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Genotoxic and carcinogenic effects of non-ionizing electromagnetic fields

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ABSTRACT

New technologies in electronics and communications are continually emerging. An increasing use of these electronic devices such as mobile phone, computer, wireless fidelity connectors or cellular towers is raising questions concerning whether they have an adverse effect on the body. Exposure to electromagnetic fields (EMF) is frequently suggested to have adverse health effects on humans and other organisms. This idea has been reported in many studies. In contrast, the therapeutic effects of EMF on different organs have also been reported. Research findings are inconsistent. This has given rise to very profound discrepancies. The duration and frequency of mobile phone calls and the association observed with various health effects has raised serious concerns due to the frequency with which these devices are used and the way they are held close to the head. The present review assesses the results of *in vitro*, *in vivo*, experimental, and epidemiological studies. The purpose of the study is to assess data concerning the carcinogenic and genotoxic effects of non-ionizing EMF. The major genotoxic and carcinogenic effects of EMF, divided into subsections as low frequency effects and radiofrequency effects, were reviewed. The inconsistent results between similar studies and the same research groups have made it very difficult to make any comprehensive interpretation. However, evaluation of current studies suggests that EMF may represent a serious source of concern and may be hazardous to living organisms.

1. Introduction

With the impact of the globalization, the world has entered a time of change and development. This is leading to rapid population growth and energy consumption (Asumadu-Sarkodie and Owusu, 2016). Fast growing wireless broadband and communication technologies have become the main source of global pollution by creating threats to the environment and human life, while at the same time providing concrete solutions to the emerging needs of globalization (Milner et al., 2012). Today, with the widespread use of electric devices, electromagnetic fields (EMF) have become a particularly important global phenomenon, and one that is creating concerns and worries among many people (Miclaus and Calota, 2010; Stather, 1997).

EMF consists of both electric and magnetic fields of force (Phillips, 2013). It was first discovered during the 19th century (Berkson, 2000), however, it has been present since life first emerged, due to its generation *via* natural phenomena (Sher, 1997). All living things are continuously exposed to EMF from natural sources at levels between 25 μT and 65 μT (Gould, 1984). In addition to natural sources of EMF, living organisms are also exposed to EMF generated by human-made sources, such as cell phones, cell phone base stations, radio stations, computer screens and many other electrical devices widely used in daily life (Berg, 1992).

The question of whether exposure to EMF is beneficial or hazardous is still the subject of much debate. This debate is encouraging research to determine whether or not it is safe to live with constant exposure to EMF (Kheifets and Ritz, 2006). Numerous studies have shown the impact of EMF on animals, tissues (Aydin and Akar, 2011; Sonmez et al., 2010), and the functional features of cells (Koch et al., 2003; Liburdy et al., 1993), but the findings are still considered preliminary. In contrast, many studies have reported therapeutic effects of EMF on various organs and body systems, including reversal of cognitive impairment in Alzheimer's disease (AD) (Arendash et al., 2010), stimulation of the repair mechanism in bone and cartilage (Bai et al., 2013; Haddad et al., 2007; Trock et al., 1994), wound healing, and nerve regeneration (Mohammadi and Mahmoodzadeh, 2015).

Some of the main features of EMF are its frequency and wavelength, both of which interact with living organisms in different ways (Grimes and Grimes, 2002; Panagopoulos et al., 2002). The biological effects of EMF depend on the frequency or wavelength. The purpose of this review is to summarize and analyze existing studies that describe the association between EMF and their carcinogenic and genotoxic effects on living organisms. A secondary aim is to contribute to the current debate on the possible impacts of EMF, and whether or not EMF exposure is dangerous to humans.

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In the first section, EMF and its main ranges are explained. Frequencies and wavelengths are described and differences set out. Then, non-ionizing range is divided into subsections based on frequency. Within the subsections, existing experimental and epidemiological studies are reviewed in terms of genotoxic and carcinogenic effects.

2. Classification of EMFs

EMF is produced by electrically charged objects and may be defined as a combination of electric fields (EF) and magnetic fields (MF). Electromagnetic waves are carried by particles known as photons (quanta) (Feynman, 1974). EMF exhibits its characteristic features *via* the interrelated parameter of wavelength and frequency. Frequency is measured in terms of number of oscillations per second (hertz) and wavelength describes the distance between one wave and the next, measured in meters. As the frequency increases, the wavelength becomes shorter and carries more energy compares to lower frequency waves (Hackmann, 1994).

EMF can be divided into two main types depending on the energy levels of electromagnetic waves. If electromagnetic waves contain enough energy per quantum to ionize molecules, they can break the bonds between molecules and cause chemical reactions (Sher, 1997). These waves are known as *'ionizing radiation'* and have the potential to damage living cells, causing cancer, tumors and genetic damage (Sukhoviia et al., 1975). High ultraviolet, X-rays and gamma rays are some forms of ionizing radiation. If the quanta energy levels are insufficient to break molecular bonds, these electromagnetic waves are known as 'non-ionizing radiation'. Low and extremely low frequency (ELF) radiofrequency (RF) microwaves and visual light are some forms of non-ionizing radiation. Common man-made sources of non-ionizing radiation include microwave ovens, computers, wireless networks, cell phones, and power lines.

3. Effects of non-ionizing radiation frequencies

3.1. Extremely low frequency effects

Frequencies up to approximately 300 Hz (Hz) are known as extremely low frequency (ELF), and are part of the non-ionizing radiation range of the electromagnetic spectrum. The fields emitted by power lines, railways, and electrical devices at home and in the workplace are in the ELF range. The effects of both EF and MF on biological systems are highly controversial. Recent studies have focused on the illumination of their potential genotoxic, carcinogenic, and neurological effects. The effects of ELF on genotoxicity and carcinogenicity are summarized (Table 1). This section therefore includes studies summarizing the genotoxic and carcinogenic effects of ELF.

3.1.1. Genotoxicity

The absence of an accepted general mechanism that explains how EMF affects biological systems poses a great challenge in interpreting experimental data from EMF studies. The effect mechanism of EMF on DNA and RNA is still unknown. As the energy level of non-ionize EMF is not sufficient to break the intermolecular chemical bonds, the intracellular effects of EMF appear indirectly. The most prominent of these indirect ways is the effect of free radicals. When the number of free radicals is increased in the cell, structures such as DNA, RNA, protein, and membrane lipids are damaged due to the oxidative stress (Cassien et al., 2015; Dinu et al., 2016; Dizdaroglu and Jaruga, 2012; Lagouge and Larsson, 2013; Storr et al., 2013). It has been shown that EMF triggers the increase of free radical in the cell by the Fenton reaction (Lai and Singh, 2004). Through the Fenton reaction, hydrogen peroxide, the oxidative respiratory product in the mitochondria, is converted to free hydroxyl molecules *via* catalysis with iron (Floyd, 1981; Henle et al., 1996).

It has been suggested that ELF shows its effect on the cell in two steps (Lai and Singh, 2004). In the first step ELF mediates iron metabolism and increases the amount of free iron in the cytoplasm, particularly in the nucleus due to of the presence of numerous numbers of iron pumps within the nuclear membrane (Meneghini, 1997). An increased iron concentration accelerates the formation of free hydroxyl radicals through Fenton reactions. The hydroxyl radicals act on DNA, RNA, cell membrane lipids, and proteins inside of the cell. As a result of lipid damage in the cell membrane (lipid peroxidation), calcium leakage increases into the cell. The increase in calcium ions accelerates the calmodulin-dependent nitric oxide synthesis and triggers the second step (Lai and Singh, 2004). Nitric oxide is more active than hydroxyl radicals to damage DNA and other macromolecules. Nitric oxide triggers iron formation from the ferritin, which increases the amount of iron ions in the cell (Reif and Simmons, 1990). This cycle continues until the cell undergoes apoptosis or necrosis (Fig. 1). It has also been suggested that ELF may act by increasing the formation of hydrogen peroxide, especially in active cells due to their constant mitochondria functions (Phillips et al., 2009).

Effects on the genetic material of the cell are among the best indicators for showing whether ELF has a genotoxic effect on the cell. *In vivo* and *in vitro* ELF studies report different results and propose different mechanisms to explain the genotoxic effects of ELF (Grundler et al., 1992).

One of the most interesting issues is whether ELF creates DNA chain breakage. In one study, hamster lung cells were exposed to 50 Hz ELF to reveal its effects on autophagy mechanism. ELF exposure did not induce double-strand breaks (DSBs) in DNA, but it elevated cell surface modifications and actin filament reorganization. Increased autophagesome formation and LC3-II expression levels were also observed after exposure to 50 Hz ELF in cultured cells. These results indicate that ELF does not directly create DNA damage, however DNA damage is an end product of molecular irregularities resulting from ELF exposure. In addition, the elevation of autophagy might help to balance homeostasis against apoptosis (Shen et al., 2016). Similarly, DNA damage, the cell cycle, and protein expression were investigated in human neuroblastoma cells exposed to menadione and 50 Hz ELF. Menadione treatment increased mitochondrial superoxide production while 24 h (h) exposure to 50 Hz ELF reduced DNA damage and altered cell cycle distribution against menadione-induced genotoxic effects in humans (Luukkonen et al., 2016). Destefanis et al. (2015) investigated the effects of 50 Hz ELF on human lens epithelial cells (LECs) using molecular and immunohistochemical methods. Genotoxicity tests revealed no significant differences between the control and experimental groups. These results suggested that neither short- nor long-term ELF exposure causes any DNA damage in LECs *in vitro*. Feng et al. (2016) reported a protective effect of 50 Hz ELF against apoptosis in human amniotic cells. Cell viability, early apoptosis, mitochondrial ROS and the level of phosphorylated Akt were evaluated. Cells were induced by staurosporine to enter early apoptosis and, as a result of ELF exposure, the level of mitochondrial ROS increased. The team also reported that ELF is able to reverse apoptotic events using the transient mitochondrial ROS release and activation of Akt. A recent study assessing the brain histopathology of freshwater fish exposed to 50 Hz ELF showed that the expression levels of some antioxidant genes expression levels may change in response to ROS as a result of exposure to ELF (Samiee and Samiee, 2017). In a similar manner, menadione was used as a cofactor to reveal the effect of 50 Hz ELF in human neuroblastoma and glioma cell lines. In contrast to the previous study, ELF increased the genotoxic effects, depending on the amount of menadione in co-exposure. 50 Hz ELF exposure increased cytosolic and mitochondrial superoxide production in rat glioma cell lines. Additionally, 50 Hz ELF significantly increased micronuclei formation – which plays a genotoxic role in the carcinogenesis mechanism and AD (Kesari et al., 2016). The effects of 50 Hz ELF have also been investigated to reveal energy re-programming and anti-glycative defence in human neuroblastoma cells. Results

Table 1
Summary of effects of ELF on genotoxicity and carcinogenicity.

Type	Frequency	Exposure Duration	Tissue/Organ	Aim	Outcome	Year	Reference
Genotoxicity	50 Hz	1 h	Salmonella typhimurium	To investigate the genotoxic and mutagenic effects of ELF	No genotoxic effect observed	2016	(Verschaeve et al., 2016)
Genotoxicity	50 Hz	24 h	Human neuroblastoma cell line (SH-SY5Y)	To investigate cell cycle distribution, DNA damage, and protein expression	Reduced DNA damage	2016	(Luukkonen et al., 2016)
Genotoxicity	50 Hz	1.5 h/ 12 d	Cultured rat femur tissue	To investigate the effects of 50 Hz magnetic field effects on bone formation and resorption and gene expression	Promoted bone formation, increased metabolism and reduced bone resorption	2016	(Zhou et al., 2016)
Genotoxicity	50 Hz	24 h	Human neuroblastoma and rat glioma cells	To investigate DNA damage and oxidative stress	Provoked DNA damage in human neuroblastoma cells, increased oxidative stress in rat glioma cells	2016	(Kesari et al., 2016)
Genotoxicity	50 Hz	24 h	Rat fibroblasts and macrophages	To investigate cell viability, DNA damage, and ROS	Increased DNA damage and decreased cell viability	2016	(Nakayama et al., 2016)
Genotoxicity	50 Hz	2 h, 6 h, 12 h, 24 h, 48 h	Human lens epithelial cells	To investigate genotoxicity, mutation DSBs, SSBs	No genotoxic effects were found	2016	(Zhu et al., 2016b)
Genotoxicity	< 10 MHz	1–9 h/d for 2–30 y	Human blood	To observe the adrenaline level, DNA damage and oxidative stress	No significant changes in adrenaline levels, induced oxidative stress	2015	(Tiwari et al., 2015)
Genotoxicity	60 Hz	9 h	Human lung epithelial cells	To observe aneuploidy and cell cycle distribution	No effects on cell cycle distribution and aneuploidy	2015	(Jin et al., 2015)
Genotoxicity	50 Hz	24 h	Human neuroblastoma cell line (SH-SY5Y)	To observe DNA damage and ROS	Induced DNA damage	2015	(Kesari et al., 2015)
Carcinogenicity	50 Hz	From 6 weeks of age until death	Heart, liver, pancreas, brain, skin, kidneys	To understand the genotoxic effects of ELF	Increased genotoxicity	2016	(Soffritti et al., 2016)
Carcinogenicity	50 Hz	14 d	Fasciola hepatica eggs	To investigate the development of the liver fluke during embryogenesis	More fluke larvae observed in the ELF exposed group	2016	(Kolodziejczyk et al., 2016)
Carcinogenicity	50 Hz	8 h/20 d during gestation	Pluripotent mouse embryonic stem cells	To observe embryonic development	Increased ROS, increased numbers of resorbed and dead fetuses, reduced VEGF and blood vessel formation	2016	(Bekhite et al., 2016)
Carcinogenicity	50 Hz	12 h/1 week before birth, 15.5 months after birth	Reproductive system	To investigate the incidence of cancer and male fertility	Increased incidence of chronic myeloid leukemia and detrimental effect on the male fertility	2015	(Qi et al., 2015)
Carcinogenicity	50 Hz	30 d	Reproductive system	To investigate the teratogenic effects of prenatal and postnatal exposure of mice to ELF	No teratogenic effects were determined	2015	(Udroiu et al., 2015)
Carcinogenicity	50 Hz	3–9 h	Rat brain	To observe DBSs in the embryonic rat brain	No DBSs observed	2015	(Woodbine et al., 2015)
Carcinogenicity	50 Hz	1 h /2 weeks	Ehrlich tumor cells, bone marrow cells	To investigate the therapeutic efficacy of low-dose cisplatin followed by exposure to ELF by examining cytotoxicity and DNA damage	Increased chemotherapeutic efficiency of cisplatin due to increased production of oxygen species by ELF	2013	(El-Bialy and Rageh, 2013)
Carcinogenicity	50 Hz	6 h/d for 8 months	Colon	To determine the expression level of P-selectin in ELF exposed cells	No significant differences in the protein expression level of P-selectin	2013	(Tuncel et al., 2013)

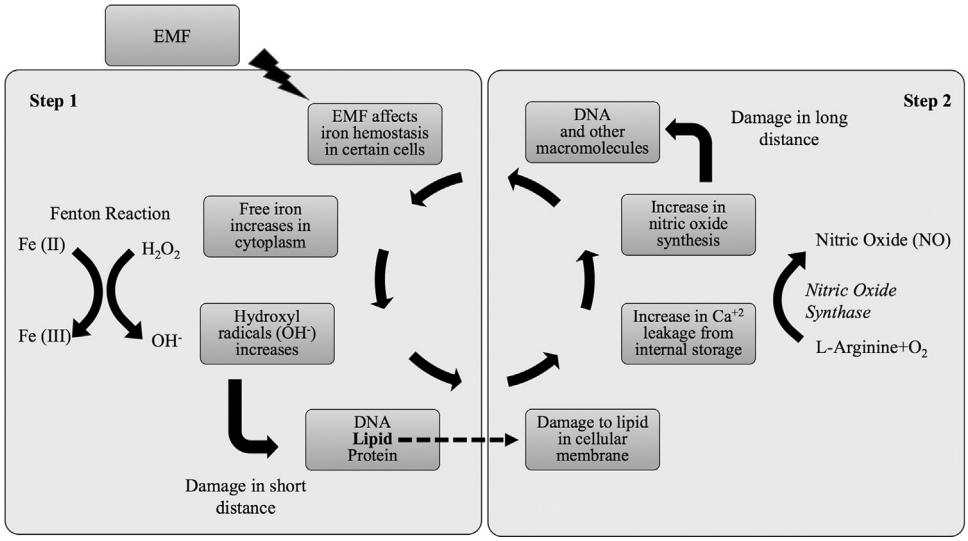

Fig. 1. The figure represents the effect mechanism of EMF in two consecutive steps within the cell.
The free radicals generated by Fenton and nitric oxide reactions show effects in the cell, modified from (Lai and Singh, 2004).

showed that ELF promoted the proliferative activity of the neuron-derived malignant cells. These finding reveals that ELF may change the balance of the cellular hemostasis by altering the features of key molecules and strength its' suspicious role on the later stages of brain-derived malignancies (Falone et al., 2016b).

The micronucleus assay is generally used as an *in vivo* and *in vitro* short-term genotoxicity-detecting test. In a 2005 study, Winker and colleagues exposed the bone marrow of mice to 50 Hz ELF continuously for 7–28 days. In comparison to the control group, the number of micronucleated erythrocytes increased three-fold (Winker et al., 2005). Similar to these results, Alcaraz et al. (2014) reported that the administration of four antioxidants that have anti-mutagenic and gen protective features exerts no protective effect against 50 Hz ELF in the mouse bone marrow. Kesari et al. (2015) investigated the effects of 50 Hz ELF on human neuroblastoma cells. Lipid peroxidation – the amount of reactive oxygen species (ROS) – and micronucleus formation were analyzed over periods of 15, 30 and 45 days. Prior to MR exposure, experimental group cells were treated with menadione and the antioxidant N-acetylcysteine to investigate the potential role of ROS. After 15 and 30 days of exposure to ELF, the number of micronuclei increased. The administration of N-acetylcysteine suppressed the effect of menadione, and cellular ROS levels then decreased. On the other hand, increased ROS levels were observed after 45 days in the N-acetylcysteine-ELF group. Lipid peroxidation levels also decreased significantly 30 and 45 days after exposure to 50 Hz ELF. These results indicate that ELF exposure may initiate the genomic instability process and that it may continue for at least 45 days.

Zhu et al. (2016a) reported the effects of 50 Hz ELF on human fetal scleral fibroblasts (HFSFs). MMP-2, FGF-2, and COL1A1 mRNA levels that are proportional to scleral structure in HFSFs were assessed. A significant decrease in COL1A1 mRNA and protein expression levels suggested that ELF may reduce collagen synthesis. In addition, an increase in the mRNA level of TGFβ − 2 might inhibit the growth of HFSFs.

Comparisons of studies using oxidative stress-inducing agents and anti-oxidant agents are helping to reveal the genotoxic effects of ELF. However, contrasting results obtained in other studies have made it difficult to explain the genotoxic effects of ELF (Table 1). In the presence of these discrepancies, it is essential to show the genotoxic effects of ELF by performing repetitive and mechanism clarifying studies.

3.1.2. Carcinogenicity

Many studies have examined the relationship between ELF exposure and cancer. The results of some epidemiological studies have shown that exposure to ELF increases the risk of developing childhood leukemia. The International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) therefore classified ELF as a possible carcinogenic in humans in 2002 and 2007 (WHO, 2007). In addition to epidemiological studies, research on experimental animals has been carried out to reveal the possible mechanisms involved.

Destefanis et al. (2015) investigated the effects of 50 Hz ELF on human cancer cell growth by observing mitochondrial activity. As a result of ELF exposure, the respiratory activity of cells was increased and mitochondrial protein expression was downregulated. The authors consequently concluded that cancer cell growth was negatively affected by 50 Hz ELF. To investigate the effects of ELF on angiogenesis, which plays an important role in cancer development, human umbilical vein endothelial cells have been exposed to 50 Hz ELF. These were then injected subcutaneously to the mice in order to observe tumor development. This exposure lowered the rate of endothelial cell proliferation and the number of migrated cells, in comparison to controls. In addition, ELF exposure significantly inhibited the protein expression level of vascular endothelial growth factor compared to a sham-exposed group. These results suggest that ELF reduced endothelial cells' ability to form new vessels. Therefore, it may be used as a therapeutic approach to cancer by reducing angiogenesis (Delle et al., 2013).

One well-known reason for cell death is the damage caused by hydroxyl free radicals. Several studies have indicated that ELF can enhance the formation of hydroxyl free radical from hydrogen peroxide *via* an iron-catalyzed process (Yakymenko et al., 2016). According to previous studies, ELF can be used to treat a variety of cancer types due to the intracellular free iron content of cancer cells, which makes them sensitive to ELF (Lai and Singh, 2010). One recent study investigated a radiofrequency identification (RFID) micro-transponder system emitting 134 kHz (KHz; 10^3 Hz) ELF. The results indicated that an RFID microchip could kill leukemia, breast cancer, and liver cancer cells. The study results also clarified one particularly important point concerning the effects of ELF. According to the data reported, ELF can affect cancer cells *via* free radicals, which form due to the Fenton reaction (Dikalova et al., 2001). RFID may therefore be an effective and target-specific alternative treatment for cancer (Lai et al., 2016).

In contrast to studies reporting therapeutic effects of ELF, several

others have indicated that ELF exhibits harmful effects. A study assessing the long-term effects of ELF exposure on rats exposed subject animals to 50 Hz ELF over 16 months, for 12 h per day. The incidence of cancer, organ weights, and male fertility were then evaluated. The only increase determined was in the incidence of chronic myelogenous leukemia in bone marrow, while no increase was observed in other tumor types (Qi et al., 2015). In addition, Kostoff and Lau (2013) reported interactive effects from combination of EMF and other agents on biological systems. They emphasized that the effect of EMF emerged or increased as a result of combination with different agents. One large-scale rodent study reported carcinogenic effects of life-span co-exposure to 50 Hz ELF and 50 mg/L-formaldehyde on rats aged 6–104 weeks. No significant changes were observed in the occurrence rate of benign tumors. Histopathological evaluation showed that the application of 50 Hz ELF did not increase the risk of cancer, but combined exposure to ELF and formaldehyde increased the carcinogenic effects in a statistically significant manner. In addition, ELF and formaldehyde exposure increased the rate of thyroid C-cell carcinomas, hemolymphoreticular neoplasias, and malignant tumors. This suggests the possibility of synergy between exposure to 50 Hz ELF and formaldehyde in terms of carcinogenicity (Soffritti et al., 2016).

3.2. Radio frequency effects

Radio frequency (RF) consists of both EF and MF in the range 10 MHz (MHz; 10^6 Hz)–300 GHz (GHz; 10^9 Hz). The effects of devices such as mobile phones and microwave ovens, which are very frequently used in daily life, are evaluated in this section. The biological effects of RF exposure are classified into cellular, pharmacological, intercellular, enzymatic, and carcinogenic categories. Publications reporting contradictory suggestions and interpretations continue to produce updated data concerning EMF. The latest reports by the WHO (WHO, 2007), the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) (SCENIHR, 2015), the German Committee for Radiation Protection (SSK) (SSK, 2011), and the Swiss Federal Office for the Environment (BAFU) (BAFU, 2014) suggest that there is insufficient evidence to show adverse health effects of EMF exposure with the exception of tissue heating levels. The International Commission on Non-Ionizing Radiation Protection (ICNIRP) published a review for the assessment of *in vivo* and *in vitro* genotoxicity studies (ICNIRP, 2009). In this section, we review the latest *in vivo* and *in vitro* studies and controversial results reported by these organizations (Fig. 2).

3.2.1. Genotoxicity

It is very difficult to determine the induction or alteration of genetic material resulting from RF due to the different methods applied and the variety of organisms recruited. Genotoxicity is generally evaluated by the comet assay, micronucleus assay, and chromosome aberrations. Table 2 summarizes both therapeutic and adverse effects of RF on genotoxicity and carcinogenicity.

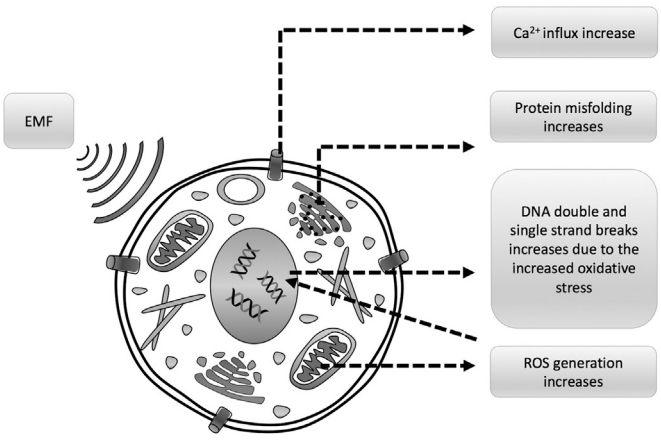

Fig. 2. EMF-induced cellular changes are summarized. The increase in permeability of calcium channels (Roux et al., 2008), misfolded protein (Mancinelli et al., 2004) and free radical production (Zeni et al., 2007), and the effects of oxidative stress on DNA and RNA (Diem et al., 2005; Zeni et al., 2007) were shown.

One subject of particular interest is the difference in effect levels between ELF and RF exposure. A number of ELF and RF studies have been conducted with genotoxic results, but the results of these are still controversial. Exposure conditions were standardized in one study, so that findings of possible genotoxicity caused by 50 MHz and 1800 MHz RF could be controlled and compared. Genotoxic effects were investigated after mouse spermatocyte-derived cell lines had been exposed to GSM-Talk mode RF and at 50 Hz ELF for 24 h. The alkaline comet assay and immunofluorescence revealed an increased DSBs in ELF exposed cells, whereas no significant difference was observed in RF exposed cells. Formamidopyrimidine DNA glycosylase (FPG) altered alkaline comet assay and RF increased oxidative damage to DNA bases at a specific absorption rate (SAR) value of 4 W/kg, whereas ELF exposure caused no significant difference. These results indicate that ELF and RF may create different patterns of DNA damage and induce genotoxicity at relative high intensities due to their alternate potential mechanisms (Duan et al., 2015).

One of the most important agents explaining the genotoxic effects of RF is ROS. The genotoxic effects that can occur in cells or tissues following exposure to RF can be easily explained by observing the levels of ROS. Drug-sensitive human neuroblastoma SH-SY5Y cells were exposed to 75 MHz RF. Mn-dependent superoxide dismutase (MnSOD)-based antioxidant protection, ROS production, and cell viability were evaluated to reveal the antioxidant response. The findings showed that RF could increase MnSOD-based antioxidant protection and cellular resistance against a pro-oxidant stimulus and reduce ROS production through an increase in mitochondrial antioxidant protection (Falone et al., 2016a). In contrast to the results of this research, many studies have reported the ROS-producing effects of RF. Spiral ganglion neurons (SGN) of rats were treated with lipopolysaccharide (LPS) to induce inflammation in an *in vitro* model before exposure to 1800 MHz RF for 24 h. ROS production, DNA damage, ultrastructural changes and expression of Beclin 1 and LC3-II were investigated. No DNA damage or ultrastructural cellular changes were observed in normal SGN groups. However, increased ROS levels, presence of lysosomes and autophagosomes, and increased expression of Beclin 1 and LC3-II were observed in LPS-induced and RF-exposed groups. Sensitivity to RF in SGN cells suggests that the resultant increase in LPS interaction represents the basis of the RF action mechanism in the ROS system (Zuo et al., 2015). Hou et al. (2015) investigated the effects of 1800 MHz exposure on mouse embryonic fibroblasts in order to analyze ROS, DNA damage, and apoptosis. Researchers found increased levels of both intracellular ROS and numbers of late-apoptotic cells in the 1-, 4- and 8-h RF exposed groups, however DSB numbers were slightly, but not significantly increased in the 2-, 4-, 6- and 8-h RF exposure groups in comparison to controls. These results once again confirmed the adverse effects of EMF in terms of ROS.

Ataxia telangiectasia mutated gene (Atm), which is regarded as a principal protector of genomic stability, was investigated in mouse embryonic fibroblasts in order to reveal the effects of 1800 MHz RF exposure on genotoxicity. DNA single-strand breaks (SSBs) and DSBs were detected using alkaline and neutral comet assays. Increased SSBs and DSBs were observed in 1800 MHz RF exposed Atm-deficient mouse embryonic fibroblasts. Additionally, the phosphorylation and expression of X-ray repair cross-complementing protein 1 (Xrcc1), which are critical to DNA damage repair mechanisms, increased in both Atm-proficient and Atm-deficient groups. The activation of DNA repair mechanisms revealed that 1800 MHz RF increased DNA damage and corrupted cellular homeostasis (Sun et al., 2016).

Table 2
Summary of effects of RF on genotoxicity and carcinogenicity.

Type	Frequency	Exposure Duration	Tissue/Organ	Aim	Outcome	Year	Reference
Genotoxicity	1950 MHz	20 h	Chinese hamster lung fibroblast cells	To investigate lung fibroblast cells exposed to RF	RF exposure induced both adverse and beneficial effects	2017	(Sannino et al., 2017)
Genotoxicity	100 MHz	80% less than 8 years, 20% more than 9 years	Human blood	To investigate the genotoxic effects of mobile phone base station effect on exposed subjects	No genotoxic effect	2016	(Gulati et al., 2016)
Genotoxicity	1800 MHz	12, 24, or 36 h	Atm +/+ and Atm −/− mouse embryonic fibroblasts	To investigate the genotoxic effects	Both beneficial and hazardous effects were observed, DNA damage repair mechanisms were activated and resulted in decreased DNA fragmentation levels	2016	(Sun et al., 2016)
Genotoxicity	2100 MHz	6 h/5 weeks	Brain	To investigate ROS and DNA damage	Increased oxidative DNA damage	2016	(Sahin et al., 2016)
Genotoxicity	≥ 10 MHz	< 5 years and 3 h a week; ≥5 years and 10 h a week	Human, head, oral mucosa	To investigate genotoxic effects	Increased micronucleus numbers and genotoxic effects	2016	(Banerjee et al., 2016)
Genotoxicity	915 MHz	72 h	Broad bean seedlings (Vicia faba)	To investigate genotoxic effects	Increased micronucleus frequencies and genotoxic effects.	2016	(Gustavino et al., 2016)
Genotoxicity	1800 MHz	120 min/d for 3 months	Rat brain	To investigate oxidative stress and DNA damage	Increased ROS and DNA damage, decreased antioxidant parameters	2016	(Hussein et al., 2016)
Genotoxicity	900 MHz	24 h	Rat neuroblastoma cells	To investigate DNA damage, oxidative stress and cell viability	Increased ROS and DNA base damage	2015	(Wang et al., 2015)
Genotoxicity	900 MHz, 1800 MHz, 2450 MHz	2 h/d 5 d/week for 180 d	Brain	To investigate cognitive functions, Hsp70 prt expression and DNA damage	Increased Hsp70 expression, DNA damage, and different behaviors observed	2015	(Deshmukh et al., 2015)
Genotoxicity	1800 MHz	0.5, 1, 1.5, 2, 4, 6, 8 h	Mouse fibroblast cells (NIH3T3)	To investigate oxidative stress, DNA damage and apoptosis	Increased oxidative stress and apoptosis	2015	(Hou et al., 2015)
Genotoxicity	50 Hz − 1800 MHz	24 h	Murine spermatocyte-derived cells (GC2)	Comparison of the genotoxic effects of 50 MHz and 1800 MHz	Both exposure frequencies exhibited genotoxic effects	2015	(Duan et al., 2015)
Genotoxicity	1966 MHz	10 and 120 min	Human lymphoblastoid T cells (Jurkat cells)	To investigate genotoxic effects on Jurkat cells	Increased DNA damage	2015	(Moraitis et al., 2015)
Carcinogenicity	800 MHz–5.2 GHz	20 h/d, 6 weeks	Pregnant dams, offspring	To investigate adverse effects on development	No adverse effects	2017	(Shirai et al., 2017)
Carcinogenicity	900–1800 MHz	30 min/4 d	Mice 2-cell-state embryos	To investigate embryonal development	No hazardous effects on embryonal development	2016	(Safian et al., 2016)
Carcinogenicity	935 −960 MHz	2–4 h	Fertilized embryo	To investigate fertilization and subsequent embryonic development	Decreased IVF rate and blastulation rate	2016	(Chen et al., 2016)
Carcinogenicity	1950 MHz	12,24,48 h	Human glioblastoma cell lines	To investigate apoptosis, cell proliferation, cell viability, and tumorigenesis	No significant differences were observed	2015	(Liu et al., 2015)
Carcinogenicity	800–1900 MHz	≥ 3 h	Tumor, glioblastoma patients	To investigate the relation between mobile phone use and p53 expression in tumor cells	Increased occurrence of p53 in the peripheral zone of glioblastomas	2014	(Akhavan-Sigari et al., 2014)

3.2.2. Carcinogenicity

Numerous studies to date have reported inconsistent results concerning the carcinogenic effects of RF. While some studies have not determined any relationship between RF exposure and tumor development (Auvinen et al., 2002; Christensen et al., 2005; Hardell and Carlberg, 2009; Hepworth et al., 2006), others have reported increased risk-related outcomes (Hardell et al., 2013; Lonn et al., 2004). Study results are also inconsistent in terms of whether RF exposure has carcinogenic effects on biological samples *in vitro* (Buttiglione et al., 2007; French et al., 1998; Zeni et al., 2012).

In one recently published study, human glioblastoma cells were exposed to 1950 MHz RF for 12, 24, and 48 h and then injected subcutaneously into mice to reveal the effects of 3G mobile phone signals on cellular parameters *in vitro* and possible carcinogenic effects *in vivo*. RF exposure caused no change in any of the parameters investigated, such as apoptosis, proliferation, migration, invasion, expression of apoptotic (bcl-2, bax) and proliferative (emp-1, c-myc) genes, and morphology of glioblastoma cell lines at the end of 28 days (Liu et al., 2015). However, Akhavan-Sigari et al. (2014) reported a significant relation between increased mutant p53 expression in the peripheral zone of tumors and mobile phone (1800 MHz) EMF exposure exceeding 3 h per day.

In addition to *in vivo* and *in vitro* studies, epidemiological studies have been conducted to clarify the relationship between cancer and mobile phones. The relationship between the incidence of malignant neoplasms of the central nervous system and increasing mobile phone use among young people was investigated in Japan. Mobile phone usage data from 7550 participants was analyzed. Between 1993 and 2010, the incidence of malignant neoplasms was significantly high in both males and females at the ages of 20 and 30. However, there was no significant increase among younger individuals aged 10–19 years. These results prevent a precise judgment because it was expected that there would be an increased risk in the young population group, as this population is exposed to daily cell phone use. The authors reported a number of limitations in that study; the estimation of cancer incidences was based on regional cancer registries, therefore the data cannot be generalized for national figures. Furthermore, the questionnaire was sent only to schools, so the data do not cover mobile phone use in the general population. Authors report the absence of data on length of cell phone usage to be another limitation of the study (Sato et al., 2016).

Despite the limitations of that research, Chapman et al. (2016) examined gender- and age-specific incidence in 19,858 males and 14,222 females diagnosed with brain cancer. The effects of mobile phone use on brain cancer incidence rates were compared with observed and expected data. Contrary to expectation, data analysis showed that observed incidence rates were lower in all age groups, except for subjects aged ≥ 70 years. The increase in the ≥ 70 age group may not be significant because the increase commenced before the use of mobile phones. Similarly, there was no consistent elevation in the incidence rates of all primary brain cancers or gliomas in the New Zealand and Korean populations over a 15-year period from 1995 to 2010 and a 5-year period from 2002 to 2007, respectively (Kim et al., 2015; Yoon et al., 2015). Hsu et al. (2013) didn't report any evident correlation between the incidence of mobile phone use and malignant brain tumors. In contrast to these results, an enhanced risk of glioma associated with mobile phone use was observed in a pool case study in Sweden in 1997–2003 and 2007–2009 (Hardell and Carlberg, 2015).

Results from *in vitro* and *in vivo* studies represent strong evidence of a carcinogenic effect of RF, but epidemiological studies have not yet confirmed this. More up-to-date and precise epidemiological studies are now needed in addition to those involving limitations. It is also expected that WHO will soon provide a more comprehensive report on the effects of RF on cancer development.

4. Conclusion

The findings reported in the current study highlight the difficulty involved in evaluating the effects of EMF is very difficult. Each of the various study types, *in vitro*, *in vivo*, animal experimental, and epidemiological, has its own specific advantages and disadvantages regarding certain frequency ranges and their specific parameters (sample size, dosimetry, study design). International authorities (WHO, ICNIRP and IARC) and local institutions have also published differing and inconsistent reports about the effects of EMF. These inconsistencies make the true situation even more difficult to analyze and interpret.

In vitro and experimental studies are more advantageous than epidemiological studies since their results are significantly more reliable. The effects of EMF can be shown using a large sample size in standardized laboratory conditions. The ability to verify the observed effects, to reveal the action mechanisms of EMF, and to test the hypotheses make the results of experimental studies more valuable. On the other hand, epidemiological studies and human experimental studies yield data concerning humans. The disadvantage of epidemiological studies is a relatively small sample size and a lack of prospective data acquisition. For this reason, it is difficult to evaluate the results on a per person basis. When the findings of different study types provide evidence that EMF has the same effect, the idea of causality may then emerge. However, most recent experimental studies clearly indicate the harmful effects of EMF. For this reason, the planning and evaluation of epidemiological studies should be more careful.

The US national toxicology program is the flagship-testing program for the US government. In 2016, they release the results of a long-term animal bioassay that studied the impact of cell phone radiation levels equivalent to that which humans received today in their lifetimes. They found that rats exposed to cell phone radiation developed significantly more highly malignant very rare tumors of the brain. They also found unusual patterns and significant rates of malignancies in the nerve leading to the heart. Epidemiologic studies have in fact found elevated rates of brain cancer's and acoustic neuroma's. Thus, the findings of this report should be taken quite seriously (Wyde et al., 2017).

There is some confusion about the fact that the report was issued as a partial report in 2016. The leaders of that program have explained that the report was issued as a partial report because they were quite concerned and surprised at these findings especially in light of the human results showing similar increased cancers. In fact, the report is an important report on the brain and heart tumors in the studies.

It is well documented that EMF exposure might cause indirect harmful effects *via* DNA damage, and DNA breaks, and oxidative stress. In very short duration and low frequencies of non-ionizing radiation exposure might be resulted in no effects. However, the average person living in a city is exposed to non-ionizing radiation whole day in different ways. Over time exposure might be resulted with the builds up ROS and creates indirect harmful effects.

To summarize, in the light of the information gathered in this study, EMF shows its biological effects by acting indirectly on cellular fragments. Long-term disruption of hemostasis may lead to the disruptive effects of EMF. Furthermore, it should not be forgotten that EMF is energy and EMF may show entropy-accelerating effects on every object present in the environment. The safety of EMF has not clearly been proved, and thus the necessary precautions must be taken to ensure our health and safety.

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Conflict of interest

Authors declare no conflict of interest.

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