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Comments on:

NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES IN Hsd:SPRAGUE DAWLEY SD RATS
EXPOSED TO WHOLE-BODY RADIO FREQUENCY RADIATION
AT A FREQUENCY (900 MHz) AND MODULATIONS (GSM AND CDMA) USED BY CELL PHONES

NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES IN B6C3F1/N MICE EXPOSED
TO WHOLE-BODY RADIO FREQUENCY RADIATION AT A FREQUENCY (1,900 MHz) AND MODULATIONS (GSM AND CDMA) USED BY CELL PHONES

We have read these two reports with interest. They show increased incidence of malignant schwannoma in the heart and brain glioma in male rats exposed either to GSM-modulated or CDMA modulated cell phone radiofrequency (RF) radiation for two years. There are also increased incidences of some other tumor types and diseases. We discuss in the following some of the major findings.

The reports the results on schwannoma and glioma are of special concern since they corroborate human epidemiology findings. Thus, it is noteworthy that similar tumors were found in the NTP study as in epidemiological studies on human use of wireless phones; mobile phones or cordless phones (DECT). Malignant schwannoma in the heart is a similar type of tumor as vestibular schwannoma in humans, also called acoustic neuroma, although acoustic neuroma is usually benign and may rarely undergo malignant transformation.

In the following we give an updated evaluation on the scientific evidence for increased risk for glioma and vestibular schwannoma (acoustic neuroma) associated with use of wireless phones. In our opinion also certain aspects on human epidemiology on this issue need to be further clarified and elaborated in the NTP report.

Our study group has since the end of the 1990's published results from case- control studies on use of wireless phones and brain tumor risk (Hardell et al 1999). An increased risk for brain tumors was found for ipsilateral use of mobile phones, the same side of the brain as the phone was used. A statistically significant increased risk was published for malignant brain tumors (Hardell et al 2002) and vestibular schwannoma (Hardell et al 2003). Further scientific evidence on the association has more recently been discussed by Carlberg and Hardell (2017).

Background

The brain is the main target for exposure to RF radiation during use of handheld wireless phones; both mobile and cordless phones (Cardis et al 2008, Gandhi et al 2012). An increased risk for brain tumors has been of concern for a long time. In May 2011 RF radiation in the frequency range 30 kHz–300 GHz was evaluated to be a Group 2B, i.e. a 'possible' human carcinogen, by the International Agency for Research on Cancer (IARC) at the World Health

Organization (WHO) (Baan et al 2011, IARC 2013). This was based on an increased risk for glioma and acoustic neuroma in human epidemiological studies.

The IARC cancer classification includes all sources of RF radiation. The exposure from mobile phone base stations, Wi-Fi access points, smart phones, laptops and tablets can be long-term, sometimes around the clock, at home, at work place, at school, and in the environment. For children this risk may be accentuated because of a cumulative effect during a long lifetime use (Hedendahl et al 2015).

The exposure guideline used by many agencies was established in 1998 by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) and was based only on established short-term thermal (heating) effects from RF radiation neglecting non-thermal biological effects (ICNIRP 1988). The ICNIRP guidelines were updated in 2009 but still do not cover cancer and other long-term or non-thermal effects (ICNIRP 2009), see also Hardell (2017).

ICNIRP gives the guideline 2 to 10 W/m^2 for RF radiation depending on frequency. This is only based on a short-term immediate thermal effect (ICNIRP 2009). ICNIRP is a private non-governmental organisation (NGO) based in Germany. New expert members can only be elected by members of the organization. Many of the ICNIRP members have ties to the industry that is dependent on the ICNIRP guidelines. The guidelines are of huge economic and strategic importance to the military, telecom/IT and power industry.

In contrast to ICNIRP, the BioInitiative Reports from 2007, updated in 2012, based the evaluation also on non-thermal health effects from RF radiation (BioInitiative Working Group 2007, 2012). The scientific benchmark for possible health risks was defined to be 30 to 60 μW/m^2. In 2012, the Bioinitiative Working Group proposed a precautionary target level of 3–6 μW/m^2, using a safety factor of 10. Using the significantly higher guideline by ICNIRP gives a 'green card' to roll out the wireless digital technology thereby not considering non-thermal health effects from RF radiation.

Since the IARC evaluation in 2011 more studies have been published that support a causal association between RF radiation and brain and head tumors. Thus, it is impertinent to make an up-dated presentation in the NTP reports on current evidence on cancer risks associated with use of wireless phones.

A Danish cohort study on 'mobile phone users' (Johansen et al 2001, Schüz et al 2006) is not included here due to serious methodological shortcomings in the study design, see (Söderqvist et al 2012). The study by Benson et al (2013) is of limited value since use of cordless phones was not included, mobile phone use was assessed only at baseline and no information on tumor laterality including ipsilateral *versus* contralateral use were given. In spite of the many shortcomings an increased risk for acoustic neuroma was reported. The study will not be further discussed below.

First human epidemiology studies on specific tumor types are discussed. Then NTPs-study findings are presented and finally an evaluation of the combined evidence from human and animal studies.

Glioma

Human studies

Glioma is the most common malignant brain tumor and represents about 60 % of all central nervous system (CNS) tumors. Most of these are astrocytic tumors divided into low-grade (WHO grades I-II) and high-grade (WHO grades III-IV). The most common glioma type is glioblastoma multiforme (WHO grade IV) with the peak incidence in the age group 45-75 years and median survival less than one year (Ohgaki, Kleihues 2005). No substantial increasing survival has been obtained during recent years. Three research groups have provided results in case-control studies on glioma, Interphone (Interphone 2010), Coureau et al (2014) and the Hardell group in Sweden (Hardell, Carlberg 2009, 2015a; Hardell et al 2006, 2011a, 2011b).

Random effects model was used for meta-analyses of published studies, based on test for heterogeneity in the overall group ("all mobile"), see also http://www.bioinitiative.org/. Note that only our group assessed also use of cordless phones. Thus the reference category in our studies included cases and controls with no use of wireless phones in contrast to the other studies investigating only mobile phone use. Including cordless phone use in the 'unexposed' group would bias the risk estimates towards unity (Hardell el at 2011a)

In Table 1 results for highest cumulative use in hours of mobile phones are given. All studies reported statistically significant increased risk for glioma and the meta-analysis yielded odds ratio (OR) = 1.90, 95 % confidence interval (CI) = 1.31-2.76. For ipsilateral mobile phone use the risk increased further to OR = 2.54, 95 % CI = 1.83-3.52 in the meta-analysis based on 247 exposed cases and 202 exposed controls. Further support for the increased risk of glioma associated with mobile phone use has been obtained in additional analyses of parts of the Interphone study (Cardis et al 2011, Grell et al 2016, Momoli et al 2017).

Table 1. Numbers of exposed cases (Ca) and controls (Co) and odds ratio (OR) with 95 % confidence interval (CI) for glioma in case-control studies in the highest category of cumulative use in hours for mobile phone use.

	All			**Ipsilateral**		
	Ca/Co	OR	95 % CI	Ca/Co	OR	95 % CI
Interphone 2010						
Cumulative use ≥1,640 h	210/154	1.40	1.03 – 1.89	100/62	1.96	1.22 – 3.16
Coureau et al 2014						
Cumulative use ≥896 h	24/22	2.89	1.41 – 5.93	9/7	2.11	0.73 – 6.08
Hardell, Carlberg 2015						
Cumulative use ≥1,640 h	211/301	2.13	1.61 – 2.82	138/133	3.11	2.18 – 4.44
Meta-analysis						
Cumulative use ≥1,640 h*	445/477	1.90	1.31 – 2.76	247/202	2.54	1.83 – 3.52

**≥896 h used for Coureau et al.*

We analyzed survival of the patients in our studies and found shorter survival in patients with glioblastoma multiforme associated with use of wireless phones compared with patients with no use (Carlberg, Hardell 2014). Interestingly mutation of the p53 gene involved in disease progression has been reported in glioblastoma multiforme in patients with mobile phone use

≥3 hours per day. The mutation was statistically significant correlated with shorter overall survival time (Akhavan-Sigari et al 2014).

NTP study
No increased incidence of glioma was reported in the mice study (*NTP TR 596*).

In male rats (*NTP TR 595*) malignant glioma and glia cell hyperplasia occurred in all groups exposed to GSM-modulated cell phone RF radiation for 2 years. No lesions were seen in sham controls. In female rats glial cell hyperplasia occurred in one rat (3 W/kg) but none in sham controls. One malignant glioma occurred in one rat in the 6 W/kg group but none in sham controls. These results were not statistically significant.
In male rates exposed to CDMA-modulated cell phone RF radiation for 2 years there was an increased incidence of malignant glioma with a statistically significant trend, p = 0.044. In females three malignant glioma occurred in the 1.5 W/kg group, but none in the other exposed groups or sham control. Glial cell hyperplasia was seen in most exposed groups, although not statistically significant.

Evaluation
Based on human epidemiology studies and the NTP animal study there is clear evidence that RF radiation causes glioma in humans.

Meningioma

Human studies
Meningioma is an encapsulated, well-demarked and rarely malignant tumor. It is the most common benign brain tumor that accounts for about 30 % of intracranial neoplasms. It develops from the pia and arachnoid membranes that cover CNS. It is slow growing and gives neurological symptoms by compression of adjacent structures. Most common are headaches and seizures. The incidence is about two times higher in women than in men and meningioma develops mostly among middle aged and older persons (Cea-Soriano et al 2012). The same research groups as for glioma included also meningioma in their case-control studies with a separate publication on meningioma by Carlberg, Hardell (2015). Results of the meta-analyses for cumulative exposure in highest exposure category are given in Table 2. A statistically significant increased risk was obtained for ipsilateral mobile phone use with OR = 1.49, 95 % CI = 1.08-2.06.

Table 2. Numbers of exposed cases (Ca) and controls (Co) and odds ratio (OR) with 95 % confidence interval (CI) for meningioma in case-control studies in the highest category of cumulative use in hours for mobile phone use.

	All			**Ipsilateral**		
	Ca/Co	OR	95 % CI	Ca/Co	OR	95 % CI
Interphone 2010						
Cumulative use ≥1,640 h	130/107	1.15	0.81 – 1.62	46/35	1.45	0.80 – 2.61
Coureau et al 2014						
Cumulative use ≥896 h	13/9	2.57	1.02 – 6.44	6/4	2.29	0.58 – 8.97
Carlberg et al 2013						
Cumulative use ≥1,640 h	141/301	1.24	0.93 – 1.66	67/133	1.46	0.98 – 2.17
Meta-analysis						
Cumulative use ≥1,640 h*	284/417	1.27	0.98 – 1.66	119/172	1.49	1.08 – 2.06

**≥896 h used for Coureau et al.*

NTP study
No increased incidence was reported in mice (*NTP TR 596*).

In the rat study (*NTP TR 595*) increased incidence of malignant or benign granular cell tumors occurred in the males exposed to GSM-modulated cell phone RF radiation for 2 years. This was not statistically significant, trend p = 0.343. In female rats granular cell tumors malignant or benign were not associated with RF radiation, p trend = 0.594.

Evaluation
Based on human epidemiology studies and the NTP animal study there is equivocal evidence that RF radiation causes meningioma in humans (may be related to exposure).

Rate/incidence of brain tumors

The Swedish Cancer Register has not shown increasing incidence of brain tumors in a study for the time period 1979-2008, and has been used to dismiss epidemiological evidence on a risk (Deltour et al 2012). We have previously published that descriptive studies cannot be used to dismiss results in analytical epidemiology with individual exposure histories such as in case-control studies. We have also published the deficiencies in reporting of brain tumors to the Swedish Cancer Register (Hardell, Carlberg 2015b). Results for more recent time periods have now been published. These articles discuss also results from studies in other countries.

We used the Swedish National Inpatient Register (IPR) and Causes of Death Register (CDR) to study the incidence of brain tumors comparing with the Swedish Cancer Register data for the time period 1998–2013 using joinpoint regression analysis (Hardell, Carlberg 2015b). In the IPR we found a joinpoint in 2007 with Annual Percentage Change (APC) +4.25%, 95% CI +1.98, +6.57% during 2007–2013 for tumors of unknown type in the brain or CNS. Figure 1 shows time trends in IPR for brain tumors of unknown type (D43), red line, and mobile phone communication; number of out-going mobile phone minutes in millions per year (blue line). The figure shows increasing rates of brain tumors with some latency in relation to increasing use of mobile phones.

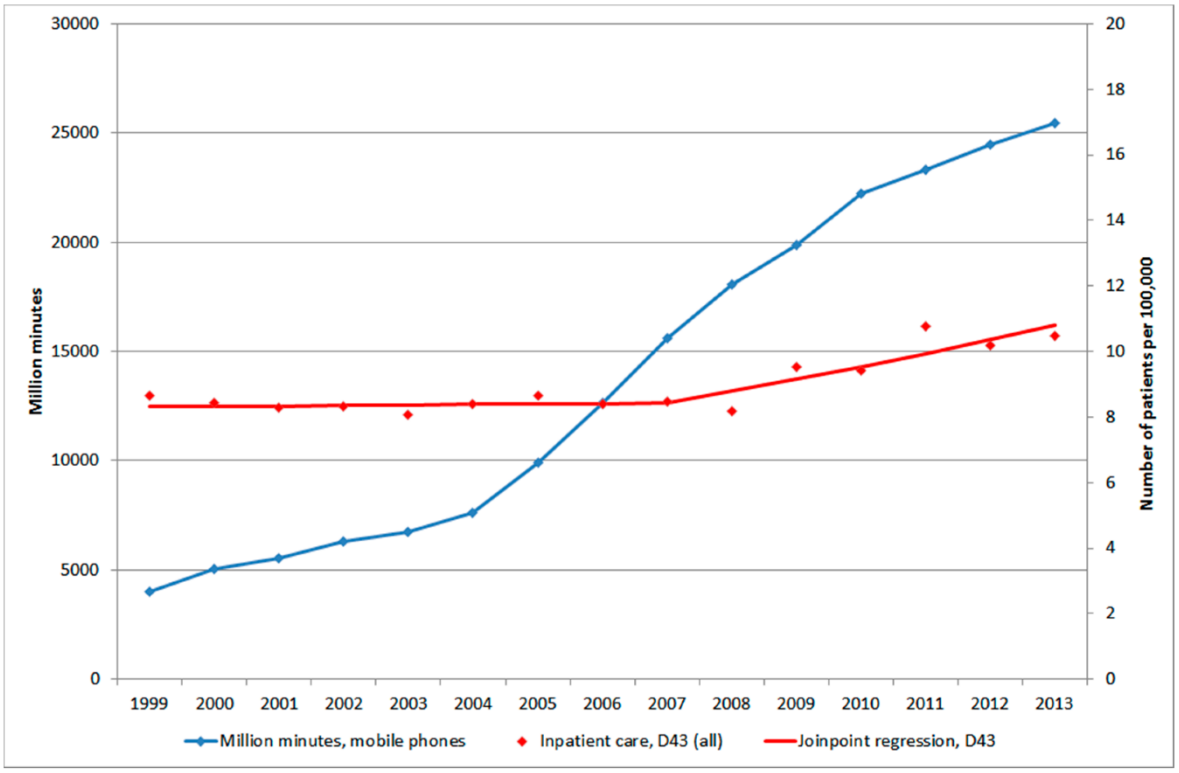

Figure 1. Number of out-going mobile phone minutes in millions during 1999–2013 (http://statistik.pts.se/pts2013/download/Svensk%20Telemarknad%202013.pdf ; accessed on 1 April 2015) and joinpoint regression analysis of number of patients per 100,000 inhabitants according to the Swedish National Inpatient Register for all ages during 1999–2013 diagnosed with D43 = tumor of unknown type in the brain or CNS (http://www.socialstyrelsen.se/statistik/statistikdatabas/diagnoserislutenvard ; accessed on 1 April 2015).

In the Causes of Death Register (CDR) joinpoint regression found one joinpoint in 2008 with APC during 2008–2013 +22.60%, 95% CI +9.68, +37.03%. These tumor diagnoses would be based on clinical examination, mainly CT and/or MRI, but without histopathology or cytology. No statistically significant increasing incidence was found in the Swedish Cancer Register during these years. We postulated that a large part of brain tumors of unknown type are never reported to the Cancer Register. Furthermore, the frequency of diagnoses based on autopsy has declined substantially due to a general decline of autopsies in Sweden adding further to missing cases. We conclude that the Swedish Cancer Register is not reliable to be used to dismiss results in epidemiological studies on the use of wireless phones and brain tumor risk.

In Figure 2 we show rates per 100,000 of deaths in unknown type of brain tumor (D43), red line, and number of out-going mobile phone minutes in millions (blue line) during 1999–2013. We postulate that the increasing rate of patients deceased with brain tumor may be associated with the increasing use of mobile phones.

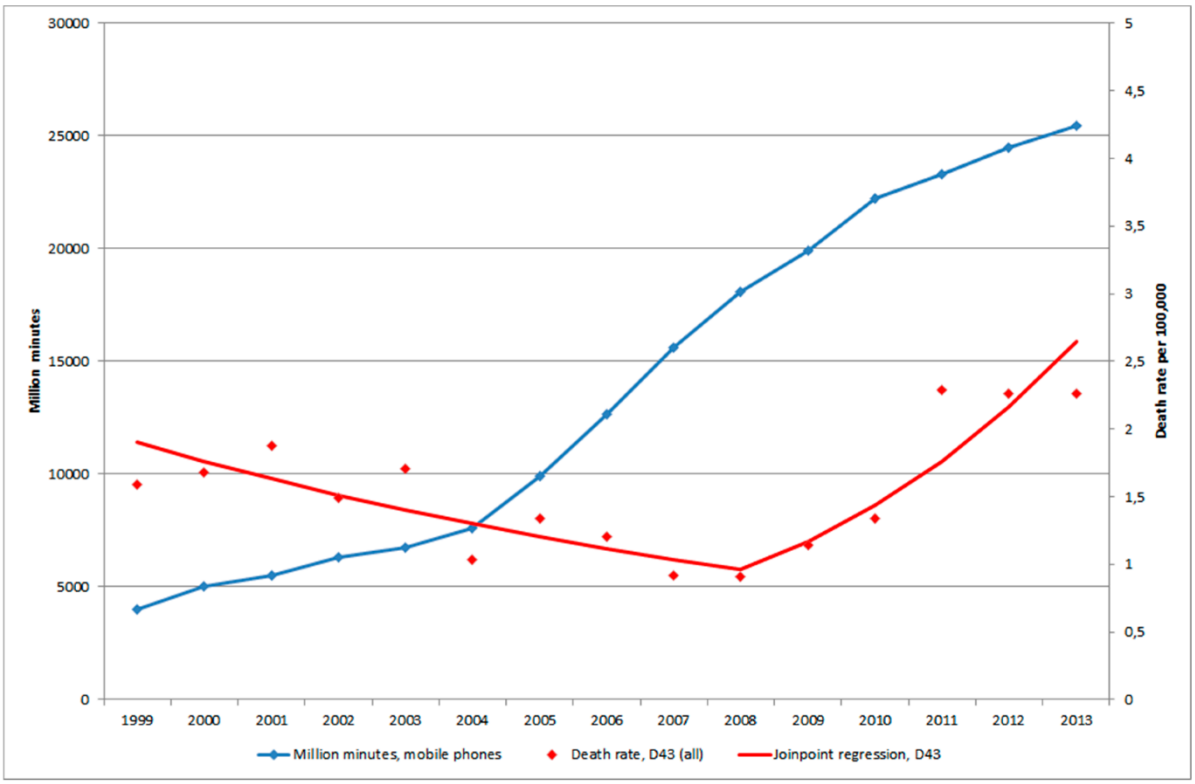

Figure 2. Number of out-going mobile phone minutes in millions during 1999–2013 (http://statistik.pts.se/pts2013/download/Svensk%20Telemarknad%202013.pdf ; accessed on 1 April 2015) and joinpoint regression analysis of age-standardized death rates per 100,000 inhabitants according to the Swedish Causes of Death Register for all ages during 1999–2013 diagnosed with D43 = tumor of unknown type in the brain or CNS (http://www.socialstyrelsen.se/ statistik/statistikdatabas/dodsorsaker ; accessed on 1 April 2015).

In an up-dated further analysis we used the Swedish Inpatient Register (IPR) to analyze rates of brain tumors of unknown type (D43) during 1998-2015 in different age groups (Hardell, Carlberg 2017). Average Annual Percentage Change (AAPC) per 100,000 increased with +2.06 %, 95 % confidence interval (CI) +1.27, +2.86 % in both genders combined. A joinpoint was found in 2007 with APC 1998-2007 of +0.16 %, 95 % CI -0.94, +1.28%, and 2007-2015 of +4.24 %, 95 % CI +2.87, +5.63 %. Highest AAPC was found in the age group 20-39 years.

In the Swedish Cancer Register the age-standardized incidence rate per 100,000 increased for brain tumors, ICD-code 193.0, during 1998-2015 with AAPC in men +0.49 %, 95 % CI +0.05, +0.94 %, and in women +0.33 %, 95 % CI -0.29, +0.45 % (Hardell, Carlberg 2017). The cases with brain tumor of unknown type lack morphological examination. Brain tumor diagnosis was based on cytology/histopathology in 83 % for men and in 87 % for women in 1980. This frequency increased to 90 % in men and 88 % in women in 2015. During the same time period CT and MRI imaging techniques were introduced and morphology is not always necessary for diagnosis. If all brain tumors based on clinical diagnosis with CT or MRI had been reported to the Cancer Register the frequency of diagnoses based on cytology/histology would have decreased in the register. The results indicate underreporting of brain tumor cases to the Cancer Register. The real incidence would be higher. Thus, incidence trends based on

the Cancer Register should be used with caution. Our results support mobile and cordless phones as risk factors for brain tumors with a reasonable latency period.

Figure 3 shows joinpoint regression analysis of age-standardized incidence rates per 100,000 in men aged 60–79 years with astrocytoma grade III or IV in the Swedish Cancer Register during 1998–2015, and Figure 4 results in women.

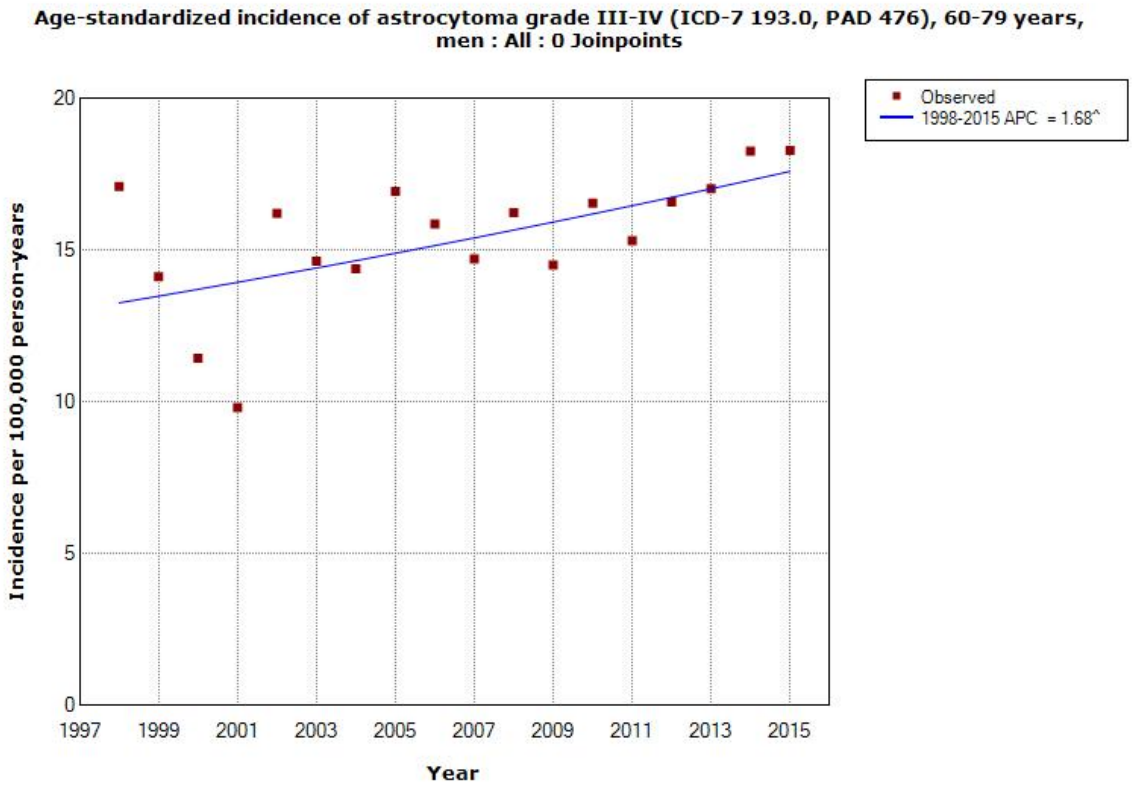

Figure 3. Joinpoint regression analysis of age-standardized incidence rates per 100,000 in men aged 60–79 years with astrocytoma grade III or IV in the Swedish Cancer Register during 1998–2015. APC/AAPC +1.68 %, 95 % CI +0.39, +2.99 %. (http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer).
https://doi.org/10.1371/journal.pone.0185461.g005

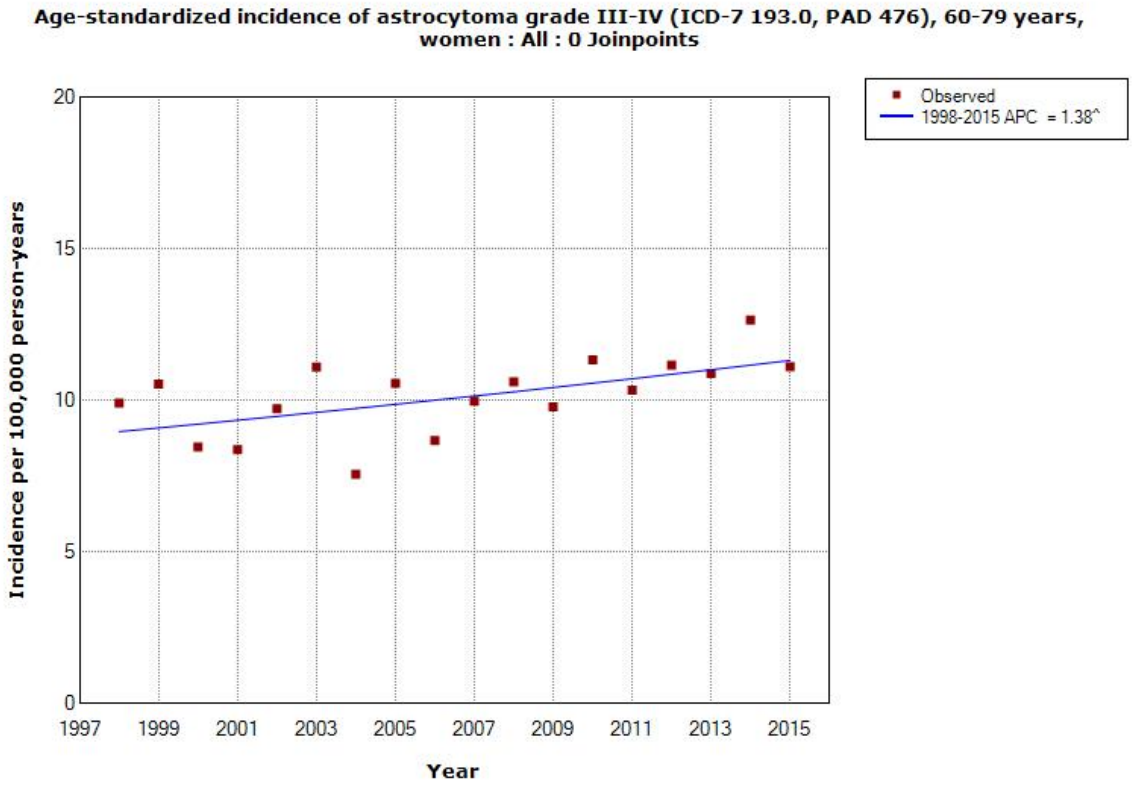

Figure 4. Joinpoint regression analysis of age-standardized incidence rates per 100,000 in women aged 60–79 years with astrocytoma grade III or IV in the Swedish Cancer Register during 1998–2015. APC/AAPC + 1.38 %, 95 % CI +0.32, +2.45 %. (http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer).
https://doi.org/10.1371/journal.pone.0185461.g006

Evaluation
Increasing rates/incidences of brain tumors in Sweden, a country with among the earliest use of wireless phones in the world, have been published. Similar findings have been reported from other countries. The results give some evidence that RF radiation causes brain tumors in humans.

Acoustic neuroma (vestibular schwannoma)

Human studies
Acoustic neuroma, also called vestibular schwannoma, is a benign tumor located on the eight cranial nerve from the inner ear to the brain. It is usually encapsulated and grows in relation to the auditory and vestibular portions of the nerve. It grows slowly and due to the narrow anatomical space may give compression of vital brain stem structures. First symptoms of acoustic neuroma are usually tinnitus and hearing problems. Results for use of mobile phones in Interphone (2011) and Hardell et al (2013a) are given in Table 3. Statistically significant increased risk was found for cumulative ipsilateral use ≥ 1,640 h yielding OR = 2.71, 95 % CI = 1.72-4.28.

Table 3. Numbers of exposed cases (Ca) and controls (Co) and odds ratio (OR) with 95 % confidence interval (CI) for acoustic neuroma in case-control studies in the highest category of cumulative use in hours for mobile phone use.

	All			**Ipsilateral**		
	Ca/Co	OR	95 % CI	Ca/Co	OR	95 % CI
Interphone 2010						
Cumulative use ≥1,640 h	77/107	1.32	0.88 – 1.97	47/46	2.33	1.23 – 4.40
Hardell et al 2013						
Cumulative use ≥1,640 h	27/301	2.40	1.39 – 4.16	19/133	3.18	1.65 – 6.12
Meta-analysis						
Cumulative use ≥1,640 h	104/408	1.73	0.96 – 3.09	66/179	2.71	1.72 – 4.28

The study by Moon et al (2014) was not included in the meta-analysis since data on cumulative mobile phone use with numbers of cases and controls were not given. Support of an increased risk was seen in the case-case part of the study (Moon et al 2014), as also reported by Sato et al (2011) in their case-case analysis. Pettersson el al made a case-control study on acoustic neuroma in Sweden not overlapping our study (Pettersson et al 2014). An increased risk for highest category of cumulative use of both mobile phone ($\geq$ 680 h OR = 1.46, 95 % CI = 0.98-2.17) and cordless phone ($\geq$900 hours OR = 1.67, 95 % CI = 1.13-2.49) was found. We did not include that study in our meta-analysis due to the many scientific shortcomings in the study, e.g. laterality analysis was not made for cordless phone and the numbers in the laterality analysis for mobile phone are not consistent in text and tables and obviously not correct, and the 'unexposed' reference category included subjects using either mobile or cordless phone (Hardell, Carlberg 2014).

The Danish part of Interphone study reported mean tumor volume 1.66 cm^3 among regular mobile phone users and 1.39 cm^3 for non-users (p = 0.03) (Christensen et al 2004). We analyzed percentage change in tumor volume per year of latency and 100 h of cumulative use (Hardell et al 2013). For all types of wireless phones the percentage of tumor volume increased, statistically significant for analogue mobile phones. Moon et al (2014) reported statistically significant larger mean tumor volume for heavy users (11.32 $\pm$ 15.43 cm^3) compared with light users (4.88 $\pm$ 5.60 cm^3) based on daily amount of mobile phone use (p = 0.026). Similar results were found for cumulative hours of use. Taken together these results support tumor promotion by RF radiation.

NTP study

No malignant schwannoma was reported in the mice study (*NTP TR 596*).

In the rat study (*NTP TR 595*) there was an increased incidence of malignant schwannoma in the heart in males exposed to GSM modulated cell phone RF radiation for 2 years; trend p = 0.041. The tumor was found in all exposed male rats, whereas no malignant schwannoma was found in sham controls. Endocardial hyperplastic Schwann cell lesions, that are preneoplastic, were found in one 1.5 W/kg and in two 6 W/kg males, but no in sham control. Two female rats were diagnosed with malignant schwannoma in the heat in the 3 w/kg group, no was found in the two other exposure groups or in sham control, p trend = 0.640.

Evaluation

Based on human epidemiology studies and the NTP animal study there is clear evidence that RF radiation causes vestibular schwannoma (acoustic neuroma) in humans

Pituitary tumor

Human studies

In a case-control study from Japan no statistically significant increased risks were found for use of mobile phone (Takebayashi et al 2008). A somewhat increased risk was found in the highest cumulative call time in hours, OR = 1.33, 95 % CI = 0.58-3.09. The cases were aged 30-69 years and diagnosed during 2000-2004.

In a UK case-control study with patients diagnosed during 2001-2005 overall no statistically significant increased risks were found (Schoemaker, Swerdlow 2009). In the group with ≥ 10 years of use a somewhat increased risk was found for analog mobile phone use, OR = 1.2, 95 % CI = 0.6-2.4, and digital mobile phone use with OR = 2.5, 95 % CI = 0.7-9.1.

In a case-control study from China with cases diagnosed 2006-2010 mobile phone use yielded an increased risk for pituitary tumor, OR = 7.6, 95 % CI = 2.6-21.4 and duration of use gave OR = 8.5, 95 % CI = 2.8-24.4 (Leng, Zhang 2016). However no more data were given.

The incidence of pituitary tumors increased during the time period 2004-2009 in USA (Gittleman et al 2014). The incidence is increasing in Sweden especially sine 2000, see Fig 5. There seems to be a drop during the latest year, but this may be explained by a time lag in the reporting to the Swedish Cancer Register.

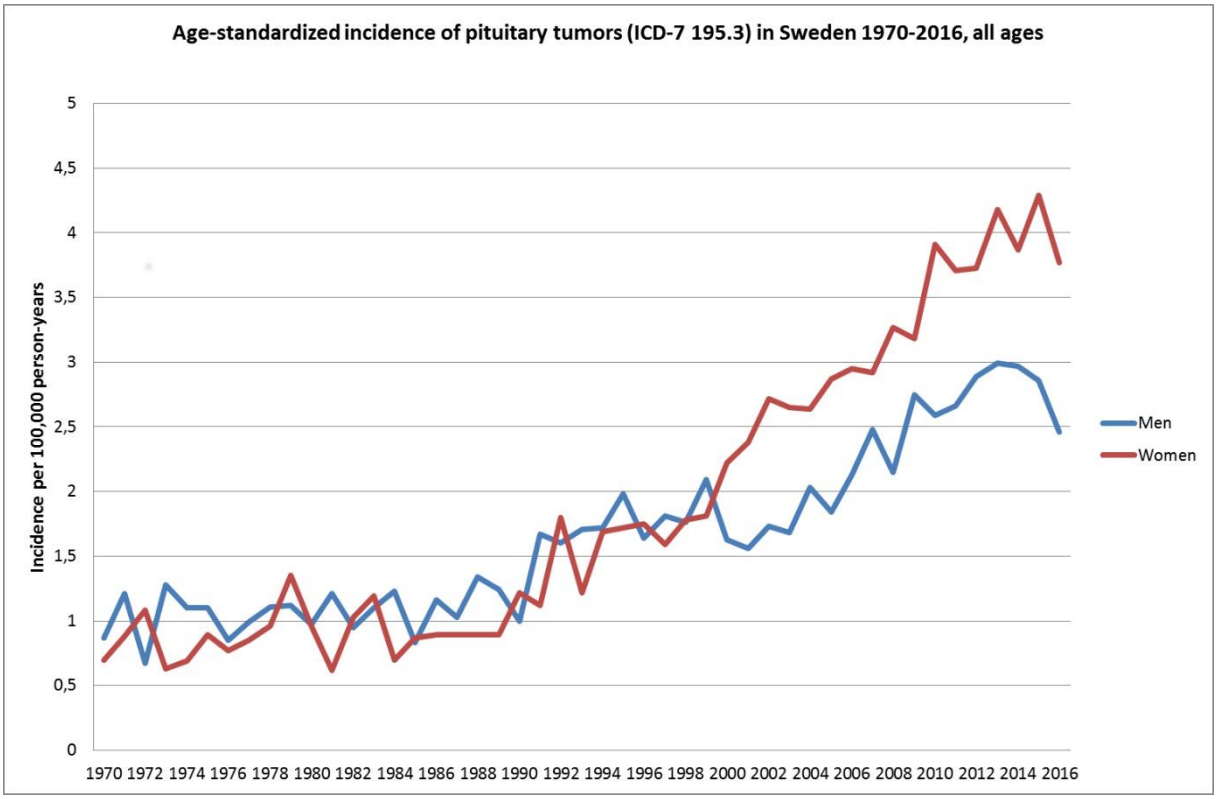

Figure 5. Age-standardized incidence of pituitary tumors (ICD-7 195.3) in Sweden 1970-2016 for men and women, all ages, according to the Swedish Cancer Register (http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer).

NTP
In male rats exposed to GSM-modulated cell phone RF radiation for 2 years (*NTP TR 595*) increased incidence of pituitary adenoma was found in all exposed groups, although not statistically significant. In females the incidence of adenoma in 1.5 W/kg and 6 W/kg were statistically significant decreased.

In male rats exposed to CDMA-modulated RF radiation for 2 years an increased incidence of pituitary adenoma was found in the 1.5 W/kg (p=0.208) and 3W/kg (p=0.030). In females there was a statistically decreased incidence of adenoma or carcinoma in the 3 W/kg group (p=0.030).

In male mice (*NTP TR 596*) exposed to CDMA-modulated RF radiation for 2 years two adenoma and one carcinoma occurred in pars distalia of the pituitary gland. No carcinoma or adenoma occurred in the sham control or the other two exposure groups. No increased incidence was seen in female mice.

Evaluation:
Based on human epidemiology studies and the NTP animal study there is equivocal evidence that RF radiation causes pituitary tumor in humans (may be related to exposure).

Thyroid cancer

Human studies
The incidence of thyroid cancer is increasing in many countries, especially the papillary type that is the most radiosensitive type. We used the Swedish Cancer Register to study the incidence of thyroid cancer during 1970-2013 using joinpoint regression analysis (Carlberg et al 2016). In women, the incidence increased statistically significantly during the whole study period; AAPC +1.19 % (95 % CI +0.56, +1.83 %). Two joinpoints were detected, 1979 and 2001, with a high increase of the incidence during the last period 2001-2013 with an APC of +5.34 % (95 % CI +3.93, +6.77 %).

In the age group 20-39 years joinpoint regression analysis of age-standardized incidence of thyroid cancer in women, aged 20–39 years, APC increased with + 10.77 % (95 % CI +5.75, +16.04 %) during the time period 2006-2013, see Figure 6.

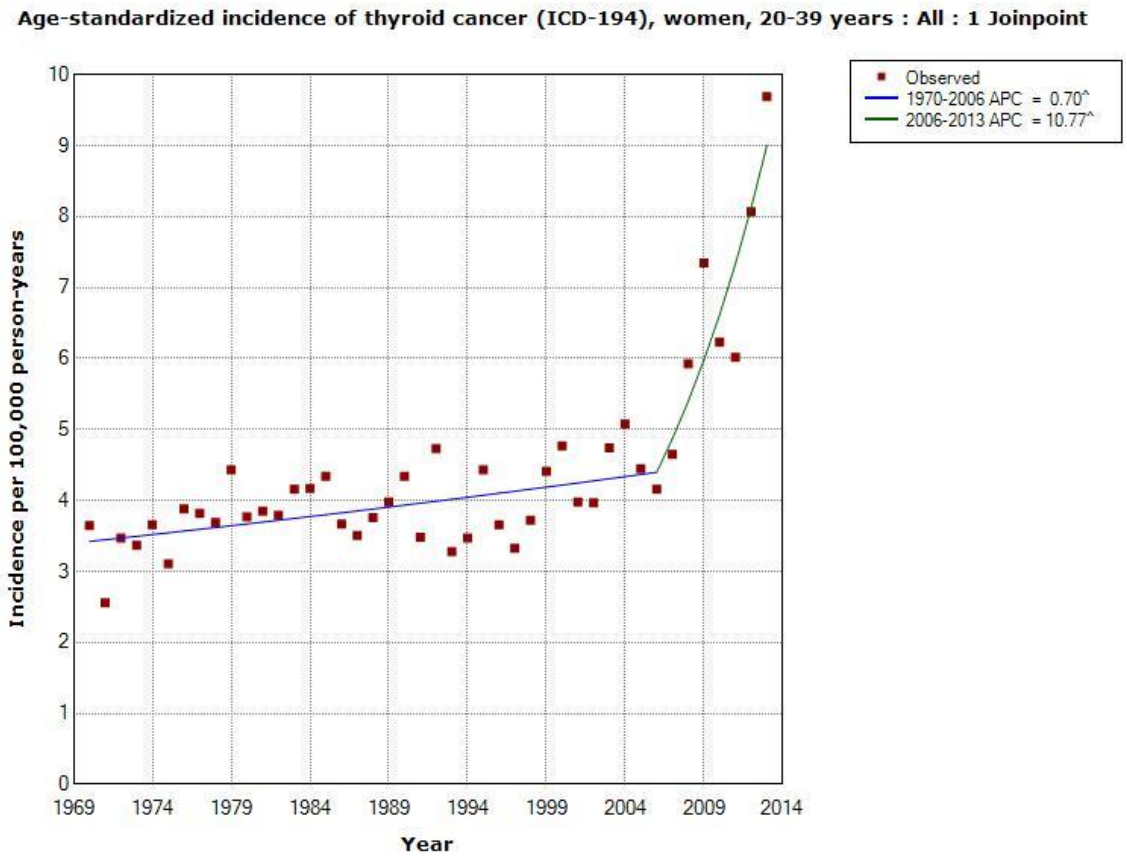

Figure 6. Joinpoint regression analysis of age-standardized incidence of thyroid cancer for women, aged 20–39 years, 1970–2013. Incidence per 100,000 inhabitants for ICD-7 code 194 according to the Swedish Cancer Register (http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer)

Analyses based on data from the Cancer Register showed that the increasing trend in Sweden was mainly caused by thyroid cancer of the papillary type. The incidence increased statistically significantly in women with an AAPC of +4.38 % (95 % CI +2.95, +5.84 %) during 1993-2013, see Figure 7. One joinpoint was detected in 2006; 1993-2006 APC +1.69 % (95 % CI +0.32, +3.08 %), 2006-2013 APC +9.58 % (95 % CI +5.85, +13.44 %). The incidence increased in men during 1993-2013 with an AAPC of +3.95 % (95 % CI +2.20, +5.73%).

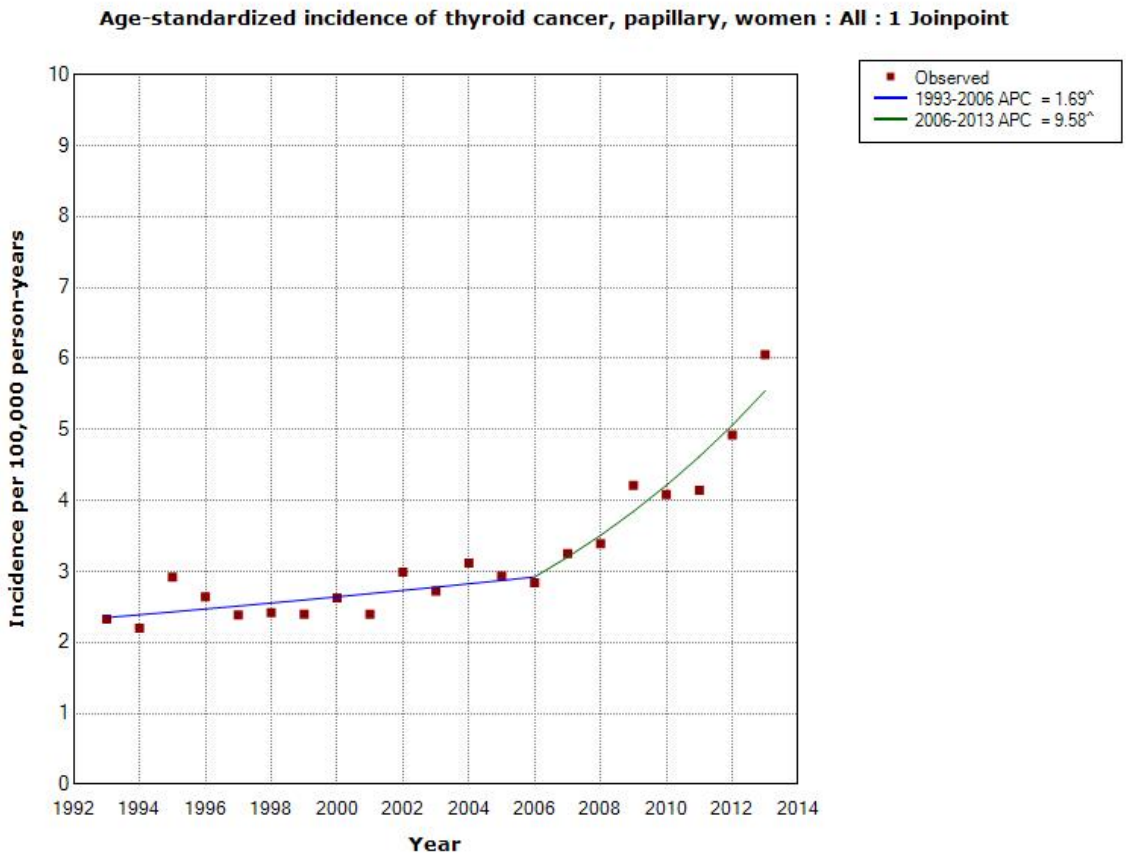

Figure 7. Joinpoint regression analysis of age-standardized incidence of papillary thyroid cancer for women, all ages, 1993–2013. Incidence per 100,000 inhabitants for ICD-7 code 194; data obtained from the Swedish Cancer Register

AAPC for all men during 1970-2013 was +0.77 % (95 % CI -0.03, +1.58 %). One joinpoint was detected in 2005 with a statistically significant increase in incidence during 2005-2013; APC +7.56 % (95 % CI +3.34, +11.96 %). Based on NORDCAN data, there was a statistically significant increase in the incidence of thyroid cancer in the Nordic countries during the same time period. In both women and men a joinpoint was detected in 2006. The incidence increased during 2006-2013 in women; APC +6.16 % (95 % CI +3.94, +8.42 %) and in men; APC +6.84 % (95 % CI +3.69, +10.08 %), thus showing similar results as the Swedish Cancer Register.

We postulate that the whole increase cannot be attributed to better diagnostic procedures. In Figure 8 Swedish data are shown on number of out-going mobile phone minutes during 2001-2013 and the incidence of thyroid cancer in men (green line) and in women (red line). Clearly, with a lag time of some years after the increasing number of out-going calls, the thyroid cancer incidence is increasing.

Increasing exposure to ionizing radiation, e.g. medical CT scans, and to RF radiation should be further studied as causative factors to this emerging thyroid cancer health problem.

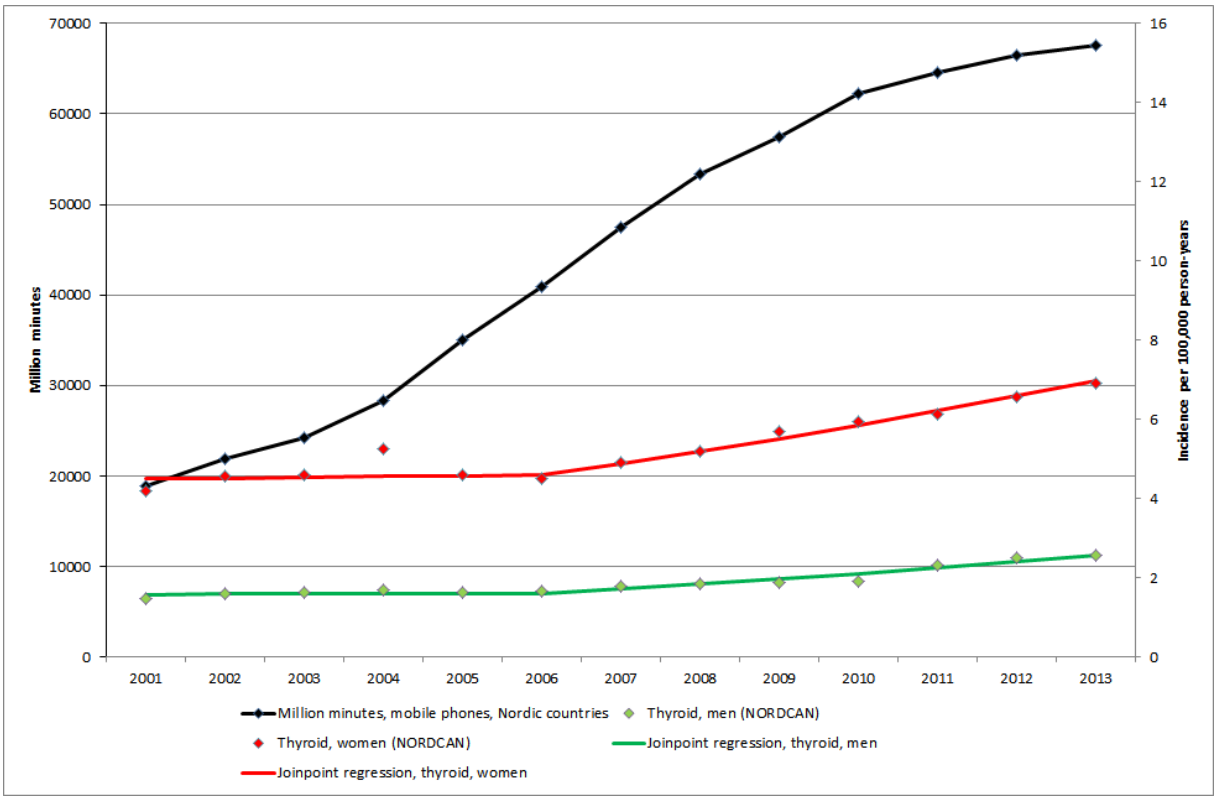

Figure 8. Number of out-going mobile phone minutes and incidence of thyroid cancer 2001–2013. Mobile phone minutes in millions in the Nordic countries (http://statistik.pts.se/PTSnordic/NordicBaltic2014/) and incidence per 100,000 person-years for all ages 2001–2013 according to NORDCAN (http://www-dep.iarc.fr/NORDCAN/english/frame.asp). Joinpoint regression analyses based on the time period 1970–2013

Figure 9 shows three developments in the antenna design in mobile phones that may be of relevance in thyroid carcinogenesis. The second generation (2G) mobile phones started in the 1990s with the external retractable monopole or helical antennas. The 2G GSM band operated at 800/900 MHz frequency band, later accompanied by 1,800 MHz band. Around the turn of the millennium, the external antennas were starting to disappear, replaced with new phone models with internal planar or microstrip antennas. The first internal antenna was introduced in 1998 and the first dual-band mobile phone, with the internal antenna, was introduced on the market in 1999 (Garg et al 2001). The internal antennas were positioned at the top of the telephone. With the emergence of the smartphones in the mid and late 2000s, the internal antenna location started to shift from the top of the phone to the bottom. Currently, the majority of smartphone models have their antenna positioned at the bottom of the phone, thus closer the thyroid gland (grey in figure). This would have a major impact on increasing radiation to the thyroid gland from smartphones.

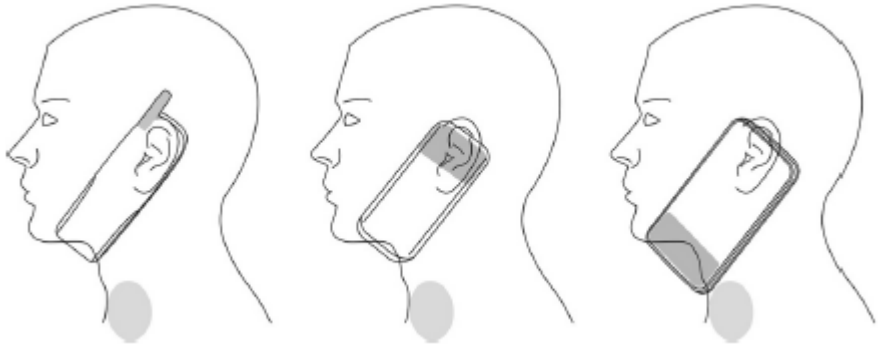

Figure 9. Mobile phone antenna placements in regard to the thyroid gland

Some published laboratory studies are of interest, Radiofrequency radiation at 2.45 GHz at a non-thermal level modified the morphology of the thyroid gland in a study on rats. The central and peripheral follicles presented increased in size and the thickness of peripheral septa decreased. Peripheral follicles increased in size with repeated exposure at 3 W power (Misa-Agustiño et al 2015).

In another study on rats, whole body exposure to 900 MHz pulse-modulated RF radiation that was similar to that emitted by the global system for mobile communications (GSM) mobile phones caused pathological changes in the thyroid gland. The gland structure was altered and caspase-dependent pathways of apoptosis were enhanced (Eşmekaya et al 2010).

NTP studies
In mice (*NTP TR 596*) no increased incidence was reported.

In female rats (*NTP TR 595*) a statistically significant increased incidence of C-cell hyperplasia was found in the 2 years GSM exposed groups (1.5, 3 and 6 W/kg, respectively). In males a statistically non-significant increased incidence was seen in the 1.5 W/kg exposure group.

Evaluation
C-cell hyperplasia as a precursor to familial medullary thyroid cancer in humans is well established. C-cell hyperplasia may be a precursor to other types of thyroid cancer but its role is not well established. Based on human cancer statistics and the NTP animal study there is some evidence that thyroid cancer is caused by RF radiation in humans.

Malignant lymphoma

Human studies
Few studies exist on malignant lymphoma and exposure to RF radiation. In a case-control study male and female subjects aged 18-74 years living in Sweden were included during a period from 1 December 1999 to 30 April 2002 (Hardell et al 2005). Controls were selected from the national population registry. Exposure to different agents was assessed by questionnaire. In total, 910 (91%) cases and 1016 (92%) controls participated. NHL of the B-cell type was not associated with the use of cellular or cordless telephones. Regarding T-cell NHL and >5 year latency period, the use of analogue cellular phones yielded: OR = 1.46, 95%; 95 % CI = 0.58-3.70, digital: OR=1.92, 95%; CI=0.77-4.80 and cordless phones: OR=2.47; 95 % CI=1.09-5.60. The corresponding results for certain, e.g. cutaneous and

leukaemia, T-cell lymphoma for analogue phones were: OR=3.41, 95%; CI=0.78-15.0, digital: OR=6.12, 95%; CI=1.26-29.7 and cordless phones: OR=5.48, 95%; CI=1.26-23.9. The results indicate an association between T-cell NHL and the use of cellular and cordless telephones, however based on low numbers and must be interpreted with caution. Regarding B-cell NHL no association was found.
A case-control study in USA used a questionnaire to assess cellular telephone use in 551 NHL cases and 462 frequency-matched population controls (Linet et al 2006). Compared to persons who had never used cellular telephones, risks were not increased among individuals whose lifetime use was more than 100 times (e.g., regular users, OR = 0.9, 95% CI= 0.6-1.4). Among regular users compared to those who had never used hand-held cellular telephones, risks of NHL were not statistically significantly associated with minutes per week, duration, cumulative lifetime or year of first use, although NHL was non-significantly higher in men who used cellular telephones for more than 8 years; OR = 2.4, 95 % CI = 0.8-7.0. Little evidence linked use of cellular telephones with total, diffuse large B-cell lymphoma or follicular NHL. No results were presented for T-cell lymphoma.

In USA primary central nervous system lymphoma (PCNSL) rates in immunocompetent men and women aged 65+ years increased statistically significantly (1.7% and 1.6% per year, respectively), but remained stable in other age groups during 1992-2011 (Shiels et al 2016). Thus, the increasing rates could not be related to HIV or immune suppression in organ transplant patients.

In Sweden increasing incidence of PCNSL was reported for the time period 2000-2013 in immunocompetent persons (Eloranta et al 2018). With 359 identified PCNSL cases (median age 66 years), overall incidence was 0.26 (95% CI= 0.24-0.29) and the average annual increase 4% (p = 0.002). The increasing trend was primarily observed among elderly individuals (70+ years). Similarly, an increase in incidence of all brain tumors was noted only among the elderly.

No etiologic factor has clearly been defined to explain the increasing incidence of brain lymphoma. However, it has occurred during a time period when RF radiation to the brain from wireless phones has increased.

It should be noted that in transgenic mouse an increased incidence of lymphoma exposed to 900 MHz GSM RF radiation was reported; p=0.006 versus sham group (Repacholi et al 1997). No increased risk for malignant lymphoma was found in mice exposed to GSM 900 MHz but the incidence in the sham exposed group was higher than in the Repacholi et al (1997) study (Utteridge et al 2002).

NTP study
In NTP TR 595 no conclusive evidence of increased incidence of malignant lymphoma was reported in rats.

In NTP TR 596 there were in female mice exposed to GSM modulated cell phone RF radiation for 2 years increased incidences of malignant lymphoma in all exposed groups compared to the controls. The increase was statistically significant in the 2.5 W/kg (p=0.004) and 5 W/kg groups (p=0.035). In the CDMA modulated cell phone RF radiation for 2 years the incidence increased in female mice in all exposed groups compared to the controls, statistically significant in the 2.5 W/kg group (p=0.035).

Evaluation
Based on human epidemiology studies and the NTP study there is equivocal evidence that malignant lymphoma is caused by RF radiation in humans (may be related to exposure).

Skin (cutaneous tissue)

Human studies

Few studies exist on RF radiation and the risk for skin tumors. In a Danish cohort on mobile phone subscribers from 1987-1995 followed to 2007 no increased risks of skin cancer was seen (Poulsen et al 2013). The same cohort has also been used for studying brain tumor risk. Due to serious methodological problems including misclassification of exposure it has been evaluated to be uninformative (Söderqvist et al 2012, IARC 2013).

In a Swedish study on cutaneous malignant melanoma diagnosed during 2000-2003 no increased risk was seen overall (Hardell et al 2011c). In the shortest latency period >1-5 years and highest cumulative use > 365 hours wireless phone use (mobile phone and/or cordless phone) yielded OR = 1.6, 95 % CI = 0.96-2.9. For melanoma in the most exposed anatomical area during use of the handheld phone, temporal, ear, cheek, the risk increased to OR = 2.1, 95 % CI = 1.1-3.8. The risk was overall highest for cases with first use of a wireless phone before 20 years of age, OR = 2.7, 95 % CI = 0.6-12, although based on low numbers. No interaction was seen with known risk factors for malignant lymphoma such as hair and eye color, skin type or sunburns as teenager.

Figure 10 displays the rapidly increasing incidence of malignant melanoma in Sweden in both genders. The increase is most marked from early 2000.

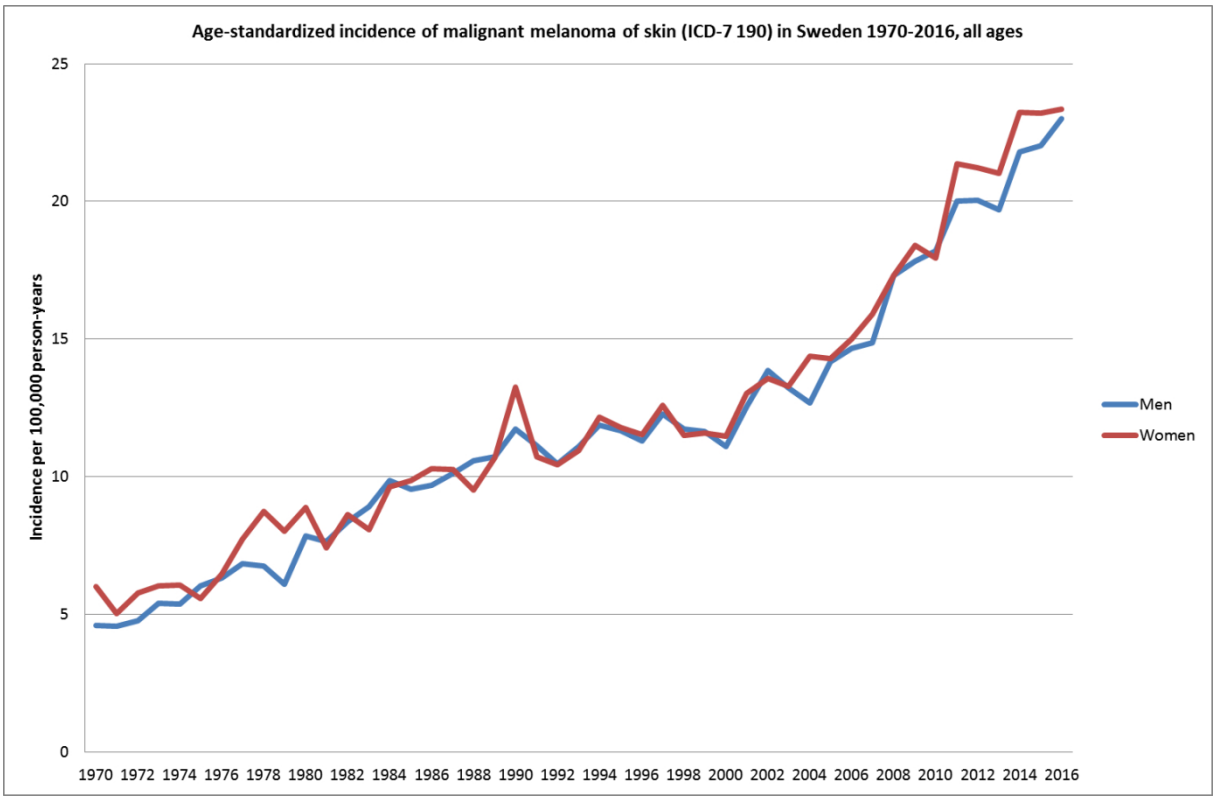

Figure 10. Age-standardized incidence of malignant melanoma (ICD-7 190) in Sweden 1970-2016 for men and women, all ages, according to the Swedish Cancer Register (http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer).

NTP study
Male rats exposed to GSM modulated cell phone RF radiation for 2 years (*NTP TR 595*) showed higher incidences of fibroma, fibrosarcoma, myxosarcoma, or malignant fibrous histiocytoma in the skin (subcutaneous tissue) in all exposed groups. The increased rates were not statistically significant. No statistically significant results were found in female rats.

The incidences of malignant fibrous histiocytoma were higher in 5 W/kg and 10 W/kg mice exposed to GSM modulated cell phone RF radiation for 2 years (*NTP TR 596*). The results were not statistically significant. The incidences of fibrosarcoma, sarcoma or malignant fibrous histiocytoma were higher in exposed mice compared with sham control, although not statistically significant, p trend = 0.093. No increased incidence was seen in female mice.

Evaluation
Based on human epidemiology studies and NTP animal studies there is equivocal evidence that RF radiation causes skin cancer in humans (may be related to exposure).

Conclusion

Based on case-control studies there is a consistent finding of increased risk for glioma and acoustic neuroma associated with use of mobile phones. Similar results are found for cordless phones in the Hardell group studies. These results are supported by the results in the NTP animal study (https://ntp.niehs.nih.gov/ntp/about_ntp/trpanel/2018/march/tr595peerdraft.pdf, https://ntp.niehs.nih.gov/ntp/about_ntp/trpanel/2018/march/tr596peerdraft.pdf). Malignant vestibular schwannoma is a similar tumor type as acoustic neuroma, also called vestibular schwannoma.

The findings are less consistent for meningioma although somewhat increased risk was seen in the meta-analysis of ipsilateral mobile phone use. A longer follow-up time is necessary for this type of slow growing tumor.

The results on glioma and acoustic neuroma are supported by results from other animal studies showing co-carcinogenic and tumor promoting effects from RF radiation (Tillman et al 2010, Lerchl et al 2015). The NTP study showed genotoxicity of RF radiation in rats and mice exposed to RF radiation (Smith-Roe et al 2017) and now presented in more detail. That result supports previous findings of DNA strand breaks in rat brain cells exposed to RF radiation (Lai, Singh 1997).

One mechanism in carcinogenesis could be oxidative stress with production of reactive oxygen species (ROS) as summarised by Yakymenko et al (2016). This could be an indirect mechanism for the increased brain and head tumor risk (Megha et al 2015) since ROS may give DNA damage.

By now carcinogenicity has been shown in human epidemiological studies replicated in animal studies. Laboratory studies on RF radiation have shown increased ROS production that can cause DNA strand brakes. We published in 2013 the conclusion that RF radiation should

be regarded as a human carcinogen Group 1 according to IARC definition, based on scientific evidence (Hardell, Carlberg 2013b) further supported in our up-dated article (Carlberg, Hardell 2017). That conclusion is reinforced by the current evaluation.

Overall evaluation of levels of evidence of carcinogenic activity

Glioma: Clear evidence
Meningioma: Equivocal evidence
Vestibular schwannoma (acoustic neuroma): Clear evidence
Pituitary tumor (adenoma): Equivocal evidence
Thyroid cancer: Some evidence
Malignant lymphoma: Equivocal evidence
Skin (cutaneous tissue): Equivocal evidence
Multi-site carcinogen: Some evidence

Based on the IARC preamble to the monographs, RF radiation should be classified as Group 1: The agent is *carcinogenic* to humans.

'This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.'
(*http://monographs.iarc.fr/ENG/Preamble/currentb6evalrationale0706.php)*

Respectfully submitted
Pro Bono Publico

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