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Radiofrequency Radiation and Cancer
A Review

David Robert Grimes, PhD

IMPORTANCE Concerns over radiofrequency radiation (RFR) and carcinogenesis have long existed, and the advent of 5G mobile technology has seen a deluge of claims asserting that the new standard and RFR in general may be carcinogenic. For clinicians and researchers in the field, it is critical to address patient concerns on the topic and to be familiar with the existent evidence base.

OBSERVATIONS This review considers potential biophysical mechanisms of cancer induction, elucidating mechanisms of electromagnetically induced DNA damage and placing RFR in appropriate context on the electromagnetic spectrum. The existent epidemiological evidence in humans and laboratory animals to date on the topic is also reviewed and discussed.

CONCLUSIONS AND RELEVANCE The evidence from these combined strands strongly indicates that claims of an RFR-cancer link are not supported by the current evidence base. Much of the research to date, however, has been undermined by methodological shortcomings, and there is a need for higher-quality future research endeavors. Finally, the role of fringe science and unsubstantiated claims in patient and public perception on this topic is highly relevant and must be carefully considered.

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It is difficult to envision any phenomenon as ubiquitous or crucial to human existence as electromagnetic radiation (EMR). We are surrounded by an invisible symphony of light that permeates everything we experience, from the visible light that illuminates our world, to the x-rays that have revolutionized diagnostic imaging and cancer treatments, to the broadcast and mobile communications transmitted worldwide by radiofrequency radiation (RFR). This last facet has of late proved especially contentious; while EMR is an inescapable part of our universe, there is increasing public concern over whether RFR poses a cancer risk. Such is the depth of feeling on the issue that it has led to a spate of arson attacks on phone masts and assaults on telecommunications engineers.

By 1 estimate, 20% of the US population believe that their cell phones cause cancer and that the government covers up harmful effects of RFR.[1] Such beliefs are passionately held and widely evangelized, despite being unrealistic. The recent adoption of 5G technology has been met by an explosion of claims on social media asserting all manner of harm, including not only claims that it can cause cancer, but even outlandish and thoroughly debunked assertions that 5G towers could cause COVID-19.[2] For cell phones, Wi-Fi, Bluetooth, and 5G, however, claims that these RFR sources can induce cancer are the most routinely invoked. For clinicians and scientists in cancer, it is important to understand the current evidence base.

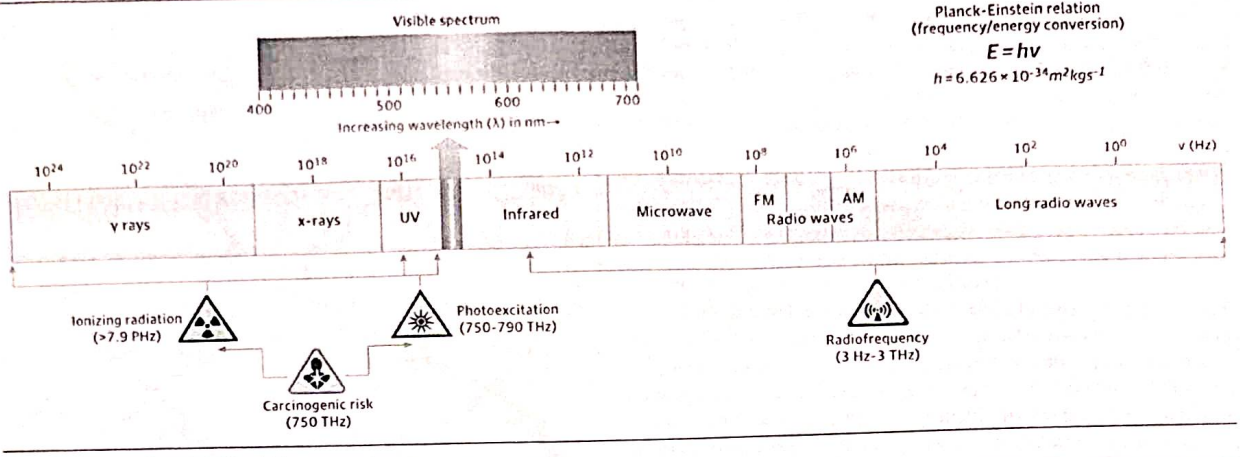
Biophysical Overview

Every enduring confusion has a grain of truth behind it. It is absolutely true that some types of EMR are capable of inducing DNA damage and are carcinogenic. However, this must be placed in context. Electromagnetic radiation is carried by photons, effectively particles of light, whose energy is proportional to their frequency. The electromagnetic spectrum is unbelievability vast, as illustrated in **Figure 1**. The energies that different forms of light carry, and the variation in their biological effect, are similarly vast. Photons with the requisite energy to eject electrons from an atom and cleave chemical bonds are defined as ionizing radiation, while light lacking this threshold energy is deemed nonionizing.[3]

When ionizing photons travel through tissue, some are absorbed by molecules in their path, surrendering their energy. This yields fast-moving charged particles. These charged particles can either directly impinge on DNA (direct effect) or can interact with water molecules, producing reactive oxygen species radicals that damage DNA (indirect effect). These 2 distinct mechanisms of damage are shown in **Figure 2**, with their net result being potentially mutagenic DNA damage and ultimately cancer. Typically, 33 eV is taken as the ionization threshold, corresponding to an extreme UV photon of 38 nm.

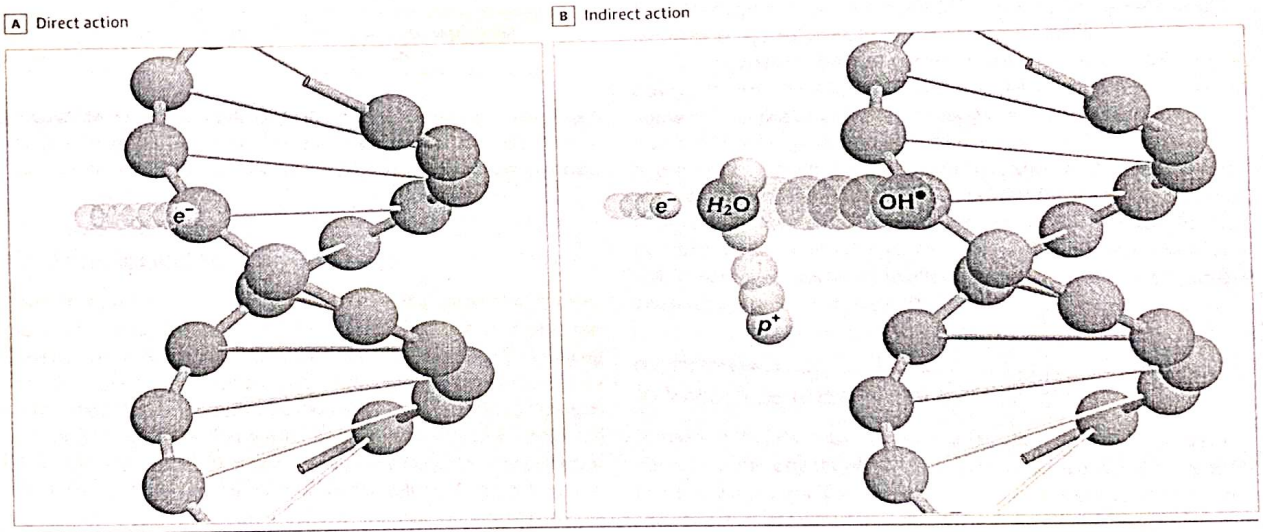
It is tempting to infer that all EMR above this threshold is carcinogenic, and all that below it is not. However, this is not strictly true; UV radiation (UVR), on the periphery of the ionization threshold, is a known carcinogen.[4] Ultraviolet B photons cannot ionize but have enough energy to raise DNA to an excited state. Through rapid internal conversion, DNA dissipates most of these events to harmless heat in mere femtoseconds (approximately 10^{-15} seconds), avoiding reactions. However, this process can fail, resulting in an incident UV-B photon absorbed by a pyrimidine base opening the bond, reacting with neighboring molecules to form pyrimidine

Figure 1. Frequencies on the Electromagnetic Spectrum



Radiofrequency regimen is to the right.

Figure 2. Mechanisms of Ionizing Radiation Damage



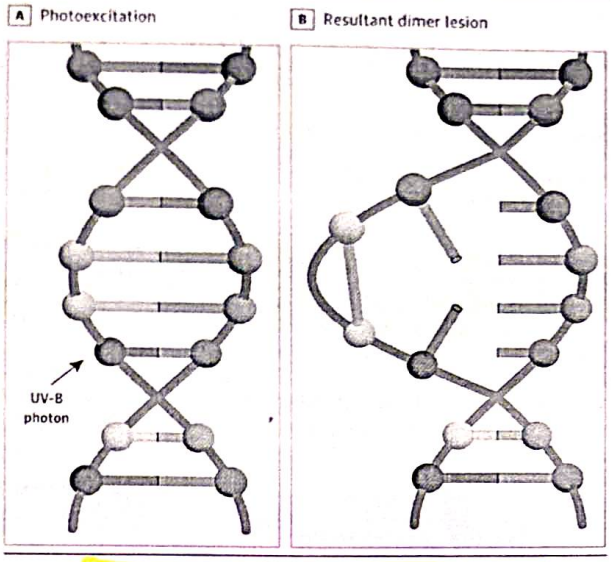
Direct action (A) occurs when an electron produced by a photon interaction impinges directly on DNA, whereas indirect action (B) occurs when the electron interacts with a water molecule to produce a reactive oxygen species, which then impinges on DNA. Owing to the relative abundance of water in the human body, roughly 70% of cell-killing events are through indirect action.

dimers, as illustrated in **Figure 3**. Lower-energy UV-A photons can react with chromophores, yielding reactive oxygen singlets.[5] Both mechanisms can initiate carcinogenesis, so the boundary of UVR (3.1 eV) is typically taken as the boundary for cancer hazard.

At UVR energies and beyond, EMR is endowed with mutagenic and apoptotic properties that can initiate cancers. The cytotoxic nature of ionizing radiation is, for example, exploited in x-ray radiotherapy to kill cancer cells, so that secondary cancer induction is a risk that must be carefully considered. Given the nuance of all these factors, confusion is entirely understandable. If light can be marshalled to obliterate cells and can even cause cancer, then could radiofrequency energies be doing us similar harm? After all, it is *radiation*, a word which itself conjures up frightening imagery, despite it simply referring to the transfer of energy through space. Compounding this, assertions that 5G in particular causes cancer have been relentlessly propagated online in recent months.

This insistence betrays a misunderstanding of the vastness of the electromagnetic spectrum; the reality is that RFR is much less energetic than even the visible photons we experience daily. In Europe, the 5G spectrum ranges from 3.6 GHz to 26 GHz. This renders the most powerful RF photon more than 15 000 times less energetic than the lowest-energy visible light, with 5G cell phone

Figure 3. Photoexcitation Damage From Nonionizing UV-B



Mutagenic DNA damage can occur from nonionizing UV light when a photoexcitation event transpires opening electronic bonds (A), resulting in dimer lesions (B). Ultraviolet radiation can also cause damage via the mechanism of singlet oxygen production (not illustrated).

frequencies (6 GHz) around 67 500 times less energetic. Were such claims of harm taken to their logical conclusion, there would be orders of magnitude more concern over lightbulbs than cell phones.

Epidemiological Human Evidence

The RFR spectrum is undoubtedly nonionizing, incapable of causing the requisite DNA damage that exogeneous carcinogenesis demands. Yet while known biophysics seem to preclude RFR having any plausible connection to carcinogenesis, the absence of any known mechanism for harm is not congruent to absence of harm. It is entirely conceivable that an unknown mechanism of action could result in the initiation of cancer. We need also look to the epidemiological evidence to see if we can infer the telltale fingerprints that might hint at harm by an unknown mechanism. It is worth noting that any existent effect would have to be exceptionally subtle and not necessarily at the ostensible site of impact; between 1992 to 2008, cell phone use in the US grew from virtually zero to practically 100%, and yet in the same period, there has been no indication that rates of common brain cancers have increased proportionally,[6] as would be expected if a direct link existed.

To ascertain any potential emergent safety signals from cell phone use, large, carefully controlled trials provide the most reliable data. The most ambitious of these to date is the 13-country INTERPHONE study,[7] a case-control study that compared 2708 patients with glioma and 2409 patients with meningioma with matched controls. The study concluded that "no increase in risk of glioma or meningioma was observed with use of mobile phones,"[7(p675)] nor did the dose-response curve from this undertaking detect any obvious correlation between cancer rates and cell phone use, although the researchers noted the potential for participant bias and unavoidable recall error.

A similar Danish cohort study the following year also yielded no evidence of a link,[8] looking at all Danes 30 years and older, subdivided into those who had subscribed to cellular networks since before 1995 and those who did not. In 10 729 cases of central nervous system tumors, there was no indication of dose-response association either by years of use or anatomical location of the tumor. A large prospective cohort study in the UK[9] found no increased incidence of central nervous system cancers associated with RFR exposure in a sample of 791 710 women. An initial result suggesting an increase in acoustic neuroma incidence in long-term users was subsequently found not to hold on reanalysis.[10]

Aside from these large studies, several smaller epidemiological studies have been performed,[11-15] which have to date not found any link between cancer incidence and cell phone usage. The exception to this is a pooled Swedish analysis[16] that reported a statistically significant trend of increasing brain cancer risk with total cell phone use in people who began using cell phones prior to age 20 years. This, however, was strongly contradicted by another analysis, which found that the increased risks reported in the pooled analysis from Sweden were not compatible with observed glioma rates in the Nordic countries,[17] with further analysis of incidence data from Nordic countries between 1974 and 2008 also showing no increase in age-adjusted brain tumor incidence.[18]

A nonexhaustive list of current scientific consensus for carcinogenicity from RFR by major public health bodies is given in the Table[19-24] for brevity. To date, findings of a lack of association between RFR and cancer are not outliers; they are the common findings of large-scale studies the world over, several of which are summarized in the Table. As the World Health Organization stated, " A large number of studies have been performed over the last two decades to assess whether mobile phones pose a potential health risk. To date, no adverse health effects have been established as being caused by mobile phone use."[25]

In Vivo Experimental Data

A major difficulty with in vivo studies for assessing possible adverse or other effects of RFR is that they are extraordinarily difficult to design. Typically, whole-body exposures are used, which are not reflective of human localized exposure. Given these and other difficulties, the US Food and Drug Administration (FDA) concluded that strong epidemiological studies tended to provide more relevant and accurate information with regard to human health. The FDA review[20] identified 37 studies that were relevant, but concluded that owing to inherent limitations, these studies have produced no clear evidence of RFR exposure being associated with tumorigenic effect, with authors of these studies suggesting a need for further research or concluding that RFR exposure did not display any tumor-initiating or tumor-promoting effects.

One possible exception to this is a 2018 National Toxicology Program preprint, which ostensibly observed increased cancer rates in rats exposed to extremely high levels of RFR. This conclusion, however, has been roundly criticized for low-power and questionable methods.[20,26] It is worth noting that the same analysis also showed that male rats in the high-RFR group lived significantly longer than

Table. Summary of Recent Conclusions by Public Health Bodies Worldwide

Public health body	Year	Evidence considered	Conclusion
International Commission on Non-Ionizing Radiation Protection[19]	2020	Updated exposure guidelines from 1998, comprising literature review of 39 relevant studies	No evidence of carcinogenic effect in epidemiological studies; no effects of radiofrequency EMFs on cancer induction substantiated
US Food and Drug Administration[20]	2020	Review of relevant literature (2008-2018) on radiofrequency and cancer, comprising 125 studies, including in vivo work	Insufficient evidence for causal association between RFR exposure and tumorigenesis, lack of clear dose-response relationship and specificity, lack of biological mechanistic plausibility
Swedish Scientific Council on Electromagnetic Fields[21-23]	2016-2019	Consensus report of relevant studies published up to 2019	No causal relationship between EMF exposure and cancer risks established; age-standardized incidence of brain tumors does not support inference of causal relationship with RFR
European Commission Scientific Committee on Emerging and Newly Identified Health Risks[24]	2015	Expert consensus on studies published between 2009 and 2014	RFR exposure did not appear to increase risk of brain tumors, other cancers of the head and neck region, or childhood cancers

Abbreviations: EMF, electromagnetic fields; RFR, radiofrequency radiation.

unexposed rodents, but it would of course be ludicrous and fallacious to suggest on this basis that RFR exposure increases life span.

Discussion

To our current knowledge, neither epidemiological evidence nor the physical reality of how EMR interacts with tissue support claims of an RFR-cancer link. Taken in concert, the epidemiological evidence and the physical reality of how EMR interacts with tissue seem to preclude any carcinogenic effect of RFR. The epidemiological evidence to date does not support the contention that RFR has any tumor-initiating or tumor-promoting properties, nor does any ostensible animal or epidemiological evidence come close to meeting Bradford Hill criteria or similar for causation. There are of course crucial limitations to our current knowledge; cell phones have only been widely used for 4 decades, and it is still possible that a negative association could be uncovered.

Radiation-induced carcinogenesis from ionizing sources is a stochastic process that typically takes 10 to 20 years to manifest for solid tumors,[3] with latency of up to 40 years reported in some cases. This is broadly similar to the latency period observed for cancer initiation from nonionizing but photoexciting UV-B radiation and skin cancers.[4,5] While cellular communications are relatively recent, they have seen rapid worldwide uptake in previous decades, and no similar cancer induction has thus far been shown in a comparable timescale. Unlike RFR, however, ionizing radiation and UV-B have known mechanisms of damage, and their ability to induce cancers is well understood. The same cannot yet be said for nonionizing RFR, and the lack of a plausible biophysical mechanism for carcinogenesis coupled with unconvincing epidemiological evidence suggests that on the balance of probability, this is currently unlikely. However, it would be pragmatic to continue monitoring epidemiological trends to ascertain whether any high-latency effects might be attributable to RFR in future.

While observations and further studies are critical for ensuring the safety of any technology, RFR research has been perhaps somewhat undermined by a perpetuation of weak studies and potentially inflated results. This is especially prevalent in in vivo studies, with the FDA review[20] noting that many in vivo studies lacked adequate controls and blinding. The majority did not even measure the animal's core temperature—a glaring omission when thermal effects of high RFR are well known. The Swedish review[22] was more direct about the poor quality of many investigations, concluding, "Many studies have been excluded due to poor quality. From a scientific perspective, studies of poor quality are irrelevant. They are also a waste of money, human resources and, in many cases, experimental animals."[22(p4)] This is an important consideration because underpowered or poorly conducted investigations are far more likely to yield ostensible effects in bioscience than high-quality investigations,[27] and RFR research is not immune to this reality.

Even epidemiological studies, when well conducted, have inherent problems—investigations to date have been adversely affected by the unavoidable influence of recall bias. As noted in the FDA report,[20] there were persistent issues in these studies, particularly concerns that recall bias strongly affected case-control and retrospective studies. Selection bias and confounding factors were common in all studies examined. While most studies found no evidence of increased risk, 1 particular group repeatedly reported increased hazards, but this was contradicted by independent analysis by other groups. The FDA noted these results included variously unjustified assumptions, questionable data methods, and interpretation bias, noting that "increased risk trends that stemmed from multiple publications by the same group (Hardell and Carlberg, 2009-2017, Sweden) were likely affected by limitations of a single data source limited to one population."[20(p4)]

There is an important question of scientific philosophy underpinning these investigations, and one that should be borne in mind for future research—that fewer works of higher quality are far more informative than multiple works of lower quality. Underpowered studies and those lacking adequate controls limit what can be inferred, and risk peppering the literature with erroneous findings. While both epidemiological and in vivo experiments in RFR are notoriously difficult to conduct, basic considerations, such as proper binding, controls, sample selection, and ensuring adequate sample size for statistical analysis, would be of major benefit to future RFR health research. More than this, if a cancer hazard due to RFR is postulated, then new or subtle biophysics would be required to explain this.[28]

We should briefly consider some more esoteric potential mechanisms that could hypothetically induce cancer after RFR exposure. Changes in protein conformation, for example, could in principle have some bearing on the evolution of cancer, but current evidence suggests that RFR exposure has no consistent effect on mammalian

cells in culture.[29] Epigenetic changes due to RFR exposure are another potential avenue of exploration, but evidence for this is currently lacking.[30] Prior reviews of evidence also do not support claims of genotoxic effects due to RFR.[31] It should be noted that there is currently no evidence beyond speculation for these mechanisms. It is also critical to note that cellular penetration is substantial, with more than 5.27 billion unique cell phone users worldwide as of April 2021.[32] Such high uptake implies that even rare or marginal cancer-inducing effects, if they exist, should be readily observable in epidemiological data. To date, this has not been observed.

Public perception is also an important consideration, especially in the context of addressing patient fears. Given the combined biophysical and epidemiological evidence base to date against the proposition that RFR is carcinogenic, it might seem surprising that this belief is so widely evangelized and propagated relentlessly. A major and unedifying part of the reason for this is the noxious influence of fringe science on confounding public understanding; the BioInitiative Report, a nonscholarly work that insists that RFR causes many harms from cancer to autism, has been widely circulated since 2007. Despite its popularity, it has been repeatedly debunked by health bodies worldwide,[30] and the attempts to treat its unsubstantiated assertions as equivalent to the weight of peer-reviewed weight of scientific evidence are archetypical false balance.[33]

Tellingly perhaps, the recent misinformation propagated around 5G is not even new—the same grave claims were made about prior mobile technologies for decades and were equally unsupported. Their renaissance now is underpinned by disinformation perpetuated across social media and a microcosm of a greater problem with online disinformation. There is, for example, a thriving online market for dubious devices that promise to protect consumers from RFR, furthering a likely misguided perception of harm. Cancer is an emotive topic, which undoubtedly increases the virulence of misguided assertions. It is accordingly important to be cognizant of the fact that while the issue may be strictly academic to researchers, it is a source of anxiety and apprehension to patients and the general public, and there is an onus on scientists to both convey the scientific consensus and to ensure that future work is conducted to a high standard.

The International Agency for Research on Cancer designation of RFR as a group 2B agent (a possible carcinogen) in 2011 is also frequently misunderstood as implying evidence of harm. However, such an interpretation is incorrect, as reiterated in the most recent International Agency for Research on Cancer communication[28] in 2020, which stated that "despite considerable research efforts, no mechanism relevant for carcinogenesis has been consistently identified to date. In the past 5 years, epidemiological research on mobile phone use and tumours occurring in the head has slowed down compared with the previous decade. Most new and previous case-control studies do not indicate an association between mobile phone use and risk of glioma, meningioma, acoustic neuroma, pituitary tumours, or salivary gland tumours."

It is worthwhile too to acknowledge a potentially political dimension to the propagation of falsehoods on 5G in particular; a *New York Times* investigation[34] found that Russian state forces were complicit in spreading falsehoods, with the European Commission finding the fingerprints of both Russian and Chinese health disinformation rising with the advent of COVID-19,[2,34-36] including false claims linking cancer to RFR. All of this undermines collective understanding and makes it imperative that scientists be at the vanguard of communicating the evidence to prevent detrimental misconceptions.

Conclusions

Radiofrequency radiation is invisible and inescapable, and it is completely understandable that apprehension exists. With cell phones only with us for a few decades, it is reasonable to be pragmatic and keep a cautious eye on any potential emergent health effects. To this end, high-quality research is to be welcomed. But equally, such pragmatism must be guided by evidence, which to date does not support the cacophonous claims of harm.

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