metastatic tumours from other organs make up about 20-40% of all brain tumours (the commonest is the bronchial carcinoma, which represents over half of all metastatic brain tumours; there are also high proportions of breast-cancer and skin-cancer metastases). Parotid-gland tumours are rather rare (1-3% of all head tumours).

The following tumours were studied in the Interphone Study: gliomas, meningiomas, acoustic neuromas and parotid-gland tumours.

Primary tumours of the brain and spinal cord comprise a wide range of tumour types, originating from different cells in the nervous system and differing considerably in their growth, response to treatment and prognosis. Little is known about the causes of primary brain tumours. Genetic predisposition is known to play a role, as does ionising radiation, but as yet there has been no conclusive evidence of a link with risk factors such as smoking. Knowledge of the induction and latency periods is also sketchy. The ‘induction period’ is the time between exposure and initiation of the illness, and the ‘latency period’ is the period from the start of the illness until it is diagnosed. In general, it is assumed that brain tumours have long latency periods (10 years or more).

The exact classification of the different tumour types as well as assessment of their biological properties – i.e. differentiation of benign and malignant tumours (gradation) – is based on characteristics determined by examining sections of the tumour tissue under a microscope. When making a diagnosis, specialists follow internationally recognised criteria outlined in the WHO Classification of Tumours of the Central Nervous System. On the basis of this WHO classification, each tumour – alongside diagnosis of the type – is assigned a WHO grade, with four WHO grades being distinguished. WHO grade I tumours are slowly growing benign tumours with a favourable prognosis and presenting a good chance of the patient being cured through surgical removal of the tumour. By contrast, WHO grade IV tumours are malignant, very fast-growing tumours with an unfavourable prognosis and which cannot generally be cured using currently available forms of treatment (surgery, radiotherapy and chemotherapy).

In principle, brain tumours and tumours of the spinal cord can occur in people of any age. Most commonly people between 50 and 70 years old are affected (with malignant gliomas and benign meningiomas being especially frequent). The second highest incidence – but significantly lower than amongst the leading group – is amongst children. It is worth pointing out that, after leukaemia, brain tumours (especially benign gliomas and malignant medulloblastomas) are the second most frequent forms of cancer occurring in children.

Gliomas are amongst the most common brain tumours. About half of all primary brain tumours are gliomas. There are different types and gradations of glioma. Astrocytomas are the most common type and occur predominantly amongst middle-aged people. The 5-year survival rate for patients with an astrocytoma is 65%. The 10-year survival rate is 40%. For glioblastomas, the average age when tumours are diagnosed is 53. The 5-year survival rate is under 2%. Gliomas are more common in men than in women.

Meningiomas are predominantly benign tumours occurring in adults. They adhere to the dura mater and arise from the arachnoidal cap cells of the pia mater. They account for about 25% of all primary brain tumours and occur mostly in people aged 50 and over. Meningiomas are twice as common in women as in men.

Acoustic neuromas are benign tumours of the acoustic-nerve sheath. They almost always affect only one acoustic nerve. Typical symptoms are reduced hearing and balance problems. The group of people with the highest occurrence of this type of tumour are people in their fifties and sixties. They occur in men and women in equal measure. Less than 10% of all head tumours are acoustic neuromas.

Parotid-gland tumours are rarely occurring mostly benign tumours of the parotid gland, located between the ear and the jaw. There are a number of different types.

Pituitary adenomas are mostly benign tumours. They originate from hormone cells of the anterior lobe of the pituitary gland. 10-15% of all head tumours are pituitary adenomas. They are most common amongst people of 35-45 years old, and more than half of them are hormone-active.

Glossary of key terms:
- adenoma: benign tumour of glandular tissue;
- blastoma: tumour in embryonic tissue;
- papilloma: benign tumour of the skin or mucous membrane;
- carcinoma: malignant tumour of epithelial tissue;
- sarcoma: malignant tumour of supporting tissue (mesoderm);
- neurinoma/schwannoma: mostly benign tumour of the nerves (or more precisely, nerve sheaths; an example is a tumour of the acoustic nerve, i.e. acoustic neuroma).

4.2 Epidemiology: case-control studies

Epidemiological studies investigate the distribution of illnesses and health risks in general among the population and are mostly large-scale statistical investigations. Often, such studies aim to find out how much greater a particular health risk is for a certain at-risk group than the population average. One factor to be borne in mind here is that the doubling of what is inherently a very low risk of illness in absolute terms is less significant than what may only be a very slight increase in the risk of a widespread illness.

Epidemiological studies have to be interpreted with care as they do not make clear statements about the cause of an illness. The more possible causes there are, the more complex an epidemiological study must be: to make claims about a cause that is of interest, all the other possible causes also need to be taken into account, so that (via appropriate statistical adjustments) an accurate assessment can be made of the risk of the relevant cause.

Consequently, where rare illnesses are concerned, there is a strong possibility that if not very many people can be studied, only a few cases will be included in the analysis, making the results not very robust and prone to the emergence of chance links that would not be observed if larger numbers of cases were considered. This is another reason why conclusions should never be drawn from a single epidemiological study. Only when a number of independently conducted investigations point in the same direction can the results be regarded as reliable.

There are three epidemiological approaches. In *cross-sectional studies* samples are taken from the population. These studies look for a relationship between exposure – e.g. to an air pollutant, a chemical or another suspect ‘agent’ – and some illness, e.g. cancer. The most robust way of doing this is to ask people questions individually. Analyses that compare not individuals, but rather the statistical characteristics of groups, are less robust.

Analytical approaches in which specific people are selected lead to more reliable results. So-called *cohort studies* investigate people from at-risk groups (e.g. from certain occupational groups) who have a particularly high level of exposure to a substance suspected to be hazardous for human health. Then the researchers check whether the feared health problems occur more frequently amongst these people than others.

So-called *case-control studies* approach the issue from the opposite side. People who are suffering from an illness – e.g. cancer – are specifically chosen (from the cancer registry in the case of cancer patients) and the researchers check whether these people were exposed to a greater extent than other people. This group of ‘other people’ must be selected to match the group with the illness as closely as possible (e.g. in terms of demographics or particular proneness to disorders). The Interphone Study was a case-control study.

Data for the cases and control group are generally gathered by asking the respondents questions (in an individual interview if possible). This is very time-consuming and expensive. For serious illnesses like cancer it is also ethically taxing, since researchers have to speak to people who may be very ill or even at death's door. Other methodological problems involved in case-control studies are discussed in the 'Robustness of the results' section.

4.3 Statistics: odds ratio

The odds ratio (OR), which represents the relationship between two values, is applied in case-control studies in a bid to assess risk.

In concrete terms (cf. Table 1), here the relationship between ill and healthy people is established, first taking into account the risk factor chain-smoking (90/2,910 = 0.03093) and second disregarding this factor (10/6,990 = 0.00143). The odds ratio (0.03093/0.00143 = 21.6) is obtained by dividing the first value by the second. For chain-smokers the risk of developing lung cancer is 20 times that for non-smokers.

	Chain	**Non-smokers**	*Total*
Lung cancer	**90**	**10**	*100*
No lung cancer	**2,910**	**6,990**	*9,900*
Total	*3,000*	*7,000*	*10,000*

Tab. 1: Cross-classified table for calculating odds ratios and relative risk

Relative risk (RR) is calculated in a different way. The probability of illness for chain-smokers is 90/3,000 = 0.03, and the probability of illness for non-smokers is 10/7,000 = 0.0014. The relative risk is the quotient of these two figures, so here the RR is 21. Random samples need to be taken from the population to calculate a relative risk. Odds ratios are used if the number of cases is specified, as in case-control studies. For rare illnesses the OR and RR are virtually the same.

5. Publications

5.1 Interphone: principal publications

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