Knowledge Gaps

Regarding RF-EMF-cancer risk assessment in Epidemiology

(Based on the expertise by Prof. Dr. Michael Kundi)

Contents

Notes

- Die Erläuterungen zu den Knowledge Gaps basieren auf Kundi und sind im Bedarfsfall ergänzt worden.
- Erläuterung von wichtigen Begriffen sollen durch Definitionen erfolgen, die per Hyperlink (hier angezeigt mit doppelter Unterstreichung) in einem extra Fenster erscheinen sollen.
- ***kursive Fragen:*** keine „Schieberfragen", sondern offene Fragen
- mit **Neu** indizierte Fragen: Knowledge Gaps, die nicht von Kundi formuliert wurden, sich aber bei der Lektüre des Gutachtens als relevant herausgestellt haben
- Text (in Klammern) unter den Knowledge Gaps: Originaltext Kundi (zur Vergleichbarkeit, intern)

1. Endpoints

New applications of mobile phones are rapidly evolving which result in different patterns of exposure to RF-EMF. However, using them as a telephone limits exposure to emissions of RF-EMF *almost exclusively to the head region.* In the head region there is a multitude of tissues that could be potential targets for exposure induced malignant transformation, for the promotion of a malignant process, or an influence on tumour growth and progression. Yet, there is currently no evidence how to select the most sensitive endpoint for epidemiological studies.

1:
1a: For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the search for cellular targets and tissues which are sensitive to exposures from RF-EMF of mobile phones?
(Which cellular targets and tissues are most sensitive to exposures from RF-EMF of mobile phones?)

1b: Which cellular targets and tissues are most sensitive to exposures from RF-EMF of mobile phones?

At present, the following partly heterogeneous endpoints have been studied: malignant primary brain tumors, benign brain tumors (meningioma and acoustic neuroma in particular), salivary gland tumors, intraocular melanoma, facial nerve tumors, non-Hodgkin lymphoma and testicular cancer. Other head and neck sites as well as other ophthalmic sites have not been studied so far. Also skin cancer and melanoma of the skin have not yet been studied with respect to mobile phone use. Because of the fact that mobile phone use starts now progressively earlier in life and already preschool children have a substantial prevalence of mobile phone use, leukemia might become an important endpoint in future studies especially in children.

2:
2a: For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the question whether there is a relationship between mobile phone use and risk of leukemia?
(Is there a relationship between mobile phone use, in particular at young age, and risk of leukemia?)

2b: For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the question whether there is a relationship between mobile phone use and risk of leukemia in particular at young age?
(Is there a relationship between mobile phone use, in particular at young age, and risk of leukemia?)

WHOs histological classification of nervous system tumors contains more than 50 different malignant entities. Tumors are graded in four groups by their survival pattern. However, molecular neuropathology is rapidly evolving and may lead to different concepts concerning prognosis of tumor growth and prediction of survival. It is mentioned, that it will be a tremendous step forward if the relative risk of mobile phone use could be related to the molecular histopathology.

3:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the search for correlations between risk of mobile phone use and certain molecular histopathological features of the neoplasm?
(Is there a correlation between risk of mobile phone use and certain molecular histopathological features of the neoplasm?)

Depending on the frequency, intensity, polarization, and distance of the antenna, RF-EMF penetrate the body and loose energy by absorption within tissues and body fluids. Specific absorption rate (SAR) is proportional to the square of the electric field strength within the tissue and is, therefore, a useful measure of the presence of the field. However, for long-term effects such as influences on cancer development, SAR may not be the only relevant aspect of exposure.

Neu1a:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the search for indicators of long-term exposure to RF-EMF?
(Nicht von Kundi als Wissenslücke benannt, u.E. sehr wichtige Frage!)

Neu1b: For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the search for indicators of exposure to pulsed RF-EMF?
(Nicht von Kundi als Wissenslücke benannt, u.E. sehr wichtige Frage!)

2. Exposure Indication

Since the early days of mobile phone technology there have been different types of mobile phones. Beginning with analogue appliances, currently the digital GSM and UMTS standards are

common, whereas the latter one is expected to further increase in distribution. Compared to GSM, UMTS works within a doubled frequency range of approx. 2.0 GHz.

There are only very few studies yet which have established exposure indicators with respect to the type of mobile phone in use. But exactly this might be indicated in order to take into account both qualitative and quantitative different patterns of RF-EMF of different transmission standards.

4:
For a better assessment of the possible link between RF-EMF and cancer: How important is it to distinguish between different types of mobile phones used (analogue phones, GSM, UMTS etc.) with respect to exposure indication?
(How should different types of mobile phones used concurrently or subsequently (analogue phones, GSM, UMTS etc.) be integrated into a single or several exposure indicators?)

→ **Für diese KG konnte im Gutachten keine Erklärung gefunden werden**

Because of the increasing usage of mobile phones for other purposes than telephony (SMS, MMS, internet, television, games etc.), and the fact that these applications result in a completely different pattern of exposures, it might be of importance to properly assess and quantify habits of use and relate them to the diverse exposure patterns.

5:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the assessment of the body-distribution of SAR-values of new applications of mobile phones (TV, internet, etc.?)
(What is the SAR distribution associated with new applications of mobile phones (TV, internet etc.)?)

To date, the only indicator which allows for assessment of exposure is SAR. But, strictly speaking, the specific absorption rate is nothing but a specific feature of human tissue to absorb a certain amount of energy. Hence, it might be ventured to doubt whether SAR is an adequate indicator of actual exposure to RF-EMF

Neu2a
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the assessment of other exposure indicators than SAR?

Neu2b
What other exposure indicators are imaginable?

Due to the efficient power regulation of modern mobile phones, distance to the base-station is an important modifier of intensity of exposure. Consequently, use of the mobile in different areas (rural, urban etc.) has been assessed in some investigations. Actual measurements of power regulation, however, indicate that power regulation differs not only between regions and indoors and outdoors but that there are also differences between countries.

6:

For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is an area-specific adjustment of exposure?
(Should there be an adjustment of exposure indicators for area of mobile phone use (rural, urban etc.) to account for power regulation?)

Neu2:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is an adjustment of exposure indicators for mobile networks (E, D1, D2, etc.)?

→ Ist unseres Erachtens sinnvoller, als regionale Gliederung)

In some studies, in addition to cellular telephone use, cordless phones have been included into risk evaluation. Although power of cordless phones is less than the maximum power of cellular mobile phones, cordless phones have no power regulation and may cause not much less cumulative exposure due to the often longer duration of calls.

7:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the inclusion of exposure indicators for cordless phones into epidemiological studies?
(Should cordless phones be included into exposure indicators, and how should this be done?)

It is supposed that RF-EMF might influence tumor development only on the side of the head, where the mobile phone is commonly held during talks. It is argued that, if exposure has only an effect on already deviating cell populations (by an influence on growth rate, survival, tumor-host interaction etc.), exposure must be assessed only for the location where the tumor is growing.

8:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the distinction between side of the head, where the mobile phone is held during talks, and the opposite side?
(How should side of the head the mobile phone is held during calls be incorporated into exposure indicators?)
(Diese Frage schein mir inhaltlich besser nach KG 9 zu passen…)

→ Knowledge Gap **9** wurde von Kundi zu unspezifisch formuliert, daher basierend auf seinen Gedanken dazu mehrere neue Knowledge Gaps formuliert:

It was argued that there are two different types of evaluations that must be part of any epidemiological investigation: One that starts from the assumption of an influence on the tumor induction process (cultivation of neoplastic cells), and one that assumes an influence on tumor progression (diffusion of metastasizing cells all over the body). Additionally, there is the possibility that RF-EMF might influence the process of tumor growth (promotion), or even each of those stages of carcinogenesis.

However, there is scientific evidence neither for an interaction effect nor for a singular effect on induction process or tumor progression yet.

Neu3a:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the search for an influence of RF-EMF on the tumor induction process?

Neu 3b
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the search for an influence of RF-EMF on the tumor promotion process?

Neu 3c
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the search for an influence of RF-EMF on the tumor progression process?

Neu 3d
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the search for an influence of RF-EMF on each stage of the tumor development (induction, promotion, progression)?

→ **Bei Kundi wird die Frage nach einem Interaktionseffekt (a) in dieser Art nicht gestellt, sondern (b) nur auf ein entweder–oder hingewiesen.**

Unfortunately, SAR values are typically only available as maximum values according to the different measurement standards (e.g. EN 50361, IEEE 1528/D1.2). The maximum occurs often at locations that are irrelevant for cancer risk considerations (e.g. the pinna). Therefore, it is not possible to use SAR values of the mobile phone a person has used to assess exposure intensity at the location of the tumor.

10:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the search for indicators of intensity of exposure to RF-EMF from mobile phones to be used in epidemiological studies?
(Which indicators of intensity of exposure to RF-EMFs from mobile phones can be used in epidemiological studies?)

→ Knowledge Gap **11** verwies auf zwei verschiedene Fragen, daher aufgeteilt:

Actual exposure could depend on a number of anatomic features. This is especially important if exposure in children and adolescents is studied, because there could be a substantial difference due to anatomical features and dielectric properties of tissues. There has been a controversy about this aspect, yielded by different studies which found both higher SAR values in children and similarity of SAR values in children and adults.

11a.
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the search for anatomic features of the user, which could modify a possible/thinkable impact of RF-EMF on cancer development?

(Can or should anatomical features of the user and habits of use be included in the assessment of exposure to mobile phone emissions?)

Current exposure could depend on a number of habits of use. For instance, this could be the side where the phone is held during talks. Another feature might be how close to the head the mobile phone is held during use. Especially in the early years of the mobile phone technology, it was almost exclusively practiced by occupational users. Although this has changed in recent years by the increasing diffusion of mobile phone use into the private sector, differing practices of mobile phone use related to either professional or private purposes still might account for differences in exposure. E.g., the more frequent use of short message services (SMS) among children and adolescents could result in an overall different pattern of exposure.

11b.
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the search for habits of use, which could be modifying the impact of RF-EMF on cancer development?
(Can or should anatomical features of the user and habits of use be included in the assessment of exposure to mobile phone emissions?)

There has been controversy about the question whether properties of different tissues might account for tissue specific susceptibility to RF-EMF. E.g., concerning brain tissue, cerebrospinal fluid and the skull, it was shown that children might have two to four times the respective SAR values of adults. Consequently, it was questioned, whether research concerning a relationship between RF-EMF and cancer should take properties of certain tissues of interest into account,

12a:
For a better assessment of the possible link between RF-EMF and cancer: How important is the evaluation of SAR for the tissue of interest (e.g. vestibular nerve, parietal lobe, eye…)?
(Should the SAR be evaluated for the tissue of interest (e.g. vestibular nerve, parietal lobe, eye) and should the dielectric properties be varied according to age?)

It is an open question whether children are specifically susceptible to RF-EMF. Different dielectric properties between children and adults are regarded one distinguishing feature. It is questioned whether different dielectric properties of tissues in children and adults possibly might modify the exposure to RF-EMF.

12b:
For a better assessment of the possible link between RF-EMF and cancer: How important is the investigation into effects of varying dielectric properties according to age?
(Should the SAR be evaluated for the tissue of interest (e.g. vestibular nerve, parietal lobe, eye) and should the dielectric properties be varied according to age?)

Concerning aspects of the time course of exposure there are a number of options including unweighted cumulative exposure, cumulative exposure with different weights for earlier and later exposures, cumulative exposures above a certain threshold, or duration of exposure above a certain threshold. It was suggested no to exclude any of these opportunities a priori, but to investigate into the consequences of using particular measures for long time exposure.

13a:
For a better assessment of the possible link between RF-EMF and cancer: How important is the accumulation of exposure intensity over time?
(For the accumulation of exposure intensity over time, which type should be chosen (unweighted sum, sum weighted according to distance from diagnosis, sum above some threshold, duration above some threshold …)?

13b:
For a better assessment of the possible link between RF-EMF and cancer: How important is the accumulation of exposure intensity over time as unweighted sum?
(For the accumulation of exposure intensity over time, which type should be chosen (unweighted sum, sum weighted according to distance from diagnosis, sum above some threshold, duration above some threshold …)?

13c:
For a better assessment of the possible link between RF-EMF and cancer: How important is the accumulation of exposure intensity over time as sum weighted for earlier or later exposure?
(For the accumulation of exposure intensity over time, which type should be chosen (unweighted sum, sum weighted according to distance from diagnosis, sum above some threshold, duration above some threshold …)?

13d:
Which one is most important?

3. Mechanisms of Action

Although it is usually not necessary to have insight into the interaction mechanism to design an epidemiological study and to assess the risk associated with the exposure, the situation is different for RF-EMF exposure from mobile phone use. In other words, choice of the appropriate exposure meter depends on the unknown mechanism of action (if there is one) and how it is linked to the neoplastic development. Since there is consistent evidence that neoplastic diseases are associated with genetic events that result in immortalization and substrate independent growth of a cell population, it might be indicated to investigate for RF-EMF effects on cancer at certain stages of neoplastic development.

14:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is an answer to the question, at which stage of the neoplastic development an effect of mobile phone use might occur?
(At which stage of the neoplastic development occurs an effect of mobile phone use?)

If RF-EMFs from mobile phones have adverse effects on health, it is almost unavoidable to assume that there is a variation of susceptibility in the population. Given that knowledge of the interaction mechanism exists, this would be instrumental in defining sensitive subpopulations and in quantifying individual risks and for recommendations about prudent use of mobile phones.

15:

For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the question whether there are subpopulations that are specifically susceptible to RF-EMF from mobile phone use?
(Are there subpopulations that are specifically susceptible to RF-EMFs from mobile phone use?)

Based on theoretical considerations children have been assigned a possibly higher risk from mobile phone use. There are no data yet about long-term effects of mobile phone use in children. Also for other (potentially) hazardous environmental factors there are rarely data to specifically address differences in susceptibility between children and adults. In a comprehensive overview of the literature in 2005, the U.S. Environmental Protection Agency detected only a handful of carcinogens for which data about early-life exposures were available. Due to the paucity of data on effects in children the U.S. EPA recommended a 10-fold adjustment for permissible exposure levels of children from birth to age 2 and a 3-fold adjustment for ages 2–16 as default values.

16:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the question whether children should be considered at increased risk of long-term adverse health effects from mobile phone use?
(Are children among those that should be considered at increased risk of long-term adverse health effects from mobile phone use?)

Epidemiology is facing the problem of fast technological development resulting in considerable changes of exposure conditions. Due to long latencies of relevant diseases such as cancer, evidence about an association can only be accumulated after considerable time has elapsed.

Along with the gradually developing evidence about earlier mobile phone technologies new types of devices and applications are evolving. Although it cannot be answered by epidemiology, epidemiologists call for clarifying the mode of action. Without insights into the mode of action, it is regarded as difficult, if not impossible, to both assess and extrapolate risks, e.g. from older to new technologies.

17a:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the clarification of the mode of action, i.e. the bio-physical basis for processes that might occur at several body-levels (cells, tissues, organs) in response to exposures to RF-EMF?

17b: What levels are most important?
(Which processes occur at the cellular level in response to exposures to weak (ELF modulated) RF-EMFs from mobile telecommunication that may have an influence on neoplastic development? Are there other mechanisms at a higher level of integration (tissue, organ,…) that have implications for neoplastic development? What is the bio-physical basis for this interaction?)

→ Knowledge Gap **34** war die einzige Frage zum Thema „Evaluation of Evidence“ und wurde daher hier zu „Mechanisms of Action“ eingeordnet

Of more than 20 epidemiological studies published so far only less than half included more than a few subjects with duration of mobile phone use of 10 or more years. The fraction of controls with

10 or more years mobile phone use varies between 1% and 10% in studies published since 2004 and is negligible in earlier investigations. With respect to possible mechanisms of carcinogenesis, currently it is subject of discussion whether the intense recent use of mobile phones might be of more importance than latency or long-term use conditions. Whereas some researchers favor this hypothesis, others reject it by pointing at an insufficient proportion of investigations into this issue.

34:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ are studies which approach reasonable latencies, in order to assess risks associated with mobile phone use for prolonged periods?
(Combining the evidence from studies approaching reasonable latencies, what is the risk associated with mobile phone use for prolonged periods of time with respect to brain tumors and other relevant endpoints?)

4. Epidemiological Designs

Due to the exponential growth of subscription rates in the past two decades, some problems are arising for ongoing and future epidemiologic research. First of all, the assumption of equivalence of environments and populations of users and non-users of mobile phones cannot be maintained anymore. All features of the populations exposed and unexposed are sampled from (or are thought to be the basis for cases and controls) should be similar except for mobile phone use. But, in many countries to date almost all persons are using a mobile phone and those that don't deviate strongly from the rest. Generally speaking, if no unexposed control group can be included, evaluation of risk cannot be anchored and affords greater knowledge of the mechanism of action to relate risk to a quantified aspect mirroring the decisive aspect of exposure.

18:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is a sufficient gradient of exposure?
(How should epidemiology address the issue of today's almost 100% prevalence of mobile phone use? How can a sufficient gradient of exposure be guaranteed if no evidence based exposure indicator is available?)

In epidemiological studies, for rare diseases such as brain tumors the sample must be extremely large and the duration of follow up and exposure assessment must be very long. Only about 4 to 6 of 1.000 subjects develop a brain tumor during their lifetime. If, for example, 250.000 subjects aged 20-39 years are sampled, the expected number of brain tumors diagnosed during a follow up of 5 years will be about 40-50 cases.

Epidemiologists argue that the expected number of cases of one of the primary endpoints might be too low to detect even a substantially increased risk within the projected initial follow-up period of five years – given that the effect is on growth rate and there are no substantial differences in exposure within the cohort.

19a:

For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the sample size for assessing RF-EMF induced influences on cancer?

19b:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the homogeneity of the sample with respect to exposure?
(How could the problems of a huge cohort population and the high prevalence of mobile phone use be overcome in a cohort study?)

In epidemiological studies, for rare diseases such as brain tumors the sample must be extremely large and the duration of follow up and exposure assessment must be very long. Only about 4 to 6 of 1.000 subjects develop a brain tumor during their lifetime. If, for example, 250.000 subjects aged 20-39 years are sampled, the expected number of brain tumors diagnosed during a follow up of 5 years will be about 40-50 cases.

Hence, it is discussed whether nested case-control approaches within large cohorts might be more feasible. A large well-defined and regularly updated cohort like the "European ChildrenGenoNetwork" or the "National Children's Study" in the United States that contains information on many relevant characteristics as well as exposure to environmental toxicants may be extended to include information on mobile phone use.

20:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ are nested case-control approaches within large cohorts for assessing cancer risks of RF-EMF?
(Is a nested case-control approach within a large cohort feasible?)

→ Knowledge Gap **21** hat Age-Bias zum Gegenstand, daher eingeordnet in „Confounder, Bias"

There are different methods of collection of cases and controls that can be applied. Cases can be drawn from cancer registries, if available, or by contact to hospitals. Whereas some countries have highly developed and permanently updated cancer registries, this is not the case for all countries as well as for all kinds of tumors. In order to get valid endpoints with critical prevalence, epidemiologists thus raise the question whether there are certain endpoints (brain tumors, salivary gland cancer, leukemia, etc.), for which a registry based sampling of cases could be substituted by a hospital based one.

22:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the introduction of a hospital based sampling of cases in order to substitute registry based ones?
(For which endpoints (brain tumors, salivary gland cancer, leukemia, etc.) can a registry based sampling of cases be substituted by a hospital based one?)

A special problem arises if endpoints with a poor prognosis are studied: if cases are sampled in a rapid fashion it may not be feasible – or even impossible – to contact them prior to death or

contact may be denied, respectively, by the attending physician due to terminal stage of the disease. Moreover, using a mobile phone might even have a protective effect, in terms of the ability to rapidly call for medical attendance in emergency. Thus, if survival is related to mobile phone use, in a case-control study leaving out dead cases may result in a bias. To overcome this problem it has been suggested to sample death controls to these cases.

23:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the sampling of dead cases as controls to the cases in epidemiological studies?
(Should dead controls be sampled for dead cases?)

Using the case-control approach has the objective to estimate the relative risk of a factor that is retrospectively assessed (or already known in the nested case-control approach). A prerequisite for an unbiased estimate is that sampling of both, cases and controls, is from the same population and that there are no differences in the sampling fraction between exposed and unexposed.

The best option to do so is to draw controls randomly from a population register matching at least for age, gender and region. However, it might not always be feasible to match controls according to this recommended procedure.

24:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the search for opportunities to randomly select controls, others than based on a population registry?
(If a random selection of controls cannot be based on a population registry, which methods of control selection should be applied?)

5. Data Issues

In case-control studies cases should be included as early as possible after diagnosis, and information about the disease should be collected. These are computer-tomography images, histopathology, tumor staging, molecular pathological findings and a complete history of the disease. Furthermore, depending on the study objectives, epidemiologists propose to include also information about therapy. For some endpoints like brain tumors there are only few centers in each region where a case can be diagnosed and registry data, if available, may only be needed to assess death certificate only cases (i.e. cases that were diagnosed only during necropsy). Thus, it is questioned whether it should be obligatory to collect details of the diagnosis (including histopathology, molecular pathology, tumor location, stage and images) from the hospital or attending physician.

25a:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the collection of detailed data of both diagnosis and therapy from the respective hospital?

(Should it be obligatory to collect details of the diagnosis (including histopathology, molecular pathology, tumor location, stage and images) from the hospital or attending physician?)

25b:

For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the collection of detailed data of both diagnosis and therapy from the attending physician?

(Should it be obligatory to collect details of the diagnosis (including histopathology, molecular pathology, tumor location, stage and images) from the hospital or attending physician?)

26: Should a data base be developed that can be shared within the scientific community containing case specific data about tumor molecular biology, histopathology etc. as well as details of mobile phone use?

(Should a data base be developed that can be shared within the scientific community containing case specific data about tumor molecular biology, histopathology etc. as well as details of mobile phone use?)

→ Ist kein Knowledge Gap und zu unspezifisch – könnte aber als offene Frage ans Ende der Data Issues gestellt werden.

An important aspect of data acquisition is the collection of exposure information. Concerning RF-EMF and a possible cancer-risk, the following methods have been used so far: subscription records from network companies, questionnaires filled in by participants, and personal interviews. Each of those procedures has both advantages and disadvantages, why the question is still unsolved which methods of data collection on mobile phone use are best suited. A proposed solution to the question of data source is to combine these three methods. Yet the question how exactly a combined approach to data collection on exposure might by feasible, is still open too.

27:

For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is finding a "gold standard" of data collection?

(In order to increase veridicality and precision of exposure data, which methods of data collection about mobile phone use (or combinations of methods) should be applied?)

While it is easy to answer the question about side of the head where the phone was used during calls, the answer may be biased. If a tumor was diagnosed on one side of the head, patients may either tend to answer having used the phone on the side of the head where the tumor was located (if they blame the mobile phone as a cause of the disease) or, to the contrary, that they used it on the opposite side. Although earlier studies may not have had problems of this kind, because only recently mobile phones were publicly discussed as a potential source of health problems, recent and ongoing investigations may have problems due to an information bias of this kind. In epidemiology it is not answered yet which methods to assess laterality of mobile phone use is best suited to minimize information bias.

28:

For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is it to assess laterality of mobile phone use?

(Which methods to assess laterality of mobile phone use should be applied to minimize information bias?)

Concerning a possible carcinogenic history, hospital and physicians records may especially be scrutinized for early hints on tumor growth, like hearing impairments, seizures, visual problems, personality changes etc. for brain tumors, weight loss, periods of unexplained exhaustion, frequent infectious diseases etc. for leukaemia, and so forth. It is hypothesized that – if standardized procedures were applicable – the time point of these early signs could be used to censor the accumulation of mobile phone use for a better assessment of the exposure duration.

29:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ are standardized procedures to assess early signs of the diseases developed?
(Should a standardized procedure to assess early signs of the diseases be developed?)

6. Confounders

→ bei Kundi hierzu nur Knowledge Gap **30,** daher bei „Confounder, Bias“ eingeordnet

7. Statistical Methods

For rare diseases, and assuming equal sampling fractions, the calculated odds ratios are estimates of the *rate ratio* (the ratio of incidences between the populations of exposed and unexposed). However, the rate ratio is a questionable measure of risk for factors that might promote tumor development under conditions of only short term exposure. The impact on the level of the exposed population will be grossly underestimated if the relative risk is assumed to be fixed, but the distribution of exposure durations is *changing* over time, revealing increasing proportions of long-term users. Therefore it was raised the question whether there is a relationship between tumor growth rate and necessary minimum exposure duration which is required to detect an increased odds-ration in a case control study.

31/32:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the statistical assessment of cancer incidences in relation to changing exposure durations?

(31: What is the relationship between tumor growth rate and minimum exposure duration necessary to detect an increased odds-ratio in a case-control study?)
(32: How should the effect of increasing exposure durations on incidence be predicted?)

While standard methods were applied for overall risk estimation, the important question of *laterality*, i.e. the association between the side of the head where the mobile phone was used and the occurrence of a tumor on this side of the head, was dealt with by different approaches. Three methods have been applied so far. Two of these methods are criticized as biased: The method developed by Inskip et al. (published 2001) includes only cases and does not consider possible

confounders such as age and gender; the method applied by Lönn et al. (published 2005) is biased due to inclusion of contralaterally exposed cases as unexposed. The third method applied by Hardell et al. (published 2001) assigns a virtual tumor to the matched control at the same side of the head as observed in the case and can, therefore, not be applied in frequency matched case-control studies. Thus, there is no well defined and accepted methodological standard for assessing ipsilateral exposure to RF-EMF by mobile phones yet.

33:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is a standardized statistical procedure to assess ipsilateral exposure?
(Which statistical method should be applied to assess ipsilateral exposure to mobile phones?)

8. Evaluation of Evidence

→ bei Kundi hierzu nur Knowledge Gap **34,** daher bei „Mechanisms of Action" eingeordnet

9. Confounder, Bias

→ bei Kundi die einzige Knowledge Gaps zu „Confounder", daher hier:

For neoplastic diseases there are at least age and gender that are likely candidates to confound the association between mobile phone use and incidence. For other variables there is less evidence that they may act as confounders. One of these variables is social status. There is weak support for an association between social status and brain tumors and because of the correlation between mobile phone use and social class it may act as confounder. If a certain endpoint has a strong association with a risk factor (such as smoking for lung cancer), it must be included as a potential confounder even if there is no prior information that there could be an association with mobile phone use. However, for none of the endpoints studied so far there are such strong risk factors. It is thus questionable, whether the search for confounders could contribute to a better evaluation of the RF-EMF–cancer link.

30a:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the inclusion of potential confounders (except age and gender) in epidemiological studies of mobile phone use and cancer?

30b:
Which potential confounders (except age and gender) should be included in studies of mobile phone use and cancer?

One important bias regarding studies of RF-EMF and cancer might be due to age, as user habits change by increasing age. Epidemiologists argue that each possible impact of RF-EMF on cancer initiation or tumor growth will be a function of average exposure duration and the age pattern of

exposures. Application of the case-control approach could lead to a bias if individual matching is not exact on age (and as well in frequency matching) and furthermore, if there is a strong correlation between age and mobile phone use.

21:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the investigation into age bias and its potential consequences on risk estimation?
(Is there a bias in the case-control approach to estimate relative risk of an agent that does have only an effect on post-induction processes, and what is the magnitude of this bias?)

At the level of both metaanalytical considerations and pooled analyses publication bias must be considered. This type of bias plays an important role in pharmaceutical research where mainly 'negative' studies carry the risk of remaining unpublished. In the case of environmental and occupational agents the opposite risk, that 'positive' studies are not published, must be considered. Concerning mobile phone use and cancer, there could be a publication bias too, as critical voices repeatedly stress. However, there is no scientific proof of a publication in RF-EMF-cancer studies yet.

Neu4:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the investigation into publication bias and its potential consequences on risk estimation?

→ Bei Kundi hieß es wörtlich: "…up to now there is no suggestion of a publication bias". Wir möchten dies dennoch als Hypothese aufgreifen.

Response bias is one kind of selection bias. It is assumed, if respondents answer questions in a manner they think the interviewer wants them to. In social sciences this phenomenon is called "social acceptability". This term refers to the theory that human interactions are driven by the desire to get social support, i.e. positive feedback. Possibly, response bias is present in epidemiological studies published so far and might have consequences on risk estimates.

35:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the investigation into response bias and its potential consequences on risk estimates?
(To what extent is response bias present in studies published so far and what are the consequences on risk estimates?)

Migration bias is one kind of selection bias. It is assumed, when respondents change their habits of using mobile phones during time. In other words, if early pathological symptoms are attributed to a possible carcinogenetic development, respondents could reduce or even discontinue mobile phone use, change the side of the head when placing a call etc. But also the opposite may occur: that patients start mobile phone use due to their disease (e.g. a patient experiencing seizures may want to call for help as soon as possible). Possibly, migration bias is present in epidemiological studies published so far and might have consequences on risk estimates.

36:

For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the investigation into migration bias and its potential consequences on risk estimates?
(To what extent is migration bias present in studies published so far and what are the consequences on risk estimates?)

A special type of migration bias is the *'healthy worker'* effect (in this context: the 'healthy user effect'). If in a cohort study someone is known to be healthy enough to subscribe for a mobile phone there will be a bias if comparison is made to a control group that is not known to be equally healthy at time of inclusion. Possibly, 'healthy user' effect is present in epidemiological studies published so far and might have consequences on risk estimates.

37:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the investigation into 'healthy user' effect and its potential consequences on risk estimates?
(To what extent is a 'healthy user' effect present in studies published so far and what are the consequences on risk estimates?)

An effect on risk estimates may also occur in the case of *survival bias*, which is a further type of selection bias. If mobile phone use results in a reduced survival, failing to include dead or terminally ill patients can result in substantially underestimating the risk. Should mobile phone use protect against early death (which might indirectly be the case, due to an earlier diagnosis), the opposite effect on risk estimates would occur. Possibly, survival bias is present in epidemiological studies published so far and might have consequences on risk estimates.

38:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the investigation into survival bias and its potential consequences on risk estimates?
To what extent is survival bias present in studies published so far and what are the consequences on risk estimates?

Hospital based selection of study participants carry the risk of the *admission-rate bias*. This bias occurs if exposure status is correlated with the hospital admission rate. Mobile phone use is recommended for some patient groups (e.g. patients with coronary heart disease) to immediately get medical aid. Possibly, admission-rate bias is present in epidemiological studies published so far and might have consequences on risk estimates.

39:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the investigation into 'admission-rate bias' and its potential consequences on risk estimates?
(To what extent is an admission-rate bias present in studies published so far and what are the consequences on risk estimates?)

Within the group of selection biases, *detection bias* is present, if due to mobile phone use the disease has a higher likelihood of being detected. While for most neoplasias such a bias is almost

impossible, for acoustic neuroma it has been speculated that mobile phone use may lead to an earlier awareness of hearing problems and, therefore, to earlier detection of the tumor.

40:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the investigation into detection bias and its potential consequences on risk estimates?
(To what extent is detection bias present in studies published so far and what are the consequences on risk estimates?)

Misclassification of disease is present if cases *do not* have the disease under study, whereas controls are selected that actually *have* or had the disease. This bias is related to the sensitivity and specificity of the diagnostic system for the endpoint under study.

Neu5
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the investigation into diagnosis misclassification bias and its potential consequences on risk estimates?

→ Frage bei Kundi so nicht gestellt

Misclassification of exposure occurs if some exposed are actually unexposed and vice versa. This error, although often assumed to be negligible in cohort studies, is – concerning mobile phone use – as likely in case control studies as in cohort investigations.

Neu6
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the investigation into exposure misclassification bias and its potential consequences on risk estimates?

→ Frage bei Kundi so nicht gestellt

Misclassification bias can be distinguished into non-differential and differential misclassification bias.

Non-differential misclassification bias is independent of disease or exposure status, and is thus rather a random error than a real "bias".

41:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the investigation into non-differential misclassification bias and its potential consequences on risk estimates?
(To what extent is non-differential misclassification present in studies published so far?)

Misclassification bias can be distinguished into non-differential and differential misclassification bias.

Differential misclassification bias is related to disease or exposure status. As it is depending on measurement it is not a random, but a systematic error. Because of the possibly impaired memory in brain tumor cases a reduced sensitivity of exposure assessment has been discussed that would consequently lead to an underestimation of risk.

42:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the investigation into differential misclassification bias and its potential consequences on risk estimates?
(To what extent is differential misclassification present in studies published so far and what are the consequences on risk estimates?)

An important source of misclassification is *interviewer bias*. If interviewers are not blinded to case status and have strong personal opinions about the role of mobile phone use they might tend to perform the interview differently in cases and controls.

43:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the investigation into interviewer bias and its potential consequences on risk estimates?
(To what extent is interviewer bias present in studies published so far and what are the consequences on risk estimates?)

A potential source of misclassification is *recall bias*. Diagnosis of cancer is likely accompanied by continuous cognitive processes in the patient circulating around the reasons for the occurrence of the disease. As long as mobile phone use is not among the factors known or speculated to be associated with cancer it is unlikely that a patient will blame the mobile phone. However, during the last years there was some media coverage of the possible association of mobile phone use with cancer and therefore, some will think about their using a mobile phone as a potential factor. These processes may lead to a differential misclassification. Other sources of recall bias, like impaired memory, will also lead to differential misclassification.

44:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the investigation into recall bias and its potential consequences on risk estimates?
(To what extent is recall bias present in studies published so far and what are the consequences on risk estimates?)

A potential source of misclassification might be *diagnostic suspicion bias*. It might be especially a problem in cohort studies if exposed cohort members are screened more efficiently for the presence of the disease.

Neu7:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the investigation into diagnostic suspicion bias and its potential consequences on risk estimates?
(Frage bei Kundi so nicht gestellt)

Confounding bias occurs if a variable that is associated with both exposure and disease is not considered, i.e. either not observed or not included in the analysis. Except for age and gender, and possibly social status, for most diseases studied so far no important risk factors have been established. For some brain tumors an association with therapeutic x-rays and other exposures to ionizing radiation has been detected, however, it is unlikely (but possible) that exposure to ionizing radiation is correlated with mobile phone use. Hereditary factors may account for a fraction of the diseases, but again correlation of these factors with mobile phone use is speculative. It is questionable, whether confounding bias is present in studies published so far and what the consequences are on risk estimates.

45:
For a better assessment of the possible link between RF-EMF and cancer: How important/of which relevance/ is the investigation into confounder bias and its potential consequences on risk estimates?
(To what extent is confounder bias present in studies published so far and what are the consequences on risk estimates?)

Definitions

→ A bias is a systematic error which results in a deviation of results or inferences from the truth, or processes leading to such deviation. In epidemiology it refers to the association between exposure (here: RF-EMF) and risk of disease (here: cancer).

→ A confounder is a variable that is associated with both the endpoint and the exposure.

→ Information bias is present if the risk estimates are affected by errors in measurement, observation, or documentation of study variables. Yet, there are several forms of information bias.

→ Migration bias occurs when there is differential factor-related migration within, into or out of each study population group. It refers to the fact that migration within, into or out of each study population group is related to the factor of interest and such migration distorts the assessment of the relationship between the exposure and outcome of interest.

→ Misclassification bias is a type of information bias. It is divided into misclassification of disease and exposure.
Misclassification of disease is present if cases do not have the disease under study, whereas controls are selected that actually have or had the disease. This bias is related to the sensitivity and specificity of the diagnostic system for the endpoint under study.
Misclassification of exposure occurs if some exposed are actually unexposed and vice versa. This error, although often assumed to be negligible in cohort studies, is – concerning mobile phone use – as likely in case control studies as in cohort investigations.

→ Selection bias refers to the sampling of the study. It is the error of distorting a statistical analysis due to the methodology of how the samples are collected. It is present, when for some or all study segments the ratio $\frac{S_{11}S_{00}}{S_{10}S_{01}}$ differs from 1 (S_{11} denotes "exposed among cases", S_{00} "not exposed among controls" – S_{10} "not exposed among cases", and S_{01} "exposed among controls" – for cohort studies cases/controls can be replaced by diseases/no diseases). There are several kinds of selection biases, which might contribute to either under- or over-assessments of possible RF-EMF-cancer links.