Somato Publications ISSN: 2643-2609

Annals of Gastroenterology and Digestive Disorders

Review Article

Increased Generational Risk of Colon and Rectal Cancer in Recent Birth Cohorts under Age 40 - the Hypothetical Role of Radiofrequency Radiation from Cell Phones

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Received: 04 August 2020; Accepted: 15 September 2020 2020; Published: 16 September 2020

Citation of this article: Davis DL., Pilarcik, AM., Miller, AB. (2020) Increased Generational Risk of Colon and Rectal Cancer in Recent Birth Cohorts under Age 40 - the Hypothetical Role of Radiofrequency Radiation from Cell Phones. Ann Gastroenterol Dig Dis, 3(1): 09-16.

Abstract

To determine if there are shifts in patterns of cancer, rates of disease can be evaluated in terms of Generational Risk (GR), comparing those born recently with those born decades earlier. Using data from the U.S. Centers for Disease Control and Prevention (CDC), the U.S. Surveillance Epidemiology and End-Results (SEER) Program and Iranian cancer registries, increases in GR of colon and rectal cancer in those under age 50 are presented. For the U.S. those born in the 1990s have a doubled risk of colon cancer (GR=2) and a fourfold increase in rectal cancer (GR=4) by the time they reach age 24 compared to those born six decades ago. Experimental studies have determined that the colon and rectum of Sprague-Dawley rats are exquisitely sensitive to both ionizing and non-ionizing radiofrequency radiation (RFR), expressing significant differences in patterns of methylation of a number of well-identified proteins and other biomarkers predictive of cancer risk. Modeling of nonionizing exposures also indicates that absorption of RFR into the colon and rectum from cell phones stored in the pocket exceeds current test limits by up to 5-fold. French government tests of phones positioned next to the body report exposures to non-ionizing radiation that are up to 11 times more than current guidelines. Based on these findings, it is prudent to develop policies to reduce direct exposures to RFR from cell phones, as occurs when they are kept next to the body, and to promote advances in hardware and software that reduce direct exposures to RFR.

Keywords: Computerized tomography, Radiofrequency radiation, Colo-rectal cancer, Cell phones, Generational risk

Abbreviations: ALARA: as Low as Reasonably Achievable; CDC: Centers for Disease Control; CRC: Colo-rectal Cancer; CT: Computerized tomography; GR: Generational Risk; GSM900: Global System for Mobile Communication; RFR: Radiofrequency Radiation; RAR: Retinoic Acid Receptor; SEER: United States Surveillance Epidemiology and End-Results Program; US: United States

Colorectal cancer (CRC) is the third most common cancer in the world, and the fourth leading cause of cancer deaths, with about 700,000 estimated annually [1].While incidence is greater in developed nations, deaths from the disease are more common in rapidly developing nations that lack the infrastructure to find and treat the disease. As with most types of cancer, rates of CRC increase with age. The disease remains relatively rare in young persons. While there has been a major increase in incidence globally [2,3]. Overall rates are dropping in the U.S. and Europe [1], but not all age groups share in that decline. The proportion of persons under age 50 diagnosed with the disease has doubled since 1990, from 6% to 13% in 2017.

Epidemiological studies have identified a number of specific risk factors for CRC including obesity, inactivity, diets high in red and cured meat, alcohol, smoking, and other factors [4]. Tremendous changes of dietary habits have occurred in both the developed and the developing world during the last decades. Recorded overall declines in CRC in those over age 50 in the U.S. and elsewhere are generally attributed to improvements in screening with colonoscopy and other procedures and do not reflect reductions in these known risk factors. Surgical removal of pre-cancerous polyps is believed to account for much of the decline in CRC in the elderly. While improvements in access to care and increases in diagnostic ascertainment may in part account for these continued declines in the elderly, they are unlikely to account in any significant way for increases that occur in those under age 50 in whom screening is neither recommended nor conducted. Inherited germ-line mutations, such as Lynch syndrome, are responsible for about 5% of all disease [5].

This review first explores trends in Generational Risk (GR) of CRC in order to document patterns in younger and older persons [5]. Secondly, potential explanations for these patterns are investigated, concentrating on the increase in exposure to non-ionizing radiation that has occurred world-wide, including the young. Finally, prudent precautionary policies in the light of these findings are advised.

We examined colon and rectal cancer incidence data from the national cancer registry of the U.S., the U.S. Centers for Disease Control and from the Iranian national cancer registry. Patterns were evaluated for secular time trends and in terms of birth cohorts, using established methods for determining GR, contrasting incidence in those born after 1990 with those born before 1950. Novel toxicological investigations of CRC cells response to ionizing and non-ionizing radiation are also presented as they provide clues regarding possible etiologic factors that could underlie these patterns of disease and inform policies aimed at reducing risk factors.

Figure 1 reveals contrasting patterns of CRC cancer for older and younger Americans. There are major declines in incidence of CRC in those over age 54, in whom 90% of all CRC occurs. In contrast, a countervailing pattern is evident in those born after 1950, with a marked increase in the past two decades of CRC incidence in those born in 1970 or later compared with rates in those under age 40 in the past two decades. Employing the GR model we conclude that by the time they reach age 24 those born after 1970 are developing more than four times more rectal cancer (right side of figure) and twice the rate of colorectal cancer (left side of figure) compared to those born before 1940. Because the numbers of cases are quite small, the standard deviation in the rates will be considerable for those in their twenties. Nonetheless, the sharp increase in rates for younger birth cohorts in whom improved access to diagnostic technology is not a likely factor signals that there is a real underlying surge in CRC underway in the young. Siegel, et al. [6] recently evaluated patterns of colon and rectal cancer in the U.S. in the 4 decades up to 2013. They found that in contrast with the modest annual increases in colon cancer of less than 1% annually for all age groups under age 55, trends in incidence of rectal cancer are considerably greater with rates growing most rapidly and sharply in those ages 20-29 in the past decade. Specifically, rectal cancer incidence rates increased annually 3.2% from 1974 to 2013 in adults age 20 to 29 years, but more recently grew 4.0% annually. In contrast, for that age 55 and over rates generally declined throughout the entire 40-year study period. Similar find-

ings have been reported from Europe and Iran [7,8].

Patterns of CRC in Iran (Figure 2) are illuminating as they indicate that for both men and women of all ages, incidence has recently risen sharply, from about 2 per 100,000 in 2000 to more than 8 and 10 per 100,000 respectively in females and males, an increase of 4 to 5-fold. Moreover, combined rates of colon and rectal cancer have risen from 5 per 100,000 in 2001 to more than 20 per 100,000 in males in 2011. In Iran, surgeons are reporting more cases of the disease in younger patients (Masood Sepephrimanesh, personal communication).

In an effort to determine whether radiofrequency radiation could be affecting rates of CRC, Iranian scientists from the Ionizing and Non-ionizing Radiation Protection Research Center of Shiraz University of Medical Sciences have reported on a series of basic research studies where they devised, validated and evaluated special chemical fingerprints for relevant cellular patterns by staining genetic and epigenetic factors associated with CRC carcinogenesis. The biochemical elements they examined include the estrogen receptor, and genes believed to be critical to inflammatory processes, including COX2, APC, MINT, and MLH1 gene promoters that may represent early stages of colorectal carcinogenesis [9,10]. The grounds for incorporating and examining these biological indicators derive from several studies that have found that a number of these well-identified proteins are hypermethylated in CRC: ER alpha and MYOD, p53 the cell cycle regulatory gene, cyclin A1, UDP-glucoronosyl transferase and retinoic acid receptor. Thus, it is possible that alterations in patterns of methylation in these genes may well constitute an early biomarker of colon carcinogenesis [11] and are considered by several investigators to be prognostic for a high risk of CRC malignancy [12]. A number of additional studies have recently confirmed that methylation of ERα, MYOD, MGMT, SFRP2, P16, APC, DCC, MINT, COX2, HLFT, SOCS1, and hMLH1 gene promoters appear to have critical functions for the onset of colorectal carcinogenesis [9,10].

Mokarram, et al. [13] compared epigenetic patterns of ERα after exposure to ionizing radiation, with those occurring after exposure to non-ionizing radiofrequency radiation. Their innovative study employed biomarkers that have previously been established to signal damaging exposures to ionizing radiation, especially γ-rays. All groups studied in this experiment had methylated ER allele, while the un-methylated band varied considerably. While all of the control group displayed un-methylated bands, not one of the rats exposed to either radiofrequency or gamma radiation had any such bands. This indicates that methylation patterns may constitute an important validated biomarker of exposure to radiofrequency radiation that has the potential to play a role in the expression and promotion of CRC.

Recently, DNA hyper-methylation has been identified as a vitally important potential biomarker of cancer risk that can be used to predict rates of recurrence and advance of the disease and can be a signal property of several forms of cancer [11]. Hypomethylation of DNA may also control gene expression and chromosomal stability. Thus, ER alpha and MYOD, p53 the cell cycle regulatory genes, cyclin A1, UDP-glucoronosyltransferase and retinoic acid receptor are hypermethylated in CRC and also can be found in early stages of the disease [11]. Several investigators now consider that the methylation status of the ER promoter in the lymph nodes constitutes a valid biomarker for the development of advanced malignancy in CRC patients with stage I and II colon cancer and can be used to indicate the likelihood of disease progression [12].

The Iranian experimental study is important because as they note: "For the first time, our data showed that the effect of exposure to mobile phone radiation and 3Gy gamma radiation are the same and both of them could decrease the U-allele in the treated colon tissues of rats compared to the controls (p=.000)."

Further support for altered DNA methylation patterns as predictors of CRC comes from Dong and Ren [14]. They note that CRC results from a multi-stage, multi-causal process, reflecting the combined impacts of a variety of genetic and epigenetic changes in CRC cells that can be signaled through epigenetic alterations in blood. Using the Food and Drug Administration approved Virtual Family 3-dimensional, anatomically-based modeling of exposures to non-ionizing radiofrequency radiation carried out by the National laboratories of the Federal University of Brazil in Porto Alegre also indicates significant absorption of non-ionizing radiation takes place within the pelvic area from phones stored in the pants pocket of men, with male reproductive organs absorbing the highest levels. The pelvis has a high dielectric constant and permittivity, because it is mostly soft tissue and fat, lacking the dense bone of the skull. As a result, radiation can be more deeply

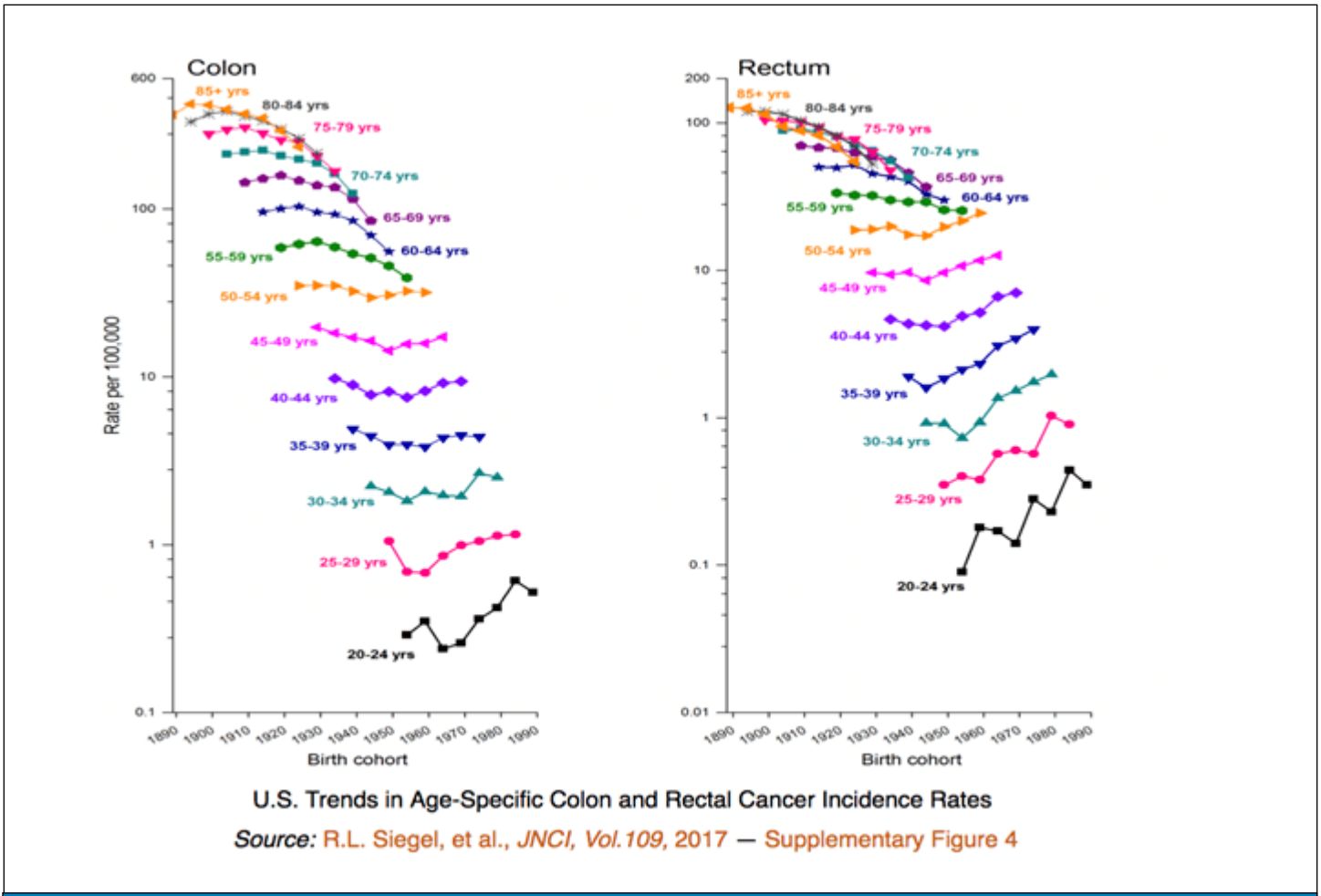

Figure 1: U.S. Trends in Age-Specific Colon and Rectal Cancer Incidence Rates.
Source: R.L. Siegel, et al., JNCI, Vol 109, 2017 – Supplementary Figure 4

absorbed into the pelvis as compared with the brain.

Despite general declines of rates of CRC in developed nations, especially in those over age 54, puzzling and substantial increases have been reported in younger persons in the U.S. and Iran [6-8]. Similar increases have been noted in Canada [15]. Population-based screening in developing nations is not widely conducted, so this cannot account for much of the reported increase in the disease in younger persons in Iran. It is important to appreciate that the underlying and distinctly diverging secular trends in colon and rectal cancer reported by these authors began decades before cellphones were widely in use. Screening certainly has played a role in the continuing decline in CRC in the elderly. But as to the unexplained relatively recent increases in the young, it is important to consider a number of potentially relevant causal factors that have changed in the past two decades. These include obesity and physical inactivity, increased exposures to HPV, HIV, and other viral factors, diagnostic radiation from computerized tomography and non-ionizing radiofrequency radiation (RFR) from cellphones, laptops, and other devices.

Belyaev [16] has noted that ionizing and non-ionizing radiation have a number of distinct properties including, polarity, wave form, power density, and frequency and that their importance to biological systems can vary with temperature, host conditions and other factors that are not always well-controlled in various studies of non-ionizing radiation. The GSM900 (Global System for Mobile Communication) includes 124 different channels/frequencies. They differ by 0.2 MHz in the frequency range between 890 MHz and 915 MHz. Depending on the number of connected users op-

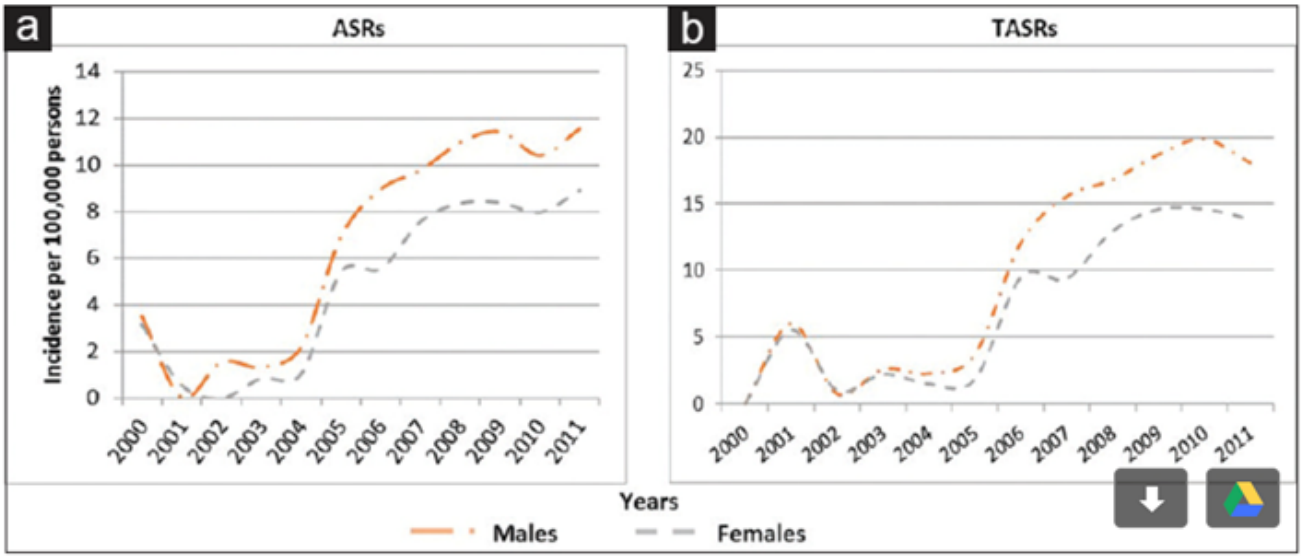

Figure 2: Trends in Age-Standardized Rates of Colorectal cancer in Iran 2000-2011. Source Dolatkhah, et al. [7]

erating at any one time, frequency is supplied by a base station to a mobile phone user and can be automatically changed to another frequency during the same call. Belyaev [16] also reports that contrary to differentiated cells, human mesenchymal stem cells do not adapt to effects of microwaves during chronic exposure. These results also suggest that less mature and differentiated cells, such as are more common in the young, may be more susceptible to proliferative responses.

When cell phones are stored next to the body, their four to six or more antennas continue to send signals to towers or hotspots up to 900 times a minute in search of an electronic handshake to maintain connectivity, especially when they are being employed when in motion. Because antennas are on the backs and sides of smartphones, keeping cell phones turned on in the pocket subjects users to frequent microwave radiation bursts. Putting cell phones on airplane mode eliminates exposures to radiofrequency radiation.

Both experimental and epidemiological evidence supports a role for RFR from cell phones in the pocket or laptop exposures. Avendaño, et al. [17] found that human sperm samples exposed ex vivo to levels of RFR from conventional laptops at a distance of 3 cm that were specially shielded not to produce battery heat developed significantly more genetic and epigenetic damage after 4 hours of continual downloading and uploading to simulate intense game-playing, video watching or other activities. Damage to human spermatozoa for 4 hours affected quality and quantity significantly--3-fold greater damage in exposed sperm in contrast to unexposed controls. These results are similar to those Houston, et al. [18] reported with in vitro studies of human sperm that found significant evidence of such damage as oxidative stress, including the DNA damage marker, 8-hydroxy-2'-deoxyguanine as well as sperm fragmentation.

For the next decade it is expected that cell phones will need to rely on 3G and 4G for voice communications, even if 5G becomes available for speedier downloading movies, games, virtual reality and videos. It is important to point out that although absorption of faster, shorter millimeter waves of 5G alone will be superficial compared to earlier generations of 2G and 3G that reached 2 inches into the brain and much more deeply into the pelvis, there are growing concerns that these higher frequencies can produce unique biochemical reactions just below the surface of the skin that effectively transform them into more powerful systemic impacts on the immune system. Although millimeter wave exposures are absorbed into 1/64 inch of human skin, the beam-forming erratic properties of 5G signals may prove highly biologically reactive. It is possible that the sweat ducts in the human body will

act as helical antennas, directing the millimeter waves deeper into the body, serving effectively as wave guides [19]. Moreover, some technologists have reported that, contrary to marketing claims that 5G is essential for autonomous vehicles, beam-forming properties are neither reliable nor easily controllable, and 4G systems are quite adequate to that task. Writing in a trade publication, technology writer and former industry executive, Desjardin [20], acknowledges that with respect to 5G no one has addressed questions of potential biological impact of complex modulation of 5G at 28.375 GHz, combined with 77 GHz from automotive radar, and 5.9 GHz from automotive infrastructure.

In addition, in considering the possible role of contemporary exposures to cellphone radiation for these unexplained patterns of CRC, it is important to consider recent reports from the French government frequency testing agency (ANFR) that most cell phones emit substantially more radiation than current test limits advise. Using FCC approved methods to conduct the testing, the agency found that 9 out of 10 phones exceeded the safety guidelines when held against the body by factors of 1.6-3.7 times for the European standard or by factors as high as 11 if 1-g SAR values were to be measured as required by the U.S. FCC [21].

Other exposures that appear relevant to these puzzling patterns of CRC include the greatly expanded use of pediatric diagnostic computerized tomographic (CT) scans. Brenner and Hall [22] estimated that a significant proportion of young adult cancer in the future would reflect CT practices that began in the 1980s, when the younger birth cohort was born. At that time, Brenner and Hall [22] reported that approximately 600,000 abdominal and head CT examinations were conducted annually in the United States on pediatric patients under the age of 15 years. Brenner and Hall [22] estimated that approximately 500 children might ultimately die of cancer attributed to CT radiation. By 2016, the number of CT scans conducted on both children and adults increased significantly to about 82 million. Although the average dose per procedure had declined, the average diagnostic radiation dose per individual has more than doubled since 1980. Currently, Americans, especially children, receive more ionizing radiation exposures from diagnostic radiation than from natural sources. The excessive use of this technology especially with infants and children led the American College of Pediatric Radiology to issue a white paper in 2007, urging that technologists be mindful of the need to keep pediatric exposures, As Low As Reasonably Achievable (ALARA). While current practices may reduce ionizing radiation overall, past scenarios involved emergency room physicians ordering repeat CT, even whole-body CT, where abuse was suspected.

Some recent evidence corroborating concerns about the long-term impacts of CT scans was provided by a retrospective study of 168,394 Dutch children that had undergone one or more CT scans, with those receiving the highest radiation having the greatest risk of brain tumors [23]. Another investigation in the UK, found that those under age 22 that underwent CT scans between 1985 and 2002 had greater risks of developing both brain cancer and leukemia [24].

In considering other known risk factors for CRC, such as obesity and inactivity, it is instructive to note that changes in these propensities have not changed as much as the rates we report here. Thus, obesity in adults 20-74 has more than doubled since 1979 and was 35% greater in 2014 [25]. However, because the latency for colorectal cancer is thought to be a decade or longer, changes in obesity are unlikely to explain much of the recent surge.

The studies reviewed here confirm statistically significant and unexplained patterns of increase in CRC in younger persons. As a multi-factoral, multi-causal disease, cancer has numerous causes. While germ line mutations are relevant in about 5% of all cancer cases [26], the bulk of CRCs stem from acquired mutations that arise as a consequence of interactions with xenobiotic agents. The appearance of increased rates of this disease in younger persons is a matter that merits the most serious concern. Improved screening or use of technologies to increase diagnostic ascertainment such as improved imaging and greater access to endoscopy as well as general improvements in health care in this younger age group seem unlikely to account for these patterns.

We suggest two plausible contributing factors underlying these unexplained increases in CRC in the young—increased exposures to RFR from cell phones and laptops and/or increased exposures to ionizing radiation through CT scans. While obesity and inactivity are also important considerations, changes in these factors cannot in and of themselves account for the changes reported here. One of the attractive aspects of these proposed risk factors

is that they can be easily addressed through education of health professionals and the general public, unlike lifestyle determinants such as diet and exercise.

The possibility that RFR and/or CT exposures in childhood could contribute to CRC in young adults should be accorded prompt attention. Methylation patterns in CRC are similar for both ionizing and non-ionizing radiation. Anatomically-based modeling investigations confirm that exposures to the colon and rectum appear to be quite substantial from cell phones held next to the body (in the pocket) and French test data show that typically cell phones emit many-fold more RFR than current test guidelines allow. Thus, it appears prudent to promote policies to reduce exposures to radiofrequency radiation and encourage ALARA during pediatric CT procedures, while continuing to promote advances in software and hardware of phones and scanners that can lower exposures to non-ionizing radiation during normal operations. In addition, major public educational programs should be developed to promote awareness of the need to practice safer technology, especially for the young, who may well be at greater risk of developing cancer due to their immunological immaturity.

The authors declare that they have no conflicts of interest in relation to this review.

Acknowledgements

Environmental Health Trust supported the preparation of this review. The Iranian study was supported by the Ionizing and Non-ionizing Radiation Protection Research Center (INIRPRC), Shiraz University of Medical Sciences (SUMS), Shiraz, Iran, and was provided by Masood Sepehrimanesh of Louisiana University. Rebecca Siegal's work was Open Access and relied on resources of the American Cancer Society.
https://academic.oup.com/jnci/article/109/8/djw322/3053481

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