

Comments on the US National Toxicology Program technical reports on toxicology and carcinogenesis study in rats exposed to whole-body radiofrequency radiation at 900 MHz and in mice exposed to whole-body radiofrequency radiation at 1,900 MHz

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Abstract. During the use of handheld mobile and cordless phones, the brain is the main target of radiofrequency (RF) radiation. An increased risk of developing glioma and acoustic neuroma has been found in human epidemiological studies. Primarily based on these findings, the International Agency for Research on Cancer (IARC) at the World Health Organization (WHO) classified in May, 2011 RF radiation at the frequency range of 30 kHz-300 GHz as a ‘possible’ human carcinogen, Group 2B. A carcinogenic potential for RF radiation in animal studies was already published in 1982. This has been confirmed over the years, more recently in the Ramazzini Institute rat study. An increased incidence of glioma in the brain and malignant schwannoma in the heart was found in the US National Toxicology Program (NTP) study on rats and mice. The NTP final report is to be published; however, the extended reports are published on the internet for evaluation and are reviewed herein in more detail in relation to human epidemiological studies. Thus, the main aim of this study was to compare earlier human epidemiological studies with NTP findings, including a short review of animal studies. We conclude that there is clear evidence that RF radiation is a human carcinogen, causing glioma and vestibular schwannoma (acoustic neuroma). There is some evidence of an increased risk of developing thyroid cancer, and clear evidence that RF radiation is a multi-site carcinogen. Based on the Preamble to the IARC Monographs, RF radiation should be classified as carcinogenic to humans, Group 1.

Introduction

Recently, the US National Toxicology Program (NTP) released results on the toxicology and carcinogenicity of radiofrequency (RF) radiation in rats and mice, as further discussed below. This initiated this article for the comparison of earlier human epidemiological studies with the NTP the findings, including a short review of animal studies.

NTP is an interagency program established in 1978 to coordinate toxicology research and testing across the Department of Health and Human Services. The program was also created to strengthen the science base in toxicology, develop and validate improved testing methods, and provide information about potentially toxic chemicals to health regulatory and research agencies, scientific and medical communities, and the public. NTP is headquartered at the National Institute of Environmental Health Sciences (NIEHS) (<https://ntp.niehs.nih.gov/about/org/index.html>).

The brain is the main target of the exposure to RF radiation during the use of handheld wireless phones; both mobile and cordless phones (1,2). Thus, an increased risk of developing brain tumors has long been a cause for concern.

Our study group has since the end of the 1990s published results from case-control studies on use of wireless phones and brain tumor risk (3). A statistically significant increased risk for ipsilateral use of mobile phones, the same side of the brain as the phone was used, was published for malignant brain tumors (4) and vestibular schwannoma (5). Further scientific evidence on the association has more recently been discussed by Carlberg and Hardell (6).

In May, 2011 the International Agency for Research on Cancer (IARC) concluded that radiofrequency (RF) radiation in the frequency range 30 kHz-300 GHz is a ‘possible’ human carcinogen Group 2B (7,8). The classification was based primarily on evidence that long-term users of wireless phones (mobile and cordless phones) have an increased risk for glioma and acoustic neuroma. One major reason that the rating was not a ‘probable’ or a ‘known’ risk was the lack of clear evidence from animal studies. IARC at the World Health Organization (WHO) is independently financed and has its own governing and scientific councils, which WHO staff

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only attend as observers (http://www.who.int/ionizing_radiation/research/iarc/en/).

Unfortunately, WHO itself has constantly refused to acknowledge the carcinogenicity of RF radiation. In fact, WHO seems to rely on the conclusion of the non-governmental organization International Commission on Non-ionizing Radiation Protection (ICNIRP) instead of the IARC evaluation. That organization is even declared to be their in-house experts (9,10). ICNIRP is a private non-governmental organization (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 are dependent on the ICNIRP guidelines (11). This creates a conflict of interest, since the former leader of the WHO International Electromagnetic Field (EMF) Project is also the founder and honorary member of the ICNIRP (11). The guidelines are of huge economic and strategic importance to the military, telecom/IT and power industry. These circumstances are further discussed in a recent publication (12).

The IARC cancer classification includes all sources of RF radiation. The exposure from mobile phone base stations, DECT base stations, Wi-Fi access points, smart phones, laptops and tablets can be long-term, sometimes around the clock, at home, at the work place, at school and in the environment. For children, this risk may be accentuated due to a cumulative effect during a long lifetime use (13).

The exposure guidelines used by many agencies and countries were established in 1998 by the ICNIRP and were based only on established short-term thermal (heating) effects from RF radiation neglecting non-thermal biological effects (14). ICNIRP provides the guideline of 2 to 10 W/m² for RF radiation, depending on the frequency. The ICNIRP guidelines were updated in 2009; however, they still do not cover cancer and other long-term or non-thermal effects (15) [see also Hardell (10)].

In contrast to the ICNIRP, the BioInitiative Reports from 2007 and 2012 based the evaluation also on the non-thermal health effects from RF radiation (16,17). The scientific benchmark for possible health risks was defined to be 30 to 60 μ W/m². In 2012, the Bioinitiative Working Group proposed a precautionary target level of 3-6 μ W/m², 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.

The evidence of RF radiation as a carcinogen was confirmed when NTP released preliminary results of a study of long-term exposure of rats and mice to cell phone radiation (18). An increased incidence of glioma in the brain and malignant schwannoma in the heart was found. The NTP study has now been published online for public consultations (19,20) and is discussed below in relation to human epidemiological studies.

Background: Evidence from previous animal studies

There are several earlier animal studies that demonstrate the carcinogenic potential of RF radiation. Szmigelski *et al* already in 1982 published a study on the co-carcinogenic effects of RF radiation exposure and benzopyrene in mice (21). Cancer promotion was found for 2,450 MHz RF radiation at either 50 or 150 W/m². The results revealed an acceleration of spontaneous and chemically-induced cancers.

Non-thermal 2,450 MHz continuous-wave RF radiation has been shown to cause a biphasic effect on glioma cells (22) and lymphocytes (23). Cell proliferation was found at a specific absorption rate (SAR) of \leq 50 W/kg, whereas a higher SAR suppressed DNA and RNA synthesis.

SAR ranged from 0.144 to 0.4 W/kg depending on the rats' weight in a study from 1992 on 200 rats exposed to 2,450 MHz pulsed RF radiation 21.5 h per day for 25 months (24). Compared with 200 sham-exposed rats, a statistically significant increased incidence of primary malignant diseases was found in exposed animals. Among the malignancies found in the exposed rats were malignant lymphoma and thyroid cancer. These findings are of interest since SAR values in the study were rather low compared to the ICNIRP guideline on SAR 2 W/kg to the brain for use of mobile phones (14).

A total of 100 mice were sham-exposed and 101 were exposed for two 30-min periods per day for up to 18 months to 900 MHz pulsed RF radiation with power densities 2.6-13 W/m² (SAR 0.008-4.2 W/kg, averaging 0.13-1.4 W/kg). The mice carried a lymphomagenic oncogene and their risk of developing lymphoma was found to be statistically significantly higher in the exposed mice than in the controls (25).

The same results were not found in the study by Utteridge *et al* (26) that has been criticized as it was not a replication study. However, the findings on lymphoma risk by Repacholi *et al* (25) and Chou *et al* (24) are of relevance in relation to the indications of an increased risk of non-Hodgkin lymphoma (NHL) in human epidemiological studies on the use of wireless phones. Thus, a statistically significant increased risk of T-Cell NHL was found in one study (27). In another study, NHL not otherwise specified was statistically significantly increased among subjects with \geq 6 years duration [odds ratio (OR) =4.4 in men] for mobile phone use (28), although based on low numbers (n=7).

The thyroid gland is among the organs with the highest exposure to RF radiation during the use of the handheld wireless phone, particularly smartphones (29,30). The finding of thyroid cancer risk in the study by Chou *et al* (24), and the sharp increase in the incidence of thyroid cancer in humans during recent years (31) are of interest in that context.

In another study, mice were exposed to universal mobile telecommunications system (UMTS) fields with intensities of 0 (sham), 4.8 and 48 W/m² up to 24 months (32). The low-dose group, exposed to 4.8 W/m², was subjected to additional prenatal ethylnitrosourea (ENU) treatment. That group showed an increased lung tumor rate and an increased incidence of lung carcinomas as compared to the controls treated with ENU only. This indicated a cocarcinogenic effect of a lifelong UMTS exposure in female mice pretreated with ENU (32).

In a follow-up study, mice were exposed to RF radiation: 0 (sham), 0.04, 0.4 and 2 W/kg SAR (33). The numbers of tumors of the lungs and livers in exposed animals were statistically significantly higher than in sham-exposed controls, and the numbers of malignant lymphoma were also higher. A tumor-promoting effect of RF radiation was found at low to moderate levels (0.04 and 0.4 W/kg SAR), well below the ICNIRP exposure limits for users of mobile phones (33).

The study by the Ramazzini Institute is the largest long-term study ever performed on the health effects of RF radiation,

including 2,448 rats (34). Male and female Sprague-Dawley rats were exposed from prenatal life until natural death to a 1.8 GHz global system for mobile communication (GSM) far field of 0, 5, 25, 50 V/m with a whole-body exposure for 19 h/day. A statistically significant increase in the incidence of malignant Schwannoma in the heart was found in male rats at the highest dose, 50 V/m, corresponding to 0.66 mW/cm² and whole-body SAR of 0.1 W/Kg. An increased incidence of heart Schwann cell hyperplasia was observed in treated male and female rats at the highest dose (50 V/m), but was not statistically significant. In treated female rats at the highest dose (50 V/m), the incidence of malignant glial tumors was increased, although this was not statistically significant. The study revealed an increased incidence of tumor types similar to those associated with the use of wireless phones, glioma and acoustic neuroma, in human epidemiological studies.

The NTP study provides additional confirmation of the carcinogenicity of RF radiation (19,20). They showed an increased incidence of malignant schwannoma in the heart and brain glioma in male rats exposed either to GSM-modulated or code division multiple access (CDMA)-modulated cell phone RF radiation for two years. There are also increased incidences of some other tumor types and diseases. Below we discuss some of the major findings.

The results on schwannoma and glioma are of particular concern since they corroborate human epidemiological findings. Thus, it is noteworthy that similar tumors were found in the NTP study as in epidemiological studies on the 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 known as acoustic neuroma, although acoustic neuroma is usually benign and rarely undergoes malignant transformation.

Below, we provide an updated evaluation of the scientific evidence of an increased risk of developing glioma and vestibular schwannoma (acoustic neuroma) associated with the use of wireless phones. It is pertinent to provide an updated presentation of the NTP reports on current evidence on cancer risks associated with the use of wireless phones.

Since the IARC evaluation in 2011, more human epidemiological studies have been published that support a causal association between RF radiation and brain and head tumors. A Danish cohort study on 'mobile phone users' (35,36) is not included herein due to serious methodological shortcomings in the study design [see Söderqvist *et al* (37)]. The study by Benson *et al* (38) is of limited value since the 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 was given. In spite of the many shortcomings, an increased risk of developing acoustic neuroma was reported. The study will not be further discussed below.

In the following, first, human epidemiological studies on specific tumor types are discussed. The NTP study findings are then presented and finally, an evaluation of the combined evidence from human and animal studies is presented.

Glioma

Human studies. Glioma is the most common malignant brain tumor and represents approximately 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 a peak incidence in the age group of 45-75 years and a median survival less than one year (39). No substantial increasing survival has been obtained in recent years. Three research groups have provided results in case-control studies on glioma, Interphone (40), Couteau *et al* (41) and the Hardell group in Sweden (42-46).

The random effects model was used for a meta-analyses of published studies, based on the test for heterogeneity in the overall group ('all mobile'), see also http://www.biointiative.org/report/wp-content/uploads/2017/11/Hardell-2017-Sec11-Update-Use_of_Wireless_Phones.pdf. Note that only our group also assessed the 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 (45).

In Table I, results of the highest cumulative use in hours of mobile phones are presented. All studies reported a statistically significantly increased risk of developing glioma and the meta-analysis yielded OR =1.90 and 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 of the increased risk of glioma associated with mobile phone use has been obtained in additional analyses of parts of the Interphone study (47-49).

We previously analyzed the survival of the patients in our studies and found a shorter survival in patients with glioblastoma multiforme associated with the use of wireless phones compared with patients with no use (50). Interestingly, the mutation of the p53 gene involved in disease progression has been reported in glioblastoma multiforme in patients using mobile phones for ≥3 h per day. The mutation was statistically significantly associated with a shorter overall survival time (51).

NTP study. No increased incidence of glioma was reported in the mouse study (20).

In male rats (19), malignant glioma and glia cell hyperplasia occurred in all groups exposed to GSM-modulated cell phone RF radiation for two years. No lesions were observed in the sham controls. In female rats, glial cell hyperplasia occurred in one rat (3 W/kg), but none in the sham controls. One malignant glioma occurred in one rat in the 6 W/kg group but none in the sham controls.

In male rats exposed to CDMA-modulated cell phone RF radiation for two 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 the sham control (P-value for trend =0.384). Glial cell hyperplasia was observed in most exposed groups, although this was not statistically significant (noted in text; P-value for trend not presented in NTP table).

Evaluation. Based on human epidemiological studies supported by the NTP animal study, there is clear evidence that RF radiation causes glioma in humans. There is also

Table I. 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.

Study (ref.)	All			Ipsilateral		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Interphone, 2010 (40)						
Cumulative use $\geq 1,640$ h	210/154	1.40	1.03-1.89	100/62	1.96	1.22-3.16
Coureau <i>et al</i> , 2014 (41)						
Cumulative use >896 h	24/22	2.89	1.41-5.93	9/7	2.11	0.73-6.08
Hardell and Carlberg, 2015 (43)						
Cumulative use $\geq 1,640$ h	211/301	2.13	1.61-2.82	138/133	3.11	2.18-4.44
Meta-analysis (40,41,43)						
Cumulative use $\geq 1,640$ h ^a	445/477	1.90	1.31-2.76	247/202	2.54	1.83-3.52

^a ≥ 896 h used for Coureau *et al*.

Table II. 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.

Study (ref.)	All			Ipsilateral		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Interphone, 2010 (40)						
Cumulative use $\geq 1,640$ h	130/107	1.15	0.81-1.62	46/35	1.45	0.80-2.61
Coureau <i>et al</i> , 2014 (41)						
Cumulative use >896 h	13/9	2.57	1.02-6.44	6/4	2.29	0.58-8.97
Carlberg and Hardell, 2015 (56)						
Cumulative use $\geq 1,640$ h	141/301	1.24	0.93-1.66	67/133	1.46	0.98-2.17
Meta-analysis (40,41,56)						
Cumulative use $\geq 1,640$ h ^a	284/417	1.27	0.98-1.66	119/172	1.49	1.08-2.06

^a ≥ 896 h used for Coureau *et al*.

evidence of an increased glioma risk in occupational studies on exposure to EMF (52-54).

Meningioma

Human studies. Meningioma is an encapsulated, well-demarcated and rarely malignant tumor. It is the most common non-malignant brain tumor that accounts for approximately 30% of intracranial neoplasms. It develops from the pia and arachnoid membranes that cover the CNS. It is slow-growing and presents neurological symptoms by the compression of adjacent structures. Most common are headaches and seizures. The incidence is greater than two-fold higher in women than in men and meningioma develops mostly among middle-aged and older individuals (55). The same research groups as for glioma also included meningioma in their case-control studies with a separate publication on meningioma by Carlberg and Hardell (56). The results of the meta-analyses for cumulative exposure in highest exposure category are presented in Table II. A statistically significant

increased risk was obtained for ipsilateral mobile phone use with OR =1.49, 95% CI =1.08-2.06.

NTP study. No increased incidence of meningioma was reported in rats or mice (19,20).

Granular cell tumors (GCTs)

Human studies. GCTs are uncommon tumors. They are believed to be of neuronal origin (57). They are soft tissue tumors, which are thought to be derived from Schwann cells (58). The immunoprofile of granular cell tumors has revealed nerve sheath differentiation, lending support to their neuronal origin (59). GCTs can affect any organ in the body, although approximately 50% are found in the head and neck region (60). In our case-control studies on brain tumors, all diagnoses were based on a histopathological examination; no one was diagnosed with a granular cell tumor (42-46).

NTP study. In the rat study (19), increased incidence of malignant or non-malignant granular cell tumors in the meninges, likely derived from Schwann cells, occurred in the

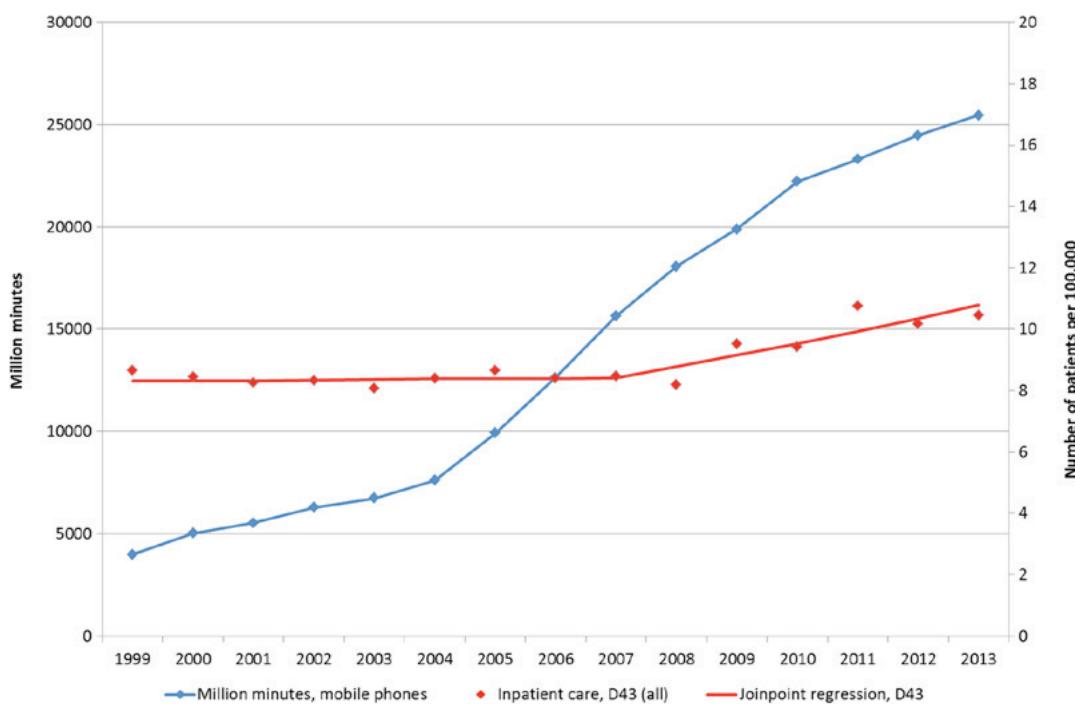


Figure 1. Number of out-going mobile phone minutes in millions during the period between 1999-2013 (<http://statistik.pts.se/pts2013/download/Svensk%20Telemarknad%202013.pdf>; accessed on April 1, 2015) and joinpoint regression analysis of number of patients per 100,000 inhabitants according to the Swedish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

males exposed to GSM-modulated cell phone RF radiation for two years. This was not statistically significant (P-value for trend =0.343). In female rats, granular cell tumors, either malignant or non-malignant were not associated with RF radiation (P-value for trend =0.594). Since GCT is neuronal in origin, the NTP study findings in male rats add to the evidence that exposure to RF radiation damage nerve sheaths.

Evaluation. Based on human epidemiological studies and the NTP animal study, there is equivocal evidence that RF radiation causes meningial tumors 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 between 1979-2008, and has been used to dismissing epidemiological evidence on risk associated with use of wireless phones (61). We have previously demonstrated 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 the reporting of brain tumors to the Swedish Cancer Register (62). The results for more recent time periods have now been published. These articles also discuss 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 between 1998-2013 using joinpoint regression analysis (62). In the IPR, we found a joinpoint in 2007 with Annual Percentage Change (APC) +4.25%, 95% CI +1.98, +6.57% during the period between 2007-2013 for tumors of unknown type in the brain or CNS. Fig. 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 the increasing use of mobile phones.

In the CDR joinpoint regression, we found one joinpoint in 2008 with APC during the period between 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 in the Cancer Register. Furthermore, the frequency of diagnoses based on autopsy has declined substantially due to a general decline of autopsies in Sweden, further adding to missing cases. We concluded 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 Fig. 2, we present the 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 the period between 1999-2013. We postulate that the increasing rate of patients deceased with brain tumor may be associated with the increasing use of mobile phones.

In an updated further analysis, we used the Swedish IPR to analyze rates of brain tumors of unknown type (D43) during the period between 1998-2015 in different age groups (63). The Average Annual Percentage Change (AAPC) per 100,000 increased with +2.06%, 95% CI +1.27, +2.86% in both sexes 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%,

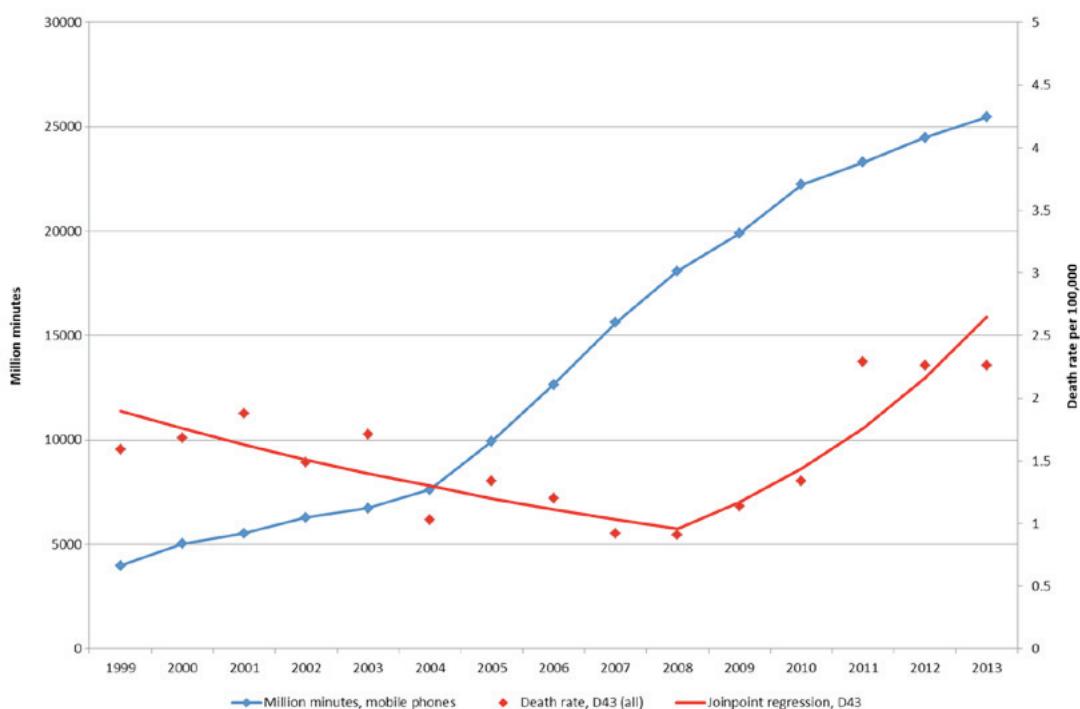


Figure 2. Number of out-going mobile phone minutes in millions during the period between 1999-2013 (<http://statistik.pts.se/pts2013/download/Svensk%20Telemarknad%202013.pdf>; accessed on April 1, 2015) and joinpoint regression analysis of age-standardized death rates per 100,000 inhabitants according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

95% CI +2.87, +5.63%. The highest AAPC was found in the age group of 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% (63). The cases with brain tumor of unknown type lack morphological examination. Brain tumor diagnoses in the Cancer Register were 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 under-reporting 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.

Fig. 3 shows joinpoint regression analyses 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 the period between 1998-2015, and Fig. 4 shows results in women (63).

Interestingly, a recent study demonstrated a similar increase in glioblastoma multiforme in England as in Sweden (64), ‘We report a sustained and highly statistically significant ASR [age-standardized incidence rates] rise in glioblastoma multiforme (GBM) across all ages. The ASR for GBM more

than doubled from 2.4 to 5.0, with annual case numbers rising from 983 to 2531. Overall, this rise is mostly hidden in the overall data by a reduced incidence of lower-grade tumours.’

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, see above and reviewed by us (62). The results have strengthened the evidence that RF radiation causes brain tumors in humans.

Acoustic neuroma (vestibular schwannoma)

Human studies. Acoustic neuroma, also known as vestibular schwannoma, is a non-malignant tumor located on the eighth 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 lead to the compression of vital brain stem structures. The first symptoms of acoustic neuroma are usually tinnitus and hearing problems. The results for the use of mobile phones in the Interphone (65) and Hardell *et al* (66) studies are presented in Table III. A statistically significant increased risk was found for cumulative ipsilateral use >1,640 h yielding an OR of 2.71, 95% CI of 1.72-4.28.

The study by Moon *et al* (67) was not included in the meta-analysis, since the data on cumulative mobile phone use with numbers of cases and controls were not given. Support of an increased risk was found in the case-case part of the study (67), as also reported by Sato *et al* (68) in their case-case analysis. Pettersson *et al* made a case-control study on acoustic neuroma in Sweden not overlapping our study (69). An increased risk for the highest category of cumulative use

Table III. 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.

Study (ref.)	All			Ipsilateral		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Interphone, 2011 (65)						
Cumulative use $\geq 1,640$ h	77/107	1.32	0.88-1.97	47/46	2.33	1.23-4.40
Hardell <i>et al</i> , 2013 (66)						
Cumulative use $\geq 1,640$ h	27/301	2.40	1.39-4.16	19/133	3.18	1.65-6.12
Meta-analysis (65,66)						
Cumulative use $\geq 1,640$ h	104/408	1.73	0.96-3.09	66/179	2.71	1.72-4.28

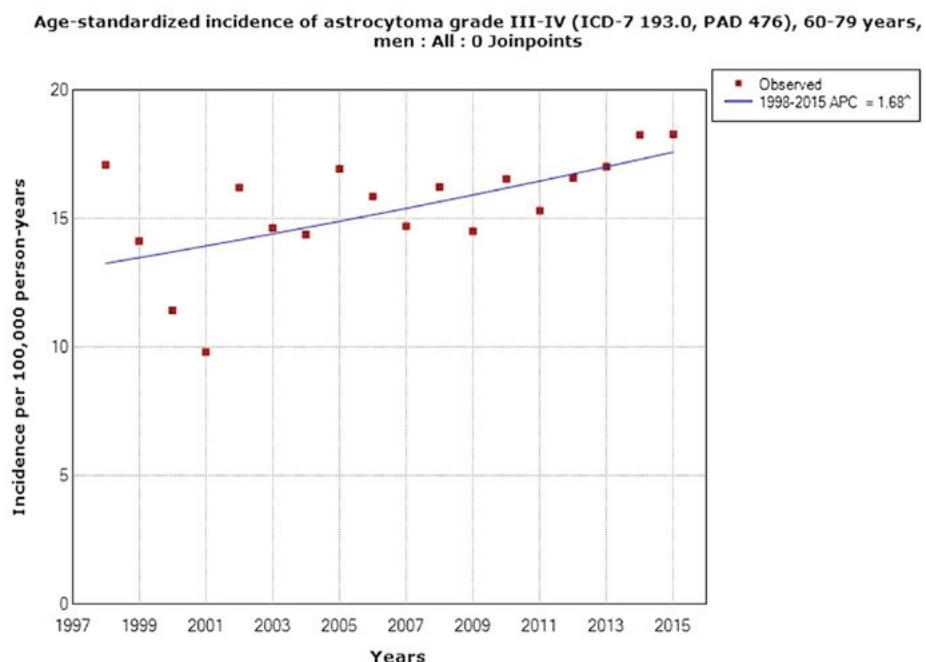


Figure 3. Joinpoint regression analysis of age-standardized incidence rates per 100,000 in men aged 60-79 years with astrocytoma grade III or IV in the Swedish Cancer Register during the period between 1998-2015. APC/AAPC +1.68%, 95% CI +0.39, +2.99% (<http://www.socialstyrelsen.se/statistik/statistik-databas/cancer>).

of both mobile phone (≥ 680 h OR =1.46, 95% CI =0.98-2.17) and cordless phone (≥ 900 h 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 (70).

The Danish part of the Interphone study reported a mean tumor volume of 1.66 cm^3 among regular mobile phone users and 1.39 cm^3 for non-users ($P=0.03$) (71). We analyzed the percentage change in tumor volume per year of latency and 100 h of cumulative use (66). For all types of wireless phones, the percentage of tumor volume increased, and was statistically significant for analogue mobile phones per year of latency ($P=0.02$) and per 100 h of cumulative use ($P=0.01$). Moon *et al* (67) reported a statistically significant larger mean

tumor volume for heavy users ($11.32 \pm 15.43\text{ cm}^3$) compared with light users ($4.88 \pm 5.60\text{ cm}^3$) based on the 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 mouse study (20).

In the rat study (19), there was a statistically significant increased incidence of malignant schwannoma in the heart of males exposed to GSM modulated cell phone RF radiation for 2 years; P -value for trend =0.041. The tumor was found in all exposure categories for male rats, whereas no malignant schwannoma was found in the 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 not in the sham control. A statistically significant trend was found in CDMA-modulated exposed males, $P=0.011$. Two female rats were diagnosed with malignant schwannoma in the heart

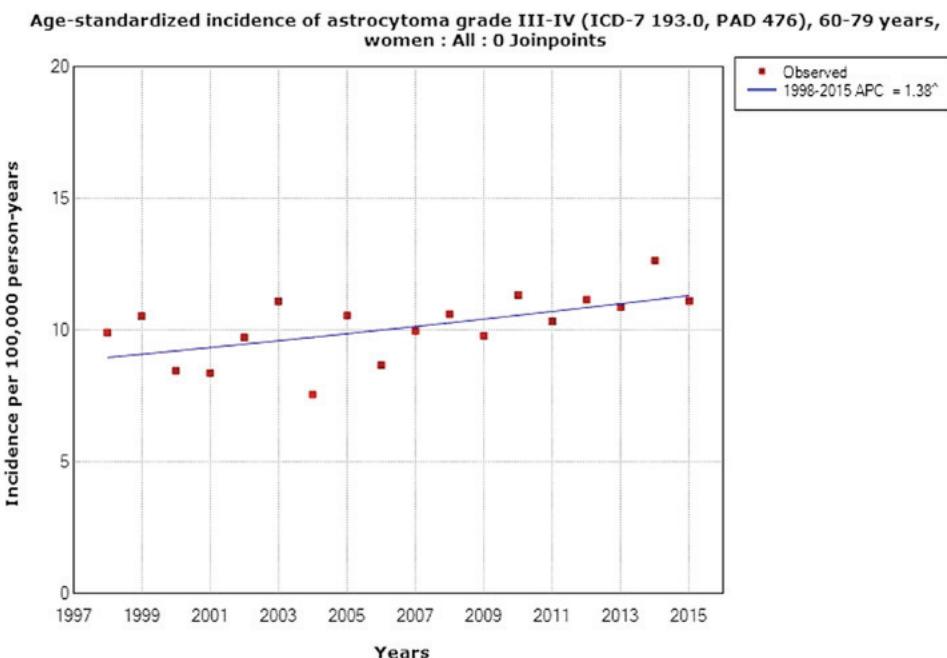


Figure 4. Joinpoint regression analysis of age-standardized incidence rates per 100,000 in women aged 60-79 years with astrocytoma grade III or IV in the Swedish Cancer Register during the period between 1998-2015. APC/AAPC +1.38%, 95% CI +0.32, +2.45% (<http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer>).

in the 3 W/kg group, but no malignant schwannomas were found in the two other exposure groups or in the sham control, P-value for trend =0.640.

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

Pituitary tumors

Human studies. In a case-control study from Japan, no statistically significant increased risks were found for the use of mobile phone (72). 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 the period between 2000-2004.

In a UK case-control study with patients diagnosed during the period between 2001-2005, overall no statistically significant increased risks were found (73). 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 between 2006-2010, mobile phone use yielded an increased risk for pituitary tumor: OR =7.6, 95% CI =2.6-21.4 and a duration of use yielded OR =8.5, 95% CI =2.8-24.4 (74). However, no more data were provided.

The incidence of pituitary tumors increased during the time period between 2004-2009 in the USA (75). The incidence is increasing in Sweden, particularly since 2000, as shown in Fig. 5. There seems to be a decrease during the latest year, but this may be explained by a time lag in the reporting to the Swedish Cancer Register.

NTP study. In male mice (20) exposed to CDMA-modulated RF radiation for two years, two adenoma and one carcinoma

occurred in the pars distalis of the pituitary gland. No carcinoma or adenoma occurred in the sham control or the other two exposure groups. No increased incidence was found in female mice.

In male rats exposed to GSM-modulated cell phone RF radiation for two years (19), an increased incidence of pituitary adenoma was found in all exposed groups, although no statistically significance was found (P-value for trend =0.301). In females, the incidence of adenoma in 1.5 and 6 W/kg was statistically significantly decreased (1.5 W/kg P=0.049; 6 W/kg P=0.038).

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

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

Thyroid cancer

Human studies. The incidence of thyroid cancer is increasing in many countries, particularly the papillary type that is the most radiosensitive type. We used the Swedish Cancer Register to study the incidence of thyroid cancer during the period between 1970-2013 using joinpoint regression analysis (31). 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 between 2001-2013 with an APC of +5.34% (95% CI +3.93, +6.77%).

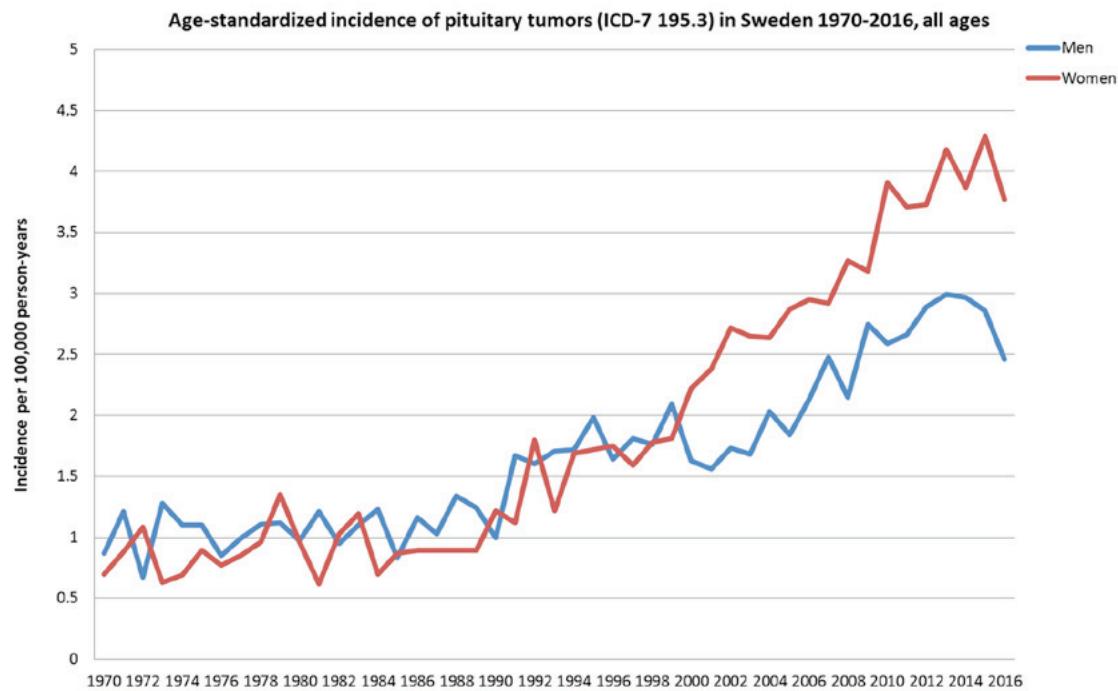


Figure 5. Age-standardized incidence of pituitary tumors (ICD-7 195.3) in Sweden between 1970-2016 for men and women, all ages, according to the Swedish Cancer Register (<http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer>).

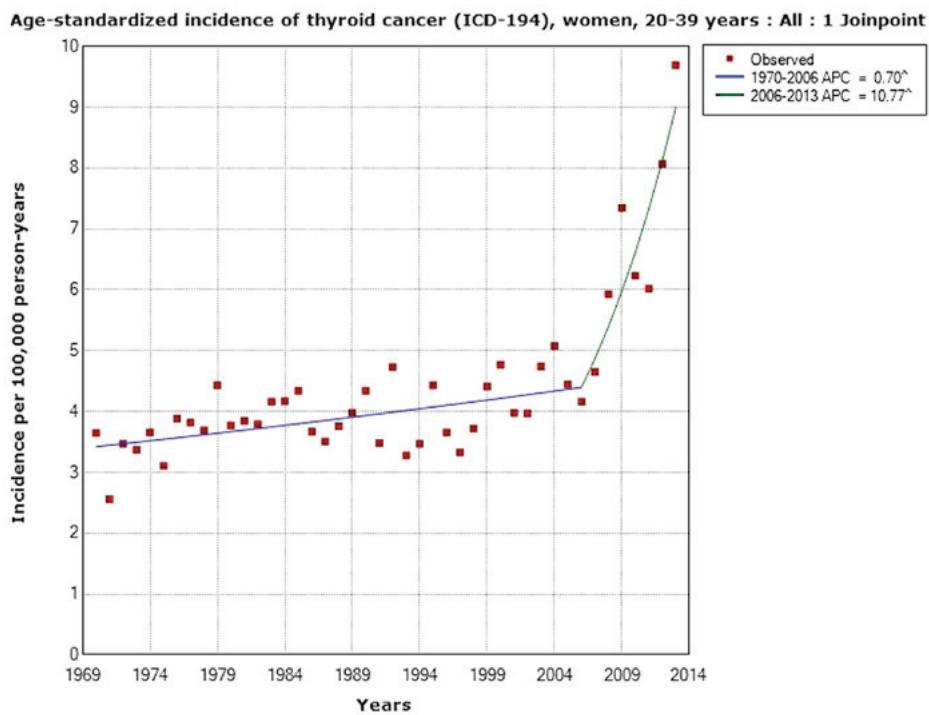


Figure 6. Joinpoint regression analysis of age-standardized incidence of thyroid cancer for women, aged 20-39 years, 1970-2013. Incidence per 100,000 inhabitants for ICD-7 code 194 according to the Swedish Cancer Register (<http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer>).

In the age group of 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 between 2006-2013 (Fig. 6).

Analyses based on data from the Cancer Register indicated 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 the period between 1993-2013 (Fig. 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 of papillary cancer increased in men during the period between 1993-2013 with an AAPC of +3.95% (95% CI +2.20, +5.73%).

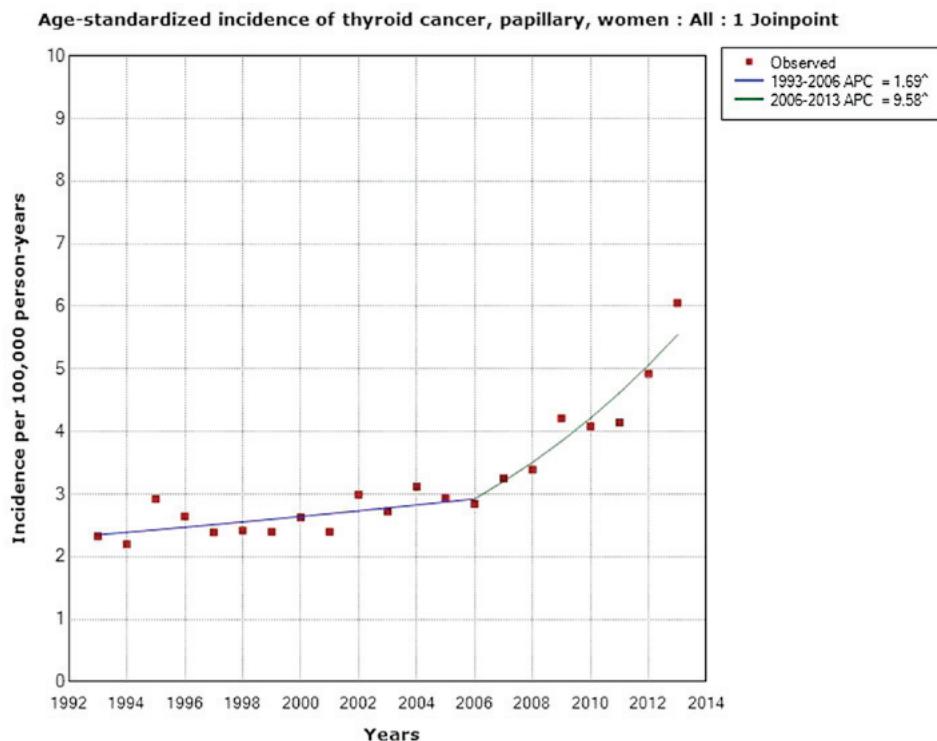


Figure 7. Joinpoint regression analysis of age-standardized incidence of papillary thyroid cancer for women, all ages, 1993-2013. Incidence per 100,000 inhabitants for ICD-7 code 194; data obtained from the Swedish Cancer Register.

AAPC for thyroid cancer in all men during the period between 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 the period between 2005-2013; APC +7.56% (95% CI +3.34, +11.96%). Based on the 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 in the Swedish Cancer Register (31).

We postulate that the whole increase cannot be attributed to better diagnostic procedures. In Fig. 8 data from the Nordic countries are shown on number of out-going mobile phone minutes during the period between 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.

Fig. 9 presents three developments in the antenna design in mobile phones that may be of relevance in thyroid carcinogenesis. The second generation (2G) mobile phones appeared in the 1990s with the external retractable monopole or helical antennas. The 2G GSM band operated at a 800/900 MHz frequency band, later accompanied by a 1,800 MHz band. Around the turn of the millennium, the external antennas

began 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 (76). 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 to the thyroid gland (shown by grey color in Fig. 9). This would have a major impact on increasing radiation to the thyroid gland from smartphones.

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 (77).

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 (78).

NTP study. In mice (20) no increased incidence was reported.

In female rats (19) a statistically significant increased incidence of C-cell hyperplasia was found in the two years of GSM-exposed groups (1.5, 3 and 6 W/kg, respectively). In males, a statistically non-significant increased incidence was observed in the 1.5 W/kg exposure group (noted in text; P-value not given in NTP table).

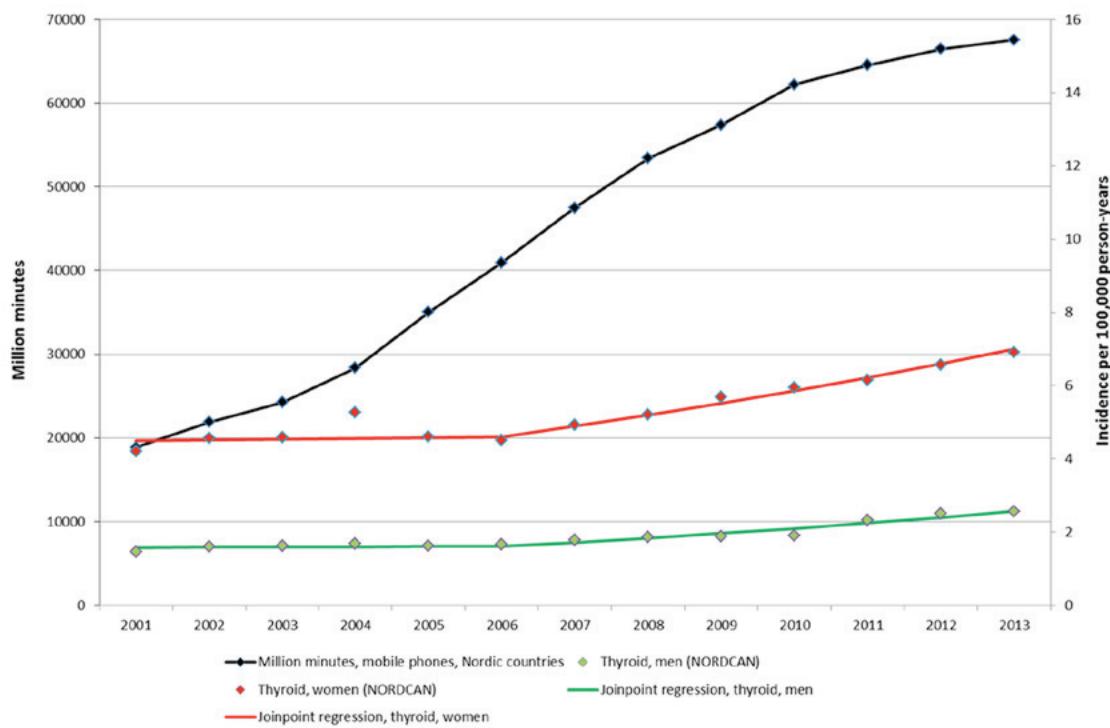


Figure 8. Number of out-going mobile phone minutes and incidence of thyroid cancer 2001-2013. Mobile phone minutes in millions in the Nordic countries (<http://statistik.pts.se/PTSNordic/NordicBaltic2014/>) and incidence per 100,000 person-years for all ages 2001-2013 according to NORDCAN (<http://www-dep.iarc.fr/NORDCAN/english/frame.asp>).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



Figure 9. Mobile phone antenna placements in regard to the thyroid gland (grey). Different localizations of the antenna depending on new generations of mobile phones are shown in the panels from left to right.

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 December 1, 1999 to April 30, 2002 (27). Controls were selected from the national population registry. Exposure to different agents was assessed by a questionnaire. In total, 910 (91%) cases and 1,016 (92%) controls participated. NHL of the B-cell type was not associated with

the use of cellular or cordless telephones. As regards T-cell NHL and the >5 year latency period, the use of analogue cellular phones yielded: OR =1.46, 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 lymphoma, e.g., of the cutaneous and leukemia types, were for analogue phones: 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, the study was based on low numbers and must be interpreted with caution. As regards 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 (28). Compared to persons who had never used cellular telephones, risks

were not increased among individuals whose lifetime use was >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 >8 years; OR =2.4, 95% CI =0.8-7.0. NHL not otherwise specified was statistically significantly increased in men for mobile phone use among subjects with ≥6 years duration, OR =4.4, 95% CI =1.3-14.6. There was little evidence to link the use of cellular telephones with total, diffuse large B-cell lymphoma or follicular NHL. No results were presented for T-cell lymphoma.

In the 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 the period between 1992-2011 (79). Thus, the increasing rates could not be related to HIV or immune suppression in organ transplant patients.

In Sweden, the increasing incidence of PCNSL was reported for the time period between 2000-2013 in immunocompetent persons (80). With 359 identified PCNSL cases (median age, 66 years), the overall incidence was 0.26 (95% CI =0.24-0.29) per 100,000 person-years 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 etiological 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 mice, an increased incidence of lymphoma exposed to 900 MHz GSM RF radiation was reported; $P=0.006$ versus the sham group (25). No increased risk of malignant lymphoma was found in mice exposed to GSM 900 MHz in another study (26). However, the incidence in the sham exposed group was higher in the study by Utteridge *et al* (26) compared with the study by Repacholi *et al* (25) which might have influenced the results.

NTP study. In female mice exposed to GSM-modulated cell phone RF radiation for two years, there were increased incidences of malignant lymphoma in all exposed groups compared to the controls (20). 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 two years, the incidence increased in female mice in all exposed groups compared to the controls, and was statistically significant in the 2.5 W/kg group ($P=0.035$).

No conclusive evidence of increased incidence of malignant lymphoma was reported in female rats (19); P-value for trend =0.537 for GSM-modulated cell phone RF radiation and P-value for trend =0.339 for CDMA-modulated cell phone RF radiation.

Evaluation. Based on human epidemiological 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 of developing skin tumors. In a Danish cohort on mobile phone subscribers from the period between 1987-1995 followed to 2007, no increased risks of skin cancer were observed (81). The same cohort has also been used for studying brain tumor risk. Due to serious methodological problems, including the misclassification of exposure the study has been evaluated to be uninformative (8,37).

In a Swedish study on cutaneous malignant melanoma diagnosed during the period between 2000-2003, no increased risk was observed overall (82). In the shortest latency period of >1-5 years and highest cumulative use of >365 h, 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 observed with known risk factors for malignant melanoma, such as hair and eye color, skin type or sunburns as a teenager.

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

NTP study. The incidences of malignant fibrous histiocytoma in the skin were higher in 5 and 10 W/kg male mice exposed to GSM-modulated cell phone RF radiation for two years (20). The results were not statistically significant (5 W/kg $P=0.124$; 10 W/kg $P=0.321$). The incidences of fibrosarcoma, sarcoma or malignant fibrous histiocytoma were higher in exposed male mice compared with sham control, although border-line significant, P-value for trend =0.093. No increased incidence was observed in female mice.

Male rats exposed to GSM-modulated cell phone RF radiation for two years (19) exhibited 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 (P-value for trend =0.428). No statistically significant results were found in female rats (P-value for trend =0.551).

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

Concluding remarks. Based on case-control studies, as discussed above, there is a consistent finding of an increased risk of developing glioma and acoustic neuroma associated with the use of mobile phones. Similar results are found for cordless phones in the Hardell group studies. These results are supported by the results of the NTP animal studies (19,20). Malignant vestibular schwannoma is a similar tumor type as acoustic neuroma, also known as vestibular schwannoma.

The findings are less consistent for meningioma although somewhat an increased risk was observed 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

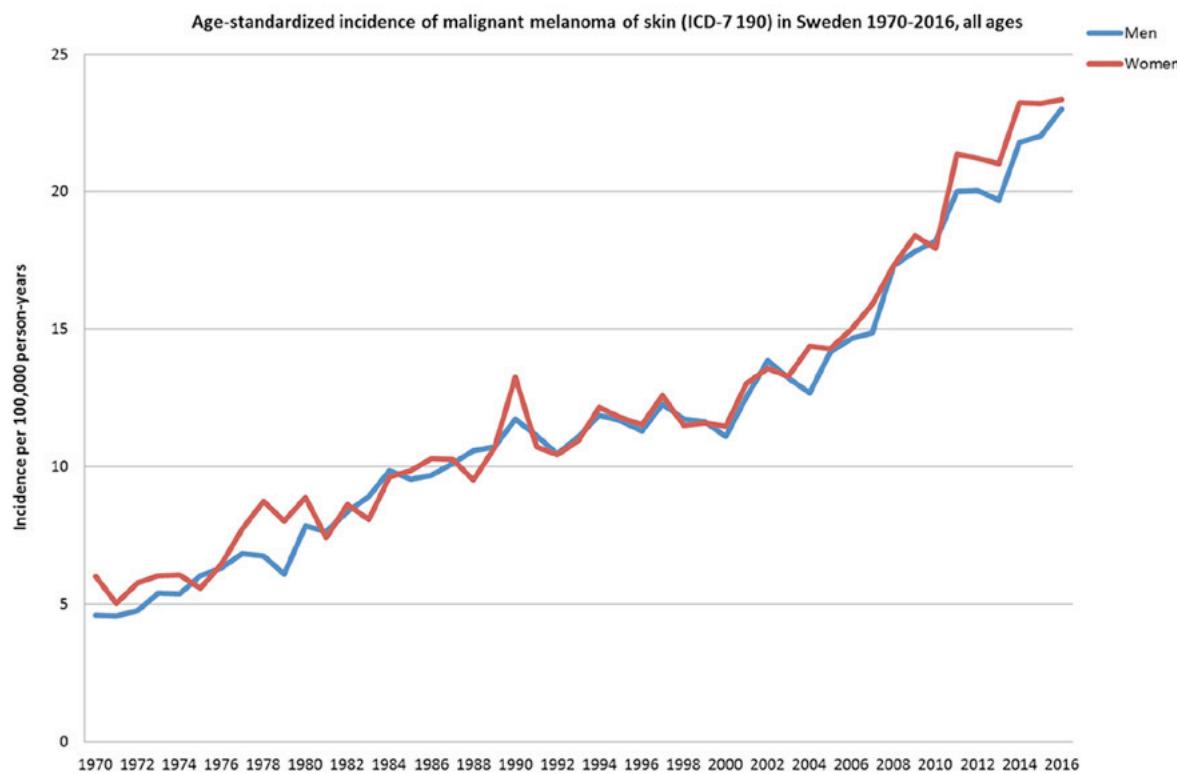


Figure 10. Age-standardized incidence of malignant melanoma (ICD-7 190) in Sweden between 1970-2016 for men and women, all ages, according to the Swedish Cancer Register (<http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer>).

carcinogenic and/or tumor promoting effects from RF radiation (21-25,32-34). The NTP study showed genotoxicity of RF radiation in rats and mice exposed to RF radiation (83). That result supports previous findings of DNA strand breaks in rat brain cells exposed to RF radiation (84).

One mechanism in carcinogenesis may be oxidative stress with the production of reactive oxygen species (ROS), as summarized by Yakymenko *et al* (85). This could be an indirect mechanism for the increased brain and head tumor risk since ROS may lead to DNA damage (86).

By now carcinogenicity has been shown in human epidemiological studies, which has been replicated in animal studies. Laboratory studies on RF radiation have shown increased ROS production that can cause DNA damage. In 2013, we published the conclusion that RF radiation should be regarded as a human carcinogen, Group 1 according to the IARC definition, fulfilling Bradford Hill causality criteria (87). This was further supported in our updated article (6). That conclusion is reinforced by the current evaluation.

The evidence that RF radiation exposure is a risk factor for cancer is particularly worrying, taking the present deployment of the fifth generation (5G) for wireless communication. More than 200 scientists and medical doctors have asked for a moratorium until studies have been performed by independent researchers on hazards to human health and the environment (88). These millimeter waves have primarily effects on the skin and eye (89). Sweat ducts in the skin may act as helical antennas and boost RF radiation exposure (90). These findings are worrying, taking the present evaluation that present RF radiation may increase the risk of developing skin cancer.

Discussion

The NTP report uses five categories for the evaluation of RF radiation carcinogenicity as follows:

Clear evidence. Clear evidence of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related i) increase of malignant neoplasms; ii) increase of a combination of malignant and benign neoplasms; or iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.

Some evidence. Some evidence of carcinogenic activity is demonstrated by studies that are interpreted as showing a test agent-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.

Equivocal evidence. Equivocal evidence of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be test agent related.

No evidence. No evidence of carcinogenic activity is demonstrated by studies that are interpreted as showing no test agent-related increases in malignant or benign neoplasms.

Inadequate study. Inadequate evidence of carcinogenic activity is demonstrated by studies that, due to major qualitative or quantitative limitations, cannot be interpreted

Table IV. National Toxicology Program (NTP) Cell Phone Radiation 2-Year Study Evaluation of Carcinogenicity of Cell Phone Radiation: NTP Draft Technical Reports (TR 595, TR 596) vs. Expert Panel Vote.^a

Animal	Sex	Cell phone modulation	Tumor types and/or location	Evidence of carcinogenicity	
				NTP draft report	Expert panel (vote yes-no-abstention)
Rat	Male	GSM ^b	Heart: Schwannoma	Some evidence	Clear evidence (8-3)
Rat	Male	CDMA ^c	Heart: Schwannoma	Some evidence	Clear evidence (8-3)
Rat	Male	GSM	Brain: Glioma	Equivocal	Some evidence (7-4)
Rat	Male	CDMA	Brain: Glioma	Equivocal	Some evidence (6-4-1)
Rat	Male	GSM	Brain: Granular cell	Equivocal	Equivocal (11-0)
Rat	Male	GSM	Prostate gland	Equivocal	Equivocal (11-0)
Rat	Male	GSM	Pituitary gland	Equivocal	Equivocal (10-1)
Rat	Male	CDMA	Pituitary gland	Equivocal	Equivocal (11-0)
Rat	Male	GSM	Adrenal medulla	Equivocal	Some evidence (6-4-1)
Rat	Male	GSM	Pancreas	Equivocal	Equivocal (11-0)
Rat	Male	CDMA	Liver	Equivocal	Equivocal (11-0)
Rat	Female	GSM	Heart: Schwannoma	No evidence	Equivocal (9-2)
Rat	Female	CDMA	Heart: Schwannoma	No evidence	Equivocal (9-2)
Rat	Female	CDMA	Brain: Glioma	Equivocal	Equivocal (8-3) (4 voted earlier for 'some evidence')
Rat	Female	CDMA	Adrenal medulla	Equivocal	Equivocal (10-0-1)
Mouse	Male	GSM	Skin	Equivocal	Equivocal (8-3)
Mouse	Male	GSM	Lung	Equivocal	Equivocal (11-0)
Mouse	Male	CDMA	Liver	Equivocal	Equivocal (10-1)
Mouse	Female	GSM	Lymphoma	Equivocal	Equivocal (9-2)
Mouse	Female	CDMA	Lymphoma	Equivocal	Equivocal (11-0)

^aJoel M. Moskowitz, School of Public Health, University of California, Berkeley, March 30, 2018 Electromagnetic Radiation Safety (<https://www.saferemr.com/2018/01/national-toxicology-program-peer-public.html>) with courtesy; ^bGSM, global system for mobile communications; ^cCDMA, code-division multiple access.

as valid for showing either the presence or absence of carcinogenic activity.

On March 26-28, 2018, a panel of 11 external scientific experts met to evaluate carcinogenicity of the NTP carcinogenicity studies (<https://factor.niehs.nih.gov/2018/4/feature/feature-2-cell-phone/index.htm>). As shown in Table IV, the carcinogenicity was upgraded for seven tumor types and/or location. Thus for glioma the vote was 'some evidence' in male rats exposed to GSM or CDMA cell modulation. Evidence for heart Schwannoma was found in male rats and was equivocal in female rats, as shown in Table IV. Note that we have herein discussed carcinogenesis only for tumor types with human epidemiological data. It is of interest that animal data indicate also increased incidence for other tumor types and/or locations such as prostate gland, adrenal medulla, pancreas, liver and lung, see also https://ntp.niehs.nih.gov/ntp/about_ntp/trpanel/2018/march/actions20180328_508.pdf.

In contrast to the NTP panel, ICNIRP has made its own evaluation (<https://www.icnirp.org/cms/upload/publications/ICNIRPnote2018.pdf>). They discuss mainly the Schwannoma findings and ignore glial tumors. ICNIRP does not recognize the pattern of increased risk for Schwannoma and glioma in

both animal studies and human epidemiology on RF radiation. They conclude that '*ICNIRP considers that the NTP (2018a, b) and Falconni et al (2018) studies do not provide a consistent, reliable and generalizable body of evidence that can be used as a basis for revising current human exposure guidelines.*' That conclusion is not based on scientific evidence, but is rather an ad hoc statement.

A recent commentary discussed 'several unfounded criticisms about the design and results of the NTP study that have been promoted to minimize the utility of the experimental data on RFR for assessing human health risks. In contrast to those criticisms, an expert peer-review panel recently concluded that the NTP studies were well designed, and that the results demonstrated that both GSM- and CDMA-modulated RFR were carcinogenic to the heart (schwannomas) and brain (gliomas) of male rats.' (91).

Our conclusion on RF radiation carcinogenicity is the following based on human epidemiology and supported by animal results in the NTP reports: 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, clear evidence.

There is clear evidence that RF radiation causes cancer/tumor at multiple sites, primarily in the brain (glioma) and head (acoustic neuroma). There is also evidence of an increased risk of developing other tumor types. The results are similar in both the NTP studies (19,20) and the Ramazzini Institute findings (34). 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>)

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Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Both LH and MC participated in the conception, design and writing of the manuscript. LH supervised the study. MC made all statistical calculations. Both authors have read and approved the final version.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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