Health Council of the Netherlands

Mobile phones and cancer

Part 1: Epidemiology of tumours in the head

Gezondheidsraad
Health Council of the Netherlands

Aan de staatssecretaris van Infrastructuur en Milieu

Onderwerp : Aanbieding advies *Mobile phones and cancer. Part 1. Epidemiology of tumours in the head*
Ons kenmerk : U-7758/EvR/pm/673-M4
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Geachte staatssecretaris,

Hierbij bied ik u het advies *Mobile phones and cancer. Part 1. Epidemiology of tumours in the head* aan. Het advies is opgesteld door de Commissie Elektromagnetische velden en getoetst door de Beraadsgroep Gezondheid en omgeving.

Blootstelling aan radiofrequente elektromagnetische velden afkomstig van mobiele telefoons en andere bronnen in de leefomgeving is vrijwel onvermijdelijk. Mobiele toepassingen bieden vele voordelen voor het dagelijks leven, maar leiden soms ook tot zorgen. Sommigen zijn bezorgd dat de continue blootstelling aan elektromagnetische velden leidt tot gezondheidsproblemen. Een belangrijke vrees in dat verband is, dat veelvuldig en intensief gebruik van een mobiele telefoon de kans op tumoren in het hoofd, met name kwaadaardige hersentumoren, kan vergroten. In juni 2011 heeft het *International Agency for Research on Cancer* (IARC) van de Wereldgezondheidsorganisatie op basis van een evaluatie van de beschikbare literatuur radiofrequente elektromagnetische velden geclassificeerd als 'mogelijk kankerverwekkend bij mensen'. Deze classificatie is vooral gebaseerd op epidemiologisch onderzoek. Al voordat het IARC met zijn project startte, was de commissie Elektromagnetische velden van de Gezondheidsraad begonnen met een systematische analyse van de epidemiologische literatuur over dit onderwerp. De conclusies van de commissie wijken enigszins af van die van het IARC. De commissie is van oordeel dat het epidemiologisch onderzoek geen duidelijk en consistent bewijs levert voor een verhoogde kans op tumoren in de hersenen of andere delen van het hoofd in relatie tot maximaal 13 jaar gebruik van een mobiele telefoon. Een klein risico kan echter ook niet met zekerheid worden uitgesloten. Nader onderzoek gedurende een langere periode kan hierover meer duidelijkheid geven. Dergelijk onderzoek wordt momenteel uitgevoerd, maar het zal nog

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een aantal jaren duren voordat de eerste resultaten worden gepubliceerd. De Gezondheidsraad zal de wetenschappelijke ontwikkelingen blijven volgen en daar zonodig over rapporteren.

Dit advies is het eerste in een serie van drie. De commissie werkt nu aan een systematische analyse van de dierexperimentele gegevens over de kankerverwekkendheid van radiofrequente elektromagnetische velden. Dat advies zal naar verwachting nog dit jaar worden uitgebracht. In een derde advies zal de commissie de gegevens uit de eerste twee adviezen integreren en bespreken in het licht van de recent gepubliceerde evaluatie van het IARC. Dat advies wordt begin volgend jaar verwacht.

Met vriendelijke groet,

prof. dr. W.A. van Gool
voorzitter

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Gezondheidsraad
Health Council of the Netherlands

To the State Secretary for Infrastructure and the Environment

Subject : Advisory report *Mobile phones and cancer.*
Part 1: Epidemiology of tumours in the head
Our reference : U-7758/EvR/pm/673-M5
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Date : June 3, 2013

Dear State Secretary,

I have the pleasure of presenting you the advisory report *Mobile phones and cancer. Part 1: Epidemiology of tumours in the head*. It has been drafted by the Electromagnetic Fields Committee and reviewed by the Standing Committee on Health and the Environment.

Exposure to the radiofrequency electromagnetic fields from mobile phones and other sources in the environment is almost inevitable. Mobile applications have brought many benefits to our daily life, but also concerns. Some people are worried that the continuous exposure to the fields may result in adverse health effects. A main fear in this respect is that the frequent and intensive use of mobile phones may increase the risk of tumours in the head, in particular malignant brain tumours. In June 2011 the International Agency for Research on Cancer (IARC) of the WHO concluded on the basis of a review of the available literature that radiofrequency electromagnetic fields should be classified as "possibly carcinogenic to humans". This classification is primarily based on evidence from epidemiological studies. Even before the IARC started its project, the EMF Committee of the Health Council initiated a systematic analysis of the epidemiogical literature on this subject. Its conclusions are slightly different from those of IARC. The Committee concludes that there is no clear and consistent evidence from epidemiological studies for an increased risk for tumours in the brain and other regions in the head in association with mobile phone use up to approximately 13 years. However, a slightly increased risk can also not be excluded. This means that further studies with a longer follow-up period will need to provide more clarity. Several studies are ongoing, but it will take a number of years before results will be published. The Health Council will continue to monitor the scientific developments and will report on them when relevant.

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This report is the first of three. The Committee is now preparing a systematic analysis of the animal studies on the carcinogenicity of radiofrequency electromagnetic fields. This report is expected to be published this year. In a third report the Committee will discuss the observations from the first two reports in the light of the recently published IARC evaluation. That report is expected early next year.

Kind regards,
(signed)
Prof. W.A. van Gool
President

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Mobile phones and cancer

Part 1: Epidemiology of tumours in the head

to:

the State Secretary for Infrastructure and the Environment

the Minister of Economic Affairs

the Minister of Health, Welfare and Sport

No. 2013/11, The Hague, June 3, 2013

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Samenvatting

Doel van het advies

Mobiele telefonie is gemeengoed geworden. Bijna iedereen in westerse landen heeft een mobiele telefoon. Maar met de toename van het gebruik van mobiele telefoons onstonden ook zorgen over mogelijke gezondheidseffecten van blootstelling aan de radiofrequente elektromagnetische velden die deze apparaten uitzenden. Die zorgen zijn vooral gericht op een mogelijke relatie met hersentumoren.

In dit advies onderzoekt de Commissie Elektromagnetische Velden van de Gezondheidsraad op basis van epidemiologische gegevens of er aanwijzingen zijn voor een oorzakelijk verband tussen blootstelling aan radiofrequente velden van mobiele telefoons en het optreden van tumoren in de hersenen en diverse andere weefsels in het hoofd (zoals hersenvliezen, gehoorzenuw en speekselklieren).

De commissie heeft daartoe op een systematische wijze volgens een vooraf vastgesteld protocol de relevante epidemiologische literatuur in kaart gebracht en geëvalueerd.

In een gerelateerd advies zal de commissie zich buigen over de resultaten van dierexperimenteel onderzoek.

Relevante typen onderzoek

Alle relevante typen epidemiologisch onderzoek zijn gebruikt, voor zover beschikbaar: cohort-onderzoek, patiënt-controle-onderzoek, patiënt-patiënt-onderzoek en ecologisch onderzoek.

Het enige relevante cohortonderzoek is een uitgebreid retrospectief onderzoek uit Denemarken. Op basis van de gegevens van de mobiele telefonieaanbieders is daarbij bepaald of de deelnemers al voor 1996 een privé-abonnement hadden.

Wat betreft de patiënt-controle-onderzoeken richt de analyse zich voornameljik op twee groepen onderzoeken. De eerste groep is een serie onderzoeken uitgevoerd door 16 onderzoeksgroepen in 13 landen, het INTERPHONE-consortium. Alle hebben ze gebruik gemaakt van een basisonderzoeksopzet die is ontwikkeld in samenwerking met het *International Agency for Research on Cancer* (IARC) en die zich richt op verschillende typen tumoren in het hoofd-halsgebied, inclusief de hersenen.

De tweede groep bevat publicaties over verschillende nauw met elkaar samenhangende onderzoeken van de onderzoeksgroep van Hardell uit Zweden. De leeftijdscategorieën zijn hier breder dan die in de INTERPHONE-onderzoeken. Omdat dit van invloed kan zijn op de uitkomsten (het vóórkomen van de meeste onderzochte tumoren is namelijk leeftijdsafhankelijk), heeft de commissie in haar analyse van deze gegevens zoveel mogelijk dezelfde leeftijdscategorieën gebruikt als in de INTERPHONE-onderzoeken.

In verschillende landen zijn ecologische onderzoeken uitgevoerd naar de relatie tussen het vóórkomen van hersentumoren en de toename van het gebruik van mobiele telefoons. Gezien de lange latentietijd van hersentumoren, die waarschijnlijk meer dan tien jaar duurt, is het mogelijk dat trends in het vóórkomen van tumoren die verband houden met het gebruik van mobiele telefoons nog niet te zien zijn.

Methodologische kwaliteit

De commissie heeft een scoringssysteem ontwikkeld om de methodologische kwaliteit van de geselecteerde publicaties te beoordelen. Toepassing hiervan brengt geen fundamentele verschillen aan het licht tussen de belangrijkste onderzoeken: het Deense cohortonderzoek en de patiënt-controle-onderzoeken van

Hardell en INTERPHONE. Op basis van de scoring is er geen reden om een van deze onderzoeken meer gewicht te geven dan de andere.

Resultaten per type tumor

In de onderzoeken zijn verschillende blootstellingskenmerken gebruikt. De commissie heeft zich in haar evaluatie gericht op (a) het aantal jaren dat een mobiele telefoon is gebruikt; (b) de totale blootstelling door het voeren van gesprekken met de mobiele telefoon, bepaald aan de hand van het totale aantal gespreksuren en (c) de zogenoemde lateralisatie; hierbij wordt gekeken of de telefoon voornamelijk gebruikt is aan de kant van het hoofd waar zich de tumor bevindt (ipsilateraal) of aan de andere kant (contralateraal).

Gliomen

Gliomen zijn kwaadaardige tumoren van het hersenweefsel. In het Deense cohort werd geen verhoogde kans op het krijgen van een glioom gevonden bij een abonnement op mobiele telefonie gedurende maximaal 13 jaar. In de patiënt-controle-onderzoeken is een vergelijkbaar criterium gebruikt: de tijd sinds het eerste gebruik van een mobiele telefoon. In het INTERPHONE-onderzoek is daarbij geen verhoogd risico gevonden. Dat was wel het geval bij de overeenkomstige leeftijdsgroep in het onderzoek van Hardell.

In de lateralisatie-analyse van de gegevens over de tijd sinds het eerste gebruik vond Hardell voor zowel ipsilateraal als contralateraal gebruik een verhoogd risico. In het INTERPHONE-onderzoek werd zowel voor ipsi- als contralateraal gebruik geen verhoogd risico gevonden. De gegevens voor dit criterium zijn dus niet consistent.

Voor de totale beltijd werd in de onderzoeken van Hardell en INTERPHONE in de hoogste blootstellingscategorie (1640 uur en meer) een verhoogd risico gevonden, waarbij het risico in het onderzoek van Hardell hoger was dan in dat van INTERPHONE. In het onderzoek van INTERPHONE werden in diverse lagere categorieën, waaronder ook de op een na hoogste, juist verlaagde risico's gevonden. Er is dus geen duidelijke blootstellings-respons relatie.

In de lateralisatie-analyse van de gegevens van de totale beltijd vond Hardell een verhoogd risico voor zowel ipsilateraal als contralateraal gebruik. In het INTERPHONE-onderzoek daarentegen werd alleen een verhoogd risico gevonden voor ipsilateraal gebruik in de hoogste van vijf categorieën (1640 uur en meer), terwijl bij de laagste twee categorieën voor contralateraal gebruik de risico's juist verlaagd bleken te zijn.

In de ecologische onderzoeken werd in de gegevens uit Scandinavische landen en Groot Brittannië geen toename gevonden in het vóórkomen van gliomen. In de Verenigde Staten werd een toename van 0,75% per jaar gevonden voor gliomen in de temporaalkwab (het gedeelte van de hersenen dat zich het dichtst bij de mobiele telefoon bevindt tijdens het voeren van een gesprek). De Amerikaanse gegevens komen niet overeen met de relatieve risico's uit de onderzoeken van Hardell. Als die relatieve risico's echt zouden zijn, zou de toename van het aantal gliomen in de VS groter moeten zijn en zou die ook in andere landen zichtbaar moeten zijn. De Amerikaanse gegevens zijn niet strijdig met een kleine verhoging van het risico zoals dat in het INTERPHONE-onderzoek voor totale beltijd is gevonden, maar ze kunnen ook verklaard worden zonder de aanname van een verhoogd risico. De gegevens over het vóórkomen van gliomen in Nederland laten geen toename zien na de periode van snelle toename van het gebruik van mobiele telefoons in de leeftijdsgroepen die deze het meest gebruiken: die van 20 tot 29 en die van 30 tot 59 jaar.

Meningiomen

Meningiomen zijn tumoren van de hersenvliezen, die de scheiding vormen tussen het zenuwweefsel van de hersenen en de schedel. In het Deense cohortonderzoek werd geen verhoogd risico voor meningiomen waargenomen. In de onderzoeken van Hardell werd een verhoogd risico gevonden in de hoogste categorie voor verstreken tijd sinds het eerste gebruik (meer dan 10 jaar), maar alleen voor analoge en niet voor digitale mobiele telefoons. In het INTERPHONE-onderzoek werden in de twee middelste van vier categorieën juist verlaagde risico's gevonden. Geen van de andere blootstellingsmaten was gecorreleerd met een risico voor meningiomen.

Akoestische neuromas of brughoektumoren

Brughoektumoren zijn tumoren van de gehoorzenuw. In het Deense cohortonderzoek werd geen verhoogd risico voor brughoektumoren gevonden in relatie tot een mobiele telefonie-abonnement gedurende 11 jaar of langer. Hardell vond een verhoogd risico in associatie met het gebruik van analoge telefoons voor alle gebruiksduren, zelfs al bij een duur van één tot vijf jaar. Voor digitale telefoons werd alleen over kortere periodes een verhoogd risico gevonden, maar niet bij gebruik gedurende 10 jaar of langer.

De lateraliteitsanalyse van de gegevens van Hardell gaf verhoogde risico's te zien voor ipsilateraal gebruik van analoge en digitale mobiele telefoons bij een

gebruiksduur van zowel meer dan een jaar als meer dan tien jaar. In het algemeen werd geen verhoogd risico gevonden. Dat was ook niet het geval in de lateraliteitsanalyse van het INTERPHONE-onderzoek en in een Japans patiënt-patiënt-onderzoek.

In de onderzoeken van Hardell werden verhoogde risico's gevonden voor alle typen telefoons bij een totale beltijd van meer dan 1000 uur. In het INTERPHONE-onderzoek werden daarentegen geen verhoogde risico's gevonden bij een totale beltijd van 1640 uur of meer, terwijl in verschillende lagere categorieën juist verlaagde risico's werden gevonden. Voor ipsilateraal gebruik was het risico verhoogd in de hoogste categorie (totale beltijd van 1640 uur of meer), en verlaagd in de op een na hoogste categorie.

Parotiskliertumoren

Parotisklieren zijn de speekselklieren die het meest zijn blootgesteld bij het bellen met een mobiele telefoon. In de onderzoeken van Hardell werden geen verhoogde risico's voor tumoren in de parotisklier gevonden voor de tijd sinds het eerste gebruik en voor de totale beltijd. Evenmin was dit het geval in de INTERPHONE-onderzoeken. Het enige verhoogde risico werd gevonden in een subgroep van een van de onderzoeken die volgens het INTERPHONE-protocol zijn uitgevoerd, en wel in de groep patiënten met zowel goedaardige als kwaadaardige tumoren die de telefoon ipsilateraal gebruikten en die een totale beltijd hadden van meer dan 266 uur.

In slechts één ecologisch onderzoek werd over parotiskliertumoren gerapporteerd, waarbij het vóórkomen vrijwel constant was. Gegevens over het vóórkomen van parotiskliertumoren in Nederland laten geen veranderingen zien over de periode 1989-2010.

Overwegingen voor de evaluatie

Latentietijd

Bij onderzoek naar langzaam groeiende tumoren is het van belang rekening te houden met de latentietijd, dat wil zeggen de tijd tussen het ontstaan van de tumor en het moment dat deze klinisch aantoonbaar wordt. Er is echter nauwelijks enige informatie beschikbaar over latentietijden voor de typen tumoren die in dit advies worden besproken. De commissie acht het mogelijk dat een periode van tien jaar te kort is om een toename in het vóórkomen van deze tumoren te kunnen meten.

Analoge versus digitale telefoons

De eerste mobiele telefoons maakten gebruik van een analoog signaaltype, terwijl de latere GSMs een digitaal signaal gebruikten. Dit betekent dat de in de epidemiologische onderzoeken opgenomen personen die het langst gebruik maakten van mobiele telefonie (tien jaar of langer) aanvankelijk belden met een analoge telefoon. De blootstelling bij gebruik van een analoge telefoon was hoger dan die bij gebruik van een digitale telefoon.

Draadloze versus mobiele telefoons

Draadloze telefoons zijn mobiele telefoons met een beperkt bereik voor gebruik binnenshuis, zoals DECT-telefoons. In verschillende onderzoeken heeft Hardell het gebruik van draadloze telefoons meegenomen, onder de aanname dat de blootstelling aan radiofrequente velden daarbij van vergelijkbare grootte is als bij mobiele telefoons. De blootstelling bij het gebruik van een draadloze telefoon is echter lager dan bij gebruik van een mobiele telefoon.

Dit betekent dat het op grond van de daadwerkelijke blootstelling moeilijk te verklaren is dat Hardell ruwweg vergelijkbaar verhoogde risico's vond bij gebruik van mobiele en draadloze telefoons. Het is niet bekend of het gebruik van beide typen telefoons gecorreleerd is, maar de commissie acht dit wel mogelijk. Dat zou dan deels een verklaring kunnen zijn voor de verhoogde risico's die zijn gevonden bij het gebruik van draadloze telefoons. De commissie is desalniettemin van mening dat de gegevens over de draadloze telefoons vragen oproepen over de interne consistentie van de onderzoeken van Hardell.

Sterke en zwakke punten in de onderzoeken

Cohortonderzoeken

Cohortonderzoeken leveren potentieel sterk bewijs, omdat de blootstelling herhaaldelijk en objectief gemeten of bepaald kan worden voordat de ziekte optreedt. Dergelijke onderzoeken hebben daarom geen last van vertekening op grond van foutieve herinnering. Wel kunnen er andere problemen zijn.

In het Deense cohortonderzoek hebben de onderzoekers alleen gekeken of de deelnemers een privé-abonnement hadden dat was gestart voor 1996. Deze groep hebben zij vervolgens vergeleken met alle inwoners van Denemarken. Het is duidelijk dat de tijd die is verstreken sinds het aangaan van een abonnement een

minder relevante parameter is dan een schatting van de mate van daadwerkelijk gebruik, die directer gerelateerd is aan de blootstelling.

In de latere publicaties over dit onderzoek, die een langere periode bestrijken, zal daarnaast in toenemende mate misclassificatie zijn opgetreden in de groep niet-gebruikers. Daar zijn twee redenen voor: zakelijke gebruikers, die mogelijk tot de meest intensieve gebruikers behoren, zijn niet opgenomen in de gebruikersgroep, en het bezit van mobiele telefoons in de Deense bevolking is na 1996 sterk toegenomen. Het Deense cohortonderzoek is om deze redenen wel afgeschilderd als een onderzoek van beperkte waarde.

Ondanks het ontbreken van gegevens over de blootstelling beschouwt de commissie het Deense cohortonderzoek echter als belangrijk voor de evaluatie. Misclassificatie in de niet-gebruikersgroep heeft namelijk slechts een zeer beperkt effect op het berekende risico, en van misclassificatie in de gebruikersgroep is geen sprake.

Patiënt-controle-onderzoeken

De commissie beschouwt de INTERPHONE-onderzoeken als vatbaar voor vertekening door selectie, vanwege de relatief lage deelnamepercentages. Omdat deze bij de controles ook nog eens lager zijn dan bij de patiënten, kan er differentiële misclassificatie optreden (dat wil zeggen dat de misclassificatie verschillend is voor patiënten en controles). Dit versterkt vertekening door selectie.

Deze vertekening is mogelijk de oorzaak van de verlaagde risico's die in sommige van de lagere blootstellingscategorieën zijn waargenomen; een beschermend effect van mobiel bellen is namelijk niet waarschijnlijk. Maar dit zou betekenen dat de verhoogde risico's in de hoogste blootstellingscategorieën ook te laag kunnen zijn als gevolg van vertekening door selectie. Anderzijds kunnen de risico's door vertekening door selectieve herinnering juist weer hoger uitvallen. Het is niet mogelijk om de omvang van deze vertekeningen in te schatten.

In de onderzoeken van Hardell worden hogere deelnamepercentages en kleinere verschillen tussen de deelname van patiënten en controles gemeld dan in de INTERPHONE-onderzoeken. Deze onderzoeken hebben daarom waarschijnlijk minder last van vertekening door selectie dan de INTERPHONE-onderzoeken. De deelnamepercentages van met name de controles in de onderzoeken van Hardell zijn echter ongewoon hoog.

Een ander punt bij de onderzoeken van Hardell is dat al na korte tijd sinds het eerste gebruik verhoogde risico's werden gevonden. Dat is onwaarschijnlijk in het licht van de naar verwachting zeer lange latentietijden van de onderzochte typen tumoren. Daarnaast zou, als deze verhoogde risico's echt zouden zijn, in de

ecologische onderzoeken gevonden moeten zijn dat het vóórkomen van deze tumoren toeneemt. Dit is echter niet het geval.

Bij zowel de onderzoeken van Hardell als die van INTERPHONE kan er ook waarnemersvertekening optreden. Ondanks de training van degenen die de interviews hebben afgenomen kunnen zij patiënten en controles ongemerkt net iets anders benaderen, al is niet bekend welke invloed dit kan hebben. Beide onderzoeken zijn ook vatbaar voor vertekening door herinnering, omdat het vaststellen van de blootstelling in patiënt-controle-onderzoeken altijd achteraf gebeurt. Het is aangetoond dat vertekening door herinnering verschillend werkt voor patiënten en controles, en dat dit tot een overschatting van het risico kan leiden.

Een ander punt dat in aanmerking moet worden genomen is dat de onderzoeken van Hardell in slechts één land zijn uitgevoerd (Zweden), terwijl de onderzoeken van INTERPHONE 16 gebieden in 13 landen bestrijken, en dus ook een veel bredere populatie omvatten. Ook de totale aantallen patiënten en controles zijn in de onderzoeken van Hardell lager dan die in de INTERPHONE-onderzoeken.

De moeilijk te verklaren verhoogde risico's samenhangend met het gebruik van draadloze telefoons en korte latentietijden die zijn gevonden in de onderzoeken van Hardell, in combinatie met de geringere omvang van deze onderzoeken in verhouding tot het INTERPHONE-onderzoek, hebben de commissie doen besluiten de onderzoeken van Hardell minder gewicht te geven in de uiteindelijke evaluatie en conclusies dan de INTERPHONE-onderzoeken.

Patiënt-patiënt-onderzoeken

Onderzoeken met twee groepen patiënten zijn potentieel sterk, omdat ze minder te kampen hebben met vertekening door selectie en waarneming. Vertekening door selectieve herinnering kan natuurlijk nog wel optreden, maar deze zal niet-differentieel zijn, omdat alleen patiënten in het onderzoek zijn opgenomen.

Ecologische onderzoeken

Ecologische onderzoeken zijn per definitie van beperkte waarde, omdat de individuele blootstelling niet wordt bepaald. Er kunnen hieruit dan ook geen blootstelling-effectrelaties worden vastgesteld. Hooguit kunnen ecologische onderzoeken laten zien dat er overeenkomsten zijn in trends van de toename van een ziekte en het gebruik van mobiele telefoons.

Als er na een toename van het bezit (en verondersteld gebruik) van mobiele telefoons geen toename gevonden wordt in het voorkomen van een ziekte, is dat echter nog geen bewijs dat er geen oorzakelijk verband is tussen blootstelling en ziekte. Alleen als de latentietijd tien jaar of minder zou zijn, zou een verhoogd risico in de trends nu al zichtbaar moeten zijn.

Conclusies over specifieke tumoren

Gliomen

De commissie concludeert dat er enkele zwakke en inconsistente aanwijzigingen zijn voor een associatie tussen langdurig intensief gebruik van een mobiele telefoon en het vaker voorkomen voor gliomen. Verschillende vormen van vertekening en toeval zouden een verklaring kunnen zijn voor deze uitkomsten, maar het kan niet worden uitgesloten dat er een oorzakelijk verband is. De commissie schat de kans hierop echter in als zeer klein.

In de bevolkingsstatistieken is, ook in Nederland, geen toename te zien in het vóórkomen van gliomen. Een toename kan echter ook nog niet zichtbaar zijn geworden vanwege de waarschijnlijk lange latentietijd bij deze tumoren.

De ecologische onderzoeken geven ook geen ondersteuning voor een verhoogd risico. Als de door de groep van Hardell gerapporteerde risico's werkelijk voorkomen, zou in de recente kankerstatistieken een toename van gliomen zichtbaar moeten zijn en zou de latentietijd veel korter moeten zijn dan de mogelijk meer dan tien jaar die nu wordt vermoed. Een risicotoename zoals gerapporteerd in de INTERPHONE-onderzoeken, die lager is dan die bij Hardell, zou in de statistieken nog niet te zien zijn.

Op grond hiervan concludeert de commissie dat er een klein risico op het verhoogd voorkomen van gliomen kan zijn in samenhang met mobiel telefoongebruik, maar dat het ook mogelijk is dat er geen risico is.

Meningiomen

De commissie concludeert dat er geen duidelijke en consistente aanwijzingen zijn dat het gebruik van een mobiele telefoon gepaard gaat met een verhoogd risico voor meningiomen.

Brughoektumoren

De commissie oordeelt dat de gegevens over een associatie tussen langdurig gebruik van een mobiele telefoon en het vóórkomen van brughoektumoren niet consistent zijn en geen duidelijke aanwijzingen geven voor een verhoogd risico.

Parotiskliertumoren

De commissie concludeert dat er geen duidelijke aanwijzingen zijn dat gebruik van een mobiele telefoon een verhoogd risico op parotiskliertumoren oplevert. Er is slechts in één subgroep in één onderzoek met een beperkt aantal patiënten een verhoogd risico waargenomen. Dit zou door toeval kunnen worden verklaard. De bevolkingsstatistieken laten, ook in Nederland, geen toename zien in het vóórkomen van parotiskliertumoren.

Andere tumoren

Er kunnen geen conclusies worden getrokken over risico's die samenhangen met het gebruik van mobiele telefoons met betrekking tot tumoren van de hypofyse, melanomas van het oog, tumoren aan andere zenuwen dan de gehoorzenuw en neuroblastomas.

Eindconclusie

De huidige systematische analyse laat zien dat er, ondanks uitgebreid onderzoek, nog steeds geen duidelijkheid is over een mogelijk verband tussen het gebruik van een mobiele telefoon en een verhoogde kans op het optreden van tumoren in de hersenen en andere delen van het hoofd.

Er zijn enkele zwakke en inconsistente aanwijzingen voor een verband tussen langdurig intensief gebruik van een mobiele telefoon en een toename van het vóórkomen van gliomen. Die aanwijzingen kunnen verklaard worden door verschillende vormen van vertekening en door toeval, maar het kan ook niet worden uitgesloten dat er een oorzakelijk verband is. De aanwijzingen voor een verhoogd risico voor andere tumoren, waaronder meningiomen en brughoektumoren, zijn veel zwakker of ontbreken geheel.

Op basis van de epidemiologische gegevens die in dit advies zijn beschreven en in aanmerking nemend de kwaliteit en de sterke en zwakke punten van de verschillende onderzoeken luidt de eindconclusie van deze systematische analyse daarom als volgt: er is geen duidelijk en consistent bewijs voor een verhoogd

risico voor tumoren in de hersenen of andere delen van het hoofd gerelateerd aan gebruik van een mobiele telefoon gedurende 13 jaar of minder; een dergelijk risico kan echter ook niet worden uitgesloten. Over langduriger gebruik kan niets worden gezegd.

Executive summary

Why this report?

Mobile telephony has become an ubiquitous commodity. In Western countries virtually everybody has a mobile telephone. But with the increase in mobile phone use, also concerns developed on possible adverse effects of exposure to the radiofrequency electromagnetic fields emitted by these devices. Much of this concern focussed on a possible relation with cancer in the brain.

In this report, the Electromagnetic Fields Committee of the Health Council of the Netherlands investigates on the basis of the epidemiological evidence whether there are indications for a causal relationship between exposure to radiofrequency fields from mobile phones and tumours in the brain and various other tissues in the head (e.g. meninges, acoustic nerve, parotid glands).

To this end, the Committee has systematically searched and reviewed the relevant epidemiological literature following an a priori defined protocol.

In a related report the Committee will evaluate the results of animal studies.

Relevant types of studies

All available relevant types of epidemiological studies have been used: cohort, case-control, case-case and ecological studies.

The only relevant cohort study is a very large retrospective study from Denmark, in which mobile phone company records were used to determine whether a private mobile phone subscription was started before 1996.

Two groups of case-control studies are primarily used in the analysis. The first group is a series of studies from 16 research groups in 13 countries, the INTERPHONE consortium. They all used a core protocol developed in collaboration with the International Agency for Research on Cancer (IARC) on different types of tumours in the head and neck area, including the brain.

The second group contains publications of several closely related studies of the Hardell group from Sweden. The age range covered in these studies is wider than that in the INTERPHONE study. This may affect the results, since the incidence of most tumours investigated is age-related. Therefore, whenever possible, the Committee used data for the same age range as used in the INTERPHONE study in the analysis.

Ecological studies that study the incidence of brain cancers in relation to the increase in use of mobile phones, have been performed in various countries. In view of the long latency period of brain tumours of likely more than 10 years, it is possible that any trends in tumour incidence related to mobile phone use may not yet be visible.

Methodological quality

The Committee developed a scoring system to evaluate the methodological quality of the selected publications. This assessment did not result in major differences between the main studies, i.e. the Danish cohort study and the INTERPHONE and Hardell case-control studies. On the basis of this scoring system there is no reason to give one type of study more weight than the other.

Results per tumour type

Several exposure characteristics have been used in the studies. In this analysis the Committee focussed on (a) the duration of mobile phone use in years; (b) the cumulative exposure from mobile phone calls in hours over the respondents' lifetime and (c) the so-called lateralisation. Lateralisation addresses if the telephone predominantly was used at the side of the head where the tumour is located (ipsilateral), or on the other side (contralateral).

Gliomas

Gliomas are malignant tumours of the brain. In the Danish cohort no increased glioma risks were observed for having a mobile phone subscription for up to 13 years. The case-control studies investigated a similar endpoint: time since first use. INTERPHONE found no increased risks, but in the corresponding age-range in the Hardell studies an increased relative risk was found.

In the laterality analysis of the time since first use data, Hardell found an increased risk for both ipsilateral and contralateral use, while INTERPHONE found no increased risks. So the data on this endpoint are not consistent.

For cumulative call time, both groups found an increased risk for the highest exposure category (1640 hours and more). In the Hardell studies it was higher than in the INTERPHONE study. However, INTERPHONE identified decreased risks in several lower categories, including the next-highest one, so there is no obvious exposure-response relation.

In the laterality analysis of the cumulative call time data, Hardell found an increased risk for both ipsilateral and contralateral use, while INTERPHONE found an increased risk only for ipsilateral use in the highest of five categories (1640 hours and more), and decreased risks for contralateral use in the lowest categories.

In the ecological studies, no increase in glioma incidence was observed in the Nordic countries and the UK, while in the USA a small increase of approximately 0.75% per year was observed of gliomas in the temporal lobe (the part of the brain closest to a mobile telephone when a call is made). These US data are not compatible with the relative risks of the Hardell studies. If these relative risks were true, the increase of the glioma rate in the USA should have been much larger and an increased rate should also have to be visible in other countries. The US data are consistent with a small increase in risk as found for cumulative call time in the INTERPHONE studies, but also with no change in risk. Brain cancer incidence data for the Netherlands indicate no increase in gliomas following the period of rapid increase in mobile phone use in the age groups that use them most: those of 20-29 and of 30-59 years.

Meningiomas

Meningiomas are tumours of the meninges, the membranes that separate the nervous tissue of the brain from the skull. No increased risk for meningioma was observed in the Danish cohort study. In the Hardell studies an increased risk was found in the highest category for time since first use (more than 10 years), but

only for analogue and not for digital mobile phones. In the INTERPHONE study decreased relative risks were observed in the two middle of four categories. All other exposure metrics were not associated with risk for meningioma.

Acoustic neuromas

Acoustic neuromas are tumours of the acoustic nerve. In the Danish cohort study no increased risk for acoustic neuroma was found for having a mobile phone subscription for more than 11 years. Hardell found an increased risk associated with the use of analogue phones for all times since first use, even as short as more than 1-5 years. For digital phones an increased risk was found only for the shorter follow-up times, but not for more than 10 years use.

In the laterality analysis of the Hardell data increased risks for both analogue and digital mobile phones were found for both more than 1 year and more than 10 years ipsilateral use. No increased risks for time since first use were found overall and in the laterality analysis of the INTERPHONE study, nor in a Japanese case-case study.

In the Hardell studies increased risks were associated with all types of phones for a cumulative call time of more than 1000 hour. No increased risks were found in the INTERPHONE study for cumulative call times of 1640 hours or more, but decreased risks were observed in several of the lower categories. For ipsilateral use the risk was increased for cumulative call times of 1640 hours or more, but decreased for the next-lower category.

Parotid glands tumours

Parotid glands are the salivary glands most exposed when making a call with a mobile phone. No increased risks associated with time since first use or cumulative call time were found for parotid gland tumours in the Hardell studies, nor in studies following the INTERPHONE protocol. The only increased risk was found in one subgroup in a study following the INTERPHONE protocol, in the group containing both benign and malignant tumours that reported ipsilateral phone use and a cumulated call time of more than 266 hour.

Only one ecological study reported on parotid gland tumours and found a rather constant incidence. Incidence data for parotid gland tumours for the Netherlands do not show changes in the incidence of this tumour over the period 1989-2010.

Issues to be considered in the evaluation

Latency time

An important point to be considered in the study of slow growing tumours is their latency time, i.e. the time between induction of the tumour and its clinical manifestation. Hardly any information is available, however, on latency periods for the tumours considered in this report. The Committee considers it possible that a follow-up time of 10 years would not be enough to measure an increase in tumour incidence.

Analogue versus digital phones

The first mobile phones used an analogue type of signal, while the later GSMs used a digital signal. This means that the subjects in the epidemiological studies that have been using mobile telephony for the longest time periods (10 years or more) will initially have used analogue phones. The exposure from the analogue phones was higher than that from the digital ones.

Cordless versus mobile phones

Cordless phones are wireless phones with a limited range used indoors, such as DECT phones. In several studies Hardell also investigated the risks from the use of cordless phones, under the assumption that the radiofrequency field exposures from that type of phone is of comparable magnitude as that from mobile phones. However, exposure from cordless phones is lower than that from mobile phones.

Thus the grossly similar increased risks for the use of mobile or cordless phones observed by Hardell are hard to explain on the basis of actual incident or total exposure. It is not known, but considered possible by the Committee, that there is a correlation between the use of both types of phones. This could in part be an explanation for the increased risks found for cordless phone use. Nevertheless the Committee feels that the cordless phone data challenge the internal consistency of the Hardell studies.

Strengths and limitations of the studies

Cohort studies

Cohort studies generate potentially strong evidence, as the exposure can be repeatedly and objectively measured or assessed before the outcome occurs. These studies therefore do not suffer from recall bias, but they may suffer from other problems.

The Danish cohort study merely considered whether or not subjects held a private subscription that was started before 1996, and compared this group to all other residents of Denmark. Clearly the time that passed since a subscription started is a less meaningful endpoint than an estimate of the actual amount of use, which is more directly associated with exposure.

In the later publications of this study with longer follow-up there will be increasing misclassification in the non-users group. This is because holders of business contracts, who are possibly among the heaviest users, were excluded from the users group, and because mobile phone possession in the Danish population strongly increased after 1996. It has been argued that because of this the Danish cohort is of limited value.

Despite the lack of actual exposure data, the Committee considers the Danish cohort important for the overall evaluation. This is because misclassification in the non-users group has only very limited effect on the calculated risk and there is no misclassification in the users group.

Case-control studies

From the case-control studies, the Committee considers the INTERPHONE studies to be prone to selection bias due to the overall relatively low response rates. Because these are also lower for the controls than for the cases, this might lead to differential misclassification (i.e. the misclassification is different for cases and controls). This reinforces the selection bias.

This is possibly reflected in the decreased risks observed in some of the lowest exposure categories: a protective effect from mobile phone use is not very likely. But this would mean that the observed increased risks in the highest categories may also be too low due to selection bias, while on the other hand they also could be too high due to recall bias. It is not possible to assess the extent of these biases.

The Hardell studies reported higher response rates and smaller differences in response rates between cases and controls than the INTERPHONE studies. So they are less likely to suffer from selection bias than the INTERPHONE studies. However, the response rates in especially the controls of the Hardell studies are unusually high.

Another issue with the Hardell studies is that increased risks were already observed with short usage times. These are unlikely in view of the presumably very long latency times of the tumours under consideration. Also, if these increased risks were true, increased incidences in the ecological studies would be expected, but these were not observed.

In both the Hardell and INTERPHONE studies there is also the possibility of observer bias. In spite of the training of the interviewers, they might in some way have been unknowingly influenced by the case or control status of the subjects. The direction of effect of this bias is unclear. Both studies are also inherently prone to recall bias, as exposure assessment in case-control studies is always retrospective. Recall bias has been shown to be different between cases and controls and is expected to cause over-estimation of risk.

Another point that is important to take into account is the fact that the Hardell studies have been performed in only one country (Sweden), while the INTERPHONE studies cover 16 areas in 13 countries, thus covering a much broader population. The total numbers of cases and controls are also lower in the Hardell studies compared to the INTERPHONE studies.

The increased risks associated with cordless phone use and short latency times observed in the Hardell studies, that are difficult to explain, combined with the smaller size of the Hardell studies compared to the INTERPHONE studies, made the Committee to give the Hardell studies less weight than the INTERPHONE studies in the overall analysis and conclusions.

Case-case studies

Case-case studies are potentially powerful, as they are less likely to suffer from selection and observer bias. There will of course still be recall bias, but this will be non-differential, since only patients are included.

Ecological studies

Ecological studies are inherently limited in their interpretation, since individual exposure is not determined. Exposure-effect relationships cannot be derived

from ecological studies. At best, they can show a similarity in trends in increase of disease and phone use.

Absence of an increase in disease incidence with a preceding increase in mobile phone possession (and presumed use) does not prove the absence of a causal relation between exposure and disease. If the latency would be a decade or less, an increased risk would have been expected in the trends by now.

Tumour-specific conclusions

Glioma

The Committee concludes that there are some weak and inconsistent indications for an association between prolonged and intensive use of a mobile phone and an increased incidence of gliomas. These might be explained by various types of bias and chance, but it cannot be excluded that there is a causal relation. However, the Committee estimates the likelihood for a causal relation to be very low.

The population statistics, also in the Netherlands, do not show an increased incidence of glioma. But since it is likely that the latency time for these tumours is very long, an increased incidence might not yet be visible.

The ecological studies also do not support an increased risk. If the risks reported by the Hardell group were true, a clearly increased glioma rate should have been visible in recent cancer statistics and the latency time should have to be much shorter than the the currently assumed possibly more than 10 years. The increased risk reported in the INTERPHONE studies, that is lower than that in the Hardell studies, would not show up yet in the statistics.

The Committee concludes that their may be a small risk for an increased glioma incidence in association with the use of mobile phones, but it is also possible that such risk does not exist.

Meningioma

The Committee concludes that there are no clear and consistent indications for an increased risk of meningioma from using a mobile telephone.

Acoustic neuroma

The Committee feels that the data on an association between long term use of a mobile phone and acoustic neuroma are inconsistent and do not really give an indication for an increased risk.

Parotid gland tumours

The Committee concludes that there are no clear indications for an increased risk of parotid gland tumours from using a mobile phone. Only one increased risk estimate in one subgroup in one study with limited numbers of cases has been observed. This could have been the result of chance. The incidence data, including those from the Netherlands, also do not show an increase.

Other tumours

For pituitary tumours, melanoma eye tumours, intra-temporal facial nerve tumours and neuroblastoma tumours no conclusions regarding risks associated with the use of mobile phones can be drawn.

Overall conclusion

The present systematic analysis shows that, despite large research efforts, there is still no clarity regarding a possible association between mobile phone use and an increased risk of tumours in the brain and other regions of the head.

There are some weak and inconsistent indications for an association between prolonged and intensive use of a mobile phone and an increased incidence of gliomas. These might be explained by various types of bias and by chance, but it can also not be excluded that there is a causal relation. For the other types of tumours, including meningiomas and acoustic neuromas, indications for an increased risk are much weaker or completely absent.

Based on the available epidemiological evidence described in this report and taking into account the quality of the different studies and their strengths and weaknesses, the final conclusion from this systematic analysis is then: there is no clear and consistent evidence for an increased risk for tumours in the brain and other regions in the head in association with up to approximately 13 years use of a mobile telephone, but such risk can also not be excluded. It is not possible to pronounce upon longer term use.

Chapter 1

Introduction

1.1 Why this report?

Since the allegation of a Florida inhabitant that his wife's brain tumour was caused by excessive use of a mobile telephone, many studies have been performed into that hypothesis. When the first publication by Hardell et al. in 1999[1] indeed suggested a relationship between the use of mobile telephones and brain cancer, this subject has become a matter of concern to the general public and to authorities.

Despite the availability of quite some data, they do not present a clear-cut picture of the possible relationship between the use of mobile or cordless phones and tumours in the head and recent reviews have reached conflicting conclusions. In June 2011, the International Agency for Research on Cancer (IARC) classified radiofrequency electromagnetic fields as 'possibly carcinogenic to humans' (group 2B).[2,3] When other recent reviews are considered, there is a lack of convergence into a common conclusion. Some reviews conclude, like IARC, that there are indications for an association between mobile phone use and an increased risk of brain cancers, and some call for (precautionary) measures.[4-9] Others conclude that the data do not show such association.[10,11] Many of these these reviews contain shortcomings and biases, but these will not be discussed.

The Electromagnetic Fields Committee of the Health Council of the Netherlands ("the Committee") performs its own analysis of the literature on this

subject. This report is the first of three to discuss this. The composition of the Committee is presented in Annex A.

1.2 The research question

The basic question the Committee investigates is, whether there are indications for a causal relationship between exposure to radiofrequency electromagnetic fields (RF EMF) from mobile phones and tumours in the brain and various other tissues in the head (e.g. meninges, acoustic nerve, parotid glands). To this end, the Committee performs systematic analyses of the epidemiological and animal experimental literature. This report contains the results of the systematic analysis of the epidemiological evidence. Any associations observed in epidemiological studies may be indicative for a causal relation, but in general it is difficult to establish a causal relation from epidemiological evidence only, unless the association is consistently observed and the risk observed is high. Observing an exposure-response relationship is also an indication for a causal association. If this is not the case, additional evidence from experimental studies need to be investigated also. Therefore a second report will deal with the systematic analysis of animal experiments. The results of these two reports will be combined in a third report, that will present an overall evaluation.

1.3 This report

The Committee has conducted an independent systematic search and review of the epidemiological literature on the relation between exposure to RF EMF from mobile phones and tumours in the brain and other tissues in the head, using objective methods. This report describes the methods used and presents the results of this study.

Following an a priori defined protocol, all relevant studies, both case-control, cohort and other types of studies, were identified, extracted, selected for further analysis and evaluated for their quality.

When analyzing epidemiological data, it is important to take into account a number of considerations formulated by Bradford Hill, in order to conclude on the possibility of a causal relation.[12] These include strength, consistency, temporality, biological gradient (or exposure-response) and plausibility and will be discussed later.

In Chapter 2 the Committee briefly describes the methods and results of the literature search; a full account of this process is provided in Annex B. In

Chapter 3 the methods of data analysis are given, including the extraction of the data (with more details in Annex C) and the evaluation of the quality of the studies (with more details in Annex D). The results of the literature selection through the processes described in Chapter 2 are presented in Chapter 4, organized by type of study (cohort, case-control, case-case and ecological), with some remarks on strengths and weaknesses of the different study types. Annex E to this chapter gives more details on the supporting literature, that is not included in the main text. Annex F to this chapter gives the results of the data extraction for core publications. The results of the quality evaluations of the selected studies are given in Chapter 5, with more details on the qualitative evaluation in Annex G. Chapter 6 presents a summary of the results of the selected studies, with more details given in Annex H. In Chapter 7 the Committee discusses and integrates the results (with detailed results of a meta-analysis presented in Annex I) and the report is finalised with the conclusions and recommendations presented in Chapter 8.

Chapter 2

Literature search

2.1 Method

A systematic approach was followed to search for relevant publications. The search strategy and the methods of data analysis were determined before the start of the study. Using a combination of different keywords (cellular phone; mobile phone; cell phone; epidemiology; exposure assessment; dosimetry; radio waves; radio frequencies; electromagnetic fields; human; tumour; cancer; neoplasms), PubMed was searched, followed by hand-searching of reviews and other key papers. Initial searches were performed in the week of 20 July 2009 with a full repeat search on 15 August 2011, updated on 10 July 2012. A full account of this process is presented in Annex B.

2.2 Results

There were 2083 publications identified in the final search. After the selection process, which is summarized in Figure 1 and Annex B, 85 publications remained that described original studies. These were subsequently analyzed as described in the next chapter.

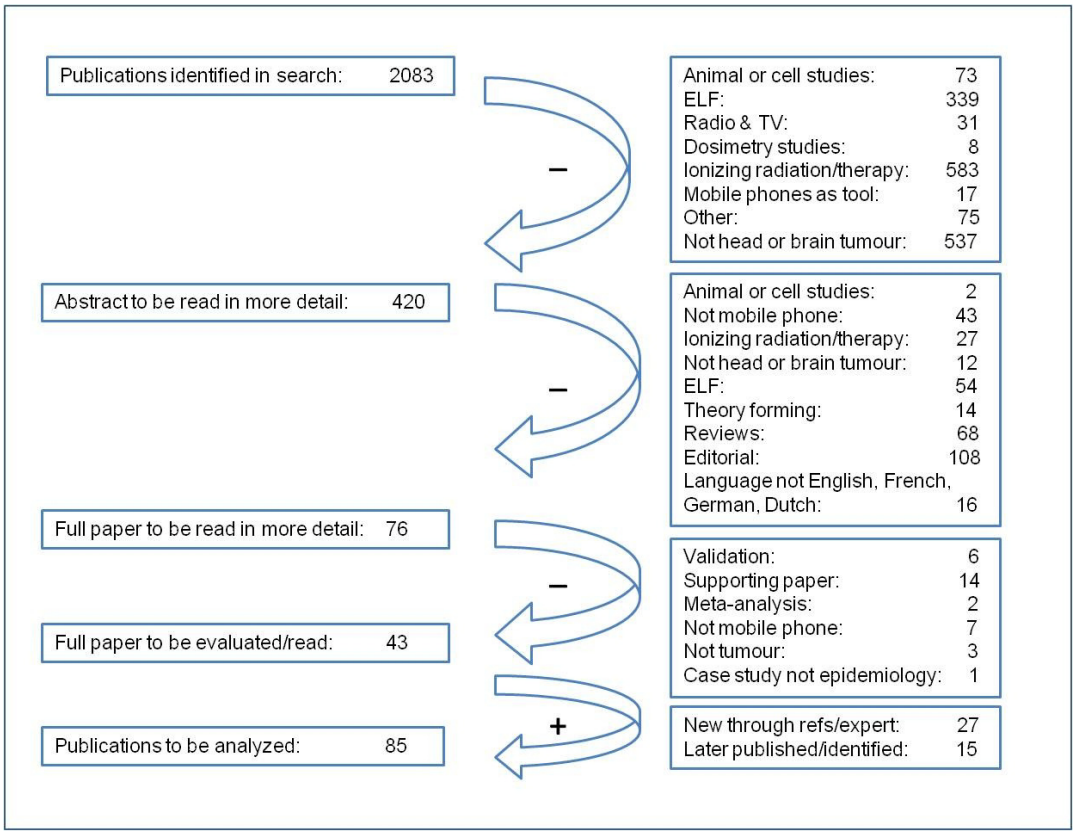

Figure 1 The selection of publications after the search.

Chapter 3

Methods of data analysis

Prior to the analysis, literature searches were conducted on methods used for systematic review of observational research data. The results were used to develop methods for data-extraction and -evaluation.

3.1 Data extraction

Searches in PubMed, Web of Science and Cochrane resources identified several systematic reviews that included elaborate descriptions of methods of data extraction.[13-21] This material was used to check and expand the most extensive checklist identified. Particularly expansion for exposure assessment aspects was found to be needed as most checklists mainly focus on disease outcomes and the selection of the study populations.

To ensure that important aspects were included, also a brief review of the epidemiology of relevant tumours was conducted. Relevant tumours were thought to be those related to the brain (including those of the acoustic system) and tumours of the parotid glands.[22-36] Potential confounders (general risk factors for the relevant tumours) identified from this literature were age, sex, allergies and atopy, ethnicity (Caucasian vs. African or Asian) and a history of head irradiation. However, the associations were different for the different tumours.

Taking these issues into account, the checklist presented in Table C1 in Annex C was developed and used in this study.

The 85 selected publications were extracted independently by two trained epidemiologists. Conflicts of interpretation were resolved by discussion. There were no disagreements that necessitated third party arbitration. All extracted data were double checked for factual correctness (numbers in tables and graphs particularly) by a third party.

Studies and publications

In several cases, a single study or dataset was described in several publications. To evaluate all aspects of study design, studies have been extracted and evaluated as a whole. Not all publications contained all the information that was to be included in the extraction. Missing information could mostly be obtained from other publications on the same study. In some cases additional information was obtained by contacting the main author of the study. This will be specifically indicated in the presentation of results.

The use of different publications to extract the results on different endpoints from a particular study carries the risk of double counting of data and therefore of overweighting the study. This has been carefully avoided. In the analysis by disease, the most recent and most complete publication from each study per tumour type was used. Only if a specific aspect was not described in the preferred publication, another paper was used to extract the data.

Other information used

Several papers generated Letters to the Editor. Most of these were identified in the literature search, others became available through other retrieval methods. They were used as supporting material together with the responses of the authors. This was also the case for editorials and commentaries.

3.2 Evaluation of the quality of studies

The Committee thought it to be helpful for the interpretation of the data to consider some form of scoring or weighting of the evidence. Several of the reviews mentioned in 1.1 have actually applied some quality evaluation, although this was not[11] or not clearly used[5] in the overall analysis.

A separate literature search for publications evaluating such scoring methods was performed and methods used by (collaborators of) Committee members were also considered. Several publications were identified that reviewed scoring methods for the quality of publications.[37-39] One paper also validated domains

for assessment used in the various methods.[40] However, various authors have been quite strongly opposed to the use of scoring in general or of specific scoring methods.[41-44] As a compromise the Committee uses the scores only to summarize the overall methodological quality of the selected papers and to present this in an overview, but not as a numerical weight in an overall analysis.

The Committee used the evaluation method of Monninckhof et al.[45] as basis. Since this method was originally developed for studies on physical activity and breast cancer risk, slight modifications were introduced for the current purpose. To evaluate the method, the opinion of external experts was sought regarding the evaluation items themselves and the weights to be allocated. The Committee further developed this into the detailed list of questions that is described in Table D1 in Annex D. They are categorized into the main domains identified in the literature on quality evaluation: selection of cases and controls, tumour diagnosis, assessment of exposure, confounding and conflict of interest. Further elaboration follows in Chapter 5.

Chapter 4

Study design and methods

The different studies identified are first described by study design: cohort, case-control, case-case and ecological studies. There are no intervention studies. Pooled analyses of studies from a particular study group are used preferentially. Meta-analyses are not included, since only primary studies were to be part of this review. Only data from the original publications are given here, additional information used in the evaluation is presented in Annex E and results of the extraction for selected publications as highlighted in the tables is presented in Annex F.

But before giving the descriptions of the studies, it is necessary to discuss briefly different biases that may occur.

4.1 Bias

Recall bias

A major problem with many epidemiological studies is obtaining accurate information on past exposure. This is usually dependent on the memory of the subjects under study. Apart from the problem that the recollection of specific exposures in the sometimes distant past is generally inaccurate, memory may also be influenced if someone is aware that he or she has a particular disease: cases may report their exposure more accurately than controls, because the latter feel less involved in the study, or cases may overestimate their exposure, because

they believe the exposure caused their disease. The accuracy of recollection of exposure may therefore differ between cases and controls. This is known as differential recall bias and can affect the outcome of the study.

Since in particular brain tumours have a very poor prognosis, it is important that cases be identified and interviewed soon after diagnosis. The accuracy of information of mobile phone use provided by family members when the patient is too ill to be interviewed or deceased, is considered to be less than that provided by the cases themselves.[46]

Observation bias

If the researchers collecting the information via interviews or questionnaires are aware of the disease status of the study subjects, this may result in observation bias that may compound the recall bias. Both types of bias may result in differential misclassification, i.e. they affect case and control data differently. This usually results in overestimation of the actual risk, although underestimation is also possible.

Selection bias

An important issue with case-control studies is the selection of cases and controls. Ideally, the two groups should come from the same population and be sampled over the same period of time. If this is not the case, this may result in selection bias. Also, relatively high response rates are important, as these will reduce the risk of selection bias. This type of bias also may result in over- or underestimation of the actual risk.

4.2 Cohort studies

In this study design a group of subjects that is initially free of the disease(s) of interest, the cohort, is followed over a certain period of time. During follow-up, the occurrence of the disease(s) of interest is registered and exposure to the factor(s) of interest is monitored or measured. At relevant follow-up times, disease incidence in different exposure groups can be determined and the risk of exposure calculated. Cohort studies can be either prospective or retrospective. The major advantage of prospective cohort studies is that the exposure is measured before the occurrence of the disease and that changes in exposure can be measured as they occur. This type of studies is thus not vulnerable to recall bias, i.e. misclassification of (past) exposure. In retrospective cohort studies the

exposure took place in the past and is reconstructed using routine data such as employment records or e.g. subscriptions. Changes in exposure or precise estimates can be difficult to assess in retrospective cohort studies. Cohort studies examining brain cancers have some drawbacks. Because the disease is relatively rare, the cohort needs to be very large. The disease has a long latency period, i.e. it may take a long time after induction before the disease becomes manifest (see Chapter 6), therefore the follow-up period of the cohort needs to be long, up to several decades. Exposure assessment over such a long time period may give problems, particularly with changing exposures such as from (mobile) phone use.

Six publications on cohort studies were identified, based on two cohorts.[47-52] Table 4.1 presents the publications of the original studies. The studies selected for evaluation and final analysis are indicated in boldface type.

With mobile phone use, the exposure may fluctuate and change over time, which can lead to non-differential misclassification. It is therefore important to perform regular exposure assessments in cohort studies.

The first of the two cohorts discussed in this report is from the USA, with publications from Rothman et al. (1996)[49] and Dryer et al. (1999).**[47]** The main problems are the short period of follow up (the median duration of a mobile phone subscription in the highest category was 3.8 years) and the fact that mortality and not incidence was investigated. Therefore the results are only relevant for the question whether mobile phone use might act as a promoter

Table 4.1 Cohort studies.

Reference	Type of tumour	Exposure assessment	Country / time period / ages
Rothman et al. (1996)[49]	None; overall mortality	Length contract, type phone, duration calls	Boston, Chicago, Dallas, Washington DC/ USA/ 1994 ≥ 20 y at start
Dreyer et al. (1999)[47]	Brain cancer	Idem	Idem ≥ 20 y at start
Johansen et al. (2001)[48]	Cancer, including brain & central nervous system tumours, parotid gland tumour	Length of contract for those with contract before 1996	Denmark, 1982-1996 ≥ 30 y at start
Schüz et al. (2006)[50]	Cancer, including glioma, meningioma, acoustic neuroma, parotid gland tumour	Idem	Denmark, 1982-2002 ≥ 30 y at start
Schüz et al. (2011)[51]	Vestibular schwannoma (acoustic neuroma)	Idem	Denmark, 1982-2006 ≥ 30 y at start
Frei et al. (2011)[52]	Brain tumours, including glioma, meningioma	Idem	Denmark, 1982-2007 ≥ 30 y at start

The publications indicated in bold were used for quality evaluation.

for brain cancers, but even then the promoting effect would have to cause a considerable acceleration of tumour growth to result in measurable changes in mortality in such a short time period.

The second cohort is from Denmark, with a maximum follow up time of 21 years, with publications from Johansen et al. (2001), Schüz et al. (2006, 2011) and Frei et al. (2011).[48,50-52] This is a very large retrospective cohort study, in which mobile phone company records were used to determine whether a private mobile phone subscription was started before 1996. These data thus do not provide information on actual exposure to radiofrequency fields such as number and duration of calls.

A large multinational prospective cohort study (COSMOS) has recently been started, but it will take many years before results are available. The study design is described by Schüz et al. (2011).[53]

There were 15 (invited) Letters to the Editor or Editorials and one supplementary publication concerning the cohort studies. They are listed in Annex E, Table E1. Results from the data extraction are presented in Annex F.

The evaluation of the methodological quality of the cohort studies is presented in Chapter 5, Table 5.1, more details are given in Annex G, Table G2.

4.3 Case-control studies

In this study design a comparison is made between a group of subjects with a given disease (cases) and a suitable control group of subjects without the disease. The past history of exposure to a suspected risk factor is determined and groups of cases and controls with similar exposures are compared. This allows the (relative) risk of exposure to be calculated, i.e. the risk of exposure to the factor under investigation relative to the combined risk of all other factors that are not studied.

In the studies of cancer in relation to mobile phone use, the case-control studies come in three ‘clusters’ according to the study protocol used. The first group of studies contains those performed by Hardell et al.; these all used the same protocol. The second group of studies contains those from the INTERPHONE program; they all used a core protocol developed in collaboration with the International Agency for Research on Cancer (IARC). The third group contains all other case-control studies identified, that used a variety of protocols.

4.3.1 *Case-control studies according to the Hardell protocol*

This group contains 18 publications of closely related studies, sometimes using the same data or combining the data used in previous publications.[1,54-70] They all used the same study protocol and the same method of data collection, such as the same questionnaire and additional interview methods. Upon request, Hardell provided the questionnaire and informed the Committee that in all cases additional information was obtained by telephone interview, during which the interviewers were blinded for case-status. The Committee did not have access to the questions used in the telephone interviews.

Hardell et al. performed three distinct case-control studies (designated 1, 2, and 3 in Table 4.2) that included only prevalent cases, i.e. respondents who were alive at the time of enrolment. A fourth study interviewed family members of deceased cases. Unfortunately there is some overlap in successive papers on the same studies, and many different subgroups are analysed. This makes it sometimes difficult to get a clear picture of the studies by the Hardell group and also increases the occurrence of significant results just by chance. Hardell et al. also performed several pooled analyses, in which the results from their studies 2 and 3 and sometimes 4 are combined. The pooled study that included the deceased cases is the most complete one, because it addresses all incident cases. Table 4.2 presents the publications on the original and pooled studies. The studies selected for evaluation and final analysis are indicated in boldface type.

There were two Letters to the Editor identified and one supporting paper and these are listed in Annex E, Table E2. Results from the data extraction are presented in Annex F.

The quality evaluation of these studies is presented in Chapter 5, Table 5.1 with details given in Annex G, Table G3.

Table 4.2 Case-control studies of the Hardell group.

Reference	Type of tumour	Original / pooled / study no.	Population / hospital based / ages	Response (%)		Time period / place/ topic of analysis
				Published	Recalculated [a]	
Hardell et al. (1999)[1]	Brain tumour (incl. glioma, meningioma, acoustic neuroma)	Original 1	Population 20-80 y old	Cases: 90% Controls: 91%	Cases: 77% Controls: 79%	1994-1996/ 2 city regions Sweden
Hardell et al. (2001)[54]	Brain tumour	Original 1	Population 20-80 y old	Cases: 90% Controls: 91%	Cases: 77% Controls: 79%	1994-1996/ 2 city regions Sweden
Hardell et al. (2002)[55]	Brain tumour (incl. glioma, meningioma, acoustic neuroma)	Original 2	Population 20-80 y old	Cases: 88% Controls: 91% but complete pairs 81% as used for analysis	Cases: 72% Controls: xx% (no details given)	1997-2000/ 4 city regions Sweden
Hardell et al. (2002)[56]	Malignant brain tumour (incl. glioma)	Original 2	Population 20-80 y old	Cases: 91% Controls: 90% but complete pairs 82%	Cases: 59% Controls: 90%	1997-2000/ 4 city regions Sweden
Hardell et al. (2003)[57]	Brain tumour (incl glioma, meningioma, acoustic neuroma)	Original 2	Population 20-80 y old	Cases: 88% but is only 63% of cases reported in cancer registry Controls: 91%	Cases:72% Controls: xx% (no details given)	1997-2000/ 4 city regions Sweden
Hardell et al. (2004)[69 b]	Parotid gland tumour	Original	Population 20-80 y old	Cases: 91% Controls: 92%	Cases: 64% Controls: 90%	1994-2000/ 6 city regions Sweden
Hardell et al. (2004)[71]	Brain tumour	Original 2	Population 20-80 y old	Cases:88% Controls: 91%	Cases: 65% Controls: xx% (no details given)	1997-2000/ central region Sweden/ Age
Hardell et al. (2005)[59]	Brain tumour	Original 2	Population 20-80 y old	Cases: 88% but is only 63% of cases reported in cancer registry Controls: 91%	Cases: 72% Controls: xx% (no details given)	1997-2000/ central region Sweden/ Rural vs. urban
Hardell et al. (2005)[60]	Acoustic neuroma, meningioma	Original 3	Population 20-80 y old	Cases: 89% (but 18 not incl. as deceased) Controls:88%	Cases:59% Controls: xx% (no details given)	2000-2003/ 2 city regions Sweden
Hardell et al. (2006)[61]	Malignant brain tumour	Original 3	Population 20-80 y old	Cases: 88% Controls: 84%	Not enough detail for calculation	2000-2003/ 2 city regions Sweden
Hardell et al. (2010)[62]	Malignant brain tumour	Original 4	Population 20-80 y old	Cases: 75% Controls 67% (average) Controls cancer: 74% Controls other diseases 60%	Cases: 65% Controls: xx% (no details given)	1997-2003/ 4 city regions Sweden
Söderqvist et al. (2012) [72]	Parotid gland tumour	Original	Population 22-80 y old	Cases: 88%, Controls: 83%	Cases: 75% Controls: 83%	2000-2003 / 3 city regions (9/21 counties) Sweden

Hardell et al. (2006)[63]	Malignant brain tumour	Pooled 2+3	Population	Cases: 90% but this is only 65% of cancer registry cases Controls: 89%	Not enough detail for calculation	1997-2003
Hardell et al. (2006)[64]	Benign brain tumour (incl. meningioma, acoustic neuroma)	Pooled 2+3	Population	Cases: 88% Controls: 89%	Not enough detail for calculation	1997-2003
Hardell et al. (2006)[67]	Brain tumour (incl. glioma, meningioma, acoustic neuroma), parotid gland tumour	Pooled 2+3	Population	Cases:88% Controls: 84%	Not enough detail for calculation	1997-2003 Mobile+cordless
Hansson Mild et al. (2007)[65]	Brain tumour (incl. glioma, meningioma, acoustic neuroma)	Pooled 2+3	Population	Cases: 90% (malignant tum.); 88% (benign tum., incl. meningioma, acoustic neuroma) Controls: 89%	Not enough detail for calculation	1997-2003
Hardell et al. (2009)[66]	Brain tumour (incl. glioma, meningioma, acoustic neuroma)	Pooled 2+3	Population	Cases: 90% (malignant tum.); 88% (benign tum., incl. meningioma, acoustic neuroma) Controls: 89%	Not enough detail for calculation	1997-2003 Mobile+cordless
Hardell et al. (2011)[68]	Malignant brain tumour	Pooled 2+3+4	Population	Cases: 85% Controls: 84%	Not enough detail for calculation but as includes deceased expected similar	1997-2003

[a] Recalculated by including excluded cases that were deceased or declared too ill by their physician. This was only done for the studies where these subpopulations had been included in the response calculations.
[b] The publications indicated in bold were used for quality evaluation.

4.3.2 *Case-control studies according to the INTERPHONE protocol*

In the INTERPHONE consortium 16 research groups conducted case-control studies on different types of tumours in the head and neck area, including the brain, in 13 countries using a common core protocol.[73,74] Several groups published their data individually, several pooled assessments of a limited number of groups were made, and for glioma and acoustic neuroma pooled analyses of the data from all groups have been published (which was the initial objective of the INTERPHONE studies). In all the studies data were collected by computer-assisted personal interview.[74]

The 20 publications on original and pooled data are presented in Table 4.3. The studies selected for evaluation and final analysis are indicated in boldface type.

Table 4.3 Case-control studies of the INTERPHONE consortium.

Reference	Type of tumour	Original / pooled	Population / hospital based / ages	Response (%)	Country [a]; specific topic
Christensen et al.(2004)[75]	Acoustic neuroma	Original	Population 20-69 y old	Cases: 82% Controls: 64%	Denmark
Lönn et al. (2004)[76]	Acoustic neuroma	Original	Population 20-69 y old	Cases: 93% Controls: 72%	3 cities Sweden
Christensen et al.(2005)[77]	Glioma, meningioma	Original	Population 20-69 y old	Cases: glioma 71%; meningioma 74% Controls: 64%	Denmark
Lönn et al. (2005)[78]	Glioma, meningioma	Original	Population 20-69 y old	Cases: glioma 74%, meningioma 85% Controls: 71%	4 cities Sweden
Klaeboe et al. (2007)[79]	Glioma, meningioma, acoustic neuroma	Original	Hospital for cases, population controls? 19-69 y old	Cases: 74% Controls: 69%	2 regions Norway
Schüz et al. (2006)[80]	Glioma, meningioma	Original	Hospital for cases, population controls? 30-59 y old	Cases: glioma 80%, meningioma 88% Controls: 63%	4 cities Germany; DECT base stations
Schüz et al. (2006)[81]	Glioma, meningioma	Original	Hospital for cases, population controls? 30-59 y old	Cases: glioma 80%, meningioma 88% Controls: 63%	4 cities Germany
Lönn et al. (2005)[82]	[b]Parotid gland tumour	Original	Population 20-69 y old	Cases: 85% overall (79% Denmark, 89% Sweden) Controls:70% overall (60% Denmark, 72% Sweden)	Denmark, 3 cities Sweden
Takebayashi et al. (2006)[83]	Acoustic neuroma	Original	Hospital for cases, population controls 30-69 y old	Cases: 84% Controls:52%	Greater Tokyo area, Japan
Hepworth et al. (2006)[84]	Glioma	Original	Population for cases, GP's for controls SE: 18-59 y NE: 18-69 y	Cases: 51% Controls: 45%	South-east, north-east UK
Sadetzki et al. (2008)[85]	Parotid gland tumour	Original	Population ≥ 18 y of age	Cases: 87% Controls: 66%	Israel
Schlehofer et al. (2007)[86]	Acoustic neuroma	Original	Hospital for cases, population controls 30-59 y old	Cases: 89% Controls: 55%	4 cities Germany

Hours et al. (2007)[87]	Glioma, meningioma, acoustic neuroma	Original	Population 30-59 y old	Cases: glioma 60%, meningioma 78%, acoustic neuroma 81% Controls: 75%	Lyon, France
Takebayashi et al. (2008)[88]	Glioma, meningioma, pituitary adenoma	Original	Hospital for cases estimated to represent 75% of total # of cases in area, population controls 30-69 y old	Cases: glioma 59%, meningioma 78%, pituitary adenoma, 76% Controls: 51%	Greater Tokyo area, Japan
Schoemaker et al. (2009)[89]	Pituitary tumours	Original	Population for cases, GP's for controls 18-59 y old	Cases: 61% (calculated) Controls 43%:	South-east UK
Schoemaker et al. (2005)[90]	Acoustic neuroma	Pooled	Mixed	Cases: 83% (69-91%) Controls: 51% (42-69%)	Nordic countries, south-east UK
Lahkola et al. (2007)[91]	Glioma	Pooled	Mixed	Cases 69%:(37-81%) Controls: 50% (42-69%)	Nordic countries, south-east UK
Lahkola et al. (2008)[92]	Meningioma	Pooled	Mixed	Cases: 74% (55-90%) Controls: 50% (42-69%)	Nordic countries, south-east UK
INTERPHONE study group (2010)[93]	Glioma, meningioma	Pooled	Mixed	Cases: glioma 64% (36-92%), meningioma 78% (56-92%) Controls: 53% (42-74%)	13 countries
INTERPHONE study group (2011)[94]	Acoustic neuroma	Pooled	Mixed	Cases: 82% (70-100%) Controls: 53% (35-74%)	13 countries

[a] Nordic countries: Denmark, Norway, Sweden & Finland;13 countries: Nordic, Australia, Canada, France, Germany, Israel, Italy, Japan, New Zealand, north-east & south-east UK.
[b] The publications indicated in bold were used for quality evaluation.

Fifteen supporting papers and 30 comments as well as Letters to the Editor and associated author responses were also considered in the context of these publications. These are listed in Annex E, Table E3. Results from the data extraction are presented in Annex F.

The quality evaluations of these case-control studies are presented in Chapter 5, Table 5.1; details are given in Annex G, Table G3.

4.3.3 *Case-control studies according to other protocols*

This group contains 14 publications on original investigations related to mobile phone use.[95-108] A wide variety of methods for data collection and population sampling was used. The information on potential exposure (retrospectively gathered as in all case-control studies) was limited in most of these studies; also the number of cases and controls in the categories with longer exposure duration

was extremely limited. For most of the studies the total number of participants was very small (often not more than 25), and the duration of exposure to mobile phones short (less than 5 years; see the details in the tables in Annex F). Therefore, the relevance to the interpretation of long-term effects is minimal. The details of the publications of case-control studies according to other protocols are presented in Table 4.4. The studies selected for evaluation and final analysis are indicated in boldface type.

Table 4.4 Other case-control studies.

Reference	Type of tumour	Original / pooled	Population / hospital based / ages	Response (%)	Time period / place / country
Inskip et al. (1999)[95]	Glioma, meningioma, acoustic neuroma	Original	Hospital ≥ 18 y old	Cases: 92% Controls: 86%	1994-1998 Phoenix, Boston, Pittsburgh, USA
Muscat et al. (2000)[96] [a]	Primary brain cancer, incl. glioma	Original	Hospital 18-80 y old	Cases: 82% Controls: 90%	1994-1998 New York, Providence, Boston, USA
De Roos et al. (2001)[97]	Neuroblastoma	Original	Hospital ≤ 19 y old	Cases: 73% Controls: 71%	1992-1994 139 hospitals, USA & Canada
Stang et al. (2001)[98]	Uveal melanoma	Original	Population 35-69 y old + Hospital 35-74 y old	Cases: 84% Controls: 81%	1994-1997 Essen+ all of Germany
Inskip et al. (2001)[99]	Glioma, meningioma, acoustic neuroma	Original	Hospital ≥ 18 y old	Cases: 92% Controls: 86%	1994-1998 Phoenix, Boston, Pittsburgh, USA
Auvinen et al. (2002)[100]	Glioma, meningioma, parotid gland tumour	Original	Population 20-69 y old	Cases: 100% Controls: 100% as register-based	1996 All Finland
Muscat et al. (2002)[101]	Acoustic neuroma	Original	Hospital ≥ 18 y old	Cases: 100%? Controls: 100%?	1997-1999 New York, USA
Warren et al. (2003)[102]	Intratemporal facial nerve tumours	Original	Hospital Cases: mean 47 y old Controls: mean 57.8, 52.6, 50.8 y old	Cases: 100%? Controls: 100%?	1995-2000 Gainesville (Fl), USA
Gousias et al. (2009)[103]	Glioma	Original	Population 22-82 y old	Cases: 100%? Controls: 100%?	2005-2007 6 districts of Greece
Stang et al. (2009)[104]	Uveal melanoma	Original	Hospital 20-74 y old	Cases: 94% Controls: 57% (hospital) & 52% (population)	2002-2004 Essen, Germany

Spinelli et al. (2010)[105]	Glioma	Original	Hospital ≥ 18 y old	Cases: 72% Controls: 100%?	2005 Marseille, Toulon, France
Duan et al. (2011)[106]	Parotid gland tumour	Original	Hospital 7-80 y old	Cases: 78% Controls: 62%	1993-2010 Beijing, China
Baldi et al. (2011)[107]	Brain tumours	Original	Population ≥ 15 y old	Cases: 70% Controls: 69%	1999-2001 Gironde, France
Aydin et al. (2011)[108]	Brain tumours children	Original	Population 7-19 y old	Cases: 83% Controls: 71%	2004-2008 All of Denmark, Sweden, Norway, Switzerland

[a] The publications indicated in bold were used for quality evaluation.

Two supporting papers were identified for these case-control studies. They are listed in Annex E, Table E4. Results from the data extraction are presented in Annex F.

The quality evaluation of the original studies is presented in Chapter 5, Table 5.1 and details are given in Annex G, Table G3.

4.4 Case-case studies

This study design compares two or more groups of cases that differ in a specific characteristic, such as exposure or location of the tumour. Comparison of for instance reported mobile phone use by cases with a tumour closer to the surface with that of cases with a tumour at more central locations in the brain, may provide supporting information on a possible causal relation between exposure and disease. Since differential recall bias is less likely (because only cases are included) the influence of recall bias in case-case studies is minimised. It is however not entirely gone, as people may be aware of the location of the tumour and thus report accordingly.

Six publications of this design were identified and details are presented in Table 4.5.[109-113] The studies selected for evaluation and final analysis are indicated in boldface type.

Table 4.5 Case-case studies.

Reference	Type of tumour	Exposure estimate	Original / pooled / meta analysis	Response (%) / ages
Ali Kahn et al. (2003)[109]	Glioma	Handedness in phone users vs. tumour location	Original	100% 20-81 y old
Salahaldin & Bener (2006)[110]	Acoustic neuroma	Possession of phone (yes / no)	Original	100%? 34-66 y old
Hartikka et al. (2009)[111]	Glioma	Distance phone - tumour	Subsample of INTERPHONE	100% (published) 69% (calculated) 20-60 y old

Sato et al. (2010)[112]	Acoustic neuroma	Intensity of phone use and laterality vs. tumour location and size	Original	51% ≥29 - ≤70 y old
Cardis et al. (2011)[114]	Glioma, meningioma	Intensity of phone use; based on calculated RF energy	Subsample of INTERPHONE Australia, Canada, France, Israel, New Zealand	Cases: glioma 42% meningioma 56% Controls: for glioma 36%, for meningioma 40% 30-59 y old
Larjavaara et al. (2011)[113]	Glioma	Case-specular* Based on calculated RF exposure	Subsample of INTERPHONE Denmark, Finland, Germany, Italy, Norway, Sweden, Southeast England	63% 18-59 y old

* Simulated case
The publications indicated in bold were used for quality evaluation.

No Letters to the Editor or supporting papers were identified. Results from the data extraction are presented in Annex F. The quality evaluation of these studies is presented in Chapter 5, Table 5.1, with details given in Annex G, Table G4.

4.5 Ecological studies

These studies investigate the occurrence of disease at population level in relation to the prevalence of (a proxy for) exposure in the population. They may analyze for instance the pattern of tumour occurrence over time (either by incidence or by mortality) in geographic entities such as countries, to identify any trends and to see whether these could be explained e.g. by trends in possession or use of mobile phones. Individual data on mobile phone use are not used in these studies. Such studies will inherently be limited by the poor level of insight into trends and patterns of mobile phone use, and hence of actual exposure, particularly for specific age, sex and other population group definitions.

It should be noted that for many countries substantial and wide-spread mobile phone use is relatively recent (Figure 2).

In most Western-European countries approximately half of the population had a mobile phone subscription in the year 2000. In the Nordic countries (Norway, Sweden, Finland and Denmark) the increase started earlier, but was caught up by the other countries around the century mark. By 2005 most people in the countries presented (except France and the USA) owned a mobile phone, but the extent of use is much less certain.

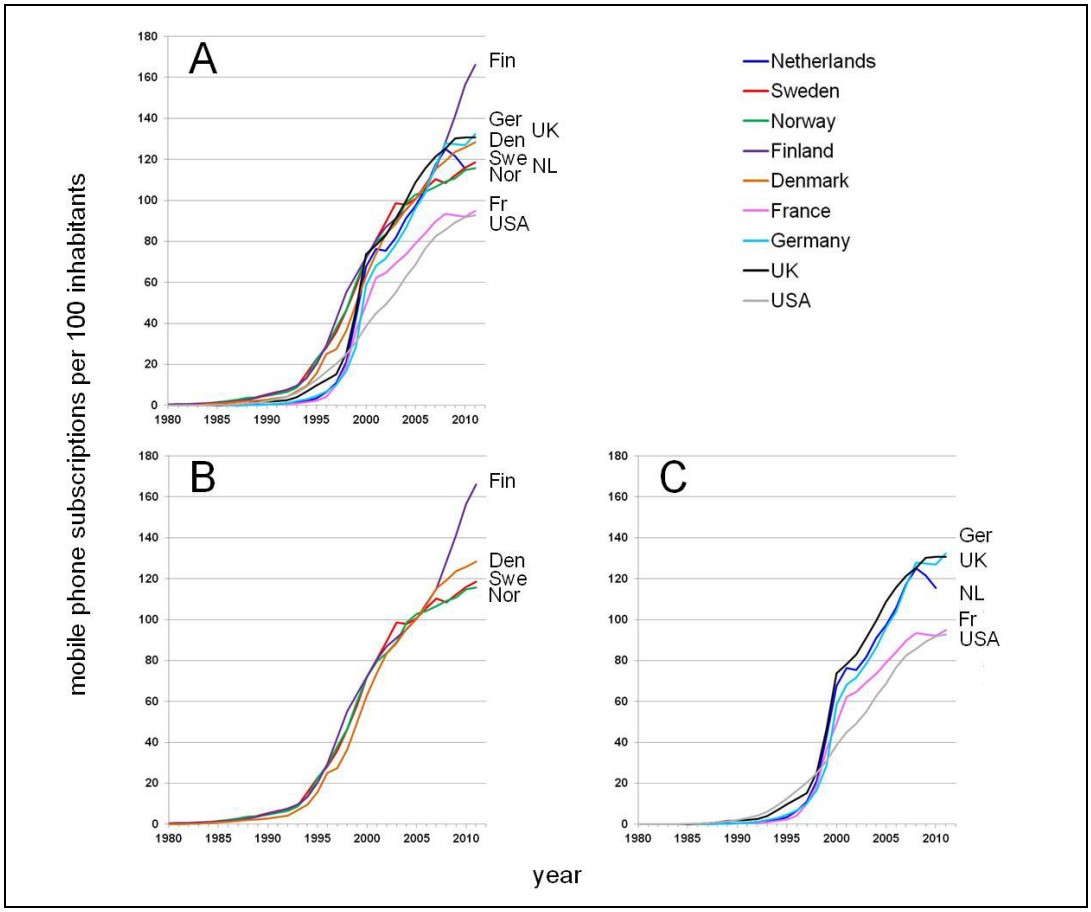

Figure 2 Number of mobile phone subscriptions for some European countries and the USA. Panels B and C show the same data as panel A, but separated for Nordic and other countries. Data from ITU (http://www.itu.int/ITU-D/ict/statistics/explorer/index.html).

Taking into account that the latency period of brain tumours is likely more than 10 years (see Chapter 6), it is thus possible that any trends in tumour occurrence related to mobile phone use may not yet be visible in most countries, with an exception perhaps for the Nordic countries, since use started earlier there.

In analyzing ecological studies, it has to be realized that trends in mortality can also be influenced by the introduction of more effective treatments and that trends in incidence can be affected by changes in diagnostic techniques.

Ecological studies identified in this search were performed in various countries and totalled 21 publications.[115-121,58,122-125,125-133] A summary of the publications is presented in Table 4.6.

Table 4.6 Ecological studies.

Reference	Tumour type, Endpoint	Exposure assessment	Time period	Country
Counsell et al. (1996)[126]	Brain tumours	Trend, not in relation to phone possession or use	1989-1990	Scotland
Howitz et al. (2000)[116]	Acoustic neuroma	Trend, not in relation to phone possession or use	1977-1995	Denmark
Gurney & Kadan-Lottick (2001)[127]	Brain tumours	Trend, not in relation to phone possession or use	1975-1997	USA, 11 states
Cook et al. (2003)[115]	Head and neck tumours	Trend, in relation to phone possession and exposure (from location of tumour)	1986-1998	New Zealand
Inskip et al. (2003)[117]	Ocular melanoma	Right- vs. left sided tumours (assuming predominantly right sided phone use): trends & contrast pre/post 1995	1974-1998	USA, 5 states & 4 metropolitan areas
Hardell et al. (2003)[58]	Brain tumours, acoustic neuroma	Trend, not in relation to phone possession or use	1960-1998	Sweden
Lönn et al. (2004)[119]	Primary brain tumours	Trend, in relation to phone subscriptions	1996-1998	Denmark, Finland, Norway and Sweden
Muscat et al. (2006)[120]	Neuronal brain cancers	Contrast pre/post 1985, in relation to phone subscriptions	1973-2002	USA, 5 states & 4 metropolitan areas
Nelson et al. (2006)[128]	Acoustic neuroma	Trend, in relation to phone subscriptions	1979-2001	England & Wales
Röösli et al. (2007)[121]	Brain tumour	Trend, in relation to predicted phone use based on subscriptions	1969-2002	Switzerland
Deltour et al. (2009)[122]	Glioma, meningioma	Trends, in relation to general mobile phone use pre/post mid 1990s	1974-2003	Denmark, Finland, Norway & Sweden
Inskip et al. (2010)[123]	Brain cancer	Trends, in relation to phone subscriptions	1997-2006	USA, 5 states & 4 metropolitan areas (10% USA population)
Lehrer et al. (2010)[124]	Primary brain tumours	Relation with subscriptions in 2007; comparison of 19 states	2007	USA, 19 states
Johansen et al. (2002)[118]	Ocular melanoma	Trend, in relation to phone subscriptions	1943-1996	Denmark
Czerninski et al. (2011)[129]	Parotid gland tumour	Trends, in relation to increase in phone use	1970-2000	Israel
De Vocht et al. (2011)[130]	Brain tumours	Trends, in relation to phone subscriptions	1998-2007	England
De Vocht (2011)[134]	Parotid cancer	Trends, in relation to phone subscriptions	1986-2008	England

Kohler et al. (2011)[131]	Brain tumours	Trends, not in relation to phone possession or use	1975-2007	USA, 46 population based cancer (93% USA population)
Larjavaara et al. (2011)[132]	Vestibular Schwannoma (acoustic neuroma)	Trends incl. birth cohorts, not in relation to phone possession or use	1987-2007	Denmark, Finland, Norway & Sweden
Deltour et al. (2012)[135]	Glioma	Trends, in relation to general mobile phone use	1974-2008	Denmark, Finland, Norway & Sweden
Little et al. (2012)[133]	Glioma	Trends, in relation to results from INTERPHONE and Hardell studies	1997-2008	USA 12 SEER regions

Only those investigations using both outcome and exposure are assessed and the most recent investigation of the same data is discussed. These publications are identified in bold type face in Table 4.6.

Two Letters to the Editor were identified and are listed in Annex E. Results from the data extraction are presented in Annex F.

The Committee deemed a quality evaluation of the ecological studies not meaningful.

Chapter 5

Evaluation of study quality

To prevent evaluation of multiple publications on the same study, only the most recent publication for each data set for a specific outcome was selected.

The full list with items used for the evaluation is shown in Table D1 in Annex D. The items are divided into several domains: *Selection bias*, referring to the selection of cases and controls (scored out of 34); *Misclassification of outcome*, referring to the method of ascertainment of tumour diagnosis (scored out of 4); *Misclassification of exposure*, referring to the assessment and classification of exposure (scored out of 69); *Confounding*, referring to the possibility of other factors influencing the outcome (scored out of 16); and *Conflict of Interest*; referring to the possibility that the outcomes were influenced by (financial or other) interests (scored out of 5). The agreed evaluations for these domains for the two scorers are presented in Table 5.1 as percentage of the maximum score for each domain. A detailed listing of the scores for each individual question is given in Tables G1, G2 and G3 in Annex G.

The Committee weighted the domains for the overall rating as 4 (Selection) : 1 (Diagnosis) : 4 (Exposure) : 1 (Confounding) : 0 (Conflict of interest). The Committee considered Conflict of Interest to be important, but it could be poorly assessed due to missing information. The information that was used for scoring were the financial interests declared in the publications. In some cases, earlier publications about the same study revealed interests that were not declared later. This may be correct, as at the time of the later publication the funding may have ceased, but some level of conflict of interest could still be suspected. The

Committee felt that the impact of such financial ties can be widely different and there was insufficient information to take this into account. Also, non-financial interests and professional commitment to an opinion about an association between mobile phone use and brain cancer could also influence the presentation of the results. Again this could not be measured. Therefore the score for Conflict of Interest was not taken into account in the overall score but is only given for information.

5.1 Results of the evaluation of study quality

The final rating is given in the last column of Table 5.1 as a number between 0 and 10. To facilitate distinguishing higher from lower rated studies, they are colour coded, but without any particular meaning of the cut-off values. Ratings of 7.0 and higher are marked green, ratings of between 3.0 and 7.0 are marked yellow, and ratings lower than 3.0 are marked red.

Table 5.1 Results for the evaluation of selected cohort, case-control and case-case studies, grouped by tumour type.

		Domains:	Selection bias	Misclas-sification of outcome	Mis-classifi-cation of exposure	Con-founding	Conflict of interest	Over-all score (0-10)
Reference	Design	Tumour	% of maximum obtainable score					
Dreyer et al.(1999)[47]	Cohort	Brain cancer	100.0	0.0	59.4	75.0	60.0	7.1
Baldi et al. (2011)**[107]**	Ca-co	Brain cancer	64.7	100.0	33.3	75.0	100.0	5.7
Aydin et al. (2011)[108]	Ca-co	Brain tumours children	76.5	100.0	66.7	75.0	100.0	7.5
Frei et al. (2011)**[52]**	Cohort	Glioma, meningioma	100.0	100.0	53.6	75.0	0.0	7.9
Muscat et al. (2000)[96]	Ca-co	Glioma	0.0	100.0	53.6	75.0	0.0	3.9
Inskip et al. (2001)**[99]**	Ca-co	Glioma, meningioma, acoustic neuroma	35.3	100.0	46.4	75.0	100.0	5.0
Auvinen et al. (2002)[100]	Ca-co	Glioma, meningioma, parotid gland tumour	100.0	100.0	66.7	75.0	60.0	8.4
Gousias et al. (2009)**[103]**	Ca-co	Glioma	0.0	100.0	27.5	0.0	100.0	2.1
Spinelli et al. (2010)**[105]**	Ca-co	Glioma	14.7	100.0	27.5	0.0	100.0	2.7
INTERPHONE study group (2010)[93]	Ca-co	Glioma, meningioma	52.9	100.0	68.1	75.0	60.0	6.6
Hardell et al. (2011)[68]	Ca-co	Glioma, meningioma	76.5	100.0	63.8	75.0	100.0	7.4
Ali Kahn et al. (2003)[109]	Ca-ca	Glioma	100.0	100.0	26.1	0.0	100.0	6.0
Hardell et al. (2009)[66]	Ca-co	Acoustic neuroma	76.5	100.0	63.8	75.0	100.0	7.4
Schüz et al. (2011)[51]	Cohort	Acoustic neuroma	100.0	100.0	53.6	75.0	0.0	7.9
Muscat et al. (2002)[101]	Ca-co	Acoustic neuroma	0.0	100.0	42.0	75.0	0.0	3.4
INTERPHONE study group (2011)[94]	Ca-co	Acoustic neuroma	64.7	100.0	68.1	75.0	60.0	7.1
Salahaldin & Bener (2006)[110]	Ca-ca	Acoustic neuroma	100.0	100.0	4.3	0.0	100.0	5.2

Sato et al. (2010)[112]	Ca-ca	Acoustic neuroma	100.0	100.0	63.8	75.0	100.0	8.3
Warren et al. (2003)[102]	Ca-co	Intratemporal facial nerve tumours	0.0	0.0	34.0	0.0	100.0	2.0
Hardell et al. (2004)[69]	Ca-co	Parotid gland tumour	52.9	100.0	63.8	75.0	100.0	6.4
Lönn et al. (2006)[82]	Ca-co	Parotid gland tumour	76.5	0.0	68.1	75.0	60.0	6.5
Sadetzki et al. (2008)[85]	Ca-co	Parotid gland tumour	47.1	100.0	68.1	75.0	60.0	6.4
Duan et al. (2011)**[106]**	Ca-co	Parotid gland tumour	0.0	100.0	63.8	75.0	100.0	4.3
Söderqvist et al. (2012)[72]	Ca-co	Parotid gland tumour	76.5	100.0	59.5	75.0	100.0	7.2
Takebayashi et al. (2008)[88]	Ca-co	Pituitary adenoma	23.5	100.0	71.0	75.0	100.0	5.5
Schoemaker et al. (2009)[89]	Ca-co	Pituitary tumours	64.7	100.0	68.1	75.0	60.0	7.1
Stang et al. (2001)[98]	Ca-co	Uveal melanoma	64.7	100.0	24.6	0.0	100.0	4.6
Stang et al. (2009)[104]	Ca-co	Uveal melanoma	76.5	50.0	79.7	75.0	60.0	7.5
De Roos et al.(2001)**[97]**	Ca-co	Neuroblastoma	0.0	0.0	18.8	0.0	100.0	0.8

Ca-co: case-control, Ca-ca: case-case

Selection bias

Selection biases are distortions that result from procedures used to select subjects and from factors that influence study participation. The common element of such biases is that the relation between exposure and disease is different for those who participate and for all those who should have been theoretically eligible for study, including those who did not participate.[136]

Maximum scores in the selection bias domain are inherently generated for the cohort studies.

A striking feature of the case-control studies in this domain is the generally high response rates of the Hardell studies. These are all population sampled for both cases and controls. Due to the early uptake of mobile phones in Sweden, the later studies have relatively high numbers of respondents with prolonged phone use. The high response rates make the studies adequately representative of population patterns for the exposures measured. However, some investigators have expressed concern that these high levels of response are virtually impossible to attain.[137,138] In their response to a Letter to the Editor on this matter, Hardell et al. claim that they have obtained (very) high response rates in a number of earlier (non-mobile telephone) studies as well; these range from 90-100% for cases and 83-100% for controls.[137] Case-control studies on other topics performed in Sweden in the 1990's using the same methods as Hardell et al., mailed questionnaires and telephone follow-up, obtained response rates of between 59% and 83% for cases and between 53% and 82% for population controls.[139-142] In view of this, the response rates in the Hardell studies are rather high.

However, in the calculation of the response rates for cases in their publications, Hardell et al. incorrectly did not include deceased cases and cases whose participation was denied by their physician, as was done in the INTERPHONE studies. In order to allow a better comparison with other studies, the Committee recalculated the Hardell response rates to include these cases as well. This led to the lower response rates shown in Table 4.3, ranging from 59-72% for cases and 79-90% for controls. The corrected response rates for cases are more in accordance with those from other Swedish studies mentioned above, but those for the controls are still high. This will be discussed later.

The INTERPHONE studies score lower in this domain as they have rather low response rates and may thus suffer more from selection bias than the Hardell studies. For the INTERPHONE study with pooled glioma and meningioma data the overall response rates were 64% for glioma cases, 78% for meningioma cases and 53% for controls.[93] In 6 of the 14 individual country studies control participation was less than 50% (on-line Annex in [93]). These poor response rates for controls may have introduced selection bias, as only the more motivated subjects with potentially different mobile phone use characteristics may have participated. Indeed, a non-response analysis showed that both cases and controls that refused to participate in the main study in general had a lower use of mobile phones than participants.[143] The underestimation of the risk due to selection bias in the INTERPHONE study is raised in the Letters to the Editor as an issue in the interpretation of differences between the findings of Hardell and INTERPHONE (see Annex E). According to the authors of the INTERPHONE study, non-participation bias may have led to a reduction in the odds ratios for regular use of 5-15%.

Comparison of the Hardell response rates with those from INTERPHONE should only be done for the Hardell study that pooled information of living and deceased cases, since that study is used in the analyses in this report. The response rate Hardell reported for cases was 85%, which does not fall into the range of the recalculated response rates of 59-72% indicated above. This might be the case because Hardell did not include those cases for which the physician refused participation as non-responders. The response rate for controls was 84%, which does fall in the range of recalculated values (79-90%). The response rates of INTERPHONE are markedly lower: 64-78% for cases and 53% for controls. The Hardell response rates might reflect a better representation of the population in question than in the INTERPHONE studies, and consequently a lower likelihood of selection bias, but this is challenged by the difference between the reported and recalculated response rates and by the fact that the response rates of the controls in the Hardell studies are much higher than those in other studies.

This has no implications for the scoring in the present (methodological) evaluation, but it does have consequences for the overall appraisal, as will be discussed in later chapters.

The strengths of the INTERPHONE studies are that large numbers of respondents could be achieved by pooling of the results, and that the authors went at great length to study various types of bias involved in these studies.[46,74,143-150] It should be mentioned, however, that there is also a limitation, since the bulk of the data of the pooled INTERPHONE studies is coming from a limited number of countries: for glioma 46.6% of cases come from the UK (with two separate studies in the north and south of the country), Australia and Germany, for meningioma 51.8% of cases come from these three countries, while for acoustic neuroma 44% of cases come from the UK, Australia and France. In the UK and Australia poor response rates were obtained. In Australia, according to information obtained from the investigators, cases were ascertained by hospital sampling and double checked in the cancer registry. Control selection was from the electoral roll and in contrast to the case selection, this would not fully include migrants, thus introducing potential selection bias. Altogether this increases the likelihood of selection bias in the overall INTERPHONE results.

Another limitation of INTERPHONE is that in many countries sampling of controls from the population is difficult. As a result, the pooled database contains a mix of respondents obtained by population sampling, hospital sampling or other sampling methods (see Table 4.5). As such, it may not be fully representative of the target population and therefore potentially biased. It is hard to tell whether this would result in under- or overreporting of the risk. However, the issue needs to be weighed with the relative contribution of certain countries to the pooled results.

Although the INTERPHONE protocol[74] states that a complete population sample for cases and controls was aimed for, case selection in some countries has been incomplete: e.g. in Germany not all hospitals in the regions were covered. Therefore further information was obtained from the authors of the German study. They stated that all cases were referred to the tertiary hospitals for further diagnostic procedures and consultation, even when primarily treated in local hospitals. As a result all cases were seen, even when not admitted, and exclusion of some local hospitals should not have caused selection bias.

For the case-case studies the domain of selection bias is inherently generating maximum scores, since only cases are involved. For some of the studies it is unclear if the included cases do represent a full or at least random selection of the cases available in the target population. In the case-case study by Sato et al.

(2010)[112] the response rate is less than 100%, but the recruiting process seems to have been consistent and transparent, even though some hospitals have been missed. Therefore, there could still have been selection bias in this group, even though this does not show in the scoring.

Misclassification of outcome

In the domain of misclassification of outcome no problems were seen for most of the studies. The outcome is always reasonably well to very well defined and uses histology and location information. For those studies that separated the types of tumours, at least histological information had to be available to do so; this was missing in some publications.

Misclassification of exposure

In the domain of misclassification of exposure the items of interest are the bias resulting from the method of collecting the information on mobile phone use and the validity of the reported information.

The most important cohort study, the Danish cohort study, used an objective but crude measure of exposure: time since first subscription as determined from provider records. The study compared a group of subjects that started a private subscription between 1 January 1982 and 31 December 1995 with the rest of the Danish population. This includes people not using a mobile phone, people that started owning and using a mobile phone after 31 December 1995, and people not owning a phone but having used one owned by others before and/or after 31 December 1995. In the formation of the cohort, business contracts were excluded, because it was not possible to relate these to individual users. This means that a number of potentially heavy users was not included in the 'exposed' group but in the 'unexposed' group (although some business users may have had a private subscription also). The advantage of considering the time since first subscription is that this is objective information. The disadvantage is that, since the subjects were not interviewed, no information is available on phone type or (intensity of) use, and hence actual exposure could not be assessed. In the first publication from 2001[48], which studied the cohort up to the end of 1996, the 'unexposed' population was probably mostly non-exposed, except for the relatively small group of business users. However, in the publications with follow-up up to 2002-2007[50-52], the originally defined group of early users is still being compared to the general population. In these later studies this 'unexposed'

group was clearly not unexposed anymore, as an estimated 100% of the Danish population currently uses mobile phones and many have been doing so for over 10 years, since subjects included in the control group might have started their subscription as early as 1996 (see also Figure 2 in 4.5).[151] Since misclassification in this cohort study is limited to the 'unexposed' group, it can be demonstrated that the effect of misclassification on the calculated risk will only be minimal.[152]

In the Hardell case-control studies, the core information has been gathered with observer blinding by using a mailed-in paper questionnaire. According to the principal investigator, this was a larger questionnaire on environmental factors that contained several questions on mobile telephone use. The Committee received only those questions, that are not very detailed, in particular with regard to assessment of mobile phone use. According to the principal investigator, in all cases additional information was gathered by telephone interviews using a protocol, but this is not available and therefore the validity of the data obtained cannot be checked. This procedure may lead to misclassification bias. Although the interviewers in the Hardell studies had no prior knowledge of the disease status of the respondents, it is likely that the disease status was revealed during the interview. This may have led to observer bias and, hence, differential misclassification with potential overestimation of the risks. As a consequence, the quality of the exposure assessment in the Hardell studies is difficult to judge.

The INTERPHONE studies have the most detailed exposure assessment and have spent much effort in validation of the questionnaire. The assessment of the use of mobile phones in the INTERPHONE studies was done in person, showing pictures of mobile phone models. This makes recall of the types of phone used, and thus of the exposure, more accurate than when phone types are asked for by mail or telephone interview, as in the Hardell studies. Since in the INTERPHONE studies the data were mostly collected by personal (computer-assisted) face-to-face interview, there may have been observer bias, as the cases will have been notably ill. The protocol states that the observers were carefully trained to reduce this effect, but still it is possible that also in the INTERPHONE studies differential misclassification may have occurred.

The INTERPHONE researchers performed several validation studies, such as a separate study on recall bias using healthy volunteers.[146] They used software-modified phones that logged the time and duration of incoming and outgoing calls. These data were compared with the data recalled by the subjects 6-12 months after the data logging period. They observed that the random error in recall was larger for the duration of calls than for the number of calls. In another study they compared call records of the operators with phone use reported by the

subjects. They observed no difference between cases and controls, except that cases over-reported phone use 3-5 years back (but this was based on few cases with long-term data).[46] It is likely that this effect will be stronger with reporting of phone use longer back. There was no operator information on phone use longer than 5 years back. There are no publications describing the validation of mobile phone use in the Hardell studies, but the INTERPHONE validation studies show that in case-control studies in general recall bias is potentially an important source of error. The possible differential long-term recall bias may have resulted in overestimation of the actual risks. This may then counteract the underestimation due to selection bias, as discussed above.

As a result of all these considerations, the scores of the Hardell and INTERPHONE studies in the domain of misclassification are approximately similar.

For the case-case studies the exposure assessment is generally very poorly described, resulting in low scores in this domain. An exception is the publication by Sato et al. (2010)[112].

Confounding

A risk factor for brain tumours is a confounder when the exposure to that factor is associated with the exposure of interest, in this case exposure resulting from the use of mobile or cordless phones.

The publications on the characteristics of mobile and cordless phone use among children and adolescents in the Nordic countries of Europe indicated a clear association between age and use and between gender and use.[153-156] However, the equivalent publications on adults did not provide adequate information.[157,158] No information was found on the extent of use of cordless handsets for landline telephones. The age and sex distributions of cordless phone users are not necessarily similar to that of mobile phone users. It is clear, however, that there is an association between age and sex and mobile phone use, so they are to be considered confounders in the study of the association between mobile phone use and brain tumours. For cordless phones this is less clear, but it is assumed to be the case.

In the domain of confounding all publications addressed these main confounders age and sex. There may be some confounding left, as little is known about the risk factors for brain tumours. The scoring for this domain does not distinguish between the different types of studies, since they all use conventional techniques for correction and all account for the standard confounders.

5.2 Conclusion

The evaluation of the methodological quality of the studies did not result in major differences between the main studies. The usefulness of several studies was very limited because of their short follow-up, but that does not necessarily mean that they were of low quality. In effect, however, only the case-control studies by Hardell et al. and INTERPHONE, and the Danish cohort study are useful for the current analysis that is aimed at an evaluation of long-term effects.

The domains in the quality score that can best differentiate between the studies are those related to selection of the subjects and exposure assessment. In both domains and overall the Hardell studies had similar scores as the INTERPHONE studies. The Danish cohort scored the maximum for selection of subjects, but lower than the case-control studies on exposure assessment, while the overall score was similar to that of the Hardell and INTERPHONE studies. So on the basis of this scoring system for methodological quality there is no reason to give one type of studies more weight than the other.

Chapter 6

Results: analysis of the data by disease

In the different studies a number of exposure characteristics has been used in the analyses. Given the availability of the exposure characteristics across publications it was decided to focus on (a) the duration of mobile phone use in years and (b) the cumulative exposure from mobile phone calls in hours over the respondents' lifetime in the analysis of effects. However, data on the estimated number of phone calls over lifetime will also be presented, even though the Committee considers the number of calls to be less relevant than the actual total call duration. On the other hand, total call duration carries a higher risk of overestimation than number of calls.[46,145,146,159]

6.1 Issues to be considered

Lateralisation

An important aspect considered in the studies was the so-called lateralisation: was the telephone predominantly used at the side of the head where the tumour is located (ipsilateral), or not (contralateral; this generally includes both use on the opposite side of the head from the location of the tumour and use on either side). These data definitely suffer from recall bias, as has been demonstrated by the INTERPHONE investigators.[160] Cases tended to indicate more often that they used the phone on the side of the head where the tumour is located than they actually did. This was not the case with the controls, since they were allocated

the same hemisphere as their matching case after they had been interviewed. This means that there is differential recall bias, i.e. it is larger in the cases than in the controls, which will lead to overestimation of the risk.[160] A clear indication for an overestimation of the ipsilateral risk is a concomitant decreased contralateral risk that seems to indicate a protective effect. This has been observed and discussed extensively in the INTERPHONE study.[93]

Latency time

Another important point to be considered in the study of slow growing tumours such as those considered in this report, is the latency time, i.e. the time between induction of the tumour and clinical manifestation. Hardly any information is available, however, on latency periods for these tumours. What is known comes from studies on secondary tumours after radiotherapy. However, since ionizing radiation is a known carcinogen, it is highly uncertain whether this information is in any way representative for the situation with exposure to RF EMF, which is at most, according to IARC, a possible carcinogen and for which, in contrast to ionising radiation, a carcinogenic mechanism of action is not known (see below). The Committee presents the data anyway, since it is all we know and it might be considered a worst-case situation.

Two reviews present information on latency of gliomas after X-rays.[161,162] From these data, latency periods of 10.6 ± 9.2 years for cases up to an age of 19 years at exposure, and of 11.6 ± 6.5 years for older cases can be derived. No clear relation between total X-ray dose and latency time was observed.

For meningioma, a mean latency time of 20.8 years was calculated for patients aged ≤12 years and 21.8 year for >12 year-olds, with an overall range of 1-63 years.[163] Only 1.4% occurred within 5 years of treatment. Shorter latency periods were observed with increasing X-ray dose.

A review on radiation-induced acoustic neuromas reported a latency time of 38.3 ± 10.1 years, with an increasing risk with X-ray dose.[164] All cases were <16 years old at the time of treatment.

So for all three major tumour types considered in this report, the latency time after X-ray exposure is very long, but with a considerable spread. The latency time is specific for a disease / exposure combination. If there would be a causal relation between RF EMF exposure and these tumours, the Committee considers it possible that the latency time will be longer than that after X-ray exposure. This would mean that a follow-up time of 10 years would not be enough to measure any increase in tumour incidence and, vice versa, that any increased

incidence observed with short follow-up times is not realistic and might indicate flaws in the study.

Mechanism of action

RF EMF such as generated by mobile phones do not act upon biological material in the way ionising radiation does. It is not known, but considered very unlikely, that RF EMF can cause direct damage to DNA that may lead to disruption of biological processes and the development of cancer (unless through thermal effects, but these do not occur when using a mobile phone). Animal studies also do not indicate that RF EMF exposure might influence the development of cancer that has been induced by another agent. This will be discussed in a separate report.

6.2 Brain tumours (not further specified)

Cohort and case-control studies

This includes the results from three publications.[47,107,108] Aydin et al. (2011)[108] conducted a case-control study in children, the other two are studies on brain cancer in adults. The detailed results are presented in Tables H1, H2 and H3 in Annex H. Neither in the cohort nor in the case-control studies significantly increased risks were found. However, the cohort study from the USA[47] only looked at duration of use of more or less than 3 years and had only one case in each category (Table H1). The case-control study of Aydin et al. (2011)[108] on childhood brain cancers (which is the first report on the MOBI-KIDS study) had a maximum follow-up time of 5 years and maximum cumulative exposures of 144 hours. The usefulness of these studies in this analysis is therefore limited. The study of Baldi et al. (2011)[107] only made a distinction between use or no use of a mobile phone and did not register duration of use, or number or duration of calls. It can therefore not be used in the present analysis.

The childhood brain cancer data[108] allowed a laterality analysis (Table H3). Several increased odds ratios (ORs) were found, but with an inconsistent pattern. For time since first use an increased OR was found only in the middle category for contralateral use. For cumulative call time an increased OR was found only for the middle category of ipsilateral use and for the two highest categories for use on the contralateral side. For cumulative number of calls increased ORs were found in the highest category for ipsilateral use and in the two highest categories for contralateral use. Decreased ORs were found for the highest categories of

cumulative call time and cumulative number of calls for tumours with a central or unknown location. In all instances the number of cases and controls is very limited and this might be an explanation for not observing clear exposure-effect relationships, that would be expected in case there would be a causal relation.

Ecological studies

Kohler et al. (2011)[131] investigated brain and other tumour incidences in the USA for the period 1980-2007, but did not link this to mobile phone use. They concluded that both malignant and non-malignant brain tumours demonstrate differing patterns of occurrence by sex, age, and race, and exhibit considerable biologic diversity.

De Vocht et al. (2011)[130] reported on brain tumour trends in England from 1998-2007. They observed overall no statistically significant increases, but identified small but systematic increases in temporal lobe tumours in both men and women and of frontal lobe tumours in men, and decreases in tumours of the cerebrum, parietal lobe and cerebellum in men. Trends indicate a rapid increase in mobile phone use between 1998 and 2003, but this study cannot draw any conclusions when latency periods of 10 or more years are assumed.

Röösli et al. (2007)[121] analysed brain tumour incidence in Switzerland over the period 1969-2002. However, since mobile phone use was shown to be rapidly increasing in this time period, this study does not address any reasonable latency period.

Cook et al. (2003)[115] described trends for brain malignancies in New Zealand over the period 1986 to 1998 in relation to the prevalence of cell phones. However this prevalence was only slightly higher than 12.5% by the end of the observation period, so was still very low compared to later time periods. This study also does not address any reasonable latency period.

6.3 Glioma

Nine different studies have been identified on gliomas, tumours of the brain nervous tissue.[52,68,93,96,99,100,103,105,109] Figures 3-6 present the main outcomes of the studies. The more complete and detailed results are presented in Annex H; the data for duration of use are in Table H4, those for cumulative use in Table H5 and the lateralisation data are in Table H6. All odds ratios presented in this report, both in the figures and in the tables, are the ones that are corrected for confounders, i.e. the adjusted odds ratios.

Cohort studies

The latest publication on the Danish cohort study by Frei et al. (2011)[52] presented overall results for duration of use. However, as has been mentioned earlier, the associations reported in the later studies of this cohort are difficult to compare to the results of the other studies. The cohort study compares a group of subjects that started a private mobile phone contract before 1996 with the rest of the Danish population, that includes people using phones through a business contract and people that started a contract as of 1996. This is different from the case-control and case-case studies that compared duration of mobile phone use with no use or that compared start of regular use. Nevertheless, the cohort data are included in Figure 3 and given in Table H4. They do not show any increased risks for any of the durations of use, for either males of females.

Case-control and case-case studies

The case-control studies are more readily comparable, but some points need attention. Hardell et al. (2011)[68] presented glioma as such, but also made a distinction between astrocytomas and 'other malignant brain tumours', which included mixed gliomas and oligodendromas. They found the strongest association for astrocytomas of the highest grade, i.e. the most malignant type. However, as the INTERPHONE study (2010)[93] does not present any subdivisions of glioma, in the figures only a comparison with the overall glioma results of the Hardell studies is made, while their astrocytoma data are presented in the tables for completeness. It should also be noted that the age range of the Hardell studies is wider (20-80 years) than that of the INTERPHONE studies (30-59 years), which for strongly age-related illnesses such as glioma might give different effects; also recall problems might be larger in the older age groups. In order to allow a better comparison, Hardell et al. (2011)[165] partially reanalyzed their data to include only the 30-59 age categories. A third issue is that Hardell et al. make a distinction between the use of mobile phones (such as GSMs) and cordless phones (the wireless phones for indoor use, such as DECT). The reanalysis they performed for the limited age range was done only for mobile phone users, and not separately for cordless phone users.

The Hardell data of the full age range for time since first use, show an increased relative risk associated with mobile phone use for all gliomas in the highest (>10 years) category (Figure 3, Table H4) and in the middle and highest categories (>5-10 and >10 years) for astrocytoma (Table H4). For cordless phone use increased relative risks were found only in the middle categories (Figure 3,

Table H4). The recalculation for the limited age range was done only for the highest category (≥10 years) and resulted in a relative risk that was lower than for the full age range, but still increased (Figure 3, Table H4). It is puzzling that the OR of 2.26 for the full age range given in the reanalysis paper[165] (95% Confidence Interval 1.60-3.39) differs from that in the pooled analysis paper[68]: 2.6 (CI 1.7-4.1), while also the numbers of cases and controls differ: 88 / 99 in the reanalysis paper and 50 / 42 in the pooled analysis paper. Hardell et al. noted in the reanalysis paper that in their original analysis they used >10 years instead of the ≥10 years in the reanalysis, but then it would expected that the numbers of cases and controls would be lower in the reanalysis, while they are in fact higher. This is one of the inconsistencies of the Hardell papers. No increased risks were found by INTERPHONE for time since first use (Figure 3, Table H4), but for two categories, 1-1.9 and 5-9 years, decreased risks were found.

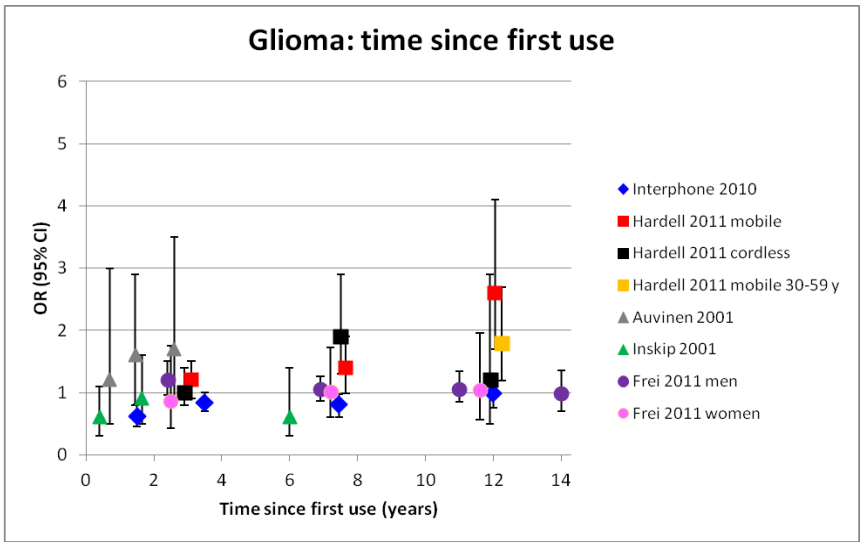

Figure 3 Adjusted Odds Ratios with 95% confidence limits for glioma for years since first use of a mobile phone.

- Data from INTERPHONE (2010)[93]; Hardell et al. (2011)[68,165]; Inskip et al.(2001)[99], Auvinen et al. (2002)[100] and Frei et al. (2011)[52].
- The midpoints of the ranges for years since first use are used, but for the highest category an arbitrary value has been chosen (7 yrs for the >5 yrs category of Inskip, 2.5 yrs for the >2 yrs category of Auvinen, 12 yrs for the >10 yrs categories of Interphone and Hardell, 14 yrs for the ≥13 yrs category for men and 12 yrs for the ≥10 yrs category for women of Frei). For the lowest category similarly arbitrary values were used (0.7 for the <1 yr for Auvinen). If necessary these values were slightly adjusted to show overlapping points.
- The data point 'Hardell 2011 mobile 30-59 y' is a subset of 'Hardell 2011 mobile'.

The data of Frei et al. (2011) [52] are results from a cohort study, therefore the point estimates refer to an Incidence Rate Ratio, not an Odds Ratio. This is a comparison with the whole population, not with a group of subjects with no or limited use.

For cumulative call time, Hardell et al. found increased risks for mobile phone users in all categories (Figure 4, Table H5), and for cordless phone users in the two highest categories, both for all gliomas and for astrocytomas. In the recalculated data (Figure 4, Table H5) the risk was lower than in the full age range data, but the category was also slightly different (>2000 h for the full age range and ≥1640 h for the limited age range).[165] The INTERPHONE data were divided over 10 categories and an increased risk was only found in the highest one (≥1640 h) (Figure 4, Table H5). In several lower categories, including the next-highest one, decreased risks were found, so there is no obvious exposure-response relationship. When the data from subjects who reported calls of on average >5 h per day were excluded, because INTERPHONE considered those to be unrealistically high usage data, the relative risk was not significantly increased anymore (Table H5).

A validation study showed that the number of calls was slightly underestimated and, as mentioned earlier, the random error in recall was larger for the duration of calls than for the number of calls.[146] This makes the number of calls potentially a more reliable endpoint then duration of calls. Nevertheless, ORs for cumulative number of calls were reported only by INTERPHONE (Table H5). In the two lowest and fourth highest of ten categories the risk was decreased, in the others it was not different from unity.

The analysis of the data in terms of laterality is presented in Figure 5 and Table H6. The Hardell publication[68] from which the data for duration and cumulative call time were derived did not present information on laterality. The laterality data were obtained from another publication[66] using the same data. For the full age range, Hardell et al. observed increase risks for ipsilateral mobile phone use already for a time since first use of >1 year (Table H6). Contralateral use of >10 year also was associated with an increased risk. For ipsilateral cordless phone use also increased risks were found already for a time since first use of >1 year. The reanalysis for the limited age range[165] was done for mobile phone use only and resulted in a lower risk than for the full age range, but it was still significantly increased (Figure 5, Table H6). No increased risks were found by INTERPHONE for time since first use, but for contralateral use the risk was decreased for the lowest and next-highest categories.

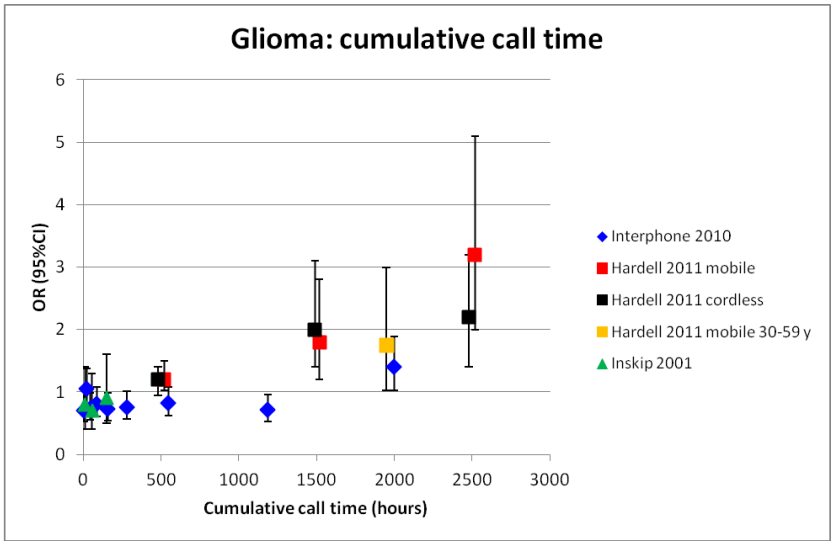

Figure 4 Adjusted Odds Ratios with 95% confidence intervals for glioma for cumulative call time.

- Data from INTERPHONE (2010)[93]; Hardell et al. (2011)[68,165]; Inskip et al. (2001)[99].
- The midpoints of the ranges for years since first use are used, but for the highest category an arbitrary value has been chosen (600 h for the >500 h category of Inskip, 2000 h for the ≥1640 h category of INTERPHONE and the reanalysis of the Hardell data and 2500 for the >2000 h category of Hardell). For the lowest category similarly arbitrary values were chosen (12 h for the <13 hr of Inskip and 4 h for the <5 h category of INTERPHONE). If necessary the values were slightly adjusted to show overlapping points.
- The data point 'Hardell 2011 mobile 30-59 y' is a subset of 'Hardell 2011 mobile'.

For cumulative call time data are not available for the full age range in the Hardell et al. studies, but they are presented in the 30-59 y age range reanalysis for a cumulative call time similar to the highest category used by INTERPHONE, ≥1640 h.[165] Hardell found that for ipsilateral use the risk was increased, but not for contralateral use (Figure 6, Table H6). INTERPHONE found an increased risk for ipsilateral phone use in the highest of five categories (≥1640 h), but a decreased risk in the one but lowest category (Figure 6, Table F6). For contralateral use the risk was decreased in the lowest, middle and next highest categories.

Only INTERPHONE also reported data for cumulative number of calls. No increased risks were found, but decreased risks for the middle of five categories for ipsilateral use, and for the 2nd and 3rd category for contralateral use (Table H6). The effect of exclusion of cases and controls with unrealistically long daily call times on the risk estimate was not reported for the laterality data.

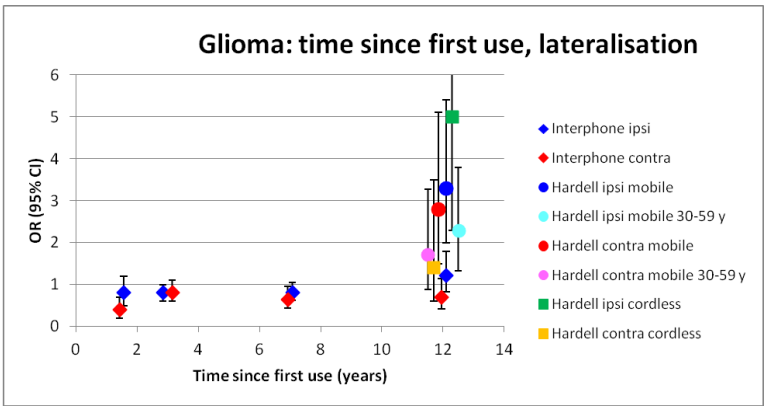

Figure 5 Adjusted Odds Ratios with 95% confidence intervals for ipsilateral and contralateral glioma for years since first use.

- Data from INTERPHONE (2010)[93]; Hardell et al. (2011)[66,165].
- The midpoints of the ranges for years since first use are used, but arbitrary values of 12 yrs for the >10 yrs categories of INTERPHONE and Hardell. The values were slightly adjusted to show overlapping points. Error bars were cut at an OR of 6.0.
- The data points 'Hardell ipsi mobile 30-59 y' and 'Hardell contra mobile 30-59 y' are subsets of 'Hardell ipsi mobile' and 'Hardell contra mobile', respectively.

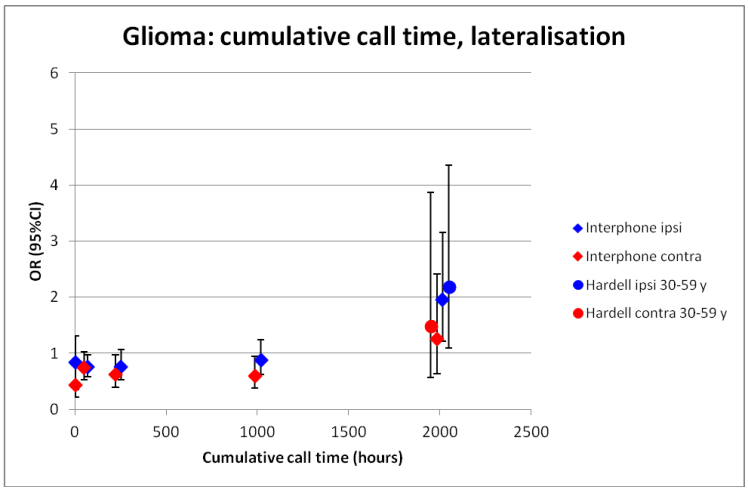

Figure 6 Adjusted Odds Ratios with 95% confidence intervals for ipsi- and contralateral glioma for cumulative call time.

- Data from INTERPHONE (2010)[93]; Hardell et al. (2011)[165].
- The midpoints of the ranges for years since first use are used, but for the highest category an arbitrary value has been chosen (2,000 h for the >1,640 h category). For the lowest category similarly arbitrary values were chosen (4 h for the <5 h category). If necessary the values were slightly adjusted to show overlapping points.

Two groups of INTERPHONE researchers also independently assessed the relation between calculated energy uptake in brain tumours (and corresponding brain tissue in controls) and various endpoints. Cardis et al. (2011)[114] calculated for a five-country subset of the INTERPHONE data (Australia, Canada, France, Israel and New Zealand) the total cumulated specific energy (in joules per kg, J/kg) in the tumours or brain tissue. The case-control pairs were selected on the basis of the estimation of the tumour centre by either a neuroradiologist or a computer algorithm. For comparison with the entire INTERPHONE dataset, risks were first calculated for cumulative call times. The risk for the highest of five categories (≥735 h) was not increased (Table H5), while it was for the highest of ten categories (≥1640 h) in the entire INTERPHONE study, as mentioned above. A decreased risk was calculated for the middle of five categories. When assessed for total cumulative energy, for the entire dataset no increased risks were found, but for the subgroup of use ≥7 years in the past an increased risk was found in the highest category (≥3124 J/kg cumulated energy) (Table H5).

Cardis et al. (2011) also calculated risks in a case-case subset, where they compared cases with the centre of the tumour within the most exposed area of the brain with cases with a tumour outside that area. An increased risk was found for time since first use of >10 years (Table H4), but no increase risk for cumulative call time (highest category ≥1147 h) (Table H5). These data are based on low numbers of cases, however.

The second INTERPHONE substudy was published by Larjavaara et al. (2011).[113] They used another subset of the INTERPHONE data (from 7 countries: Denmark, Finland, Germany, Italy, Norway, Sweden, and Southeast England) to calculate for cases the distance of the tumour midpoint to the source of exposure, where it was assumed that the mobile phone was always kept at the side of the head where the tumour was located, thus avoiding recall bias (but most likely introducing misclassification errors). A second approach was what they called a ‘case-specular’ analysis, where the actual cases were compared with hypothetical or ‘specular’ cases. The specular locations were constructed by mirroring the location of the tumour to the opposite side of the brain. These hypothetical cases thus represented the exposure that would have been incurred if the tumour had been located in another location. This counterfactual ‘control’ was contrasted in the analysis with the actual case. Neither approach resulted in higher or lower percentages of tumours in locations receiving the highest exposure, in relation to time since first use, total duration of use and laterality. The data for the case-case analysis are given in Tables H4, H5 and H6. Those for

the case-specular analysis are not given, since the Committee has doubts about the usefulness of that analysis.

The case-control studies by Auvinen et al. (2002)[100] and Inskip et al. (2001)[99] each concern small numbers of cases, as well as relatively short durations of phone use. Therefore the results from those studies, although presented in the figures and tables, and although the study by Auvinen had a high score for the quality evaluation, are not really useful for the current analysis. In general, no increased risks were found. The only exception is an increased risk for 1-2 years use of analogue mobile phones by Auvinen et al. (Table H4).

The case-control study by Spinelli et al. (2010)[105] also included only a small number of cases. They presented the data as hour-years, based on the number of monthly hours of call time available in the subscriptions (so not actual call time) and years of subscription held. These data, that do not show increased risks, are not readily comparable to the duration and cumulative call time data of the other publications and are therefore not included in the figures, but only given in Table H5. They cannot be used in the current analysis. The study by Muscat et al. (2000)[96] on unspecified brain tumours also contained data for specific tumour types, including gliomas. However, these data were pooled for all follow-up times and are therefore incomparable to the INTERPHONE and Hardell data. These data are also not shown in the figures, but are given in Table F4. Gousias et al. (2009)[103] performed a case-control study in Greece and determined minute-years of mobile phone use, but they only report on overall mobile phone use without providing any number on minute-years. Data from this study cannot be included in the figures and are only given in Table H5; they also cannot be used in the current analysis.

Ali Kahn et al. (2003)[109] investigated in a case-case study on glioma patients the relation between the location of the tumour and handedness. They hypothesized that handedness would be indicative of the preferred side of use of a mobile phone and only included patients with a unilateral cortical glioma. However, in later studies handedness has been shown to be a poor indicator of the preferred side of phone use.[84,166] No associations were observed. However, they did not determine the duration of use or number of calls, therefore these data cannot be compared to those of the case-controls studies and this study is therefore not included in the figures and tables.

Ecological studies

Several recent studies investigated the incidence of brain tumours over time. The studies reporting on unspecified brain tumours have been discussed in 6.2. Here the studies reporting gliomas will be discussed.

The publication by Little et al. (2012)[133] is the most recent analysis of data from the United States of America (USA) Surveillance, Epidemiology and End Results (SEER) programme using population based cancer registries. The SEER data is generally held to be informative and trustworthy. The results show that both lower grade gliomas as well as those with poorly specified anatomical locations have decreased by 2.4-3.0% per year over the period 1997-2008. Gliomas with temporal lobe locations and other specified sites have increased by approximately 0.75% per year. This study uses mobile phone usage data to calculate scenarios of glioma incidence development, given the results of some important case-control studies. Assuming a latency time of 10 years and a relative risk of 1.5, the underlying glioma rate was expected to increase from 17.7 per 100 000 people per year to 19.5 in 2008. When the relative risks of Hardell et al. (2011)[167] were used, all predicted rates were substantially higher than the observed rates, i.e. if these risks were true, a clearly increased glioma rate should have been visible. However, using the (lower) relative risks from the INTERPHONE studies[93] the predicted rates were within the observed patterns, i.e. the observed patterns are consistent with a small increase in risk, but also with no change in risk. It is unclear how much these calculations take the age range difference between the Hardell and INTERPHONE studies into account.

Deltour et al. (2012)[135] described the incidence data up to 2008 from the Nordic countries, that have the longest mobile phone use. They observed no clear increases in glioma incidence overall, but slight increases among the oldest age group of 60-79 year olds. They also carried out simulations for men aged 40-59 and concluded that a relative risk of 1.5 should be visible in the incidence rates when a latency time of 10 years for all users is assumed, but when the latency time would be 15 years this should be less likely.

In an editorial on the Frei et al. (2011) study, Ahlbom and Feychting (2011)[151] presented brain tumour incidence data from the Swedish cancer registry over 1970-2009. They concluded that incidence has not changed, not in general nor for different age groups and genders. They argued that handheld mobile phones were introduced in Sweden in 1987 and that by 2002 87% of 16-75 year olds were mobile phone users. Since almost 90% of the population had been using mobile phones for at least seven years in 2009, and probably a

significant proportion used them for 10 years or even 15 years, they state that any increased risk should have shown up in the incidence rates by 2009.

The Committee has obtained brain cancer incidence data from the Netherlands Cancer Registry (NCR) for the period 1989-2010. Incidences are reported in Figure 7 for gliomas, including astrocytomas, oligodendromas, oligoastrocytomas and malignant gliomas, for different age categories.

It is clear from this data that there is no increase in gliomas in the Netherlands during the period of rapid increase in mobile phone use in the age groups that use them most: 20-29 and 30-59 years. There is an continuous increase in the highest age group of 60-79 years, but this started already before mobile phones started to be used. These data correspond to those from other countries, for instance Inskip et al. (2010)[123] for the USA, De Vocht et al. (2011)[130] for the UK and Deltour et al. (2012)[135] for Nordic countries.

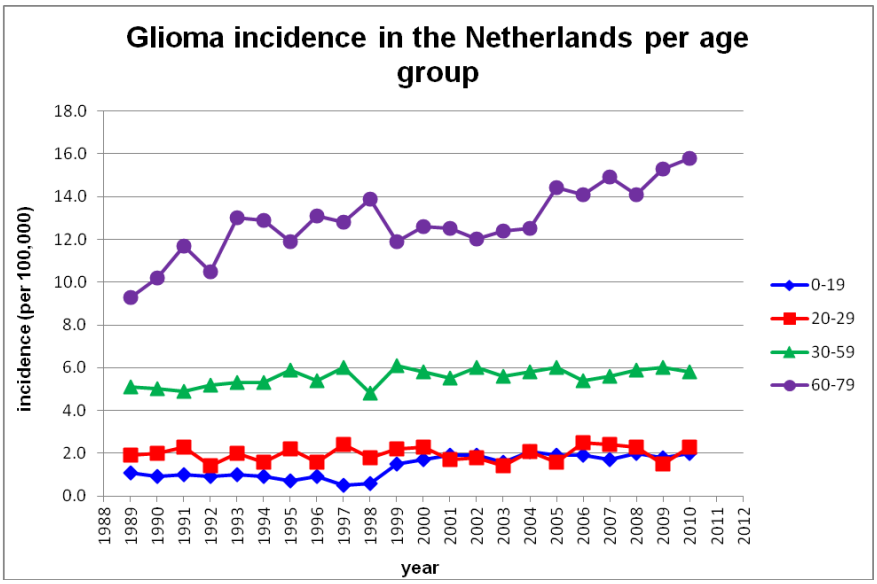

Figure 7 Glioma incidence in the Netherlands for different age groups. Source: Netherlands Cancer Registry managed by CCCNL.

6.4 Meningioma

Meningiomas are tumours of the meninges, the membranes that separate the nervous tissue of the brain from the skull, so they have no neurological origin. Five publications report on the association between mobile phone use and the risk of meningiomas.[52,65,93,99,100]

Cohort studies

The latest publication on the Danish cohort study[52] reported for meningioma overall results for duration of use. As mentioned with gliomas, in this cohort study the definition of cases and controls is substantially different from that in the case-control studies. Nevertheless, they are included in Figure 8 and presented in Table H7. They do not show any increased risks for any of the durations of use, for either males of females.

Case-control studies

The publication of the Hardell group that was used to obtain the odds ratios for meningioma (Hansson Mild et al., 2007[65]) does not present the numbers of cases and controls for the individual tumour types, but merely gives the total numbers for all types of brain tumours (2671 cases and 3723 controls). It could be derived from another publication that this study included 916 cases of meningioma.[66] Hansson Mild et al. made a distinction between analogue, digital and cordless phones. For time since first use an increased risk was found for analogue phones in the highest category of >10 years use, for digital phones no increased risks were found and for cordless phones the risk was increased in the middle category of >5-10 years use (Figure 8, Table F7). The results from the INTERPHONE study show decreased relative risks in the two middle of four categories.[93] So no exposure-response relationships were observed. The studies by Auvinen et al. (2002)[100] and Inskip et al. (2001)[99] are not really useful for the current analysis for reasons mentioned with the gliomas (see 5.1.2). They are, again, presented in Figure 8 and Table F7 for completeness only.

The Hardell group did not publish any data on cumulative call time for meningiomas. The INTERPHONE data for both cumulative call time and cumulative number of calls do not show any increased risks, but for several intermediate categories of both endpoints decreased risks were observed

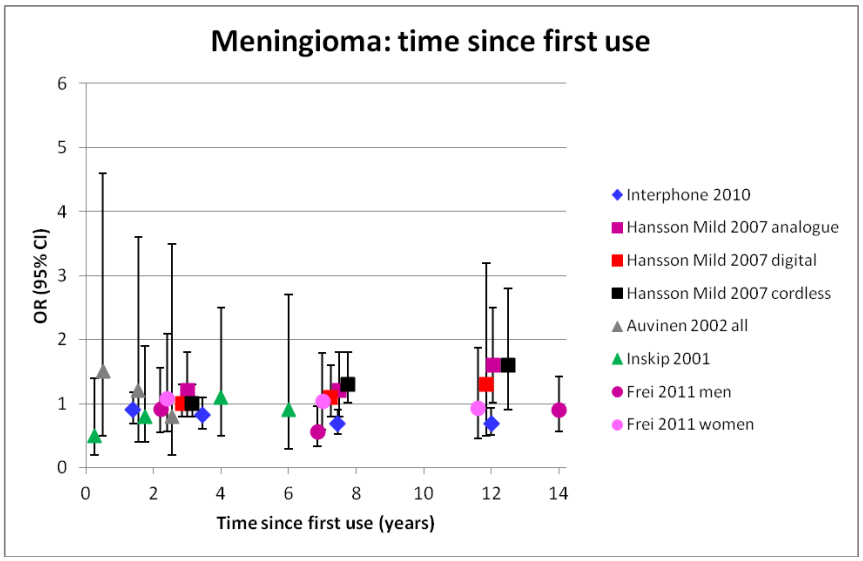

Figure 8 Adjusted Odds Ratios with 95% confidence limits for effects on meningioma for years since first use of a mobile phone.

- Data from INTERPHONE (2010)[93]; Hansson Mild et al. (2007)[65]; Auvinen et al. (2002)[100]; Inskip et al. (2001)[99] and Frei et al. (2011)[52].
- The midpoints of the ranges for years since first use are used, but for the highest category an arbitrary value has been chosen (4 yrs for the >3 yrs category of Inskip, 2.5 yrs for the >2 yrs category of Auvinen, 12 yrs for the >10 yrs categories of INTERPHONE and Hardell,14 yrs for the ≥13 yrs category for men and 12 yrs for the ≥10 yrs category for women of Frei). If necessary the values were slightly adjusted to show overlapping points.
- The data of Frei et al. (2011) [52] are results from a cohort study, therefore the point estimates refer to an Incidence Rate Ratio, not an Odds Ratio.

(Figure 9, Table H8). The data from Inskip et al. (2001)[99] are presented for completeness only.

One publication from the Hardell group also presents analyses for duration of use as continuous variable.[65] No increased risks were observed for the analysis per 100 h of use, but the analysis per 1 year of use an increased risk was found for analogue and cordless phones (Table H9).

The publication of the Hardell group from which the data for exposure duration was derived did not present information on laterality.[65] The laterality data were obtained from another publication on this study using the same data.[66] For time since first use, the Hardell group found an increased risk for ipsilateral use >1 year, but not for >10 years of use of mobile phones (only the latter data are

shown in Figure 10). Also they observed an increased risk associated with >10 years ipsilateral use of cordless phones (Figure 10, Table H10). In the INTERPHONE study no increased risks were observed, but in the two middle of four categories a decreased risk was observed for contralateral use (Figure 10, Table H10). For cumulative call time and cumulative number of calls decreased risks were observed for the 2nd and 4th of five categories for contralateral use (Table H10).

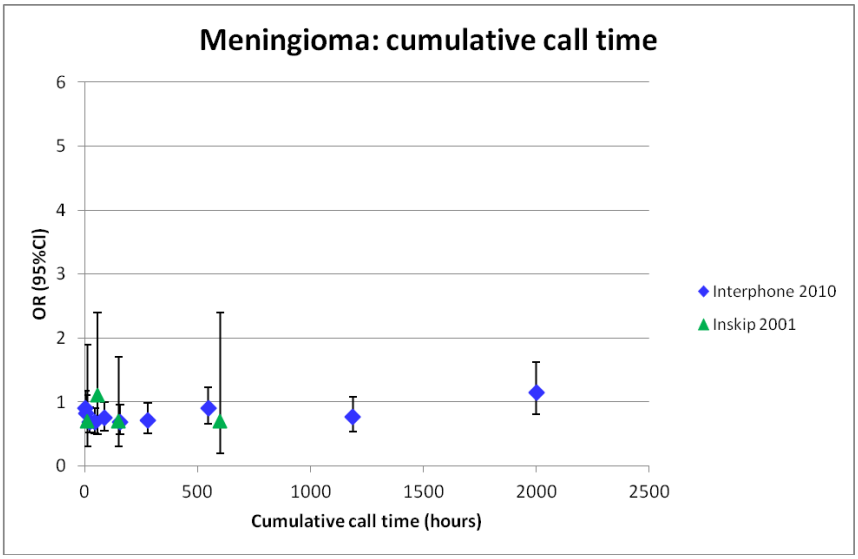

Figure 9 Adjusted Odds Ratios with 95% confidence limits for effects on meningioma for cumulative call time.

- Data from INTERPHONE (2010)97; Inskip et al. (2001)144.
- The midpoints of the ranges for years since first use are used, but for the highest category an arbitrary value has been chosen (1200 h for the >1640 h category of INTERPHONE and 600 h for the >500 h category of Inskip). For the lowest category similarly arbitrary values were chosen (12 h for the <13 hr of Inskip and 4 h for the <5 h category of INTERPHONE). If necessary the values were slightly adjusted to show overlapping points.

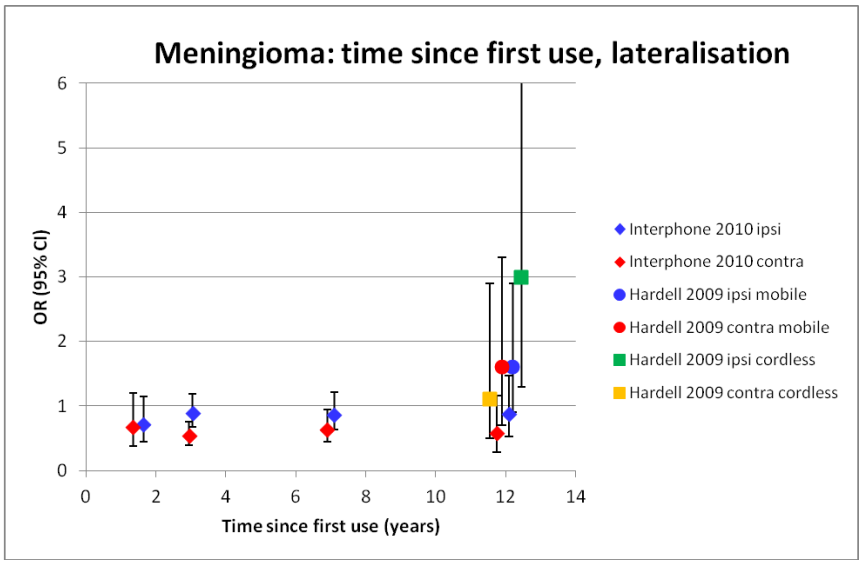

Figure 10 Adjusted Odds Ratios with 95% confidence intervals for ipsilateral and contralateral meningioma for years since first use.

- Data from INTERPHONE (2010)[93]; Hardell et al. (2009)[66].
- The midpoints of the ranges for years since first use are used, but for the highest category an arbitrary value has been chosen (12 yrs for the >10 yrs categories of INTERPHONE and Hardell). If necessary these values were slightly adjusted to show overlapping points. Error bars were cut at an OR of 6.0.

Data on cumulative call time were presented by Hardell et al. only for benign tumours, that encompassed both meningiomas and acoustic neuromas.[65] No data for meningiomas from the Hardell studies can thus be presented for this endpoint. The INTERPHONE data show decreased risks in the 2nd and 4th of five categories for contralateral use (Table H10).

6.5 Acoustic neuroma

Acoustic neuromas are tumours that originate from the nerve sheath of the acoustic nerve. Six studies on the association between mobile phone use and the risk of acoustic neuroma are reported.[51,65,94,99,101,112]

Cohort studies

Schüz et al. (2011)[51] published results for acoustic neuroma from the Danish cohort study. As mentioned with gliomas, in this cohort study the definition of cases and controls is substantially different from that in the case-control studies. Nevertheless, they are included in Figure 11 and presented in Table H11. In contrast to the publications on gliomas and meningiomas, for acoustic neuromas only results for men were reported, and only for having a mobile phone subscription ≥11 years. No increased risk was found. In women, no acoustic neuromas were observed in the study period.

Case-control and case-case studies

In the acoustic neuroma data Hardell et al. again made a distinction between analogue, digital and cordless phones.[65] An increased risk was found for all follow-up times for the older types of analogue phones (Figure 11, Table H11). For digital phones an increased risk was found only for the shorter follow-up times, but not for follow-up times >10 years. For cordless phones an increased risk was found only for follow-up times >1- 5 years, but not for >5 years. No increased risks were found in the INTERPHONE[94] and other case-control studies[99,101], but in the INTERPHONE study in the 7th and 9th of ten categories a decreased risk was observed (Figure 11, Table H11). Sato et al. (2010) presented the results of a case-case study of acoustic neuroma.[112] They calculated risks for two groups: those cases that did not show acoustic neuroma-related symptoms at 1 or at 5 years before diagnosis. For each group risks were calculated for years since first use before the reference date. No increased risks were observed (Figure 11, Table F11).

The publication of the Hardell group from which the data for duration of phone use were derived did not present information on cumulative call time.[65] Another publication describing the same data was used to obtain data cumulative call time.[64] Hardell et al. found increased risks associated with analogue, digital and cordless phone use for cumulative call times of >1000 h (Figure 12, Table H12). No increased risks were found in the INTERPHONE study for cumulative call times up to ≥1640 h and by Muscat et al (2002) for call times >60 h. Decreased risks were observed in the INTERPHONE study for the 6th and 8th of ten categories (Figure 12, Table H12).

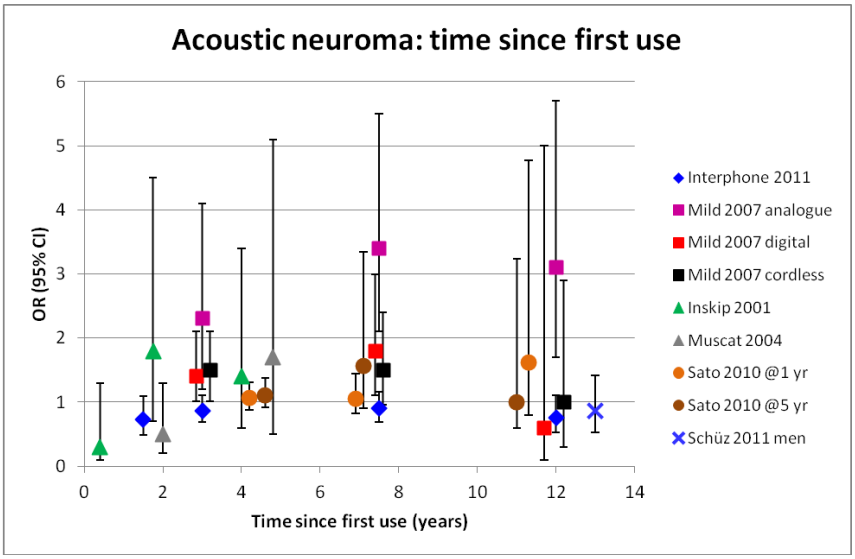

Figure 11 Adjusted Odds Ratios with 95% confidence intervals for acoustic neuroma for years since first use.

- Data from INTERPHONE (2011)[94]; Hansson Mild et al. (2007)[65]; Inskip et al. (2001)[99]; Muscat et al. (2002)[101]; Schüz et al. (2011)[51].
- The midpoints of the ranges for years since first use are used, but for the highest and lowest category an arbitrary value has been chosen (1.4 yrs for the < 0.5 yrs category of Inskip et al. (2001)[99], 4 yrs for the >3 yrs category of Inskip et al. (2001)[99], 4.5 yrs for the <5 yrs category of Sato et al. (2010[112]), 12 yrs for the >10 yrs category of INTERPHONE (2011)[94] and for the >10 yrs category of Hansson Mild et al. (2007)[65] and 11 yrs for the > 10 yrs category of Sato et al. (2010)[112] and 13 yrs for the ≥11 yrs category of Schüz et al (2011)[51]. If necessary these values were slightly adjusted to show overlapping points.
- The data of Schüz et al (2011)[51] are results from a cohort study, therefore the point estimates refer to an Incidence Rate Ratio, not an Odds Ratio.

The INTERPHONE study group also analyzed the data on the basis of total number of calls.[94] No increased risks were found, but in the 6th and 8th of ten categories the risk was decreased (Table H12).

One publication from the Hardell group also presents analyses for duration of use as continuous variable.[65] Only for analogue phones an increased risk was observed, both for the analyses per 100 h of use and per 1 year of use (Table H13).

The Hardell publication[65] from which the data for duration of phone use were derived did not present information on laterality for acoustic neuroma. Another publication describing the same data was used to obtain these data.[66]

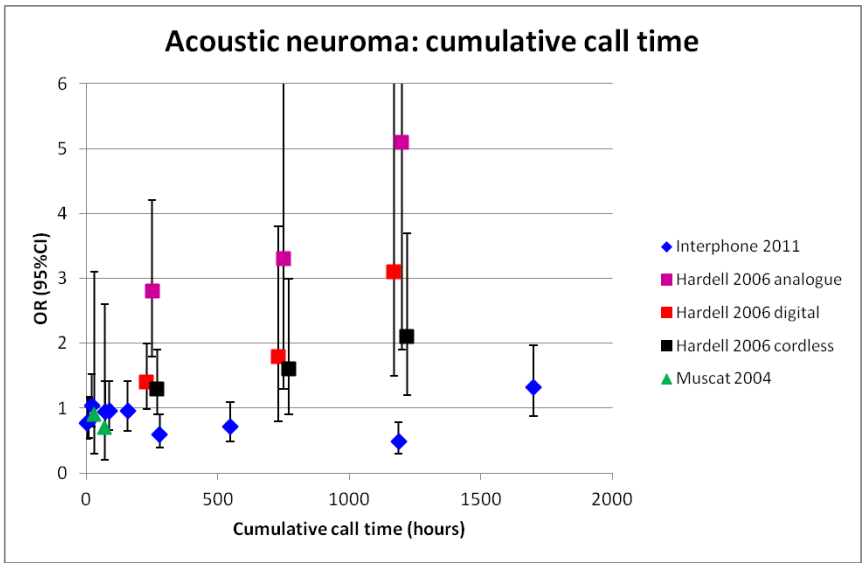

Figure 12 Adjusted Odds Ratios with 95% confidence intervals for acoustic neuroma for cumulative exposure.

- Data from INTERPHONE (2011)[94]; Hardell et al. (2006)[64]; Muscat et al. (2002)[101].
- The midpoints of the ranges for cumulative exposure are used, but for the highest category an arbitrary value has been chosen (70 h for the >60 h category of Muscat et al. (2002)[101], 1700 h for the ≥1640 h category of INTERPHONE (2011)[94], and 1200 h for the >1000 h category of Hardell et al. (2006)[64]. If necessary these values were slightly adjusted to show overlapping points. Error bars were cut at an OR of 6.0.

The laterality data for years since first use of the Hardell group show increased risks for all mobile phones (analogue and digital) for both >1 year and >10 years ipsilateral use, and an increased risk for cordless phones only for >1 year ipsilateral use (Figure 13, Table H14). No increased risks were observed for contralateral use by Hardell. The INTERPHONE study did not find any increased risk for ipsi- or contralateral use when looking at time since first use, but for cumulative call time the risk was increased for ipsilateral use and exposure ≥1640 h (Figure 14, Table H14). For the next-lower category the risk was decreased. For cumulative number of calls, both for ipsilateral and contralateral use a decreased risk was found in the middle one of the five categories (Table H14). Hardell did not present data on laterality and cumulative call time or number of calls.

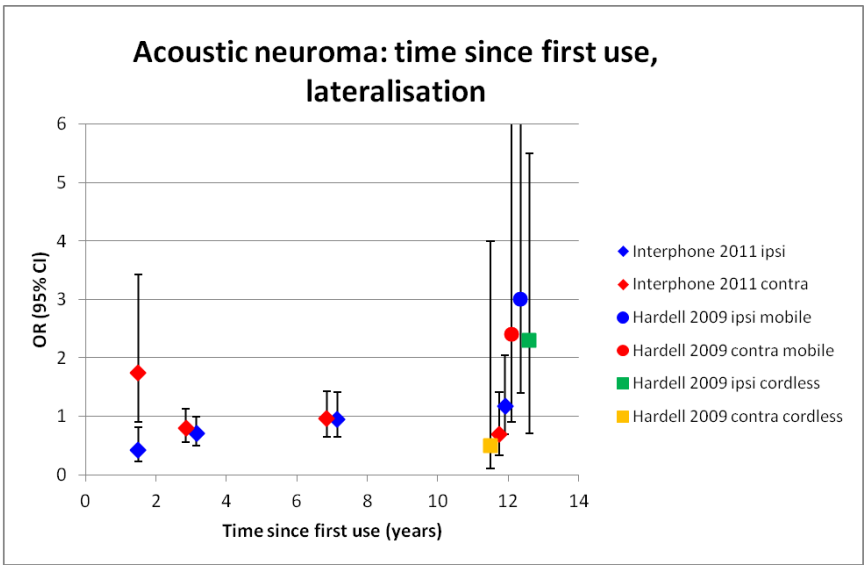

Figure 13 Adjusted Odds Ratios with 95% confidence intervals for ipsilateral and contralateral acoustic neuroma for years since first use.

- Data from INTERPHONE (2011)[94]; Hardell et al. (2009)[66].
- The midpoints of the ranges for years since first use are used, but for the highest category an arbitrary value has been chosen (12 yrs for the >10 yrs categories of INTERPHONE and Hardell). If necessary these values were slightly adjusted to show overlapping points. Error bars were cut at an OR of 6.0.

Ecological studies

Larjavaara et al. (2011)[132] addressed trends in the incidence of acoustic neuroma, which is a very slow growing tumour. The results indicated a higher incidence for later birth cohorts in practically all age groups. Patterns in trends were also analysed, with widely differing results. The timing of some of the increased incidences observed was thought to be linked to improvements in diagnostics and registration or to increasing risk, but no relation with mobile phone use was considered.

Incidence data for the Netherlands are not available, since registration of acoustic neuromas is not complete.

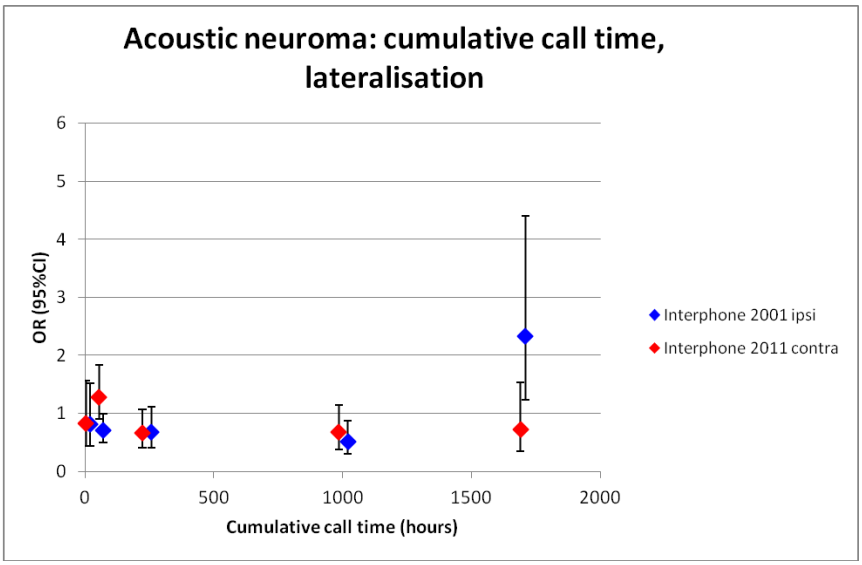

Figure 14 Adjusted Odds Ratios with 95% confidence intervals for ipsilateral and contralateral acoustic neuroma for cumulative call time.

- Data from INTERPHONE (2011)[94].
- The midpoints of the ranges for years since first use are used, but for the highest category an arbitrary value has been chosen (12 yrs for the >10 yrs categories of INTERPHONE). If necessary these values were slightly adjusted to show overlapping points.

6.6 Parotid gland tumours

Parotid glands are the largest salivary glands and located below the ears. Thus they are the salivary glands most exposed when making a call with a mobile phone.

Case-control studies

Five publications report on parotid gland tumours.[69,72,82,85,100] Since no pooled analysis of the parotid gland tumour data has been published at this time, these studies are presented separately. The publications from the Hardell group[69,72] only presented cumulative categories of exposure. As this did not allow a direct comparison with the other material, only the non-overlapping information is presented.

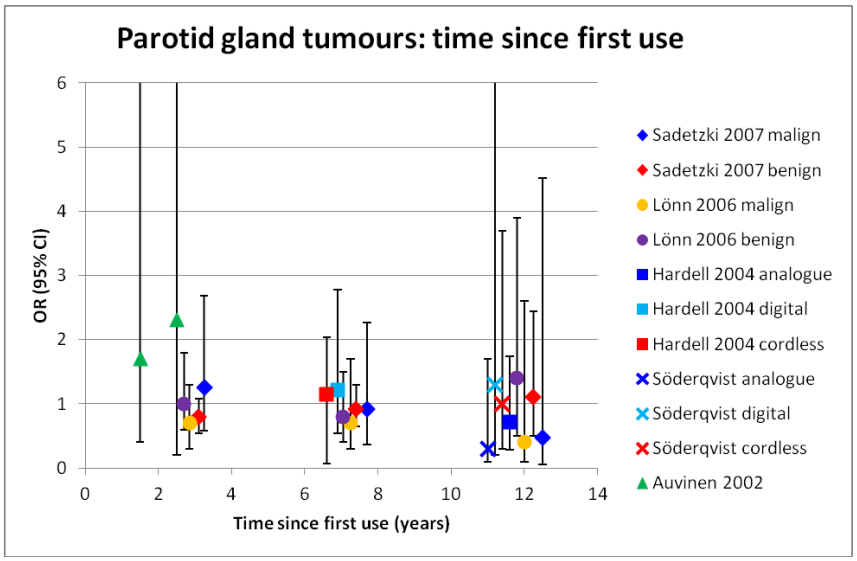

Figure 15 Adjusted Odds Ratios with 95% confidence intervals for parotid gland tumours for years since first use.

- Data from: Sadetzki et al. (2007)[85], Lönn et al. (2006)[82]); Hardell et al. (2004)[69]; Auvinen et al. (2002)[100]; Söderqvist et al. (2012)[72].
- The midpoints of the ranges for years since first use are used, but for the highest category an arbitrary value has been chosen (1.4 yrs for the < 0.5 yrs category of Auvinen et al. (2002)[100], 4 yrs for the >3 yrs category of Auvinen et al. (2002)[100], 12 yrs for the >10 yrs category of INTERPHONE, Hardell and Söderqvist). If necessary these values were slightly adjusted to show overlapping points. Error bars were cut at an OR of 6.0.

The analyses of the Hardell group data by duration of exposure[69,72] did not result in any increased risks for use of analogue, digital or cordless phones, and neither did the data of Sadetzki et al. (2007)[85] and Lönn et al. (2006)[82] following the INTERPHONE protocol, and Auvinen et al. (2002)[100] (Figure 15, Table H15).

The analyses of these studies by cumulative call time also did not result in any increased risks (Figure 16, Table H16).

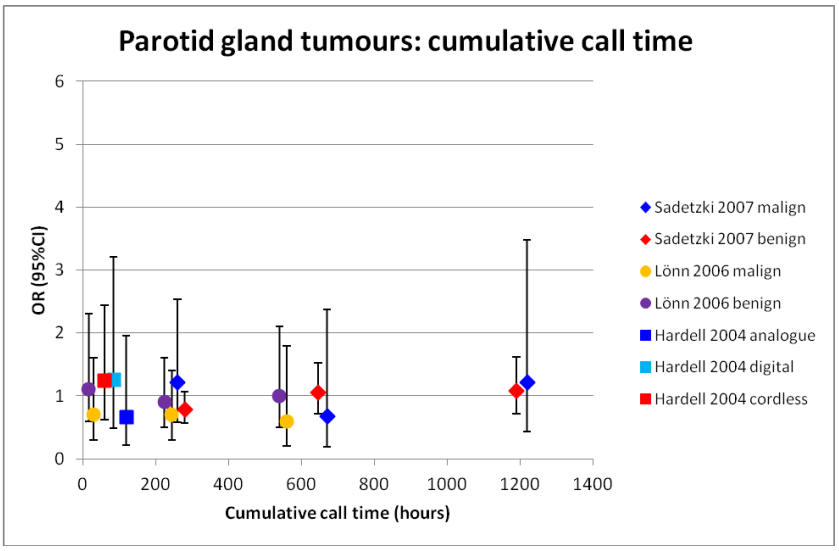

Figure 16 Adjusted Odds Ratios with 95% confidence intervals for parotid gland tumours for cumulative call time.

- Data from: Sadetzki et al. (2007)[85], Lönn et al. (2006)[82]; Hardell et al. (2004)[69].
- The midpoints of the ranges for cumulative exposure are used, but for the highest category an arbitrary value has been chosen (12 yrs for the >10 yrs category of INTERPHONE and Hardell). If necessary these values were slightly adjusted to show overlapping points.

No data on lateralisation were presented by the Hardell group. Only the two publications according to the INTERPHONE protocol provide this.[82,85] No increased risks were found for time since first use in either study (Figure 17, Table H17).

The only increased risk was found for one subgroup analysis in the study by Sadetzki et al. (2007)[85] in the group containing both benign and malignant tumours that reported ipsilateral phone use and a cumulated call time >266 h (Figure 18, Table H17).

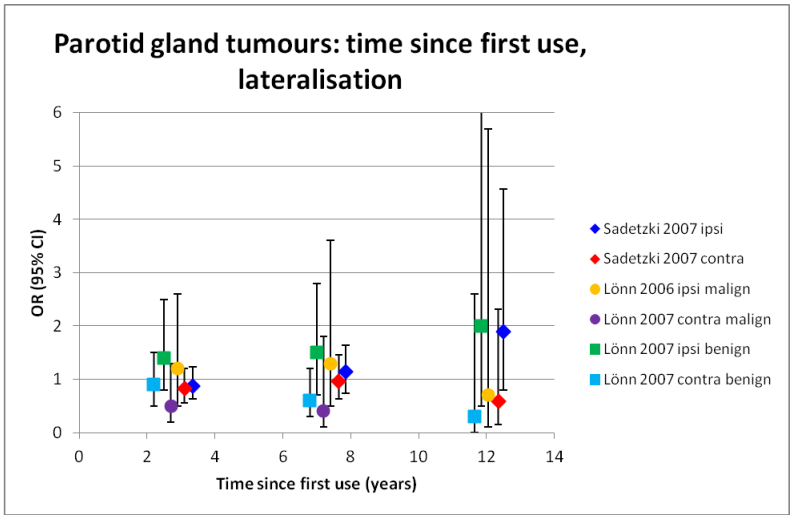

Figure 17 Adjusted Odds Ratios with 95% confidence intervals for ipsilateral and contralateral parotid gland tumours for years since first use.

- Data from Sadetzki et al. (2007)[85], Lönn et al. (2006)[82].
- The midpoints of the ranges for years since first use are used, but for the highest category an arbitrary value has been chosen (12 yrs for the >10 yrs category). If necessary these values were slightly adjusted to show overlapping points. Error bars were cut at an OR of 6.0.

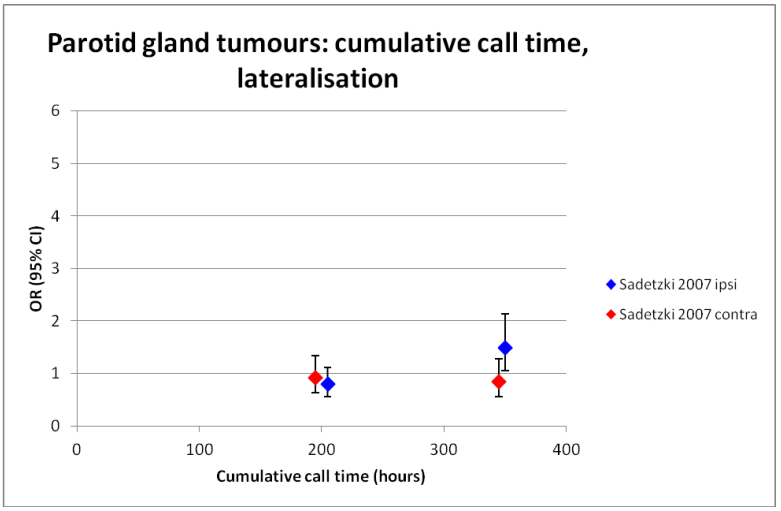

Figure 18 Adjusted Odds Ratios with 95% confidence intervals for ipsilateral and contralateral parotid gland tumours for cumulative call time.

- Data from Sadetzki et al. (2007)[85].
- Arbitrary values have been chosen: 200 h for the <266.3 h category and 350 h for the > 266.3 h category.

Ecological studies

De Vocht et al. (2011) published a brief report on the trends in parotid gland tumours in England over the period 1998-2008, but this study cannot draw any conclusions when latency periods of 10 or more years are assumed.

The brief report by Czerninski et al. (2011)[129] described a quite steady incidence of most parotid gland tumours in Israel and a rapid increase in incidence of sublingual gland cancers. These data are not linked to mobile phone use.

The Committee has obtained incidence data for parotid gland tumours from the Netherlands Cancer Registry for the period 1989-2010. These do not show changes in the incidence of this tumour (Figure 19).

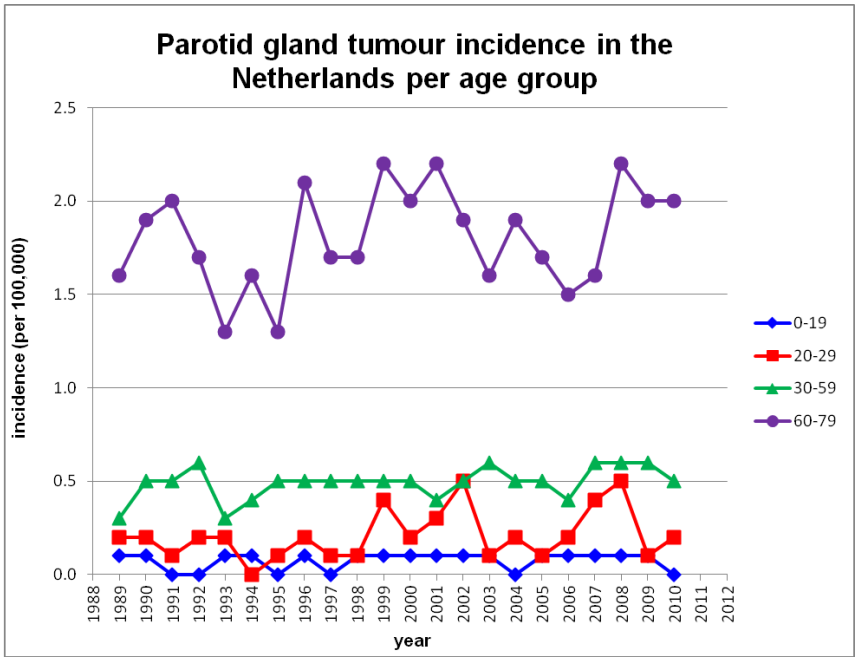

Figure 19 Parotid gland tumour incidence in the Netherlands for different age groups. Source: Netherlands Cancer Registry managed by CCCNL.

6.7 Pituitary tumours

The pituitary gland, or hypophysis, is an endocrine gland at the bottom of the hypothalamus at the base of the brain. It secretes important hormones such as growth hormone and thyroid stimulating hormone.

Two publications reported on case-control studies on pituitary tumours.[88,89] The detailed results are presented in Annex G, Tables H18 and H19. No associations were found.

6.8 Malignant melanoma of the eye

The structure giving rise to the colour of the eye is the uvea, which includes the iris. It contains pigment cells (melanocytes) from which cancer (melanoma) may arise.

Also for this tumour results from two publications are available.[98,104] The detailed results are presented in presented in Annex G, Tables H20 and H21. No associations were found

6.9 Intra-temporal facial nerve tumours

This includes the results from one publication.[102] However, the analysis presented in this publication does not allow any comparison with the other studies, as only the individual answers to a questionnaire are presented. Combinations of duration of mobile phone use while corrected for confounders are not given.

6.10 Neuroblastoma

Neuroblastoma is a neuroendocrine tumour that originates in neural tissue outside the central nervous system. Only one publication reports the risk of this type of tumour in children in relation to mobile phone use by the parents.[97] Also in this case, the analysis presented in this publication does not allow any comparison with the other studies, as only the individual answers to a questionnaire are presented. Combinations of duration of mobile phone use while corrected for confounders are not given.

Chapter 7

Discussion

7.1 The research questions

In this report, the Committee addresses the question whether there is evidence from epidemiological studies that exposure to radiofrequency electromagnetic fields (RF EMF) from mobile phones is associated with an increased risk of tumours in the brain and various other tissues in the head.

In assessing the evidence for a causal association based on the epidemiological data discussed in the previous chapters, the Committee uses the considerations of Bradford Hill[12] (see 7.6). A causal association is more likely when there is an exposure-response relationship, such that the risk increases with increasing intensity and/or time of exposure, and when there is consistency between the studies. These points will be explicitly discussed in this chapter.

An important issue is the assumption that there is a long latency time between the induction and the clinical manifestation of tumours in the head. As was discussed in Chapter 6, for the main tumours considered in this report, latency times of 10-15 years are assumed.

7.2 Strengths and limitations of this analysis

The strength of this investigation is that it has been systematic in both the identification of the information available through original study publications

and the way it has evaluated the methodological quality of the available information.

A limitation is that there are only limited possibilities for pooling of the data from the publications selected, as the data were generated with very different protocols and are thus not always sufficiently compatible. Another limitation is that there are only few studies with long-term users.

7.3 Mobile vs. cordless phones

An issue that needs to be discussed before going into detail on the strengths and weaknesses of the different studies, is the exposure from cordless phones versus that of mobile phones. Hardell claims in his studies that the RF EMF exposures from both types of phones are of comparable magnitude, and that the observed increased risks associated with cordless phone use he observed in his studies are consistent with this. But is this claim valid?

Vrijheid et al. (2009)[144] used software modified mobile phones used by over 500 volunteers in 12 countries to measure the output power of mobile phones. The 900 MHz phones transmitted with an average power of 133.3 mW (maximum 250 mW, based on 46994 calls), and the 1800 MHz phones with an average of 64.2 mW (maximum 125 mW, based on 29505 calls).*

The maximum power of a cordless DECT phone is 10 mW and during a call transmission is always at this maximum. There is no transmission in standby mode.** This means that exposure to radiofrequency electromagnetic fields from DECT phones is considerably lower than exposure from mobile phones.

Some authors, however, have concluded otherwise. Redmayne et al. (2010)[172] discussed the exposure by cordless phones and compared that with the data for mobile phones as assessed by Vrijheid et al. (2009).[144] Vrijheid et al. state that "Analyses included data recorded during speech communication only." This means: not during texting, but for the entire duration of a call, both during speaking and listening. However, Redmayne et al. (2010)[172] erroneously interpreted this statement that power was only registered during speaking and not during listening. They conclude from this that the average exposure from mobile

* Maximum SAR values of mobile phones vary from 0.07 up to 1.59 W/kg (with similar models having sometimes different SAR values in different countries).[168-170] This corresponds to 3.5-80% of the ICNIRP limit (=2 W/kg).Since the average power is just over half of the maximum, the average SAR will also be.

** For one type of handset the manufacturer supplies the SAR_{10g}, which is 0.06 W/kg. The maximum peak SAR for several types of DECT handsets was calculated at 0.00794 – 0.052 W/kg.[171] This corresponds to 0.4 – 2.6% of the ICNIRP limit (=2 W/kg).

phones is likely to be much lower than the levels given by Vrijheid et al . (2009)[144] and that the exposure from cordless phones during a conversation might be considerably higher than that from a mobile phone. This incorrect conclusion is adopted by Hardell et al. (2011)[68,165] to explain the increased risks observed with cordless phone use.

Hardell et al. (2011)[68] distinguished two exposure categories on the basis of call time: below and above the median. The median for mobile phones is a call time of 74 h, while for cordless phones it is 243 h. That means that at the median the total 'exposure' (calling time x output power) is 9864 mWh for GSM 900 MHz phones (assuming the average power of 133.3 mW), 4751 mWh for GSM 1800 MHz (assuming the average power of 64.2 mW) and 2430 mWh for DECT (assuming the output power of 10 mW). So there is a considerable difference in 'exposure' between especially the 900-MHz GSM and DECT phones. If only the output power would be the relevant parameter this difference is even greater.

Another, related, issue is that of analogue versus digital phones. When mobile phones were first introduced, the signal type was an analogue one, i.e., a continuous signal that was amplitude and frequency modulated to transfer information. Since the capacity and speed of data transfer using these signals proved insufficient, a digital type signal was developed. This uses pulsed transmissions with a complex modulation for speech and data transfer. The most widespread type is the GSM standard, which is in use in most of the countries included in the studies in this report.

The output power of the (now outphased) analogue phones was higher than that of the digital ones. While the digital phones have a facility called adaptive power control, that regulates the output power according to need in order to establish and maintain a connection with the nearest base station, analogue phones did not, and the average distance to a base station was also higher than with the digital systems. Kelsh et al. (2011)[173] measured the output in various types and models of mobile phones using 4 different operating systems, including an analogue one and GSM 1900 MHz. They did not measure while actual phone calls were made by volunteers, as in the Vrijheid et al. (2009)[144] studies, but measured in a standardized setup while driving along fixed routes in different environments (urban and rural). The mean output of the analogue phones was 171.40 mW, while that of the GSM 1900 MHz phones was 25.76 mW. This value for the GSM phones is lower than the 64.2 mW measured by Vrijheid et al. (2009).[144] Apart from the differences in methods of data collection, this difference may also have to do with the fact that the Kelsh et al. (2011)[173] study was performed in 2005/2006 in the USA, and the Vrijheid et al.

(2009)[144] study between 2001 and 2005 in 12 of the 13 INTERPHONE countries, so the results of both studies are probably not directly comparable. In any case, the Kelsh et al. (2011)[173] study clearly shows that exposure from analogue phones is considerably higher than that of GSM phones.

The GSM standard was first commercially introduced in Europe in 1990 (in Finland) and started being used at a large scale in the mid-1990's. Recruitment in the case-control studies took place between 2000 and 2004 (INTERPHONE) and 1997-2003 (Hardell), and in the Danish cohort study in 1997. This means that the subjects in the epidemiological studies that have been using mobile telephony for the longest time periods (10 year of more) will initially have used analogue phones. So the exposure in that period of use was likely to be considerably higher than that in the later period when GSM phones were used. This makes the difference in exposure with cordless phones even larger.

These differences are at odds with the conclusion by Hardell et al. (2011)[68] that exposure from both types of phones is of the same order. Hardell found grossly similar odds ratios for the use of mobile or cordless phones, that are thus hard to explain on the basis of actual incident or total 'exposure'. It is not known, but considered possible by the Committee, that there is a correlation between the use of cordless phones and mobile phones. This could in part be an explanation for the increased risks found for cordless phone use. Hardell et al. did not clarify whether the risk estimates for cordless phones were adjusted for mobile phone use. The Committee feels that the cordless phone data challenge the internal consistency of the Hardell et al. studies.

7.4 Strengths and limitations of the different study types and studies

Cohort, case-control, case-case and ecological studies all have different strengths and limitations.

Cohort studies generate potentially strong evidence, as the exposure can be repeatedly and objectively measured or assessed before the outcome occurs. These studies therefore do not suffer from recall bias. However, it is often difficult to perform cohort studies in the optimal way, as the investment in (preferably longitudinal) exposure measurements can be high and the cohort will have to be followed for a long time, up to several decades. The main cohort study in this evaluation (the Danish cohort study[48,50-52,174]) merely considered the duration of the subscription for those people that started a private subscription before 1996, and compared that to all other residents of Denmark. No

information has been gathered on the intensity and duration of use, such as the number of calls and the total duration of calls, as has been done in the case-control studies. Clearly the mere time that passed since a subscription started (which was also assessed in the case-control studies) is a less meaningful endpoint than an estimate of the amount of use, which is more directly associated with exposure.

Two other points need to be discussed with respect to the Danish cohort. The first is that business contracts were excluded from the 'exposed' group, since these subscriptions could not be related to individuals. This means that a number of business users, who are possibly among the heaviest users in the period before 1996, are included in the control group. The second issue is that the mobile phone use in the control group, the rest of the Danish population, also strongly increased after 1996. This means that in the later publications with longer follow-up there will be increasing misclassification in the control group. However, it can be demonstrated that, because there is no misclassification in the 'exposed' group, any misclassification in the control group has only limited effect on the calculated risk.[152] Therefore the cohort study is potentially well suited to examine risks also long after first use.

So, because a cohort is a strong study design and the score of the Danish cohort in the quality evaluation was good, the Committee considers the Danish cohort, despite the lack of actual exposure data, important for the overall evaluation.

The Committee considers the other cohort studies identified of little value for the overall data analysis, mainly because of the only short periods of follow-up, which are not relevant for very slow growing tumours.

Case-control studies are very efficient in their data collection, since they focus on new cases arising in a restricted time period. This has great advantages over cohort studies, especially in case of relatively rare diseases such as brain tumours, where large cohorts are needed to obtain sufficient cases. However, exposure assessment in case-control studies is always retrospective, therefore these studies potentially suffer from some major sources of bias, as discussed in Chapter 4. The main case-control studies identified in this analysis are those from the Hardell group and the INTERPHONE studies. The other case-control studies have much lower overall 'exposure' and considered much shorter times since first phone use. They are therefore not really relevant under the assumption of the Committee that, if there would be a risk associated with mobile phone use, it would be increasing with increasing exposure and usage time. They will not further be discussed here.

The Committee considers the INTERPHONE studies to be prone to selection bias due to the overall relatively low response rates. Because these are also lower for the controls than for the cases, this might lead to differential misclassification bias. The Hardell studies reported higher response rates and smaller differences in response rates between cases and controls than the INTERPHONE studies. These response rates were for the controls still higher than the response rates in the Swedish part of INTERPHONE (see 5.1). So also on the basis of the recalculated response rates, the Hardell studies are less likely to suffer from selection bias than the INTERPHONE studies, but the response rates in especially the Hardell controls are unusually high.

In both study protocols there is also the possibility of observer bias. The interviews of the INTERPHONE studies were all done in person at the participants' home. In spite of the training of the interviewers, they might in some way have been unknowingly influenced by the case or control status of the subjects. This is also the case with the Hardell studies. Although in these studies the initial information has been gathered by postal questionnaire, all participants received a follow-up interview by phone. The investigators state that this was conducted in a blinded fashion, but during the interview disease status may well have become known. So observer bias is not a likely explanation for any differences in outcomes between the two studies.

Both the Hardell and INTERPHONE studies are also inherently prone to recall bias. A recent publication evaluated a subsample of the INTERPHONE study with the aim of improving the exposure assessment by taking the location of the tumour relative to the preferred position of the mobile phone into consideration.[114] However, as this still relies on recall of both the position of the phone and the extent of its use, it is a refinement of the analysis but it does not solve the fundamental problem of recall bias.

The Committee has spent a great deal of effort in systematically assessing the methodological quality of the various studies (see Chapter 5) and the issue of bias discussed above plays an important role in that analysis. It did not result in any major differences in quality between the two main research groups, Hardell and INTERPHONE. The overall rating of the Hardell studies was 7.6 for the glioma + meningioma and the acoustic neuroma studies, and 6.7 and 7.4 for the parotid gland tumour studies. For INTERPHONE the ratings were 6.7 (glioma+meningioma), 7.2 (acoustic neuroma), and 6.7 and 6.5 (parotid gland tumours) (Table 5.1). However, this quality analysis has not taken into account a number of issues relating to internal and external consistency.

The first issue is that of the cordless phones. In view of the lower exposure resulting from the use of these phones in comparison to mobile phones as discussed in 7.3, the Committee considers it highly unlikely that similar odds ratios would be observed, as was the case in the Hardell studies. But, as discussed earlier, an explanation for these findings might also be that there is a correlation between the use of mobile and cordless phones.

The second issue is that of the increased risks observed by Hardell et al. at very short usage times. These are unlikely in view of the presumably very long latency times of the tumours under consideration. Also, if these increased risks were true, increased incidences in the ecological studies would be expected, but these were not observed.

According to the Committee these issues cast some doubt on the validity of the Hardell et al. studies.

Another point that is important to take into account is the fact that the Hardell et al. studies are performed in only one country (Sweden), while the INTERPHONE studies cover 16 areas in 13 countries, thus covering a much broader population. The total numbers of cases and controls are also lower in the Hardell et al. studies compared to INTERPHONE (Table 7.1).

Effectively this comparison can only be made for the glioma studies. It should also be born in mind that for the full data set the age ranges are dissimilar. As the incidence of brain tumours is very much age-dependent, this is a major issue and a direct comparison between the Hardell and INTERPHONE data should only be made with the age-limited Hardell dataset that has the same age range as the INTERPHONE dataset. This effectively limits this comparison to the highest categories for 'Time since first use' and 'Cumulative call time'. In the studies on other tumours, Hardell et al. always make a distinction between users of cordless and mobile phones, with sometimes also a division between analogue and digital mobile phones. The numbers for these categories are sometimes provided, but there is overlap when subjects have used more than one type of phone, and the overall total numbers are not provided.

Table 7.1 Comparison of numbers of cases and controls in the Hardell and INTERPHONE studies.

		Hardell[66,165]	INTERPHONE[93]
		Cases / controls	Cases / controls
Glioma	Time since first use	529 / 963 (20-80 yrs)	1666 / 1894 (30-59 yrs)
	Cumulative call time	529 / 963 (20-80 yrs)	1666 / 1894 (30-59 yrs)
Glioma 30-59 yrs	Time since first use ≥10 yrs	56 / 74	252 / 232
	Cumulative call time ≥1640 h	29 / 37	210 / 154

In summary, there is doubt on the internal and external consistency of the Hardell data on account of (1) the increased risk observed already with very short usage times; (2) the unusually high response rates in the controls; and (3) the increased risks observed for cordless phone use, again in some cases for very short usage time. For these reasons, in combination with the lower numbers of subjects, the Committee has given the Hardell et al. studies less weight than the INTERPHONE studies in the overall analysis and conclusions.

Case-case studies are potentially powerful, as they are less likely to suffer from selection and observer bias. There will of course still be recall bias, but this will be non-differential, since only patients are involved. However, case-case studies are limited because they are often single-hospital based and thus will have very limited numbers of cases for rare diseases such as brain cancers. This applies to all the case-case studies discussed in this report, with the exception of the multi-hospital study by Sato et al. (2010)[112] that included 1589 cases, and two subsamples of the INTERPHONE study that have been analysed in a case-case fashion, including respectively 2692[147] and 888 cases.[113]

Ecological studies are inherently limited in their interpretation, since individual exposure is not determined. Instead, these studies investigate trends in the incidence (or prevalence) of disease and, in this case, the development of the number of mobile phone subscriptions. However, as indicated, for the tumours considered in this report there is only limited information on the latency time. Exposure-effect relationships cannot be derived from ecological studies. At best, they can show a similarity in trends in increase of disease and phone use. Absence of an increase in disease incidence following an increase in mobile phone possession (and presumed use) does not prove the absence of a causal relation between exposure and disease, but might give support to it when the period of strong increase in phone use is a decade or longer in the past, if it is assumed that the latency period is more than a decade. If the latency would be a decade or less, an increased risk would have been expected in the trends by now.

7.5 Overall discussion per tumour type

7.5.1 Brain tumours not further specified

It is not possible to draw any conclusions with respect to the relation between mobile phone use and the occurrence of brain tumours in general.

No increased risks were found in the two case-control studies and in the cohort study. However, even though the quality of the case-controls studies is reasonable, the follow-up is too short for them to be meaningful. The cohort study has limitations with respect to exposure categorization.

7.5.2 Glioma

The Committee concludes that there are some weak and inconsistent indications for an association between prolonged and intensive use of a mobile phone and an increased incidence of gliomas. These might be explained by various types of bias and chance, but it cannot be excluded that there is a causal relation. However, the Committee considers the likelihood for a causal relation very low. The population statistics also do not show an increased incidence of glioma. But since it is likely that the latency time for these tumours is very long, an increased incidence might not yet be visible.

Time since first use, overall usage

Most cohort studies had a follow-up period that is too short to show a possible increase in glioma risk and they are therefore not useful for the current analysis. The only long-term cohort study, the Danish cohort, gives no indication of an increased risk at follow-up times of ≥13 years for those who started to use a mobile phone before 1996.

The measure of exposure used in this cohort study, length of subscription, is only a crude measure. It is also used in some of the case-control studies, mostly as time since first use. The Committee considers other endpoints used in the case-control studies that give a more direct measure of exposure – cumulative number of calls and, even more, cumulative call time – to provide the most relevant data, even though they are suffering from various types of bias, as discussed earlier.

For time since first use the INTERPHONE study did not find any increased risks, only two decreased risks for intermediate follow-up times. The only explanation for this is bias (mainly selection bias) and chance. Case-case analyses of two subsets of the INTERPHONE data provided contradictory results: in one subset an increased risk was found for the highest category of time since first use, >10 years, while in the other study no increased risks were found. So nothing can be concluded from these case-case analyses.

Hardell observed increased risks for all glioma in the highest category of >10 years, and for aggressive brain tumours, astrocytomas, in the two highest

categories, >5-10 years and >10 years. This is a pattern that can be expected if there would be a causal relation between mobile phone use and brain tumours. However, Hardell also found an increased risk for cordless phone use, both for all gliomas and for astrocytomas, in the two highest categories. An increased risk with cordless phone use is not consistent with the lower exposure from cordless phones compared to that from mobile phones. It is also unlikely and not consistent with other data to observe an increased risk already after 5-10 years of phone use.

A meta-analysis of the data from the longest usage time categories has been performed. A full description and all data are given in Annex I. The data were tested for heterogeneity and datasets for which the p-value was <0.05 were considered to be too heterogeneous for a meaningful meta-analysis and are not reported here. They are shown in Annex I for completeness, however.

The data for time since first use >10 y using the Hardell data for the full age range of 20-80 y were too heterogeneous for a combined analysis (Annex I, tables I1). When the Hardell et al. data were not included, there was no heterogeneity (Annex I, tables I2), meaning that the Hardell data strongly deviate from the Frei et al. and INTERPHONE data. When the subset of the Hardell data for the age range of 30-59 y was used (which is similar to that of the INTERPHONE study) a non-significantly increased overall OR of 1.14 (95% CI: 0.90, 1.45) was calculated (Figure 20; Annex I, Tables I3).

Cumulative call time, overall usage

For cumulative call time INTERPHONE found an increased risk only in the highest category (cumulative call time ≥1640 h), and a decreased risk in the next-highest (and several lower ones). So there is no obvious exposure-response relationship. Since it is not very likely that mobile phone use results in a protective effect, there should be another explanation for the decreased risks. The authors of the INTERPHONE publication conclude that the bias inherent to case-control studies could in part (thus not completely) explain their results.

Especially selection bias associated with the poor response rates of the INTERPHONE studies could result in the decreased risks. But this would mean that the observed increased risk in the highest category may also have been underestimated due to selection bias, while on the other hand it also could have been overestimated due to recall bias. It is not possible to fully assess these differential effects. The INTERPHONE researchers also analysed the data for the highest category while excluding subjects that indicated a very high average

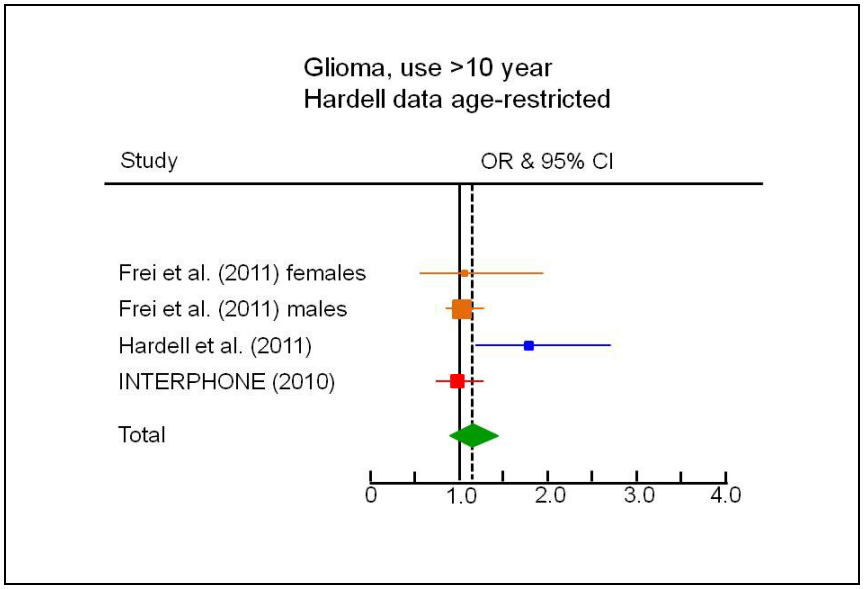

Figure 20 Forest plot of the glioma data for use >10 y. Data from Frei et al. (2011)[52], Hardell et al. (2011)[165], INTERPHONE (2010)[93].
NB: this meta-analysis has only been performed on the data for the highest 'exposure' category. It does not take into account any exposure-response relationships, and the possible influence of bias and other factors that have been discussed in this report has not been accounted for. Therefore this analysis does not provide an estimate of the true risk increase.

daily call time of >5 h (that was deemed implausible by some). This resulted in no increased risk. It is questionable, however, whether this procedure is justified, since it concerned quite some subjects: 41 of 210 cases (19.5%) and 20 of 154 controls (13%).

Two subsets of the INTERPHONE study were also analysed for cumulative call time. Neither found an increased risk. For one of the subsets the total accumulated energy in the tumour was calculated also, and in the highest category for the subset that had used the phone ≥7 years in the past the risk was increased. Since the calculated cumulated energy still relies on reported phone use, this method does not avoid the influence of recall bias.

Hardell observed increased risks for both all glioma and astrocytoma in all categories of cumulative call time (1-1000 h, 1001-2000 h and >2000 h) for mobile phone use, and in the two highest categories for cordless phone use. The latter is inconsistent with the lower exposure from cordless phones compared to that from mobile phones. The Committee also considers an increased risk even in the lowest category of 1-1000 h not very likely.

The heterogeneity analysis of data for cumulative call time for the full age range Hardell data (>2000 h) and INTERPHONE (>1640 h) resulted in a p-value <0.05, i.e. the data are too heterogeneous for a meta-analysis (Annex I, I4). When the limited age range Hardell data were used (in which they used a cumulative call time >1640 h to be more comparable to the INTERPHONE data), heterogeneity was less and the overall OR was significantly increased at 1.48 (95% CI: 1.13, 1.93) (Figure 21; Annex I, I5).

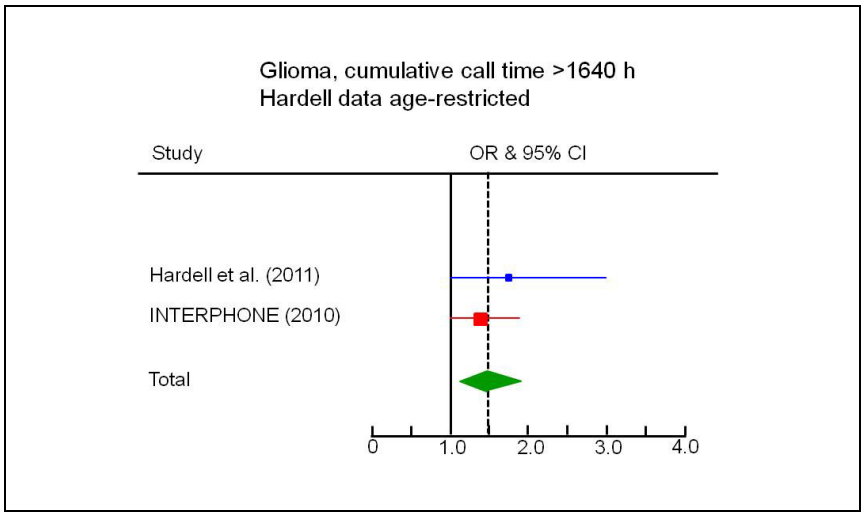

Figure 21 Forest plot of the glioma data for cumulative call time >1640 h. Data from Hardell et al. (2011)[165] and INTERPHONE (2010) [93].
NB: this meta-analysis has only been performed on the data for the highest 'exposure' category. It does not take into account any exposure-response relationship, and the possible influence of bias and other factors that have been discussed in this report has not been accounted for. Therefore this analysis does not provide an estimate of the true risk increase.

Number of calls, overall usage

INTERPHONE was the only study also to analyze the number of calls, a measure that was shown to be less prone to recall bias than duration of calls (and consequently total call time).[146] No increased risk was observed in any of the categories (maximum > 27,000 calls). Decreased risks were observed in some of the lower categories, indicating some form of bias. No meta-analysis for this endpoint is possible, since there is only one study.

Time since first use, laterality

In the laterality analyses of time since first use INTERPHONE did not observe any increased risks with either ipsilateral (side of the head where the tumour is located) or contralateral use (side of the head opposite from the tumour location). Decreased risks were observed in two intermediate categories for contralateral use. Again, bias and chance are the most likely explanations for this. Hardell on the contrary observed increased risks for ipsilateral use for both mobile and cordless phone use of even total usage times as short as >1 year, and for contralateral use of a mobile phone for >10 years. The Committee considers it highly unlikely that, with these slowly growing tumours, an increased risk would be visible already after 1 year of phone use, and even more unlikely that this could be the case after >1 year use of a cordless phone, which results, as discussed earlier, in a considerably lower exposure than a mobile phone. Moreover, the increased risk for contralateral use of a mobile phone is also unlikely, since most of the energy of the phone that enters the head is deposited within several centimetres of the antenna.[114,147,175]

The heterogeneity analysis indicated that the data for both ipsi- and contralateral use with the Hardell data for the full age range had a p value <0.05 (Annex I, I6, I7). They are therefore too heterogeneous for a meta-analysis. This is also the case for the contralateral use data with the age-limited Hardell data set (Annex I, I9). Only the ipsilateral data using this set had a p value >0.05; the meta-analysis resulted in a non-significantly increased OR of 1.62 (95% CI: 0.87, 3.01) (Figure 22; Annex I, I8).

Cumulative call time, laterality

The only increased risk in the INTERPHONE glioma studies was found for ipsilateral use and the highest category of cumulative call time (≥1640 h). In a reanalysis of his data limiting it to the age range used by INTERPHONE (39-50 years), Hardell also found an increased risk for ipsilateral exposure (although based on very few subjects). If there would indeed be an association between mobile phone use and glioma risk, this is a situation where this might be expected. However, in several other categories of both ipsi- and contralateral use, INTERPHONE observed decreased risks. The INTERPHONE investigators went at great length to find an explanation for this, but finally concluded that bias (mainly selection bias) and chance were the most likely explanations. The Committee agrees with that, and sees no reason why the only increased risk

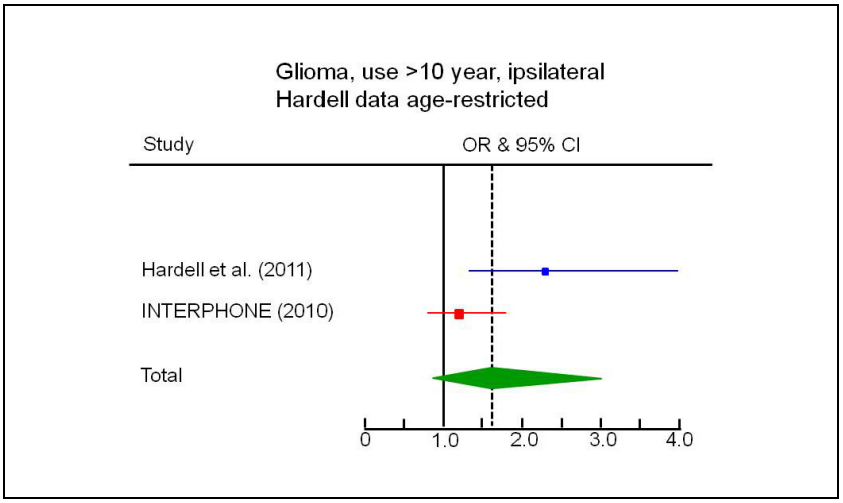

Figure 22 Forest plot of the glioma data for time since first use >10 y, ipsilateral use. Data from Hardell et al. (2011)[165] and INTERPHONE (2010) [93].
NB: this meta-analysis has only been performed on the data for the highest 'exposure' category. It does not take into account any exposure-response relationship, and the possible influence of bias and other factors that have been discussed in this report has not been accounted for. Therefore this analysis does not provide an estimate of the true risk increase.

estimate could not also be explained by this. This point of view is supported by the fact that for cumulative number of calls, an endpoint that is closely related to cumulative call time, no increased risk was observed in the INTERPHONE studies, but again several decreased risks. It has been indicated earlier that this could be the result of selection bias.

The heterogeneity analysis showed that the datasets including the age-restricted Hardell data for both ipsi- and contralateral use had p-values >0.05 and are therefore suitable for a meta-analysis. For ipsilateral use a statistically significantly increased OR of 2.03 (95% CI: 1.37, 3.00) was found, and for contralateral use the OR was not significantly increased: 1.32 (95% CI: 0.76, 2.28) (Figure 23; Annex I, I10, I11).

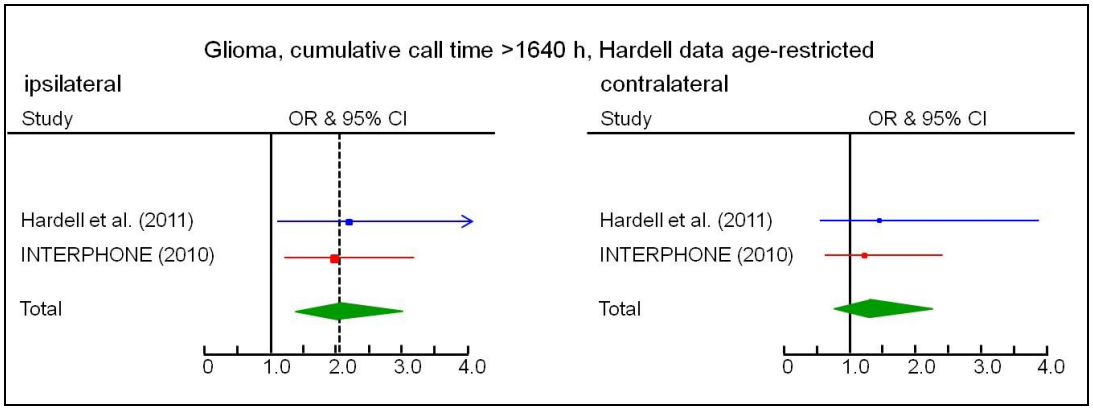

Figure 23 Forest plot of the glioma data for cumulative call time >1640 h; left panel: ipsilateral use, right panel: contralateral use. Data from Hardell et al. (2011)[165] and INTERPHONE (2010) [93].
NB: this meta-analysis has only been performed on the data for the highest 'exposure' category. It does not take into account any exposure-response relationship, and the possible influence of bias and other factors that have been discussed in this report has not been accounted for. Moreover, the INTERPHONE data include a number of subjects that reported an unlikely high daily calling time. Therefore this analysis does not provide an estimate of the true risk increase.

Ecological studies

The ecological studies support the absence of an increased risk. Little et al. (2011)[133] showed that if the risks Hardell et al. (2011)[167] reported were true, a clearly increased glioma rate should already have been visible. If the increased risk reported in the INTERPHONE studies[93] were true, that would be consistent with the observed incidence patterns. So there could be a small risk, but there could also be no risk at all. The incidence of brain tumours in the Netherlands has been constant over the period 1998-2010 in the age groups <60 y, supporting the absence of an increased risk from mobile phone use.

7.5.3 *Meningioma*

The Committee concludes that there are no clear and consistent indications for an increased risk of meningioma from using a mobile telephone.

The INTERPHONE studies showed no increased risk at all for meningioma in any of the groups for any of the endpoints, only several decreased risk, but without a clear exposure-response relationship. These findings can be regarded as the result of (selection) bias and/or chance. For overall exposure Hardell observed an increased risk only for analogue phones and a time since first use of >10 years, and for cordless phone use for >5-10 years. The latter is inconsistent

with an exposure-response relation and with the lower exposure caused by cordless phones, but there might be a correlation between cordless and mobile phone use. The laterality data only show increased risks for ipsilateral use of mobile phones for >1 year (and not for >10 years) and for cordless phones of >10 years. Again, these data from Hardell et al. are inconsistent and cannot logically be explained.

The Danish cohort study did not show any increased meningioma risks. The other two case-control studies had too short follow-up times and too few cases in the highest duration category to be meaningful.

7.5.4 *Acoustic neuroma*

The Committee feels that the data on an association between long term use of a mobile phone and acoustic neuroma are inconsistent and do not really give an indication for an increased risk.

INTERPHONE found an increased risk only in the ipsilateral subgroup with the highest cumulative call time. This is not contradictory to expectations, but the lack of any exposure-response and even a decreased risk in the next-highest category are not supportive of a real increase in risk. In the data for cumulative number of calls, that are highly correlated to those of cumulative call time, decreased risks were found for both ipsi- and contralateral use in the middle one of five categories. The Committee feels that such results cannot logically be explained and that these data therefore should be regarded as being the result of bias and/or chance, as discussed before. It is likely that this is also true for the only increased risk, although this could work both ways: the actual risk could both be higher and lower than the observed one. No changes in risk were observed by INTERPHONE for time since first use for both ipsi- and contralateral use.

The Hardell data show an increased risk for ipsilateral mobile phone use >10 years, but also for ipsilateral use >1 year, for both mobile and cordless phones. The overall data (so including both ipsi- and contralateral use) for time since first use show increased risks for analogue phone use in all categories (>1-5, >5-10 and >10 years), for digital phones only for >1-5 and >5-10 years and for cordless phones only for >1-5 years. For cumulative call time the Hardell data show increased risks only in the highest category, but for all three phone types. So these data are not really consistent. It is highly unlikely that any increased risk would show up already after >1 year of phone use.

The data from the Danish cohort are very limited but also do not indicate any effect. The data from other case-control studies lack an adequate follow-up time and sufficient subjects, and are therefore practically of no value.

A heterogeneity analysis was performed on the data for time since first use >10 y, both for all use and for ipsi- and contralateral use, and on the data for cumulative call time >1000/1640 h (Annex I, I12-I15). In all cases the p-value was <0.05, indicating too much heterogeneity for a meta-analysis.

7.5.5 Parotid gland tumour

The Committee concludes that there are no clear indications for an increased risk of parotid gland tumours from using a mobile phone. The data from the various studies on parotid gland tumours have shown only one increased risk estimate in one subgroup in one study with limited numbers of cases. This could have been the result of chance. The incidence data including those from the Netherlands also do not show an increase.

7.5.6 Other (pituitary, melanoma eye, intra-temporal facial nerve tumours and neuroblastomas)

For pituitary tumours, melanoma eye tumours, intra-temporal facial nerve tumours and neuroblastomas tumours no conclusions regarding risks associated with the use of mobile phones can be drawn.

In case of the studies on pituitary tumours and malignant melanoma of the eye, the numbers of cases and controls were very small in all exposure categories, and particularly in the groups with longer or heavier exposure. The studies on intra-temporal facial nerve tumours and neuroblastomas were of a nature that did not allow risks to be determined.

7.6 The Bradford Hill considerations

The Committee has focused in this report on epidemiological studies. In such observational studies the quality of exposure assessment is crucial, especially in deriving exposure-response relations.[176] Moreover, the extent of selection bias and the adjustment for confounding factors are important in assessing the evidence for causality of associations. A standard tool in assessing evidence for causality are Bradford Hill's considerations.[12] Of these, in more recent epidemiological literature, strength, consistency, temporality, biological gradient

(or exposure-response) and biological or physical plausibility are considered. It should be borne in mind that presence of these items is considered a contributing argument that causality is likely, but their absence does not prove that there is no causality.

Strength

A relative risk or odds ratio higher than 2 is usually considered to be a relatively strong association. Most relative risks observed in the studies discussed in this report are lower than 2. It is likely that in the studies described, misclassification of exposure occurs. This will mostly lead to underestimation of the odds ratio, thus decreasing the strength of the observed association. Nevertheless, an odds ratio of less than 2 could also be indicative of causality if it is consistently observed. This is not really the case in the studies described in this report.

Consistency

Consistency of results from different studies strengthens the causality argument. However, the consistency across and within the studies discussed here is not very high. In several studies some increased risks have been observed in subgroups, while in particular in the INTERPHONE studies many decreased risks were found. Mostly, however, no increased or decreased risks were observed. However, where one would expect the effect to occur if an effect exists, such as in the ipsilateral side of the exposure after longer or heavier exposure, some consistency might be perceived.

Temporality

This refers to the fact that the occurrence of the disease should always follow the exposure. In case-control studies exposure is always measured retrospectively, so temporality can never truly be addressed. Cohort studies could provide more insight into this, but the cohort studies described in this report do not report increased risks. So no conclusions on temporality can be made.

Biological gradient or exposure-response

Exposure-response relationships can only be assessed if exposure can be measured adequately and with sufficient precision.[176] However, since the case-control studies used questionnaires to retrospectively assess exposures which

often occurred long ago, recall bias will decrease the accuracy of exposure assessment. Where in the INTERPHONE studies an increased risk was observed, this was only in the highest out of 10 exposure categories for cumulative call time. This does not constitute a clear exposure-response association. No increased risks were found for cumulative number of calls. Hardell observed several exposure-responses in the analysis of time since first use and cumulative use for gliomas.

Plausibility

This refers to the understanding of the biological model underlying a true association between mobile phone use and brain tumours. Many reviews have concluded that there is no known biological model to explain a relation between mobile phone use and an increased risk of cancer.[7,11,177,178]

In conclusion, application of the Bradford Hill considerations to the available epidemiological data is not supportive of a causal relation between the use of mobile phones and the occurrence of tumours in the head. This may be because there really is no causal relation, but it may also reflect inadequacies of the methods used in the studies up to date or in the ability to measure exposure and outcome.

Chapter 8

Conclusions and recommendations

On the basis of the data presented in this systematic analysis, the conclusions can only be based on the results of three groups of studies: the case-control studies of Hardell et al. and of INTERPHONE, and the Danish cohort. All three study groups scored approximately similar in the analysis of the methodological quality. But since there is doubt on the internal and external consistency of the results of Hardell et al. and since the numbers of subjects in these studies are much lower than in the other two studies, the Committee gives the studies by Hardell et al. less weight than the other studies in the overall analysis and conclusions.

No proven risk

Based on the available epidemiological evidence described in this report and taking into account the quality of the different studies and their strengths and weaknesses, the final conclusion from this systematic analysis is then, that there is no clear and consistent evidence for an increased risk of tumours in the brain and other regions in the head in association with up to approximately 13 years use of a mobile telephone. For longer term use, for which no data are available, such risk cannot be excluded at present. In general it can be stated that the use of mobile phones has considerably increased since the studies described in this report were conducted, but what the long-term health effects of this, if any, may be is impossible to predict. Currently ongoing cohort studies, that include a better

characterization of exposure than in the studies described in this report, might allow more firm conclusions in due time. A challenge in these studies will be to take account of the rapidly changing intensity of use and patterns of exposure, due to the changing types and use of mobile phones.

The present systematic analysis shows that, despite substantial research efforts, there is still insufficient clarity and consistency regarding a possible association between mobile phone use and an increased risk of tumours in the brain and other regions of the head. There is some weak and inconsistent evidence for an association between prolonged and intensive use of a mobile phone and an increased incidence of gliomas. This is most likely explained by various types of bias and chance, but it cannot be excluded that there is a causal relation. For the other types of tumours, including meningiomas and acoustic neuromas, indications for an increased risk are much weaker or completely absent. The Committee notes that the meta-analyses as presented in the forest plots have only been performed on the data for the highest 'exposure' category. They do not take into account any exposure-response relationships, and the possible influence of bias and other factors that have been discussed has not been accounted for. Therefore they do not provide estimates of the true risk increase.

The case-control studies have severe limitations due to their inherent vulnerability to several biases. Any increased risks observed for long-term or extensive use might be related to use of the – now obsolete – analogue mobile phones. Since most studies did not make a distinction between exposures from analogue and digital phones it is not possible to conclude anything on this issue. It is also possible that the follow-up period in the available studies is too short for an effect on the slow growing types of tumours to become manifest. However, up to now there is no indication from cancer registry data, including those from the Netherlands, that the incidence of brain or other tumours in the head is increasing, despite the very fast and sharp increase in mobile phone use that occurred from the mid-1990's onwards. But again, the time period for this might be too short, in view of the slow development of the types of tumour under study.

With the currently available data, consideration of the Bradford Hill criteria is not supportive of a causal relation between the use of mobile phones and the occurrence of tumours in the head.

Measures

There are currently in the Netherlands no legally binding exposure limits, but the government policy is that the ICNIRP guidelines are observed. Without implying

that either the exposures currently experienced in daily life or the exposure limits such as those proposed by ICNIRP are too high, the Committee would like to suggest that there is no reason not to apply the ALARA principle to exposure to RF EMF, meaning that exposures should be As Low As Reasonably Achievable. This is fully in line with the suggestions from the Health Council's advisory report 'Prudent precaution'.[229]

It is possible that some individuals would like to reduce their exposure, despite the conclusion of the Committee that there is no consistent evidence for an increased risk for tumours in the brain and other regions in the head associated with mobile phone use. The Knowledge Platform Electromagnetic Fields provides a number of suggestions for exposure reduction.[179]

Better focussed research

According to the Committee there still is a need for further, focused, research. A large multinational prospective cohort study of mobile phone users (COSMOS) has recently been started, but it will take many years before results are available. Further results of the MOBI-KIDS case-control study investigating mobile phone use and brain tumours in children are awaited. When necessary, the Committee will report on new developments.

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A	The Committee
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Annexes

Annex **A**

The Committee

The membership of the Electromagnetic Fields Committee at the time of preparation of this advisory report was as follows:

- Prof. G.C. van Rhoon, *chair*
  Professor of Physical Aspects of Electromagnetic Fields and Health, Erasmus University Medical Centre Rotterdam
- Prof. A. Aleman
  Professor of Cognitive Neuropsychiatry, University of Groningen
- Prof. H. Kromhout
  Professor of Epidemiology of Health Effects from Exposure to Electromagnetic Fields, Institute for Risk Assessment Sciences, University of Utrecht
- Prof. F.E. van Leeuwen
  Professor of Cancer Epidemiology, Free University of Amsterdam, Epidemiologist, Netherlands Cancer Institute, Amsterdam
- Prof. H.F.J. Savelkoul
  Professor of Cell Biology and Immunology, Wageningen University
- Prof. W.J. Wadman
  Professor of Neurobiology, University of Amsterdam
- D.H.J. van de Weerdt, MD
  Toxicologist and Specialist in Environmental Medicine, Central Gelderland Municipal Health Services (GGD), Arnhem

- Prof. A.P.M. Zwamborn
  Professor of Electromagnetic Fields and Health, Eindhoven University of Technology, physicist, TNO (Netherlands Organisation for Applied Scientific Research), The Hague
- Dr. G. Kelfkens, *advisor*
  Physicist, Netherlands Institute for Public Health and the Environment, Bilthoven
- R.M. van der Graaf, *observer*
  Executive Director, Knowledge Platform Electromagnetic fields, Bilthoven
- Prof. E. Lebret, *observer*
  Professor of Environmental Health Impact Assessment, Institute for Risk Assessment Sciences, Utrecht University, and Chairman Science forum, Knowledge Platform Electromagnetic Fields, Bilthoven
- Dr. H.K. Leonhard, *observer*
  Physicist, Ministry of Economic Affairs, Groningen
- Prof. I.A. Kreis, *scientific secretary*
  Epidemiologist and Specialist in Social Medicine, Health Council of the Netherlands, The Hague
- Dr. E. van Rongen, *scientific secretary*
  Radiobiologist, Health Council of the Netherlands, The Hague

Dr. M.C. Cardous-Ubbink, epidemiologist, assisted in the extraction and scoring of the data, and dr. W.L.J. van Putten, statistician, assisted with the forest plots. The registration teams of the Comprehensive Cancer Centre Netherlands and Comprehensive Cancer Centre South collected the data for the Netherlands Cancer Registry and the scientific staff of the Comprehensive Cancer Centre Netherlands provided the analysis of the data.

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for

the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **B**

Search strategy and results

A search strategy consists of the keywords and databases used. For this systematic review, a comparison of several important databases was carried out and the publications identified were evaluated for the relevance of the topics identified.

Keywords

Both intuitively relevant terms and MeSH (Medical Subject Headings) in PubMed were used as keywords. For exposure, the MeSH terms were “cellular phone”, “radio frequencies” and “electromagnetic fields”, but “mobile phone”, “radio waves” and “cell phone” were also used. To assess the impact of different words for telephone both “phone” and “*phone” were tried and gave identical numbers of hits. The keyword “telephone” give substantially fewer hits and was taken as included in “*phone”. As outcome parameter the MeSH was “neoplasms”, but “tumour” and “cancer” were also used. These keywords individually resulted in different numbers of hits, therefore they were all included in the search strategy. For methodology “epidemiology” (a MeSH term) and “exposure assessment” plus “dosimetry” were added.

Databases

Initially both PubMed Central and PubMed were searched and compared for the number of hits. Since PubMed appeared a broader database then PubMed Central, only PubMed was used.

Searches

Initial searches were performed in the week of 20 July 2009 and fully repeated on 15 August 2011. The results of the search from August 2011 are presented in tables B.1 and B.2, where the number of hits for the different keywords and combinations of keywords is given.

Using the combinations of the search terms that were evaluated, a combined search was conducted. The combined search used the terms:

cellular phone* OR mobile phone* OR cell phone* OR radio waves OR electromagnetic fields OR radio frequency AND human AND (tumour OR cancer OR neoplasms) AND (epidemiology OR dosimetry OR exposure assessment).

There were no restrictions on years, language or any other placed on this search. This resulted in 2083 hits.

Based on title 420 papers were identified as possibly of interest. The rest was discarded as animal or cell studies (73), extremely low frequency fields (339), radio- or tv- or GSM masts (11), SAR (8), ionising radiation or therapy (583), using mobile phones as research tool (17), other (76), and tumours not in head or brain (537).

The 420 remaining papers were evaluated using the abstracts. This resulted in 76 publications on original studies of interest, 108 editorials, 68 reviews and 14 of potential interest as theory forming papers. The rest was discarded as animal or cell studies (2), extremely low frequency fields (54), tumours not in head or brain (12), ionising radiation or therapy (27), language not English, French, German or Dutch (16), not mobile phones (43).

Table B.1 PubMed search results in number of hits per single or two-term combination.

	solo	+ H	+ T	+ C	+ N	+ Epi	+ EA	+ D
Cellular phone*	2639	2247	314	343	2914	367	138	266
Mobile phone*	1799	1366	203	230	1768	266	177	192
Cell phone*	716	551	65	80	61	95	12	24
Radio waves	15322	7098	2230	2228	2065	402	204	1279
Electromagnetic fields	14720	8381	1843	1890	1657	1044	557	1570
Radio frequency	7779	4538	1743	1780	1644	1863	123	399
Human (H)	12116038	-	-	-	-	-	-	-
Tumour (T)	2568569	2111767	-	-	-	269665	5566	23874
Cancer (C)	2537766	2075920	-	-	-	280169	6737	25520
Neoplasms (N)	2274624	1918981	-	-	-	263885	5121	22233
Epidemiology (Epi)	1391216	-	-	-	-	-	-	-
Exposure Assessment (EA)	37814	-	-	-	-	9300	-	-
Dosimetry (D)	106491	-	-	-	-	5080	-	-

* operator term allowing for plural + : operator term “AND”;.?????

Table B.2 PubMed search results in number of hits per multiple term combination.

	Cellular phone*	Mobile phone*	Cell phone*	Radio waves	Electromagnetic fields	Radio frequency
+ T/C/N	362	249	84	2361	2040	1854
+ H + T	276	178	60	1839	1565	1591
+ H + C	314	202	72	1842	1598	1612
+ H + N	266	167	59	1748	1446	1545
+ H + T/C/N	321	208	73	1915	1691	1649
+ H + Epi)	362	253	93	366	998	1754
+ H + EA	125	101	9	160	483	113
+ H + D	198	151	18	670	940	286
+ H + Epi + T	149	98	24	210	667	979
+ H + Epi + C	157	101	29	213	692	995
+ H + Epi + N	149	97	24	210	663	973
+ H + Epi + T/C/N	157	101	29	213	694	999

* operator term allowing for plural + : operator term “AND”, / : operator term “OR”, ????

The resulting list of 76 publications was evaluated using full text publications. Thirty-three were set aside as validation studies (6), supporting papers (14), meta-analyses (2), not mobile phone studies (7), not tumour studies (3) and case study (1).

The remaining 41 publications were checked for completeness by an expert (EvR) and compared to the reference lists of recent reviews as well as searching for other publications by the main authors. This identified a further 27 publications that were missing and 15 that were published in 2011 or later and probably missed for that reason. These experiences clearly indicate that

searching needs to include a snowballing component and cannot solely rely on protocol-driven search strategies, as has also been observed by others.[180]

This resulted in a total of 85 publications on original or pooled studies that were to be analysed. A complete list of all publications identified at any of the stages of the search is available upon request. The full flow of searches, decisions and numbers is presented in Figure 1 in the main text of this report.

Duplicate publications

It can be argued that overlapping publications should be excluded to avoid double counting and overweighting limited evidence. However, this would exclude potentially important evidence, so pooled and overlapping evidence is included in the extracted papers with due recognition of the problem. After the extractions were performed, a selection of papers was made that were used for presenting unique results. In some cases information on e.g. methods of numbers of cases and controls was obtained from related publications, but the data on odds ratios was taken from one single publication per study, to avoid overweighting.

Updating search

As there were many ‘later identified’ publications and the whole process took a long time, an update search was conducted on 10 July 2012 with a limited timeframe starting 01 January 2011. This confirmed the identification of 15 ‘later’ publications which were all included in the evaluation process taking the total of publication evaluated to 85.

Annex **C**

Data extraction

Table C1 was used for the extraction of data from the selected studies.

Table C1 Data extraction items.

Reference no. for extraction; file no. EMFcommittee, Reference no. document		
1st Author (Year)		
Title (short)		
GENERAL		
A	1	Why was the study done?
	2	What were the prior hypotheses, if any?
	3	What hypotheses were actually tested?
B	1	What type of study was done?
	2	Was this design appropriate to the study question?
	3	How might some other design have been better?
	4	What was the follow-up period?
	5	Was the follow-up period relevant to the study questions?
C	1	How was the size of the study population determined?
	2	How might some other size have been better?
	3	Was a power based assessment of adequacy of sample size done?
D	1	How was the ratio case/controls or exposed/non–exposed determined?
	2	How might some other ratio have been better?
E	1	What would be possible ethical issues in relation to the design and conduct of this study?
	2	Was the study cleared by an ethics committee?
DATA COLLECTION		
F	1	What was the source of the subjects?
	2	How might another source have been better?

G	1	What were the response rates?
	2	Were the response rates adequate for interpretation of the results?
	3	What were the final numbers in the study?
	4	What was the percentage of follow-up?
	5	Was the follow-up percentage adequate for interpretation?
	6	What was the follow-up no. of years?
H	1	Could there have been selection bias?
	2	What was the likely effect of selection bias on the data if identified?
I	1	Could there have been responders bias?
	2	What was the likely effect of responders bias on the data if identified?
J	1	Could there have been information bias?
	2	What was the likely effect of the information bias on the data if identified?
K	1	Could there have been observation bias?
	2	What was the likely effect of the observation bias on the data if identified?
L	1	What confounding bias was possible?
	2	Were the confounders measured?
M	1	Could there have been misclassification bias?
	2	What were the sources of misclassification bias?
N	1	How was exposure measured?
	2	Would other exposure measures have been better?
	3	Do exposure measures reflect person-dose or population-dose?
	4	What was the exposure among the controls?
	5	Can the exposure measures allow for a dose gradient measure?
O	1	Was there a major influence of measurement error?
P	2	Was there a major influence of random error?
ANALYSIS		
Q	1	What were the methods used to control confounding bias?
	2	Would other methods have been better?
R	1	What were the methods used to measure the association between exposure and disease?
	2	Would other methods have been better?
S	1	What were methods used to measure the stability of the association between exposure and disease?
	2	Would other methods have been better?
T	1	Was there internal consistency among the data presented in the paper?
INTERPRETATION		
U	1	What were the major results of the study?
	2	What were the key results in numbers?
	3	Was the temporal relationship correct?
	4	Was there a dose-response gradient?
V	1	How might bias including confounding have affected these results?
W	1	How might misclassification have affected these results?
X	1	Are the references up to date and relevant?
	2	Are there any glaring omissions in the references?
Y	1	To whom may the results of this study be generalised?
Z	1	Is the interpretation of the data conservative?
note1		
note2		
post-hoc power calculation		

Annex **D**

Evaluation of quality of the studies

Table D1 shows the method used to evaluate cohort, case-control and case-case studies. Ecological studies were not evaluated.

Questions 1-4 are contributing to the domain of selection, with a maximum score of 34; question 5 contributes to the domain of diagnosis, with a maximum score of 4; questions 6-14 contribute to the domain of exposure, with a maximum score of 69; questions 15 and 16 contribute to the domain of confounding, with a maximum score of 16; and question 17 contributes to the domain of conflict of interest, with a maximum score of 5.

Table D1 Evaluation system used for cohort, case-control or case-case studies on mobile phone use and head and neck tumours.

nr	Question		Evaluation	Score	Remarks
SELECTION					
1	Did cases & controls come from the same source population?	a	No or unknown	0	Consider Berkson's bias if hospital based.
		b	Yes	12	
		c	Not applicable (cohort or case-case)	12	
2	Were the same inclusion/ exclusion criteria applied to cases and controls?	a	No or unknown	0	
		b	Yes	6	
		c	Not applicable (cohort or case-case)	6	

3	What was the % response of the cases?	a	< 76% or unknown or unclassifiable	0	Include deceased cases and refusals by physician in (re)calculated response rates
		b	76-90%	4	
		c	> 90%	8	
		d	Not applicable (cohort or case-case)	8	
4	Was the absolute difference in % response between cases and controls <20%?	a	No or unknown	0	
		b	Yes	4	
		c	Not applicable (cohort or case-case)	8	
DIAGNOSIS					
5	Was the cancer diagnosis valid?	a	No or unknown	0	If they use cancer registry they probably have histology and imaging but if they have glioma vs. meningioma they certainly have histology
		b	Yes, but imaging only	1	
		c	Yes, but imaging plus location only	2	
		d	Yes, including histology	3	
		e	Yes, including histology and location	4	
EXPOSURE					
6	Could the type of administration of the (exposure) questionnaire lead to observer bias?	a	Participant or proxy, interview (in person or by phone) administered	0	
		b	Participant or proxy, self administered	5	
		c	Register-based	5	
7	Were all cases and controls treated equally?	a	No or not provided	0	No is if there is clearly a different data collection protocol or people involved between the groups
		b	Yes	5	
		c	Yes as is cohort study	5	
8	Was there potential for non-differential misclassification?	a	Yes: register based data-collection	0	
		b	somewhat: self administered data collection	5	
		c	No: interview-based data collection	5	
9	Completeness of type mobile telephone history?	a	Total of 2 points	2	Accumulate points for phone type history Mobile phone, non-specified analogue or digital: 3 points Mobile phone, specified analogue or digital: 4 points Cordless or DECT phone: 2 points Change in phone type: 3 points
		b	Total of 3 points	3	
		c	Total of 4 points	4	
		d	Total of 5 points	5	
		e	Total of 6 points	6	
		f	Total of 7 points	7	
		g	Total of 8 points	8	
		h	Total of 9 points	9	

10	Did the measure of exposure include frequency and duration and start date?	a	No	0	
		b	Start date or call-duration or frequency	4	
		c	Start date and call-duration or frequency	6	
		d	All three, but no changes	8	
		e	All three, including changes in use for all types	10	
11	Did the exposure assessment include lateralisation of phone use?	a	No	0	
		b	Indirectly via handedness	5	
		c	Yes, directly via questions and allowing for combinations	10	
12	Were changes over time considered in the analysis?	a	No	0	If changes asked for and total hours called calculated: assumed changes incorporated
		b	Yes	5	
13	Was the exposure questionnaire validated or was reliability tested?	a	No or unknown	0	
		b	Validated in another (related) study such as subsample	5	
		c	Provider data verified	10	
14	Was the exposure assessed before the cancer diagnosis (thus avoiding recall bias)?	a	No (case-control)	0	
		b	Yes (cohort or nested case-control)	10	
CONFOUNDING					
15	Were confounders adjusted in a correct way?	a	No or unknown	0	Potential confounders: age, sex
		b	Yes	8	
16	Could residual confounding influence the results?	a	Yes or unknown	0	As little known about potential confounders, this is likely to always be partly true
		b	Partly	4	
		c	No	8	
CONFLICT OF INTEREST					
17	Was there evidence of potential conflict of interest?	a	Yes	0	
		b	Yes, but with firewall	3	
		c	No	5	

Annex **E**

Additional information for the publications used

In this Annex, all Letters to the Editors, Editorials and supplementary publications used in the evaluation of the original publications are listed.

Cohort studies

There were 15 (invited) Letters to the Editors and responses from authors and one supporting paper. These are listed in Table E1.

The main issue identified was the possibility of socio-economic bias due to the selection of early adopters in the Danish cohort, but this was corrected for in the latest publication.[52] Kundi (2012)[194] pointed out that the total number of cases, in spite of the relatively large person-number of years in the publication, is small, much smaller than in the large case-control studies, and that although there is no recall bias, there still may be a substantial underestimation of risk. This is due to the fact that about 50% of the subjects labelled non-exposed have actually been exposed for over 10 years and because it is unclear if those labelled exposed were actually the ones using the phones. Rough calculations by Kundi showed a potential relative risk of 1.63 for the >10 years exposure category. Leszczynski (2011)[189] also criticized the roughness of the exposure characterization, as people with widely different phone use would be grouped as exposed. This comment also addresses the small number of cases. Morgan (2011)[187] felt that

Table E1 Supporting literature and Letters to the Editor for the cohort studies.

Reference	Supporting paper / Letter to the Editor	Subject
Hardell et al. (2001)[181]	Letter to the Editor	Comment to Johansen et al. (2001)[48]
Ahlbom et al. (2007)[182]	Letter to the Editor	Comment to Schüz et al. (2006)[50]
Ahlbom et al. (2011)[151]	Invited editorial	Comment to Frei et al. (2011)[52]
Charlier (2011)[183]	Letter to the Editor	Comment to Frei et al. (2011)[52]
Henshaw (2011)[184]	Letter to the Editor	Comment to Frei et al. (2011)[52]
Gujral (2011)[185]	Letter to the Editor	Comment to Frei et al. (2011)[52]
Davis (2011)[186]	Letter to the Editor	Comment to Frei et al. (2011)[52]
Morgan (2011)[187]	Letter to the Editor	Comment to Frei et al. (2011)[52]
Frey (2011)[188]	Letter to the Editor	Comment to Frei et al. (2011)[52]
Leszczynski (2011)[189]	Letter to the Editor	Comment to Frei et al. (2011)[52]
Glaser (2012)[190]	Letter to the Editor	Comment to Frei et al. (2011)[52]
Khurana (2011)[191]	Letter to the Editor	Comment to Frei et al. (2011)[52]
Philips & Lamburn (2011)[192]	Letter to the Editor	Comment to Frei et al. (2011)[52]
Frei et al. (2011)[193]	Response from authors	Reply to comments from Khurana (2011) [191] and Philips & Lamburn (2011) [192]
Kundi (2012)[194]	Letter to the Editor	Comment to Frei et al. (2011)[52]
Schüz et al. (2011)[53]	Original publication	Study design COSMOS cohort

the entire results had to be dismissed as the publications seemed to indicate for all cancers combined (the Danish cohort study not only considered cancers of the head but also other cancers) a protective effect of being a subscriber, thus indicating a clear healthy subscriber effect (i.e. the group of subscribers is not representative for the population as a whole, but has a better than average health). The comments by Davis (2011)[186] and Gujral (2011)[185] closely echo these points. Henshaw (2011)[184] and Frey (2011)[188] address the issue that there is no biological model that might explain any risk. Both argue that the current lack of an agreed model should not be used as an argument against the existence of a risk. They call for more well-designed studies that can actually address plausible effect models; the cohort study does not do this. The authors responded that there are indications from other sources that the early subscribers were on average heavier users than later subscribers.[193] They agree that not incorporating the business subscriptions would not allow the detection of a small risk increase such as in subsets of the INTERPHONE study.

Case-control studies

Case-control studies according to the Hardell protocol

There were 2 (invited) Letters to the Editor and responses from authors and one supporting paper. These are listed in Table E2.

Table E2 Supporting literature and Letters to the Editor for the Hardell studies.

Reference	Supporting paper / Letter to the Editor	Subject
Ahlbom & Feychting (1999)[137]	Letter to the Editor	Comment on Hardell et al. (1999)[1]
Boice & McLaughlin (2006)[195]	Letter to the Editor	Rebuttal to allegations in Hardell & Hansson Mild (2006)[196]
Hansson Mild et al. (2005)[197]	Supporting paper	Combining mobile and cordless phone data

The main issue on the Hardell case-control studies identified by Ahlbom and Feychting (1999)[137] is a seeming discrepancy between the number of cases identified in the initial case-control study and those in the Swedish cancer registry for the same period, but this was refuted by the authors with substantial detail about the in- and exclusion criteria. The letter by Boice and McLaughlin (2006)[195] mainly refutes perceived conflict of interest claims.

The supporting paper by Hanson Mild et al. (2005)[197] analyses the likely contribution of different mobile and cordless phones to the total exposure and argues against simple cumulative measures, but proposes a weighting with exposure from GSM phones weighing 1/10th of that of NMT (analogue) phones and cordless (DECT) phones weighing 1/100th. However, such weighting has not been used in any of the publications used in this report.

Case-control studies according to the INTERPHONE protocol

Thirty (invited) Letters to the Editor and responses from authors and 15 supporting papers were considered in the context of these publications. These are listed in Table E3.

Table E3 Supporting literature and Letters to the Editor for the INTERPHONE publications.

Reference	Supporting paper / Letter to the Editor	Subject
Tarone & Inskip (2005)[198]	Letter to the Editor	Comment on Lönn et al. (2004)[76]
Stang et al. (2005)[199]	Letter to the Editor	Comment on Lönn et al. (2004)[76]
Hardell & Hansson Mild (2005)[200]	Letter to the Editor	Comment on Lönn et al. (2004)[76]
Thomas et al. (2005)[201]	Letter to the Editor	Comment on Lönn et al. (2004)[76]

Johnston & Scherb (2005)[202]	Letter to the Editor	Comment on Lönn et al. (2004)[76]
Lönn et al. (2005)[230]	Response from Authors	Comments on Lönn et al. (2004)[76]
Savitz (2004)[203]	Commentary	Comment on Lönn et al. (2004)[76]
Hardell & Hansson Mild (2004)[204]	Letter to the Editor	Comment on Christensen et al. (2004)[75]
Kundi (2004)[205]	Letter to the Editor	Comment on Christensen et al. (2004)[75]
Gale & Juran (2006)[206]	Letter to the Editor	Comment on Christensen et al. (2004)[75]
Hardell et al. (2005)[207]	Letter to the Editor	Comment on Lönn et al. (2005)[78]
Milham (2005)[208]	Letter to the Editor	Comment on Lönn et al. (2005)[78]
Morgan (2006)[209]	Letter to the Editor	Comment on Lönn et al. (2005)[78]
Morgan (2006)[209]	Letter to the Editor	Comment on Schüz et al. (2006)[81]
Schüz (2006)[210]	Response from Authors	Comment on Schüz et al. (2006)[81]
Hardell & Hansson Mild (2006)[211]	Letter to the Editor	Comment on Hepworth et al. (2006)[84]
Kundi (2006)[212]	Letter to the Editor	Comment on Hepworth et al. (2006)[84]
Maier (2006)[213]	Letter to the Editor	Comment on Hepworth et al. (2006)[84]
Morgan (2006)[214]	Letter to the Editor	Comment on Hepworth et al. (2006)[84]
Hocking (2008)[215]	Letter to the Editor	Comment on Takebayashi et al. (2008)[88]
Hocking (2006)[216]	Letter to the Editor	Comment on Schoemaker et al. (2005)[90]
Hardell & Hansson Mild (2006)[196]	Letter to the Editor	Comment on Schoemaker et al. (2005)[90]
Milham (2006)[217]	Letter to the Editor	Comment on Schoemaker et al. (2005)[90]
Schoemaker et al. (2006)[218]	Response from authors	Reply to comments on Schoemaker et al. (2005)[90]
Noone (2009)[219]	Letter to the Editor	Comment on Lahkola et al. (2008)[92]
Milham (2010)[220]	Letter to the Editor	Comment on Lahkola et al. (2008)[92]
Morgan (2010)[221]	Letter to the Editor	Comment on Lahkola et al. (2008)[92]
Auvinen et al. (2010)[231]	Response from authors	Reply to comments on Lahkola et al. (2008)[92]
Saracci & Sammet (2010)[222]	Commentary	Comment on INTERPHONE (2010)[93]
Clouston (2011)[223]	Letter to the Editor	Comment on INTERPHONE (2010)[93]
Cardis & Kilkenny (1999)[73]	Supporting paper	Feasibility study results
Berg et al. (2005)[148]	Supporting paper	German validation of exposure
Samkange-Zeeb et al. (2004)[149]	Supporting paper	German self report validation study
Behrens et al. (2004)[224]	Supporting paper	Limits to exposure assessment
Lahkola et al. (2005)[150]	Supporting paper	Finnish selection bias study
Schoemaker et al. (2006)[225]	Supporting paper	Other determinants analysis
Berg et al. (2006)[226]	Supporting paper	Occupational exposure to RF
Vrijheid et al. (2006)[146]	Supporting paper	Mobile phone use recall bias validation
Vrijheid et al. (2006)[145]	Supporting paper	Recall and selection bias
Cardis et al. (2007)[74]	Supporting paper	Study design
Schüz & Johansen (2007)[159]	Supporting paper	Self-report versus subscriber data
Vrijheid et al. (2009)[46]	Supporting paper	Recall bias
Vrijheid et al. (2009)[143]	Supporting paper	Selection bias
Schüz (2009)[160]	Supporting paper	Laterality issues*
Vrijheid et al. (2009)[144]	Supporting paper	Mobile phone output power

* These refer to a possible relationship between the location of the tumour in the head and the preferential side of use of the mobile telephone

The main issues identified in the supporting papers of the INTERPHONE study are related to the possible effects of recall and selection bias. The publications by Vrijheid et al. (2006)[145,146], Schüz & Johansen (2007)[159], Vrijheid et al. (2009)[46,143,144] and Schüz (2009)[160] indicate the expectation of a considerable effect of random error in recall of phone use, which might result in an underestimation of the effect. Indications for differential recall bias (thus different between cases and controls) were observed for recall periods of 4-5 years.[46] This could result in overestimation of the effect, but it is not possible to indicate to what extent this occurred in the main studies, where phone use up to more than 10 years back was investigated. Selection bias, particularly the measured selective non-response of non-phone users, also is expected to result in lower risk estimates. Another finding was that possibly the number of calls would be a better (more robust) measure of exposure than the cumulative hours called.

For the main INTERPHONE publications[93,94] Clouston (2011)[223] stated that there was clear evidence of selection bias related to socioeconomic class and that this in turn could have led to confounding, as socioeconomic class is closely related to the survival related to glioma (if not the incidence also) which likely results in underestimation of an effect. Saracci and Samet (2010)[222] in an editorial pointed out that even now widely established cancer risks such as from tobacco smoking would not have been possible to be identified within the first 10 years or so after start of exposure. They also pointed at the high number of significantly decreased relative risks, for which is it not realistic to assume a protective effect, but for which in particular participation bias (i.e. differences in participation between cases and controls, as reflected in the different response rates) is the most likely explanation, as was also concluded by the INTERPHONE authors. They therefore concluded that the question on effect remains open and much more research is needed. Kundi (2006)[212], in addressing the paper by Hepworth et al. (2006)[84], stated the same in view of the on average short follow up period, as there are no occupational or other factors known that are associated with effects in such a short period. Kundi considered only the laterality analysis to be relevant and this showed a statistically significant association. Hepworth et al. (2006)[84] discussed that when the odds ratio for contralateral tumours is lower than 1, this proves that the increased ipsilateral risk is the result of recall bias. Kundi however considered this a consequence of the method of analysis.

The more methodological issues had often already been raised after the publications of results from individual or small number of countries. The main issues are:

- Since many odds ratios are statistically significant below unity, either mobile phone use protects (which is unlikely), or there is selection bias in the study population (Milham (2005)[208], Noone (2009)[219])
- There is evidence of selection bias, as there is low response and the cases have higher affluence (Morgan (2006)[214])
- There is selection bias, as visible in the distribution of gender (Thomas et al. (2005)[201])
- The total number of cases was too small for realistic conclusions to be drawn (Morgan (2006)[209], Johnston & Scherb (2005)[202])
- The interview method was too stressful for patients and there was possible exclusion of patients living in remote areas (Hardell et.al (2005)[207])
- There was recall bias resulting in underestimation of the risk (Hocking (2006)[216])
- There is a high non-response and the resulting bias leads to underestimation of the risk (Milham (2006)[217])
- There is a high non-response in the cases of the Japanese study[88] and over-representation of the more affluent in the controls, resulting in substantial underestimation of the risk due to selection bias (Hocking (2008)[215])
- The method used for analyzing laterality in Lönn et al. (2005)[78] is incorrect, as cases with contralateral use are labelled unexposed. The authors of this letter conclude on the basis of calculations that the risks reported in this study are substantially underestimated (Hardell et al (2005)[207])
- The laterality analysis indicates misclassification of exposure (Hardell and Hansson Mild (2004)[204])
- The laterality analysis is fundamentally flawed (Tarone and Inskip (2005)[198])
- Several odd hypotheses seem to underlie the analysis, such as the assumption that the effect of mobile phones should be associated with increasing aggressiveness of the tumour histology (Morgan (2006)[209])
- Odd data regarding histological verification of acoustic neuroma cases (Hardell & Hanson Mild (2005)[200])
- An extremely low cut-off for regular cell phone use (at least once a week for six months or more) (Morgan (2006)[209]).
- Wrong assumptions about latency for the acoustic neuroma studies as ever/never would be better (Stang et al. (2005)[199])
- Not all wireless phones are considered, in particular cordless phones, and changes in phone use are insufficiently taken into account (change from analogue to digital phones) (Hardell and Hansson Mild (2004)[204])

- There is potential conflict of interest as some investigations were (partly) financed by the mobile phone industry (Hardell and Hansson Mild[196], Morgan (2006)[214])
- Several inconsistencies in the publications were identified (Hardell et al (2005)[207], Morgan (2006)[214], Hardell & Hansson Mild (2005)[200]) but these were mostly accepted by the authors as typographical errors and corrected.

Authors responses came from Schoemaker et al. (2006)[218] who addressed the issue of conflict of interest and pointed at the firewall construction to prevent this and concluded that the biases that were elaborately discussed in the publication in their view did not amount to a likely substantial underestimation of risk. Schüz et al. (2006)[210] replied to the comments on their publication by stating that they deliberately identified 'regular users' with a low cut-off, in order to get a reference group consisting of subjects with extremely low to no exposure; they discussed the issue of selection bias, thinking that their results are in line with others and thus not underestimated; and they addressed again potential conflicts of interest by stating that this is taken care of with a good firewall construction.

In a more general remark in relation to the partial INTERPHONE publications, Savitz (2004)[203], reacting to the publication by Lönn et al. (2004)[76], came to the conclusion that this publication shifted the likelihood of there being an effect from 'highly unlikely to slightly more likely but still highly uncertain'. The publication by Hepworth et al. (2006)[84] was discussed by Maier (2006)[213] in an editorial concluding that, even though effects on tumours cannot be excluded, the most important effects of mobile phones are a positive one on the quality of people's lives and a negative one as their use is dangerous while driving. Noone (2009)[219] stated in relation to the publication by Lahkola et al. (2008)[92] that there cannot be a conclusion yet, as too many widely different associations could still hold true.

Case-control studies according to other protocols

Two supporting papers were considered in the context of these publications. These are listed in Table E4. No Letters to the Editor were identified.

Table E4 Supporting literature and Letters to the Editor for the case-control studies according to other protocols.

Reference	Supporting paper / Letter to the Editor	Subject
Schmidt-Pokrzywniak et al. (2004)[227]	Supporting paper	Study design of Stang et al. (2009)[104]
Aydin et al. (2011)[228]	Supporting paper	Error issues for Aydin et al. (2011)[108]

Schmidt-Pokrzywniak et al. (2004)[227] described design issues related to the study by Stang et al. (2009)[104]. They mainly focused on the feasibility of case recruitment and concluded that cases can be recruited and exposure can be measured in the way proposed in the study design.

Aydin et al. (2011)[228] published an evaluation of the errors in measurement related to the case-control study in children by Aydin et al. (2011)[108]. The paper concludes that there is overestimation of exposure, but that this does not differ between cases and controls but is associated with age and sex, making these factors clear confounders that need to be accommodated for in the analysis.

Case-case studies

No Letters to the Editors and no supporting papers were considered in the context of these publications.

Ecological studies

Two Letters to the Editor, no responses from authors and no supporting papers were found in the context of these publications. The letters are listed in Table E5.

Table E5 Letters to the Editor for the ecologic studies.

Reference	Supporting paper / Letter to the Editor	Subject
Hardell et al. (2010)[125]	Letter to the editor	Comment on Deltour et al. (2009)[122]
Davis (2011)[186]	Letter to the editor	Comment on Ahlbom & Feychting (2011)[151]

Hardell et al (2010)[125] commented on the publication by Deltour et al. (2009)[122] that their data collection stopped in 2003, while in any case in Sweden according to the information in the Hardell studies, the use of mobile phones sharply increased after 2003. Thus according to Hardell et al, the conclusions from this publication cannot be definitive. In the later publication by Deltour et al. (2012)[135], the analysis extends to 2008, but this would still be not long enough to reflect any increase due to the increased mobile phone use indicated by Hardell, assuming an latency period of at least 10 years and a small relative risk. Hardell et al. concluded that to allow firm conclusions to be drawn, at least another 10 years of observations is needed.

Davis (2011)[186] challenged the conclusion of Ahlbom and Feychting (2011)[151], by arguing that the Swedish cancer registry is not complete. In a personal communication to the Committee, Feychting denied this.

Annex **F**

Results of the data extraction

These tables show the results of the data extraction for the publications used in the evaluation of the quality of studies in Annex G.

Cohort studies

Table F1 Extractions from Dreyer NA, Loughlin JE, and Rothman KJ. Cause-specific mortality in cellular telephone users. JAMA, 1999; 282(19): 1814-1816.[47]

A1	concerns about potential biological effects, including brain cancers due to radiofrequency energy transmitted from mobile phones; additional to a previous study (1010), cause-specific mortality in expanded cohort
A2	not described, probably same as in 1010
A3	overall & specific mortality and length of mobile service contract
B1	cohort study
B2	design ok, detailed comparison with general population is missing
B3	design is ok, reasonably efficient because using registrations that have been linked, however many issues to make this method work for the study question; different time period would have been better (longer)
B4	not described, but highest category: >3 years of use
B5	too short to prove cancer, to not even consider prove cancer mortality
C1	based on registration of 2 US cellular telephone carriers; all subscribers to these
C2	size ok, very big cohort
C3	no
D1	all exposed to at least 1 phone type (cordless or mobile)
D2	include truly nonexposed
E1	that is done without consent, participants are not aware of all the privacy sensitive data that have been used for this investigation
E2	not mentioned

F1	all cellular telephone users covered by two US cellular telephone carriers serving several metropolitan areas
F2	source ok; but very restricted: only one contract per household, only households that clearly were not companies (might exclude single medical practices or trades people)
G1	not described, but in 1010 clear that substantial exclusion occurred: linking 2 registries, linking far from perfect; original cohort 770390 records (before which already excluded corporate users, multiple telephone users), finally after various eliminations and exclusions: 255868 records over (33,2%)
G2	no
G3	285561 records
G4	till category > 3 years nothing else described
G5	very short for interpretation cancer, to not even talk about cancer mortality
G6	highest category: > 3 years
H1	not described in this article but it is in 1010: yes but: in the early years who used mobile phones: predominantly working people, so healthy subpopulation, also various exclusions made that make it an indescribable study population, every exclusion factor probably results in selection bias
H2	can go either way
I1	no, because data linked without interference of research personnel
I2	n.a.
J1	yes, for information completely dependent on registrations, dependent on their quality, dependent if good data were delivered to them, missing information about duration of phone use, how much phone used etc., however in analyses only info used about which phone and this seems quite easily traced using an ESN, so for analyses not such a big problem
J2	so not much for analysis
K1	no, registrations used, at the most if extraction of data from the database not done well e.g. if someone has been selectively searching for people, however, this seems quite unlikely
K2	n.a.
L1	yes, sex, possibly particularly healthy working subpopulation that used mobile phones (and less risk of dying (early) than a ill non-working population), socio-economic status
L2	sex yes, nothing else
M1	everything if ESN does not lead to correct phone type
M2	n.a.
N1	see 1010, not given in this letter: only if used yes/no, and minimal 1 (or 2 or 3) years registered and 2 active accounts:
N2	your exact exposure, through duration of plan, duration and amount and frequently of phone calls, poss. Urban or rural etc.
N3	person-dose
N4	no controls, all exposed, 2 groups: portable (no risk to be expected) and mobile phone
N5	no, no information of how often, how long etc.
O	yes, limited info about measurement of exposure, so can contain all sorts of errors, really only known what type of phone is present and that has been used in the last 2 months
P	no, not to be expected, normal random error
Q1	none, except adjustment for sex and age and metropolitan area
Q2	correct for more variables (including SES), if need be stratify
R1	sex and age-specific mortality rates
R2	at least compare mortality rate with the general population, but really the mortality rate is not a good indicator with such a short latency time, incidence of specific health effects should be compared (e.g. cancer); compare with non-users and in a cohort logistic regression (outcome ill/not-ill and then mobile phone use in duration and frequency and type phone etc as variables in the model incl confounders and such to adjust for)
S1	95% CI

S2	ok
T	almost no numbers described, only tabular info, cannot be checked well, not all seems to add up
U1	no indication that risk is increasing with increasing minutes (except maybe for motor vehicle collisions)
U2	see Annex H
U3	yes because outcome is death so all exposure before
U4	no, not really, 2 and 3 years…. However, in this analysis this says nothing about dose
V	so much bias, can really go any direction, but anyway not the correct method and too short to say anything
W	everyone exposed, so at that level no misclassification, at the most in type of phone, so effect can go either way
X1	yes
X2	yes, only 4 references, this really is very limited even though at the time not much was known
Y	to no one as too much selection bias
Z	yes

Table F2 Extractions from Schüz J, Steding-Jessen M, Hansen S, e.a. Long-term mobile phone use and the risk of vestibular schwannoma: a Danish nationwide cohort study. Am J Epidemiol, 2011; 174(4): 416-422.[51]

A1	to investigate cancer (acoustic neuroma) risk among Danish cellular telephone users who were followed for up to 21 years
A2	none, before no clear hypotheses if there would be an increased or decreased risk, more general: is there a relation between use of cellular telephones and tumours of head and neck
A3	was cellular telephone use associated with increased risk of brain tumours?
B1	cohort study (combination of 2 cohort studies actually)
B2	yes
B3	n.a. (experiment, practically almost impossible)
B4	1987-2006
B5	yes, but still relatively short for largest part of cohort < 10 years and few people in the groups with the long follow-up, longer follow-up information simply does not exist given recent use of mobile phones
C1	cohort based on people who between 1982 and 1995 first used a mobile phone
C2	super big cohort, only suggestion for improvement: now many exclusions because professional connections could not be personalised; due to combination now more limited but more information on confounders
C3	no
D1	exposed: total cohort, unexposed: rest general population
D2	rest general population: assumed that they did not use telephone, not entirely correct even though the most recent users (1995-2006) have to short follow up for cancer
E1	no permission by members of the cohort, after announcements in the media, possibility for refusing participation
E2	yes
F1	cohort cellular telephone subscriptions
F2	good source
G1	420095 of the 723421 records received are included: 58%% but the paper does not say how many of these remain in the combined cohort which as no acoustic neuroma was observed in long-term exposed women (but almost as many casesd as in men!) was reduced (50%?) to men only; 404 cases
G2	no, certain subgroups now excluded which hinders interpretation, double addresses: use more than 1 phone? So higher exposure? Corporate subscriptions: those people are now in the rest general population but in reality they were exposed
G3	420095 exposed; rest of general population assumed as unexposed in general population, basis onto which expected is calculate as unexposed in Danish cancer registry
G4	no data given other than the conceptual that they would have been exposed since before 1995, how many stopped after 1995 is not presented

G5	not really, follow-up should be longer due to the latency time for developing cancer
G6	max follow-up not really given but few person years in top follow-up
H1	yes, particularly group that uses mobile phones for work has been excluded, while this is possibly a highly exposed group
H2	effect in reality present, or in any way OR >1
I1	no
I2	n.a.
J1	no, because respondents were not approached themselves, but yes, information missing about exact use, time, frequency, preferred ear, however this is more a limit for the analyse than bias
J2	now all the use put together and no difference made in amount of use, only duration of use in years, so no analyse done on this and possible distortion of results, various levels of exposure now all on one heap
K1	no, cohort was not linked to cancer cases during phase of including, so blind for case and non-case; no interview or anything used, hard data from registrations used so no influence observer
K2	n.a.
L1	might still be possible that there is unknown or unmeasured confounder, because the cohort seemed to be a unique subgroup of persons with higher income and therefore risk profile; exposure to other factors that might cause brain cancer?
L2	income is measured, occupation and exposure to certain substances not measured
M1	yes
M2	regular use cellular telephone (compared with interphone case control data) also non regular subscribers are now in exposed group
N1	subscriber or not; duration use by cohort members compared to case control interphone, no information on frequency, duration of calls, preferred ear etc
N2	real use of received and send phones and their duration, number, how often, how long; via questionnaire such as this these cannot be traced at the telephone company
N3	person-dose
N4	n.a., no controls in cohort study rest of the general population assumed to be unexposed but isn't as many have used mps for long time and also includes all non-personal subscriptions
N5	no, no information of how often, how long etc
O	yes, possibly, now frequent and less frequent users together and in ref population (to calculate expected) also professional users
P	no
Q1	corrected for confounding using regression as a lot of information available through linked cohort
Q2	despite it all being based on routine data this is quite elaborate
R1	person year analysis resulting in SIR but a lot of it is in %
R2	appropriate association for cohort, possibly regression analysis as addition and to control for variables in a multivariate analysis
S1	95% CI
S2	no, ok
T	can not really check as insufficient information given
U1	no evidence for association between acoustic neuroma risk and cellular telephone use among short and long-term users
U2	see Annex H
U3	yes, subscribers known and then checked is someone became a case, however not known if exposure and brain tumour not too close in time and so probably not associated given latency cancer
U4	not really, only years of having a cellular phone, with very few people in the long use group
V	some level of correction applied but always tricky as limited
W	unknown exposed from corporate subscriptions biased towards the null, so in this group possibly cases missed

X1	as far as I can see yes
X2	as far as I can see no
Y	only to the included cohort members, rest population no good info about use mobile phone
Z	yes, effect would in reality only be bigger

Table F3 Extractions from Frei P, Poulsen AH, Johansen C, e.a. Use of mobile phones and risk of brain tumours: update of Danish cohort study. BMJ, 2011; 343: d6387.[52]

A1	to investigate cancer (all central nervous tumours) risk among Danish cellular telephone users who were followed for up to 17 years (cancers had to occur between 1990 and 2007)
A2	none, before no clear hypotheses if there would be an increased or decreased risk, more general: is there a relation between use of cellular telephones and tumours of head and neck
A3	was cellular telephone use associated with increased risk of brain tumours?
B1	cohort study
B2	yes
B3	n.a. (experiment, practically almost impossible)
B4	claims all Danes born after 1925 but based on those exposed before 1995
B5	yes, but still relatively short for largest part of cohort < 10 years and few people in the groups with the long follow-up, longer follow-up information simply does not exist given recent use of mobile phones
C1	cohort based on people who between 1982 and 1995 first used a mobile phone; combined with cohort on those born in Denmark after 1925
C2	super big cohort, only suggestion for improvement: now many exclusions because professional connections could not be personalised; due to combination now more limited but more information on confounders
C3	no
D1	exposed: total cohort, unexposed: rest general population cohort
D2	rest general population cohort: assumed that they did not use telephone, not entirely correct even though the most recent users (1995-2007) have to short follow up for cancer
E1	no permission by members of the cohort, after announcements in the media, possibility for refusing participation
E2	yes
F1	cohort cellular telephone subscriptions
F2	good source
G1	358403 of the 723421 records received are included: 50% but the paper has 1853 glioma cases for men, 1455 for women; 429 meningioma cases for men and 1248 for women
G2	no, certain subgroups now excluded which hinders interpretation, double addresses: use more than 1 phone? So higher exposure? Corporate subscriptions: those people are now in the rest general population but in reality they were exposed
G3	358403 exposed; rest of general population cohort assumed as unexposed in gen population, basis onto which expected is calculate as unexposed in Danish cancer registry
G4	among glioma cases only 37 men had exposure over 13 yrs (37/324=11%) and no women; for meningioma cases only 65 men (65/162=40%) were over 10 yrs exposed and only 12 women (12/35=34%),
G5	not really, follow-up should be longer due to the latency time for developing cancer
G6	max follow-up not really given but few person years in top follow-up
H1	yes, particularly group that uses mobile phones for work has been excluded, while this is possibly a highly exposed group
H2	effect in reality present, or in any way OR >1
I1	no
I2	n.a.

J1	no, because respondents were not approached themselves, but yes, information missing about exact use, time, frequency, preferred ear, however this is more a limit for the analyse than bias
J2	now all the use put together and no difference made in amount of use, only duration of use in years, so no analyse done on this and possible distortion of results, various levels of exposure now all on one heap
K1	no, cohort was not linked to cancer cases during phase of including, so blind for case and non-case; no interview or anything used, hard data from registrations used so no influence observer
K2	n.a.
L1	might still be possible that there is unknown or unmeasured confounder, because the cohort seemed to be a unique subgroup of persons with higher income and therefore risk profile; exposure to other factors that might cause brain cancer?
L2	income is measured, occupation and exposure to certain substances not measured
M1	yes
M2	regular use cellular telephone (compared with interphone case control data) also non regular subscribers are now in exposed group
N1	subscriber or not; duration use by cohort members compared to case control interphone, no information on frequency, duration of calls, preferred ear etc
N2	real use of received and send phones and their duration, number, how often, how long; via questionnaire such as this these cannot be traced at the telephone company
N3	person-dose
N4	n.a., no controls in cohort study rest of the general population assumed to be unexposed but isn't as many have used mps for long time and also includes all non-personal subscriptions
N5	no, no information of how often, how long etc
O	yes, possibly, now frequent and less frequent users together and in ref population (to calculate expected) also professional users
P	no
Q1	corrected for confounding using regression as a lot of information available through linked cohort
Q2	despite it all being based on routine data this si quite elaborate
R1	person year analysis resulting in SIR
R2	appropriate association for cohort, possibly regression analysis as addition and to control for variables in a multivariate analysis
S1	95% CI
S2	no, ok
T	yes
U1	no evidence for association between glioma or meningioma risk and cellular telephone use among short and long-term users
U2	see Annex H
U3	yes, subscribers known and then checked if someone became a case, however not known if exposure and brain tumour not too close in time and so probably not associated given latency cancer
U4	not really, only years of having a cellular phone, with very few people in the long use group
V	some level of correction applied but always tricky as limited
W	unknown exposed from corporate subscriptions biased towards the null, so in this group possibly cases missed
X1	as far as I can see yes
X2	as far as I can see no
Y	only to the included cohort members, rest population no good info about use mobile phone
Z	yes, effect would in reality only be bigger

Case-control studies of the Hardell group

Table F4 Extractions from Hardell L, Hallquist A, Hansson Mild K, e.a. No association between the use of cellular or cordless telephones and salivary gland tumours. Occup Environ Med, 2004; 61(8): 675-679.[69]

A1	to investigate the association between the use of cellular or cordless telephones and the risk for salivary gland tumours because the parotid gland is located in an area where some phones give a high exposure to microwaves
A2	use of cellular and cordless phones increases the risk for salivary gland tumours
A3	use of cellular and cordless phones increases the risk for salivary gland tumours
B1	case-control; population based
B2	yes
B3	observational cohort, so minimising all sorts of bias (experiment would be best but not feasible)
B4	no clearly described follow-up period. Info asked back to start use. In analysis latency period >10 years is used, but only for a very small subgroup more than 10 years follow-up
B5	longer follow-up better, but not available, as only since 1981 start first use analogue phones and since 84 use without fixed antennae, and particularly need to collect more cases and controls in longer follow-up group for stronger conclusions
C1	cases diagnosed in cancer registries between 1 Jan 1994 and 31 December 1999 for Stockholm and Linkoping; between 1 Jan 1994 and 30 June 2000 for Uppsala- Orebro and between 1 Jan 1994 and 30 June 1999 for rest of Sweden (Umea, Goteborg, Lund); incident cases
C2	size ok
C3	yes, to detect OR >=1,4 (alpha 0,05 and beta 0,20)
D1	ratio 1:4
D2	ok, based on available cases and power calculation
E1	psychological burden for cancer patients
E2	yes
F1	cancer registry for whole Sweden and population registry for controls
F2	source ok
G1	415 cases, 293 included, 267 responders = 64,3%; 815 from other study + 357 additional, 750+303 (1053) responded = 89,9%
G2	cases quite low, but that is due to the exclusion of the deceased (n=96), controls good response,
G3	415 cases invited; 96 dead, 26 excluded 16 refused, so 267 cases and 1053 controls
G4	n.a., only 6 cases had used a phone for more than 10 years
G5	duration of use is still relatively short, so nothing can be said over longer periods, but for short term use yes, however in this study unclear how many people exactly used mobile phones for more than 5 years
G6	highest category > 10 years, but only 6 cases in this group
H1	yes as a substantial group of deceased cases were not included (96/415= 23%)
H2	is the question, worst cases also the most exposed?, you do not know so effect could go either way
I1	yes, but limited as response around 90% (response 415 original cases: 267/415= 64.3%, so is quite low, mostly caused by death)
I2	could go either way: particularly users of mobile phones interested in participating, or particularly not as busy working population?
J1	yes, measurement errors in exposure variables due to recall bias
J2	possibly overestimation because memory in cases could lead to higher exposure
K1	yes

K2	minimal, questionnaire i.s.o. interview, in case of additional phone interview: blinded for case-control status and tumour details assessed without information about exposure data
L1	age, sex has been corrected, in 1 analysis also for study areas corrected for, also SEI, occupation or other exposures could be confounders
L2	yes
M1	yes misclassification exposure, due to recall bias, cases have been histologically verified so minimal chance for misclassification cases
M2	recall problems, different types of phones used, duration of use wrongly estimated, changes over time not correctly remembered (e.g. change from analogue to digital)
N1	questionnaire if needed with additional telephone interview
N2	phone habits prospectively monitored, phone habits traced at telecompany; additional questionnaire through telephone interview particularly for phone habits of early years where recall the biggest problem, not know how this exactly is asked
N3	person dose
N4	ever use analogue: cases 11,6% controls 13,0%; digital: cases 16,9% en controls 16,1%; cordless: cases 18,0% en controls 19,0%; overall: cases 34,1% en controls 33,4%
N5	yes
O	possible yes due to recall bias, however, probably particularly for the early years, recent memory possibly more reliable
P	not to be expected
Q1	all analyses adjusted for age, sex and 1 analysis also adjusted for region
Q2	ok
R1	unconditional logistic regression analyses for matched studies
R2	not described it incomplete pairs, than ok, if they are complete pairs, conditional logistic regression analysis would be better
S1	95% CI
S2	ok
T	yes
U1	no association between the use of cellular or cordless phones and salivary gland tumours was found, although this study does not permit conclusions for long term heavy use
U2	see Annex H
U3	debatable, only few >10 years exposure and > 5 years still relatively few cases digital, < 5 years almost certainly no temporal relationship in carcinogenesis
U4	no
V	most bias can go either way, but possibly the results are slightly overestimated due to overestimation of exposure by the cases and results not corrected for e.g. occupational exposures, however for important confounders corrected, sex and age, no correction for other exposures
W	can go either way, depends on errors in recall bias and accompanying misclassification of exposure, possibly to be expected overestimation of exposure by cases, so overestimation OR
X1	yes
X2	as far as I can see: ok, no major missing references
Y	Swedish population
Z	yes

Table F5 Extractions from Hardell L and Carlberg M. Mobile phones, cordless phones and the risk for brain tumours. Int J Oncol, 2009; 35(1): 5-17.[66]

A1	further and more detailed results of the pooled analysis of 2 case control studies
A2	is there an association between mobile phones and brain tumours (benign en malignant)?
A3	is there an association between mobile phones and brain tumours (benign en malignant)?
B1	population based case-control (in discussion talked about a hospital based study, but this is not correct as cancer registry is used?)
B2	yes
B3	observational cohort, so minimising all sorts of bias (experiment would be best but not feasible)
B4	no clearly described follow-up period. Info asked back to start use. In analysis latency period >10 years is used
B5	reasonably good, study long enough now to have sufficient numbers in the category > 10 years
C1	all incident cases aged 20-80 diagnosed between 1 Jan 1997 and 30 June 2000 in 4 regional cancer registries in 4 medical regions & all living cases, aged 20-80 in time period 1 July 2000 and 31 deck 2003, living in Uppsala/Örebro or Linkoping region (recruited through cancer registry) but only if living so actually prevalent cases
C2	nationwide and including all cases, also the ill and dead ones (via proxy)
C3	no
D1	malignant ratio 1:2,4 ; benign ratio 1:1,7 (all controls used)
D2	ok, enough numbers
E1	psychological burden for cancer patients and people can become anxious about mobile phones
E2	yes
F1	1997-2000 for cases 4 Swedish medical regions (Uppsala/Örebro or Linkoping, Stockholm, Gothenburg) and for controls population registries and 2000-2003 region of Uppsala/Orebro or Linkoping, Sweden, for cases; cancer registry, for controls population registry; possible delay between diagnosis and notification, as living only: selecting out the early deceased
F2	national cancer registry, so all regions in Sweden; source controls is ok
G1	benign cases 88% and malignant cases 90% controls 89%
G2	quite high, however still chance of responders bias, 1 of the 10 after all refused to take part, note that selection based on inclusion criteria, is not included in the response %
G3	1254 benign cases and 905 malignant cases and 2162 controls
G4	n.a., in analysis a latency period of >10 years is used
G5	particularly for group with latency period > 10 year follow up time is long enough to develop cancer as thus make an inference
G6	highest category > 10 years
H1	yes, due to ill and dead cases and physician refusal, this can contain selection as these are particularly the cases with poor prognosis, other exclusion criteria will not generate selection; 3729 cases cancer registry, exclusion metastases, misdiagnosis, deceased (748!), refusal via physician etc, ultimately only 2437 eligible (65%)
H2	if particularly the cases with poor prognosis were users of mobile phone the effect would be underestimated, as those people are now missing. However, if they are particularly non-users there is overestimation of effect
I1	yes, but limited as response around 90%
I2	limited effect expected as the response is quite high, no info about non responders, possibly particularly non-users of mobile phones so less interested in participating, or particularly not participated as it is the busy working population (so the users)?
J1	yes, measurement errors in exposure variables due to recall bias
J2	cases would probably refer to higher exposures than controls, which would lead to overestimation of effect

K1	questionnaire not, but additional interviews can, way of asking questions by interviewer can direct answer a certain way, particularly since this is often about the detail of the phone use
K2	possible so not applicable, otherwise a slight overestimation of effect as observer directed towards relation phone and tumour.
L1	age, sex and SES has been corrected for, also occupation or other exposures could be confounders
L2	yes, including socio-economic status and various occupational exposures
M1	yes, due to recall bias, cases are usually histologically verified, so minimal chance on misclassification of cases
M2	recall problems, different types of phones used, duration of use wrongly estimated, changes over time not correctly remembered (e.g. change from analogue to digital)
N1	questionnaire if needed with additional telephone interview
N2	for phone use: monitor calling habits prospectively or if possible ask about calling habits at telecompany, but questionnaire bar recall good method
N3	person dose
N4	exposures overall not described separately
N5	yes
O	possible yes due to recall bias
P	not to be expected
Q1	analysis adjusted for age, sex, SEI and year of diagnosis
Q2	ok, possibly correct for ionising radiation
R1	unconditional logistic regression analyses for matched studies
R2	ok, as not exactly 1 to 1 matching, all controls included
S1	95% CI
S2	ok
T	yes
U1	a consistent association between use of mobile or cordless phones and astrocytoma grade I-IV and acoustic neuroma, highest for ipsilateral exposure using > 10 year latency; especially high risk for persons that started use of mobile phone before the age of 20 years. Results are supported by increasing incidence of astrocytoma during 2000-2007 in Sweden
U2	see Annex H
U3	for longer latency group >10 years yes, for < 10 years this is debatable
U4	yes
V	adjusted for important confounders
W	can go either way, depends on errors in recall bias and accompanying misclassification of exposure and possibly overestimation
X1	yes
X2	no
Y	Swedish population (assuming the 4 regions representative for Sweden)
Z	unclear, probably not as not corrected for other variables (ionising radiation, other occupations exposures)

Table F6 Extractions from Hardell L, Carlberg M, and Hansson Mild K. Pooled analysis of case-control studies on malignant brain tumours and the use of mobile and cordless phones including living and deceased subjects. Int J Oncol, 2011; 38(5): 1465-1474.[68]

A1	to investigate the use of mobile or cordless phones and the risk for malignant brain tumours in a group of living and deceased cases
A2	not a clear hypothesis is described; there is an association between cellular and cordless phone use and malignant brain tumours
A3	Is there an association between cellular and cordless phone use and malignant brain tumours?

B1	population based case-control
B2	yes
B3	observational cohort, so minimising all sorts of bias
B4	n.a., not a clear follow-up period. Information starts at the beginning of the use of a cellular and/ or cordless telephone. In analysis the latency period >10 years is used, so a subgroup has more than 10 years of follow-up (of using a cellular phone)
B5	yes, all right, use of mobile phone long enough to have enough cases in the group of long-term users (>10 years).
C1	all living and deceased cases aged 20-80 diagnosed between 1 Jan 1997 and 30 June 2000 in 4 regional cancer registries in 4 medical regions (Uppsala-Örebro, Stockholm, Linkoping, Göteborg) & diagnosed in time period 1 July 2000 and 31 deck 2003, living in Uppsala/Örebro or Linkoping region (recruited through cancer registry)
C2	nationwide
C3	no
D1	ratio 1:1 for living and deceased cases, but for living cases also controls of benign tumours are included, so ratio is 1:2
D2	enough cases and controls
E1	psychosocial burden for cancer patient and relatives of deceased cases and controls and possibility for anxiety for mobile phone use
E2	Yes
F1	1997-2000 for cases 4 Swedish medical regions (Uppsala/Örebro or Linkoping, Stockholm, Gothenburg) and 2000-2003 region of Upssala/Örebro or Linkoping, Sweden, for cases; cancer registry, for controls population registry or death registry
F2	national cancer registry, so all regions in Sweden; sources controls are ok
G1	living cases: 90%, living controls 89%; deceased cases 75% and deceased controls 60%
G2	for living cases and controls good response; for deceased cases and controls moderate response
G3	905 living cases 2162 controls; 346 deceased cases and 276 deceased controls; total: 1251 cases and 2438 controls
G4	n.a., in analysis a latency period of >10 years is used
G5	especially for group with latency period > 10 years reliable conclusions possible, time is long enough for cancer to develop
G6	highest category: > 10 years
H1	yes, partly due to the fact that the physician could refuse participation of the cases
H2	if cases for who participation is refused by the physician are the most ill people who may be used mobile phone the most, the effect will be underestimated, but the physician probably did not know about mobile phone history. So the real effect is unknown
I1	yes, possibly, but not a large effect due to the relatively high response
I2	no information about non-responders, so the effect can go both ways, but little effect due to high response
J1	yes, recall bias especially for mobile phone use in the earliest years, so a long time ago
J2	cases possibly refer to higher exposure than controls, leading to an overestimation of the risk
K1	for questionnaires no observation bias, for the extra phone interviews this plays possibly a role
K2	small effect, if observer is focussing on phone and cancer relation possibly a little overestimation of the risk
L1	for age, sex, year of diagnosis and SEI is adjusted in analysis, but blue colour worker or radiation could be a confounder
L2	yes, including socio-economic status and several occupational exposures
M1	yes, due to recall bias, according to Hardell this effect is little, cases are histologically confirmed, so minimal chance of misclassification case
M2	recall problems (different phones used, lifetime use in wrong category, changes over time
N1	questionnaires, if necessary completed with interview over the phone

N2	collect data of use of mobile phone prospectively and/ or use data of phone company about phone use provided that these data can be connected with the correct persons. But questionnaire is good measurement, except for the recall problems
N3	person dose
N4	727 of 1251 cases exposed (58,1%) and 1267 of 2438 controls exposed (52,0%)
N5	yes
O	possible yes due to recall bias
P	is not expected
Q1	analysis adjusted for age, sex, SEI, year of diagnosis and vital status
Q2	appropriate method, possibly also adjustment for ionizing radiation
R1	unconditional logistic regression analyses for matched studies
R2	no
S1	95% CI
S2	ok
T	yes
U1	the risk for glioma increased with latency period and cumulative use in hours for both mobile and cordless phone and was highest in subjects with first use before the age of 20
U2	see Annex H
U3	for long latency period (> 10 year) the temporal relationship is correct, for < 10 year latency time the temporal relationship is doubtful, especially for < 5 year
U4	yes
V	possibly little overestimation due to overestimation use of mobile phones by cases
W	misclassification in recall bias? classification of categories of exposition can go both ways so leading to over and underestimation of the risk
X1	yes
X2	no
Y	Swedish population, provided that 4 regions are representative for Swedish population
Z	unclear

Table F7 Extractions from Söderqvist F, Carlberg M, and Hardell L. Use of wireless phones and the risk of salivary gland tumours: a case-control study. Eur J Cancer Prev, 2012.[72]

A1	some indications of effect of mobile phones on parotid gland tumour risk
A2	association between having acoustic neuroma and reporting use of mobile phones
A3	as in A2
B1	case-control
B2	is ok
B3	cohort as exposure independently measured form outcome
B4	n.a.
B5	n.a.
C1	incident cases in designated area during designated period
C2	larger so more years or wider area
C3	not presented
D1	1 case : 4 controls
D2	is supposedly optimal
E1	burden for very ill patients

E2	not mentioned but assumed to be yes
F1	patients with salivary gland tumours (ICD-7 142.0, 142.6 and 142.8) were recruited continuously between the years 2000 and 2003 as reported by the Regional Oncology Centre of Uppsala / Örebro and Linkoping, including nine of 21 Swedish counties.
F2	is ok but wider or longer would have been better
G1	88% of cases and 83% of controls responded with filled in questionnaire
G2	ok
G3	in total, 92 cases were reported and of these, six were dead, four had treating doctors who did not permit their patients' participation and an additional four cases had wrong diagnoses
G4	n.a.
G5	n..
G6	n.a.
H1	always some possible but response rates case/control very similar so not very likely
H2	n.a.
I1	yes as cases know they are ill so this is likely
I2	either direction
J1	yes somewhat
J2	other direction
K1	for certain
K2	either direction
L1	age, sex, sex
L2	yes as far as possible for SES
M1	some for mostly exposure
M2	mp use questionnaire
N1	questionnaire
N2	checking bills
N3	Person-dose
N4	57%
N5	yes
O	some
P	some
Q1	no association seen
Q2	see Annex H
R1	regression
R2	ok
S1	85% CI
S2	ok
T	seems ok
U1	the data presented in this short report do not support an association between the use of wireless phones (including both the mobile phone and the cordless desktop phone) and the risk for salivary gland tumours.
U2	see Annex H
U3	cannot tell
U4	no
V	could have underestimated
W	could cause underestimation
X1	ok

X2	no
Y	other similar countries
Z	ok

Case-control studies of the INTERPHONE consortium

Table F8 Extractions from Lönn S, Ahlbom A, Christensen HC, e.a. Mobile phone use and risk of parotid gland tumor. Am J Epidemiol, 2006; 164(7): 637-643.[82]

A1	potential concern of increased risk of acoustic neuroma due to its close position to the handset of a mobile phone
A2	is there an association between mobile phone use and acoustic neuroma?
A3	does mobile phone use increases acoustic neuroma?
B1	population-based case-control
B2	yes
B3	observational cohort, so minimising all sorts of bias (experiment would be best but not feasible)
B4	info mobile phone use retrospectively asked, highest usage category > 10 years
B5	not long enough, because the development of this tumour is slow and mobile phones are only recently used at a large scale, only few cases and controls have been using mobile phones for a long time
C1	all cases in specific area of cancer registry
C2	national registry, include all regions so more cases in general and more cases and controls that have been using mobile phones for a long time, now is a small subgroup
C3	no
D1	1 per brain tumour cases, 2 per acoustic neuroma case, 3 per parotid gland tumour, all controls included in this study.
D2	2 or 3 controls for all cases
E1	development of fear for mobile phones and burden for cases
E2	not mentioned
F1	residents of 3 geographical areas covered by the regional cancer registries in Stockholm, Gotenburg, and Lund; incident cases of an in 3 cancer registries (Stockholm, Gotenburg, Lund) Sept 2000 - Aug 2002, 20-69 yrs old, controls from pop register
F2	national registry, use all regions
G1	93% of 160 eligible cases: n=148; 72% of 838 controls: n=604
G2	cases yes, controls: relatively low response rate, information of some variables of the non-responders is necessary
G3	148 cases and 604 controls
G4	n.a.
G5	no, follow-up relatively short for developing cancer due to mobile phone use.
G6	n.a., highest category mobile phone use: > 10 years
H1	not likely
H2	n.a.
I1	yes, refusal and illness can generate selection in other variables, not reached is less of an issue; most non-response among cases possibly due to illness (too ill or dead): excluding the very ill if illness assoc with exposure causes underestimation. Among controls refusal very high so most motivated left in study, possibly overestimating control exposure.
I2	can go either way
J1	yes, measurement errors due to recall bias
J2	can be either under- or overestimation of the exposure
K1	yes, personal interview, so observer has much influence on the way the questions is asked and is not blinded for case/ control status

K2	overestimation because interviewer could (subconsciously) also be looking for effect higher phone use: greater risk cancer
L1	yes, e.g. no info known on occupations situations and exposure to other substances that can influence cancer
L2	sex, age, residential areas and education level yes, adjustment for hearing loss and tinnitus, use in rural or urban area
M1	yes, depending on memory phone use misclassified in wrong exposure group?; use different types of phones, which how long and when exactly used,
M2	recall problems, different type of phones used, duration of use wrongly assigned, recall bias due to occupation and other exposure factors?
N1	majority personal interview, 5% cases and controls interviewed by phone; 1% cases and 7% controls mailed questionnaire
N2	mailed questionnaire has advantage of minimising observer bias, but personal interview allows clarification of unclear questions and probing so hopefully you still get the right answer.
N3	person dose
N4	59% regular use mobile phone, comparable cases, but many fewer people with long use > 10 years
N5	yes
O	possibly yes (recall problems)
P	no, by laterality analysis yes, because controls randomised in different groups
Q1	analysis adjusted for age, sex, residential area and education
Q2	for large differences poss. stratify and present results per category
R1	unconditional logistic regression analysis
R2	ok, controls not matched
S1	95%CI
S2	ok
T	no, this is to mean total number of controls assumed, unclear how they got assembled precisely (which were matched to which diagnose e.g.), table 2 and 3 almost no summing of subcategories is right… How can this be?? missing values??
U1	no increased risk of mobile phone use and acoustic neuroma, however suggestion of increased risk > 10 year
U2	see Annex H
U3	cannot say, possible exposure before development of tumour, but given the short duration of phone use and long latency time for development of tumour possibly exposure only after start subclinical phase tumour
U4	possibly: longer use, so more exposure, higher risk
V	most bias can go either way, but most likely the results were overestimated due to overestimation of exposure by the cases (even so mobile phone), possibly also influenced by interviewer?
W	can go either way, depends on errors in recall bias and accompanying misclassification of exposure, possible overestimation
X1	yes
X2	probably not because at the time not much was known about this topic, did not do own literature search, however relatively few references in total, only 1 hard ell article in refs
Y	3 regions used in study, not clear if 3 regions are a good reflection of all of Sweden, e.g. for urban-rural and occupations
Z	too mild given results?

Table F9 Extractions from Sadetzki S, Chetrit A, Jarus-Hakak A, e.a. Cellular phone use and risk of benign and malignant parotid gland tumors--a nationwide case-control study. Am J Epidemiol, 2008; 167(4): 457-467.[85]

A1	to assess the association between cellular phone use and development of parotid gland tumours
A2	is there an association between cellular phone use and development of parotid gland tumours
A3	do patients with meningioma, glioma, acoustic neuroma or parotid gland tumours have higher mp use
B1	nationwide population based case-control study in Israel

B2	yes
B3	observational cohort, so minimising all sorts of bias (experiment would be best but not feasible)
B4	info mobile phone use retrospectively asked, highest category of use > 10 year
B5	group > 10 year yes, but only relatively few cases in this group, but relatively many heavy users in <10 year group, possibly promotor function i.s.o. initiation
C1	all incident cases of PGT diagnosed in Israel at age 18 years or more, in 2001-2003, all 22 otolaryngology departments throughout the country participated, all Jewish (not Arab) patients with (confirmed) tumour aged 18-59 between jan.2001-dec.2003,
C2	ok, nationwide
C3	no
D1	all controls Interphone Israel used, resulting total ratio 1:3
D2	ok
E1	develop fear for mobile phone use and burden for cases
E2	yes
F1	all otolaryngeal units in Israel, all Jewish (not Arab) patients with (confirmed) tumour aged 18-59 between 2001-2003; controls from whole country from population registry, up to 7 controls potentially assigned to a case (?)
F2	all residents? Checking against the cancer registry for missed cases in e.g. mortality (inoperable so not referred to specialist unit?): this is probably marginal though
G1	cases 87%, controls 66%
G2	cases sufficient, controls much too few
G3	460 cases (58 malignant, 264 pleomorphic, 117 warthins tumour and 21 others) and 1266 controls
G4	n.a.
G5	highest category > 10 years, long enough, but still relatively small numbers
G6	n.a.> 10 years category
H1	unclear, all incident cases included, but not clearly how many e.g. deceased, n=531, is probably the group where cases that did not fulfil all inclusion criteria have been removed, how many deceased, how many too sick? Is this last group in the refusals?
H2	unclear, if 531 were all cases, than no selection bias; if underrepresentation of iterant workers than underrepresentation of heavy mobile phone users in controls so underestimation of effect.
I1	very high refusal rate; refusers that were interviewed seemed 'less connected': systematically different from total
I2	participating controls particularly users, gives underestimation
J1	the ill could be over representing their exposure plus proxy interviews and telephone interviews would be different also (more proxy for cases, more phone for controls and always in questionnaire research as people answer what they think you want to hear
J2	if cases report higher use, than overestimation of risk
K1	yes, personal interview, so observer has much influence on way of asking questions and has not been blinded for case/ control status
K2	overestimation because interviewer possibly (subconsciously) is also looking for effect of higher phone use: greater chance of cancer
L1	sex, age, year of interview, ionizing radiation, SES
L2	yes
M1	yes, depends on memory of phone use thus allocated to wrong exposure group?; use of different types of phones, which how long and when precisely, cases have been histologically verified, so probably no misclassification in this aspect
M2	recall problems, different types of phones used, duration of use incorrectly allocated
N1	face to face interview
N2	questionnaire to avoid observation bias, but best will be to get information from registries about phone use from telecom companies

N3	person dose
N4	regular use cases: 285 (62%) and controls 691 (55%)
N5	somewhat but limited as it relies on memory and personal estimation
O	possibly yes (recall problems)
P	not to be expected
Q1	adjustment for age, sex, year of interview (adjustment for ethnic origin did not influence the results, so not included)
Q2	ok, pos stratify if there are big difference, e.g. in sex
R1	conditional logistic regression analysis
R2	yes as individually matched
S1	95% CI
S2	ok
T	yes
U1	increased risk estimates were found for ipsilateral regular use 5 and 10 years in the past, although the latter was based on small numbers, significantly elevated odds ratios were observed consistently in the highest category of each of the measures of cellular phone use on the ipsilateral side, supporting a dose-response association.
U2	see Annex H
U3	for longer latency group >10 year yes, for < 10 year this is debatable
U4	yes
V	adjusted for important known confounders, but recall particularly for cases and non response for controls can respectively over and under estimate results underestimated were
W	can go either way, depends on errors in recall bias and associated misclassification in exposure, possibly overestimation in assessment of higher exposition cases
X1	yes
X2	no
Y	somewhat but exposure levels (and possibly output power levels) are higher in Israel than elsewhere
Z	yes, they seriously consider particularly a recall bias among the cases which might exaggerate the assoc

Table F10 Extractions from Takebayashi T, Varsier N, Kikuchi Y, e.a. Mobile phone use, exposure to radiofrequency electromagnetic field, and brain tumour: a case-control study. Br J Cancer, 2008; 98(3): 652-659.[88]

A1	to investigate whether mobile phone use increased brain tumour risk in Japan
A2	mobile phone use increases brain tumour risk in Japan
A3	mobile phone use increases brain tumour risk in Japan
B1	population-based case-control (in several departments region Tokyo)
B2	yes
B3	observational cohort, so minimising all sorts of bias (experiment would be best but not feasible)
B4	info mobile phone use retrospectively asked, highest usage category > 10 years
B5	to short follow-up < 10 years and group > 10 years has only very few cases
C1	newly diagnosed meningiomas, gliomas, and pituitary adenomas aged 30-69 who were treated in the 21 participating hospitals between 1 Dec. 2000 to 30 Nov. 2004
C2	nationwide
C3	no
D1	ratio 1:4 according to text, but given very high non-response about 1:2
D2	1:3 for a bit more power
E1	development of fear for mobile phone use and burden of cases
E2	yes

F1	area of Tokyo, including 23 wards (metropolitan area) and 14 cities (municipal area) and 25 cities adjacent to Tokyo; see and c but not all cases histologically verified, some diagnosed more than 6 months before start of study (those were eliminated but that means some less than 6 months pre were still in the study)
F2	nationwide
G1	cases 58,7% glioma, 77,6% meningioma, 75,6% pituitary adenoma, controls 52,5% glioma, 51,6% meningioma, 49,4% pituitary adenoma
G2	glioma cases and all controls much too few, meningioma cases and pituitary cases just too few, but better than glioma cases
G3	83 glioma, 128 meningioma, 101 pituitary adenoma; 208 controls
G4	n.a.
G5	to short follow-up for development of cancer, to small numbers in long follow-up group
G6	n.a.> 10 years category
H1	yes, unclear of the mentioned wards cover the area of Tokyo, no check with e.g. a cancer registry (30 out of 172 departements in Tokyo treated 90% of brain tumour in the area, only 21 participated)
H2	can go either way
I1	yes, particularly for glioma and controls low response, but also meningioma and pituitary somewhat marginal
I2	the questions whether for controls particularly those participated who are users, or particularly not as they were young workers who are possibly high users of mobile phones than non working people??
J1	yes, due to recall problems and incorrectly estimated SAR
J2	as cases report higher use, overestimation results of the risk, and if particularly non-respondent controls were users that would also result in overestimation
K1	yes, personal interview, so observer has much influence on way of asking questions (and is not blinded for case/ control status?)
K2	overestimation effect because interviewer is possibly (subconsciously) also looking for effect higher phone use: greater risk of cancer
L1	sex, age, ionizing radiation, SES, occupation marital status
L2	yes
M1	yes, depending on memory of phone use classified in the wrong exposure category?; use of different types of phones, which how long and when precisely, many cases have been histologically verified, so probably no misclassification here, and global estimated SAR values can contain much misclassification
M2	recall problems, use of different types of phones, duration of usage wrongly classified
N1	face to face interview
N2	questionnaire to avoid observation bias, but best will be to get information from registries about phone use from telecom companies
N3	person dose
N4	regular use cases: glioma 68%, meningioma 43% and pituitary 61%, controls glioma 65%, meningioma 52% and pituitary 65%
N5	yes
O	possibly yes (recall problems), and errors in SAR measurement
P	not to be expected
Q1	adjusted for educational level and marital status and matched on age, sex and residency
Q2	ok, assuming analyse stratified for matching variables, but has not been clearly stated
R1	conditional logistic regression analysis
R2	ok, because controls are matched
S1	95% CI
S2	ok
T	yes

U1	no consistent increase was observed in the overall risk of glioma or meningioma among mobile phone users, nor increasing trend in risk in relation to cumulative length of use or cumulative call time; no substantial increase in risk was observed for glioma or meningioma
U2	see Annex H
U3	cannot know, possible exposure for development of tumour, but given short duration of use and long latency time for development of tumour probably exposure after start subclinical phase tumour
U4	no
V	it has been adjusted for confounding by education and marital status, but results can certainly be biased by recall, possibly resulting in overestimation, additionally high non-response for controls, can lead to over- and underestimation, cannot know, hardly info non responders
W	can go either way, depends on errors in recall bias and associated misclassification of exposure, possibly overestimation by estimation of the highest exposed cases
X1	yes
X2	no
Y	population of the area of Tokyo, or Japan if this area is representative for Japan
Z	they put a lot of store in it being similar results to the others (that are also too small to come to a conclusion)

Table F11 Extractions from Schoemaker MJ and Swerdlow AJ. Risk of pituitary tumors in cellular phone users: a case-control study. Epidemiology, 2009; 20(3): 348-354.[89]

A1	specific tumour location, could be associated with mobile phone use
A2	association between having tumour and reporting mobile phone use.
A3	as in A2
B1	case-control
B2	ok
B3	cohort
B4	n.a.
B5	n.a.
C1	no of cases in study area
C2	larger or longer
C3	not presented in this paper but done earlier
D1	1:4
D2	is ok
E1	burden for patients
E2	yes
F1	cancer registry data
F2	ok
G1	63% of cases and 43% for controls
G2	ok but not lush
G3	317 cases and 630 controls
G4	n.a.
G5	n.a
G6	n.a
H1	good response rates so not overly likely
H2	n.a.
I1	yes

I2	could go either way
J1	yes some
J2	could go either way
K1	yes certainly
K2	could go either way
L1	age, sex and SES
L2	age/sex=x yes
M1	slightly
M2	anyways, most often underestimation
N1	questionnaire
N2	checking against bills
N3	person-does
N4	64%
N5	yes, theoretically
O	always some
P	slight
Q1	regression
Q2	ok
R1	regression coefficient or OR
R2	ok
S1	85% CI
S2	ok
T	ok
U1	no association seen
U2	see Annex H
U3	n.a
U4	no
V	underestimation
W	some is possible as always
X1	ok
X2	no
Y	similar countries
Z	ok

Table F12. Extractions from INTERPHONE study group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. Int J Epidemiol, 2010; 39(3): 675-694.[93]

A1	to determine whether mobile phone use increases the risk of these tumours and, specifically, whether RF energy emitted by mobile phones is tumourigenic.
A2	null hypothesis of no association would be expected to produce an approximately symmetric pattern of negative and positive log ORs.
A3	is there an (positive or negative) association between mobile phone use and brain cancer?
B1	international population-based case-control study in sixteen study centres from 13 countries
B2	yes
B3	observational cohort, so minimising all sorts of bias (experiment would be best but not feasible)
B4	info mobile phone use retrospectively asked, highest usage category > 10 years

B5	reasonable, mobile phones only recently in wide spread use, only a few cases that have long (>10 years) mobile phone use, category > 5 years use relatively large number of cases and controls to come to conclusions
C1	all eligible cases with glioma or meningioma of the brain diagnosed in the study regions during study periods of 2-4 years between 2000 and 2004, aged 30-59
C2	ok
C3	no
D1	ratio 1:1, and ratio Germany 1:2. 7 centres individual matching, frequency matching elsewhere
D2	ok, sufficient power due to large numbers
E1	development of fear for mobile phones and burden for cases
E2	not found in text but as far as I know the part studies all had
F1	16 study centres in 13 countries (Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden and the UK), aged 30-59 years, mainly large urban areas, all patients with glioma diagnosed 2000-2004 (different years in this period for the study centres, 2-4 years for each centre), cases from all neurological and neurosurgical facilities (bar in Paris and Tokyo where some did not participate); controls selection as locally appropriate
F2	non-neurological clinics as some case may not have made it in? (checked in cancer registry so maybe not that much of an issue?) some cases are totally missed but no other strategy would have gotten those. Worry about catchment area of what are mostly tertiary clinics: unlikely to be a small geographic area so would need exclusions to match with possible control selection, main problem is with control selection is several areas. also note that problems are listed for Paris and Tokyo but the German study also had incomplete case ascertainment (see 8051)
G1	response meningioma cases: 78% (range 56-92), glioma cases 64% (36-92), controls, 53% (42-74) (analyse matched sets only, some smaller numbers used)
G2	no, not really, the lower ends of the ranges are much too low to ensure that there is no selection bias, the upper range would have been fine but the averages are not great
G3	2409 (i.s.o. 2425) meningioma, 2662 matched controls/ 2708 (i.s.o. 2765) glioma, 2972 matched controls
G4	n.a., highest category: > 10 year mobile phone use
G5	not even 5% of all meningioma cases and not even 10% of all glioma cases have > 10 years mobile phone use, so it stay relatively small numbers, group that has 5-9 year use of mobile phones is substantially larger
G6	n.a.> 10 years category
H1	yes given the very poor response rates this seems likely, also the results are mostly driven by 2 countries (UK and Australia) and the control selection there is highly selective for SEC particularly (the control selection for Australia is not described in a separate article and cannot be traced at this time but there is no proper control selection method in Australia)
H2	underestimation as it is likely to make cases and controls more alike; also worrying is the reasons for non-response as far as known: to ill (1-20%), refusal (11-30%) and not reached (5-15%)
I1	yes, some countries very low response
I2	can go either way, particularly users of mobile phones participated? Deceased, so worst glioma cases particularly the group most intensively and longest mobile phone use? Particularly working young population that uses mobile phones a lot in the non responders group?
J1	yes, measurement errors in exposure variables due to recall bias, all cases histologically verified or based on unequivocal diagnostic imaging, so chance of information bias here probably small
J2	could be either underestimation or overestimation of the exposure, for cases the expectation is for overestimation
K1	as the study used interviews at home, this could have been very substantial as interviewers were not blinded, even though there is no observation as such, the questions could have been given a leading tone, emphasis or more detail could have been sought of the cases than of the controls
K2	overestimation effect because interviewer possibly (subconsciously) also searching for effect higher phone use: greater chance of cancer
L1	age, sex, educational level, occupation
L2	yes

M1	yes, depends on memory phone use wrongly allocated to an exposure group?; use different types of phones, which how long and when exactly used
M2	recall problems, different types of phones used, duration of use wrongly classified, recall bias for occupational and other exposure factors?
N1	personal interview
N2	questionnaire to avoid observation bias, but best will be to get information from registries about phone use from telecom companies, than you will also avoid recall bias
N3	person dose
N4	regular use meningioma cases: 52,4% and controls 55,9%; glioma cases 61,5% controls 63,7%
N5	yes
O	possibly yes (recall problems), probably not for case ascertainment, mostly using (?) pathology reports
P	not to be expected
Q1	adjustment for sex, age, study centre, ethnicity in Israel, education
Q2	ok, possibly stratify if there are large differences for e.g. sex or centre
R1	conditional logistic regression analysis on the matched case-control datasets
R2	ok
S1	95%CI
S2	ok
T	yes
U1	quote: For meningioma, there is little evidence to counter a global null hypothesis, and we conclude that INTERPHONE finds no signs of an increased risk of meningioma among users of mobile telephones. For glioma, an increased OR was seen in analyses in the highest decile of cumulative call time, including tumours in the temporal lobe and subjects who reported having used the mobile phone mainly on the same side as where the tumour occurred. Still, the evidence for an increased risk of glioma among the highest users was inconclusive, as the increase could be due to one or more of the possible sources of error discussed ....
U2	see Annex H
U3	probably for a part of the cases, but for another part of the cases the latency period is too short
U4	no
V	most bias can go either way, but possibly the results are overestimated due to e.g. the overestimation of exposure by cases, possibly additionally influenced by the interviewer?, but also possibly underestimated by the very substantial non-response
W	can go either way, depends on errors in recall bias and accompanying misclassification of exposure, possibly overestimation effect due to overestimation exposure in cases
X1	yes
X2	no
Y	participating countries? Depends a bit on the size of the differences between the countries, whether you can generalise the overall results over the countries
Z	yes

Table F13 Extractions from INTERPHONE study group. Acoustic neuroma risk in relation to mobile telephone use: Results of the INTERPHONE international case-control study. Cancer Epidemiol, 2011.[94]

A1	is AN caused by use of mobile phones
A2	is having AN associated with a history of using a mobile phone
A3	is having AN associated with a history of using a mobile phone
B1	case-control
B2	ok

B3	n.a.
B4	n.a.
B5	n.a.
C1	available areas etc
C2	ok
C3	in a previous paper
D1	1:2
D2	ok given large numbers
E1	burden for patients
E2	in individual papers it did say so mostly
F1	16 sites in 13 countries
F2	wider region?
G1	82% for cases (70-100%) 53% for controls
G2	quite poor for the controls
G3	1105 cases 2145 controls
G4	n.a.
G5	n.a.
G6	n.a.
H1	certainly as poor response rates
H2	underestimation?
I1	yes
I2	can't tell, either way
J1	yes
J2	can't tell, either way
K1	yes
K2	can't tell, either way
L1	age, sex, SES
L2	yes
M1	some
M2	various
N1	interview
N2	more checking with bills?
N3	person-dose
N4	1308 / 2145 = 61%
N5	theoretically
O	some as measurement imprecise
P	no
Q1	regression
Q2	ok
R1	regression coefficient / OR
R2	ok
S1	95% CI
S2	ok
T	ok

U1	there was no increase in risk of acoustic neuroma with ever regular use of a mobile phone or for users who began regular use 10 years or more before the reference date.
U2	see Annex H
U3	unclear
U4	no
V	some left due to selection bias and observer bias
W	underestimation
X1	ok
X2	no
Y	quite widely
Z	ok

Other case-control studies

Table F14 Extractions from Muscat JE, Malkin MG, Thompson S, e.a. Handheld cellular telephone use and risk of brain cancer. JAMA, 2000; 284(23): 3001-3007.[96]

A1	public health concerns about the safety of cellular telephones
A2	using handheld cellular telephones is related to the risk of primary brain cancer
A3	is using handheld cellular telephones related to the risk of primary brain cancer
B1	case-control
B2	yes
B3	poss. cohort, however given low incidence one would need a long time to get enough cases
B4	highest category >= 4 years, in US start cellular phones in 1984
B5	still very short
C1	unclear description of how group exactly defined, eligible cases diagnosed as having primary brain cancer within the past year (which last year? Interviews have been conducted between '94 and '98) and spoke English
C2	deceased patients not in study, should include those, now exclusion worst cases, spoke English actually vague definition: how well?
C3	no
D1	ratio 1:1, frequency matched by age, sex, race, month of admission, hospital
D2	poss. ratio 1: 2 given relatively small numbers and now wide confidence intervals
E1	burden for hospital patients, both cases and controls (have another reason for hospital visit)
E2	not mentioned
F1	New York (Memorial Sloane Kettering) cancer centre, NY university medical centre and Columbia University Presbyterian hospital), Providence (Rhode Island hospital), Boston (Massachusetts General Hospital)
F2	population controls as the hospitals used were tertiary specialist units for all specialities so 'normal' cases might not be present as many more hospitals present in NY
G1	not presented, written as if 100% response rate in both cases & controls but Response rate cases: 82% (469/571; 2 dead, 25 refused, 75 to ill), (97 not approached as to ill or do not speak English); response rate controls: 90%
G2	for cases certainly not, for controls ok
G3	469 cases and 422 controls
G4	17 cases (3,6%) and 22 controls (5,2%) >= 4 years use and 2-3 years follow-up: 6% cases and 5.7 controls
G5	very small numbers for long follow-up, cannot say anything about longer duration and short duration only effect on speeded up subclinical stages instead of development of new tumour
G6	≥4 years highest category

H1	yes, 97 not approached, particularly the most ill and the group that does not speak English (so possibly the group with lower SES)
H2	can go either way, depends if the most ill particularly use or not use mobile phones, not speak English, lower SES probably lower use of mobile phones (particularly in the early years before the use became wide spread)
I1	yes 82% response cases not terribly bad, but still a substantial group non-responders that can differ systematically from responder cases, also for controls responders bias possible, chance smaller as response higher at 90%
I2	possibly particularly users of mobile phones participated? In that case overestimation risk
J1	yes, particularly due to recall bias, in text spearman correlation coefficients calculated and recall seems ok when compared to hours registered on accounts (is however also an estimate because accounts were not well traced at the telecom company), however recall will always play a role in retrospective investigations, also on the bills no info about call received, not described how all is comparable.
J2	can go either way but most likely overestimation of exposure by cases
K1	yes
K2	overestimation effect if interviewer convinced of existence of possible effects
L1	yes, (matching variables: age, sex, race, hospital) en potential confounders: SES, medical history, occupational exposure
L2	yes, except SES
M1	yes, due to recall bias
M2	all sorts of errors can occur in the measurement of the exposure (recall, type phone, how many minutes, how often, which ear used, how much with a 'cord', how much direct exposure to the head...)
N1	structured interview
N2	registrations via telecom companies, than no more information and observation bias
N3	person-dose
N4	cases: 14.1% user; controls 18,0% user
N5	yes, but with loads of issues attached
O	possibly yes due to information bias
P	not to be expected
Q1	multivariate analysis, in which adjustment for confounders is contained in the model and stratify
Q2	ok
R1	multivariate unconditional logistic regression analysis and test for trend and nonparametric regression analysis (alternative method assessing dose response relationship)
R2	ok, because frequency matched and not individually matched
S1	95% CI
S2	ok
T	yes, but some numbers missing, e.g. how many potential cases there were.
U1	use of handheld telephones is not associated with risk of brain cancer
U2	see Annex H
U3	is the question, because unclear when tumour developed exactly and if all types of exposure really did occur before
U4	no, still to small numbers and to wide confidence intervals to be able to say anything about this, effect cannot be excluded but these numbers of not indicate a dose-response relation
V	has been corrected for as analysis was multivariate, so in theory clean OR
W	can go either way depending on recall and allocation to user categories, possible overestimation exposure by cases so overestimation risk, but OR already below 1
X1	yes
X2	as far as I can see no
Y	to patients of the hospitals involved but too many problems to generalise
Z	reasonably as they consider the need for longer duration studies

Table F15 Extractions from De Roos AJ, Teschke K, Savitz DA, e.a. Parental occupational exposures to electromagnetic fields and radiation and the incidence of neuroblastoma in offspring. Epidemiology, 2001; 12(5): 508-517.[97]

A1	determinants of neuroblastoma
A2	what is the (parental) mobile phone history In children with neuroblastoma
A3	as A2 but way too early for exposure to mps
B1	case-control
B2	ok
B3	cohort but would need to be extremely large
B4	n.a.
B5	n.a.
C1	total number of eligible pateints
C2	longer duration
C3	not presented
D1	1:1
D2	ok but generally assumed 1:4 better
E1	burden for patients
E2	not mentioned but assumed to be ok
F1	patients at 139 hospitals in the US, less than 19 yrs of age, 01/05/92-30/04/94
F2	newer as for mobile phones this is way too early
G1	73% of cases and 74% for controls
G2	yes
G3	n.a.
G4	n.a.
G5	n.a.
G6	n.a.
H1	very small number but good response rate so possibly not too bad . however, to be eligible many criteria were applied
H2	could go either way
I1	yes as ill
I2	could go either way
J1	yes as ill
J2	could go either way
K1	yes as interviews
K2	could go either way
L1	yes as always as poorly measured
L2	yes as far as possible
M1	yes
M2	many as poorly measured
N1	interview
N2	more elaborate but it was a tiny bit of many other interests
N3	person dose but poorly specified
N4	4 / 503 so minimal
N5	not really
O	as always
P	as always

Q1	regression
Q2	ok
R1	regression coeff / OR
R2	ok
S1	95% CI
S2	ok
T	numbers seem to add up
U1	overall, there was scant supportive evidence of strong associations between parental exposures in electromagnetic spectrum and neuroblastoma in offspring. (quote)
U2	see Annex H
U3	no
U4	no
V	poor measurements so could go either way
W	poor measurements so could go either way
X1	ok
X2	ok
Y	limited as study is limited
Z	ok

Table F16 Extractions from Stang A, Anastassiou G, Ahrens W, e.a. The possible role of radiofrequency radiation in the development of uveal melanoma. Epidemiology, 2001; 12: 7-12.[98]

A1	interest in determinants of uveal melanoma and different sources of radiation
A2	what is the mobile phone (and other determinants) history in people with uveal melanoma
A3	A2 tested
B1	case-control
B2	ok
B3	cohort but would have to be extremely big
B4	n.a.
B5	n.a.
C1	total number of incident cases
C2	more hospitals, wider region?
C3	not presented
D1	1:12 for hospital study and ca 1:2 for population study
D2	1:4 is considered optimal
E1	burden for pateints
E2	not mentioned but assumed
F1	mixed model of hospital cases, hospital, family and populations controls for limited regions in Germany
F2	clearer choices and good population controls selection
G1	hospital based study: cases 84%, controls 48%; population based study cases 88% controls 79%
G2	population study yes, hospital controls response is poor
G3	57 cases and 699 controls in hospital study; 81 cases and 148 controls in population study
G4	n.a.
G5	n.a.
G6	n.a.

H1	given poor response rates: yes
H2	could go either way
I1	yes
I2	could go either way
J1	yes
J2	could go either way
K1	as there were interviews: yes
K2	could go either way
L1	age, sex
L2	yes
M1	somewhat
M2	misunderstanding questions etc
N1	mostly interviews, some questionnaires
N2	all one or the other as this mix makes it hard to interpret
N3	personal dose
N4	person-dose
N5	12% (?)
O	as always
P	as always
Q1	regression
Q2	ok
R1	regression coeff/ OR
R2	ok
S1	95% CI
S2	ok
T	numbers do seem to add up
U1	we found an increased risk of uveal melanoma in relation to RFR as transmitted by radio sets and mobile phones. The association between electromagnetic fields and uveal melanoma was limited to RFR (quote)
U2	see Annex H
U3	some indications but unclear
U4	not clearly
V	could go eithr way
W	yes and could go either way
X1	ok
X2	ok
Y	limited as small scale study
Z	ok

Table F17 Extractions from Inskip PD, Tarone RE, Hatch EE, e.a. Cellular-telephone use and brain tumors. N Engl J Med, 2001; 344(2): 79-86.[99]

A1	because of concern about the risk of brain cancer associated with the use of hand-held cellular phones
A2	recent use of hand-held cellular telephones causes brain tumours
A3	does recent use of hand-held cellular telephones cause brain tumours?

B1	case-control
B2	yes
B3	poss. cohort, however given low incidence one would need a long time to get enough cases
B4	n.a., cases and controls are at most allocated to use >= 5 years
B5	to short for the development of brain tumours, but assumed that if magnetic fields cause cancer, they act at a late stage in the process sand than it could potentially have an influence, exact mechanism unclear
C1	power calculation
C2	for subgroup analysis to small numbers still
C3	yes
D1	ratio cases: controls: 1:1
D2	power calculation done: sufficient power, so good ratio, however for subgroup analysis not sufficient power
E1	burden for hospital patients, however can refuse cooperation if they want, extra blood sampling for investigation
E2	yes, in this article can be found that institutional review boards approved the protocol
F1	2 hospitals in Arizona, 1 in Boston, 1 in Pennsylvania, all newly diagnosed cases over 4 years; controls admitted to same wards + general surgical, urology, cardiac, pulmonary, gastrointestinal & trauma
F2	nationwide, particularly include smaller hospitals, would give better reflection of population?, these 3 centres are truly referral hospitals
G1	cases: 92 %; controls 86 %
G2	yes, relatively high, although a non-response analyses would be preferable
G3	782 cases and 799 controls
G4	maximal category >= 5 years phone use, but all sorts of variables for exposure asked far back
G5	no, really too short for cancer to develop, possibly influence on the speeding up of a sub clinical state of the cancer
G6	category >= 5 years
H1	yes, but unclear which cases and controls did not participate and how many that were. E.g. why has not everyone been asked by a doctor? Also possibly selection bias because only large urban hospitals included. However, tight protocol about who is and who isn't included so hopefully no selection bias due to choice of doctors themselves if someone was to participate or not in the study
H2	possible so very small
I1	yes, 92 and 86% are quite high %, but also this can still contain bias, e.g. particularly people with an affinity with the topic are more prepared to participate
I2	relatively more people who use mobile phones may have participated? However, effect is not there so will not have changed this much
J1	yes, recall bias can be a big problem here, but is minimized by often having a partner present at the interviews, but maybe this was less often the case for controls.
J2	over reporting by cases for the various exposures assessed
K1	on the one hand yes because the interviewer has influence on the way of asking the questions and if needed explain them, on the other hand no because it is all according to a strict protocol
K2	overestimation of effect if interviewer convinced of existence of possible effects, however also taped interviews checked so probably no effect
L1	matching variables: (age, sex, race, hospital and distance to hospital) and education, self-reported income, date of interview, interview respondent
L2	yes
M1	yes
M2	limitations to capture historical changes, inaccuracies in recall, variations in levels of exposure, different types of telephones and different circumstances of use. (misclassification mainly in level of use than in use itself)

N1	interview and questionnaire
N2	very many exposures depend on memory, so use of registries would be better, e.g. phone companies and poss. Registration of exposure through occupation in registries? (e.g. dosimetry for people that worked with X-rays)
N3	person-dose
N4	358 of 799 used mobile phone, 172 regular use
N5	yes
O	possible as recall plays a role, but very detailed reconstruction asked for
P	no, not to be expected. Just normal random error
Q1	confounders included in model for logistic regression and thus adjusted OR´s
Q2	ok
R1	conditional logistic regression
R2	ok, because controls are matched
S1	95% CI
S2	ok
T	yes
U1	the study does not support the view that exposure to low-power microwave radiation from hand-held, analogue cellular telephones causes malignant or benign tumours of the brain or nervous system (note says nothing about long term and enormous increase in use in whole population)
U2	see Annex H
U3	is the question because unclear when tumour exactly developed and/if all sorts of exposure did occur before than
U4	yes
V	has been corrected for
W	can go either way depending on recall and allocation to user categories
X1	as far as I can see yes; ok (points to specific no-effect literature and wireless company literature)
X2	as far as I can see no
Y	urban US population of the three 3 regions
Z	no as they cannot prove or disprove the association given the lack to latency time in the study

Table F18 Extractions from Auvinen A, Hietanen M, Luukkonen R, e.a. Brain tumors and salivary gland cancers among cellular telephone users. Epidemiology, 2002; 13(3): 356-359. [100]

A1	possible health hazards of radiofrequency electromagnetic fields emitted by cellular phones
A2	not really formulated, but is about the question : increased risk brain and salivary gland tumour in cellular telephone users
A3	is the risk for brain and salivary gland tumour increased in cellular telephone users?
B1	case-control
B2	yes
B3	design is ok, reasonably efficient because uses registries that have been linked, however many issues with the method to answer the study questions, case control with individual exposure data or prospective cohort
B4	couple of years, average duration of subscription 2-3 year for analogue & less than 1 year for digital; highest category used > 2 years
B5	not at all
C1	all cases from population based Finnish cancer registry, 5 controls per case
C2	ok
C3	yes, to detect an OR of 1,4 or higher for brain tumours and 2,8 or higher for salivary gland cancers with $\alpha = 0,05$, two-sided and $1-\beta = 0,8$

D1	ratio 1: 5 not described why (undoubtedly to do with power calculation but it is not presented)
D2	fine ratio, possibly 1:3 or 1:4 ok also good?? 5 controls is quite much
E1	that is done without consent, participants are not aware of all the privacy sensitive data that have been used for this investigation
E2	yes
F1	Finnish Cancer Registry (cases) and Population Registry Centre of Finland (controls); all cases in Finland in 1996, controls from population registry
F2	ok, however this way exposure cannot be asked back in detail (exposure now via subscribers list from the 2 cellular network providers)
G1	n.a., registry data
G2	n.a.
G3	cases: 432 (398 brain tumour and 34 salivary gland) controls: 2156 (1986 brain and 170 salivary gland)
G4	n.a.
G5	no highest category > 2 years, so much to short and very small numbers
G6	> 2 years
H1	no, all cases in registry included
H2	n.a.
I1	no, all cases in registry included
I2	n.a.
J1	yes, unclear if phone was really used by the case or control rather than e.g. a family member, also missing info about duration of use etc, maybe phone and phone plan was bought but was is hardly if ever used?; also very important that only private subscribers were included so no company subscriptions, these people are now if they are either a case or a control in the study taken as non-exposed
J2	overestimation exposure because you do not know for certain if the subscribers are users; underestimation because in unexposed group also people who do use mobile phones via a company plan and so are exposed
K1	no, not to be expected, all registry based
K2	n.a.
L1	overestimation because part effect due to other exposures
L2	yes some are, urban residence, SES, occupation farming or electromagnetic fields
M1	yes
M2	people labelled as exposed due to the phone provider data, while this may not be the person who actually uses the phone and users of company phones are missed and incorrectly labelled as unexposed
N1	subscription at telecom provider, and duration subscription; private subscription, little detail on non-private definition for exclusion (trades people etc?) duration was used for dose
N2	yes recall through questionnaire or interview, this information does not mean much
N3	should be person dose, but the question remains if it was the correct person
N4	13% brain cancer, 12% salivary gland and 11% controls ever had personal subscription to a cellular telephone
N5	no
O	yes, who really used the phone, case or control or maybe a family member and substantial measurement error because all company subscriptions are missing
P	not to be expected
Q1	not, only looked in the frequency tables if distribution for cases and controls comparable
Q2	correct in multivariate analysis
R1	conditional logistic regression
R2	ok

S1	95% CI
S2	ok
T	yes
U1	cellular phone use was not associated with brain tumours or salivary gland tumours overall, a weak association between gliomas and analogue cellular phones
U2	see Annex H
U3	no, exposure much too short to cause cancer
U4	no
V	overestimation because not corrected for confounders
W	can go either way, overestimation if users are not the actual users, and underestimation of unexposed people maybe use a company phone
X1	yes
X2	very limited number of references
Y	cannot be generalised, way too many shortcomings in this study to generalise conclusions
Z	yes as they themselves do not say they don't find an association, they realise you need better detailed data and longer period of observation

Table F19 Extractions from Muscat JE, Malkin MG, Shore RE, e.a. Handheld cellular telephones and risk of acoustic neuroma. Neurology, 2002; 58(8): 1304-1306.[101]

A1	public health concerns about the safety of cellular telephones
A2	intracranial energy disposition from handheld cellular telephones causes acoustic neuroma
A3	intracranial energy disposition from handheld cellular telephones causes acoustic neuroma
B1	case-control
B2	yes
B3	poss. cohort, however given low incidence one would need a long time to get enough cases
B4	highest category 3-6 years use of cellular phone
B5	very short, particularly since acoustic neuroma has long latency time
C1	part of larger case-control study on brain tumour, form that this subgroup used
C2	small numbers, so use more than the indicated 2 hospitals as a source
C3	no
D1	ratio 1:1
D2	1:4 given small numbers
E1	burden for hospital patients, both cases and controls (have other reason for hospital visit)
E2	not described in the text
F1	18-80 yrs old, patients @ 3 NY, 1 RI, 1 Boston tertiary hospitals with brain tumours, diag 94-98; controls same hospitals daily admissions (benign illness other than 2 hospitals) excl leukaemia or lymphoma
F2	population controls as the hospitals used were tertiary specialist units for all specialities so 'normal' cases might not be present, in many places many more hospitals present
G1	only described that 90 cases and 86 controls were selected from a larger case control study (from 1020: Response rate cases: 82% (469/571; 2 dead, 25 refused, 75 to ill), (97 not approached because to ill or did not speak English); response rate controls: 90%)
G2	for cases certainly not, for controls ok
G3	90 cases, 86 controls
G4	only 11 (12,2%) patients and 6 (7,0%) controls have 3-6 years follow-up
G5	to begin with small numbers, miniscule small numbers in category with longest use

G6	3-6 years highest category
H1	unknown, not described (see 1020)
H2	unknown, not described (see 1020)
I1	unknown, not described (see 1020)
I2	unknown, not described (see 1020)
J1	yes, particularly due to recall bias
J2	overestimation exposure by cases (so overestimation effect)
K1	yes because the interviewer's way of asking can influence
K2	overestimation effect if interviewer is convinced of the existence of possible effects
L1	yes, (matching variables: age, sex, race, hospital) and potential confounders: SES, medical history, occupational exposure
L2	yes, except SES
M1	yes, due to recall bias
M2	all sorts of errors can occur in measuring exposure and e.g. exposure to substances in occupation
N1	personal, structured interview
N2	use registrations of telecom companies and occupation related registries
N3	person-dose
N4	26,7% controls regularly using handheld cellular telephone versus 20,0 % cases
N5	potentially yes
O	bill seize is an approximation but reasonably close (not entirely matched as distance of call increases bill but not necessarily exposure)
P	not to be expected
Q1	multivariate analysis, with adjustment for confounders in the model
Q2	ok
R1	multivariate unconditional logistic regression analysis
R2	ok, because frequency matched and not individually matched
S1	95% CI
S2	ok
T	yes
U1	reasonably as they consider the need for longer duration studies and the analogue/digital issue (use at the time mainly analogue)
U2	see Annex H
U3	reasonably as they consider the need for longer duration studies and the analogue/digital issue (use at the time mainly analogue)
U4	reasonably as they consider the need for longer duration studies and the analogue/digital issue (use at the time mainly analogue)
V	reasonably as they consider the need for longer duration studies and the analogue/digital issue (use at the time mainly analogue)
W	reasonably as they consider the need for longer duration studies and the analogue/digital issue (use at the time mainly analogue)
X1	reasonably as they consider the need for longer duration studies and the analogue/digital issue (use at the time mainly analogue)
X2	reasonably as they consider the need for longer duration studies and the analogue/digital issue (use at the time mainly analogue)
Y	reasonably as they consider the need for longer duration studies and the analogue/digital issue (use at the time mainly analogue)

Z	reasonably as they consider the need for longer duration studies and the analogue/digital issue (use at the time mainly analogue)

Table F20 Extractions from Warren HG, Prevatt AA, Daly KA, e.a. Cellular telephone use and risk of intratemporal facial nerve tumor. Laryngoscope, 2003; 113(4): 663-667.[102]

A1	to determine whether cellular telephone use is associated with an increased risk of intratemporal facial nerve tumours
A2	is cellular telephone electromagnetic radiation exposure a causative agent of facial nerve tumours?
A3	is cellular telephone use associated with an increased risk of intratemporal facial nerve tumours?
B1	hospital based case-control
B2	ok bar for inherent limitations
B3	poss. Cohort or case control over more years
B4	n.a.; cases and controls included from 1 July 1995 - 1 July 2000 and use phone , occupation, medical history, social habits etc retrospectively asked
B5	average number of years of use varies from 1-5,67, to short, long follow-up is for acoustic neuroma, but that is a slow growing tumour so also for this group to short follow-up
C1	all cases diagnosed with IFN between July 1995-2000 in the academic tertiary care medical centre
C2	small numbers, so if possible also include other hospitals or use larger region, are there other specialist centres?
C3	no
D1	1 to 12 for the non tumour controls, all acoustic neuromas (?)
D2	very few cases, so many controls needed to get some power, also included 3 different reference groups in controls
E1	burden for patients; too small so never a real result so unethical to conduct in the first place
E2	yes
F1	fiscal database at academic, tertiary-care medical centre: all newly diagnosed patients over 1 year in one (main?) hospital, controls from same department for both non-tumour and tumour controls, University hospital (unclear if based in Florida or in Minnesota, probably Florida)
F2	larger region, include more specialist hospitals
G1	not described, but all 18 cases have been included and 192/216 controls (88,9%), the intention was to use 12 controls per case and those cannot be traced in the tables
G2	if the numbers in the previous answer were right yes but unclear if and who were excluded
G3	18 cases, 192 controls (51 acoustic neuroma, 72 rhino sinusitis, 69 dysphonia or gastroesophageal reflux)
G4	n.a., use of mobile asked back, but only number of years of use described: (1 for cases and 1 for controls and 5,67 for acoustic neuroma patients), except for acoustic neuroma for the other tumours is the time to short anyway
G5	n.a.
G6	not real follow-up of course but time since first use: average 1 for IFN cases and controls and 5,67 years for acoustic neuroma
H1	if all 18 cases are included and if these were indeed the only cases, than not, for controls possible but unclear how people recruited (all people with named diagnosis of a selection?)
H2	probable so negligibly small
I1	for cases not as all 18 participated, controls only limited non-response so responder bias will be relatively small, however nothing presented about who the non responders are
I2	not really a large effect to be expected possibly overestimation for people with acoustic neuroma and underestimations rhinosinusitis (possibly also inclined to report higher exposure given illness history)
J1	yes, recall bias, although mobile phones have been used relatively recently only and memory might still be quite good
J2	possible over reporting cases INF and acoustic neuroma and rhinusitis (all in area head/ear)
K1	yes because interviewer can influence the conversation
K2	possible overestimation effect if interviewer convinced of the existence of a possible effect

L1	many confounders measured (age, sex, occupation etc), SES,
L2	yes some have been, SES not, unclear how corrected for in multivariate regression: nowhere to be found which variables were included in the model
M1	yes
M2	exposure definition, duration, frequency use of phone, however in this analysis they were not used...
N1	structured interview about phone
N2	questionnaire to reduce observation bias or use telecom companies to get exact phone habits
N3	person-dose
N4	2 or 18 patients (11,1%) regular use (average 1 call a week), 11 of 51 acoustic neuroma (21,6%), 31 of 141 non-tumour control (22,0%)
N5	probably yes, given that many details were asked for of the various exposures, l however nothing said about in this article
O	possible due to recall
P	not to be expected
Q1	multivariate analysis, however nowhere to be found which variables corrected for
Q2	ok, assuming correct corrections, poss. Stratify
R1	multivariate unconditional logistic regression analysis
R2	conditional logistic regression analysis (because of matched data)
S1	95% CI
S2	ok
T	yes, except that it is unclear how they got the 192 controls with a ratio of 1 to 12 and in tables 2 and 3 the total number of non tumour controls doe not compute 5 times, 4 times 1 missing: probably a missing answer but also 1 time 3 controls to many??
U1	regular cellular telephone use does not appear to be associated with a higher risk of IFN tumour development
U2	see Annex H
U3	probably not as the period of phone use is very short and the tumour therefore probably existed a long time before the start of the phone use
U4	no
V	if the confounders have been corrected for in the multivariate analysis than the results are pure estimates, however cannot be traced if and how corrected for
W	misclassification in diagnose: nowhere described if diagnoses histologically verified and for the exposure: overestimation of use by the cases, so overestimation of effect?? However no effect found
X1	as far as I can see at this time yes
X2	as far as I can see not entirely, e.g. only 1 article by Hardell referenced
Y	patients of other academic tertiary care medical centres with 1 of the diagnoses used, unclear
Z	yes as they recognise that the numbers are too small for any conclusions and therefore do not present one

Table F21 Extractions from Gousias K, Markou M, Voulgaris S, e.a. Descriptive epidemiology of cerebral gliomas in Northwest Greece and study of potential predisposing factors, 2005-2007. Neuroepidemiology, 2009; 33(2): 89-95.[103]

A1	the aim of the study was to investigate the epidemiologic and clinical characteristics of glioma patients in a defined area of northwest Greece with a total population of about 500,000 inhabitants
A2	not really stated but is about the question : cellular telephone use increases the risk of brain tumour? (and descriptive incidence rate)
A3	cellular telephone use increases the risk of brain tumour?
B1	case-control study
B2	yes

B3	observational cohort or maybe poss. experiment
B4	not described how long the phones were used for
B5	follow-up has not been used in this study
C1	all patients with newly diagnosed cerebral glioma during period 1 June 2005 and 31 May 2007, referred to the departments of neurosurgery and neurology of the university hospital of Ioannina as well as the other hospitals of the study area (6 districts, Ioannina, Arta, Preveza, Thesprotia, Corfu, Lefkada)
C2	nationwide
C3	no
D1	ratio 1:2
D2	ratio 1:3 of 1:4 for power
E1	burden on very ill patients and also on controls as they were neurologically assessed
E2	not mentioned
F1	the study area consisted of 6 districts: Ioannina, Arta, Preveza, Thesprotia, Corfu, Lefkada, source were hospitals within this area
F2	nationwide cancer registry
G1	first 41 of the 56 cases participated and 82 controls, nothing described about response
G2	not known what response rate is, possibly all included given small numbers? In that case good response
G3	41 cases and 82 controls (no drop-outs described but there very well might be non-response)
G4	nothing described
G5	unknown what follow-up is
G6	unknown how long people used their mobile phone
H1	unclear is this is complete, possibly some elderly rural areas missed due to wrong diagnosis stroke, however free access to all patients in hospital, so probably no or little selection bias
H2	probably so negligibly small
I1	unknown what response rate was, 100%?
I2	probably not or not much, but not described what response is
J1	yes, cases are likely to recall better and the controls are likely to have been the interested or SEC better off and thus more exposed+ yes as the mobile phone use had to be recalled as well as alcohol and tobacco which are always tricky
J2	possible overestimation use by cases, so overestimation effect??
K1	yes, because interviewer can influence conversation
K2	possible overestimation effect if interviewer convinced of the existence of an effect
L1	yes, age, sex, SES etc
L2	no, SES not and in analysis only alcohol consumption, smoking, use mobile phone and history severe cranial trauma included, matched op age and sex and district (unclear how this was included in the analysis)
M1	yes
M2	mobile phone use per minute years, very recall sensitive, so quickly wrong number of minute years
N1	interview
N2	questionnaire to reduce observation bias or use telecom companies to get exact phone habits
N3	yes, questions about time of start, minute-years and hands-free use
N4	not described
N5	could be
O	possibly yes due to recall
P	not to be expected
Q1	in analysis only alcohol consumption, smoking, use mobile phone and history severe cranial trauma included, matched op age and sex and district, but unclear how matching variables were included in the analysis
Q2	stratify for age, sex and district (probably to small numbers to do this?)

R1	logistic regression analysis
R2	conditional logistic regression analysis (due to matched data)
S1	95% CI and p-value
S2	ok
T	yes (not many absolute numbers given to check, cannot check in the table how many cases and controls per group)
U1	there is no significant association between glioma and mobile phone use
U2	see Annex H
U3	unclear, not described how long ago the use of the mobile phone started
U4	no that is to say not per minute -year, otherwise nothing investigated of a dose-response
V	unclear how exactly included in analysis so really not much to say
W	overestimation use due to cases, overestimation effect
X1	yes
X2	references particularly focussed on incidence rate, interphone references missing but some Hardell referred to and some others
Y	if 6 districts are representative for Greece, all Greece, otherwise only population 6 districts
Z	bit overstated given the very small numbers

Table F22 Extractions from Stang A, Schmidt-Pokrzywniak A, Lash TL, e.a. Mobile phone use and risk of uveal melanoma: results of the risk factors for uveal melanoma case-control study. J Natl Cancer Inst, 2009; 101(2): 120-123.[104]

A1	recently reported increased risk of uveal melanoma now conducted with more valid exposure measurements more power
A2	mobile phone use increases the risk of uveal melanoma
A3	does mobile phone use increases the risk of uveal melanoma?
B1	hospital-based case-control study
B2	yes
B3	observational cohort or poss. experiment
B4	not described how long the phones were used for, highest usage category > 10 years
B5	no, only very small group >5 years use and only a few cases and controls in >10 years group
C1	subjects first diagnosed with uveal melanoma, aged 20-74, lived in Germany, proficient in German language between Sept. 25 2002 and September 24 2004 at University of Duisburg-Essen's referral centre for eye cancers
C2	bigger region, or nationwide
C3	not in this paper but in one referred: if achieving 380 cases & 760 controls an OR of 1.5 would be detectable
D1	3 control groups: population controls: 455 cases, 827 controls, ratio 1: 1,8 ophthalmologist: 133 cases, 180 controls, ratio 1:1,4 sibling controls: 187 cases, 187 controls, ratio 1:1
D2	all groups 1:2 for more power (here reasonable numbers of cases and controls in total, but subgroups to few people)
E1	burden for patients due to interview, fear for mobile phones
E2	not mentioned
F1	region of Duisburg/ Essen, Germany, University of Duisburg-Essen's referral centre for eye cancers; all newly diagnosed cases of uveal melanoma between 09/02 and 09/04 in the main tertiary clinic in one place supposedly missing 10 from another clinic in the state, controls form population census
F2	nationwide
G1	cases 94%, population controls 57%, sibling controls 57%, ophthalmologists controls 52%
G2	cases yes, controls: not at all
G3	455 cases, 827 population controls, 180 ophthalmologist controls (133 cases), 187 sibling controls (187 cases)
G4	n.a.

G5	no, too few cases and controls > 10 years follow-up (also > 5 years relatively few people)
G6	highest category > 10 years
H1	yes, unclear if referral centre gets all cases, or e.g. only the worst cases
H2	can go either way, depends if the most ill particularly use or particularly do not use a phone
I1	yes for controls only a bit over 50% response, so substantial bias possible
I2	possible underestimation risk because for controls particularly users mobile phones participated
J1	yes recall problems
J2	possible overestimation use by cases, so overestimation effect??
K1	yes, in additional phone interviews possibly influenced by interviewer
K2	overestimation effect if interviewer "intend on proving" effect
L1	yes, age, sex, region of residence, SES etc
L2	yes, SES however unclear is this was measured
M1	yes
M2	recall bias, exposure definition, type, duration, frequency use phone
N1	questionnaire + additional phone interviews
N2	only questionnaire use to minimise observation bias, unclear what the aim was of the additional interviews (more details about exposure?)
N3	person-dose
N4	regular use (interphone definition) 36% of 827 population controls and 30% of 455 cases; 30% of 180 opth. controls and 31% of 133 cases; 35% of 187 sibling controls and 37% of 187 cases
N5	yes
O	possible, due to recall bias
P	not to be expected
Q1	log regression accounting for matching variables
Q2	multivariate analyse with also correction for e.g. SES
R1	conditional logistic regression
R2	ok
S1	95% CI
S2	ok
T	cannot be checked
U1	risk of uveal melanoma was not associated with regular mobile phone use, and no trend was observed for cumulative measures of exposure
U2	see Annex H
U3	no, much to small numbers > 10 years and also even > 5 years to small numbers to infer anything.
U4	no
V	can go either way, depends which bias has most influence
W	overestimation of use by cases, overestimation effect
X1	ok if a bit '1sided'
X2	no
Y	to population of Duisburg Essen
Z	reasonably as they recognise the time period problem

Table F23 Extractions from Spinelli V, Chinot O, Cabaniols C, e.a. Occupational and environmental risk factors for brain cancer: a pilot case-control study in France. Presse Med, 2010; 39(2): e35-e44.[105]

A1	what are deteminants of brain tumours
A2	in people with a brain tumour, what is the reported use of mobile phones (and other)
A3	ok A2 (note this is a pilot study)
B1	case-control
B2	ok
B3	cohort but would have to be very large
B4	n.a.
B5	n.a.
C1	all patients in 2 hospitals and very strict criteria
C2	larger but then this was a pilot
C3	not presented
D1	1:1
D2	1:4 considered better
E1	burden for respondents
E2	not mentioned
F1	patients in 2 hospitals, controls also hospitalised
F2	populations controls
G1	71% for cases and 90% for controls (?? unclear)
G2	would be ok
G3	122 cases and 122 controls
G4	n.a.
G5	n.a.
G6	n.a.
H1	yes
H2	could go either way
I1	yes
I2	could go either way
J1	yes
J2	could go either way
K1	yes
K2	could go either way
L1	some left
L2	could go either way
M1	yes
M2	could go either way
N1	interview
N2	yes, more detail, currently does have cumulative hrd
N3	hardly as too limited but if anything it is person
N4	cannot say
N5	potentially
O	as always
P	as always

Q1	regression
Q2	ok
R1	regression coeff / OR
R2	ok
S1	95% CI
S2	ok
T	no seem to add up
U1	no effect seen but small numbers
U2	see Annex H
U3	cannot be assessed
U4	cannot be assessed
V	as always
W	as always
X1	ok
X2	ok
Y	very limited see next answer
Z	overstated as this is only a pilot so numbers are way too limited

Table F24 Extractions from Duan Y, Zhang HZ, and Bu RF. Correlation between cellular phone use and epithelial parotid gland malignancies. Int J Oral Maxillofac Surg, 2011; 40(9): 966-972.[106]

A1	deteminants of parotid gland tumours including mobile phone use
A2	is there an association between having a parotid gland tumour and having a history of mobile phone use
A3	A2
B1	case-control
B2	ok
B3	cohort
B4	n.a.
B5	n.a.
C1	all cases in 1 hospital
C2	wider ranging?
C3	not presented
D1	1: 15 and 1: 30
D2	1:4 is considered optimal
E1	burden for the patients
E2	not mentioned
F1	all cases in 1 hospital (as all confirmed by 1 surgeon); controls in hospital too
F2	wider?
G1	62% for cases and 78% for controls
G2	yes but bit low for cases
G3	136 cases and 2051 controls (as only the living were on the study)
G4	n.a.
G5	n.a.
G6	n.a.

H1	response rates are quite similar so possibly not too much?
H2	could go either way
I1	as responders are ill: yes
I2	could go either way
J1	as always
J2	could go either way
K1	as there were interviews yes
K2	could go either way
L1	age, sex, SES
L2	yes but SES poorly as always
M1	as always
M2	could go eitherway
N1	interview (face-2-face or telephone)
N2	more detail and verification
N3	person-dose
N4	57%
N5	potentially yes
O	as always
P	as always
Q1	regression
Q2	ok
R1	regression coeff / or
R2	ok
S1	95% Ci
S2	ok
T	seems ok, numbers add up
U1	the results suggest a possible dose–response relationship of cellular phone use with epithelial parotid gland malignancy
U2	see Annex H
U3	not obvious but maybe too limited range
U4	more consistently an association in highest exposure categories only
V	always
W	always
X1	ok
X2	ok
Y	to similar countries
Z	ok

Table F25 Extractions from Baldi I, Coureau G, Jaffre A, e.a. Occupational and residential exposure to electromagnetic fields and risk of brain tumors in adults: a case-control study in Gironde, France. Int J Cancer, 2011; 129(6): 1477-1484.[107]

A1	widely assess possible determinants for brain tumours in adults
A2	do people with brain tumours have a different history of e.g.. mobile phone use
A3	A2 plus loads of other hypotheses
B1	case-control
B2	ok

B3	cohort but would have to be extremely alrge
B4	n.a.
B5	n.a.
C1	all cases between 01/05/99 and 30/04/01 in one region
C2	larger?
C3	not presented
D1	1:2 matched
D2	ok but 1:4 would be better as numbers are not that large
E1	burden for patients to answer questions
E2	not mentioned but assumed
F1	incident cases Gironde, France, all cases between 01/05/99 and 30/04/01 in one region
F2	larger
G1	70% for cases and 69% for controls
G2	ok
G3	221 cases and 442 controls
G4	n.a.
G5	n.a.
G6	n.a. and duration of mp exposure is not given
H1	response rates are quite equal but there could be difference in non-response reasons and thus selection bias
H2	could go either way
I1	yes, they were ill and would have analysed for reasons
I2	could go either way
J1	yes
J2	could go either way
K1	yes, data collected by interview
K2	could go either way
L1	age, sex, SES
L2	yes but SES as that is always inadequately measured
M1	interview but limited on the phone information
M2	more detail
N1	person but limited on dose
N2	more detail at least
N3	not really
N4	112 / 441 = 25%
N5	barely probably not
O	yes as measurements are crude
P	yes as measurments are crude
Q1	regression
Q2	ok
R1	regression coeff / OR
R2	ok
S1	95% CI
S2	ok
T	seems ok

U1	no stat sig association seen
U2	see Annex H
U3	not measured
U4	no but not measured
V	underestimation
W	underestimation
X1	ok
X2	ok
Y	limited
Z	ok

Table F26 Extractions from Aydin D, Feychting M, Schüz J, e.a. Mobile phone use and brain tumors in children and adolescents: a multicenter case-control study. J Natl Cancer Inst, 2011; 103(16): 1264-1276.[108]

A1	several exposures such as mobile phones could be associated with brain tumours in children
A2	is there an association between having a brain tumour (as a child/adolescent) and having been exposed to mobile phones
A3	A2 was kind of tested
B1	case-control
B2	yes sort of with the inherent problems
B3	cohort but would have to be extraordinarily big
B4	n.a. but max exposure is 5 yrs
B5	n.a.
C1	total no of cases in region
C2	larger, longer
C3	not presented in this paper
D1	1:2
D2	1:4 is considered optimal
E1	burden for patients (and parents)
E2	not mentioned but assumed yes
F1	patients from Denmark, Sweden, Norway and Switzerland
F2	more countries?
G1	83% (68%-76%) for cases and 71% for controls (range for controls not given)
G2	ok good
G3	352 cases and 646 controls
G4	n.a. but longest exposure was 5 yrs
G5	n.a.
G6	n.a.
H1	yes as response rates are inequal
H2	could go either way
I1	yes as respondents were aware of hypotheses
I2	could go either way
J1	yes as cases will differ from controls in interest in the study questions
J2	could go either way
K1	yes as information gathered through interview so no blinding
K2	could go either way

L1	age, sex and SES
L2	yes
M1	yes somewhat
M2	could go either way
N1	interview
N2	checking in bills (some of that was done but not always possible)
N3	person-dose
N4	317 / 636 = 50%
N5	theoretically yes
O	yes somewhat
P	yes somewhat
Q1	regression
Q2	ok
R1	regression coefficient /OR
R2	ok
S1	95% CI
S2	ok
T	yes numbers add up
U1	there was no consistent exposure–response relationship either in terms of the amount of mobile phone use or by the location of the tumor. In a small subset of study participants with operator recorded data (n = 163), however, time since the start of a mobile phone subscription was statistically significantly related to brain tumor risk.
U2	see Annex H
U3	unclear, too short
U4	unclear
V	underestimate
W	could go either way but ususally underestimate
X1	ok
X2	ok
Y	similar countries
Z	ok

Case-case studies

Table F27 Extractions from Ali Kahn A, O'Brien DF, Kelly P, e.a. The anatomical distribution of cerebral gliomas in mobile phone users. Ir Med J, 2003; 96(8): 240-242.[109]

A1	patients of the Beaumont neurosurgical unit have expressed concern regarding the possible role of mobile phones, concerns fuelled by various media reports on the subject
A2	were a cellular phone to cause a glioma, then it would do so on the dominant hand site
A3	correlation between handedness of patient and side of tumour and correlation between use, non use of mobile phone and location of tumour.
B1	unclear description, case-series of patients with supratentorial glioma
B2	no clear design
B3	cohort
B4	not described how long the mobile phones were used only category of how many minutes per day
B5	so unclear

C1	study carried out between October 2000 and September 2001 of adult patients, histological diagnosis of supratentorial glioma at Beaumont neurological unit (diagnosed or interviewed between 2000-2001? unclear)
C2	more hospitals, larger region?
C3	no
D1	no controls, but also no comparisons with the general population e.g. pure handedness has been compared in this study with the location of the tumour
D2	n.a.
E1	burden for patients due to interview even though this seems to have been quite a short interview so probably not to bad
E2	not described in the text so possibly not
F1	all cases of glioma in 1 hospital 10/00 to 09/01; Beaumont neurosurgical unit (Ireland)
F2	all of Ireland??, maybe this is the only centre, unclear as not described
G1	response 100%, via case themselves otherwise via close family; 73/92= 79%, due to exclusion of centrally located tumours or tumours of which the lateralisation was hard to establish
G2	80% is a bit low, however still acceptable to infer, reasons non-response would be interesting to trace
G3	73 cases
G4	nothing described
G5	therefore nothing to say
G6	unknown how long people used their mobile phone
H1	yes if people were excluded before the 92 that were left over, e.g. deceased patients who are not among the 92, and also because the centrally located tumours and those that were hard to localise were excluded, particularly that last group could have been influenced by phone use??
H2	unknown, possible underestimation effect, on the other hand possibly at the most some lack of power because some people were excluded who did not have a tumour localised in the part of the head that was exposed, while possibly this tumour had been located in the exposed part
I1	no, everyone participated and for those that did not give permission close family members did
I2	so no
J1	yes recall problems
J2	overestimation phone use, however that information is not used in the analysis and the location of the tumour and right-left handedness is not dependent on memory
K1	yes, because interviewer can influence the conversation
K2	possible overestimation effect if interviewer convinced of the existence of an effect
L1	relation location tumour and right or left handedness does not get influenced by confounders?,
L2	age , sex, clinical features have been measured, unclear if used in analysis, cannot trace id corrected for potential confounders
M1	for location tumour, theoretically yes, in practice this should be ok, and right or left handedness should not easily be misclassified either
M2	exposure mobile phones but that is not used in the analysis
N1	questionnaire, however also described that patients were visited, unclear if this was only to hand in the questionnaire or if the questionnaire was filled in using an interview
N2	right and left handedness and localisation and lateralisation tumour ok; exposure mobile phones via provider
N3	person-dose
N4	n.a.
N5	yes, but nothing done with the exposure as measured
O	possible recall, however concerns relatively short period of phone use and for localisation and lateralisation tumour and right /left handedness no misclassification to be expected. Cases have been histologically diagnosed, so also no misclassification to be expected

P	not to be expected
Q1	no correction for confounding done
Q2	??, this is mostly an explorative article
R1	Fisher's exact test to test homogeneity of Odds ratios for case control comparing left and right sides cerebral gliomas
R2	logistic regression?
S1	p-value
S2	ok
T	yes, but few numbers mentioned and not clear how they got to the original 92 cases
U1	no statistical significance for glioma location based on the handedness of the patient in the mobile phone users group and location of the tumour in both user and non-user group
U2	see Annex H
U3	n.a.
U4	n.a.
V	can go either way, limited info on selection and such so little to say
W	misclassification will be limited. Cases have been histologically verified and use mobile yes/no and handedness should be answerable and correctly assigned
X1	yes
X2	very limited and short list
Y	Irish glioma patients
Z	bit overstated given the very small numbers

Table F28 Extractions from Salahaldin AH and Bener A. Long-term and frequent cellular phone use and risk of acoustic neuroma. Int Tinnitus J, 2006; 12(2): 145-148.[110]

A1	interest in descriptive epi of acoustic neuromas, no clear exposure hypothesis but some mention of mobile phones
A2	not obvious
A3	not obvious
B1	case-series
B2	no control structure at all
B3	case-control over more years
B4	unclear
B5	n.a.
C1	unclear
C2	more years, controls etc: anything really
C3	not presented
D1	n.a.
D2	n.a.
E1	too small so never a real result so unethical to conduct in the first place
E2	not mentioned
F1	all newly diagnosed patients over an unspecified period in one (main?) hospital, no controls
F2	all cases in the country and population controls in 1 to 4 ratio over more years
G1	seemingly 100%
G2	n.a.
G3	13 cases
G4	n.a.
G5	n.a.

G6	n.a.
H1	yes in the initial presentation and diagnosis of the patients
H2	n.a.
I1	unclear
I2	n.a.
J1	yes in answers to the mp questions but as they are not really used
J2	unclear
K1	yes as it is unclear if the interviewers were blinded for the location of the tumour
K2	could go either way
L1	age, sex, SEC
L2	nothing presented
M1	yes
M2	mp use
N1	questionnaire
N2	many ways
N3	personal
N4	n.a.
N5	not really
O	yes
P	yes
Q1	unclear, seemingly none
Q2	stratification, regression etc: anything really
R1	unclear
R2	anything really
S1	unclear
S2	anything really
T	there are always 13 patients in the tables
U1	incidence higher than expected no mention of mps
U2	see Annex H
U3	not addressed
U4	n.a.
V	unclear
W	n.a.
X1	bit sparse
X2	see previous
Y	limited
Z	bit overstated given the very small numbers

Table F29 Extractions from Sato Y, Akiba S, Kubo O, e.a. A case-case study of mobile phone use and acoustic neuroma risk in Japan. Bioelectromagnetics, 2010.[112]

A1	literature on acoustic neuroma and mobile phones
A2	if there is an association there should be lateralisation
A3	is there an association between laterality of acoustic neuroma and reported mobile phone use

B1	case-case or case-series
B2	yes as has non-differential recall bias
B3	is ok
B4	n.a.
B5	n.a.
C1	patients in a number of hospitals
C2	is ok as quite large
C3	not presented
D1	n.a.
D2	n.a.
E1	should be ok but burden to patients possible (likely even)
E2	not mentioned
F1	patients in named hospitals
F2	more hospitals?
G1	51%
G2	bit poor but given design not issue
G3	816 cases
G4	n.a.
G5	n.a
G6	n.a.
H1	no
H2	n.a.
I1	no, not differential
I2	n.a.
J1	no, not differential
J2	n.a.
K1	no, not differential
K2	n.a.
L1	age, sex, SES
L2	yes
M1	no, not differential
M2	n.a.
N1	questionnaire
N2	checking bills etc
N3	person-dose
N4	n.a.
N5	yes
O	yes
P	yes
Q1	regression
Q2	is ok
R1	regression coefficient
R2	is ok
S1	95% CI
S2	is ok

T	ok
U1	so effect of lateralisation seen?
U2	increased risk of acoustic neuroma was observed in cases who reported having used mobile phones on the affected ear for >20 min/day on average. Risk ratio was 2.74 (95% CI, 1.18–7.85) for use until 1 year before diagnosis and 3.08 (95% CI, 1.47–7.41) for use until 5 years before diagnosis.
U3	cannot be seen
U4	slightly
V	slightly
W	slightly
X1	ok
X2	no
Y	similar countries
Z	ok

Ecological studies

Table F30 Extractions from Cook A, Woodward A, Pearce N, e.a. Cellular telephone use and time trends for brain, head and neck tumours. N Z Med J, 2003; 116(1175): U457.[115]

A1	controversy about mp and tumours and now increasing use of mp
A2	if mp causes tumours we might start seeing it in cancer incidence
A3	what is the pattern in cancer incidence and what is the pattern in mp use
B1	ecological
B2	ok bar for inherent limitations
B3	ok but longer duration
B4	assumption was that as of 1987 mps started to be used so (theoretically) 11 yrs
B5	real use started up since 1995 so real fu was ca 3 yrs
C1	nationwide
C2	ok
C3	not presented
D1	n.a.
D2	n.a.
E1	identification of vulnerable subgroups but relatively minor issue, privacy as no consent possible
E2	not mentioned
F1	cancer registry (nationwide) and national data on mp subscriptions
F2	ok
G1	n.a.
G2	n.a.
G3	n.a.
G4	n.a.
G5	n.a.
G6	12 yrs: 1986-1998
H1	no
H2	n.a.
I1	n.a.
I2	n.a.

J1	no
J2	n.a.
K1	no
K2	n.a.
L1	age, sex, SEC
L2	age and sex were
M1	no
M2	n.a.
N1	national data on mp subscriptions
N2	ok
N3	population
N4	9% at end of observation period
N5	not really
O	no
P	no
Q1	standardisation (unclear if direct or indirect)
Q2	ok
R1	trend & regression analysis
R2	ok
S1	not presented
S2	95%CI
T	probably ok given national registry data
U1	no evidence of an increase in brain tumour incidence in since with use of mps
U2	no increase in aa incidence (around10/100000 for bt's)
U3	as well as possible
U4	n.a.
V	has been taken care of
W	n.a.
X1	ok
X2	no
Y	somewhat
Z	yes

Table F31 Extractions from Röösli M, Michel G, Kuehni CE, e.a. Cellular telephone use and time trends in brain tumour mortality in Switzerland from 1969 to 2002. Eur J Cancer Prev, 2007; 16(1): 77-82.[121]

A1	controversy about mp and tumours and now increasing use of mp
A2	if mp causes tumours we might start seeing it in mortality
A3	was the mortality for brain tumours higher in a period with (predicted use of) mps than in a previous one without
B1	ecological
B2	ok bar for inherent limitations
B3	cancer incidence based study?
B4	assumption was that as of 1987 mps started to be used so (theoretically) 15 yrs
B5	real use started up since 1995 so real fu was ca 7 yrs

C1	nationwide
C2	ok
C3	not presented
D1	n.a.
D2	n.a.
E1	identification of vulnerable subgroups but relatively minor issue, privacy as no consent possible
E2	not mentioned
F1	national mortality data and national mp stats plus 2 surveys on mp use
F2	cancer registry data
G1	n.a.
G2	n.a.
G3	n.a.
G4	n.a.
G5	n.a.
G6	33 years: 1969-2002
H1	no
H2	n.a.
I1	n.a.
I2	n.a.
J1	no
J2	n.a.
K1	no
K2	n.a.
L1	age, sex, SEC
L2	age and sex were
M1	no
M2	n.a.
N1	national data on mp subscriptions and supporting surveys
N2	commercial verification but it is ok
N3	population
N4	around 0% till ca 1988, 20% in ca 1998, ca 70% in 2002
N5	not really
O	no
P	no
Q1	standardisation (unclear if direct or indirect)
Q2	ok
R1	predicted mortality rates vs. observed mortality rates
R2	this is ok
S1	95%CI
S2	ok
T	probably ok given national registry data
U1	no evidence of an increase in brain tumour mortality in since with use of mps
U2	no increase in aa rates in relevant ages for bt's
U3	as well as possible
U4	n.a.

V	has been taken care of
W	n.a.
X1	ok
X2	no
Y	somewhat
Z	yes

Table F32 Extractions from Czerninski R, Zini A, and Sgan-Cohen HD. Risk of parotid malignant tumors in Israel (1970-2006). Epidemiology, 2011; 22(1): 130-131.[129]

A1	possibly ass parotid tumours and mp use
A2	if an increase in mps then an increase in parotid land tumours
A3	do trends seem to go in the expected direction but no trends for mps use given
B1	ecological
B2	somewhat but always limited as no association at personal level possible
B3	unclear
B4	unclear
B5	unclear but possibly too short
C1	whole population of Israel
C2	more countries
C3	not presented and n.a.
D1	n.a.
D2	n.a.
E1	involuntary
E2	as anonymous not an issue
F1	cancer registry of Israel
F2	is OK but more countries would be better
G1	n.a.
G2	n.a.
G3	n.a.
G4	n.a.
G5	n.a.
G6	n.a.
H1	no as all data
H2	n.a.
I1	no as routine data
I2	n.a.
J1	no as routine data
J2	n.a.
K1	no
K2	n.a.
L1	age, sex and SEC
L2	age and sex yes
M1	not really
M2	n.a.

N1	vague data on mobile phone subscriptions/plans/ownership
N2	actual data
N3	no
N4	n.a.
N5	no not really
O	no
P	no
Q1	age standardised rates
Q2	is ok
R1	not done
R2	many options
S1	not done
S2	many options
T	can't be judged but assumed yes
U1	marked increase in incidence of parotid gland tumours
U2	as no association measured not relevant
U3	can't be judged
U4	can't be shown
V	some level of confounding by SEC possible
W	n.a.
X1	ok
X2	no
Y	Israel and similar countries
Z	is ok

Table F33 Extractions from de Vocht F, Burstyn I, and Cherrie JW. Time trends (1998-2007) in brain cancer incidence rates in relation to mobile phone use in England. Bioelectromagnetics, 2011; DOI 10.1002/bem.20648.[130]

A1	aAssess if there are trends in incidence of brain tumours in association with trends in mp use
A2	if there is an association then incidence of brain tumours should be increasing (soon)
A3	is there a trend
B1	ecological
B2	as no association at personal level measured it is always limited
B3	cohort
B4	n.a.
B5	n.a.
C1	all country
C2	n.a
C3	n.a.
D1	n.a.
D2	n.a.
E1	involuntary participation
E2	as all information is anonymous limited problems so not relevant
F1	cancer registry
F2	is ok

G1	n.a.
G2	n.a.
G3	n.a.
G4	n.a.
G5	n.a.
G6	n.a.
H1	no
H2	n.a.
I1	no
I2	n.a.
J1	no
J2	n.a.
K1	no
K2	n.a.
L1	age, sex and EC
L2	age and sex were
M1	limited
M2	n.a.
N1	trends in mp ownership
N2	actual use data
N3	population
N4	n.a.
N5	no
O	no
P	no
Q1	age and sex standardisation
Q2	ok
R1	not done
R2	regression
S1	no
S2	95% CI
T	should be ok as routine data but cannot be checked
U1	no evidence of an increasing trend
U2	reasonably stable numbers
U3	can't tell
U4	n.a.
V	SEC and detection bias?
W	n.a.
X1	yes
X2	ok
Y	similar countries
Z	is OK

Table F34 Extractions from de Vocht F. Cell phones and parotid cancer trends in England. Epidemiology, 2011; 22(4): 608-609.[134]

A1	given use of mps is there a trend in parotid gland tumours
A2	if there is an association, trends should be starting to go up (if the effect is reasonably immediate)
A3	is there a trend
B1	ecological
B2	is inherently limited
B3	cohort
B4	n.a.
B5	n.a.
C1	n.a.
C2	n.a.
C3	n.a.
D1	n.a.
D2	n.a.
E1	involuntary participation s routine data used
E2	as is anonymous not much of an issue and often signed off by ethics committees without much of a problem
F1	cancer registry data
F2	is ok
G1	n.a.
G2	n.a.
G3	n.a.
G4	n.a.
G5	n.a.
G6	n.a.
H1	n.a.
H2	n.a.
I1	n.a.
I2	n.a.
J1	n.a.
J2	n.a.
K1	n.a.
K2	n.a.
L1	age, sex and SEC
L2	age and sex yes
M1	n.a.
M2	n.a.
N1	trend in mp ownership
N2	actual use
N3	population
N4	n.a.
N5	no
O	no
P	no

Q1	age and sex standardised
Q2	is OK
R1	not done
R2	regression
S1	no
S2	n.a.
T	presumed ok
U1	there is increase
U2	2-fold increase in incident cases
U3	no: increase started before widespread use of mp
U4	n.a.
V	SES? detection bias?
W	n.a.
X1	ok
X2	no
Y	similar countries
Z	ok

Table F35 Extractions from Deltour I, Auvinen A, Feychting M, e.a. Mobile phone use and incidence of glioma in the Nordic countries 1979-2008: Consistency check. Epidemiology, 2012; 23(2): 301-307.[135]

A1	if mobile phone use causes brain tumors, the marked increase in prevalence of use over a 20-year period will eventually influence the time trends of the incidence rates of these tumors. (quote)
A2	compare trends in glioma vs. trends in use of mobile phone
A3	as vague association it might see something, duration of mps is possibly long enough
B1	ecological
B2	reasonably
B3	cohort as it would actually measure use rather than compare groups
B4	1979-2008: only in last 10 years have almost all had mobile phones, in Nordic countries several years earlier than elsewhere: still bit short?
B5	getting there
C1	all cases in Denmark, Finland, Norway and Sweden
C2	should have been big enough
C3	not stated
D1	n.a.
D2	n.a.
E1	effectively involuntary participation as routine data are used
E2	if anonymous as is here, generally not considered a problem if no individuals can be traced
F1	cancer registries in all 5 countries
F2	good source
G1	n.a.
G2	n.a.
G3	n.a.
G4	n.a.
G5	n.a.
G6	n.a.

H1	no unless not diagnosed but mortality is often also included if post-mortem diagnosis
H2	n.a.
I1	n.a.
I2	n.a.
J1	n.a.
J2	n.a
K1	n.a.
K2	n.a.
L1	age and sex and possibly SEC
L2	age and sex were and were corrected for
M1	no not really
M2	n.a.
N1	as in population wide no. of subscriptions/plans etc
N2	this is quite crude: actual use would be better
N3	no
N4	n.a.
N5	not really
O	n.a.
P	yes in the mobile phone use data
Q1	age and sex standardised rates
Q2	is ok
R1	log linear model
R2	is ok
S1	95% CI
S2	is ok
T	yes
U1	there is no upward turn in the trends
U2	results compatible with those of studies showing no effect but INTERPHONE seize effects could still be true
U3	weak as it is possibly still too early
U4	n.a.
V	SEC is not controlled for as those higher up get diagnosed more and would have had phones earlier but this is all weak
W	n.a.
X1	ok
X2	no
Y	similar countries such as northern Europe
Z	ok

Table F36 Extractions from Little MP, Rajaraman P, Curtis RE, e.a. Mobile phone use and glioma risk: comparison of epidemiological study results with incidence trends in the United States. BMJ, 2012; 344: e1147.[133]

A1	looking a trends in brain tumour incidence
A2	is mp use is associated with brain tumours the trends should be starting to go up
A3	is there a trend
B1	ecological
B2	kind of yes

B3	cohort
B4	n.a.
B5	n.a.
C1	n.a.
C2	n.a.
C3	n.a.
D1	n.a.
D2	n.a.
E1	involuntary as routine data use
E2	anonymous data so ethics committee mostly say yes
F1	cancer registry data
F2	is ok, longer period would not have helped
G1	n.a.
G2	n.a.
G3	n.a.
G4	n.a.
G5	n.a.
G6	n.a.
H1	n.a.
H2	n.a.
I1	n.a.
I2	n.a.
J1	n.a.
J2	n.a.
K1	n.a.
K2	n.a.
L1	n.a.
L2	n.a.
M1	n.a.
M2	n.a.
N1	n.a.
N2	n.a.
N3	n.a.
N4	n.a.
N5	n.a.
O	n.a.
P	n.a.
Q1	age standardised rates
Q2	is ok
R1	regression
R2	is ok
S1	95% CI
S2	is ok
T	should be ok as routine data

U1	raised risks of glioma with mobile phone use, as reported by one (Swedish) study forming the basis of the IARC's re-evaluation of mobile phone exposure, are not consistent with observed incidence trends in US population data, although the US data could be consistent with the modest excess risks in the Interphone study.
U2	n.a.
U3	not obvious
U4	not possible
V	n.a.
W	n.a.
X1	ok
X2	no
Y	similar countries
Z	ok

Annex **G**

Results of the evaluation of quality of the studies

The results of the scores per question are presented in Tables G1, G2 and G3. These are the combined scores for the two evaluators (IK and MC). These final scores were the result of independent scoring, comparison and mediation (EvR).

Table G1 Results of the quality scores for the cohort studies.

	Question																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Dreyer et al. (1999)[47]	c	c	d	c	a	c	c	a	b	d	a	a	c	b	b	b	b
Schüz et al. (2011)[51]	c	c	d	c	e	c	c	a	b	b	a	a	c	b	b	b	a
Frei et al. (2011)[52]	c	c	d	c	e	c	c	a	b	b	a	a	c	b	b	b	a

Table G2 Results of the quality scores for the case-control studies.

	Question																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Hardell et al. (2004)[69]	b	b	a	a	e	a	b	c	h	e	c	b	a	a	b	b	c
Hardell et al. (2009)[66]	b	b	b	b	e	a	b	c	h	e	c	b	a	a	b	b	c
Hardell et al. (2011)[68]	b	b	b	b	e	a	b	c	h	e	c	b	a	a	b	b	c
Söderqvist et al. (2012)[72]	b	b	b	b	e	a	b	c	h	e	b	a	a	b	b	b	c
Lönn et al. (2006)[82]	b	b	b	b	a	a	b	c	f	e	c	b	b	a	b	b	b
Sadetzki et al. (2008)[85]	b	a	b	a	e	a	b	c	f	e	c	b	b	a	b	b	b
Takebayashi et al. (2008)[88]	a	a	b	b	e	a	b	c	h	e	c	b	b	a	b	b	c

Schoemaker et al. (2009)[89]	b	b	a	b	e	a	b	c	f	e	c	b	b	a	b	b	b
INTERPHONE (2010)[93]	b	b	a	a	e	a	b	c	f	e	c	b	b	a	b	b	b
INTERPHONE (2011)[94]	b	b	b	a	e	a	b	c	f	e	c	b	b	a	b	b	b
Muscat et al. (2000)[96]	a	a	a	a	e	a	b	c	f	e	c	a	a	a	b	b	a
De Roos et al. (2001)[97]	a	a	a	a	a	a	b	c	b	a	a	a	a	a	a	a	c
Stang et al. (2001)[98]	b	b	b	a	e	a	b	c	b	b	a	a	a	a	a	a	c
Inskip et al. (2001)[99]	a	a	c	b	e	a	b	c	c	d	c	a	a	a	b	b	c
Auvinen et al. (2002)[100]	b	b	c	c	e	c	b	a	f	b	a	b	c	b	b	b	b
Muscat et al. (2002)[101]	a	a	a	a	e	a	b	c	b	c	c	a	a	a	b	b	a
Warren et al. (2003)[102]	a	a	a	a	a	a	b	c	e	d	c	a	a	a	a	a	c
Gousias et al. (2007)[103]	a	a	a	a	e	a	b	c	b	c	a	a	a	a	a	a	c
Stang et al. (2009)[104]	b	b	c	a	c	a	b	c	f	d	c	b	b	a	b	b	b
Spinelli et al. (2010)[105]	a	a	a	b	e	a	b	c	b	c	a	a	a	a	a	a	c
Duan et al. (2011)[106]	a	a	a	a	e	a	b	c	h	e	c	b	a	a	b	b	c
Baldi et al. (2011)[107]	b	b	a	b	e	a	b	c	b	a	a	a	a	b	b	b	c
Aydin et al. (2011)[108]	b	b	b	b	e	a	b	c	e	d	c	b	b	a	b	b	c

Table G3 Results of the quality scores for the case-case studies.

	Question																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Ali Kahn et al. (2003)[109]	c	c	d	c	e	a	b	c	b	a	b	a	a	a	a	a	c
Salahaldin & Bener (2006)[110]	c	c	d	c	e	a	a	a	b	a	a	a	a	a	a	a	c
Sato et al. (2010)[112]	c	c	d	c	e	b	b	b	c	e	c	b	a	a	b	b	c

Annex **H**

Results from the selected publications

This Annex presents all the detailed results in tables, organized by tumour type. Statistically significant increased risks are in boldface type and highlighted in yellow, statistically significantly decreased risks are highlighted in light blue only.

The publications of Hardell et al.[64-66,68,69,72,165] and Stang et al.[98] from which the data are obtained do not provide information on the numbers of cases and controls in the reference categories, nor can these be derived.

Abbreviations used:
Obs / Exp: observed and expected numbers of cases;
SIR: standardized incidence ratio;
SMR: standardized mortality ratio;
CI: confidence interval;
Ca / Co: numbers of cases and controls;
OR: odds ratio.

Brain tumours, not specified

Table H1 Brain tumours (not otherwise specified) and duration of use, results corrected for confounders.

Cohort	Exposure	Person years	Obs / Exp	SMR	95%CI
	Time since 1st use (yrs)				
Dryer et al. (1999)[47] (adults)	≤3	88152	1 / --	1.4	
	>3	14447	1 / --	8.4	

Case-control	Time since 1st use (yrs)	Ca / Co	OR	95%CI
Muscat et al. (2000)**[96]** (adults)	0	403 / 306	1.0	
	1	21 / 30	0.7	0.4 -1.3
	2-3	28 / 24	1.1	0.6 -2.0
	≥4	17 / 22	0.7	0.4 -1.4
Aydin et al. (2011)[108] (children)	0	158 / 317	1.0	
	≤3.3	95 / 165	1.35	0.89-2.04
	3.3-5.0	53 / 83	1.47	0.87-2.49
	>5.0	46 / 81	1.26	0.70-2.28

Table H2 Brain tumours (not otherwise specified) and cumulative use, results corrected for confounders.

Case-control	Exposure	Ca / Co	OR	95%CI
	Cumulative call time (h)			
Muscat et al. (2000)**[96]** (adults)	0	403 / 306	1.0	
	>0-≤8.7	17 / 18	1.0	0.5-2.0
	>8.7-≤60	12 / 19	0.6	0.3-1.3
	>60-≤480	19 / 19	0.9	0.5-1.8
	>480	14 / 19	0.7	0.3-1.4
Aydin et al. (2011)[108] (children)	0	158 / 317	1.0	
	≤35	94 / 162	1.33	0.89-2.01
	36-144	48 / 81	1.44	0.85-2.44
	>144	49 / 81	1.55	0.86-2.82
	Cumulative number of calls			
	0	158 / 317	1.0	
	≤936	94 / 163	1.34	0.89-2.02
	937-2638	50 / 80	1.47	0.86-2.51
	>2638	47 / 79	1.42	0.79-2.53

Table H3 Brain tumours (not otherwise specified) in children and laterality, results corrected for confounders.

Aydin et al. (2011)[108]	Ipsilateral			Contralateral			Central / unknown		
	Ca / Co	OR	95%CI	Ca / Co	OR	95%CI	Ca / Co	OR	95%CI
Time since 1st use (yrs)									
0	146 / 267	1.0		141 / 257	1.0		147 / 257	1.0	
≤3.3	29 / 40	1.73	0.87-3.44	24 / 36	1.86	0.82-4.21	36 / 68	0.81	0.41-1.57
3.3-5.0	15 / 25	1.53	0.62-3.76	16 / 16	**3.27**	**1.10-9.68**	19 / 31	0.82	0.34-1.94
>5.0	18 / 18	2.75	0.93-8.06	9 / 11	2.39	0.67-8.57	13 / 36	0.36	0.13-1.02
Cumulative call time (h)									
0	146 / 267	1.0		141 / 257	1.0		147 / 257	1.0	
≤35	28 / 48	1.46	0.74-2.91	19 / 35	1.65	0.73-3.74	40 / 59	0.97	0.50-1.85
36-155	17 / 17	**2.66**	**1.05-6.71**	13 / 17	**4.14**	**1.25-13.7**	15 / 37	0.43	0.18-1.03
>155	17 / 18	2.64	0.92-7.59	16 / 9	**6.19**	**1.57-24.4**	12 / 36	0.24	0.08-0.73
Cumulative number of calls									
0	146 / 267	1.0		141 / 257	1.0		147 / 257	1.0	
≤936	30 / 46	1.59	0.81-3.12	22 / 38	1.74	0.78-3.90	37 / 57	0.98	0.51-1.92
937-2638	13 / 19	2.06	0.72-5.93	14 / 12	**5.37**	**1.54-18.7**	17 / 38	0.54	0.24-1.23
>2638	19 / 18	**2.91**	**1.09-7.76**	12 / 11	**4.82**	**1.21-19.2**	13 / 37	0.31	0.11-0.87

Glioma

Table H4 Glioma and duration of use, results corrected for confounders.

Cohort	Gender	Exposure	Cases	IRR	95%CI
		Time since subscription (yrs)			
Frei et al. (2011)[52]	Males	0	4397	1.00	
		1-4	85	1.20	0.96-1.50
		5-9	122	1.05	0.87-1.26
		≥10	117	1.04	0.85-1.26
		10-12	80	1.06	0.85-1.34
		≥13	37	0.98	0.70-1.36
	Females	0	5486	1.00	
		1-4	8	0.87	0.43-1.75
		5-9	14	1.02	0.60-1.72
		≥10	10	1.04	0.56-1.95
Case-control	Type of phone	Exposure	Ca / Co	OR	95%CI
		Time since 1st use (yrs)			
Hardell et al. (2011)[68] All glioma	Mobile	>1-5	250 / 571	1.1	0.9 -1.4
		>5-10	156 / 286	1.3	0.99-1.6
		>10	123 / 106	**2.5**	**1.8 -3.4**
	Cordless	>1-5	205 / 463	1.2	0.9 -1.5
		>5-10	152 / 244	**1.5**	**1.2 -1.9**

		>10	45 / 55	**1.7**	**1.1 -2.6**
Astrocytoma (all)	Mobile	>1-5	197 / 571	1.2	0.9 -1.5
		>5-10	132 / 286	**1.4**	**1.04-1.8**
		>10	110 / 106	**2.7**	**1.9 -3.7**
	Cordless	>1-5	157 / 463	1.2	0.9 -1.5
		>5-10	135 / 244	**1.7**	**1.3 -2.2**
		>10	41 / 55	**1.8**	**1.2 -2.9**
Hardell et al. (2011)[165] 30-59 y old	Mobile (cordless = unexposed)	≥10	56 / 74	**1.79**	**1.19-2.70**
INTERPHONE study group (2010)[93]	Mobile (excl. cordless)	0	1042 / 1078	1.00	
		1-1.9	156 / 247	0.62	0.46-0.81
		2-4	644 / 725	0.84	0.70-1.00
		5-9	614 / 690	0.81	0.60-0.97
		≥10	252 / 232	0.98	0.76-1.26
Cardis et al. (2011)[114]	Mobile	0	14 / 178	1.00	
	Case-case*	1-4	12 / 133	1.37	0.59-3.19
		5-9	7 / 147	0.72	0.27-1.90
		≥10	11 / 54	**2.80**	**1.13-6.94**
Larjavaara et al. (2011) [113]	Mobile	0	**	1.00	
	Case-case	1.5-4		0.85	0.57-1.25
		5-9		0.71	0.43-1.18
		≥10		0.85	0.39-1.86
		Duration of subscription (yrs)			
Auvinen et al. (2002)[100]	Mobile analogue	0	172 / 921	1.0	
		<1	4 / 13	1.6	0.5 -5.1
		1-2	11 / 24	**2.4**	**1.2 -5.1**
		>2	11 / 31	2.0	1.0 -4.1
	Mobile digital	0	188 / 938	1.0	
		<1	3 / 20	0.8	0.2 -2.6
		1-2	7 / 25	1.4	0.6 -3.4
		>2	0 / 6	0.0	-
	Mobile all	0	-	1.0	
		<1	-	1.2	0.5 -3.0
		1-2	-	1.6	0.8 -2.9
		>2	-	1.7	0.9 -3.5
Inskip et al. (2001)[99]	Mobile (excl. cordless)	0	398 / 625	1.0	
		<0.5	24 / 56	0.6	0.3 -1.1
		0.5-<3	31 / 55	0.9	0.5 -1.6
		>3	30 / 60	0.9	0.5 -1.5
		>5	11 / 31	0.6	0.3-1.4
Muscat et al. (2000)[96]	Mobile	>1	41 / 76	0.8	0.5-1.2

* Case-case study: cases with tumour within most exposed area vs. cases with tumour outside most exposed area
** Case-case study, no numbers provided

Table H5 Glioma and cumulative use, results corrected for confounders.

	Type of phone	Exposure	Ca / Co	OR	95%CI
		Cumulative call time (h)			
Hardell et al. (2011)[68] All glioma	Mobile	1-1000	427 / 879	**1.2**	**1.03-1.5**
		1001–2000	44 / 51	**1.8**	**1.2 -28**
		>2000	58 / 33	**3.2**	**2.0 -5.1**
	Cordless	1-1000	297 / 643	1.2	0.95 -1.4
		1001-2000	50 / 60	**2.0**	**1.4 -3.1**
		>2000	55 / 59	**2.2**	**1.4 -3.2**
Astrocytoma	Mobile	1-1000	346 / 879	**1.3**	**1.1 -1.6**
		1001-2000	42 / 51	**2.2**	**1.4 -3.5**
		>2000	51 / 33	**3.4**	**2.1 -5.6**
	Cordless	1-1000	240 / 643	1.2	0.96-1.5
		1001-2000	45 / 60	**2.3**	**1.5 -3.6**
		>2000	48 / 59	**2.4**	**1.5 -3.6**
Hardell et al. (2011)[165] 30-59 y old	Mobile (cordless = unexposed)	≥1640	29 / 37	**1.75**	**1.02-3.00**
INTERPHONE study group (2010)[93]	Mobile (excl. cordless)	0	1042 / 1078	1.0	
		<5	141 / 197	0.70	0.52-0.94
		5-12.9	145 / 198	0.71	0.53-0.94
		13-30.9	189 / 179	1.05	0.79-1.38
		31-60.9	144 / 196	0.74	0.55-0.98
		61-114.9	171 / 193	0.81	0.61-1.08
		115-199.9	160 / 194	0.73	0.54-0.98
		200-359.9	158 / 194	0.76	0.57-1.01
		360-734.9	189 / 205	0.82	0.62-1.08
		735-1639.9	159 / 184	0.71	0.53-0.96
		≥1640	210 / 154	**1.40**	**1.03-1.89**
		≥1640 (excl. >5 h/d)	169 / 134	1.27	0.92-1.75
		Cumulative number of calls (x 100)			
INTERPHONE study group (2010)[93]	Mobile (excl. cordless)	0	1042 / 1078	1.0	
		<1.5	147 / 182	0.74	0.55–0.99
		1.5-3.4	141/ 200	0.71	0.54–0.95
		3.5-7.4	161 / 201	0.76	0.58–1.00
		7.5-13.9	174 / 179	0.90	0.68–1.20
		14-25.4	180 / 206	0.78	0.59–1.02
		25.5-41.4	156/ 190	0.83	0.62–1.10
		41.5-67.9	163 / 194	0.71	0.53–0.94
		68-127.9	186 / 200	0.93	0.70–1.23
		128-269.9	193 / 180	0.96	0.72–1.28
		≥270	165 / 162	0.96	0.71–1.31

		Cumulative call time (h)			
Cardis et al. (2011)[114]	Mobile	0	196 / 617	1.00	
		<13	44 / 174	0.83	0.55-1.26
		13-60.9	68 / 223	0.93	0.65-1.32
		61-199.9	63 / 264	0.66	0.46-0.96
		200-734.9	90 / 237	1.07	0.76-1.50
		≥735	90 / 205	1.25	0.88-1.77
		Total cumulative specific energy (J/kg)			
	Mobile, all users	0	196 / 617	1.00	
		<76.7	67 / 265	0.76	0.53-1.09
		76.7-284	68 / 227	0.94	0.66-1.35
		284.1-978.9	60 / 207	0.80	0.54-1.18
		979-3123.9	57 / 197	0.89	0.61-1.30
		≥3124	103 / 207	1.35	0.96-1.90
	Mobile, use ≥7 y in past	0	421 / 1445	1.00	
		<76.7	20 / 63	1.11	0.61-2.02
		76.7-284	23 / 53	1.53	0.85-2.78
		284.1-978.9	24 / 53	1.50	0.81-2.78
		979-3123.9	25 / 49	1.69	0.91-3.13
		≥3124	38 / 57	**1.91**	**1.05-3.47**
		Cumulative call time (h)			
	Mobile Case-case*	0	14 / 178	1.00	
		<39	6 / 65	1.19	0.40-3.51
		39-220	4 / 67	0.93	0.27-3.14
		220-520	5 / 68	1.38	0.42-4.53
		520-1147	10 / 66	2.55	0.94-6.91
		≥1147	5 / 68	0.99	0.30-3.27
Larjavaara et al. (2011)[113]	Mobile	0	**	1.00	
		0.001-46		0.82	0.51-1.31
		46-339		0.97	0.60-1.56
		>339		0.58	0.35-0.96
Inskip et al. (2001)[99]	Mobile (excl. cordless)	0	398 / 625	1.0	
		< 13	26 / 55	0.8	0.4 -1.4
		13-100	26 / 58	0.7	0.4 -1.3
		>100	32 / 54	0.9	0.5 -1.6
		>500	11 / 27	0.5	0.2-1.3
		Cumulative potential use (hour-years)			
Spinelli et al. (2010)[105]	Mobile	0	37 / 42	1.0	
		≤ 4	8 / 11	0.86	0.30-2.44
		4-36	58 / 48	1.45	0.75-2.80

		≥ 36	13 / 15	1.07	0.41-2.82
		Cumulative use (minute-years)			
Gousias et al. (2009)[103]	Mobile	Not provided	41 / 82	1.00	0.99-1.01

* Case-case study: cases with tumour within most exposed area vs. cases with tumour outside most exposed area
** Case-case study, no numbers provided

Table H6 Glioma and laterality, results corrected for confounders.

		Ipsilateral			Contralateral		
	Exposure	Ca / Co	OR	95%CI	Ca / Co	OR	95%CI
	Time since first use (yrs)						
Hardell et al. (2009)[66] * Astrocytoma	Mobile > 1	229 / 374	**2.0**	**1.5 - 2.5**	98 / 308	1.0	0.7 -1.4
	Mobile >10	50 / 45	**3.3**	**2.0 - 5.4**	26 / 29	**2.8**	**1.5 -5.1**
	Cordless >1	167 / 309	**1.8**	**1.4 - 2.4**	81 / 235	1.2	0.8 -1.6
	Cordless >10	19 / 15	**5.0**	**2.3 -11**	8 / 20	1.4	0.6 -3.5
Hardell et al. (2011)[165] 30-59 y old Glioma	Mobile ≥10 (cordless = unexposed)	35 / 30	**2.29**	**1.33-3.79**	20 / 24	1.71	0.89-3.28
INTERPHONE (2010)[93] Glioma	0	773 / 832	1.00		721 / 718	1.00	
	1-1.9	69 / 91	0.77	0.49-1.20	24 / 58	0.34	0.20-0.71
	2-4	261 / 300	0.80	0.62-1.04	145 / 178	0.81	0.57-1.14
	5-9	239 / 280	0.81	0.62-1.05	110 / 145	0.65	0.44-0.95
	≥10	108 / 82	1.21	0.82-1.80	49 / 56	0.70	0.42-1.15
	Cumulative call time (h)						
Hardell et al. (2011)[165] 30-59 y old Glioma	≥1640	20 / 18	**2.18**	**1.09-4.35**	8 / 11	1.48	0.57-3.87
INTERPHONE (2010)[93] Glioma	0	773 / 838	1.00		721 / 718	1.00	
	<5	64 / 76	0.83	0.53-1.31	23 / 50	0.43	0.22-0.84
	5-114.9	253 / 321	0.75	0.58-0.97	135 / 170	0.74	0.53-1.03
	115-359.9	121 / 147	0.75	0.53-1.07	67 / 93	0.62	0.39-0.97
	360-1639.9	139 / 147	0.88	0.62-1.24	64 / 93	0.60	0.38-0.94
	≥1640	100 / 62	**1.96**	**1.22-3.16**	39 / 31	1.25	0.64-2.42
Larjavaara et al. (2011)[113]	**	51 / 195	0.80	0.52-1.22	37 / 133	0.77	0.47-1.24
	Cumulative number of calls (x100)						
INTERPHONE (2010)[93] Glioma	0	773 / 838	1.00		721 / 718	1.00	
	<1.5	61 / 71	0.66	0.41-1.07	26 / 44	0.61	0.32-1.17
	1.5-25.4	263 / 318	0.80	0.62-1.04	138 / 179	0.69	0.49-0.96
	25.5-67.9	115 / 159	0.69	0.49-0.97	64 / 91	0.59	0.38-0.92
	68-269.9	164 / 145	1.09	0.78-1.52	72 / 86	0.81	0.51-1.28
	≥270	74 / 60	1.51	0.91-2.51	28 / 37	0.61	0.32-1.18

* This publication groups ipsilateral and ipsi/contralateral, so the subjects that call at the side of the tumour and those who do this and alternate it with the other side are grouped, the other publications do not group these.
** Case-case study; comparison only for ipsi- vs. contralateral use.

Meningioma

Table H7 Meningioma and duration of use, results corrected for confounders.

Cohort	Gender	Exposure	Cases	IRR	95%CI
		Time since subscription (yrs)			
Frei et al. (2011)[52]	Male	1-4	15	0.92	0.55-1.56
		5-9	14	0.56	0.33-0.96
		≥10	21	0.90	0.57-1.42
	Female	1-4	9	1.08	0.56-2.09
		5-9	13	1.04	0.60-1.79
		≥10	8	0.93	0.46-1.87
Case-control	Type of phone	Exposure	Ca / Co	OR	95%CI
		Time since 1st use (yrs)			
Hansson Mild et al. (2007)[65]	Analogue	>1-5	NR*	1.2	0.8 -1.8
		>5-10	NR	1.2	0.8 -1.8
		>10	NR	**1.6**	**1.02-2.5**
	Digital	>1-5	NR	1.0	0.8 -1.3
		>5-10	NR	1.1	0.8 -1.6
		>10	NR	1.3	0.5 -3.2
	Cordless	>1-5	NR	1.0	0.8 -1.3
		>5-10	NR	**1.3**	**1.01-1.8**
		>10	NR	1.6	0.9 -2.8
INTERPHONE study group (2010)[93]	Mobile (excl. cordless)	0	1147 / 1174	1.0	
		1-1.9	178 / 214	0.90	0.68-1.18
		2-4	557 / 675	0.77	0.65-0.92
		5-9	417 / 487	0.76	0.63-0.93
		≥10	110 / 112	0.83	0.61-1.14
		Duration of subscription (yrs)			
Auvinen et al. (2002)[100]	Mobile analogue	0	121 / 615	1.0	
		<1	3 / 7	2.3	0.6 -9.2
		1-2	3 / 10	1.6	0.4 -6.1
		>2	2 / 11	1.0	0.2 -4.4
	Mobile digital	0	126 / 623	1.0	
		<1	1 / 9	0.6	0.1 -4.4
		1-2	2 / 10	1.0	0.2 -4.6
		>2	0 / 1	0.0	-
	Mobile all	0	NR	1.0	
		<1	NR	1.5	0.5 -4.6
		1-2	NR	1.2	0.4 -3.6
		>2	NR	0.8	0.2 -3.5

		Time since 1st use (yrs)			
Inskip et al. (2001)[99]	Mobile (excl. cordless)	0	165 / 625	1.0	
		<0.5	6 / 56	0.5	0.2 -1.4
		0.5-<3	12 / 55	0.8	0.4 -1.9
		≥3	14 / 60	1.1	0.5 -2.5
		≥5	6 / 31	0.9	0.3-2.7

* NR: not reported

Table H8 Meningioma and cumulative use, results corrected for confounders.

	Type of phone	Exposure	Ca / Co	OR	95%CI
		Cumulative call time (h)			
INTERPHONE study group (2010)[93]	Mobile (excl. cordless)	0	1147 / 1174	1.00	
		<5	160 / 197	0.90	0.69-1.18
		5-12.9	142 / 159	0.82	0.61-1.10
		13-30.9	144 / 194	0.69	0.52-0.91
		31-60.9	122 / 145	0.69	0.51-0.94
		61-114.9	129 / 162	0.75	0.55-1.00
		115-199.9	96 / 155	0.69	0.50-0.96
		200-359.9	108 / 133	0.71	0.51-0.98
		360-734.9	123 / 133	0.90	0.66-1.23
		735-1639.9	108 / 103	0.76	0.54-1.08
		≥1640	130 / 107	1.15	0.81-1.62
		Cumulative number of calls (x 100)			
INTERPHONE study group (2010)[93]	Mobile (excl. cordless)	0	1147 / 1174	1.00	
		<1.5	159 / 180	0.95	0.72–1.27
		1.5-3.4	136 / 182	0.62	0.46–0.83
		3.5-7.4	148 / 176	0.90	0.68–1.19
		7.6-13.9	176 / 173	0.80	0.61–1.07
		124-25.4	122 / 181	0.60	0.45–0.81
		25.5-41.4	111 / 126	0.81	0.58–1.13
		41.5-67.9	129 / 146	0.79	0.58–1.09
		68-127.9	134 / 126	0.92	0.67–1.26
		128-269.9	100 / 100	0.81	0.57–1.16
		≥270	80 / 98	0.80	0.55–1.17
		Cumulative call time (h)			
Inskip et al. (2001)[99]	Mobile (excl. cordless)	0	165 / 625	1.0	
		<13	8 / 55	0.7	0.3 -1.9
		13-100	13 / 58	1.1	0.5 -2.4
		>100	11 / 54	0.7	0.3 -1.7
		>500	6 / 27	0.7	0.2-2.4

Table H9 Meningioma, analysis as continuous variables (Hansson Mild et al. (2007)[65]).

Variable	Type of phone	OR	95% CI
Per 100 h of use	Digital	0.99	0.96-1.02
	Analogue	1.02	0.99 -1.05
	Cordless	1.01	0.997-1.02
Per 1 yr of use	Digital	1.02	0.98-1.06
	Analogue	**1.05**	**1.01 -1.09**
	Cordless	**1.04**	**1.01 -1.07**

Table H10 Meningioma and laterality, results corrected for confounders.

		Ipsilateral			Contralateral		
	Exposure	Ca / Co	OR	95%CI	Ca / Co	OR	95%CI
	Time since first use (yrs)						
Hardell et al. (2009)[66] [a]	Mobile >1	167 / 374	1.3	1.01-1.7	125 / 308	1.1	0.8 -1.4
	Mobile >10	18 / 45	1.6	0.9 -2.9	12 / 29	1.6	0.7 -3.3
	Cordless >1	134 / 309	1.2	0.9 -1.6	101 / 235	1.1	0.8 -1.5
	Cordless >10	11 / 15	3.0	1.3 -7.2	7 / 20	1.1	0.5 -2.9
INTERPHONE study group (2010)[93]	0	821 / 898	1.00		832 / 841	1.00	
	1-1.9	54 / 79	0.71	0.44-1.15	41 / 59	0.67	0.38-1.20
	2-4	198 / 203	0.89	0.67-1.19	118 / 196	0.54	0.39-0.76
	5-9	132 / 155	0.87	0.63-1.21	100 / 126	0.64	0.44-0.94
	≥10	40 / 42	0.88	0.52-1.47	20 / 25	0.58	0.29-1.16
	Cumulative call time (h)						
	0	821 / 828	1.00		832 / 841	1.00	
	<5	48 / 71	0.76	0.48-1.21	36 / 54	0.75	0.42-1.31
	5-114.9	185 / 209	0.86	0.65-1.15	125 / 190	0.55	0.40-0.75
	115-359.9	65 / 96	0.64	0.42-0.97	42 / 69	0.64	0.39-1.06
	360-1639.9	80 / 68	1.09	0.72-1.64	50 / 65	0.54	0.32-0.94
	≥1640	46 / 35	1.45	0.80-2.61	28 / 28	0.62	0.31-1.25
	Cumulative number of calls (x100)						
	0	821 / 891	1.00		832 / 841	1.00	
	<1.5	51 / 72	0.77	0.49-1.22	32 / 49	0.76	0.41-1.40
	1.5-25.4	187 / 229	0.80	0.60-1.05	131 / 191	0.59	0.44-0.81
	25.5-67.9	80 / 81	0.89	0.59-1.35	51 / 77	0.61	0.37-1.00
	68-269.9	76 / 61	1.22	0.77-1.95	49 / 66	0.39	0.23-0.68
	≥270	30 / 36	1.01	0.56-1.82	18 / 23	0.66	0.30-1.46

[a] This publication groups ipsilateral and ipsi/contralateral so the subjects that call at the side of the tumour and those who do this and alternate it with the other side are grouped, the other publications do not group these.

Acoustic neuroma

Table H11 Acoustic neuroma and duration of use, results corrected for confounders.

Cohort	Gender	Exposure Time since subscription (yrs)	Cases	IRR	95%CI
Schüz et al. (2011)[51]	Men	≥11	15	0.87	0.52-1.46
Case-control	Type of phone	Exposure Time since 1st use (yrs)	Ca / Co	OR	95%CI
Hansson Mild et al. (2007)[65]	Analogue	>1-5	NR	**2.3**	**1.2 -4.1**
		>5-10	NR	**3.4**	**2.1 -5.5**
		>10	NR	**3.1**	**1.7 -5.7**
	Digital	>1-5	NR	**1.4**	**1.01-2.1**
		>5-10	NR	**1.8**	**1.1 -3.0**
		>10	NR	0.6	0.1 -5.0
	Cordless	>1-5	NR	**1.5**	**1.01-2.1**
		>5-10	NR	1.5	0.96-2.4
		>10	NR	1.0	0.3 -2.9
INTERPHONE Study Group (2011)[94]	Mobile (excl. cordless)	0	462 / 837	1.00	
		1-1.9	63 / 169	0.73	0.49–1.09
		2-4	276 / 554	0.87	0.69–1.10
		5-9	236 / 444	0.90	0.69–1.16
		≥10	68 / 141	0.76	0.52–1.11
Muscat et al. (2002)[101]	Mobile (excl. cordless)	0	72 / 63	1.0	
		1-2	7 / 17	0.5	0.2 -1.3
		3-6	11 / 6	1.7	0.5 -5.1
Inskip et al. (2001)[99]	Mobile (excl. cordless)	0	74 / 625	1.0	
		<0.5	4 / 56	0.3	0.1 -1.3
		0.5-<3	8 / 55	1.8	0.7 -4.5
		≥3	10 / 60	1.4	0.6 -3.4
		≥5	5 / 31	1.9	0.6-5.9
Case-case	Reference date (years before diagnosis)	Exposure Time since first use at reference date (yrs)	Ca	RR[a]*	95%CI
Sato et al. (2010)[112]	1	≤5	112	1.06	0.88-1.31
		5-10	56	1.05	0.82-1.45
		>10	12	1.62	0.79-4.77
	5	≤5	123	1.11	0.92-1.38
		5-10	21	1.56	0.90-3.34
		>10	6	1.00	0.59-3.23

[a] RR: risk ratio.

Table H12 Acoustic neuroma and cumulative use, results corrected for confounders.

Case-control	Type of phone	Exposure	Ca / Co	OR	95%CI
		Cumulative call time (h)			
Hardell et al. (2006)[64]	Analogue	1-500	55 / 252	2.8	1.8-4.2
		501-1000	7 / 29	3.3	1.3-8.0
		>1000	6 / 16	**5.1**	**1.9-14**
	Digital	1-500	83 / 667	1.4	0.99-2.0
		501-1000	10 / 64	1.8	0.8-3.8
		>1000	12 / 45	**3.1**	**1.5-6.4**
	Cordless	1-500	60 / 502	1.3	0.9-1.9
		501-1000	15 / 97	1.6	0.9-3.0
		>1000	21 / 102	**2.1**	**1.2-3.7**
INTERPHONE Study Group (2011)[94]	Mobile (excl. cordless)	0	462 / 837	1.00	
		<5	58 / 144	0.77	0.52–1.15
		5-12.9	63 / 129	0.80	0.54–1.18
		13-30.9	80 / 136	1.04	0.71–1.52
		31-60.9	66 / 131	0.95	0.63–1.42
		61-114.9	74 / 137	0.96	0.66–1.41
		115-199.9	68 / 128	0.96	0.65–1.42
		200-359.9	50 / 144	0.60	0.39–0.91
		360-734.9	58 / 126	0.72	0.48–1.09
		735-1639.9	49 / 126	0.48	0.30–0.78
		≥1640	77 / 107	1.32	0.88–1.97
		Cumulative number of calls (x 100)			
INTERPHONE Study Group (2011)[94]	Mobile (excl. cordless)	0	462 / 837	1.00	
		<1.5	59 / 135	0.76	0.51–1.14
		1.5-3.4	60 / 137	0.68	0.45–1.03
		3.5-7.4	73 / 135	1.11	0.76–1.61
		7.5-13.9	87 / 138	1.22	0.84–1.77
		14-25.4	79 / 132	1.11	0.75–1.64
		25.5-41.4	55 / 137	0.64	0.42–0.98
		41.5-67.9	50 / 133	0.74	0.49–1.12
		68-127.9	62 / 133	0.65	0.43–0.98
		128-269.9	56 / 115	0.67	0.44–1.02
		≥270	62 / 113	0.93	0.61–1.41
		Cumulative call time (h)			
Muscat et al. (2002)[101]	Mobile (excl. cordless)	0	72 / 63	1.0	
		1-60	9 / 11	0.9	0.3 -3.1
		>60	9 / 12	0.7	0.2 -2.6

Table H13 Acoustic neuroma, analysis as continuous variables (Hansson Mild et al. (2007)[65])

Variable	Type of phone	OR	95% CI
Per 100 h of use	Digital	1.03	0.998-1.06
	Analogue	**1.05**	**1.02 -1.9**
	Cordless	1.01	0.997-1.02
Per 1 yr of use	Digital	1.06	0.995-1.13
	Analogue	**1.12**	**1.06 -1.17**
	Cordless	1.04	0.99 -1.10

Table H14 Acoustic neuroma and laterality, results corrected for confounders.

		Ipsilateral			Contralateral		
	Exposure	Ca / Co	OR	95%CI	Ca / Co	OR	95%CI
	Time since first use (yrs)						
Hardell et al., (2009)[66] [a]	Mobile >1	80 / 374	**1.8**	**1.2 -2.6**	48 / 308	1.4	0.9 -2.1
	Mobile >10	13 / 45	**3.0**	**1.4 -6.2**	6 / 29	2.4	0.9 -6.3
	Cordless >1	67 / 309	**1.7**	**1.2 -2.5**	28 / 235	1.1	0.7 -1.7
	Cordless >10	3 / 15	2.3	0.6 -8.8	1 / 20	0.5	0.1 -4.0
INTERPHONE Study Group, (2011)[94]	0	416 / 615	1.00		405 / 625	1.00	
	1-1.9	23 / 62	0.42	0.22-0.81	32 / 51	1.75	0.90–3.42
	2-4	103 / 204	0.70	0.49-1.00	123 / 189	0.80	0.56–1.13
	5-9	101 / 153	0.95	0.64-1.41	89 / 120	0.96	0.64–1.43
	≥ 10	44 / 52	1.18	0.69-2.04	17 / 30	0.69	0.33–1.42
	Cumulative call time (h)						
	0	416 / 615	1.00		405 / 625	1.00	
	<5	23 / 44	0.81	0.43-1.52	28 / 56	0.83	0.44–1.56
	5.0-114.9	108 / 200	0.71	0.50-1.00	131 / 151	1.28	0.90–1.83
	115-359.9	47 / 95	0.67	0.40-1.12	49 / 92	0.66	0.41–1.07
	360-1639.9	46 / 86	0.51	0.30-0.88	37 / 65	0.67	0.38–1.15
	≥1640	47 / 46	**2.33**	**1.23-4.40**	16 / 26	0.72	0.34–1.53
	Cumulative number of calls (x 100)						
	0	416 / 615	1.00		405 / 625	1.00	
	<1.5	24 / 46	0.67	0.35-1.28	29 / 49	0.98	0.52-1.84
	1.5-25.4	108 / 193	0.81	0.57-1.14	143 / 158	1.36	0.96-1.93
	25.5-67.9	48 / 108	0.56	0.34-0.90	34 / 90	0.51	0.31-0.86
	68-269.9	50 / 81	0.68	0.40-1.13	44 / 66	0.67	0.39-1.14
	≥270	41 / 43	1.67	0.90-3.09	11 / 27	0.52	0.21-1.26

[a] This publication groups ipsilateral and ipsi/contralateral so the subjects that call at the side of the tumour and those who do this and alternate it with the other side are grouped, the other publications do not group these.

Parotid gland tumours

Table H15 Parotid gland tumours and duration of use, results corrected for confounders.

	Type of tumour	Type of phone	Exposure	Ca / Co	OR	95%CI
			Time since first use (yrs)			
Hardell et al. (2004)[69]	All	Analogue	>1	31 / 137	0.92	0.58-1.44
			>5	17 / 88	0.78	0.44-1.38
			>10	6 / 35	0.71	0.29-1.74
		Digital	>1	45 / 170	1.01	0.68-1.50
			>5	8 / 27	1.22	0.54-2.78
			>10	-	-	-
		Cordless	>1	48 / 200	0.99	0.68-1.43
			>5	18 / 66	1.15	0.07-2.03
			>10	0 / 5	-	-
		All	>1	91 / 352	1.02	0.75-1.38
			>5	32 / 145	0.90	0.58-1.39
			>10	6 / 38	0.65	0.27-1.59
Söderqvist et al. (2012)[72]	All	Analogue	≤ 52 h > 10 y	2 / 7	0.7	0.1-4.3
			> 52 h > 10 y	0 / 10	-	-
			All >10 y	2 / 17	0.3	0.1-1.7
		Digital	≤ 69 h > 10 y	0 / 0	-	-
			> 69 h > 10 y	2 / 5	1.3	0.2-7.4
			All >10 y	2 / 5	1.3	0.2-7.4
		Cordless	≤ 304 h >10y	1 / 4	1.0	0.1-9.6
			> 304 h >10y	3 / 8	1.1	0.2-5.2
			All >10 y	4 / 12	1.0	0.3-3.7
		Mobiles	≤ 66 h > 10 y	0 / 2	-	-
			> 66 h > 10 y	2 / 18	0.3	0.1-1.4
			All >10 y	2 / 20	0.3	0.1-1.4
Sadetzki et al. (2007)[85]	All	Mobile (excl. cordless)	0	175 / 575	1.0	
			1-4.9	148 / 405	0.84	0.63-1.12
			5-9.9	124 / 264	0.92	0.67-1.27
			≥10	13 / 22	1.0	0.48-2.09
	Benign		0	150 / 469	1.0	
			1-4.9	127 / 351	0.79	0.54-1.08
			5-9.9	113 / 234	0.92	0.65-1.29
			≥10	12 / 18	1.11	0.50-2.44
	Malignant		0	25 / 106	1.0	
			1-4.9	21 / 54	1.25	0.58-2.68
			5-9.9	11 / 30	0.92	0.37-2.27
			≥10	1 / 4	0.47	0.05-4.51

Lönn et al. (2006)[82]	Benign	Mobile (excl. cordless)	0	35 / 119	1.0	
			<5	47 / 104	1.0	0.6 -1.8
			5-9	23 / 76	0.8	0.4 -1.5
			≥10	7 / 15	1.4	0.5 -3.9
	Malignant		0	35 / 280	1.0	
			<5	14 / 228	0.7	0.3 -1.3
			5-9	8 / 128	0.7	0.3 -1.7
			≥10	2 / 36	0.4	0.1 -2.6
			Duration of subscription (y)			
Auvinen et al. (2002)[100]		Analogue	0	31 / 155	1.0	
			<1	0 / 3	-	-
			1-2	2 / 11	0.9	0.2 -4.9
			>2	1 / 1	4.4	0.3 -71.6
		Digital	0	33 / 167	1.0	
			<1	0 / 2	-	-
			1-2	1 / 1	5.0	0.3 -80.0
			>2	0 / 0	-	-
		All phones	<1	-	-	-
			1-2	-	1.7	0.4 -7.5
			>2	-	2.3	0.2 -25.3

Table H16 Parotid gland tumours and cumulative use, results corrected for confounders.

	Type of tumour	Type of phone	Exposure	Ca / Co	OR	95%CI
			Cumulative call time (h)			
Hardell et al. (2004)[69]	All	Analogue	>1 y, >91 h	15 / 68	0.90	0.49-1.66
			>5 y, > 91 h	10 / 52	0.78	0.38-1.61
			>10 y, >91 h	4 / 25	0.66	0.22-1.95
		Digital	>1 y, >64 h	23 / 81	1.07	0.67-1.71
			>5 y, >64 h	6 / 20	1.25	0.48-3.21
			>10 y, >64 h	-	-	-
		Cordless	>1 y, >183 h	21 / 97	0.89	0.53-1.50
			>5 y, >183 h	12 / 41	1.24	0.62-2.44
			>10 y, >183h	0 / 4	-	-
		All	>1 y, >182 h	42 / 175	0.94	0.63-1.39
			>5 y, >182 h	21 / 100	0.86	0.51-1.44
			>10 y, >182h	4 / 31	0.53	0.18-1.55
Söderqvist et al. (2012)[72]	All	Analogue	1-1000 h	9/31	0.9	0.3-2.4
			1001-2000 h	0 / 1	-	-
			>2000 h	0 / 0	-	-
		Digital	1-1000 h	28 / 95	1.9	0.4-1.7
			1001-2000 h	2 / 4	1.4	0.2-8.8
			>2000 h	0/ 5	-	-

		Cordless	1-1000 h	17 / 80	0.6	0.3-1.3
			1001-2000 h	2 / 4	1.2	0.2-2.8
			>2000 h	0 / 9	-	-
		Mobiles	1-1000 h	28 / 98	0.9	0.4-1.7
			1001-2000 h	2 / 8	0.86	0.1-3.6
			>2000 h	0 / 5	0.53	-
Sadetzki et al. (2007)[85]	All	Mobile (excl. cordless)	0	176 / 578	1.0	
			≤266.3	121 / 390	0.82	0.62-1.09
			266.4-1034.9	80 / 155	1.03	0.72-1.47
			≥1035	83 / 134	1.09	0.75-1.60
	Benign		0	151 / 480	1.0	
			≤266.3	103 / 336	0.78	0.57-1.06
			266.4-1034.9	75 / 139	1.05	0.72-1.53
			≥1035	73 / 117	1.08	0.72-1.62
	Malignant		0	25 / 107	1.0	
			≤266.3	18 / 54	1.21	0.58-2.53
			266.4-1034.9	5 / 16	0.67	0.19-2.38
			≥1035	10 / 17	1.22	0.43-3.48
Lönn et al. (2006)[82]	Benign	Mobile (excl. cordless)	0	35 / 119	1.0	
			<30	20 / 45	1.1	0.6 -2.3
			30-449	34 / 92	0.9	0.5 -1.6
			>450	22 / 52	1.0	0.5 -2.1
	Malignant		0	35 / 280	1.0	
			<30	7 / 110	0.7	0.3 -1.6
			30-449	11 / 184	0.7	0.3 -1.4
			>450	5 / 90	0.6	0.2 -1.8

Table H17 Parotid gland tumours and laterality, results corrected for confounders.

			Ipsilateral			Contralateral		
	Type of tumour	Exposure	Ca / Co	OR	95%CI	Ca / Co	OR	95%CI
		Time since first use (yrs)						
Sadetzki et al. (2007)[85]	All	0	175 / 575	1.00		175 / 575	1.00	
		1-4.9	84 / 220	0.88	0.63-1.24	53 / 166	0.82	0.56-1.21
		5-9.9	83 / 148	1.13	0.78-1.64	45 / 118	0.96	0.63-1.46
		≥10	10 / 13	1.89	0.79-4.57	3 / 10	0.58	0.15-2.32
		Cumulative call time (h)						
		0	176 / 583	1.00		175 / 578	1.00	
		<266.3	67 / 224	0.79	0.56-1.11	53 / 162	0.92	0.63-1.34
		>266.3	115 / 158	**1.49**	**1.05-2.13**	48 / 129	0.84	0.55-1.28
		Time since first use (yrs)						
Lönn et al. (2006)[82]	Benign	0	58 / 210	1.0		74 / 209	1.0	
		<5	30 / 57	1.4	0.9-2.2	24 / 60	0.9	0.5-1.5
		5-9.9	17 / 41	1.5	0.7-2.8	10 / 40	0.6	0.3-1.2
		≥10	4 / 8	2.0	0.5-7.0	1 / 8	0.3	0.0-2.6

Malignant	0	36 / 452	1.0		45 / 460	1.0	
	<5	9 / 125	1.2	0.5-2.6	5 / 130	0.5	0.2-1.3
	5-9.9	6 / 72	1.3	0.5-3.6	2 / 66	0.4	0.1-1.8
	≥10	1 / 23	0.7	0.1-5.7	0 / 16	-	-

Pituitary tumours

Table H18 Pituitary tumours and duration of use, results corrected for confounders.

	Type of phone	Exposure	Ca / Co	OR	95%CI
		Time since first use (yrs)			
Takebayashi et al. (2008)[88]	All	0	39 / 56	1.00	
		<2.4	14 / 25	0.86	0.39-1.88
		2.4-4.5	13 / 27	0.75	0.31-1.81
		4.5-7.2	22 / 26	1.64	0.74-3.66
		>7.2	13 / 27	0.75	0.31-1.82
Schoemaker et al. (2009)[89]	All	0	116 / 545	1.0	
		1.5-4	89 / 197	1.0	0.7-1.5
		5-9	62 / 140	0.8	0.5-1.2
		10-17	24 / 48	1.0	0.5-1.9
	Analogue	0	116 / 245	1.0	
		1.5-4	2 / 13	0.4	0.1-2.1
		5-9	18 / 44	0.9	0.5-1.9
		≥10	19 / 41	1.2	0.6-2.4
	Digital	0	116 / 245	1.0	
		1.5-4	103 / 236	1.0	0.7-1.4
		5-9	53 / 120	0.7	0.4-1.1
		≥10	10 / 6	2.5	0.7-9.1

Table H19. Pituitary tumours and cumulative use, results corrected for confounders.

	Type of phone	Exposure	Ca / Co	OR	95%CI
		Cumulative call time (h)			
Takebayashi et al. (2008)[88]	All	0	39 / 56	1.00	
		<39	15 / 26	1.00	0.46-2.16
		39-190	14 / 26	0.97	0.40-2.32
		190-560	12 / 26	0.72	0.31-1.70
		>560	21 / 27	1.33	0.58-3.09
Schoemaker et al. (2009)[89]	All	0	116 / 245	1.0	
		<113	79 / 190	0.9	0.6-1.3
		113-596	44 / 91	1.1	0.7-1.8
		>596	51 / 95	1.1	0.7-1.7
	Analogue	0	116 / 245	1.0	
		<96	13 / 48	0.7	0.3-1.4

		96-371	11 / 24	1.2	0.5-2.9
		>371	15 / 24	1.5	0.7-3.4
	Digital	0	116 / 245	1.0	
		<94	75 / 178	0.9	0.6-1.3
		94-453	37 / 88	0.9	0.5-1.5
		>453	53 / 89	1.2	0.7-1.9
		Cumulative number of calls			
Schoemaker et al. (2009)[89]	All	0	116 / 245	1.0	
		<2203	72 / 191	0.8	0.6-1.2
		2203-8300	45 / 94	1.1	0.7-1.8
		>8300	57 / 95	1.2	0.7-1.9

Malignant melanoma of the eye

Table H20 Malignant melanoma of the eye and duration of use, results corrected for confounders.

		Exposure	Ca / Co	OR	95%CI
Stang et al. (2001)[98]	Possible / probable / certain mobile phone exposure	Ever	7 / 25	2.8	1.0-7.9
		≥5 yrs before reference date	4 / 10	4.1	0.7-24.0
		≥3 yrs	6 / 16	3.0	0.9-9.7
	Type of controls	Duration of regular use (y)	Ca / Co	OR	95%CI
Stang et al. (2009)[104]	Population controls	0	24 / 20	1.0	
		≤4	17 / 19	0.8	0.5-1.2
		>5-9	11 / 14	0.6	0.4-1.0
		≥10	2 / 3	0.6	0.3-1.4
	Ophthalmologist controls	0	32 / 24	1.0	
		≤4	17 / 19	1.0	0.5-2.2
		>5-9	10 / 8	1.3	0.5-3.2
		≥10	4 / 3	1.5	0.3-6.6
	Sibling controls	0	14 / 17	1.0	
		≤4	21 / 18	1.4	0.6-3.3
		>5-9	13 / 13	1.1	0.4-2.8
		≥10	2 / 3	0.7	0.2-3.0

Table H21 Malignant melanoma of the eye and cumulative use, results corrected for confounders.

	Type of controls	Exposure	Ca / Co	OR	95%CI
		Cumulative call time (h)			
Stang et al. (2009)[104]	Population controls	0	24 / 20	1.0	
		≤44	11 / 15	0.6	0.4-1.0
		>44-≤195	9 / 8	0.9	0.5-1.5
		>195	10 / 12	0.8	0.5-1.3
	Ophthalmologist controls	0	23 / 24	1.0	
		≤44	14 / 13	1.2	0.6-2.8
		>44-≤195	7 / 8	0.9	0.3-2.4
		>195	10 / 8	1.2	0.4-3.6
	Sibling controls	0	14 / 17	1.0	
		≤44	12 / 16	0.8	0.3-2.1
		>44-≤195	11 / 8	1.7	0.7-4.5
		>195	13 / 11	1.5	0.5-4.3
		Cumulative number of calls			
	Population controls	0	24 / 20	1.0	
		Sporadic	47/44	0.9	0.7-1.3
		≤1176	17 /19	0.8	0.5-1.2
		>1176-≤4350	11 / 14	0.6	0.4-1.0
		>4350	2 / 3	0.6	0.3-1.4
	Ophthalmologist controls	0	23 / 24	1.0	
		Sporadic	47/46	1.2	0.7-2.2
		≤1176	17 / 19	1.0	0.5-2.2
		>1176-≤4350	10 / 8	1.3	0.5-3.2
		>4350	4 / 3	1.5	0.3-6.6
	Sibling controls	0	14 / 17	1.0	
		Sporadic	49/48	1.3	0.6-2.5
		≤1176	21/18	1.4	0.6-3.3
		>1176-≤4350	13/13	1.1	0.4-2.8)
		>4350	2/3	0.7	0.2-3.0

Annex I

Meta-analysis and forest plots

Two models have been used to calculate the pooled estimates, using metaan.ado in Stata. The first is a fixed effects model, the second a random effects model (DerSimonian-Laird).The pooled variance includes the spread between the different studies and is therefore sometimes considerably larger than the variance of the individual studies. When there is no heterogeneity, the fixed and random effect estimates of the pooled effect are equal. Heterogeneity between studies has been determined using the Cochrane Q with p-value. A high Q and low p-value indicate heterogeneity between studies. When p was <0.05, heterogeneity was considered to be too large for a meaningful pooling of the data. This has nevertheless be done, but in those cases the data are only shown in this Annex in the tables, to show the differences. If p >0.05, heterogeneity was considered small enough to perform a meta-analysis. The figures drawn from the data in the tables are in those cases shown in the main text.

OR, CI1 and CI2 are the odds ratio, lower and upper 95% confidence intervals, respectively, as reported in the papers. The log(OR) should be exactly the mean of log(CI1) en log(CI2). This is not always the case, as a result of rounding and reporting not enough decimal numbers.

Tables I1 Glioma, time since first use ≥10 years, Hardell 20-80 year.

Data

Study	logOR	logCI1	logCI2	OR	CI1	CI2
Frei et al. (2011)[52], females, ≥10 yr	0.039	-0.580	0.668	1.04	0.56	1.95
Frei et al. (2011)[52], males, ≥10 yr	0.039	-0.163	0.247	1.04	0.85	1.28
Hardell et al. (2011)[68], ≥10 yr	0.916	0.588	1.194	2.50	1.80	3.30
INTERPHONE (2010)[93], ≥10 yr	-0.020	-0.274	0.231	0.98	0.76	1.26

Fixed-effects model

Study	Effect	[95% Conf. Interval]		% Weight	OR	CI1	CI2
Frei et al. (2011)[52], females	0.039	-0.585	0.663	4.85			
Frei et al. (2011)[52], males,	0.039	-0.165	0.244	45.05			
Hardell et al. (2011)[68]	0.916	0.613	1.219	20.55			
INTERPHONE (2010)[93]	-0.020	-0.273	0.233	29.54			
Overall effect	0.202	0.065	0.339	100.00	1.22	1.07	1.40

Random-effects model

Study	Effect	[95% Conf. Interval]		% Weight	OR	CI1	CI2
Frei et al. (2011)[52], females	0.039	-0.585	0.663	18.86			
Frei et al. (2011)[52], males,	0.039	-0.165	0.244	27.92			
Hardell et al. (2011)[68]	0.916	0.613	1.219	26.12			
INTERPHONE (2010)[93]	-0.020	-0.273	0.233	27.10			
Overall effect	0.252	-0.197	0.701	100.00	1.29	0.82	2.02

Heterogeneity

	Value	df	p-value
Cochrane Q	27.00	3	0.000

Tables I2 Glioma, time since first use ≥10 years, without Hardell. This is the same analysis as the previous one, except without the Hardell data.

Study	logOR	logCI1	logCI2	OR	CI1	CI2
Frei et al. (2011)[52], females, ≥10 yr	0.039	-0.580	0.668	1.04	0.56	1.95
Frei et al. (2011)[52], males, ≥10 yr	0.039	-0.163	0.247	1.04	0.85	1.28
INTERPHONE (2010)[93], ≥10 yr	-0.020	-0.274	0.231	0.98	0.76	1.26

Fixed-effects model

Study	Effect	[95%Conf.Interval]		%Weight	OR	CI1	CI2
Frei et al. (2011)[52], females	0.039	-0.585	0.663	6.11			
Frei et al. (2011)[52], males,	0.039	-0.165	0.244	56.71			
INTERPHONE (2010)[93]	-0.020	-0.273	0.233	37.19			
Overall effect	0.017	-0.137	0.171	100.00	1.02	0.87	1.19

Random-effects model							
Study	Effect	[95%Conf.Interval]		%Weight	OR	CI1	CI2
Frei et al. (2011)[52], females	0.039	-0.585	0.663	6.11			
Frei et al. (2011)[52], males	0.039	-0.165	0.244	56.71			
INTERPHONE (2010)[93]	-0.020	-0.273	0.233	37.19			
Overall effect	0.017	-0.137	0.171	100.00	1.02	0.87	1.19

Heterogeneity			
	Value	df	p-value
Cochrane Q	0.13	2	0.935

Tables I3 Glioma, time since first use ≥10 years, Hardell 30-59 year.

Study	logOR	logCI1	logCI2	OR	CI1	CI2
Frei (2011)[52], females, ≥10 yr	0.039	-0.580	0.668	1.04	0.56	1.95
Frei (2011)\[52], males, ≥10 yr	0.039	-0.163	0.247	1.04	0.85	1.28
Hardell et al. (2011)[165], ≥10 yr	0.582	0.174	0.993	1.79	1.19	2.70
INTERPHONE (2010)[93], ≥10 yr	-0.020	-0.274	0.231	0.98	0.76	1.26

Fixed-effects model							
Study	Effect	[95% Conf. Interval]		% Weight	OR	CI1	CI2
Frei et al. (2011)[52], females	0.039	-0.585	0.663	5.35			
Frei et al. (2011)[52], males	0.039	-0.165	0.244	49.68			
Hardell et al. (2011)[165]	0.582	0.173	0.992	12.40			
INTERPHONE (2010)[93]	-0.020	-0.273	0.233	32.57			
Overall effect	0.087	-0.057	0.231	100.00	1.09	0.94	1.26

Random-effects model							
Study	Effect	[95% Conf. Interval]		% Weight	OR	CI1	CI2
Frei et al. (2011)[52], females	0.039	-0.585	0.663	11.42			
Frei et al. (2011)[52], males	0.039	-0.165	0.244	36.36			
Hardell et al. (2011)[165]	0.582	0.173	0.992	20.29			
INTERPHONE (2010)[93]	-0.020	-0.273	0.233	31.94			
Overall effect	0.130	-0.110	0.371	100.00	1.14	0.90	1.45

Heterogeneity			
	value	df	p-value
Cochrane Q	6.54	3	0.088

Tables I4 Glioma, cumulative call time, Hardell 20-80 year.

Study	logOR	logCI1	logCI2	OR	CI1	CI2
Hardell et al. (2011)[68], >2000 hr	1.163	0.693	1.629	3.20	2.00	5.10
INTERPHONE (2010)[93], >1640 hr	0.336	0.030	0.637	1.40	1.03	1.89

Fixed-effects model

Study	Effect	[95%Conf.Interval]		%Weight	OR	CI1	CI2
Hardell et al. (2011)[68]	1.163	0.695	1.631	29.60			
INTERPHONE (2010)[93]	0.336	0.033	0.640	70.40			
Overall effect	0.581	0.327	0.836	100.00	1.79	1.39	2.31

Random-effects model

Study	Effect	[95%Conf.Interval]		%Weight	OR	CI1	CI2
Hardell et al. (2011)[68]	1.163	0.695	1.631	47.58			
INTERPHONE (2010)[93]	0.336	0.033	0.640	52.42			
Overall effect	0.730	-0.079	1.539	100.00	2.08	0.92	4.66

Heterogeneity

	value	df	p-value
Cochrane Q	8.44	1	0.004

Tables I5 Glioma, cumulative call time, Hardell 30-59 year.

Study	logOR	logCI1	logCI2	OR	CI1	CI2
Hardell et al. (2011)[165], >1640 hr	0.560	0.020	1.099	1.75	1.02	3.00
INTERPHONE (2010)[93], >1640 hr	0.336	0.030	0.637	1.40	1.03	1.89

Fixed-effects model

Study	Effect	[95%Conf.Interval]		%Weight	OR	CI1	CI2
Hardell et al. (2011)[165]	0.560	0.020	1.099	24.05			
INTERPHONE (2010)[93]	0.336	0.033	0.640	75.95			
Overall effect	0.390	0.126	0.655	100.00	1.48	1.13	1.93

Random-effects model

Study	Effect	[95%Conf.Interval]		%Weight	OR	CI1	CI2
Hardell et al. (2011)[165]	0.560	0.020	1.099	24.05			
INTERPHONE (2010)[93]	0.336	0.033	0.640	75.95			
Overall effect	0.390	0.126	0.655	100.00	1.48	1.13	1.93

Heterogeneity

	value	df	p-value
Cochrane Q	0.50	1	0.480

Tables I6 Glioma, time since first use ≥10 year, ipsilateral, Hardell 20-80 year.

Study	logOR	logCI1	logCI2	OR	CI1	CI2
Hardell et al. (2009)[66], ipsilateral, ≥10 yr	1.194	0.693	1.686	3.30	2.00	5.40
INTERPHONE (2010)[93], ipsilateral, ≥10 yr	0.191	-0.198	0.588	1.21	0.82	1.80

Fixed-effects model

Study	Effect	[95%Conf.Interval]		%Weight	OR	CI1	CI2
Hardell et al. (2009)[66]	1.194	0.697	1.691	38.52			
INTERPHONE (2010)[93]	0.191	-0.202	0.584	61.48			
Overall effect	0.577	0.269	0.885	100.00	1.78	1.31	2.42

Random-effects model

Study	Effect	[95%Conf.Interval]		%Weight	OR	CI1	CI2
Hardell et al. (2009)[66]	1.194	0.697	1.691	48.81			
INTERPHONE (2010)[93]	0.191	-0.202	0.584	51.19			
Overall effect	0.680	-0.303	1.663	100.00	1.97	0.74	5.28

Heterogeneity

	value	df	p-value
Cochrane Q	9.64	1	0.002

Tables I7 Glioma, time since first use ≥10 year, contralateral, Hardell 20-80 year.

Study	logOR	logCI1	logCI2	OR	CI1	CI2
Hardell et al. (2009)[66], contralateral, ≥10yr	1.030	0.405	1.629	2.80	1.50	5.10
INTERPHONE (2010)[93], contralateral, ≥10yr	-0.357	-0.868	0.140	0.70	0.42	1.15

Fixed-effects model

Study	Effect	[95%Conf.Interval]		%Weight	OR	CI1	CI2
Hardell et al. (2009)[66]	1.030	0.418	1.642	40.39			
INTERPHONE (2010)[93]	-0.357	-0.860	0.147	59.61			
Overall effect	0.203	-0.186	0.592	100.00	1.23	0.83	1.81

Random-effects model

Study	Effect	[95%Conf.Interval]		%Weight	OR	CI1	CI2
Hardell et al. (2009)[66]	1.030	0.418	1.642	49.18			
INTERPHONE (2010)[93]	-0.357	-0.860	0.147	50.82			
Overall effect	0.325	-1.033	1.684	100.00	1.38	0.36	5.39

Heterogeneity

	value	df	p-value
Cochrane Q	11.76	1	0.001

Tables I8 Glioma, time since first use ≥10 year, ipsilateral, Hardell 30-59 year.

Study	logOR	logCI1	logCI2	OR	CI1	CI2
Hardell et al. (2011)[165], ipsilateral, ≥10 yr	0.829	0.285	1.379	2.29	1.33	3.97
INTERPHONE (2010)[93], ipsilateral, ≥10 yr	0.191	-0.198	0.588	1.21	0.82	1.80

Fixed-effects model

Study	Effect	[95%Conf.Interval]		%Weight	OR	CI1	CI2
Hardell et al. (2011)[165]	0.829	0.282	1.375	34.08			
INTERPHONE (2010)[93]	0.191	-0.202	0.584	65.92			
Overall effect	0.408	0.089	0.727	100.00	1.50	1.09	2.07

Random-effects model

Study	Effect	[95%Conf.Interval]		%Weight	OR	CI1	CI2
Hardell et al. (2011)[165]	0.829	0.282	1.375	45.38			
INTERPHONE (2010)[93]	0.191	-0.202	0.584	54.62			
Overall effect	0.480	-0.142	1.103	100.00	1.62	0.87	3.01

Heterogeneity

	value	df	p-value
Cochrane Q	3.45	1	0.063

Tables I9 Glioma, time since first use ≥10 year, contralateral, Hardell 30-59 year.

Study	logOR	logCI1	logCI2	OR	CI1	CI2
Hardell et al. (2011)[165], contralateral, ≥10 yr	0.536	-0.117	1.188	1.71	0.89	3.28
INTERPHONE (2010)[93], contralateral, ≥10 yr	-0.357	-0.868	0.140	0.70	0.42	1.15

Fixed-effects model

Study	Effect	[95%Conf.Interval]		%Weight	OR	CI1	CI2
Hardell et al. (2011)[165]	0.536	-0.116	1.189	37.36			
INTERPHONE (2010)[93]	-0.357	-0.860	0.147	62.64			
Overall effect	-0.023	-0.422	0.376	100.00	0.98	0.66	1.46

Random-effects model

Study	Effect	[95%Conf.Interval]		%Weight	OR	CI1	CI2
Hardell et al. (2011)[165]	0.536	-0.116	1.189	47.20			
INTERPHONE (2010)[93]	-0.357	-0.860	0.147	52.80			
Overall effect	0.065	-0.809	0.939	100.00	1.07	0.45	2.56

Heterogeneity

	Value	df	p-value
Cochrane Q	4.51	1	0.034

Tables I10 Glioma, cumulative call time, ipsilateral, Hardell 30-59 year.

Study	logOR	logCI1	logCI2	OR	CI1	CI2
Hardell et al. (2011)[165], ipsilateral, >1640 hr	0.779	0.086	1.470	2.18	1.09	4.35
INTERPHONE (2010)[93], ipsilateral, >1640 hr	0.673	0.199	1.151	1.96	1.22	3.16

Fixed-effects model

Study	Effect	[95%Conf.Interval]		%Weight	OR	CI1	CI2
Hardell et al. (2011)[165]	0.779	0.087	1.471	32.11			
INTERPHONE (2010)[93]	0.673	0.197	1.149	67.89			
Overall effect	0.707	0.315	1.099	100.00	2.03	1.37	3.00

Random-effects model

Study	Effect	[95%Conf.Interval]		%Weight	OR	CI1	CI2
Hardell et al. (2011)[165]	0.779	0.087	1.471	32.11			
INTERPHONE (2010)[93]	0.673	0.197	1.149	67.89			
Overall effect	0.707	0.315	1.099	100.00	2.03	1.37	3.00

Heterogeneity

	Value	df	p-value
Cochrane Q	0.06	1	0.804

Table I11 Glioma, cumulative call time, contralateral, Hardell 30-59 year.

Study	logOR	logCI1	logCI2	OR	CI1	CI2
Hardell et al. (2011)\[165], contralateral, >1640 hr	0.392	-0.562	1.353	1.48	0.57	3.87
INTERPHONE (2010)[93], contralateral, >1640 hr	0.223	-0.446	0.884	1.25	0.64	2.42

Fixed-effects model

Study	Effect	[95%Conf.Interval]		%Weight	OR	CI1	CI2
Hardell et al. (2011)[165]	0.392	-0.566	1.350	32.53			
INTERPHONE (2010)[93]	0.223	-0.442	0.888	67.47			
Overall effect	0.278	-0.268	0.824	100.00	1.32	0.76	2.28

Random-effects model

Study	Effect	[95%Conf.Interval]		%Weight	OR	CI1	CI2
Hardell et al. (2011)[165]	0.392	-0.566	1.350	32.53			
Interphone (2010)[93]	0.223	-0.442	0.888	67.47			
Overall effect	0.278	-0.268	0.824	100.00	1.32	0.76	2.28

Heterogeneity

	value	df	p-value
Cochrane Q	0.08	1	0.776

Table I12 Acoustic neuroma, time since first use ≥10 years.

Study	logOR	logCI2	logCI1	OR	CI1	CI2
Schüz et al. (2011)[51]	-0.1	0.38	-0.7	0.87	0.52	1.46
Hansson Mild et al. (2007)[65], analogue	1.1	1.74	0.5	3.10	1.70	5.70
Hansson Mild et al. (2007)[65], digital	-0.5	1.61	-2.3	0.60	0.10	5.00
Hansson Mild et al. (2007)[65], cordless	0.0	1.06	-1.2	1.00	0.30	2.90
INTERPHONE (2011)[94]	-0.3	0.10	-0.7	0.76	0.52	1.11
Sato et al. (2010)[112]	0.5	1.56	-0.2	1.62	0.79	4.77

Fixed-effects model

Study	Effect	[95% Conf.	Interval]	% Weight	OR	CI1	CI2
Schüz et al. (2011)\[51]	-0.139	-0.655	0.377	23.88			
Hansson Mild et al. (2007)[65], analogue	1.131	0.526	1.736	17.39			
Hansson Mild et al. (2007)[65], digital	-0.511	-2.467	1.445	1.66			
Hansson Mild et al. (2007)[65], cordless	0.000	-1.134	1.134	4.94			
INTERPHONE (2011)[94]	-0.274	-0.654	0.105	44.26			
Sato et al. (2010)[112]	0.482	-0.417	1.381	7.87			
Overall effect (fe)	0.071	-0.181	0.324	100.00	1.07	0.83	1.38

Random-effects model

Study	Effect	[95% Conf.	Interval]	% Weight	OR	CI1	CI2
Schüz et al. (2011)[51]	-0.139	-0.655	0.377	21.84			
Hansson Mild et al. (2007)[65], analogue	1.131	0.526	1.736	20.32			
Hansson Mild et al. (2007)[65], digital	-0.511	-2.467	1.445	5.93			
Hansson Mild et al. (2007)[65], cordless	0.000	-1.134	1.134	12.34			
INTERPHONE (2011)[94]	-0.274	-0.654	0.105	24.07			
Sato et al. (2010)[112]	0.482	-0.417	1.381	15.50			
Overall effect (dl)	0.178	-0.360	0.716	100.00	1.19	0.70	2.05

Heterogeneity

	value	df	p-value
Cochrane Q	16.79	5	0.005

Table I13 Acoustic neuroma, cumulative call time >1000/1640 h.

Study	logOR	logCI2	logCI1	OR	CI1	CI2
Hardell et al. (2006)[64], analogue, >1000 hr	1.6	2.6	0.64	5.10	1.90	14.00
Hardell et al. (2006)[64], digital, >1000 hr	1.1	1.9	0.41	3.10	1.50	6.40
INTERPHONE (2011)[94] >1640 hr	0.3	0.7	-0.13	1.32	0.88	1.97

Fixed-effects model

Study	Effect	[95% Conf. Interval]		% Weight	OR	CI1	CI2
Hardell et al. (2006)[64], analogue	1.629	0.631	2.628	11.07			
Hardell et al. (2006)[64], digital	1.131	0.406	1.857	20.97			
INTERPHONE (2011)[94]	0.278	-0.125	0.681	67.97			
Overall effect	0.606	0.274	0.938	100.00	1.83	1.32	2.55

Random-effects model

Study	Effect	[95% Conf. Interval]		% Weight	OR	CI1	CI2
Hardell et al. (2006)[64], analogue	1.629	0.631	2.628	26.81			
Hardell et al. (2006)[64], digital	1.131	0.406	1.857	33.01			
INTERPHONE (2011)[94]	0.278	-0.125	0.681	40.18			
Overall effect	0.922	0.102	1.742	100.00	2.51	1.11	5.71

Heterogeneity

	value	df	p-value
Cochrane Q	8.60	2	0.014

Tables I14 Acoustic neuroma, time since first use ≥10 years, ipsilateral.

Study	logOR	logCI2	logCI1	OR	CI1	CI2
Hardell et al. (2009)[66], ipsilateral	1.1	1.8	0.34	3.00	1.40	6.20
INTERPHONE (2011)[94], ipsilateral	0.2	0.7	-0.37	1.18	0.69	2.04

Fixed-effects model

Study	Effect	[95% Conf. Interval]		% Weight	OR	CI1	CI2
Hardell et al. (2009)[66]	1.099	0.355	1.843	34.67			
INTERPHONE (2011)[94]	0.166	-0.376	0.708	65.33			
Overall effect	0.489	0.051	0.927	100.00	1.63	1.05	2.53

Random-effects model

Study	Effect	[95% Conf. Interval]		% Weight	OR	CI1	CI2
Hardell et al. (2009)[66]	1.099	0.355	1.843	46.12			
INTERPHONE (2011)[94]	0.166	-0.376	0.708	53.88			
Overall effect	0.596	-0.316	1.507	100.00	1.81	0.73	4.51

Heterogeneity

	value	df	p-value
Cochrane Q	3.95	1	0.047

Tables I15 Acoustic neuroma, time since first use ≥10 years, contralateral.

Study	logOR	logCI2	logCI1	OR	CI1	CI2
Hardell et al. (2009)[66], contralateral	0.88	1.8	-0.1	2.40	0.90	6.30
INTERPHONE (2011)[94], contralateral	-0.37	0.4	-1.1	0.69	0.33	1.42

Fixed-effects model

Study	Effect	[95% Conf. Interval]		% Weight	OR	CI1	CI2
Hardell et al. (2009)[66]	0.875	-0.097	1.848	36.00			
INTERPHONE (2011)[94]	-0.371	-1.101	0.359	64.00			
Overall effect	0.078	-0.506	0.661	100.00	1.08	0.60	1.94

Random-effects model

Study	Effect	[95% Conf. Interval]		% Weight	OR	CI1	CI2
Hardell et al. (2009)[66]	0.875	-0.097	1.848	46.53			
INTERPHONE (2011)[94]	-0.371	-1.101	0.359	53.47			
Overall effect	0.209	-1.010	1.428	100.00	1.23	0.36	4.17

Heterogeneity

	value	df	p-value
Cochrane Q	4.04	1	0.045