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Review article
Cancer prevention and public health

The impact of cell phone use on the formation of brain tumors

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Cell phone use is increasing and now includes nearly 6.9 billion subscribers. A common concern is the effect of long-lasting phone calls on the formation of brain tumors, due to the proximity of this region. The aim of the following review was to verify this association along with a potential molecular background. The results of epidemiological studies are inconclusive. Most of them do not indicate a significantly increased risk of central nervous system cancers in phone users. However, some indicate that there is an increased risk of gliomas and a worse prognosis for patients with long-term phone use (in terms of cumulative hours and number of calls). Experimental studies show that radiation emitted by phones is able to induce changes in cell biology by generating oxidative stress, causing DNA damage and affecting gene expression. Therefore, further observation of the population and evaluation of the results of ongoing studies is needed to accurately assess this risk.
Keywords: brain tumors, cell phones, carcinogenesis, public health

Introduction

Tumors of the central nervous system (CNS) are a group of more than a hundred histologically distinct subtypes of neoplasms with varying clinical characteristics, treatment and epidemiology. While their incidence in the world community is relatively low, they have a disproportionately high mortality rate (only 1 in 3 patients achieve survival of at least 5 years from diagnosis) [1]. They are the most common solid tumors diagnosed in children aged 0–14 years and the second most common in adolescents aged 15–19 years in the world pediatric population. What is more, they are the eighth most common among all cancers (3%) in the world adult population above 40 years of age. They are three times more frequent in men than in women [2, 3]. In Poland, their frequency is estimated on 2% of all tumors [2].

The most frequent type is glioma (up to 70% of primary brain tumors worldwide, 40% in Poland) [2, 3]. It is a group of neoplasms originating from glial cells. The World Health Organization (WHO) has made a four-stage classification for their grade of malignancy, where grade I is considered to be a benign lesion, while grade IV is the highest and represents lesions with very high malignancy (the most common malignant brain tumor, glioblastoma multiforme, is also in this category) [3]. Other malignant lesions, such as anaplastic astrocytomas and oligodendrogliomas, are far less common. Although their localization can be the entire CNS, their most common location is in the supratentorial region of the brain [1]. Non-malignant lesions (22.38 per 100000) are far more common than malignant ones (8.5 per 100000) among patients form around the world [3]. Malignant brain cancer is the sixth most common cause of death in people over the age of 40 in the world. Despite its poor prognosis (average life expectancy estimated at 12.6 months after diagnosis), in recent years there has been an increase in survival rates in Western developed countries due to significant improvements in medical care [4, 5].

Many risk factors for the disease have been discovered to date — both environmental and genetic. However, interestingly, the exact etiology of these tumors is still not understood [5]. Approximately 5% of gliomas are family-related, while an even smaller percentage are associated with so-called Mendelian disorders and hereditary syndromes [3, 6]. Recent studies have coherently demonstrated that increased birth weight (> 4000g) leads to increased risk of CNS tumors, as confirmed by a meta-analysis by Georgakis et al [7]. Caucasians are at higher risk for the disease. It has also been proven that the incidence is higher in people before 12 and after 65 years of age. The only fully confirmed environmental risk factor for all brain tumors is ionizing radiation. This correlation is most strongly seen in children receiving cranial radiotherapy as part of treatment for acute lymphoblastic leukemia [8]. Research is constantly being conducted to identify other factors that may influence the increased risk of brain tumors. One such factor might be electromagnetic radiation from cell phones. This radiation was classified by the International Agency for Research on Cancer as a potential carcinogen [9].

Since the first introduction of cell phones in the mid-1980s, they have become an irreplaceable part of daily life in developed countries. Numerous studies have been done since then to prove the relationship between cell phone use and the increased incidence of brain tumors in the world population. The main aim of this paper was to explore if any relationship exists between cell phone use and the incidence of brain cancer.

Material and methods

A review of scientific publications in PubMed and Google Scholar databases and relevant data published by the WHO and the National Cancer Institute [10–12] was conducted. The following keywords were used to search for articles: “mobile phone,” “cell phone,” “brain cancer,” “glioma,” “risk,” and a combination of these. Initially, 541 articles from 1993-2014 were found, and then repeated articles and abstracts were eliminated, obtaining 396 articles. The time criterion was set to 2014–2024 (the review was conducted in March 2024). Finally, 141 articles were found, which were analyzed substantively by title and abstract. Finally, 38 articles were included in the review.

Cell phone use and formation of CNS tumors

Cell phone usage is extremely widespread, accounting for up to 97% of US adults and about 6.9 billion people worldwide [10, 11]. Phones also used by younger and younger children. There are equally prevalent concerns about the impact of cell phones on CNS tumors due to the proximity of the head during calls. Cell phones emit radiofrequency non-ionizing electromagnetic radiation (450–2700 MHz) with a peak power of 0.1–2 W [11]. The controversial fifth-generation (5G) phones use frequencies above 80 GHz. However, it is still far lower than that of ionizing radiation, a proven risk factor for CNS tumors [12, 13]. The different types of wireless phone technology generations and frequencies they use are shown in Table I.

Experimental studies

Ionizing radiation is a known factor affecting the cycle and function of cells [13]. Researchers are also trying to answer the question of such an effect induced by radiofrequency radiation (RFR). In a study on mice [frequency (f) = 1900 MHz, specific absorption rate (SAR) = 2.5/5/10 W/kg] and rat (f = 900 MHz, SAR = 1.5/3/6 W/kg) models, it was shown that exposure to RFR for 10 hours a day after 14 (mice) and 19 weeks (rats) caused a significant increase in DNA damage in the cortex cells of the frontal lobes of mouse brains and the hippocampus of rat brains. The frequencies mentioned above correspond to the 2nd and 3rd generations of telephone network technology (2G and 3G), but the exposure was of a much higher dose and duration than standard cell phone usage [14]. The probable mechanisms are the production of reactive oxygen species (ROS) and the resulting oxidative stress which cause oxidative damage to DNA cells as well as disruption of the repair of damaged DNA [15, 16]. Some authors indicate that even short-term exposure to this type of

radiation is capable of increasing ROS levels, causing DNA damage [17–19]. Such exposure is able to induce the activation of p53-related pathways and, with longer exposure, activation of Bcl-2, Ras and Akt1-related pathways, thus promoting cell survival and impairing apoptosis. Radiofrequency radiation is also able to affect the genes responsible for angiogenesis (inhibition of *VEGF*, *TNFSF15*, stimulation of *EPO*, *IL8*, *STAT5B*, *HPSE*) [20]. Moreover, the thermal effect generated by RFR is also noted, leading to increased ROS production and enhanced neuronal cell excitability [20]. Furthermore, RFR can cause an increase in intracellular nitric oxide (NO) levels in neurons and activation of the CaM/NO/cGMP signaling pathway, thereby impairing the response of nerve cells to ischemic or injury damage. This can affect not only the process of neurogenesis and cognitive function, but also the development of CNS tumors [21]. Gupta et al. [22] observed that f = 2450 MHz radiation results in changes in neuronal structure and function. It is caused by destroying mitochondria and releasing cytochrome-c, activating the apoptotic agents caspase-3 and caspase-9 in hippocampal cells [22]. Similar conclusions were reached by Zhao et al. [23] as they observed increased expression of caspase-2, caspase-6 and Asc protein genes in neurons and astrocytes, and Bax protein only in astrocytes after 2-hour exposure to RFR with f = 1900 MHz. This shows that even short-term exposure to RFR can increase the expression of genes encoding apoptotic proteins. However, Durdik et al. [24] indicated that RFR induces ROS and oxidative stress, but not DNA damage and apoptosis of CD34+ bone marrow progenitor cells. Hou et al. [25] observed a significant increase in ROS levels after 1-hour exposure to RFR at f = 1800 MHz and enhanced apoptosis of NIH/3T3 mouse fibroblasts. Shahabi et al. [26] noted that another morphological change in rat neural cells induced by long-term exposure (6 hours a day for 4 and 8 weeks) to RFR (f = 900 MHz) is their vacuolization, although with an unknown pathophysiological role. In addition, Falcioni et al. [27] indicated that with exposure to RFR (f = 1.8 GHz) in rats, there was an increase in the incidence of cardiac schwannoma and proliferation of cardiac Schwann cells and brain glial tissue, which also indicates the induction of radiation-induced changes in neurons. The effects of RFR on glioblastoma multiforme cells have also been explored. Al-Serori et al. [28] showed that RFR at f = 1950 MHz caused DNA damage in the U87 cell line, one of the most common among malignant brain tumors. However, the results of a study by Liu et al. [29] contradict these observations. Ouadah et al. [30] while testing rats with implanted glioma cells noted that exposure to f = 900 MHz radiation did not affect the survival, tumor volume, mitotic index, vascularization and necrosis of tumor cells. There is much more concern about the widespread introduction of 5G technology. Karipidis et al. [31], in a review of 107

experimental and 31 epidemiological studies, concluded that there is no confirmed evidence of any harm from this type of radiation on the human body, including the CNS. Russell, on the other hand, noted that the effects of 5G exposure have not been sufficiently studied, although there are reports of induced oxidative stress and altered gene expression [32]. While the results of the above are ambiguous, they show that RFR exposure is capable of inducing changes in cell biology that may have a potential impact on the onset of CNS diseases, including neurodegenerative disorders and tumors. The effects of RFR on cell biology are shown in Figure 1.

Epidemiological studies

Data on the impact of cell phone radiation on the growth of CNS tumors is still controversial. Some authors categorically state that it is one of the factors of carcinogenesis and should be restricted [33]. Moon, who analyzed the nationwide cell phone subscription rate and the incidence of CNS tumors, observed a statistically significant correlation between these variables for benign tumors [benign meningeal neoplasm (ICD-10: D32. 0); benign neoplasm of the brain and other parts of the central nervous system (ICD-10: D33)] and malignant ones [malignant neoplasm of the brain except lobes and ventricles (ICD-10: C71.0), frontal lobe (ICD-10: C71.1), temporal lobe (ICD-10: C71.2)]. The strongest correlation was reported for tumors of the frontal lobe [r = 0.85; 95% confidence interval (CI): 0.63–0.93], a region exposed to close contact with the phone during conversation [34]. In contrast, Schüz et al. [35] in a study in a group of 776,156 women during a 14-year follow-up, noted that the relative risk of ever or never using a cell phone for all brain tumors was close to 1.0 [relative risk (RR) = 0.97; 95% CI: 0.90–1.04]. No significant increase or decrease in the risk of the disease was observed for daily phone use or > 10 years. No difference in tumor location was also noted [35]. Feychting et al. [36] found that phone use for > 15 years did not affect the risk of formation of CNS tumors: glioma [hazard ratio (HR) = 0.97; 95% CI: 0.62–1.52], meningioma (HR = 1.24; 95% CI: 0.60-2.59) and acoustic neuroma (HR = 0.76; 95% CI: 0.33–1.73). Villeneuve et al. [37] came to similar conclusions when they analyzed the increase in the number of phone users and the incidence of brain gliomas in Canada. They indicated that the increase in incidence was mainly related to the aging of the population, rather than phone use [37]. Choi et al. [38] conducted a similar study in South Korea's population. They observed that the age-adjusted incidence rate for brain tumors increased almost by 4% in people > 60 years old, but this was not correlated with cell phone use [38]. In another Korean study, Yoon et al. [39] noted that the age-adjusted odds

ratio (aOR) for the development of glioma for regular phone users was 1.17 (95% CI: 0.63–2.14). They found no association with time of use or type of phone. However, a statistically insignificant increase was observed for urban residents (aOR = 1.42; 95% CI: 0.66–2.89) compared to rural residents (aOR = 0.50; 95% CI: 0.22–1.13). In addition, they found a statistically insignificant, although noticeable, difference in aOR between prevalence of tumors located ipsilateral and contralateral to the side of the head on which the cell phone was used most often [39]. Karipidis et al. [40], in an Australian ecological study (n = 16825), found no increase in the incidence of gliomas during the period of intensive cell phone expansion (2003–2013) in that country [annual percentage change (APC) = –0.6; 95% CI: –1.4 to 0.2). There was also no correlation with the incidence of temporal lobe tumors (APC = 0.5; 95% CI: –1.3 to 2.3). Elwood et al. [41], in a New Zealand study (n = 6677), similarly found no association between the increase in cell phone use (in 2006 almost the entire country's population) and the incidence of gliomas. What is more, the results suggested a decline in the 10–69 age group, the most intensive users of mobile devices [41]. Most interestingly, Uddin et al. [42] analyzed Taiwan's epidemiological data, finding that as the number of phone users increased by each percent (in 2002, the number of phone subscribers exceeded the population), there was a 0.5% increase in the incidence of brain tumors. However, the authors noted that further research was needed, and the conclusions so far are ambiguous [42]. A similar study conducted in Nordic countries by Deltour et al. [43] found no significant association between cell phone use and the incidence of gliomas, including among the most intensive users of mobile devices. The observations apply not only to gliomas, but also to other intracranial tumors. Shrestha et al. [44] investigated the effect of cell phone use on the development of pituitary tumors. They determined that the risk did not increase over at least 10 years of phone use [odds ratio (OR) = 0.69; 95% CI: 0.25–1.89] in relation to duration, total hours of use, cumulative number of calls and type of device [44]. Pettersson et al. [45] verified the correlation between the occurrence of acoustic neuromas and phone use for at least 6 months. They identified this risk as OR = 1.18 (95% CI: 0.88–1.59), and for histopathologically verified tumors as OR = 0.99 (95% CI: 0.65–1.52). For exposures lasting at least 10 years, the risk was OR = 1.11 (95% CI: 0.76–1.61). The authors also found no correlation between tumor location and the side of the head to which the phone was being held [45]. In a similar way, Carlberg et al. [46] found no statistically significant increase in meningioma risk (OR = 1.0; 95% CI: 0.8–1.2). They observed an increase in OR for cell phone use for > 25 years, but this was not statistically significant, and neither was the difference in tumor location [46]. Some authors suggest that there is no increased risk of CNS

tumor development in casual, moderate phone use. Instead, it appears in the group of users who use these devices most intensively. A French study by Coureau et al. [47] showed that there was no significant increase in the risk of gliomas (OR = 1.24; 95% CI: 0.86–1.77) or meningiomas (OR = 0.90; 95% CI: 0.61–1.34) for normal phone users. On the other hand, it was significantly higher for intensive cell phone use, considering the cumulative time > 896 h (OR = 2.89; 95% CI: 1.41–5.93 for gliomas; OR = 2.57; 95% CI: 1.02–6.44 for meningiomas) and > 18360 calls (OR = 2.10; 95% CI: 1.03–4.31) [47]. Furthermore, Momoli et al. [48] in the Canadian subgroup of the INTERPHONE study noted an increased risk of glioma formation in a group of people who used the phone for at least 558 hours of cumulative use (OR = 2.0; 95% CI: 1.2–3.4). Alarming results were observed by Hardell and Carlberg [49] in a study in a group of 1,380 glioma patients. They found a significantly higher risk of this tumor on the ipsilateral side relative to phone use (OR = 1.8; 95% CI: 1.4–2.2), especially in the 18-39 age group (OR = 2.2; 95% CI: 1.2–3.8) [49]. Similar observations were noted by de Voght [50], who indicated that there was a 35% increase in the incidence of parietal lobe tumors over a 10-year period, corresponding to 188 additional cases per year. A statistically significant increase in the incidence of tumors on the ipsilateral side was also found by Grell et al. [51] in a study in the INTERPHONE group (n = 792) (α = 9.66; 95% CI: 2.84–39.3). This association was unrelated to cumulative time and number of calls [51]. In addition, Carlberg and Hardell [52] noted that cell phone use >20 years was associated with lower survival for patients with gliomas in general (HR = 1.8; 95% CI: 1.3–2.5) and glioblastoma multiforme (HR = 2.0; 95% CI: 1.4–2.9). The major concerns about phone use are among the youngest users. However, Castaño-Vinyals et al. [53] in a study in a group of 899 patients with CNS tumors aged 10–24 years did not observe a significantly increased risk of developing gliomas (OR = 0.85; 95% CI: 0.62–1.18) — regardless of the duration and intensity of phone use and RFR dose. In fact, the risk seemed to decrease in the 15–19 age group with increasing number and duration of calls [53]. Similar conclusions were reached by Sato et al. [54] in a Japanese study in a group of children aged 6–18 years (n = 82). Data from the above studies are summarized in Table II.

It should not be forgotten that most experimental and epidemiological studies have their limitations. The results of experimental studies on animal models are often hard to relate to the human body, while studies on human cell lines are rare. In addition, they often take into account the extremes of exposure, practically impossible to replicate in the daily use of phones. Many epidemiological studies report a long latency period (> 15 years), ignore rare

subtypes of brain tumors, and overlook the impact of phone use in childhood, during the period of greatest CNS development [55].

Summary

The majority of available epidemiological studies do not identify an increased risk of developing brain tumors in the context of cell phone use. However, experimental studies and some epidemiological studies suggest the effects of radiation emitted by phones on neural cells (oxidative stress, thermal effect) and the potential impact on the formation of CNS tumors with long-term use. It should also be remembered that widespread mobile telecommunication is a new invention, available for about 20 years, and brain tumors are characterized by a long latency period. Therefore, it is necessary to conduct further studies and evaluate the results of previous ones in order to further define the impact of cell phone use on the formation of brain tumors.

Article information and declarations

Author contributions

Maciej Dubaj — conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing — original draft preparation, writing – review & editing.
Karol Bigosiński — conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing — original draft preparation, writing – review & editing.
Marcin Caliński — conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing — original draft preparation, writing – review & editing.
Katarzyna Słomczyńska — conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing — original draft preparation, writing – review & editing.
Marzena Furtak-Niczyporuk — conceptualization, data curation, funding acquisition, methodology, project administration, supervision, validation, visualization, writing — review & editing.

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Conflicts of interest

The authors declare no conflict of interest.

Supplementary material

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Table I. Types of wireless phone technology generations [32]

Abbreviation	Full name	Date of introduction	Frequency (f)
1G	Analog-Advanced Mobile Phone Service (AMPS)	1980’	800 MHz
2G	Global System for Mobile Communications (GSM) and Code Division	1990’	850–1900 MHz

	Multiple Access (CDMA)		
3G	Universal Mobile Telecommunications Service (UMTS)	1998	800–2100 MHz
4G	Long Term Evolution (LTE)	2008	700–2690 MHz
5G	Device-to-Device Communication	2018	> 30 GHz (even to 300 GHz)

Table II. The impact of cell phone use on brain tumors formation [34–54]

Study	Country	Test group	Observation period	Conclusions
Moon 2023 [34]	South Korea	Nationwide cell phone subscription rate	10 years	↑ benign tumors ↑ malignant tumors of the temporal and frontal regions
Schüz et al. 2022 [35]	The United Kingdom	n = 776 156	14 years	No risk
Feychting et al. 2024 [36]	The United Kingdom, Denmark, Finland, the	n = 264 574	7 years	No risk

	Netherlands, Switzerland			
Villenueve et al. 2021 [37]	Canada	Nationwide cell phone subscription rate, patients with gliomas (n = 43 350)	23 years	No risk
Choi et al. 2021 [38]	South Korea	Patients with brain tumors (n = 29 721)	18 years	No risk
Yoon et al. 2015 [39]	South Korea	Patients with gliomas (n = 285)	5 years	No risk
Karipidis et al. 2018 [40]	Australia	Patients with gliomas (n = 16 825)	10 years	No risk
Elwood et al. 2022 [41]	New Zealand	Patients with gliomas (n = 6677)	25 years	No risk, ↓ incidence in 10-69 age group
Uddin et al. 2023 [42]	Taiwan	Nationwide cell phone subscription rate	20 years	Correlation cannot be excluded
Deltour et al. 2022 [43]	Sweden, Finland, Norway,	Patients with gliomas (n = 18 232)	20 years	No risk

	Denmark			
Shrestha et al. 2015 [44]	Finland	Patients with pituitary tumors (n = 80), healthy controls (n = 240)	10 years	No risk
Pettersson et al. 2014 [45]	Sweden	Patients with neuromas (n = 451), healthy controls (n = 710)	> 6 months	No risk
Carlberg et al. 2015 [46]	Sweden	Patients with meningiomas (n = 1625), healthy controls (n = 3530)	9 years (881 hours of calls)	No risk
Coureau et al. 2014 [47]	France	Patients with gliomas (n = 253), patients with meningiomas (n = 194), healthy controls (n = 892)	2 years (> 896 hours of calls)	No risk for normal use, ↑ risk in the group with the longest time of use
Momoli et al.	Canada	Patients with	3 years	↑ risk in the

2017 [48]		gliomas (n = 253)	(> 558 hours of calls)	group with the longest time of use
Hardell et al. 2017 [49]	Sweden	Patients with gliomas (n = 1380)	17 years	↑ risk on the ipsilateral side
Grell et al. 2016 [51]	Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden, the United Kingdom	Patients with gliomas (n = 792)	4 years	↑ risk on the ipsilateral side
Carlberg et al. 2016 [52]	Sweden	Patients with gliomas (n = 1678)	20 years	↓ survival of glioma patients
Castaño-Vinyals et al. 2022 [53]	Australia, Austria, Canada, France, Germany, Greece, India,	Patients aged 10–24 with brain tumors (n = 899), healthy controls (n =	5 years	No risk

	Israel, Italy, Japan, Korea, the Netherlands, New Zealand, Spain	1910)		
Sato et al. 2017 [54]	Japan	Patients aged 6–18 with brain tumors (n = 82)	5 years	No risk

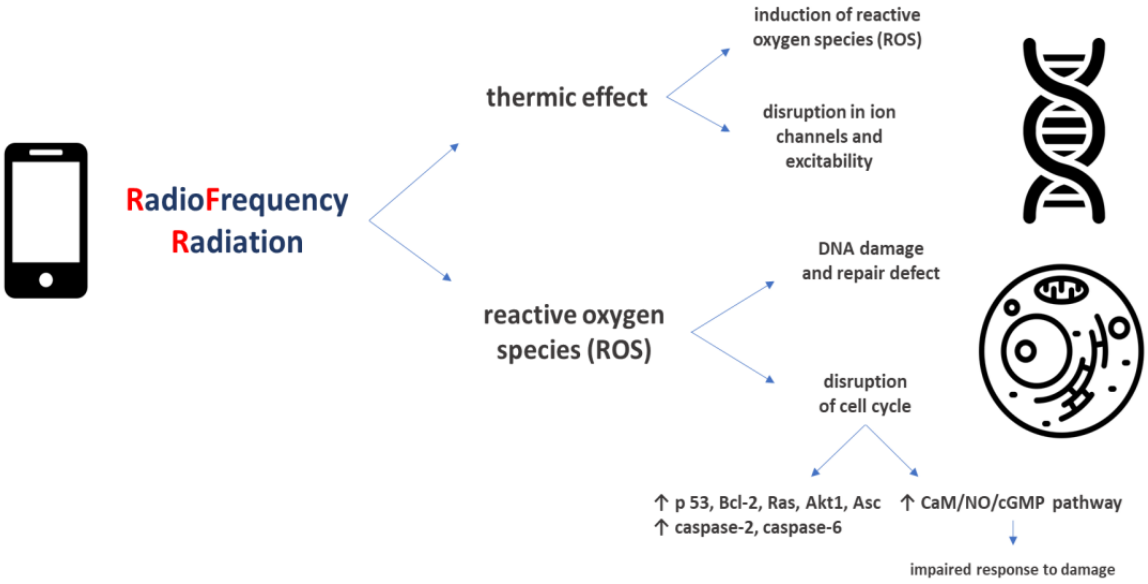

Figure 1. The effects of radiofrequency radiation (RFR) on cell biology [15–32]