

## Section 9

# Epidemiological Studies on the Risk of Head and Neck Tumours and Cancers Associated with the Use of Mobile Phones

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## Summary

- In the general population, tumours of the head and neck (including brain tumours) are relatively rare. Because of their rarity, in order to demonstrate the possible effects of mobile phone exposure on the occurrence of these tumours, cases must be identified from large populations and over many years. Because many of the studies have involved international collaboration, common classification of tumours and common assessment of mobile phone use is a challenge. Comparing results between studies is also challenging.
- Considerations in assessing epidemiological studies of cancer in humans related to exposure to mobile phones include the age group studied, the type of cell phone to which they were exposed, the intensity and duration of exposure and the location of cancer with respect to where the mobile phones were typically held.
- We identified 10 reviews of epidemiological studies published between 2007–2012 relating head and neck tumours to mobile phone exposure.
- No published reviews assessing the relationship of mobile phone exposure to tumours other than to tumours of the head and neck were identified and there were no reviews of tumours associated with exposure to radiofrequency (RF), other than that from mobile phones.
- The most consistent result from the reviews and original studies was of no relationship between long term use of mobile phones and meningiomas (tumours in tissue surrounding the brain and spinal cord) or of parotid tumours (salivary gland tumours).
- Most of the original studies cited in the reviews did not find an increased risk of head and neck tumours associated with long-term use of digital phones. The exceptions were principally from one academic research group that demonstrated increased risks of head tumours related to use of the older analog mobile phones, cordless phones, as well as digital phones.
- Many of the meta-analyses (combining study results) and a few of the original studies found increased risks of specific head tumours with longer term use of mobile phones (typically, at least 10 years since first use of mobile phones), along with recall of using mobile phones preferentially at the same side of the head as the tumour. The tumours implicated were gliomas (originating from glial cells which surround neurons and can be malignant) and acoustic neuromas (benign (non-cancerous) cranial nerve tumours).
- An extensive review of scientific studies by the IARC Working Group in May 2011 concluded that exposure to RF from wireless phones was “possibly carcinogenic to humans” (Group 2B).

- Evidence that there may be a higher risk of head tumours from long term use of mobile phones and concerns about the vulnerability of children has led to calls for further research.

## 9.1 Introduction

Can the widespread use of devices which emit radiofrequency fields (RF) cause cancer? Brain cancer is of particular concern since hand-held mobile phones and cordless phones are used in close proximity to the head, resulting in the highest near field exposure to the brain of all sources of RF. The only known environmental risk factor for malignant brain tumours (gliomas) is ionizing radiation<sup>1</sup>, emitted from such sources as medical x-rays, which have the ability to penetrate cells and deliver high levels of energy to intra-cellular structures and damage DNA. Although RF is non-ionizing, there is concern that tumours may arise through biological mechanisms that do not directly damage DNA.

The carcinogenicity of RF was assessed in detail by a working group of 30 scientists from 14 countries at the International Agency for Research on Cancer (IARC) in May 2011. Their finding of limited evidence of an association of RF and head tumours in humans was based on positive associations found in some of the studies linking glioma and acoustic neuroma to RF exposure from mobile phones. As well, they cited limited evidence of malignancy in animals and weak evidence for endpoints relating to the mechanisms of carcinogenesis, such as genotoxicity and gene and protein expression, cell signalling and oxidative stress.<sup>2</sup> Overall, the IARC classification of RF was supported by the majority of the panel of scientists as Group 2B “possibly carcinogenic to humans.”<sup>3</sup> An IARC monograph “Non-ionizing radiation, Part 2: Radiofrequency electromagnetic fields” (Volume 102; 421 pages) was recently released following completion of the toolkit.<sup>4</sup>

Prior to the May 2011 meeting, reports from the World Health Organization and the US National Cancer Institute had concluded that there was no conclusive or consistent evidence that RF emitted by mobile phones is associated with cancer risk.<sup>5,6</sup> According to the 2011 publication of the standing committee of the International Commission on Non-Ionizing Radiation Protection (ICNRP): “Although there remains much uncertainty, the trend in the accumulating evidence is increasingly against the hypothesis that mobile phone use can cause brain tumours in adults.”<sup>7</sup>

What is the scientific evidence that supports (or refutes) that an association exists between exposure to RF and an elevated risk of cancer?

## 9.2 Purpose

The objective of this section is to assess the findings of recent reviews of the epidemiologic literature concerning the risk of brain tumours and cancers in relation to long term use of mobile phones.

### 9.3 Methods

A database search of epidemiological literature pertaining to cancer outcomes from exposure to RF was conducted for the five-year period 2007 to January 2012 using Ovid Medline, EBSCO and Google scholar. Search terms and keywords for “RF” or “radiofrequency radiation” or “mobile phones” or “cell phones” were combined with terms for “cancer” or “malignancy” or “tumours.” Upon review of titles and abstracts, all systematic and narrative reviews for which the focus was the relationship of RF exposure with brain tumours or any type of cancer were included. Further hand searching for relevant reviews was done from bibliographies of the reviews obtained. Narrative reviews for which cancer outcomes were described in brief as one of many effects of exposure to RF were not included. Excluded were reviews or outcomes where types of brain tumours were not specified, but instead were grouped together. Reviews on animal studies and other biological effects also were excluded, as they are the subject of Section 6 on cellular and animal studies of RF. Relevant critiques of the scientific literature and specific epidemiological studies were included for illustrative purposes.

Meta-analysis is a statistical technique used to combine the results of selected original studies to obtain a summary statistic, typically a summary odds ratio (OR). The OR represents the odds that an outcome will occur given the exposure (RF), compared to the odds of the outcome occurring in the absence of that exposure. A statistically significant association is reflected in an odd ratio where the 95% confidence interval (CI) does not overlap with OR=1. Ideally, systematic reviews are preferred to narrative reviews by providing clear descriptions of the literature search process and criteria for selecting articles that could then be duplicated by others. Not all systematic reviews apply meta-analysis, particularly when studies differ substantially in research design. Conversely, the publication may provide results of a meta-analysis, but detailed information on the review process literature search and selection criteria is not given.

A tumour is an abnormal mass of tissue that may be benign (non-cancerous) or malignant (cancerous). In the general population, tumours of the head and neck (including brain tumours) are relatively rare. There are approximately 100 specific intracranial tumours including more than 50 neuroepithelial tumours, almost 40 meningeal tumours and more than 10 peripheral nerve tumours.<sup>8</sup> The head and neck tumours described in the reviews included: 1) gliomas, 2) meningiomas, 3) acoustic neuroma and 4) parotid (salivary) gland tumours.

- 1) Glioma is a broad category of neuroepithelial brain and spinal cord tumours that arise from glial cells that surround neurons. They comprise approximately 60% of all nervous system tumours. Approximately 77% of malignant brain tumours are gliomas. Subtypes of glioma, include astrocytoma, oligodendroglioma, ependymoma and glioblastoma multiforme (having the worst prognosis).<sup>9</sup>

Gliomas are classified as low grade (I or II) or high grade (III or IV), the latter being malignant.

- 2) Meningiomas are neoplasms arising from the meningeal tissue covering the brain and spinal cord. As they grow, meningiomas compress adjacent brain or spinal cord tissue. Most (over 97%) are benign tumours that are encapsulated.
- 3) Acoustic neuroma, also termed Vestibular Schwannoma, is a slow-growing benign intracranial primary tumour that arises from the Schwann cells which enfold the vestibulocochlear nerve (eighth cranial nerve leading from the brainstem to the inner ear).
- 4) Parotid cancer is a malignant neoplasm of the parotid gland (a type of salivary gland). Most parotid tumours (80%) are benign. The incidence of this rare cancer is increasing, but risk factors are unknown.<sup>10</sup>

Other cancers, including testicular cancer, leukemia, uveal melanoma, non-Hodgkin's lymphoma and pituitary adenoma have also been suggested as possibly having a relationship to exposure to RF.

## 9.4 Results

In order to demonstrate the possible effects of mobile phone exposure on the occurrence of head and neck cancers, cases must be identified from large populations and over many years. Because many of the studies require international collaboration, common classification of tumours and common assessment of mobile phone use is a challenge. Comparing results between studies is also challenging.

Considerations in assessing epidemiological studies of cancer in humans related to exposure to mobile phones include the age group studied, the type of cell phone to which they were exposed, the intensity and duration of exposure and the location of cancer with respect to where the mobile phones were typically held.

Tumours become evident years after the exposures which may initiate and promote them. It would be expected, therefore, that any increase in brain cancer attributed to exposure from mobile phones would occur after many years since their first use. Early studies on brain cancer risk from mobile phones compared cancer in “never” vs “ever” users. Doing so disregards cumulative exposure, based on duration and intensity of use. The primary focus of this section is long term use of mobile phones, which allows for a more appropriate assessment of period of time since first use.

### 9.4.1 Characteristics of reviews

In the five years since 2007, there have been 16 scientific review publications which evaluated the relationship between long term exposure to mobile phone RF and head and neck tumours (Table 1). No reviews of the literature were found for which the

focus was the relationship of RF to any cancer, other than brain cancer. The RF exposures of interest were from wireless phones, almost exclusively from mobile phones. Note that many of the reviews include some common original studies, and therefore the summary odds ratios are not necessarily independent.

Reviews were excluded where the outcome information was insufficient for the following reasons: a) the type of tumour could not be distinguished, for example “all brain tumours” doesn’t distinguish differential RF effects on specific tumours;<sup>11,12</sup> b) there was no individual study odds ratios presented for a narrative<sup>13</sup> or c) a limited pooled analysis included only the one author’s studies.<sup>14</sup> The studies chosen for review and meta-analysis by Khurana and colleagues in 2009<sup>15</sup> were exact duplicates of those presented by Hardell et al. (2009)<sup>16</sup> and therefore were not repeated in the tables by tumour type. Kan et al. (2008)<sup>11</sup> did present summary odds ratios for individual brain tumours for regular use of mobile phones vs. no use, but for the analysis of 10+ years of use all brain tumours were combined.

Table 1 below describes the characteristics of the 16 reviews and the rationale for excluding five of the reviews.

Table 1. Characteristics of reviews of studies assessing the association of use of mobile phones with head and neck tumours (N=narrative review; M=meta-analysis; S=systematic review)

Reference	Type of Review	Time Frame	# Studies Selected/ Searched	Inclusion Criteria	Outcomes	Comments
Corle et al. (2012) <sup>17</sup>	N	2005–2010	15 / NA	NA	Gliomas	Compared Hardell & Interphone studies
Hardell et al. (2011) <sup>14</sup>	M	2002–2010	4 / 4	Hardell studies only	Malignant brain tumours	EXCLUDED – Pooled own case-control studies only
Levis et al. (2011) <sup>18</sup>	SM	2000–2010	30 / NA	Mobile phone use $\geq$ 10-yrs & laterality analysis	Glioma, head tumours	Also others' results on analog, digital and cordless phones
Ostrom et al. (2011) <sup>19</sup>	N	2000–2010	13 / NA	NA	Glioma, head tumours	Compared long-term and ever/never use & genome associations
Repacholi et al. (2012) <sup>20</sup>	SM	< Nov. 2010	8 / 96	All languages	Glioma, head & neck tumours	Applied quality criteria for narrative review
Alhbom et al. (2009) <sup>21</sup>	M	2000–2008	14 / NA	NA	Glioma, head & neck tumours	Evaluated methods
Hardell et al. (2009) <sup>16</sup>	M	2001–2008	12 / NA	Mobile phone use $\geq$ 10-yrs & laterality analysis	Glioma, head & neck tumours	
Khurana et al. (2009) <sup>15</sup>	SM	< Dec. 2008	10 / NA	Mobile phone use $\geq$ 10-yrs & laterality analysis	Glioma, head & neck tumours	NOT TABULATED as used same data as Hardell et al. (2009) review
Kundi (2009) <sup>22</sup>	N	1999–2008	25 / NA	NA	Head tumours	Included a meta-analysis of subset of studies
Morgan (2009) <sup>23</sup>	N	< Mar. 2009	5/ NA 11/ NA	NA	Gliomas, head & neck tumours	Presented early and later (interphone) studies & critique of methods
Han et al. (2009) <sup>24</sup>	S	2001–2008	12/NA	NA	Acoustic neuromas	

Reference	Type of Review	Time Frame	# Studies Selected/ Searched	Inclusion Criteria	Outcomes	Comments
Myung et al. (2009) <sup>12</sup>	SM	1968–2008	28/463	Case-control studies with risk estimates	Tumours	EXCLUDED – Not specific for type of tumour
Croft et al. (2008) <sup>13</sup>	N	< 2007	14 / NA	English only	Head tumours	EXCLUDED – Not specific for type of brain tumour
Hardell et al. (2008) <sup>25</sup>	M	2001–2007	21 / NA	Excluded mortality studies	Glioma, head tumours	Compared by laterality
Kan et al. (2008) <sup>11</sup>	SM	< April 2006	10 / 48	Exclude case reports, animal studies, non brain tumours	Head tumours	EXCLUDED – Not specific for type of brain tumour for long term analysis
Hardell et al. (2007) <sup>26</sup>	N	2001–2006	28 / NA	Excluded mortality studies	Gliomas, head tumours	Also studied effects of cordless phones

As shown in Table 1, six of the reviews had a systematic review format, incorporating details of the search process, and the majority of reviews conducted a meta-analysis without providing the search criteria. Only three of the reviews provided information on the number of studies searched. The time frame for the search strategy was not mentioned in eight of the reviews; in these cases it was assumed to be the range of years of the tabulated studies. Most of the reviewed studies were initially published in 2000 or 2001. The end date of reviewed studies was usually one year prior to publication.

Except for the review by Hardell et al. (2007)<sup>26</sup> which also evaluated brain tumour effects from use of cordless phones, all of the reviews were of studies of mobile phones. For the most part, the term “mobile phones” was used in all reviews to indicate digital phones (commencing with 2<sup>nd</sup> generation mobile phones). Some of the individual studies specifically conducted analyses on use of older analog phones which had much higher RF power output (phone technology is discussed in Section 5 on Exposure Assessment). The highest levels of exposure to RF from mobile phones are in the “near field,” approximately less than 5 cm from the head.

#### ***9.4.2 Review findings***

Some of the reviews, chosen for their analysis of effects of long-term use of mobile phones on head and neck tumours, also presented results for ever versus never use of mobile phones, which is useful for comparison purposes (Table 2). Note that the summary statistics are not independent for comparison between reviews, as they are each derived from many of the same individual studies.

None of the reviews which had also presented meta-analyses of “ever versus never” use of mobile phones showed elevated summary ORs for the head tumours glioma, meningioma or acoustic neuroma attributable to ever having used mobile phones. Most summary odds ratios were close to the no effect value of OR=1. For meningioma, the majority of combined odds ratios were lower than one, implying a protective effect of use of mobile phones. Only one review<sup>20</sup> included a meta-analysis on parotid gland tumours, with seven studies yielding a combined risk estimate for ever use (versus never use) of mobile phones of OR 0.87, with a 95% confidence interval of 0.73 to 1.04.

Table 2. Summary odds ratios and 95% confidence intervals for the relationship of head tumours with ever use versus never use of mobile phones

Reference	# Studies Glioma	Summary OR (95% CI)	# Studies Meningioma	Summary OR (95% CI)	# Studies Acoustic Neuroma	Summary OR (95% CI)
Repacholi et al. (2012) <sup>20</sup>	8	1.07 (0.89-1.29)	6	0.93 (0.77-1.12)	10	1.05 (0.77-1.42)
Alhbom et al. (2009) <sup>21</sup>	16	1.0 (0.8-1.2)	14	0.9 (0.8-1.0)	15	1.0 (0.8-1.4)
Hardell et al. (2009) <sup>16</sup>	11	1.0 (0.9-1.1)	9	0.9 (0.8-0.9)	9	1.0 (0.8-1.1)
Hardell et al. (2008) <sup>25</sup>	10	0.9 (0.8-1.1)	7	0.8 (0.7-0.99)	9	0.9 (0.7-1.1)
Kan et al. (2008) <sup>11</sup>	NA	0.86 (0.7-1.5)	NA	0.64 (0.56-0.74)	NA	0.96 (0.83-1.10)

Analysis of length of time since first use of mobile phones of at least 10 years is more appropriate than analysis of ever having used mobile phones, when considering the period of time needed for development of head and neck tumours, as well as cumulative exposure. Tables 3a to 3d present analyses of the association of potentially higher exposures to RF due to longer term use of mobile phones or longer latency (time since first use) and/or ipsilateral use on four major types of brain tumours studied. Ipsilateral refers to recall of use of mobile phones at the same side of the head as the tumour. The summary risk estimate (odds ratio for case-control studies) was tabulated where available; otherwise the number of positive studies was given, along with their citations. The comparison group for the calculation of the risk estimates were subjects with minimal or no wireless phone use. Note that the particulars of the significant studies, such as the type of wireless phone and laterality, may differ according to which type of study analysis was included in the review.

Gliomas were the most common brain tumour studied, shown in Table 3a.

Table 3a. Findings on the association of long-term use of mobile phones with *GLIOMAS* in the reviews assessed

Reference	Long-Term Use	#Studies	Summary Risk Estimate*	Significant Studies
Corle et al. (2012) <sup>17</sup>	≥ 10 yrs	6 6	Increased risk of high grade gliomas in 2 studies No effect on low grade gliomas	Hardell et al. (2006a, 2006b) <sup>27,28</sup> of astrocytoma, digital and analog
Levis et al. (2011) <sup>18</sup>	≥ 10 yrs & ipsilateral	4	1.56 (1.21–2.00)	Hardell et al. (2008) <sup>25</sup> pooled analysis Lahkola et al. (2007) <sup>29</sup>
Ostrom et al.(2011) <sup>19</sup>	>2- to ≥10-yrs use	13	Increased risk in 1 study	Hardell et al. (2006b) <sup>28</sup> analog & digital on high grade astrocytomas
Repacholi et al.(2012) <sup>20</sup>	≥10 yrs or cumulative	5	1.40 (0.84–2.31)	Hardell et al. (2006b, 2010) <sup>28,30</sup> analog
Ahlbom et al. (2009) <sup>21</sup>	≥6 yrs	12	1.1 (0.8–1.4)	Hardell et al. (2006a, 2006b) <sup>27,28</sup> (pooled)) analog & digital
Hardell et al.(2009) <sup>16</sup>	≥10 yrs & ipsilateral	6 4	1.3 (1.1–1.6) 1.9 (1.4–2.4)	Lahkola et al. (2007) <sup>29</sup> Hardell et al. (2006b) <sup>28</sup> (for all glioma & high grade glioma)
Kundi (2009) <sup>22</sup>	>4 yrs & ipsilateral	9 3	Increased risk in 3 of 9 studies 1.5 (1.2–1.8)	Hepworth et al. (2006) <sup>31</sup> Lahkola et al. (2007) <sup>29</sup> Hardell et al. (2006b) <sup>28</sup>
Hardell et al. (2008) <sup>25</sup>	≥10 yrs & ipsilateral	6 5	1.2 (0.8–1.9) 2.0 (1.2–3.4)	Hardell et al. (2006b) <sup>28</sup> (high grade and all gliomas) Lahkola et al. (2007) <sup>29</sup> (ipsilateral only)
Hardell et al. (2007) <sup>26</sup>	≥5 yrs & ipsilateral	8	Increased risk for 3 of 8 studies	Lahkola et al.(2007) <sup>29</sup> Auvinen et al. (2002) <sup>32</sup> Analog Hardell et al. (2006b) <sup>28</sup> also cordless

\*A brief description is given when no summary risk estimate has been computed.

The number of studies included in each review on glioma ranged from 4 to 13, with exclusions due to short latency of use (less than 10 years) and/or contralateral phone exposure. In the most recent review,<sup>17</sup> distinction was made between an increased risk associated with high grade (malignant) glioma (as found in studies of astrocytomas by the Hardell group) and no effect found for low grade glioma. Significantly elevated summary ORs for head tumours related to long term use of mobile phones were shown in the review by Hardell and colleagues,<sup>16</sup> confirmed for ipsilateral use in a later review.<sup>25</sup> Reviews by Kundi et al.<sup>22</sup> and Levi et al.<sup>18</sup> also found an elevated summary risk estimate for glioma for ipsilateral exposure of at least 10 years' duration.

Original studies by Hardell and colleagues stand out by repeatedly demonstrating increased risks of brain tumours from wireless phone use, whereas most of the other primary studies from the reviews were negative. An exception was the positive findings by Lahkola and colleagues for risk of glioma (2005, 2006, 2007),<sup>29,33,34</sup> published as part of the INTERPHONE groups of studies. Differences in the number and choice of studies included in each review can be attributed, in part, to the time period covered and exclusion criteria. Arbitrariness in the choice of included studies is another consideration; for example, some reviews excluded the positive findings from Lahkola's studies.<sup>29,33,34</sup>

Each of the nine reviews on meningioma (Table 2b) included between 2 and 11 individual studies. None of the summary odds ratios from the reviews on the association of long-term use of mobile phones with meningioma were significantly elevated; the lower confidence limit for the pooled OR of 1.7 for ipsilateral exposure from Hardell et al.'s (2008)<sup>25</sup> review just missed statistical significance at 0.99. All of the positive individual studies were from Hardell et al.'s group, for which the risk was increased with use of analog (and not digital) mobile phones but also for cordless phones with greater than 10 years of use.

Table 3b. Findings on the association of long-term use of mobile phones with *MENINGIOMAS* in the reviews assessed

Reference	Long-Term Use	#Studies	Summary Risk Estimate*	Significant Studies
Levis et al. (2011) <sup>18</sup>	≥ 10 yrs & ipsilateral	3	1.27 (0.89–1.82)	All NS
Ostrom et al. (2011) <sup>19</sup>	>2 to ≥10 yrs	11	Increased risk in 1 study	Hardell et al. (2006b) <sup>28</sup> analog only
Repacholi et al. (2012) <sup>20</sup>	≥ 10 yrs or cumulative	2	1.25 (0.51–3.10)	Hardell et al. (2005) <sup>35</sup> , analog Interphone study group(2010) – NS
Hardell et al. (2009) <sup>16</sup>	≥10-yrs use & ipsilateral	5 3	1.1 (0.8–1.4) 1.3 (0.9–1.8)	All studies NS
Kundi (2009) <sup>22</sup>	>5-yrs use & ipsilateral	9	Increased risk in 1 study	Hardell et al. (2005) <sup>35</sup> analog, ≥ 10-yrs use
Hardell et al. (2008) <sup>25</sup>	≥10-yrs use & ipsilateral	4 2	1.3 (0.9–1.8) 1.7 (0.99–3.1)	All studies NS All studies NS
Hardell et al. (2007) <sup>26</sup>	≥5-yrs use & ipsilateral	5	Increased risk in 1 study	Hardell et al. (2006b) <sup>28</sup> ≥ 10-yrs use of cordless phones (increased)

NS: Study risk estimates were not statistically significant (95% CI included “1”)

\*A brief description is given when no summary risk estimate has been computed.

The same nine reviews which evaluated meningioma also presented results (from 3 to 10 studies) on the risk of acoustic neuroma associated with long-term use of mobile phones (Table 2c). A consistent pattern was apparent in which the summary risk estimates for acoustic neuroma were elevated, particularly for ipsilateral exposure and longer duration of use. In addition to the original studies by Hardell and colleagues,<sup>28,25,34,39</sup> studies by Lonn et al. (2004)<sup>36</sup> of the INTERPHONE group, as well as Schoemaker et al. (2005),<sup>37</sup> supported findings of an increased risk of acoustic neuroma with ipsilateral exposure.

Table 3c. Findings on the association of long-term use of mobile phones with *ACOUSTIC NEUROMAS* in the reviews assessed

Reference	Exposure	#Studies	Summary Risk Estimate*	Significant Studies
Levis et al. (2011) <sup>18</sup>	≥10-yrs use & ipsilateral	3	1.73 (1.17–2.56)	Hardell et al. (2008) <sup>25</sup> Lonn et al.(2004) <sup>36</sup>
Ostrom et al. (2011) <sup>19</sup>	≥3- to ≥10-yrs use	9	Increased risk in 1 of 9 studies	Hardell et al. (2006b) <sup>28</sup> analog only
Repacholi et al. (2012) <sup>20</sup>	≥10-yrs use or cumulative	4	1.37 (0.74–2.52)	All NS
Hardell et al. (2009) <sup>16</sup>	≥10-yrs use & Ipsilateral	4 3	1.3 (0.97–1.9) 1.6 (1.1–2.4)	≥10 yrs and ipsilateral for Hardell et al. (2006b) <sup>28</sup> Lonn et al. (2004) <sup>36</sup> ipsilateral only
Kundi (2009) <sup>22</sup>	≥3-yrs use & Ipsilateral	6	Increased risk 3 of 6 studies	Lonn et al. (2004) <sup>36</sup> Hardell et al. (2005) <sup>35</sup> Schoemaker et al. (2005) <sup>37</sup>
Han et al. (2009) <sup>24</sup>	≥3-yrs use ipsilateral	12	Increased risk in 5 of 12 studies	Hardell et al. (2002,2005, 2008) <sup>35,38,25</sup> Lonn et al. (2004) <sup>36</sup> Schoemaker et al. (2005) <sup>37</sup>
Hardell et al. (2008) <sup>25</sup>	≥10-yrs use & ipsilateral	3	2.4 (1.1–5.3)	Hardell et al. (2006b) <sup>28</sup> Lonn et al. (2004) <sup>36</sup>
Hardell et al. (2007) <sup>26</sup>	≥3-yrs use & ipsilateral	7	Increased risk in 3 of 7 studies	Lonn et al. (2004) <sup>36</sup> Schoemaker et al. (2005) <sup>37</sup> Hardell et al. (2006b) <sup>28</sup>

NS: Study risk estimates were not statistically significant (95% CI included “1”)

\*A brief description is given when no summary risk estimate has been computed.

As shown in Table 3d, only two reviews presented data on the risk of parotid gland tumours from mobile phone use and both calculated a summary odds ratio of less than one (not statistically significant) for greater than 10 years of use. As was found for meningioma, Hardell et al.'s review (2009)<sup>16</sup> found an elevated but not statistically significant OR of 1.7 for ipsilateral use (the lower bound of the confidence interval was 0.96).

Table 3d. Findings on the association of long-term use of mobile phones with *PAROTID GLAND TUMOURS* in the reviews assessed

Reference	Exposure	# Studies	Summary Risk Estimate	Comments
Repacholi et al. (2012) <sup>20</sup>	≥10-yrs use or cumulative	5	0.83 (0.52-1.33)	All studies NS
Hardell et al. (2009) <sup>16</sup>	≥10-yrs use & ipsilateral	4 4	0.8 (0.5-1.4) 1.7 (0.96-2.9)	All studies NS

NS: Study risk estimates were not statistically significant (95% CI included "1")

There were no reviews which focussed on the relationship of RF to cancer outcomes, other than for brain tumours. The few narrative reviews which addressed this topic as part of a general review of health risks associated with exposure to RF did not present summary risk estimates on the few studies available.

#### 9.4.3 Comparison of two reviews

Specific findings on glioma from two more recent review studies (having opposite conclusions) are described in Table 4a and 4b below.

A) Repacholi MH, Lerchl A, Röösl M, Sienkiewicz Z, Auvinen A, Breckenkamp J, et al. *Systematic review of wireless phone use and brain cancer and other head tumours. Bioelectromagnetics. 2012; 33(3);187-206.*<sup>20</sup>

**Purpose:** To conduct a systematic review to determine whether there is an increase in incidence of head tumours associated with use of wireless phones.

**Methods:** Five of eight studies selected evaluated long-term use of mobile phones (>6 years) on the risk of glioma, as shown in Table 4a. Data on analog rather than digital phones from Hardell et al.'s earlier studies were presented.

**Results & Conclusion:** A non-significant summary OR of 1.40 was found, with the greatest weighting from the INTERPHONE study. No consistent relationship was found between glioma or the other three head tumours and wireless phone use. There are insufficient data to make any determinations of the effect of longer-term use (>10 years) by adults.

**Evaluation:** Many of the European co-authors of Repacholi et al.'s review<sup>20</sup> have been involved in INTERPHONE studies. Although results for phone use were divided into short- and long-term use, there were no tables on ipsilateral exposure results. The 2006 study by Schuz et al. was a retrospective cohort study. Including a cohort study with case-control studies in a meta-analysis is not appropriate since the interpretation of a summary risk estimate relies on the assumption of common study design attributes in the combined data sets.

Table 4a. Results of studies selected by Repacholi and colleagues (2012)<sup>20</sup> on the risk of glioma from long-term use of mobile phones

Study First Author	Exposed Cases	Odds Ratio	95% Confidence Interval	Notes
Hardell et al. (2002) <sup>38</sup>	43	1.2	0.8-1.8	Analog phones Brain tumours
Hardell et al. (2006) <sup>27</sup>	48	3.5	2.0-6.4	Analog phones Brain tumours
Schuz et al. (2006) <sup>39</sup>	28	0.66	0.44-0.95	Cohort study on brain tumours Interphone collaborator
Interphone study group (2010) <sup>40</sup>	252	0.98	0.76-1.26	Multi-centre study
Hardell et al. (2010) <sup>30</sup>	38	2.4	1.4-4.1	Deceased subjects
Combined OR		1.40	0.84-2.31	

B) Levis AG, Minicuci N, Ricci P, Gennaro V, Garbisa S. Mobile phones and head tumours. The discrepancies in cause-effect relationships in the epidemiological studies – how do they arise? *Environ Health*. 2011;10:59.<sup>18</sup>

**Purpose:** A critical evaluation of publications concerning the association of mobile phones and head tumours was supplemented by a meta-analysis limited to subjects with ipsilateral tumours using mobile phones since, or for at least, 10 years.

**Methods:** Odds ratios were given separately for selected studies determining the risk of gliomas associated with long-term use of mobile phones (at least 10 years of use), with further restrictions to recalled ipsilateral exposures (Table 4b).

**Results & Conclusion:** The literature review and meta-analysis showed large and statistically significant increases in the risk of ipsilateral brain gliomas (summary OR 1.56, 95% CI 1.21-2.00) and as well for acoustic neuromas for subjects using mobile phones for at least 10 years.

**Evaluation:** All authors for the review were from Italian institutions and had no known affiliation with either the INTERPHONE or the Hardell group. Meta-analysis forest plot

results were given for data restricted to at least 10 years of latency, and contralateral and ipsilateral as well as combined results were shown. However, details on the data such as the size of the exposed sample were not readily apparent. Instead of using the combined INTERPHONE results, the smaller sample size of individual collaborator’s data was used. The reference to Hardell et al. (2006) is a different study to that cited by Repacholi et al (2012). Bias in the recall of laterality could have affected the validity of the risk estimates.

Table 4b. Results of studies selected by Levis and colleagues (2011)<sup>18</sup> on the risk of glioma after ≥10 years since first use of mobile phones and with ipsilateral exposure

Study First Author	Exposed Cases	Odds Ratio (Ipsilateral)	95% Confidence Interval (Ipsilateral)	Notes
Lonn et al. (2005) <sup>41</sup>	25	1.60	0.80-3.40	Interphone collaborator
Hepworth et al. (2006) <sup>31</sup>	66	1.60	0.92-2.76	Interphone collaborator
Lahkola et al. (2007) <sup>29</sup>	77	1.39	1.01-1.92	Interphone collaborator
Hardell et al. (2006) <sup>28</sup>	50	3.3	2.0-5.4	Astrocytomas: Analog & digital
Combined OR		1.56*	1.21-2.00	

## 9.5 Discussion

The findings of an increase in risk for glioma and acoustic neuroma after prolonged use and ipsilateral exposure from mobile phones (and perhaps cordless phones), as indicated in the combined analysis of original studies in many of the reviews, requires confirmation by further, more thorough research. Combining the results of individual studies allows for better power to determine an effect since many of the case-control studies are based on small numbers due to the rarity of tumours, and therefore the effect estimates have poor precision. However, the choice of study included in a meta-analysis is somewhat arbitrary, which results in differing summary estimates between reviews.

Acoustic neuroma is of particular interest as it grows within the skull where most of the RF energy from wireless phones is absorbed.<sup>42</sup> Nevertheless, given that many of the glioma tumours become malignant; these have a greater impact on health. The extensive review of epidemiological studies by the IARC Working Group which concluded that exposure to RF was “possibly carcinogenic to humans” was influenced by the positive associations of glioma and acoustic neuroma with longer-term exposure to RF from mobile phones found in a few epidemiological studies.<sup>2</sup>

Significant elevated risks were apparent only in two of the 10 studies of acoustic neuroma, with both studies from the Hardell group. Separate tables for case-control studies of the effects of longer term use of mobile phones and latency for development of tumours were not presented, yet there was a table of the two retrospective cohort studies which showed no effect on the incidence of glioma in males with long-term use (11–13 years).

The AGNIR report concluded that there was no evidence of an elevated risk of brain tumours within 15 years of mobile phone use, adding that data on longer latencies and long-term or heavy use of mobile phones were limited.

The most consistent negative findings from the recent reviews were for the relationship of exposure to mobile phones RF with meningioma and parotid tumours. The IARC Working Group concludes that the available evidence was insufficient to reach a conclusion concerning these two types of tumours.<sup>2</sup>

### ***9.5.1 Cancers other than head and neck tumours***

Reviews on health effects associated with exposure to RF stressed that there were methodological shortcomings in the few studies of non-CNS cancer and replication of the few positive studies either discounted the findings or have not been attempted.<sup>43,44</sup> The few studies available for leukaemia, lymphoma and other tumour types, including uveal melanoma (of the eye) and cancers of the testes, breast, lung and skin, were deemed by the IARC working group to be inconclusive due to methodological limitations and inconsistent findings.<sup>2</sup> Similar conclusions were given in the AGNIR report<sup>45</sup> which cited negative studies on testicular cancer and uveal melanoma (one study each) and in two studies of pituitary adenoma. Elevated risk estimates were found for leukemia associated with use of GSM mobile phones in one of three studies and for the less common T-cell lymphoma type of non-Hodgkin's lymphoma (one of two studies). The incidence of childhood leukemia has been associated with exposure to magnetic fields from Extremely Low Frequency (ELF) waves, but not specifically to RF.<sup>25,43</sup> Hardell and colleagues<sup>46</sup> found no overall increased risk for malignant melanoma in the head and neck region from use of wireless phones but recommend further study due to low subgroup numbers and methodological shortcomings inherent in a case-control study.

### ***9.5.2 Case-control studies***

Because brain tumours are quite rare, the most practical study design is a case-control approach in which cases (subjects diagnosed with specific tumours) are compared to controls, with exposures determined retrospectively, usually by interview or by questionnaire. The retrospective exposure assessment process is subject to biases, such as recall bias (due to differential recall of mobile phone use between cases and controls) and selection bias from low participation especially among controls.

In 1999, IARC initiated a large multi-centre case control study (the INTERPHONE study), involving 13 countries, to assess the potential risk of brain tumours associated with RF exposure due to mobile phone use. The resulting May 2010 publication described the analysis of a large number of subjects (2,708 cases of glioma and 2,409 cases of meningioma) diagnosed at ages 30 to 59 between 2000 and 2004 with comparable controls matched by age, sex and region of residence.<sup>40</sup> Key findings were a significantly reduced risk of both glioma and meningioma in regular users compared to non-users (including occasional use), no trend in risk with cumulative hours of use, but an increased risk of glioma 1.40 (95% CI 1.03–1.89) in the highest decile of recalled cumulative call time (>1640 hours of use). However, years of use or years since first use (> 10 years) were not related to risk. The researchers concluded that “biases and errors limit the strength of the conclusion we can draw from these analyses and prevent a causal interpretation.”<sup>47</sup>

A number of methodological issues affect the quality of evidence from INTERPHONE and other case-control studies.<sup>7,30,43,47,48</sup>

1. A reduced risk implies a protective effect of mobile phone use, which is counterintuitive to expected effects, and may be a result of selection bias.
2. Misclassification of exposure may occur, for example, when the minimal requirement of “exposed” is using a mobile phone once a week for at least six months. Random errors would lead to underestimation of risk. Some systematic bias would result from underestimation of number of calls and overestimation of duration of calls, as demonstrated by validity studies.<sup>8</sup>
3. Differential recall of use of mobile phones by cases and controls is possible and prodromal symptoms (early symptoms associated with disease onset) among cases may reduce or stop their use of mobile phones.
4. A greater risk of reported ipsilateral than contralateral use is consistent with causation but also with bias if subjects over-reported use of the phone on the side of the head where the tumour was found.<sup>49</sup>
5. Most of the subjects are from metropolitan areas, yet exposures to RF are higher when mobile phones are used in rural areas (see Section 5).
6. A relatively short period of observation since first exposure to RF ignores the long induction and latency periods for cancer.<sup>8</sup> Defining the etiologically relevant period requires knowledge of the biological mechanism, which is currently unknown.

The major advantage of the INTERPHONE study was its size although the numbers were relatively small for the category of highest duration of use. The studies by Hardell and colleagues (discussed in 2011; 2010; 2009),<sup>14,16,30</sup> focussed on RF exposures after greater than 10 years of wireless phone use. The results of the smaller studies by the Hardell group usually differed from most studies in that the risk estimates obtained

were often increased for cases versus controls. The positive aspects of the Hardell studies included blinding to case status (avoiding observational bias) and better participation rates (reducing the possibility of selection bias) through use of mail questionnaires.<sup>8,30</sup> An analysis of methodological quality of 23 case-control studies on mobile phone use and tumours found the highest scores (8 of 9 possible points) for studies by Hardell and associates.<sup>12</sup> Replication of the results of the Hardell group by independent investigators would strengthen the credibility of their findings.

A unique aspect of the Hardell studies was including desktop cordless phones (Digital Cordless Telecommunications or DECT) as a source of RF (see Section 5). Long-term use of DECT resulted in elevated risks of specific brain tumours particularly with long duration of use and ipsilateral exposure.<sup>14</sup>

Children may potentially be at greater risk for adverse health outcomes resulting from exposure to RF. Vulnerability to the risk of brain tumours from mobile phone use is especially a concern due to the smaller distance to brain tissues and greater amount of marrow which increases transmission of RF.<sup>50</sup> According to Wiedemann and Schutz (2011),<sup>51</sup> there is no indication of an association between RF exposure and brain cancer in children, or for childhood leukemia. The few case-control studies generally have been negative<sup>52,53</sup> and are affected by limited power, bias and non-differential exposure misclassification (random error). A multi-centre international case control study of brain tumours involving approximately 2000 10–24 year olds (Mobi-Kids) is underway to investigate the role of RF exposures from mobile phones and other sources. However, according to Feychting (2011),<sup>52</sup> further case-control studies on children based on recall of past mobile phone use are unlikely to provide firm evidence, whereas monitoring of brain incidence trends in cancer registers are likely to provide the most robust evidence on potential effects of RF on the risk of brain tumours.

### ***9.5.3 Cohort studies and incidence***

To date there have been very few cohort studies designed to mitigate recall bias, selection bias and exposure misclassification. A recent retrospective cohort study by Frei and colleagues<sup>54</sup> found no evidence of increased risks of glioma and meningioma in just over 350,000 Danish mobile phone subscribers. While the problem of non-response and selection bias was avoided by using a computerized cohort and recall bias was not a factor with digitized subscriber data, exposure assessment was questionable, given that mobile phone subscription is not equivalent to actual mobile phone use (e.g. others, besides the subscriber may have use of the phone)<sup>55</sup> and information on length of call was not available. Similar limitations were apparent in a retrospective cohort study of acoustic neuroma, which concluded that there was no risk related to mobile phone use, determined by subscription to mobile phones.<sup>56</sup>

For all types of study designs, exposure assessment is a major problem, as accurate measurement of RF exposure is affected by technology used (see Section 5), use of hands-free devices, and the ubiquitous nature of EMF exposures from all sources. Large

prospective cohort designs, in which a cohort is followed over time, have the best potential for determining risks from exposure to RF. In this regard, a European multicentre prospective cohort study (COSMOS) was initiated in April 2010, which will follow 250,000 adult subjects over the next 20–30 years to assess the long-term health consequences of mobile phone usage, including cancer and neurological disorders.<sup>42</sup> Mobile phone use will be collected prospectively through questionnaires as well as network operator records.

Worldwide, there has generally been no increase in rates of brain cancer incidence in the last 20 years. For example, in the US between 1992 and 2006 the trends were downward or flat. The exception was for females aged 20–29 years, particularly for the frontal lobes which are less exposed to mobile phone RF.<sup>57</sup> The common belief is that a noticeable increase in the incidence of brain cancer should have occurred by now.<sup>10</sup> However Kundi (2011)<sup>58</sup> cite the long latencies of brain tumours and length of time needed to show an increase in incidence. According to Cardis and Sadetzki (2011),<sup>59</sup> a co-investigator with the INTERPHONE study, the identification of increased risks of solid tumours requires very long follow-up periods of subjects even with substantial exposure. For instance, no elevation in the risk of brain tumours was detected in survivors of Hiroshima and Nagasaki, Japan, for almost 40 years.

Close monitoring of national cancer registries remains an important endeavour to assess the potential for carcinogenicity associated with expanding use of multiple RF devices. In addition, there is a need to attempt to replicate positive study findings, increase study power and improve upon research designs, including better exposure assessment of RF from mobile phones and cordless phones, with consideration of technological changes.

#### ***9.5.4 Expert opinion on the IARC classification***

Expert evaluation of the scientific literature regarding cancer risks associated with exposure to RF is ongoing. Quoted below are excerpts from statements by two well-respected international organizations in reaction to the classification of RF as a possible human carcinogen by the IARC Working Group in May 2011:

***World Health Organization:*** “A large number of studies have been performed over the last two decades to assess whether mobile phones pose a potential health risk. To date, no adverse health effects have been established as being caused by mobile phone use.... WHO will conduct a formal risk assessment of all studied health outcomes from RF exposure by 2012.”<sup>5</sup>

***International Commission on Non- Ionizing Radiation Protection:*** “ICNIRP awaits with interest the full Monograph that explains the justification and arguments put forward by IARC in arriving at this conclusion. ICNIRP has been conducting a review of the potential health effects of RF including carcinogenicity as well as other aspects. The Commission will be publishing a revision of the ICNIRP guidelines on limiting RF exposure for the

general public and occupational groups. It will take into account all aspects of the literature including the material put forward in the IARC Monograph.”<sup>60</sup>

### ***9.5.5 Limitations of review***

Due to the large number of epidemiological studies published on the association cancer from exposure to RF from wireless phones, this section was developed as a synthesis of reviews published in the past five years. As such, the results and discussion of each individual review may reflect biases of the authors. Heterogeneity of study inclusion and exclusion criteria was obvious from the different number and authorship of studies selected in each review. Some representative studies were selected more often in the different reviews, which would result in weighting of their study odds ratios to influence the overall summary risk estimates. However, use of specific criteria for choosing eligible studies in this section, the number of reviews included (ten), and the variety of review authors who were associated with either the international collaborative study INTERPHONE, Hardell’s group of investigators, or were independent researchers, does support the representativeness of these findings with that of the scientific community.

### ***9.5.6 Research gaps***

A number of issues were apparent from the literature reviews and commentaries which emphasize the need for:

- More studies, not only of effects of RF exposure on brain tumours, but other cancers of interest; most of the positive studies that were repeatedly cited were published by one research group
- Improved research design and exposure assessment of case-control and retrospective cohort studies to minimize biases and random errors, and development of prospective cohort studies
- Applying knowledge of brain tumour latencies when defining case status in terms of a minimum period since first use of mobile phones.
- Validation of recall of ipsilateral versus contralateral use of mobile phones
- Evaluating effects of technology and use of hands-free options on exposure from different mobile phone devices (including smart phone uses) and also from cordless phones
- Assessing effects of multiple near-field and far-field exposures (i.e., WiFi, smart meters) to RF from different sources
- Assessing vulnerability to the effects of RF according to age group (including maternal exposures during pregnancy) and other personal factors.

## 9.6 Conclusion

Many of the reviews incorporating a meta-analysis, showed some evidence of an association of long-term exposure to RF (e.g., at least 10 years since first use) from mobile phones with gliomas and acoustic neuromas, especially with ipsilateral exposures (to the same side of the head as the tumour was found). This finding was not unanimous among the reviews and was observed mainly in the original studies of one group of researchers. Replication of these positive longer-term exposure studies by other research groups is needed to support suggestions of increased cancer risks from exposure to RF from mobile phones. Future research investigations must not only allow for longer latency times when determining the relationship of cancer to RF, but also apply more precise measurement of RF exposure taking into account the evolving and expanding use of RF devices.

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