



A META-ANALYSIS : THE EFFECT OF MOBILE PHONE RADIATION ON THE INCIDENCE OF MALIGNANT TUMOURS IN ANIMALS

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This meta-analysis was conducted in 2013 by second-year Biomedical Sciences students.

Two authors recently translated and revised the textual part of the report to make it eligible for publication.*

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Abstract

Meta-Analysis

BACKGROUND: In the last few years, the use of mobile phones has increased exponentially. We are warned by media stations for unhealthy consequences of the mobile phone radiation. Among those is a Belgian thesis from 2008 that stated that mobile phone radiation is harmful to our health. Furthermore, the International Agency for research on cancer of the World Health Organisation reported a possible risk of cancer caused by exposure to electromagnetic radiation. However, no meta-analysis has been performed on this subject yet. Most of the studies on this subject are animal studies, because in those studies we can completely control the amount of radiation received while keeping the possible confounders to a minimum.

OBJECTIVE: To clarify whether mobile phone radiation leads to a higher incidence of malignant tumours in animals.

METHODS: An extensive search was performed in Pubmed and Embase using a search filter created by SYRCL (the SYstematic Review Center for Laboratory animal Experimentation) to include all test animals. After the critical appraisal, we deducted the incidence of malignant tumours in the animal population for each study and used these to compute odds ratios according to the Mantel-Haenszel method. We looked at whole body tumour incidence, brain tumours, breast tumours and lymphomas.

RESULTS: The search resulted in 15 relevant articles for our research question. The computed odds ratio (OR) of whole body tumour incidence was 1.01; 95% CI [0.86-1.20]. The computed OR of brain tumour incidence was 0.94; 95% CI [0.75-1.17], the breast tumour incidence was 1.11; 95% CI [0.83-1.47] and the lymphoma incidence was 0.77; 95% CI [0.46-1.29].

CONCLUSION: The evidence found shows that there is no etiological connection between mobile phone radiation and tumour growth in rats and mice. More research is needed to clarify whether this also holds true for humans.

WHAT'S KNOWN: It is known that other types of radiation can increase the risk of cancer. Controlled clinical trials on humans regarding mobile phone radiation are hard to conduct because almost everybody is exposed to mobile phone radiation. Therefore, a lot of animal studies are conducted regarding this subject, while the amount of radiation can be controlled and the confounders can be kept to a minimum in animal studies.

WHAT'S NEW: Although systematic reviews have been published about the effect of mobile phone radiation on tumour incidence in animals, a meta-analysis wherein all the existing data is combined has not yet been conducted. It is of great importance that this meta-analysis is performed to achieve the highest level of evidence on this topic.

KEYWORDS: mobile phone radiation, cancer, tumour, animals

Introduction

The last twenty years, the use of mobile phones has increased significantly. More people than ever before own mobile phones and phones are used more hours per day. To keep connected with satellites, mobile phones use electromagnetic radiation between 450-3800 MHz. Amongst the population, it is thought that this electromagnetic radiation used, could increase the risk of getting cancer. The idea that tumours might arise due to this radiation is partly fed by messages originating from the media. For example, in 2007, a Belgian thesis was published which concluded that mobile phone radiation is harmful to our health [1]. This conclusion led to turmoil amongst the population and also in the House of Representatives of the Netherlands. The Health Council of the Netherlands asked the Commission of Electromagnetic Fields (CEF) to critically review the thesis to identify the risk of the population [2]. After an extensive research, the CEF concluded that the thesis contained invalidations and imperfections. First of all, the report seemed written by only three persons, instead of a full commission with several independent

specialists. One of those persons did not have a scientific background, which was noticeable in the incomplete and selective search strategy. Lastly, the aim of the report was "to document the reasons why current public exposure standards for non-ionizing electromagnetic radiation are no longer good enough to protect public health" [1], meaning they never aimed to make an objective analysis.

In 2011, the International Agency for Research on Cancer (IARC) of the World Health Organisation (WHO) evaluated the available literature on the possible carcinogenic effects of electromagnetic fields [3]. They reported a possible risk of (brain)cancer caused by exposure to electromagnetic fields, based on epidemiological and (animal) experimental data. However, they also reported that the evidence was limited for brain tumours and inadequate for other types of cancer. They concluded that more scientific research is needed to clarify the possible risk.

Table 1: Our search strategy was made up of three parts: mobile phone radiation, tumours and an animal search filter made in SYRCLE [22,23]. It resulted in 337 studies in PubMed and 265 in Embase.

Database	Search term	Results
PubMed	<p>(GSM[Title/Abstract] OR cell phone[Title/Abstract] OR mobile phone[Title/Abstract] OR mobile phones[Title/Abstract] OR cellular phone[Title/Abstract] OR cellular phones[Title/Abstract] OR cellular telephone[Title/Abstract] OR cellular telephones[Title/Abstract] OR Radio Wave[Title/Abstract]) OR radio frequency[Title/Abstract] OR radio frequencies[Title/Abstract] OR radio-wave[Title/Abstract] OR radio-frequency[Title/Abstract] OR radio-frequencies[Title/Abstract] OR radio-waves[Title/Abstract] OR global system mobile[Title/Abstract] OR radio waves[Title/Abstract] OR radio wave[Title/Abstract] OR "Cellular Phone"[Mesh] OR "Radio Waves"[Mesh])</p> <p>AND</p> <p>(neoplasm[Title/Abstract] OR neoplasms[Title/Abstract] OR neoplasia[Title/Abstract] OR cancer[Title/Abstract] OR brain tumour[Title/Abstract] OR brain tumours[Title/Abstract] OR malignancy[Title/Abstract] OR malignancies[Title/Abstract] OR brain tumor[Title/Abstract] OR brain tumors[Title/Abstract] OR malignant tumor[Title/Abstract] OR malignant[Title/Abstract] OR tumor[Title/Abstract] OR tumour[Title/Abstract] OR tumors[Title/Abstract] OR tumours[Title/Abstract] OR carcinogenic[Title/Abstract] OR carcinogenesis[Title/Abstract] OR cancers[Title/Abstract] OR "Neoplasms"[Mesh])</p> <p>AND animal search filter [2]</p>	337
Embase	<p>(GSM OR cell phone OR mobile phone OR mobile phones OR cellular phone OR cellular phones OR cellular telephone OR cellular telephones OR Radio Wave OR radio frequency OR radio frequencies OR radio-wave OR radio-frequency OR radio-frequencies OR radio-waves OR global system mobile OR radio waves OR radio wave).ti,ab. OR exp mobile phone/ OR exp radiofrequency radiation/</p> <p>AND</p> <p>(neoplasm OR neoplasms OR neoplasia OR cancer OR brain tumour OR brain tumours OR malignancy OR malignancies OR brain tumor OR brain tumors OR malignant tumor OR malignant OR tumor OR tumour OR tumors OR tumours OR carcinogenic OR carcinogenesis OR cancers).ti,ab. OR exp neoplasm/</p> <p>AND animal search filter [3]</p>	265

Although the IARC made an analysis of the available literature and several systematic reviews have been published, no meta-analysis on this topic has been conducted yet. Most of the trials conducted regarding mobile phone radiation are animal studies. This can be easily explained while in these type of studies we are able to control the environment, expose the population to a preferred amount of radiation and keep possible confounders to a minimum. Therefore, in this report we provide an independent overview of the evidence concerning mobile phone radiation as a possible cause of the development of tumours based on animal experimental data and combined it in several meta-analyses.

Methods

Search strategy and study selection

Many synonyms for the determinant "cell phone radiation" and the outcome measure "tumour incidence" were used to conduct our search strategy. The animal filter of SYRCLE (the SYstematic Review Center for Laboratory animal Experimentation) was used for the research population to include all types of animals. Since the interest in the mobile phone radiation topic has only arisen recently, we chose to search for studies published in the last ten years (2003- February 2013). Title and abstracts

were screened based on the following exclusion criteria: systematic reviews, studies in humans, *in-vitro* studies, studies using radiofrequency as a therapy, studies without abstract or full-text version, studies not written in English or Dutch and studies with another primary outcome measure than tumours. The remaining studies were screened on full-text. If eligible for our research question, a critical appraisal based on the Cochrane Risk of bias tool was performed. Both screening and appraising of the studies were done independently by two researchers and compared afterwards. A discussion was started until consensus was reached, when differences between the two researchers in screening or appraising were encountered.

Critical appraisal

The articles were scored on their validity by scoring different domains using the Cochrane risk of bias tool [4]. For each type of bias we assessed if the authors did or did not take any measurements to reduce the risk of bias, or did not report measurements taken to reduce the risk of bias. The risk of selection bias was assessed by scoring the type of sequence generation and allocation concealment. The subgroup "baseline characteristics" was supplemented to the original Cochrane tool to assess the risk of selection bias in studies that were lacking a clear explanation of the

used techniques for sequence generation and allocation concealment. In these cases, the population characteristics of the different groups were checked on comparability at baseline.

The risk of performance bias was assessed depending on blinding of the researcher and/or caregiver. The risk of detection bias was assessed by identifying which measures were used to blind outcome assessors from knowing of which animal received which intervention. Attrition bias was assessed by reviewing if the outcome data was complete.

Outcome measures

The primary outcome was whole body tumour incidence in the animals exposed to cell phone radiation compared to sham radiation, last-mentioned meaning that the animals have been placed in the radiation apparatus without being exposed to actual radiation. The amount of received radiation or absorbed energy per time unit was expressed in specific absorption ratio (SAR) in Watt per kilogram. We also chose to report brain tumours separately, since the IARC reported that electromagnetic radiation could be a possible risk factor for these specific types of tumours. Also breast tumours and lymphomas were frequently reported tumours after radiation in literature and were therefore separately reported besides the whole body tumour incidence. For all these tumour incidences, separate meta-analyses were performed.

The SAR in the studies differed. Therefore, we pooled the amount of exposure into three groups, ≤ 1.0 W/kg defined as low, 1.1-2.9 W/kg as medium and ≥ 3 W/kg as high exposure. To see whether the amount of exposure could increase the risk of developing tumours, we compared the incidence of whole body tumours and brain tumours of each different SAR groups to sham radiation.

Statistical analysis

Using ReviewManager 5.0, we performed the meta-analyses computing a Mantzel Haenszel odds ratio for the tumour risk in each exposure group. We also calculated I^2 of Higgins et al., to assess whether the data used for the meta-analyses were heterogeneous, with cut-off points $<25\%$ as low heterogeneity, 25-50% medium heterogeneity, $>50\%$ high heterogeneity [5].

Results

Studies

The search strategy resulted in 337 articles on Pubmed and 265 articles in Embase (Figure 1). After removal of the duplicates, 456 articles remained. Screening on title and abstract resulted in 20 studies eligible for full text screening. Five studies were excluded after full text screening, because one appeared to be a review and four articles did not have the right outcome measures for the meta-analysis. Critical appraisal of the 15 remaining studies showed a lack in the reporting of used measures to decrease the risk of bias (Figure 2a, 2b) [6-20]. Saran et al. and Sommer et al. did not even report one of the domains used in the critical appraisal tool [13,17]. Furthermore, Tillman et al. did not take any measurements to randomise the outcome assessment, resulting in a high risk of bias regarding the outcome measurements [18].

An overview of the baseline characteristics of the research population and the radiation exposure method of each study can be found in the appendix. Ten studies used rats [6-10,14-16,19,20], the other five used mice [11-13,17,18]. Five studies used only female animals [6,8,9,17,19] and the remaining ten studies used both males and females [7,10-16,18,20]. Six studies exposed only the head to radiation [7,10,12,14,15,20] and the other nine studies exposed the whole body [6,8,9,11,13,16-19].

Whole body tumour incidence

Three studies reported whole body tumour incidence as an outcome measure [12,16,18]. None of the studies showed a statistically significant increase in tumour incidence after radiation.

All the data combined resulted in an OR of 1.01; 95% CI [0.86-1.20] for whole body tumour incidence in exposed groups compared to the control groups (Figure 3), with an I^2 of 32%.

When pooled in the different SAR groups, the combined OR, compared to sham radiation, for low exposure was 1.04; 95% CI [0.71-1.53], for medium exposure the OR was 1.11; 95% CI [0.73-1.70] and for high exposure the OR was 0.94; 95% CI [0.69-1.29].

Table 2: Risk of bias per item for each article. Each study was scored on (the reporting of) measurements taken for various items that could lead to a risk of bias.

	Sequence generation	Allocation concealment	Blinding researcher	Blinding care- giver	Blinding outcome	Randomisation outcome assessment	Incomplete outcome data	
Anane [6]	○	○	○	○	○	○	○	○: Yes (low risk of bias) ○: Unclear risk of bias ○: No (high risk of bias)
Anderson [7]	○	○	○	○	○	○	○	
Heikkinen [8]	○	○	○	○	○	○	○	
Hruby [9]	○	○	○	○	○	○	○	
La Regina [10]	○	○	○	○	○	○	○	
Lee [11]	○	○	○	○	○	○	○	
Oberto [12]	○	○	○	○	○	○	○	
Saran [13]	○	○	○	○	○	○	○	
Shirai2005 [14]	○	○	○	○	○	○	○	
Shirai2007 [15]	○	○	○	○	○	○	○	
Smith [16]	○	○	○	○	○	○	○	
Sommer [17]	○	○	○	○	○	○	○	
Tillmann [18]	○	○	○	○	○	○	○	
Yu [19]	○	○	○	○	○	○	○	
Zook [20]	○	○	○	○	○	○	○	

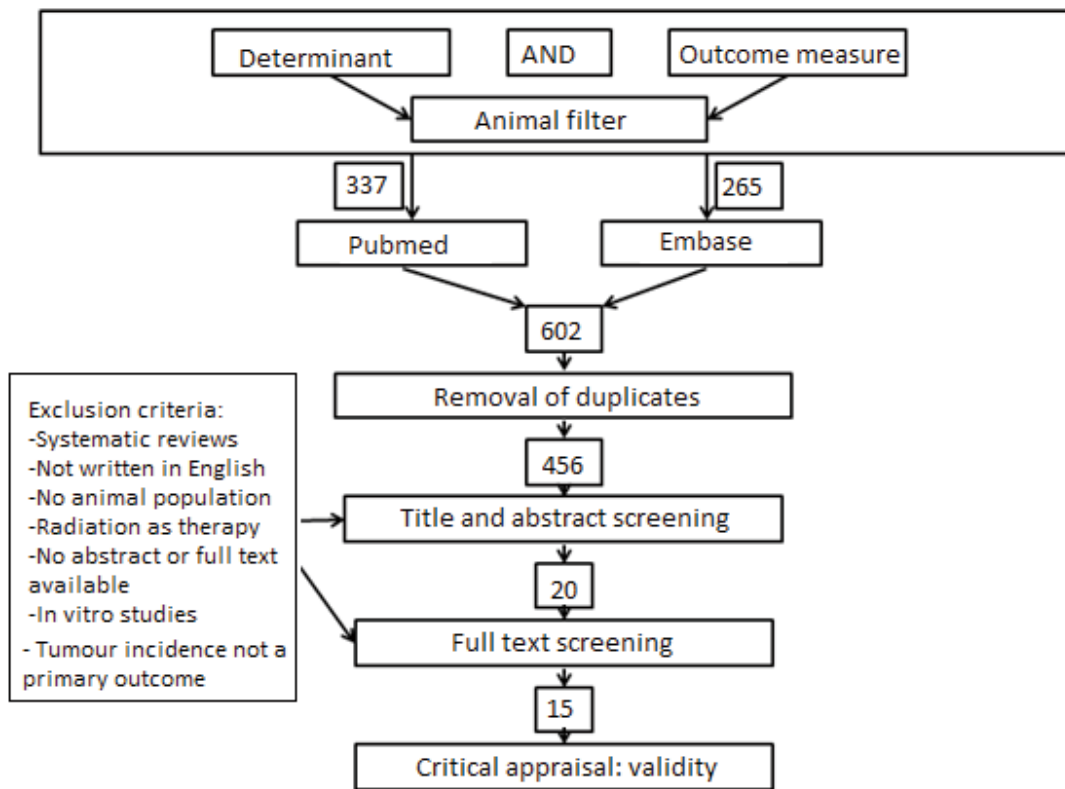


Figure 1: Flowchart of search strategy and critical appraisal. We found 602 studies using our search strategy, of which 146 were duplicates. The 456 remaining studies were screened on title and abstract resulting in 20 eligible studies. After full text screening 15 studies were included in the meta-analyses.

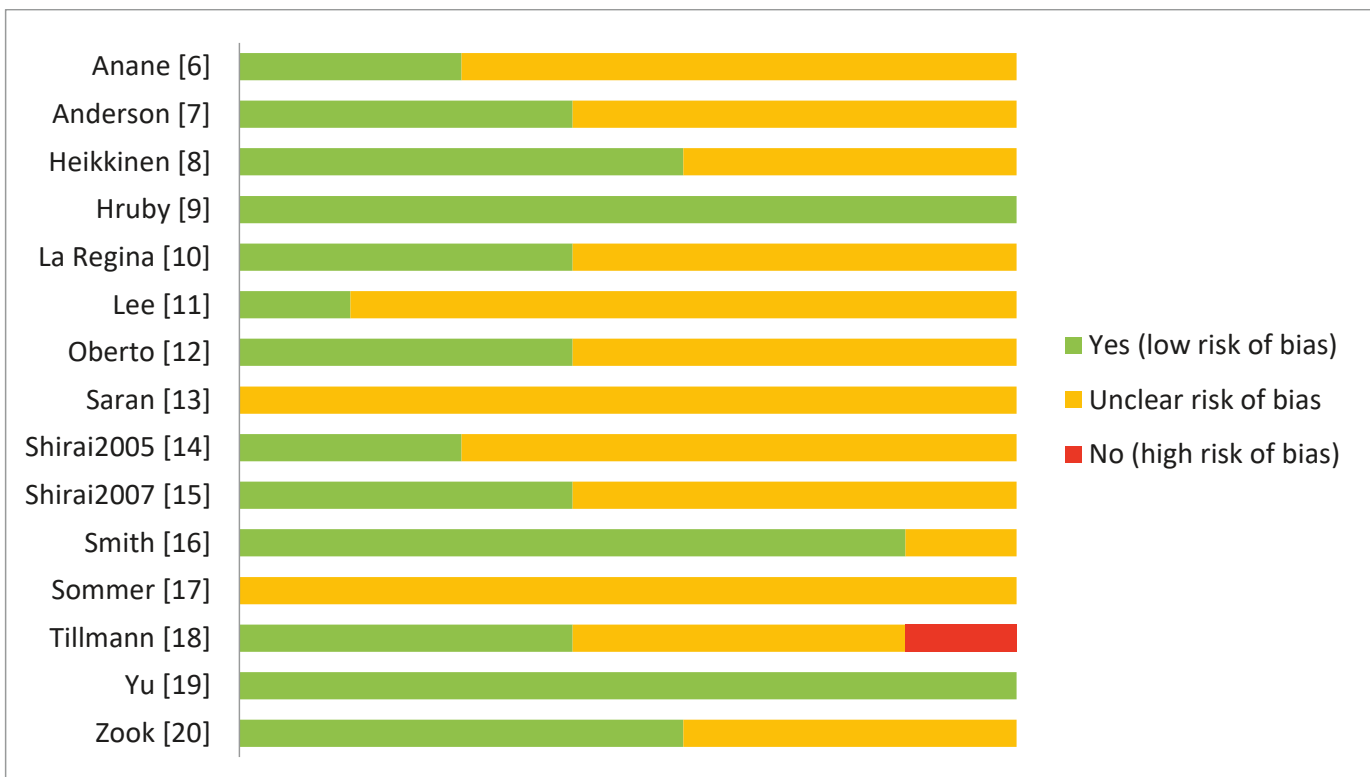


Figure 2a: Risk of bias per article. An overview of the risk of bias for each study.

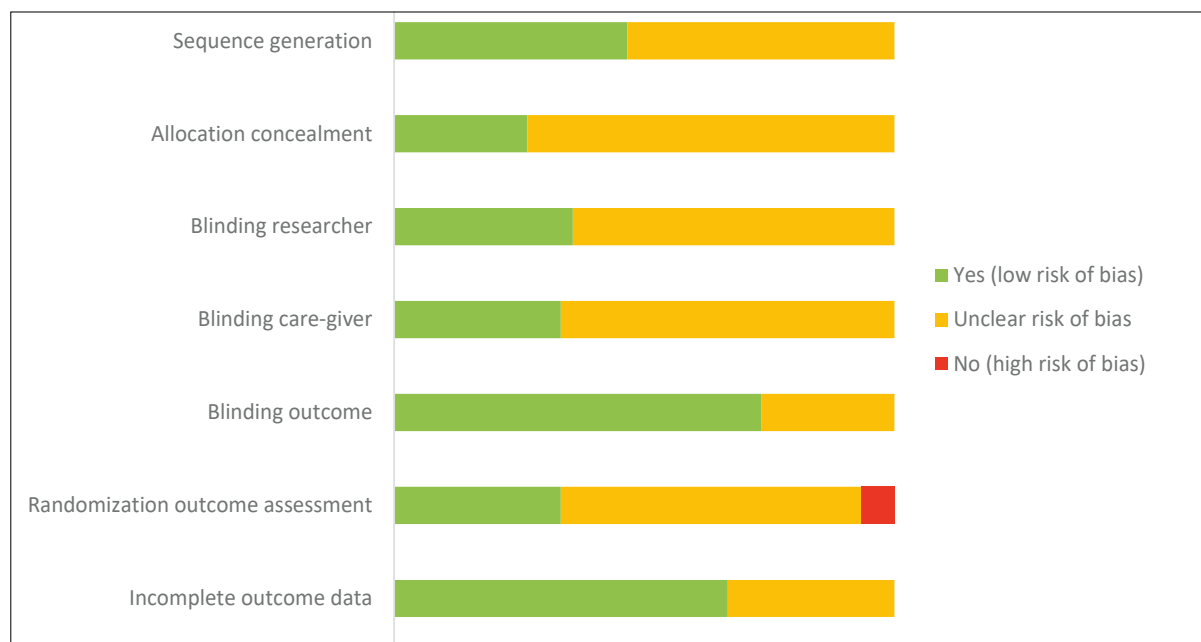


Figure 2b: Risk of bias per item. An overview of how often measurements were taken for the different items that could lead to risk of bias.

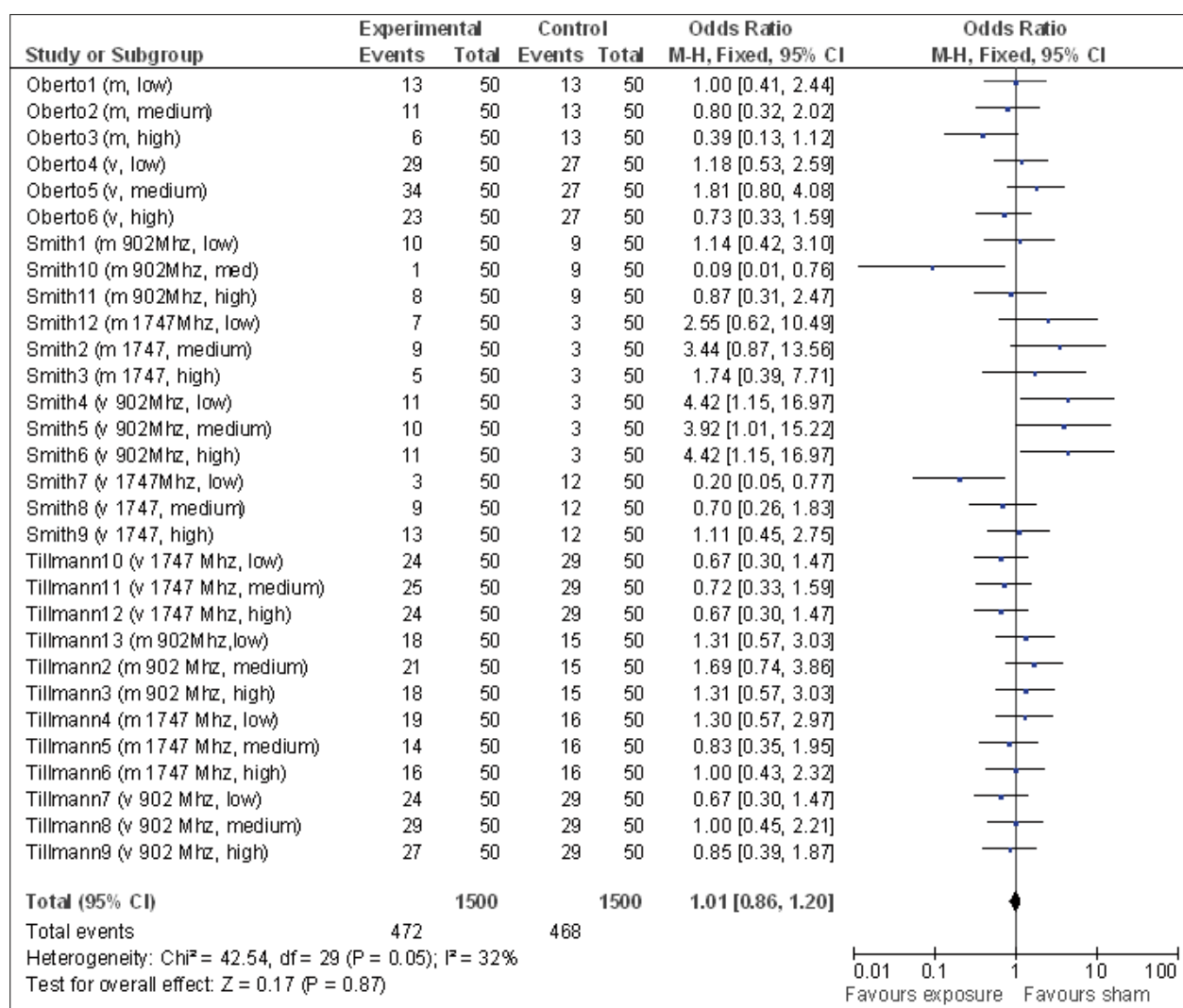


Figure 3: Meta-analysis of whole body tumour incidence. A forest plot including all studies found that researched whole body tumour incidence [12,16,18]. We separated each study population in female (v) and male (m). Furthermore, we separated the populations according to the amount of exposure they received: low was defined as ≤ 1.0 W/kg, medium as 1.1-2.9 W/kg and high as ≥ 3 W/kg. Where possible we reported the frequency (in Megahertz) used.

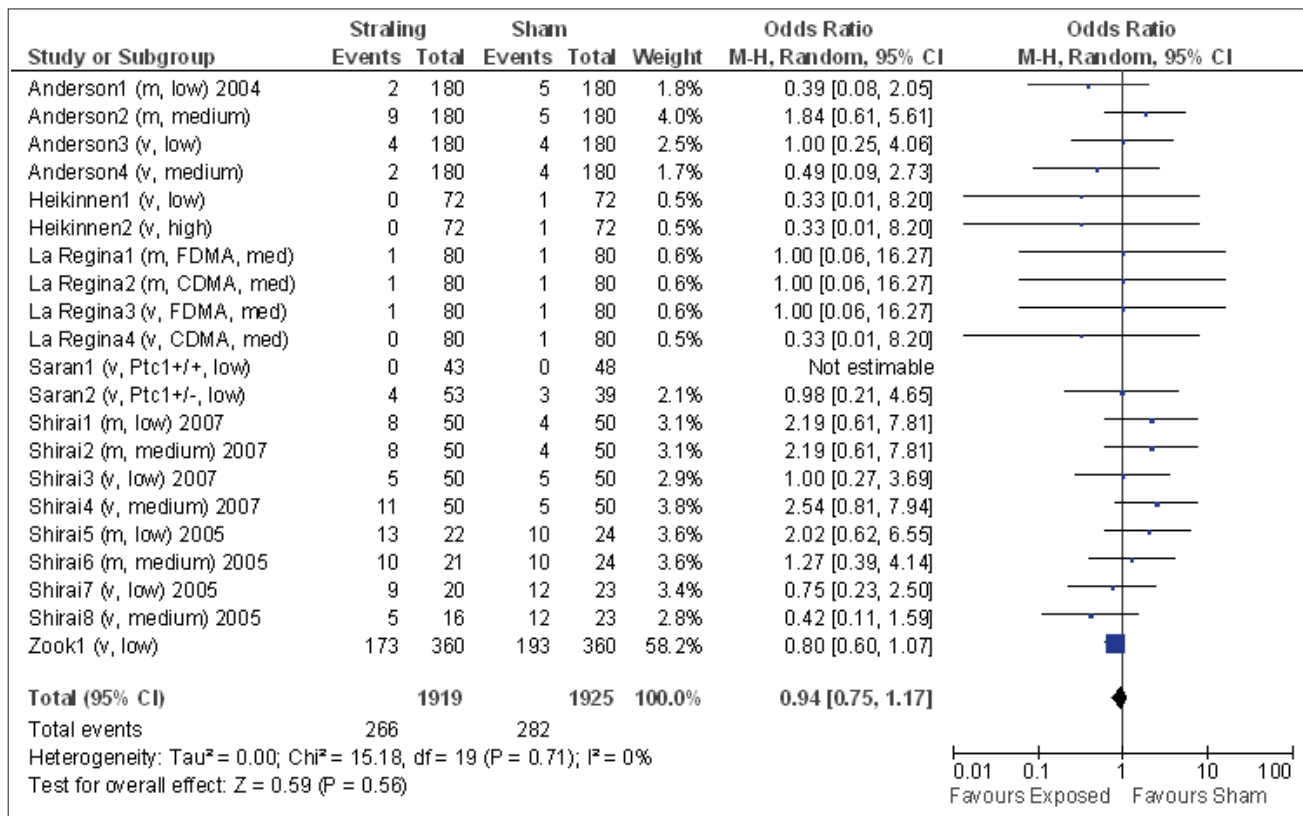


Figure 4: Meta-analysis of brain tumour incidence. A forest plot including all studies found that researched brain tumour incidence [7,8,10,13,14,15,20]. We separated each study population in female (v) and male (m). Furthermore, we separated the populations according to the amount of exposure they received: low was defined as ≤ 1.0 W/kg, medium as 1.1-2.9 W/kg and high as ≥ 3 W/kg. Where possible we reported the type of model used in the study (FDMA, CDMA, Ptc1+/-, Ptc1+/-).

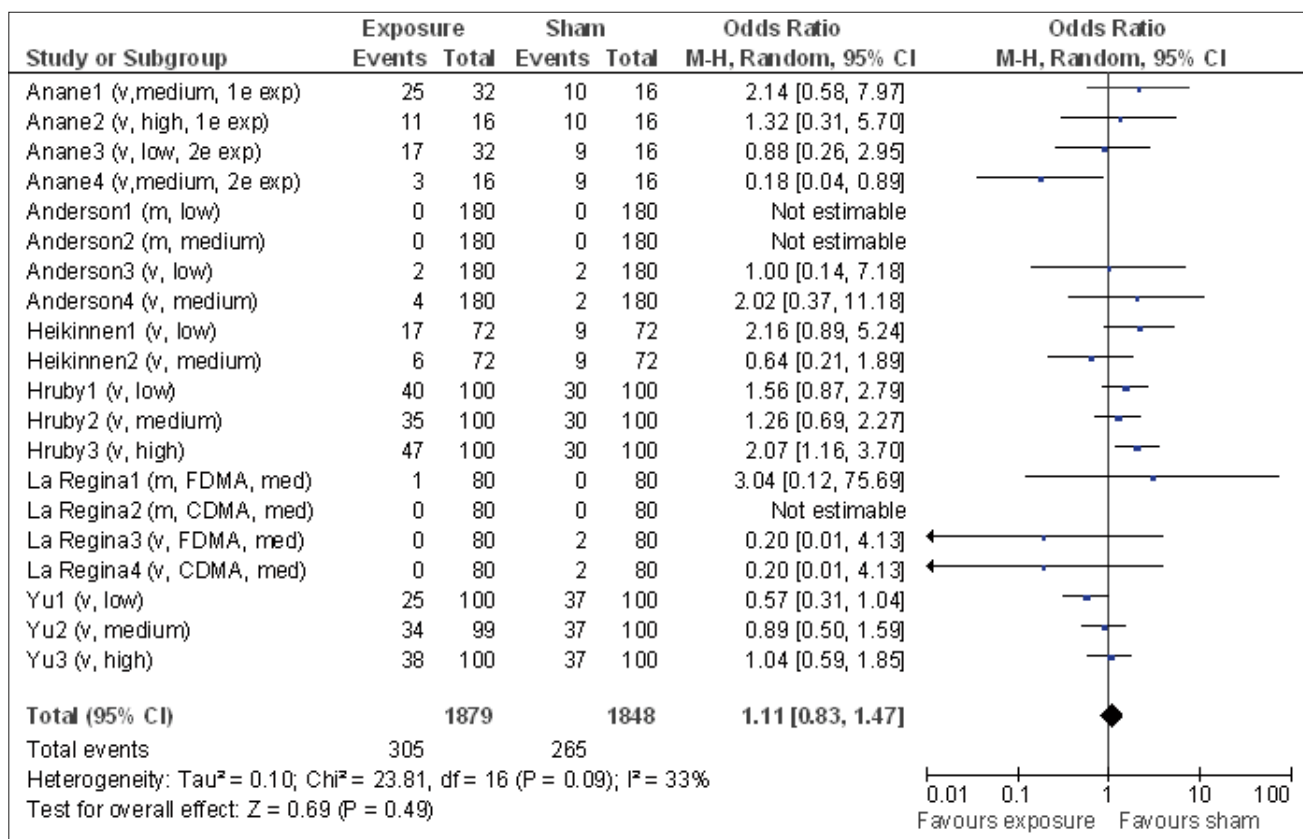


Figure 5: Meta-analysis of breast tumour incidence. A forest plot including all studies found that researched breast tumour incidence [6-10,19]. We separated each study population in female (v) and male (m). Furthermore, we separated the populations according to the amount of exposure they received: low was defined as ≤ 1.0 W/kg, medium as 1.1-2.9 W/kg and high as ≥ 3 W/kg. Where possible we reported the type of model used in the study (FDMA, CDMA).

Brain tumour

Six studies reported brain tumours as an outcome measure [7,8,10,13-15,20]. None of the studies showed a statistically significant increase in brain tumour incidence after radiation. The largest of these studies (Zook et al.) reported that 193 of the 360 exposed rats developed at least one brain tumour compared to 173 of the 360 rats in the sham group (OR 0.80; 95% CI [0.60-1.07]) [20].

All the data combined resulted in an OR of 0.94; 95% CI [0.75-1.17] for the incidence of brain tumours in exposed groups versus control groups (Figure 4), with an I^2 of 0%.

When pooled in the different SAR groups, the combined OR, compared to sham radiation, for low exposure was 0.87; 95% CI [0.67-1.11], for medium exposure the OR was 1.27; 95% CI [0.78-2.06] and for high exposure the OR was 0.33; 95% CI [0.01-8.20].

Breast tumour

Six studies reported breast tumours as an outcome measure [6-10,19]. Hruby et al. found a statistically significant increase in the incidence of breast tumours in the high exposure group (OR 2.07; 95% CI [1.16-3.70]) [9]. They conducted a big trial with 400 rats and found a statistically significant increase in the amount of tumours in other organs after exposure to radiation. However, they discussed that, based on literature, their results might be accidental since the used rat model leads to a great variety in results.

Anane et al. performed two almost identical trials [6]. The first trial showed a higher incidence of breast tumours in the medium exposure group. However, when performed for the second time, this result could not be replicated. Due to the inconsistency of the results they concluded that no valid evidence on the possible co-promoting effect of mobile phone radiation on breast tumour incidence in rats could be deduced from these results alone. The other studies did not find a statistically significant increase in breast tumour incidence after exposure to radiation.

All the data combined resulted in an OR of 1.11; 95% CI [0.83-1.47] for the incidence of breast tumours in exposed groups versus control groups (Figure 5), with an I^2 of 33%.

Lymphomas

Three studies reported lymphoma incidences as an outcome measure [8,11,17]. None of the studies reported a statistically significant increase in lymphoma incidence after exposure to radiation. All the data combined resulted in an OR of 0.77, 95% CI [0.46-1.29] for the incidence of lymphomas in exposed groups versus control groups (Figure 6), with an I^2 of 0%.

Discussion

This is the first meta-analysis on the existing data of the effect of mobile phone radiation on tumour incidence in rats and mice. Although some studies did find a statistically significant increase in tumour development after exposure to radiation, when combined with other data in several meta-analyses, no statistically significant increase was found for any of the tumour types. Furthermore, the amount of exposure to radiation did not statistically significant influence the development of tumours.

We consider our data to be of high validity, because of the clear and systematic method used. The inclusion of the relevant articles was done independently by two researchers to decrease the risk of excluding any relevant article. As with the inclusion, the appraisal of the relevant studies was done independently by two researchers, reducing the risk of observer bias. Lastly, all our included studies used mice or rats, which makes the data more comparable than it would be when different types of animal were used. This is also confirmed by the low to slightly medium percentages of I^2 .

However, for a more valid extrapolation of the results to humans, studies on bigger animals exposed to mobile phone radiation are needed. We expect that bigger animals would resemble us humans more in the body content exposed to radiation while the content in relation to the surface area is more comparable. Furthermore, the methods used in the studies were not always comparable. Firstly, there was a variety of mouse and rat models used. Some studies used genetically modified animals while others used chemical substances to induce tumour growth. Therefore it can be discussed whether the data of these studies can be combined in one meta-analysis. Secondly, the studies used different amounts of SAR. It is imaginable that a higher amount radiation dose will lead to more

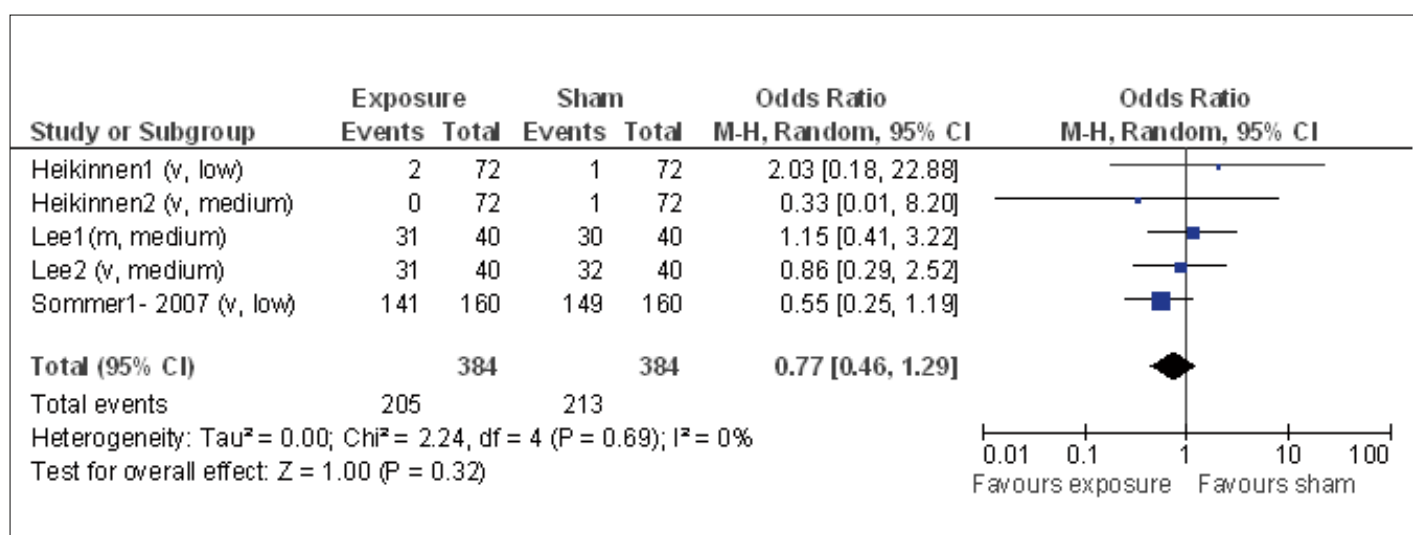


Figure 6: Meta-analysis of lymphoma incidence. A forest plot including all studies found that researched lymphoma incidence [8,11,17]. We separated each study population in female (v) and male (m). Furthermore, we separated the populations according to the amount of exposure they received: low was defined as ≤ 1.0 W/kg, medium as 1.1-2.9 W/kg and high as ≥ 3 W/kg.

DNA damage and therefore more tumour growth. However, we aimed to correct for this by pooling the different SAR amounts in three levels (low, medium, high). Thirdly, the duration of exposure differed between the studies, varying from 45 minutes to 24 hours per day. A longer exposure to radiation will possibly lead to more tumour growth. By combining the data of these studies with different exposure lengths, the effect of radiation may be underestimated.

In September 2014, the CEF released a systematic analysis regarding mobile phones and cancer based on animal studies [21]. They concluded that it is highly unlikely that exposure to electromagnetic radiation may have initiating or promoting effects on the development of cancer.

Unfortunately, we cannot report anything on the long-term effect of exposure to mobile phone radiation, since rats and mice have a short lifespan. Studies on long-term effect should therefore use animals with a longer lifespan. Furthermore, it is difficult to extrapolate data from studies with small animals, like rats and mice, to humans. Controlled clinical trials in primates would be helpful, since primates have more resembles with humans and have a longer life-span than rats and mice. Moreover, more data on the consequences of mobile phone radiation for humans is needed. However, clinical trials in humans are very hard to conduct, but epidemiological data could support the consequences for humans.

Conclusion

Based on the evidence found by the extended literature search, we conclude that mobile phone radiation is not a risk factor for the development of tumour growth in rats and mice, regardless of the amount of exposure. Further research should be performed to investigate whether this also holds true for humans.

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