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Cancer epidemiology update, following the 2011 IARC evaluation of radiofrequency electromagnetic fields (Monograph 102)☆

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ABSTRACT

Epidemiology studies (case-control, cohort, time trend and case studies) published since the International Agency for Research on Cancer (IARC) 2011 categorization of radiofrequency radiation (RFR) from mobile phones and other wireless devices as a possible human carcinogen (Group 2B) are reviewed and summarized. Glioma is an important human cancer found to be associated with RFR in 9 case-control studies conducted in Sweden and France, as well as in some other countries. Increasing glioma incidence trends have been reported in the UK and other countries. Non-malignant endpoints linked include acoustic neuroma (vestibular Schwannoma) and meningioma. Because they allow more detailed consideration of exposure, case-control studies can be superior to cohort studies or other methods in evaluating potential risks for brain cancer. When considered with recent animal experimental evidence, the recent epidemiological studies strengthen and support the conclusion that RFR should be categorized as carcinogenic to humans (IARC Group 1). Opportunistic epidemiological studies are proposed that can be carried out through cross-sectional analyses of high, medium, and low mobile phone users with respect to hearing, vision, memory, reaction time, and other indicators that can easily be assessed through standardized computer-based tests. As exposure data are not uniformly available, billing records should be used whenever available to corroborate reported exposures.

1. Introduction

With rapidly increasing applications for wireless devices targeting populations of all ages, exposures to the associated radiofrequency radiation (RFR) are increasing in number and diversity. Radiation sources include communications devices such as mobile (cell) or cordless phones, laptops and tablets, baby monitors, wearable devices and associated infrastructure (e.g. routers, antennae on towers, and distributed antennae systems (DAS) that can employ directional couplers or wireless amplifiers to enhance accessibility). Thus, the technology entails direct and growing personal exposures to an expanding array of wireless transmitting devices (WTDs).

In 2011, a Working Group of the World Health Organization's International Agency for Research on Cancer (IARC) classified RFR as a possible human carcinogen (Group 2B) (IARC, 2013). In this paper we review the human epidemiology and some other relevant studies published since the IARC Working Group meeting.

1.1. Wireless phone types

The principal sources of exposure of humans to RFR are cell and cordless phones. The radiated power and technologies for cell phones have evolved over the years, as summarized in Table 1 (Hardell and Carlberg, 2015).

2. Case-control studies; glioma

Aydin et al. (2011) reported the results of CEFALO, a multicenter

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Table 1
Wireless phone types, year introduced and average radiated power.

Phone type	Year introduced	Average radiated power	Comment
Analogue[a]	1983	1 or 2 W	No longer in use
2 G, GSM	1991	10 s of mW	Adaptive power control
3 G, UMTS	2004	10 s of μW	(APC)
4 G, LTE[b]	2010	< 10 s of μW	
Cordless[a]	1992	250 mW	Base station radiates continuously

[a] At maximum power; in-home base station is also a source.
[b] Too recent for epidemiological studies.

Table 2
Risks for glioma from and mobile phone use from Aydin et al. (2011).

Exposure	Source	OR	95% CI	p-trend
Regular use[a]	Recall	1.36	0.92–2.02	
Time since first use:				
Never regular user	Recall	1.00		
0.5- ≤ 3.3 years	Recall	1.35	0.89–2.04	0.37
3.3–5.0 years	Recall	1.47	0.87–2.49	
> 5.0 years	Recall	1.26	0.70–2.28	
Time since first subscription:				
Never regular user	Operator	1.00		
≤ 1.8 years	Operator	0.78	0.43–1.40	0.001
1.8–2.8 years	Operator	1.71	0.85–3.44	
> 2.8 years	Operator	2.15	1.07–4.29	
Ipsilateral use				
Regular ipsilateral use	Recall	1.74	0.91–3.33	
< 936 cumulative number of calls	Recall	1.59	0.81–3.12	0.08
937–2638 cumulative number of calls	Recall	2.06	0.72–5.93	
> 2638 cumulative number of calls	Recall	2.91	1.09–7.76	
Contralateral use				
Regular contralateral use	Recall	2.07	0.95–4.52	
< 936 cumulative number of calls	Recall	1.74	0.78–3.90	0.06
937–2638 cumulative number of calls	Recall	5.37	1.54–18.72	
> 2638 cumulative number of calls	Recall	4.82	1.21–19.24	

[a] At least once a week for 6 months or more.

case–control study conducted in Denmark, Sweden, Norway, and Switzerland that included children and adolescents aged 7–19 years (median age 13 years) diagnosed with a brain tumor between 2004 and 2008. In person interviews were conducted with 352 case patients (participation rate: 83%) and 646 control subjects (participation rate: 71%) and their parents. The authors concluded that there was no consistent evidence of increased risk. Self-reported use of mobile phones and billing records were the basis of the estimate of exposure. Overall, regular users of mobile phones were not statistically significantly more likely to have been diagnosed with brain tumors compared with never regular users (odds ratio (OR) 1.36; 95% CI 0.92–2.02) (Table 2). However, their data suggest that another interpretation might be offered. Analysis of a subset of cases (58% of all cases) based on operator-recorded information showed significant brain cancer risks for children with a significant trend of increase in risk with increasing years of use. Based on children's memory of both ipsilateral and contralateral use there were significant increased risk of brain cancer along with a marginal increase of risk with an increasing number of calls (Table 2).

Regular use was defined as making at least one call a week for 6 or more months.

Because both ipsilateral and contralateral self-reported use of phones in children show significant trends toward increasing brain cancer risk, the authors dismissed this finding. Three factors could account for this result. First, children's capacity to recall their phone use habits accurately may not be correct. Second, young children (25% were between 7 and 9 years; the median age of the study participants overall was 13 years) will absorb considerably more radiation further into their brains than adults (Fernandez-Rodriguez et al., 2015). Given that many of these cases began to use phones before age 5, their exposures would certainly have been extensive no matter what side of the head they reported having placed the phone. Therefore, the fact that the differences between the ORs for ipsilateral and contralateral use of cell phones and brain cancer were not significant while both ipsilateral and contralateral reported regular use showed a significant risk could signal that use of the phone on either side of the head by children involves proportionally more exposure than adults. The third potential explanation is recall bias.

Table 3
Glioma Risk relative to hours of phone use and Specific Absorption (J/kg) (Cardis et al., 2011).

Exposure	OR	95% CI
Hours of use		
61.0–199.9 h	0.74	0,55–0.99
735 + hours	1.72	1.07–2.77
Specific Absorption (SA)		
< 3 years in the past		
76.7–248 J/kg	0.63	0.41–0.96
987.3123.8 J/kg	0.56	0.32–0.99
3123.9 + J/kg	1.66	1.03–2.67
7 + Years in the past		
< 76.7 J/kg	1.11	0.61–2.02
76.7–284.1 J/kg	1.53	0.85–2.78
284.1–978.9 J/kg	1.50	0.81–2.78
978.9–3123.8 J/kg	1.69	0.91–3.13
3123.9 + J/kg	1.91	1.05–3.47

Cardis et al. (2011) evaluated the absorbed radiation dose from cellphones and the risk of glioma and meningioma in five countries contributing to the Interphone study (Australia, Canada, France, Israel, New Zealand). Analyses included 553 glioma and 676 meningioma

cases and 1762 and 1911 controls, respectively. Employing radiological records, information on phone type, network properties, condition of use and tumor location, they estimated and analyzed absorbed radiation dose as total cumulative specific energy (TCSE), also known as Specific Absorption (SA) in Joules per kilogram of tissue. The authors state "~16% of brain volume received 50% of the total absorbed energy." Table 3 summarizes the results for glioma. All Specific Absorption (SA) results (J/kg) indicate total energy absorbed by the brain tumor. The highest exposures during 735 + total hours of reported use or 3123.9 J/kg 3 or 7 years prior to diagnosis, resulted in statistically significant increases of risk, with evidence of increasing risk with increasing dose.

In the original pooled 13-country Interphone study report it was noted that "…non-participation bias may have led to a reduction in the ORs for regular use of 5–15%, which is less than the observed reductions below the null in the ORs in even regular mobile phone users for… glioma." (19%, 95% CI 30–6; Table 2) (INTERPHONE Study Group, 2010). Morgan and Carlberg (2010) calculated that the reduced odds ratio bias was 25% with a binomial p-value = 0.0002.

Hardell et al. (2013b) reported on the risk from RFR of brain cancers diagnosed in Sweden between 2007 and 2009. Of the cases with a malignant brain tumor, 87% (n = 593) participated, and 85% (n = 1368) of controls in the whole study answered the questionnaire. Table 4 shows the risk of brain cancer for various phone types with a reference value (OR = 1.0) for no use of a mobile or cordless phone, or use for ≤ 1 years or ≤ 39 h of cumulative use. The odds ratios were higher in some of the short term follow up groups than the longer perhaps because few people have 25 years of extensive cell phone use, in part because they are not old enough.

Carlberg and Hardell (2012) analyzed the association of brain cancer with mobile phone use and heredity. The results were based on 1251 cases with malignant brain tumor (response rate 85%) and 2438 controls (response rate 84%). Heredity was defined in two ways: either

Table 4
Risk of brain cancer in Sweden, by years of use of wireless phones (Hardell et al., 2013b).

Phone type	Latency[a]	OR	95% CI
Analogue	1–5	–	–
	5–10	0.6	0.1–3.1
	10–15	1.4	0.7–3.0
	15–20	1.4	0.7–2.7
	20–25	2.1	1.1–4.0
	> 25	3.3	1.6–6.9
	Total	1.8	1.04–3.3
Digital (2G)	1–5	1.8	1.01–3.4
	5–10	1.6	0.97–2.2
	10–15	1.3	0.8–2.2
	15–20	2.1	1.2–3.6
	Total	1.6	0.996–2.7
Mobile phone, Total	1–5	1.8	1.0–3.4
	5–10	1.7	0.98–2.8
	10–15	1.3	0.8–2.2
	15–20	1.5	0.8–2.6
	20–25	1.9	1.1–3.5
	> 25	2.9	1.4–5.8
	Total	1.6	0.99–2.7
Cordless phone	1.5	2.0	1.1–3.4
	5–10	1.6	0.95–2.7
	10–15	1.6	0.9–2.8
	15–20	2.1	1.2–3.8
	20–25	1.5	0.5–4.6
	> 25	–	–
	Total	1.7	1.1–2.9

[a] Time since first use (years).

having a first degree relative with any cancer except brain cancer; or having a first degree relative with brain cancer. They confirmed increased risk of brain cancer from mobile phone use and found that having a first degree relative with brain cancer (but no other cancers) increases the risk of brain cancer, but there was no interaction with mobile phone use.

Carlberg and Hardell (2013) also reported that persons diagnosed with a glioblastoma multiforme (GBM) exposed to RFR emanating from WTDs had a significantly shorter survival period than those without such exposures.

Coureau et al. (2014) reported on a French national study of mobile phone use and brain tumors (glioma and meningioma) between 2004 and 2006. Out of the subjects defined as eligible, 95% of cases and 61% of controls were contacted, and a total of 596 (73%) cases and 1192 (45%) controls were finally included in the study. Participation rate was 66% for glioma and 75% for meningioma cases. This resulted in a total of 253 gliomas, 194 meningiomas and 892 matched controls selected from the local electoral rolls being analyzed. The meningioma results can be found in the next section. This study defined heavy users as those with ≥ 896 h of use. The risk of glioma for heavy users was OR = 2.54, 95% CI = 1.19–5.41. There was a marginal increase in risk with increasing hours of use ($p_{trend} = 0.07$). A small number of urban users showed a significant 8-fold increased risk for brain tumors excluding temporal or frontal lobes (OR 8.2. 1.37–49.07). The authors commented: "Finally, we observed increased OR for urban use for gliomas, a result inconsistent with the hypothesis of a higher RF power output during calls in rural areas, documented by some Swedish study. However, our results are consistent with a recent international study showing no difference between rural and urban exposition in most countries except in Sweden, and a Hardell study when considering gliomas separately." These and other findings are shown in Table 5.

Hardell and Carlberg (2015) conducted a pooled analysis of gliomas from 1997 to 2004 and 2007–2009 with > 25 years and for > 1486 h of use, by wireless phone types. In total, 1498 (89%) cases and 3530 (87%) controls were included in the analysis. Glioma risk by years or hours of use by phone types is shown in Table 8 and in Table 9. They reported increased risk with increasing latency since first use. For

Table 5
Risk of brain cancer for various measures of exposure in the CERENAT case-control study (Coureau et al., 2014).

Condition	OR	95% CI
Average calling time/hours/month		
Not regular user	1.00	
< 2	0.91	0.57–1.46
2–4	0.57	0.30–1.10
5–14	1.70	0.97–2.99
15 or more	4.21	1.84–8.86
Heavy User		
≥ 1 year	2.89	1.41–5.93
≥ 2 years	3.03	1.47–6.26
≥ 5 years	5.30	2.12–13.23
Temporal lobe	3.94	0.81–19.08
Other brain locations excluding temporal and frontal lobes	3.61	1.00–12.96
Urban use only	8.20	1.37–49.07
Urban and rural use	2.03	0.93–4.40
Analogue phone use	3.75	0.97–14.43
Digital phone use only	2.71	1.03–7.10

Table 6
Risk of glioma for years of use by phone type (Hardell and Carlberg, 2015) for 1498 cases.

Years of use	Phone type	OR	95% CI
> 1	Analogue	1.6	1.2–2.0
	2G, GSM	1.3	1.1–1.6
	3G, UMTS	2.0	1.0–4.4
> 1, temporal lobe	Analogue, 2 G, 3 G	1.3	1.1–1.6
		4.3	2.0–9.3
> 5–10	2G, GSM	1.7	1.3–2.2
	3G, UMTS	4.1	1.3–12
	Cordless	1.4	1.1–1.8
> 10–15	Analogue	1.4	1.04–1.9
	Cordless	1.4	1.1–1.9
> 15–20	Analogue	2.4	1.5–3.7
	2G, GSM	2.1	1.5–3.0
	Cordless	1.7	1.1–2.5
> 15–20 Astrocytoma I-II, ipsilateral	Cordless	3.2	0.99–10
> 20–25	Analogue	3.2	1.9–5.5
> 25	Analogue	4.8	2.5–9.1
> 25 temporal lobe	Wireless	4.2	1.9–9.1
> 1 Astrocytoma III-IV	Analogue + 2G	1.4	1.1–1.8
> 20		2.5	1.6–3.8
> 20, ipsilateral		3.3	1.9–5.7

Table 7
Risk of glioma by hours of use (Hardell and Carlberg, 2015).

Hours of Use	Phone Type	OR	95% CI
Per 100 h	Analogue	1.043	1.026–1.061
	2 G, GSM	1.014	1.009–1.018
	3 G, UMTS	1.047	1.002–1.093
	Cordless	1.014	1.008–1.019
1st Quartile: 1–122	2 G, GSM	1.3	1.05–1.5
2nd Quartile: 123–511	Analogue	1.8	1.3–2.5
	2 G, GSM	1.3	1.01–1.7
	Cordless	1.2	0.97–1.6
3rd Quartile: 512–1486	Analogue	1.8	1.2–2.8
	2 G, GSM	1.5	1.1–1.9
	3 G. UMTS	3.0	1.2–8
	Cordless	1.6	1.3–21
4th Quartile: > 1486[a]	Analogue	4.8	2.8–8.2
	2 G, GSM	2.3	1.7–3.1
	Cordless	2.3	1.8–3.1
p-trend	Analogue	0.0001	
	2 G, GSM	0.0001	
	Cordless	< 0.0001	

[a] ~25 min per day over 10 years.

example, the OR for tumors in the temporal lobe with latency of > 25 years was 4.2 (95% CI 1.9–9.1), while the OR for analogue phone use was 4.8 (95% CI 2.5–9.1). (Tables 6 and 7)

Manufacturers indicate that the 3G-UMTS phones' average radiated power (10s of μW) is lower than 2G-GSM (10 s of mW). Nonetheless, the glioma risks for exposure to 3 G-UMTS are higher in this analysis. To explain this counter-intuitive finding, the authors cite three in vitro studies (Belyaev et al., 2009; Belyaev, 2010; Markova et al., 2010) that found UMTS inhibits significantly more DNA repair genes relative to GSM modulation.

Total absorbed radiative power is one important factor in determining risk (Hardell et al., 2005). But as Belyaev et al. (2009), Belyaev (2010) and Markova et al. (2010) have noted, modulation technology and signals for information content may be more important determinants of biological impact. Thus, the increased glioma risk reported with weaker 3-G-UMTS could reflect the fact that modulation is more critical than power alone.

Grell et al. (2016) examined the location of brain cancers diagnosed from 2000 to 2004 in the INTERPHONE study. The authors located brain cancers at various distances from the ear where the phone was held using neuro-radiologists to estimate peak areas of exposure in centers of gravity of the tumor within the brain. The main analysis included 792 regular mobile phone users diagnosed with a glioma between 2000 and 2004. Table 8 summarizes the significant results from the report's Table 3 (there are 7 additional tables reporting similar results) at the two closest ranges of out of four longer distances from the ear. The authors commented, "Our results concur with the observation of a statistically significant excess of gliomas on the self-reported side of mobile phone use." They showed significantly increased glioma risk with greater absorption, greater hours spent on phone and longer time since phone use began.

Momoli et al. (2017) undertook a re-analysis of the Canadian data from the 13-country case-control Interphone Study (2001–2004). They applied a probabilistic multiple-bias model to address possible biases simultaneously, using validation data from billing records and non-participant questionnaires as information on recall error and selective participation. For glioma, when comparing those in the highest quartile of use (> 558 lifetime hours) to those who were not regular users, the odds ratio was 2.0 (95% confidence interval: 1.2, 3.4). After adjustment for selection and recall biases, the odds ratio was 2.2 (95% limits: 1.3, 4.1), thus allaying concerns that bias could explain the positive findings in the Interphone study.

Akhavan-Sigari et al. (2014) reported that patients with glioblastoma multiforme who had used cellphones ≤ 3 h per day had better survival than those with cellphone use of ≥ 3 h per day. The authors investigated p53 mutant gene expression in peripheral (within 2 cm of the area of MRI enhancement) and central (region of necrosis) zones within the tumor. They found that 41 out of 63 patients (65%) with the highest level of cell phone use (≥ 3 h per day) had higher mutant type p53 expression in the peripheral zone of the glioblastoma; the difference [compared to cellphone use of < 3 h per day] was statistically significant (P = 0.034). They noted that occupational exposure to other electromagnetic fields was excluded in all patients. This study shows that genetic changes, compatible with carcinogenic effects, result from higher exposure to RFR.

Table 8
Estimated Elevation in Brain Tumor Risk for Regular Mobile Phone Users with Information on Preferred Side of Use - by distance from the ear to the tumor in millimeters (Grell et al., 2016).

	Distance from preferred ear to gravity center of tumor				
	Distance from Ear, 15–55 mm			Distance from Ear, > 55–75 mm	
Sex	**Count**[a]	**OR**[b]	**95% CI**	**OR**	**95% CI**
Female	284	1.85	1.41–4.04	1.85	1.36–2.96
Male	508	3.04	1.63–7.54	1.68	1.26–2.33
Age					
≤ 46	379	1.86	1.45–4.37	1.86	1.38–2.76
> 46	413	3.06	1.63–7.29	1.69	1.25–2.51
Grade					
1 or 2	331	2.59	1.15–6.61	1.82	1.25–2.75
2 or 4	417	2.16	1.05–5.01	1.64	1.34–2.39
Size (cm^3)					
≤ 18	461	1.96	1.51–3.66	1.96	1.48–2.97
> 18	331	4.09	1.90–12.0	1.51	1.17–2.25
Use, Years					
≤ 6	461	2.02	1.31–4.28	1.39	1.13–1.99
> 6	331	3.27	1.92–11.6	2.32	1.57–3.57
Use, Hours					
≤ 200	435	1.57	1.29–3.36	1.57	1.27–2.22
> 200	357	4.06	2.03–11.6	1.94	1.32–3.02
Use, Calls					
≤ 4000	420	1.55	1.25–3.42	1.44	1.19–2.02
> 4000	372	3.56	2.05–9.88	2.26	1.51–3.38

[a] Total count from 4 distance ranges from the ear.
[b] Risk of observing brain cancer within distance range.

3. Case-control studies; meningioma

Little increased risk of meningioma was found in the five country Interphone analysis, except for the highest category of exposure in those with 7 or more years of use (Table 9).

Carlberg et al. (2013) reported on risk of meningioma from exposure to wireless phone radiation between the years 2007 and 2009, but found no overall association.

Table 10 summarizes the results for meningioma from the report on the French CERENAT case-control study (Coureau et al., 2014). There was only significant excess risk for "heavy users" (≥ 896 h of use).

Carlberg and Hardell (2015) performed a pooled analysis from 1997 to 2003 and 2007–2009 of the risk of meningioma from cell and cordless phone use. In total, 1625 meningioma cases and 3530 controls were analyzed. Overall no association with use of mobile or cordless phones was found. However, they reported an increased risk among heavy users of both mobile and cordless phones from various wireless phone types (wireless combines all phone types) (Table 11). The risk increased significantly per 100 h of use from four wireless phones categories.

4. Case-control studies of other cancers and other tumors

Case-control studies have also been performed on other cancers suspected as being associated with RFR exposure. Those examining thyroid and skin cancers are not considered here, as over-diagnosis of thyroid cancer and sun exposure, respectively, result in uncontrolled confounding. As limited studies have been reported thus far on leukemia risks tied with mobile phones, we do not consider these risks here.

In a population-based case-control study of children Li et al. (2012) included 939 leukemia and 394 brain neoplasm cases newly diagnosed between 2003 and 2007, aged 15 years or less. Controls were randomly

Table 9
Meningioma risk by years of use and by Specific Absorption (SA) (Cardis et al., 2011).

Specific Absorption (SA)	OR	95% CI
7 + Years of use		
Never regular user	1.00	
< 76.7 J/kg	1.07	0.64–1.78
76.7–284.1 J/kg	0.74	0.33–1.67
284.1–978.9 J/kg	0.88	0.47–1.64
978.9–3123.9 J/kg	1.00	0.52–1.92
3123.9 + J/kg	2.01	1.03–3.93

Table 10
Risks for meningioma from the CERENAT study (Coureau et al., 2014).

Exposure	OR	95% CI
Cumulative duration of calls (hours)		
Not regular user	1.00	
< 43	1.12	0.61–2.04
43–112	0.85	0.45–1.61
113–338	0.52	0.25–1.07
339–895	0.52	0.18–1.45
≥ 896 total hours	2.57	1.02–6.44
Temporal lobe	7.89	0.48–130.14
Frontal lobe	4.82	0.78–29.63

Table 11
Risk of meningioma by hours of use for type of wireless phone (Carlberg and Hardell, 2015).

Phone Type	Hours of use	OR	95% CI
Analogue	Per 100	1.019	1.003–1.035
	1000	1.207	
	2000	1.457	
	3000	1.759	
Cellphone (2G, 3G)	Per 100	1.005	1.0001–1.010
	1000	1.051	
	2000	1.105	
	3000	1.161	
Cordless	Per 100	1.010	1.005–1.014
	1000	1.105	
	2000	1.220	
	3000	1.348	
Wireless	Per 100	1.006	1.003–1.009
	1000	1.062	
	2000	1.127	
	3000	1.197	
Analogue	> 1486	1.8	0.9–3.6
Cellphone (2G, 3G)	> 3358	1.5	1.0005–2.3
Cordless phone	> 1486	1.7	1.3–2.2
	> 3.358	2.0	1.4–2.8

selected, with a case/control ratio of 1:30 and matched on year of birth, from all non-neoplasm children insured in the same year when the index case was admitted. The Average Power Density (APD) was calculated for each township in Watt-Years per square kilometer (WYs/km^2) 5 years prior to diagnoses. The median power density was 167.02 WYs/km^2. They reported that a higher than median averaged APD was significantly associated with an increased Adjusted Odds Ratio (AOR) for all neoplasms (1.13; 1.01–1.28), and for leukemia (1.23; 0.99–1.52), but not for all brain neoplasms (1.14, 0.83–1.55). They did not specifically analyze data on gliomas.

Hardell et al. (2013a) pooled acoustic neuroma results from case-control studies conducted in 1997–2003 and 2007–2009, including 316 participating cases and 3530 controls. Their main results by phone type are shown in Table 14. There is some evidence of a dose-response relationship is evident with mobile and cordless phones associated with ORs of 4.5 and 6.5 respectively for 20 or more years of use. There were similar results per cumulative hours of use (Table 12).

Additionally, the authors reported tumor volume increases from

Table 12
Risk of acoustic neuroma for years of wireless phone use (Hardell et al., 2013).

Years of use	All mobile phones		Cordless phones	
	OR	95% CI	OR	95% CI
> 1–5	1.3	0.9–1.8	1.5	1.1–2.1
> 5–10	2.3	1.6–3.3	1.6	1.1–2.5
> 10–15	2.1	1.1–3.5	1.4	0.8–2.6
> 15–20	2.1	1.02–4.2	0.5	0.1–2.1
> 20	4.5	2.1–9.5	6.5	1.7–26

Table 13
Findings for tumor volume from Moon et al. (2014).

	Tumor size (cm^3)	OR	95% CI
< 10 years	5.57	1.045	0.987–1.107
> 10 years	9.83		
Non-regular user	2.71	1.125	1.041–1.216
Regular user	8.10		

analogue cellphone use per 100 h of use (7.4%, 95% CI = 1.0–14.2%) and per year of use (10.4%, CI = 2.4–18.7%).

Moon et al. (2014), in a matched case-control study from Korea examining 119 cases of vestibular schwannoma and 238 controls attending for routine examinations in the same institution found no difference between cases and controls in the duration, time of use or cumulative use of mobile phones. However, in a case-case analysis they found that vestibular Schwannoma tumor volume was greater in those with higher use compared to lower use of mobile phones and in those with regular compared to non-regular use (Table 13).

Pettersson et al. (2014) conducted a population-based, nation-wide, case-control study in Sweden for acoustic neuroma (vestibular Schwannoma) diagnosed between 2002 and 2007. In total, 542 eligible acoustic neuroma cases and 1095 controls were identified, of whom 83% of the cases but only 65% of the controls participated. Detailed findings were presented for all mobile phones and types of mobile phones, as well as by laterality of the tumor in relation to mobile phone used. Table 14 presents the data for time since first regular use of mobile phones and regular use of cordless phones. The low proportion of controls participating could explain these findings, as mobile phone users would be more likely to participate than non-users.

5. Cohort studies

In an update of the Danish cohort study of fewer than half a million persons over more than a decade, Frei et al. (2011) reported that when analyses were restricted to individuals with the longest mobile phone use, ≥ 13 years of subscription, the incidence rate ratio was 1.03 (95% CI 0.83–1.27) in men and 0.91 (0.41–2.04) in women. Among those with subscriptions of ≥ 10 years, ratios were 1.04 (0.85–1.26) in men and 1.04 (0.56–1.95) in women for glioma and 0.90 (0.57–1.42) in men and 0.93 (0.46–1.87) in women for meningioma. There was no indication of dose-response relation either by years since first subscription for a mobile phone or by anatomical location of the tumor. However, corporate users, people who would have been the heaviest users, were included in the unexposed group, while those who began using phones after the first cohort was established were also placed in the category of non-exposed. Thus, misclassification of exposure could have been responsible for the lack of risk observed. In addition, the study

Table 14
Data on Acoustic Neuroma in Sweden (Pettersson et al., 2014).

	All cases		Histologically confirmed cases	
Use	OR	95% CI	OR	95% CI
Ever used mobile phones regularly[a]	1.18	0.88–1.59	0.99	0.65–1.52
Time since regular[a] use of mobile phones began				
< 5 years	1.04	0.72–1.52	0.94	0.56–1.57
5–9 years	1.40	0.98–2.00	1.11	0.66–1.86
10 or more years	1.11	0.76–1.61	0.94	0.55–1.62
Ever used cordless phones regularly[a]	1.41	1.07–1.86	1.24	0.83–1.86

[a] Regular use is defined as having ever called or received a call at least once per week on average during 6 months or more.

lacked statistical power to detect a change in risk because of the small size of the population under surveillance and the relatively low rate of glioma.

In the UK Million Women cohort study the participants were asked only two questions at two points in time (1990 and 2005) about their cellphone use: “How often do you use a cellphone?”; “How long have you used it?” (Benson et al., 2013). These limited measures do not provide an accurate indicator of cellphone exposure. The authors reported no increase in glioma risk but an increased risk of a vestibular Schwannoma: the Relative Risk for ever use of a mobile phone was 1.44 (95% CI 0.91–2.28) and for 10 + years of use was 2.46 (1.07–5.64).

6. Brain tumor incidence, descriptive and trend analyses

Tos et al. (2004) examined Danish incidence rates of vestibular Schwannoma from 1996 to 2001. There is a slow and steady increase from 1976 to 1990, then from 1990 to 1995 a marginal increase followed by a significant increase with a mean incidence per 100,000 population of 1.74 in 1996–2001.

Lehrer et al. (2011) reported a significant correlation between number of cell phone subscriptions and brain tumors in nineteen US states ($r = 0.950$, $P < 0.001$) for years 2000–2004 using 2007 cellphone subscription data. Latency for brain cancer is believed to extend from 7 to 40 years. The effect of cell phone subscriptions ($P = 0.017$) was independent of the effect of mean family income ($P = 0.894$), population ($P = 0.003$) and age (0.499). While phone subscriptions in 2007 are not directly indicative of use in prior decades, it may provide a surrogate indicator of relative use.

Baldi et al. (2011) reported age-adjusted incidence trends for CNS tumors from 2000 to 2007 in the Gironde CNS Tumor Registry, France (Table 15). The lack of significant trends in the APC for all categories except meningeal tumors could be a reflection that the time period studied was one of relatively early use of mobile phones.

Ding and Wang (2011) reported that brain and nervous system cancers had been increasing in Shanghai during the period 1983–2007, but for males age-adjusted data showed no significant increase, annual percent change in incidence (APC) 1.2, 95% CI 0.4–1.9, though it did for females (APC 2.8, 95% CI 2.1–3.4). The authors concluded, however, that the latter increase was unlikely to be related to increasing cell phone use. The authors did not examine glioma specifically, nor did they examine age-specific glioma trends in individuals ages 20–39 who have used phones heavily and regularly enough to have incurred a change in baseline rates. They also did consider that women generally use their phones for talking up to three times more than men, according to some global surveys by the Pew Foundation (pewglobal.org).

Dobes et al. (2011) reported increasing incidence in Australia from 2000 to 2008 for glioblastoma multiforme (GBM), especially in those age 65 or more, and increasing incidence of meningiomas in males but significant decreasing incidence of Schwannomas (Table 16).

Zada et al. (2012) examined data from three major U.S. cancer registries: Los Angeles County, California Cancer Registry, and the National Cancer Institute's Surveillance, Epidemiology and End Result for 12 U.S. states (SEER 12) from 1992. The APC for GBM (grade IV glioma) and Glioma was reported by brain region. Table 17 shows APC changes by cancer registry for GBM and for glioma located in three anatomical regions of the brain, showing significant increases compatible with increasing use of mobile phones.

Table 15
CNS tumor incidence rate changes in Gironde, France 2000–2007 (Baldi et al., 2011).

Category	APC[a]	95% CI
All CNS tumors	2.33	0.20–4.52
Men	0.65	− 2.69 to 4.09
Women	3.88	− 0.22 to 8.14
Urban residence	2.13	− 0.29 to 4.60
Rural residence	3.07	− 2.36 to 8.81
Neuroepithelial tumors	1.14	− 2.95 to15.41
Meningeal tumors	5.40	1.15–9.83

[a] Annual percent change in incidence rates.

Table 16
Trends in incidence of glioblastoma multiforme, meningioma and Schwannoma in Australia (Dobes et al., 2011).

Category	APC	95% CI
All GBMs	2.5	0.4–4.6
Males	2.6	− 0.1 to 5.4
Females	2.2	− 1.5 to 6.0
All, ≥ 65 years	3.0	0.5–5.6
Meningioma – Males	5.3	2.6–8.1
Meningioma – Females	0.6	− 3.6 to 5.0
Schwannomas –Males	− 1.0	− 7.9 to 6.3
Schwannomas –Females	− 5.3	− 9.4 to 0.5

Consistent with the study above, Cardis et al. (2011) reported that the combined percentage of the total radiation absorbed by the frontal lobe (19%), the temporal lobe (50%) and the cerebellum (18%) was 81% at 900 MHz and was 86% at 1800 MHz (frontal lobe 14%, temporal lobe 50%, cerebellum 13%).

Chapman et al. (2016a), using national cancer registration data, examined age and gender specific incidence rates for males and females diagnosed with brain cancer in Australia between 1982 and 2012, and mobile phone usage data from 1987 to 2012. They modeled expected age specific rates based on published reports of relative risks (RR) of 1.5 in ever-users of mobile phones from the Interphone study, and RR of 2.5 in a proportion of ‘heavy users’ (19% of all users), assuming a 10-year lag period between use and tumor incidence. Significant increases in brain cancer incidence were observed (in keeping with modeled rates) only in those aged $\geq$ 70 years. They suggested that the observed increases in brain cancer incidence in the older age group are unlikely to be related to mobile phone use.

The methods used by Chapman et al. (2016a), which involved several assumptions and conclusions were challenged (Bandara, 2016; Morgan et al., 2016; Wojcik, 2016) and defended (Chapman et al., 2016b). Bandara (2016), Morgan et al. (2016) and Wojcik (2016) noted that the data used by Chapman et al. (2016a) were based on estimates, due to an unavailability of data and mobile phone user was calculated using number of subscriptions, which the authors state uses invalid assumptions and is unreliable for accurately assessing mobile phone exposure. Overall, the Australian trend data are not definitive of an increased risk, but they are also not a clear indication of no risk in the most exposed age group, in light of the long latency of GBM.

de Vocht (2016) studied cancer trends and inferred the impact of cellphone use in England for selected brain tumor types. The author concluded that the annual incidence of malignant neoplasms of the temporal lobe has been increasing faster than expected during the period of 10 years post-1995, and that post-2005 an additional increase of 35% (95% CI 9–59%) was evident.

Sato et al. (2016) examined brain cancer incidence rates in Japan (Table 18). The authors considered whether use of a mobile phone for $\geq$ 1640 h (from the Interphone study (5,6)) correlates with the increases in brain cancer incidence found in young people between 1993 and 2010 in Japan and concluded that the increase cannot be explained by heavy mobile phone use, but did not provide an explanation as to what might be the cause of these significant and unexplained increases in brain cancer. Notably the rate of increase in 2002–2010 was more than three times that since 1993.

Kleijwegt et al. (2016) examined vestibular Schwannoma (VS) incidence rates from 2001 to 2012 in the Netherlands. The authors chose to focus on the Leiden region because they considered that the incidence of VS in the Netherlands may best be estimated on the basis of

Table 17
The Average Percent Change for Glioma by 3 anatomical brain regions from the Los Angeles, California, and SEER − 12 cancer registries (Zada et al., 2012).

		Los Angeles Cancer Registry		California Cancer Registry		SEER 12 Registry	
Cancer	**Brain Region**	**APC**	**p**	**APC**	**p**	**APC**	**p**
GBM	Frontal lobe	3.0	0.001	2.4	< 0.001	2.5	0.027
Glioma		1.7	0.012	1.4	0.004	1.6	< 0.001
GBM	Temporal lobe	2.3	0.010	2.3	0.026	1.3	0.027
Glioma		0.9	NS	0.07	NS	0.05	NS
GBM	Cerebellum	NA		11.9	< 0.001	0.06	NS
Glioma		0.04	NS	− 3.4	0.014	1.4	0.014

NA: Not available; NS: Not significant.

Table 18
Japanese brain cancer increases 1993–2010 in age groups 20–29 and 30–39 (Sato et al., 2016).

Age	Period	Sex	APC[a]	95% CI
20–29	1993–2010	M	3.9%	1.6–6.3%
	2002–2010	F	12.3%	3.3–22.1%
30–39	1993–2010	M	2.7%	1.3–22.1%
		F	3.0%	1.4–47%

[a] APC Average percent change per year.

the incidence rates observed for the Leiden region. This region showed a fourfold increase from 2001 to 2012 from about 0.8 to about 3.3 per 100,000.

The Central Brain Tumor Registry of the United States (CBTRUS) has published annual reports from 2007 to 2016 with data from 2004 to 2013 (www.CBTRUS.org). The annual incidence rate of VS tumors (based on their published percentage of VS among all nerve sheath tumors) doubled from 0.88 to 1.73 per 100,000.

Gittleman et al. (2015) examined changes in incidence rates for malignant and non-malignant brain tumors (approximately two-thirds of all brain tumors) across all age groupings in the United States between 2000 and 2010 (Table 19). The authors concluded "The incidence of the most common cancers in adults decreased between 2000 and 2010, as did the incidence of MCNST [Malignant Central Nervous System Tumors]. However, the incidence of NMCNST [Non-Malignant Central Nervous System Tumors] increased significantly. In comparison, adolescents had increasing rates of MCNST and NMCNST, and children had increasing rates of … MCNST." We note that late ascertainment is a major problem in the 51 cancer registries in the U.S. It is likely that in later reports, there will be cases added in the recent 3-year bins, increasing the APC for the most recent periods.

Table 19
Trends in Brain Tumor Incidence in the United States (Gittleman et al., 2015).

Age Groups	Type[a]	Years	APC	95% CI
Children				
0–14	Ma	2000–2010	1.0	0.5–1.5
5–9	Ma	2000–2010	1.4	0.8–2.0
10–14	Ma	2000–2010	1.3	0.8–1.7
0–14	N-M	2004–2010	1.6	− 0.0.3 to − 3.6
10–14	N-M	2004–2010	3.9	0.4–7.5
Adolescents				
15–19	N-M	2004–2010	3.9	0.7–7.2
Adults				
≥ 20	Ma	2008–2010	− 3.1	− 6.1 to − 0.1
45–54	Ma	2000–2010	− 0.8	− 1.2 to − 0.4
55–64	Ma	2000–2004	1.1	0.1–2.1
		2004–2010	− 1.1	− 1.6 to − 0.7
20–44	N-M	2004–2010	3.5	0.9–6.1
45–54	N-M	2004–2010	2.2	0.2–4.2
≥ 75	N-M	2004–2010	3.6	0.8–4.9

[a] Ma: Malignant; N-M: Non-Malignant.

Philips et al. (2018) analyzed UK Office of National Statistics data covering 81,135 ICD10 C71 brain tumors diagnosed in England (1995–2015) and calculated age standardized incidence rates (ASR) per 100k person–years. They reported a sustained and highly statistically significant ASR rise in glioblastoma multiforme (GBM) across all ages and a decline in earlier stage disease. The ASR for GBM more than doubled from 2.4 to 5.0, with annual case numbers rising from 983 to 2531. Overall, the rise was mostly hidden by a reduced incidence of lower grade tumors.

7. Case series

West et al. (2013) reported multiple primary breast cancers in young women who had regularly placed a cellphone in their bras (Table 20). Tumors were reported to have occurred subcutaneously directly under the antennas of the phones. Subsequently, a number of other such cases have come to light with unusually located breast tumors relative to reported cell phone storage in the bra.

Peleg (2012) discussed a cancer cluster among young workers at an Israeli Antenna Range Facility. It was believed that significant RFR exposures took place as a result of workplace conditions. Five of about 30 workers were diagnosed with cancer. This was regarded as significantly greater than the expectation. Peleg et al. (2018) extended this analysis to 47 patients with cancer previously exposed to whole-body prolonged RFR, mainly from communication equipment and radar. They found that the percentage frequency of haemo-lymphatic (HL) cancers in the case series was very high, at 40% with only 23% expected for the series age and gender profile, 95% confidence interval: 26–56%, $p < 0.01$; 19 out of the 47 patients had HL cancers.

Stein et al. (2011) studied 56 cancers among 49 military personnel (47 male, 7 females) exposed to intense prolonged RFR between 1992 and 2011. Based on exposure information reconstructed from reported histories, it was assumed that significant RFR exposures took place as a result of workplace conditions. The average duration of exposure was 13 years; the average age at diagnoses was 43. There appeared to be an excess of both haemolymphatic and testicular cancers.

8. Discussion

Because they allow more detailed consideration of exposure and more precision of diagnoses, case-control studies can be superior to prospective cohort studies, or other methods, in evaluating potential risks for cancers. Carrying out a credible, statistically valid cohort study with sufficient power to find a change in rate of a rare cancer such as glioma that occurs at between 7 and 10 per 100,000 in industrialized countries would require a costly detailed prospective study following cellphone users (and other RF exposures) of about 10 million persons over 10 years or more. Further, exposures will change over time and cannot easily be tracked in large cohorts and it is usually difficult to collect sufficient information on exposure, and especially exposure during follow-up. It may also be difficult to select an appropriate comparison cohort.

Table 20
Placement of cellphone in bras associated with multiple primary breast cancers (West et al., 2013).

Case	Age	Bra Placement	Diagnosis
1	21	Several hours per day	"…extensive ductal carcinoma in situ (DCIS) with multifocal micro invasion."
2	21	She had been placing her [cellphone] in her bra for ≥ eight hours a day for 6 years	Four multifocal invasive cancer with extensive DCIS. Two of nine axillary lymph nodes were positive for metastatic disease.
3	33	Intermittently for 8 years. 2 years prior to Dx while jogging 3–4 times/week.	Six cancers with a 5 mm metastasis in one sentinel lymph node.
4	39	Four hours/day, 10 years	Four invasive ductal carcinomas ranging from 1 to 3 cm in size with 10 cm of DCIS.

However, estimates of exposure in case-control studies typically rely on either self-reports from patients recently operated on for brain cancer, or reports from surviving relatives about the case's cell phone patterns and habits, and thus potentially suffer from selection and recall bias, though the latter can be avoided if operator-generated data, collected equally from cases and controls, are available. To overcome the problems of self-report, Public Health organizations should mandate the collection of long-term cellphone use data that would be available to the user or researcher, with the user's permission.

Cross-sectional studies may point to issues that need evaluation, but do not permit a causal inference. Case series are useful to indicate a potential issue for action and better studies but these are not definitive and need to be followed by appropriately designed case-control or cohort studies.

Misclassification, the erroneous measurement of one or several categorical variables, is a major concern in many scientific fields. All epidemiological studies of cell phone radiation and brain cancer carry a risk of misclassification that will bias the risks towards the null. Even in rather simple scenarios, unless the misclassification probabilities are very small, major bias can arise in estimating the extent of association assessed in terms of the risk or odds ratio. Only in very special cases - for example, if misclassification takes place solely in one of two binary variables and is independent of the other variable, is misclassification non-differential, otherwise the estimates are biased towards a finding of no effect.

Nevertheless, recent case-control studies from Sweden and France corroborate findings of earlier studies in providing support for making a causal connection between cell phone use and brain cancer, as well as acoustic neuroma, also called Vestibular Schwannoma. Hardell and Carlberg (2013) concluded that the Bradford Hill criteria for causality have now been fulfilled. It is notable that three recent meta-analyses all confirm significant increased risk of glioma after 10 or more years of use of cell phones (Bortkiewicz et al., 2017; Prasad et al., 2017; Yang et al., 2017). The Aydin et al. (2011) data that relied on billing records along with children's recall of their uses of phones approaches and in some instances met conventional tests of statistical significance and indicated that four years or more of heavy cell phone radiation causes glioma in children. This finding is consistent with that of Hardell and Carlberg (2015) who showed that those who began using cell phones and/or cordless phones regularly as children had between 4 and 8-fold increased risk of glioma as adults.

Studies of time trends in cancer are of limited value in estimating the impact of cellphones. Such trends can simply suggest etiological hypotheses but cannot prove or disprove any single hypothesized factor, as was also true with tobacco use and lung cancer. Thus, time trends cannot be used to test hypotheses, but can be employed to generate them. In that regard several of the unexplained trends of GBM reported here indicate that there have been shifts in avoidable causal factors over time. As different causes can contribute to GBM at relatively greater proportions at different points of time, the interpretation of time trends remains highly problematic.

Since almost half of all brain cancers occur in persons age 60 and older, and the relatively recent increase in use by cell phones by those age 40 and under, the absence of an overall increase in rates is to be expected when the whole brain is considered; but when only the temporal lobe, frontal lobe and cerebellum are considered a different picture arises. Some incidence trend studies suggest that rates of brain tumors are increasing in the younger population. In addition, some case series suggest concern, perhaps particularly about breast cancers occurring in young women who kept cell phones in their bras.

Although cohort data continue to provide no confirmation of increased brain cancer risks tied with cell phones, both cohort studies on which data have so far been reported had limited exposure data, while the Danish cohort study (Frei et al., 2011) placed corporate subscribers (likely heavy users of mobile phones) in the unexposed group. This misclassification of exposure will have biased the relative risks observed towards the null. Continuation of these existing Danish and British cohort studies would be unproductive because of the serious exposure misclassification and the related lack of statistical power to be able to detect significant associations. Further, the Mobi-kids study (Sadetzki et al., 2014) might also result in negative findings because it may not have been started at the correct time to correctly identify exposure and is focusing on chronic disease endpoints rather than relatively short-term impacts such as memory, reaction time, hearing and visual acuity, addiction and other endpoints in children.

Any new epidemiological studies of brain cancer to be carried out should include validated measures of exposure and/or biomarkers of possible impact of RFR on biological processes. However, if this need for validated exposure indicators implied the use of a monitor there could be a problem, because few are likely to consent to wear a monitor, unless a monitor could be incorporated as a part of the operating system of a smartphone. This has been proposed with the app Quanta, for which validation remains to be ascertained. In the meantime, studies that rely on surrogates of exposure such as billing records can still yield useful information.

Potential cancer sites and other outcomes for consideration in new studies include breast cancer because of the case reports of breast cancer in women carrying cell phones in their brassieres (West et al., 2013), haematolymphatic cancers, given the apparent excess of these cancers in a case series from the Israel army in young soldiers exposed to radar and communication transmitters in military settings (Stein et al., 2011; Peleg et al., 2018) and as reported previously from the armies in Poland (Szmigielski, 1996) and Belgium (Degrave et al., 2009). Other sites than brain and acoustic neuroma could potentially increase in incidence when untested whole-body exposure occurs, this may be the case with several evolving technologies. Thus, recently introduced and untested technologies include Wireless Power Transfer that involves sending recharging signals short distances between a central charging station and an untethered wireless device. In addition, other possible sources of exposures that have not been evaluated include areas close to cellular base station antennas, the yet-to-be introduced 5 G communication systems, and rapidly evolving occupational exposure and novel systems for Wi-Fi (Peleg, 2009).

Several studies have found increases in the incidence of brain cancer, especially glioblastoma multiforme (e.g. Kleijwegt et al., 2016, Sato et al., 2016, Philips et al., in press). However, additional data are needed to evaluate cancer risk from RFR in relation to national cancer trends, especially critical analysis to determine accurately if age-specific glioma incidence is rising in children and adolescents and in special occupational groups. In addition to this outcome trend data on

hematopoietic malignancies, testicular cancer and other cancers should also be considered. Such trends are ecologic, depend on good cancer registration and require data to exclude the role of changes in cancer registration and diagnostic practices. In evaluating these trends, it would be necessary to consider any data available concerning other environmental exposures such as MRI and CT scans as well as exposure to RFR.

To determine the overall public health importance of EMF, serious consideration should be given to epidemiological studies that have shorter latency non-cancer outcomes; examples are studies using motility in sperm along with sperm DNA fragmentation as end-points (Adams et al., 2014; Houston et al., 2016), and studies of Electrical Hypersensitivity (EHS) (Belpomme et al., 2015, 2016; McCarty et al., 2011; Genuis and Lipp, 2012), as well as studies of reaction time, hearing and visual acuity, memory, addiction, and sleep patterns. Recently experimental evidence has shown that RFR can affect the testicular proteome (Sepehrimanesh et al., 2017) and thus play a role in growing patterns of male infertility.

Susceptibility factors (e.g. age, genetic variability) and EHS have not yet been adequately evaluated in epidemiological studies of RFR. Age has generally been considered, but not germline or acquired genetic factors. There is a case for including detailed measures of RFR exposure in currently ongoing cohort studies in many countries designed to evaluate genetic susceptibility in disease causation and with suitable biologic specimens collected and stored. The role of RFR could be evaluated by carefully designed case-control studies nested within the cohort. There are indications particularly from the Ramazzini animal studies that other environmental exposures might make people more susceptible to a combination of exposures (Falcioni et al., 2018). This combinatorial issue been noted in studies of occupational exposure to chemicals, metals and electromagnetic fields (Navas-Acien et al., 2002). Separately, no effects were observed but when combined with EMF strong results were found. In the Ramazzini studies finding a synergistic interaction between RFR and ionizing radiation, RFR served as a promoter while in the NTP animal studies RFR served as a direct carcinogen and genotoxic agent (National Toxicology Program, a, b, 2018.). In studies of case series of human cancers, it is important to take note of multiple primaries in proportion to the total number of cases observed as a possible indicator of unusual environmental risk or unusual environmental-susceptibility interactions (Stein et al., 2011).

Individual hypersensitivity to electric and radiofrequency fields (EHS) is a relatively newly reported phenomenon in the west, although cases of radiation sickness have been found in the former Soviet literature from the 1960s and 1970s. Case studies and individual reports together identify a population which would benefit from RFR exposure reduction (Davis et al., 2017). Because of serious methodological difficulties in operationalizing the concept and a lack of investment in research, definitive epidemiological studies of EHS have not yet been conducted.

In addition, it is important to identify sentinel outcomes potentially related to RFR exposure. Cancers other than brain to consider include breast, vestibular schwannoma/acoustic neuroma, parotid gland tumors, hematopoietic malignancies, testicular cancer, and even colorectal cancer, all tumors on sites of the body with close contact with RFR “hotspots”. However, non-cancer outcomes such as sperm damage, hearing loss and loss of visual acuity are likely to be more commonly linked to mobile phone use. Awareness of these non-cancer outcomes related to RFR exposure might be more likely to change policy, technology and behavior, which would have the effect of decreasing exposure. The major data gap is detail on actual personal exposure which could be obtained on specific occupational groups, as growing numbers of employers are requiring use of mobile phones. A critical priority is to close the major gap in the time trends in population wide impacts of screen time and RFR on children. There may also be issues with mixtures of exposures. All identified occupational groups with excess exposure to RFR should be fully studied.

9. Synthesis and conclusions

The Epidemiological studies reported since the 2011 IARC Working Group meeting are adequate to consider RFR as a *probable* human carcinogen (Group 2 A). However, they must be supplemented with the recently reported animal data as performed at the Ramazzini Institute and the US National Toxicology Program as well as by mechanistic studies. These experimental findings together with the epidemiology reviewed here are sufficient in our opinion, to upgrade the IARC categorization of RFR to Group 1, carcinogenic to humans.

It would be useful to know more about the association of additional tumor types such as parotid gland, testicular, breast, hematopoietic malignancies and multiple primaries with RFR. Case studies should continue to be conducted in the absence of a better exposure assessment system to increase awareness and understand the relationship between exposure to RFR and disease causation, as well as trial-error experiments and interventions.

In light of the evolving science concerning mobile phone and screen time exposures and the longer-term risk of cancer established by both epidemiological and toxicological studies, current evidence is strong enough to go from precaution concerning possible risk to prevention of known risks. Although the benefits of connectivity are extremely important, safety considerations demand reconciling use of information vs. risk of perceived rare outcomes. Thus, a concerted program of public and health professional education should be undertaken throughout society explaining current knowledge and devising policies to promote safer technology in partnership with designers of software and hardware. In addition, methods should be developed and validated to reduce exposures in schools, workplaces, hospitals and other workplaces. The precautionary principle should be applied now and suitable warning messages provided to adults and critically to children and their parents. Until technology has been devised that substantially lowers exposures, special efforts should be advanced to ensure that the exposures of children are limited to those deemed essential. Children should be encouraged to text to reduce their exposure to RFR, while every attempt should be made to reduce exposure to RFR in schools, as well as homes.

Research has so far been performed on technologies that have already been introduced, but is critically needed on new, untested technology prior to its use. Epidemiological studies necessarily confirm the impact of past exposures, while experimental studies provide indications of future risk. Thus, experimental evaluations and modeling are essential before distributing newer systems (e.g. 5 G) for which no safety data have been obtained. The absence of systematic testing of such technologies should not be confused with proof of safety. Better modeling through anatomically based systems, such as the Virtual Family, should be encouraged.

In the meantime, the evidence amassed thus far from epidemiology strengthens the case for instituting the precautionary principle with respect to exposures to RFR, especially to young children and men and women that wish to reproduce. The lack of detailed studies at this point reflects a myopic attitude toward the technology that may well prove to be wishful and dangerous thinking. Where studies have been carried out on human sperm quantity and quality there are increasing indications of serious human health impacts. To ignore those findings and subject humans to unevaluated novel RFR frequencies places current and future generations at risk.

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