Exp Oncol 2010
32, 2, 54–60

REVIEWS

Experimental ONCOLOGY

RISKS OF CARCINOGENESIS FROM ELECTROMAGNETIC RADIATION OF MOBILE TELEPHONY DEVICES

*I. Yakymenko[1, 2] *, E. Sidorik[2]*

[1]*Bila Tserkva National Agrarian University, Soborna square 8/1, Bila Tserkva 09117, Ukraine*
[2]*R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of NAS of Ukraine, Vasylkivska str. 45, Kiev 03022, Ukraine*

Intensive implementation of mobile telephony technology in everyday human life during last two decades has given a possibility for epidemiological estimation of long-term effects of chronic exposure of human organism to low-intensive microwave (MW) radiation. Latest epidemiological data reveal a significant increase in risk of development of some types of tumors in chronic (over 10 years) users of mobile phone. It was detected a significant increase in incidence of brain tumors (glioma, acoustic neuroma, meningioma), parotid gland tumor, seminoma in long-term users of mobile phone, especially in cases of ipsilateral use (case-control odds ratios from 1.3 up to 6.1). Two epidemiological studies have indicated a significant increase of cancer incidence in people living close to the mobile telephony base station as compared with the population from distant area. These data raise a question of adequacy of modern safety limits of electromagnetic radiation (EMR) exposure for humans. For today the limits were based solely on the conception of thermal mechanism of biological effects of RF/MW radiation. Meantime the latest experimental data indicate the significant metabolic changes in living cell under the low-intensive (non-thermal) EMR exposure. Among reproducible biological effects of low-intensive MWs are reactive oxygen species overproduction, heat shock proteins expression, DNA damages, apoptosis. The lack of generally accepted mechanism of biological effects of low-intensive non-ionizing radiation doesn't permit to disregard the obvious epidemiological and experimental data of its biological activity. Practical steps must be done for reasonable limitation of excessive EMR exposure, along with the implementation of new safety limits of mobile telephony devices radiation, and new technological decisions, which would take out the source of radiation from human brain.
Key Words: **tumor, radiofrequency radiation, microwaves, mobile phone, risk assessment, non-thermal effects.**

Apparently, any technical device was not introduced in everyday human life so fast and so close as mobile phone. Starting from first commercial mobile phone network in Japan in 1979 the number of active users of mobile telephony increased to over 3 billion all over the world. In developed countries the number of mobile phone users today is close to saturation. The initial age of youngest users of mobile phone is estimated as 3 years old [1]. The distinguishing feature of the mobile telephony technology is immediate vicinity of source of electromagnetic radiation (EMR) — handset to the human brain. These specificities lead to public concern about the safety of this technology for human health. From scientific point of view the main problem of a mobile telephony technology can be formulated as the lack of research on biological effects of low-intensive EMR, especially long-term studies, on the moment of active implementation of technology. It suffice to say that safety limits for mobile telephony are based only on thermal effects of EMR [2]. At the same time a principally new data about non-thermal biological effects of non-ionizing EMR have been revealed during the last years. These data are not taken into account by mobile phones manufacturers and most authorities for today. That is why some scientists call the situation with intensive implementation of mobile phone technology the biggest biophysical experiment in human history.

In 1996 World Health Organization started the wide-ranging epidemiological research on the risk of development of some cancer types in mobile phone users. The research was carried out in term of Interphone project and was substantially supported by industry. The project included national researches in 13 countries, and was finished in 2005, but until now the final report was not published [1]. At the same time project data published in some countries and data of the epidemiological studies of independent research groups have indicated statistically significant increase in the risk of development of brain tumors in chronic users of mobile phone.

It is clear that safety problem of mobile telephony technology must be a special concern of industry and authorities. This problem must be also the special concern of profile experts and researchers. In this review the main attention is drawn to published data on potential risk of cancer development, and the aim of the review is to discuss the recent publications on the topic and pay attention to the "harmful" effects of EMR. In most cases we used peer-reviewed journal publications. For more comprehensive insight into the problem of biological effects of RF EMF we can recommend some other reviews (see, for example [3–9]).

MAIN PHYSICAL CONCEPTS OF MOBILE TELEPHONY TECHNOLOGY

Mobile telephony technology utilizes electromagnetic waves of radio frequency (RF) for connection between base station and mobile phone (handset). The frequencies of electromagnetic waves (frequency of electromagnetic field oscillations) used in most modern mobile phones are

Received: April 15, 2010.
*Correspondence: Fax: +38456351288
E-mail: iyakymen@gmail.com

Abbreviations used: AM – amplitude modulation; EMR – electromagnetic radiation; HSP – heat shock proteins; MDA – malondialdehyde; NO – nitric oxide; OR – odds ratio; ROS – reactive oxygen species; RF – radio frequency; SAR – specific absorption rate; SIR – standardized incidence ratio; SOD – superoxide dismutase.

850–1900 MHz. These waves actually belong to extreme part of radiofrequency which calls microwaves (MWs). The useful (voice) information is carried by small modulation of electromagnetic wave frequency. This range of electromagnetic waves is a non-ionizing radiation because it has not enough energy for ionizing molecules.

Thus, both base station and mobile phone irradiates EMR. The levels of radiation are different from base station and handset, and for handset it depends significantly on the state of the system. The radiation power of base station antenna is about 60 W, and the intensity of radiation depends on the geometry of irradiated beam. The pick power of mobile phone handset radiation is up to 2 W. But the intensity of radiation (power density) near a user head is much more from handset than from base station due to the big difference in distance from the sources of radiation. For example, the power density in the main beam of base station at the distance of 150–200 m from antenna is about tenths of a $\mu W/cm^2$ [10]. At the same time the power density in immediate vicinity to handset can be tens $\mu W/cm^2$. The biggest level of irradiation mobile phone produces during the connection process (calling), smaller (lower) — during the talk, and minimal (close to zero) in a stand by position. Modern international safety limits for the level of power density of non-ionizing EMR are set approximately up to 100 $\mu W/cm^2$ [2].

The level of EMR energy absorbed by human body is estimated by index of specific absorption rate (SAR), which indicates the EMR energy absorbed per mass unit of tissue. The safety limit for this index is 1.6 W/kg for USA and 2 W/kg for most other countries. This index is mandatory technical passport index for each model of mobile phone for today. SAR is estimated and calculated on the models of human head and body. It is important that real SAR value depends on the structure of tissue and, for example, can be much more for child head than for adult [11]. Least-emitting models of mobile phone give SAR just a few tenths of W/kg.

PRE-MOBILE-PHONE DATA (MILITARY, BROADCASTING AND OCCUPATIONAL STUDIES)

One of the first publications about the possible link between anthropogenic non-ionizing EMR and cancer risk was published by Wertheimer and Leeper in 1979 [12]. The authors have indicated the association of children cancer with "excess of electrical wiring configuration" in Colorado, USA in 1976–1977. Children lived close to high-current configuration had twice more cases of leukemia and 1.6 times more cases of lymphoma as compared with the control population. Later the same authors have found less but still significant association between high-current environment and cancer in adults [13]. It was proposed that low frequency magnetic fields from high-current wiring could be the risk factor of cancer development.

The military data indicate the influence of radiofrequency and microwaves radiation on the development of cancer. So, among Polish soldiers of 20–29 years old exposed to microwave and radar during 1970–1979 the cancer incidence rates were 5.5 times higher then in non-exposed soldiers [14]. Greatest excess of cancer cases were in blood-forming organs and lymphatic tissues (ratio = 6.7). Examination of 40,000 US naval personnel served during the Korean War (1950–1954) has indicated almost two times more cases of cancer in the high-exposed personnel compared with the low-exposed one [15].

In Honolulu (1978–1981) in broadcasting towers' locations (100–150 feet from the towers) the standardized incidence ratio (SIR) for total cancer cases was indicated 1.88 compared with 1.07 in the locations without towers [3]. For leukemia SIR was 2.08 and 0.59 for the locations with and without broadcasting towers [3]. Increased incidence in childhood leukemia was also detected near the low-frequency radio tower (23.4 KHz) in Hawaii (1979–1990) [16]. The odds ratio (OR) for people lived within 2.6 miles of the radio towers before diagnosis was 2.0 as compared with unexposed residences of Hawaii. South Korean study (1993–1999) of leukemia and brain cancer patients under 15 years age has revealed the OR = 2.15 for all types of leukemia among children resided within 2 km of the nearest amplitude modulation (AM) radio transmitter as compared with those resided more than 20 km from it [17]. Brain cancer and infantile cancer were not associated with AM radiofrequency radiation in this research.

Analysis of occupational studies which was done by Savitz and Calle [18] revealed that the highest risk ratio for any occupational group for acute myelogenous leukemia was in telegraph, radio and radar operators (2.6). It's significant that among the members of American Physical Therapy Association (females), who used microwave or radiofrequency diathermy for treatment of patients, the percent of miscarriages occurring before the seventh week of gestation was 47.7% in comparison with 14.5% in non-exposed control women [19].

THE USAGE OF MOBILE PHONES AND TUMOR RISK ASSOCIATION

During the last few years data about the association of long-term usage of mobile phone with tumor risk have been published. The most researches were focused on possible association of mobile phone usage and brain tumors development, because brains are mostly exposed to irradiation by mobile phone. In series of epidemiological studies by Swedish oncologists (Dr. L. Hardell group) a significant increase of some types of brain tumors risk in long-term (10 years or more) users of mobile and cordless phones has been detected [20–26]. As to the short-term users of mobile phone, similar effects were absent or less expressive [6]. It must be indicated that Sweden was one of the first countries, where commercial mobile networks were implemented. Analogue mobile phones were used in Sweden since 1981 and digital system (GSM; Global System for Mobile Communication) were introduced in 1991 [1]. The risk of meningioma increased among Swedish users of mobile and cordless phones with term of usage over 10 years. Case-control OR for analogue mobile phones was 1.6, 95%, for digital

mobile phones 1.8, 95%, for cordless phone 1.8, 95%. For acoustic neuroma the risk of development increased with increasing period of usage of mobile phone, and it was the highest for users of analogue phone with term of usage over 15 years, OR = 3.5, 95% [22].

In recent publication by L. Hardell *et al.* [4] the authors analyzed the majority of published case-control studies on possible association of the usage of mobile phones with tumor risk for long-term users. For acoustic neuroma the analysis of 9 case-control studies has revealed the increasing risk for over 10 year users of mobile phone (OR = 1.3, 95%) and further increase of risk in cases of ipsilateral exposure (OR = 1.6, 95%). Similar results were revealed for glioma. The risk of glioma significantly increased for 10 year users (OR = 1.3, 95%) and especially for ipsilateral usageof mobile phone (OR = 1.9, 95%). It was indicated the highest risk of malignant brain tumors OR = 2.7, 95% for users of mobile phone with first use less 20 years age. It correlates with previous published data of L. Hardell group about highest OR = 5.9, 95% of brain tumour in 20–29 years age ipsilateral users of analogue mobile phone among different age groups [27].

Parotid gland is another potential target for mobile phone handset radiation. Israel team study in term of Interphone research indicated an association between the mobile phone use and parotid gland tumor [28]. The study included 402 benign and 58 malignant cases of parotid gland tumor diagnosed in Israel at age over 18 years in 2001–2003. The OR in the highest category of cumulative number of calls for ipsilateral use was 1.58, 95%. It is important that previous study performed in Finland detected the OR = 5.0, 95% for salivary gland cancers among Finland digital mobile phone subscribers compared with control population (used mobile phone just for 1–2 year) [29].

As was shown by L. Hardell group, for non-Hodgkin's lymphoma (NHL) of T cell, cutaneous and leukemia types, the ORs for analogue phone users were found to be 3.4, 95%; for digital phone users — 6.1, 95%; for cordless phone users — 5.5, 95% [30]. American researchers found that for NHL the OR for ⩾ 8 years users of mobile phone was 1.6, 95%, and the risk was increasing with number of years [31].

Regarding the uveal melanoma, the analysis of 118 cases of this pathology and 475 controls in Germany has indicated the OR = 4.2, 95% for people probably/certainly exposed to mobile phone [32]. The OR = 1.8, 95% was shown for seminoma for men keeping the mobile phone during stand by in one trousers pocket, and OR = 1.0, 95% — in different pockets [33]. The results were based on 542 cases study of seminoma performed in Sweden.

MOBILE PHONE BASE STATIONS AND TUMOR RISK

Starting from early 1990s tens of thousands of mobile phone base stations have been mounted over the world. So fast and extensive implementation of new technology base stations naturally had induced public concerns. But the World Health Organization International EMF Project had a priority to study effects of mobile phone and discouraged the base stations effects studies (except 2003–2006, when WHO recommended studies of base station possible effects) [5]. That is why only a few publications on the topic could be found, and two are about the association with cancer risk [34, 35].

The comparison of cancer cases among population living up to 400 m near mobile phone base station and further then 400 m from base station was carried out in Germany (1994–2004) [36]. The increase of cancer cases among people from area close to base station over the control population was 1.26 times during the first five year period (1994–1998), and 2.11 times during the second five year period (1999–2004). For the second period of analysis the increase of cancer cases among people living near base station was statistically significant both compared to the population from further area and to the expected background incidence.

Even more expressive results were obtained in Israel, Netanya [37]. People living in the area near (up to 350 m) to mobile phone base station (850 MHz, 1500 watt of full power) during 1 year of station operation (n = 622) and matched individuals from other area (n = 1222) participated in this study. There were 4.15 times more cases of cancer in base station close area than in the control area. Relative cancer rate for females from close to base station area was 10.5, relative rate was 0.6 for control area as compared with the whole town of Netanya female population (relative rate equals 1). Cancer incidence of women in close to base station area was significantly higher ($p < 0.0001$) compared with the control area and the whole city area. Authors emphasized the enormously short latency period (only 1 year) for such dramatic increase of cancer incidence in the area [37].

ANIMAL MODEL STUDY

Just a few studies have been designed to estimate an association of non-ionizing EMR exposure and cancer development on animal models. In one study mice with high incidence of spontaneous breast cancer and mice treated with 3,4-benzopyrene (BP) were irradiated by 2,450 MHz microwaves in an anechoic chamber at 5 or 15 mW/cm^2 (2 h daily, 6 sessions per week, 3 months) [38]. Irradiation with MWs at either 5 or 15 mW/cm^2 resulted in acceleration of the development of BP-induced skin cancer (285 days in control, 230 days for 5 mW/cm^2 and 160 days for 15 mW/cm^2). Microwaves-exposed mice with high incidence of spontaneous breast cancer had breast tumors earlier than control (332 days in control, 261 days for 5 mW/cm^2 and 219 days for 15 mW/cm^2). Authors had indicated that the acceleration of cancer development and lowering of natural antineoplastic resistence was similar in mice exposed to MWs at 5 mW/cm^2 or to chronic stress caused by confinement, but differed significantly from the results obtained on animals exposed at 15 mW/cm^2, where local thermal effects were possible.

The most cited study was performed by Repacholi, *et al.* [39] on transgenic mice moderately predisposed

to develop lymphoma spontaneously. One group of mice (101 females) was exposed during two 30-min periods per day for up to 18 months in plane-wave electromagnetic fields of 900 MHz with pulse repetition frequency of 217 Hz and a pulse width of 0.6 ms, incident power densities were 2.6–13 W/m^2 and average SAR 0.13–1.4 W/kg. Another group of mice (100 females) was an unexposed control. Lymphoma risk was significantly higher in the exposed mice than in the control (OR = 2.4, 95%). And follicular lymphoma was the major contributor to the increased tumor incidence.

POSSIBLE PATHWAYS OF BIOLOGICAL ACTIVITY OF LOW-INTENSIVE EMR

One of the strong evidences that living cells perceive low-intensive EMR as a stress factor is a heat shock proteins (HSP) overexpression under the exposure. So, effective experiment with low-intensive microwaves irradiation of transgenic nematode *Caenorhabditis elegans* carrying reporter-gene constructs regulated by homologous HSP16 heat-shock promoters has revealed non-thermal-induced overexpression of HSPs [40]. Nematodes were exposed overnight to continuous-wave radiation (750 MHz, calculated SAR = 0.001 W/kg). Expression of HSP16 reporter rose steeply through 24.5 to 25.5 °C ($p < 0.001$) in exposed nematodes. Meantime in non-exposed control nematodes heat-induced reporter expression increased sharply only above 27 °C. There was a disparity of 3 °C between exposed and control induction profiles and authors of research rejected thermal explanation for this disparity.

RF radiation from GSM digital system (1800 MHz, SAR = 1.5–2 W/kg, exposure duration 22 or 72 h) induced a significant upregulation of mRNA levels of the HSP70 in p53-deficient pluripotent embryonic stem cells differentiating *in vitro*, paralleled by a low and transient increase of c-jun, c-myc, and p21 levels in p53-deficient cells, but not in wild-type cells [41]. One-hour non-thermal exposure of human endothelial cells changed the phosphorylation status of numerous proteins. One of the affected proteins was identified as HSP27 [42]. Authors underlined that changes in protein phosphorylation is an early sign of cell response to a stress factor.

Series of studies of researchers from Columbia University, USA on *HSP70* gene expression induced by low frequency EMR was performed [43–49]. Specific DNA sequence in gene *HSP70* promoter sensitive to EMR was identified. The EMR sensitive region on the *HSP70* promoter was not sensitive to increased temperature. The EMR domain contained three nCTCTn myc-binding sites at −230, −166 and −160 positions relatively to the transcription initiation site and upstream of the binding sites for the heat shock (nGAAn) and serum responsive elements. The sensitivity of the DNA sequences nCTCTn to EMF exposures has been demonstrated by transfecting these sequences into CAT and Luciferase reporter genes. Authors have indicated that the *HSP70* promoter contains different DNA regions that are specifically sensitive to different stressors, thermal and non-thermal [44].

Some studies suggest the possibility of DNA damage under the RF EMR exposure. So, it was reported the increase in DNA double-strand breaks and micronucleation in lymphocytes obtained from mobile phone users [50]. The number of single and double-strand breaks of DNA in brain cells of rat exposed to 2.450 MHz RF radiation (SAR = 0.6–1.2 W/kg of whole body) for 2 h was shown to be increased [51]. The same the exposure of mice to 2,450 MHz radiation (power density 1 mW/cm^2, 2 h per day over 120–200 days) has led to breakage of DNA in testis and brain [52]. The exposure of human fibroblasts or rat granulose cells to mobile phone radiation (1800 MHz, SAR = 1.2 or 2 W/kg, 4, 16 or 24 h) has induced single- and double-strand breaks of DNA after 16 h of exposure [53]. Molt-4 human lymphoblastoid cells exposed to TDMA (Time Division Multiple Access) and iDEN (Integrated Digital Enhanced Network) mobile phone radiation (2.4–26 μW/g, 2–21 h) had opposite effect on DNA breakage depending on the type of signal, intensity and duration of the exposure [54].

A few studies were devoted to the RF EMR exposure effects on apoptosis. So, yeast cells of wild-type and cdc-48-mutant were exposed to 900 or 872 MHz radiation (SAR = 0.4 or 3.0 W/kg) with or without exposure to ultraviolet radiation (UV) [55]. It was found that amplitude modulated RF exposure significantly enhanced UV induced apoptosis in cdc-48-mutated cells, but not in cells exposed to unmodulated radiation. The exposure of human epidermoid cancer KB cells to non-thermal RF EMR (1950 MHz) induced time-dependent apoptosis (45% after 3 h) [56]. The exposure induced a differential activation of stress-dependent pathways with an increase of JNK-1 activity and expression of HSP70 and HSP27 and decrease of p38 kinase activity and HSP90 expression.

In other study primary cultures of neurons and astrocytes were exposed to GSM mobile phone radiation (1900 MHz) for 2 h in “on” and “stand-by” mode [57]. Up-regulation of caspase-2, caspase-6 and *Asc* (apoptosis associated speck-like protein) gene expression occurred in both “on” and “stand-by” modes in neurons, but only in “on” mode in astrocytes.

Free radical processes could mediate many noxious effects in living cell. It’s important that series of studies demonstrated the change of the level of reactive oxygen species (ROS) and antioxidant enzymes’ activity in cells after the EMR exposure. So, rat exposed to 900 MHz radiation (SAR = 0.016 W/kg for whole body, applied 30 min/day, for 10 days using an experimental exposure device) had significantly increased level of malondialdehyde (MDA) and nitric oxide (NO) in renal tissue while superoxide dismutase (SOD), catalase and glutathione peroxidase activities significantly decreased [58]. In myocardial tissue of exposed rats the increased levels of MDA and NO were detected too, while SOD, CAT and GSH-Px activities were reduced [59]. Caffeic acid phenethyl ester treatment of rats reversed these effects. In other research rabbits were exposed to 900 MHz GSM mobile phone irradiation (0.02 mW/cm^2,

30 min/day, 7 days) [60]. Serum SOD activity increased, and serum NO level significantly decreased (more then twice) in exposed animals.

A significant increase in the MDA and carbonyl group concentration in Wistar rat brain tissue was registered during exposure of animals to a mobile test phone (SAR = 0.043–0.135 W/kg) during 20, 40 and 60 days. Decreased activity of catalase and increased activity of xanthine oxidase (XO) remained after 40 and 60 days of exposure to mobile phones. Melatonin treatment significantly prevented the increase in the MDA content and XO activity in the brain tissue after 40 days of exposure [61].

It was found that treatment of rats immediately before and after irradiation exposure (2450-MHz, power density 2 mW/cm^2, average whole body SAR = 1.2 W/kg, 2 h) with either melatonin or the spin-trap compound N-tert-butyl-alpha-phenylnitrone (PBN) blocks an increase in DNA single- and double-strand breaks in brain cells [62]. Since both melatonin and PBN are efficient free radical scavengers, authors hypothesized that free radicals are involved in exposure-induced DNA damage in the brain cells of rats.

Only one-hour exposure of men semen samples by standard mobile phone has led to significant decrease of semen mobility and viability, increase in ROS level and decrease in ROS-TAC (total antioxidant capacity) score [63].

50 Hz magnetic fields induced free radical formation in mouse bone marrow-derived promonocytes and macrophages [64]. It was demonstrated that mainly superoxide anion radicals were produced after 50 Hz magnetic field exposure, and the NADH-oxidase pathway to produce superoxide anion radical was activated, but not the NADPH pathway. Treatment with Trolox or iron chelator blocked the effects of exposure of rats to a 60 Hz magnetic field (0.01 mT, 24 h) caused a significant increase in DNA breaks [65]. Authors suggested that magnetic field initiates an iron-mediated process (Fenton reaction) that increases free radical formation in brain cells, leading to DNA damages.

Well-composed experimentally determined mechanism of radiofrequency radiation effect on living cell was proposed by Israel researchers [66]. They used the signaling inhibitors in irradiated to 875 MHz, 0.07 mW/cm^2 electromagnetic waves Rat1 and HeLa cells. It was found that the first step in EMR interaction with cell structures is mediated in the plasma membrane by NADH-oxidase, which rapidly (during the minutes) generates ROS. ROS directly stimulate matrix metalloproteinases and allow them to cleave and release heparin-binding epidermal growth factor (EGF). This secreted factor activates the EGF receptor, which activates the extracellular-signal-regulated kinase (ERK) cascade and thereby induces transcription and other cellular processes. Authors underlined that intensity of radiation applied in the study was well below the average intensity of a regular mobile phone (approximately 0.45 mW/cm^2 in Israel), and no changes in temperature were detected in the medium during irradiation.

Among very primary physical mechanisms of non-ionizing EMR interaction with biological systems the mobile charge interaction model of M. Blank should be noted. Model is based on the magnetic field interaction with moving charges (Lorentz force). If charge flow is associated with biological function in living cell, the function may be altered [67]. Magnetic field-induced changes in enzyme activities of Na, K-ATPase and cytochrome oxidase, proportional to charge flow, was demonstrated [67]. Moreover the effect of acceleration of the Belousov-Zhabotinski reaction by low frequency electromagnetic fields was demonstrated Blank and Soo [68]. Authors affirmed that the effect apparently was due to electromagnetic field interaction with electrons transferred during the reaction.

Another biophysical model for the action of oscillating electromagnetic fields on cell is based on mechanism of forced-vibration of all the free ions on the surface of a cell's plasma membrane, caused by an external oscillating field [69]. Representative data was published recently [70] where low-strength magnetic fields (0.1 mT, 0.2 ms) triggers onset and offset evoked potentials, indicating that the detection process was a form of sensory transduction. Authors [70] hypothesized that the evoked potentials were initiated by a force exerted by the induced electric field on an ion channel in the plasma membrane.

CONCLUSION

Recent studies in the field of electromagnetic biology have given sufficient grounds for more strict experts' estimation of possible association of cancer development and radiation of mobile telephony devices. First of all the results of epidemiological studies indicated significant increase of tumor development risk in long-term (over 10 years) users of mobile phone [4, 20–22, 24, 27, 30, 33]. It's significant that first expressive epidemiological data were revealed in Sweden, country with one of the longest history of mobile telephony. It is significant too that essential increase of risks was detected for brain tumors and salivary gland tumour. It means that direct association of tumor development and the location of EMR exposure exists. Two studies from developed countries (Germany and Israel) indicated a significant increase of cancer cases in population living near mobile base stations [36, 37]. Just a one year operation of powerful (1500 W) base station in Israel has led to dramatic increase of cancer cases among people living in base station area. Such significant increase of cancer incidence in mobile phone base station area correlates with previous data on significant increase of leukemia rate in habitants of broadcasting tower areas in Honolulu [3] and Hawaii [16].

These data arouse the concern about adequacy of safety limits for mobile telephony, which are now solely based on the conception of thermal mechanism of biological activity of RF radiation. Bulk of recent publications demonstrated the significant metabolic changes in living cells under the low-intensive EMR. The strong conception of mechanism of non-thermal biological effects of RF (MW) radiation remains to be developed. Preliminary studies indicate that typical

metabolic pathways at list partially are involved in mediating the effect of EMR on living systems. It includes NADH-oxidase activation [64, 66] and overproduction of free radicals in cell [58, 59, 64, 66], subsequent activation of extracellular-signal-regulated kinase cascade [66] or free radical damage of DNA [62]. Some pathways may lead to apoptosis of exposed cells [56, 57]. On other hand some high-specific mechanisms of low-intensive EMR interaction with cell structures were revealed, such as the existence of EMR sensitive region on the HSP70 gene promoter [43]. The very first step of non-ionizing EMR interaction with living cell must include its physical interaction with electrical charges (electrons, ions). A few biophysical models were proposed for explanation of transformation of this interaction to biological response [67, 69, 70].

There is great insufficiency in animal studies of the potential carcinogenic effect of low-intensive EMR. From epidemiological studies it is clear that possible terms for effective experiments may last up to 10 years. Animal models should be used to shorten the period of studies and give insights to the role of EMR in tumor development.

Most discussions of potential hazards of EMR of mobile telephony devices have ended with the recommendation of the further study and the necessity of precautionary principle implementation. Of course, we insistently support both of these recommendations. But we see that the bulk of published data for today allows researchers to recommend significantly more strict limitations for excessive and often needless using of mobile telephony devices, especially for children. Authorities must recommended to restrict the level of MWs radiation from mobile telephony devices through the implementation of more strict safety limits, new technological decisions (moving off the source of radiation from human brain), and constant awareness activity.

ACKNOWLEDGMENTS

We thank for partial financial support of Fulbright Scholar Program, USA (grant to I. Yakymenko, No. 68431821).

REFERENCES

1. **Khurana VG, Teo C, Kundi M, *et al.*** Cell phones and brain tumors: a review including the long-term epidemiologic data. Surg Neurol 2009; **72**: 205–14.

2. ICNIRP. Guidelines for limiting exposure to time-varying elecrtic, magnetic and electromagnetic fields (up to 300 GHz). Health Phys 1998; **74**: 494–522.

3. **Goldsmith JR.** Epidemiologic Evidence of Radiofrequency Radiation (Microwave) Effects on Health in Military, Broadcasting, and Occupational Studies. Int J Occup Environ Health 1995; **1**: 47–57.

4. **Hardell L, Carlberg M, Hansson Mild K.** Epidemiological evidence for an association between use of wireless phones and tumor diseases. Pathophysiology 2009; **16**: 113–22.

5. **Kundi M, Hutter HP.** Mobile phone base stations-Effects on wellbeing and health. Pathophysiology 2009; **16**: 123–35.

6. **Morgan LL.** Estimating the risk of brain tumors from cellphone use: Published case-control studies. Pathophysiology 2009; **16**: 137–47.

7. **van Rongen E, Croft R, Juutilainen J, *et al.*** Effects of radiofrequency electromagnetic fields on the human nervous system. J Toxicol Environ Health B Crit Rev 2009; **12**: 572–97.

8. **Habash RW, Elwood JM, Krewski D, *et al.*** Recent advances in research on radiofrequency fields and health: 2004–2007. J Toxicol Environ Health B Crit Rev 2009; **12**: 250–88.

9. **Vanderstraeten J.** [GSM fields and health: an updated literature review]. Rev Med Brux 2009; **30**: 416–24.

10. **Hyland GJ.** Physics and biology of mobile telephony. Lancet 2000; **356**: 1833–6.

11. **Gandhi O, Lazzi G, Furse C.** Electromagnetic absorption in the human head and neck for mobile telephones at 835 and 1900 MHz. IEEE transactions on microwave theory and techniques 1996; **44**: 1884–97.

12. **Wertheimer N, Leeper E.** Electrical wiring configurations and childhood cancer. Am J Epidemiol 1979; **109**: 273–84.

13. **Wertheimer N, Leeper E.** Adult cancer related to electrical wires near the home. Int J Epidemiol 1982; **11**: 345–55.

14. **Szmigielski S.** Polish epidemiological study links RF/MW exposures to cancer. Microwave news 1985; **5**: 1–2.

15. **Robinette CD, Silverman C, Jablon S.** Effects upon health of occupational exposure to microwave radiation (radar). Am J Epidemiol 1980; **112**: 39–53.

16. **Maskarinec G, Cooper J, Swygert L.** Investigation of increased incidence in childhood leukemia near radio towers in Hawaii: preliminary observations. J Environ Pathol Toxicol Oncol 1994; **13**: 33–7.

17. **Ha M, Im H, Lee M, *et al.*** Radio-frequency radiation exposure from AM radio transmitters and childhood leukemia and brain cancer. Am J Epidemiol 2007; **166**: 270–9.

18. **Savitz DA, Calle EE.** Leukemia and occupational exposure to electromagnetic fields: review of epidemiologic surveys. J Occup Med 1987; **29**: 47–51.

19. **Ouellet-Hellstrom R, Stewart WF.** Miscarriages among female physical therapists who report using radio- and microwave-frequency electromagnetic radiation. Am J Epidemiol 1993; **138**: 775–86.

20. **Hardell L, Mild KH, Carlberg M, *et al.*** Tumour risk associated with use of cellular telephones or cordless desktop telephones. World J Surg Oncol 2006; **4**: 74.

21. **Hardell L, Carlberg M, Soderqvist F, *et al.*** Long-term use of cellular phones and brain tumours: increased risk associated with use for > or = 10 years. Occup Environ Med 2007; **64**: 626–32.

22. **Hardell L, Carlberg M, Mild KH.** Case-control study of the association between the use of cellular and cordless telephones and malignant brain tumors diagnosed during 2000–2003. Environ Res 2006; **100**: 232–41.

23. **Hardell L, Carlberg M.** Mobile phones, cordless phones and the risk for brain tumours. Int J Oncol 2009; **35**: 5–17.

24. **Hardell L, Carlberg M, Hansson Mild K.** Case-control study on cellular and cordless telephones and the risk for acoustic neuroma or meningioma in patients diagnosed 2000–2003. Neuroepidemiology 2005; **25**: 120–8.

25. **Hardell L, Sage C.** Biological effects from electromagnetic field exposure and public exposure standards. Biomed Pharmacother 2008; **62**: 104–9.

26. **Hardell L, Carlberg M, Soderqvist F, *et al.*** Meta-analysis of long-term mobile phone use and the association with brain tumours. Int J Oncol 2008; **32**: 1097–103.

27. **Hardell L, Mild KH, Carlberg M, *et al.*** Cellular and cordless telephone use and the association with brain tumors in different age groups. Arch Environ Health 2004; **59**: 132–7.

28. **Sadetzki S, Chetrit A, Jarus-Hakak A, *et al.*** Cellular phone use and risk of benign and malignant parotid gland tumors — a nationwide case-control study. Am J Epidemiol 2008; **167**: 457–67.

29. **Auvinen A, Hietanen M, Luukkonen R, *et al.*** Brain tumors and salivary gland cancers among cellular telephone users. Epidemiology 2002; **13**: 356–9.

30. **Hardell L, Eriksson M, Carlberg M, *et al.*** Use of cellular or cordless telephones and the risk for non-Hodgkin's lymphoma. Int Arch Occup Environ Health 2005; **78**: 625–32.

31. **Linet MS, Taggart T, Severson RK, *et al.*** Cellular telephones and non-Hodgkin lymphoma. Int J Cancer 2006; **119**: 2382–8.

32. **Stang A, Anastassiou G, Ahrens W, *et al.*** The possible role of radiofrequency radiation in the development of uveal melanoma. Epidemiology 2001; **12**: 7–12.

33. **Hardell L, Carlberg M, Ohlson CG, *et al.*** Use of cellular and cordless telephones and risk of testicular cancer. Int J Androl 2007; **30**: 115–22.

34. **Abdel-Rassoul G, El-Fateh OA, Salem MA, *et al.*** Neurobehavioral effects among inhabitants around mobile phone base stations. Neurotoxicology 2007; **28**: 434–40.

35. **Hutter HP, Moshammer H, Wallner P, *et al.*** Subjective symptoms, sleeping problems, and cognitive performance in subjects living near mobile phone base stations. Occup Environ Med 2006; **63**: 307–13.

36. **Eger H, Hagen K, Lucas B, *et al.*** Einfluss der räumlichen Nähe von Mobilfunksendeanlagen auf die Krebsinzidenz. Umwelt-Medizin-Gesellschaft 2004; **17**: 273–356.

37. **Wolf R, Wolf D.** Increased incidence of cancer near a cell-phone transmitted station. In: Columbus F, editor. Trends in cancer prevention: Nova Science Publishers, Inc, 2007: 1–8.

38. **Szmigielski S, Szudzinski A, Pietraszek A, *et al.*** Accelerated development of spontaneous and benzopyrene-induced skin cancer in mice exposed to 2450-MHz microwave radiation. Bioelectromagnetics 1982; **3**: 179–91.

39. **Repacholi MH, Basten A, Gebski V, *et al.*** Lymphomas in E mu-Pim1 transgenic mice exposed to pulsed 900 MHZ electromagnetic fields. Radiat Res 1997; **147**: 631–40.

40. **de Pomerai D, Daniells C, David H, *et al.*** Non-thermal heat-shock response to microwaves. Nature 2000; **405**: 417–8.

41. **Czyz J, Guan K, Zeng Q, *et al.*** High frequency electromagnetic fields (GSM signals) affect gene expression levels in tumor suppressor p53-deficient embryonic stem cells. Bioelectromagnetics 2004; **25**: 296–307.

42. **Leszczynski D, Joenvaara S, Reivinen J, *et al.*** Non-thermal activation of the hsp27/p38MAPK stress pathway by mobile phone radiation in human endothelial cells: molecular mechanism for cancer- and blood-brain barrier-related effects. Differentiation 2002; **70**: 120–9.

43. **Lin H, Blank M, Goodman R.** A magnetic field-responsive domain in the human HSP70 promoter. J Cell Biochem 1999; **75**: 170–6.

44. **Blank M, Goodman R.** Electromagnetic initiation of transcription at specific DNA sites. J Cell Biochem 2001; **81**: 689–92.

45. **Lin H, Blank M, Rossol-Haseroth K, *et al.*** Regulating genes with electromagnetic response elements. J Cell Biochem 2001; **81**: 143–8.

46. **Blank M, Goodman R.** Electromagnetic fields stress living cells. Pathophysiology 2009; **16**: 71–8.

47. **Ananiev EV, Phillips RL, Rines HW.** Complex structure of knob DNA on maize chromosome 9. Retrotransposon invasion into heterochromatin. Genetics 1998; **149**: 2025–37.

48. **Lin H, Opler M, Head M, *et al.*** Electromagnetic field exposure induces rapid, transitory heat shock factor activation in human cells. J Cell Biochem 1997; **66**: 482–8.

49. **Blank M, Goodman R.** Do electromagnetic fields interact directly with DNA? Bioelectromagnetics 1997; **18**: 111–5.

50. **Gandhi G, Anita.** Genetic damage in mobile phone users: some preliminary findings. Indian J Hum Gent 2005; **11**: 99–104.

51. **Lai H, Singh NP.** Single- and double-strand DNA breaks in rat brain cells after acute exposure to radiofrequency electromagnetic radiation. Int J Radiat Biol 1996; **69**: 513–21.

52. **Sarkar S, Ali S, Behari J.** Effect of low power microwave on the mouse genome: a direct DNA analysis. Mutat Res 1994; **320**: 141–7.

53. **Diem E, Schwarz C, Adlkofer F, *et al.*** Non-thermal DNA breakage by mobile-phone radiation (1800 MHz) in human fibroblasts and in transformed GFSH-R17 rat granulosa cells *in vitro*. Mutat Res 2005; **583**: 178–83.

54. **Phillips JL, Singh NP, Lai H.** Electromagnetic fields and DNA damage. Pathophysiology 2009; **16**: 79–88.

55. **Markkanen A, Penttinen P, Naarala J, *et al.*** Apoptosis induced by ultraviolet radiation is enhanced by amplitude modulated radiofrequency radiation in mutant yeast cells. Bioelectromagnetics 2004; **25**: 127–33.

56. **Caraglia M, Marra M, Mancinelli F, *et al.*** Electromagnetic fields at mobile phone frequency induce apoptosis and inactivation of the multi-chaperone complex in human epidermoid cancer cells. J Cell Physiol 2005; **204**: 539–48.

57. **Zhao TY, Zou SP, Knapp PE.** Exposure to cell phone radiation up-regulates apoptosis genes in primary cultures of neurons and astrocytes. Neurosci Lett 2007; **412**: 34–8.

58. **Ozguner F, Oktem F, Ayata A, *et al.*** A novel antioxidant agent caffeic acid phenethyl ester prevents long-term mobile phone exposure-induced renal impairment in rat. Prognostic value of malondialdehyde, N-acetyl-beta-D-glucosaminidase and nitric oxide determination. Mol Cell Biochem 2005; **277**: 73–80.

59. **Ozguner F, Altinbas A, Ozaydin M, *et al.*** Mobile phone-induced myocardial oxidative stress: protection by a novel antioxidant agent caffeic acid phenethyl ester. Toxicol Ind Health 2005; **21**: 223–30.

60. **Irmak MK, Fadillioglu E, Gulec M, *et al.*** Effects of electromagnetic radiation from a cellular telephone on the oxidant and antioxidant levels in rabbits. Cell Biochem Funct 2002; **20**: 279–83.

61. **Sokolovic D, Djindjic B, Nikolic J, *et al.*** Melatonin reduces oxidative stress induced by chronic exposure of microwave radiation from mobile phones in rat brain. J Radiat Res (Tokyo) 2008; **49**: 579–86.

62. **Lai H, Singh NP.** Melatonin and a spin-trap compound block radiofrequency electromagnetic radiation-induced DNA strand breaks in rat brain cells. Bioelectromagnetics 1997; **18**: 446–54.

63. **Agarwal A, Desai NR, Makker K, *et al.*** Effects of radiofrequency electromagnetic waves (RF-EMW) from cellular phones on human ejaculated semen: an *in vitro* pilot study. Fertil Steril 2009; **92**: 1318–25.

64. **Rollwitz J, Lupke M, Simko M.** Fifty-hertz magnetic fields induce free radical formation in mouse bone marrow-derived promonocytes and macrophages. Biochim Biophys Acta 2004; **1674**: 231–8.

65. **Lai H, Singh NP.** Magnetic-field-induced DNA strand breaks in brain cells of the rat. Environ Health Perspect 2004; **112**: 687–94.

66. **Friedman J, Kraus S, Hauptman Y, *et al.*** Mechanism of short-term ERK activation by electromagnetic fields at mobile phone frequencies. Biochem J 2007; **405**: 559–68.

67. **Goodman R, Blank M.** Insights into electromagnetic interaction mechanisms. J Cell Physiol 2002; **192**: 16–22.

68. **Blank M, Soo L.** Electromagnetic acceleration of the Belousov-Zhabotinski reaction. Bioelectrochemistry 2003; **61**: 93–7.

69. **Panagopoulos DJ, Karabarbounis A, Margaritis LH.** Mechanism for action of electromagnetic fields on cells. Biochem Biophys Res Commun 2002; **298**: 95–102.

70. **Marino AA, Carrubba S, Frilot C, *et al.*** Evidence that transduction of electromagnetic field is mediated by a force receptor. Neurosci Lett 2009; **452**: 119–23.