Lost opportunities for cancer prevention: historical evidence on early warnings with emphasis on radiofrequency radiation

Abstract: Some historical aspects on late lessons from early warnings on cancer risks with lost time for prevention are discussed. One current example is the cancer-causing effect from radiofrequency (RF) radiation. Studies since decades have shown increased human cancer risk. The fifth generation, 5G, for wireless communication is about to be implemented world-wide despite no comprehensive investigations of potential risks to human health and the environment. This has created debate on this technology among concerned people in many countries. In an appeal to EU in September 2017, currently endorsed by more than 400 scientists and medical doctors, a moratorium on the 5G deployment was required until proper scientific evaluation of negative consequences has been made (www.5Gappeal.eu). That request has not been taken seriously by EU. Lack of proper unbiased risk evaluation of the 5G technology makes adverse effects impossible to be foreseen. This disregard is exemplified by the recent report from the International Commission on non-ionizing radiation protection (ICNIRP) whereby only thermal (heating) effects from RF radiation are acknowledged despite a large number of reported non-thermal effects. Thus, no health effects are acknowledged by ICNIRP for non-thermal RF electromagnetic fields in the range of 100 kHz – 300 GHz. Based on results in three case-control studies on use of wireless phones we present preventable fraction for brain tumors. Numbers of brain tumors of not defined type were found to increase in Sweden, especially in the age group 20–39 years in both genders, based on the Swedish Inpatient Register. This may be caused by the high prevalence of wireless phone use among children and in adolescence taking a reasonable latency period and the higher vulnerability to RF radiation among young persons.

Keywords: asbestos; cancer prevention; DDT; dioxins; early warnings; glyphosate; phenoxyacetic acids; radiofrequency radiation; tobacco.

Introduction

The International Agency for Research on Cancer (IARC) at the World Health Organization (WHO) initiated in 1969 a program to evaluate human cancer risks of chemicals. It was later expanded to include chemical mixtures, radiation and viruses. So far, this program has resulted in 125 Monographs. Mostly, as the history shows, it has taken a long time between the first reports of increased cancer risk and cancer classification of the agent. Thereby preventive measures have not been taken in due time with high costs to society as a consequence in terms of increased numbers of cases with diseases leading to suffering and costs for treatment, loss of professional activity and eventually premature deaths [1–3]. Thus, early warnings should not be neglected. In fact, false positives on environmental risks are extremely rare [4]. In the following some historical examples are discussed, followed by a review of the current controversy on radiofrequency (RF) radiation and cancer. These examples serve as lessons for early warnings [5, 6].

No doubt the reports from the European Environment Agency on late lessons from early warnings may serve as important documents for the precautionary approach. Volume 1 was published in 2001 [5]. It dealt with 12 key lessons on health and environmental hazards. The 2013 volume on late lessons was grouped into five parts including e.g., health, ecosystems, justice, and governance [6]. Both volumes give examples on action that could have
been taken to prevent harm. In the following some examples are discussed partly based on our own research experiences.

Examples of early warnings on cancer risks

The first history on occupational diseases was written by the Italian physician Bernardini Ramazzini in his book “De morbis artificum” (Diseases of Workers) printed in Modena, Italy 1700. He is regarded to be the ‘father of occupational medicine’. A second extended version was printed in Padua 1713. In the book 53 chapters deal with different occupations and diseases occurring in these occupations [7].

Regarding specific occupational exposures the English physician Percival Pott was the first to describe that men working as chimneysweeps, and thereby exposed to soot, had an increased risk for scrotal cancer. He published his findings in 1775 [8]. This disease was known as chimney-sweepers’ cancer. It is regarded to be the first report of an environmental factor causing cancer. It took a long time of campaigning to stop little boys being used to clean chimneys by climbing up them. More than 200 years later soot was classified as a human carcinogen Group 1 (carcinogenic) by IARC in 1985 [9].

Asbestos

Another both occupational and environmental toxic substance is asbestos. Already in 1899, a UK Factor Inspector observed the sharp glass-like jagged nature of asbestos particles [10]. The author noted asbestos dust in the air of the factory rooms and that “the effects have been found to be injurious“. Numerous reports have since then described increased risks primarily of lung cancer and mesothelioma. Already in 1935, a man with asbestosis and lung cancer was reported [11]. In 1953 it was reported that a man who had worked with asbestos died of pleural mesothelioma [12]. South African researchers published in 1960 a report on increased risk for mesothelioma for both occupational and environmental exposure to asbestos [13]. The American physician Dr. Irving Selikoff gave to a broader public insight into a dramatic increased cancer mortality among American insulation workers exposed to asbestos. Also, that environmental exposure increased the risk of mesothelioma [14]. This started a long-standing battle between a multinational industry defending its product, and public health and regulatory bodies [15, 16]. Asbestos was in 1977 evaluated by IARC to be carcinogenic to humans, Group 1 [17]. This was almost 20 years since the clear evidence of cancer risks was published in the early 1960s. Years were lost for prevention and yielded increased numbers of deaths.

Tobacco

Tobacco has a long history of reported adverse health effects. When first introduced in Europe smoking was recommended for medical purposes, in fact as prophylaxis for many diseases. In 1604 King James I of United Kingdom wrote against the use of tobacco [18]. Sömmering stated in a thesis in 1795 that tobacco pipes induced an increased risk for lip cancer [19]. Cancer of the tongue was described some 100 years later in 1890 [20]. A high proportion of diseases including lung cancer among cigar makers and sellers, waiters, and innkeepers was reported in 1914 [21]. A clearly increased incidence of lung cancer was first reported by Müller in 1940 [22]. This evidence and other cancer studies in the 1940s in Germany [23] and in the Netherlands [24] were mainly disregarded thereby omitting the possibility of early prevention. It was not until the 1950s when more studies showed health risks from tobacco, primarily for diseases such as cancer of the lung, myocardial infarction, peripheral vascular diseases, and chronic obstructive lung disease. Tobacco was in 1986 classified by IARC as a human carcinogen, Group 1 [25]. No doubt the history of smoking shows that early warnings were mainly neglected. Greenwashing by industry and its allied experts has a history of countering preventive measurements [26].

DDT

The marine biologist Rachel Carson was the first to write a general picture of chemical damage to the environment, human and animal health in her book Silent Spring published in 1962 [27]. She gave the first comprehensive description of the bioaccumulation of the insecticide DDT (para,para’-DDT –1,1′-(2,2,2-trichloro-ethylidene)bis (4-chloro benzene)). DDT was discovered in 1939 by the Swiss researcher Paul Müller. For that he received the Nobel Prize in medicine in 1948. No doubt the book by Rachel Carson was opposed by the chemical industry that even tried to stop the publication. In fact, DDT was defended by the American Medical Association and the US Nutrition Foundation unified with 54 companies in the food, chemical and allied industries [28]. The main human studies on human carcinogenicity of DDT and its main metabolite DDE (1,1′-(2,2-dichloroethyldene)– bis(4-chlorobenzene)) were performed from the 1990s and onward [29].
The Stockholm Convention on Persistent Organic Pollutants was adopted in 2001. It provided initially evidence for the elimination of 12 chemicals, one of which was DDT [30]. The use of DDT was banned in most countries in the 1970s [31]. In 1972, the US EPA issued a cancellation order for DDT [32]. DDT was evaluated by IARC in 2018 to be probably carcinogenic to humans, Group 2A [29]. It had previously been evaluated as a possibly human carcinogen, Group 2B [33]. One of the main toxic issues is the bioaccumulation of DDT and its metabolites with long half-time in the environment [27]. DDT is still used in some countries, e.g. for malaria control. Due to its chemical behavior its metabolites can be found in human tissue [34, 35].

Phenoxyacetic acids

In 1977, a report was published on a series of patients who had been spraying phenoxy herbicides for the Swedish Forestry and who subsequently developed soft-tissue sarcoma [36]. Herbicides of this type include 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). 2,4,5-T was contaminated by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), one of the most toxic chemicals in the world. This clinical observation was the first to indicate a possible increased cancer risk for these chemicals. Based on that report an increased risk for soft-tissue sarcoma was found both for these phenoxy herbicides and the chemically related chlorophenols, mostly exposure to pentachlorophenol, in a following case-control study [37]. These results were corroborated in further studies by our research group and others, for an overview see [2].

Another set of studies included malignant lymphoma, also initiated by a clinical observation [38]. This clinical observation resulted in further studies. An increased risk was found for both non-Hodgkin lymphoma (NHL) and Hodgkin’s disease for persons exposed to phenoxy herbicides or chlorophenols [39]. Also, the increased lymphoma risk was confirmed in other studies, for overview see [2, 40].

One of the main types of chlorophenols, pentachlorophenol, was classified by IARC in 2019 to be carcinogenic to humans, Group 1 [41]. The phenoxy herbicide 2,4-D was in 2018 classified by IARC as possibly carcinogenic to humans, Group 2B [29]. It was the same classification as in 1977 including also 2,4,5-T [42].

Dioxins

The phenoxy herbicides 2,4-D, 2,4,5-T and chlorophenols were contaminated with dioxins. Of large concern was TCDD that contaminated 2,4,5-T and trichlorophenol. The initial Swedish results on cancer risks from this group of chemicals were followed by studies in other countries that confirmed the findings, for overview see [2,40]. Vietnam veterans exposed to the defoliating agent Agent Orange, including 2,4-D and 2,4,5-T, with TCDD contamination suffering from soft-tissue sarcoma or malignant lymphoma were in 1991 judged to be eligible for service-related compensation [43].

In 1976 an accident occurred in a chemical plant at Seveso, Italy producing 2,4,5-trichlorophenol. Thereby the surrounding area was contaminated with dioxins and the general population was exposed to TCDD. In the aftermath an increased incidence in malignant diseases, notably soft-tissue sarcoma and hematolymphatic malignancies was found in the population [40, 44].

Various ad hoc explanations were postulated by the chemical industry and its allied experts to discredit the cancer risks [2]. However, in 1997 IARC classified TCDD as a human carcinogen, Group 1 [45]. It had previously been evaluated in 1977 by IARC to be a possibly human carcinogen, Group 2B [42]. This was about two decades after the first epidemiological publications on increased cancer risk for TCDD contaminated herbicides.

Glyphosate

In the case-control studies by the Hardell group on risk factors for NHL exposure to all types of herbicides was assessed. In addition to phenoxyacetic acids also glyphosate turned out to increase the risk [46, 47]. Hairy cell leukemia (HCL) is regarded to be a subtype of NHL. In a separate study on HCL glyphosate was a risk factor also for that malignancy [48]. Similar results were also found in other studies [49, 50].

Glyphosate was in 1970 tested as herbicide and was patented by Monsanto [51]. It was registered for use in USA in 1974 with the trade name ‘Roundup’. Since the patent has expired it is produced nowadays by many manufactures. In 1996 genetically engineered glyphosate tolerant crops were introduced (Roundup Ready) and since then the global use has increased 15-fold. Glyphosate has in recent years been the most widely used pesticide [52].

IARC at WHO evaluated glyphosate in March 2015 and classified it as a Group 2A, a probable human carcinogen [53, 54]. This was based on “limited” evidence of cancer in humans (from real-world exposures that occurred) and “sufficient” evidence of cancer in experimental animals (from studies of “pure” glyphosate). IARC also concluded
that there was “strong” evidence for genotoxicity, both for “pure” glyphosate and for glyphosate formulations.

The European Food Safety Authority (EFSA) is the EU agency for risk assessment regarding food safety. In October 2015, that is seven months after the IARC evaluation, EFSA published its own evaluation [55]. In summary EFSA dismissed without clear explanation any association of glyphosate with cancer. All findings on carcinogenesis in animal studies were incorrectly discarded as chance findings. Mechanistic evidence on genotoxicity was ignored. Oxidative stress was confirmed but dismissed as a ground for carcinogenesis [56]. It should be noted that EFSA did not reveal the names of the authors of the chapters and references were redacted.

Monsanto, the main glyphosate producer, hired a panel of scientists to defend glyphosate. Thus, in 2016 a 17-page article was published in Critical Reviews in Toxicology, known to be an industry friendly product defense journal [57]. It was concluded that “In summary, the totality of the evidence, especially in light of the extensive testing that glyphosate has received, as judged by the Expert Panels, does not support the conclusion that glyphosate is a “probable human carcinogen” and, consistent with previous regulatory assessments, the Expert Panels conclude that glyphosate is unlikely to pose a carcinogenic risk to humans.”

This review was made by four expert panels. In the initial publication no conflicts of interest were stated. All but six of the 16 authors appeared with their university or hospital affiliation. During lawsuits in USA on glyphosate exposure and NHL it was revealed that the authors were not independent, and that Monsanto was deeply involved in organizing, reviewing and editing the review. In fact, Monsanto paid the authors through a consulting firm, Intertek [58].

As a consequence Critical Reviews in Toxicology was forced to make a Corrigendum two years later: “When this article was originally published on 28th September 2016, the contributions, contractual status and potential competing interests of all authors and non-author contributors were not fully disclosed to Critical Reviews in Toxicology. Specifically, the Acknowledgments and Declaration of Interest were not complete. After further clarification from the authors, these sections are corrected to reflect the full contributions, contractual status and, potential competing interests of all authors and non-author contributors and read as follows … This overview paper (paper) is part of a supplement, the preparation of which was coordinated by Intertek Scientific & Regulatory Consultancy (Intertek) under the leadership of Ashley Roberts. It was prepared subsequent to completion of the four manuscripts as an overview and presented the opinions and conclusions of four groups of the expert panel. The expert panels were organized and supported administratively by Intertek. Funding was provided to Intertek by Monsanto Company, which is a primary producer and marketer of glyphosate and related products. All the expert panelists other than John Acquavella and Larry D. Kier were compensated through a contract with Intertek. John Acquavella and Larry D. Kier were compensated through existing consulting contracts with Monsanto Company” [59].

Product defense by downplaying risk seems to have been one of Monsanto’s strategies [60].

The German chemical company Bayer purchased Monsanto in 2018. It is facing a magnitude of lawsuits on NHL and glyphosate exposure. So far in three lawsuits about 200 million USD have been awarded by the juries [58]. No doubt the use of glyphosate is of large economic importance both for the producers and the agriculture. In 2017 the EU Commission extended the use of glyphosate until 2022 [61].

Radiofrequency radiation

In 2011 radiofrequency electromagnetic fields (RF-EMF) in the frequency range 30 kHz–300 GHz were evaluated by IARC at WHO to be possibly carcinogenic to humans, Group 2B [62, 63]. This was based on evidence of increased risk for glioma and acoustic neuroma in human epidemiology studies on use of mobile and/or cordless phone (DECT) [64–69]. The increased cancer risk was supported by laboratory studies [70, 71].

Extremely low frequency (ELF)-EMF was in 2001 evaluated by IARC to be a possible human carcinogen, Group 2B [72]. This was the first time that non-ionizing radiation at low intensity levels can be a possible cause of cancer. It predated the IARC finding for RF-EMF by a decade.

Since then the evidence on RF-EMF carcinogenesis has strengthened based on further human studies on use of wireless phones, as reviewed [73, 74]. Also animal studies show increased cancer risk, both near field RF-EMF exposure [75–77] and far field exposure [78, 79]. Mechanistic studies show increase of reactive oxygen species (ROS) [80] as well as DNA damage [81]. These results give support to the increased cancer risk in humans and laboratory tested animals for RF radiation. In fact, RF-EMF may now be classified as a human carcinogen, Group 1 [82, 83]. However, such classification can only be made by IARC.

Of course, these well documented health hazards from RF-EMF are not well accepted by the telecom industry and its allied experts. Several methods are used to create doubt.
Studies are discredited, only partly cited, or even not cited at all [84–86]. Thereby the uniformed reader gets the wrong information on actual risks. This includes also regulatory agencies and policy makers. Even agencies aimed at setting exposure guidelines may include pro-industry and biased scientists that obscure the true risks [87, 88].

ICNIRP

The International Commission on Non-Ionizing Radiation Protection (ICNIRP) is a private non-governmental (NGO) organization registered in Munich, Germany. ICNIRP appoints its own members and is closed to transparency. It was started in 1992 with the biophysicist Michael Repacholi as the first chairman, now emeritus member. ICNIRP has published three articles with guidelines on RF-EMF exposure [86, 89, 90]. Only thermal (heating) effects from RF radiation are recognized, thereby excluding all studies showing harmful effects at lower non-thermal intensities.

In contrast to ICNIRP, some other expert panels such as European Academy of Environmental Medicine [91], the Bioinitiative group [92], and the Russian Commission for Protection from Non-Ionizing Radiation [93], take into account non-thermal RF effects and suggest much lower guidelines for RF exposure.

ICNIRP has managed to get collaborative status with WHO, as discussed previously [88]. The aim is to harmonize the RF-radiation guidelines all over the world. For that purpose ICNIRP has been successful. The guidelines are set to allow very high exposure levels so that the deployment of this technology is not hampered, in favor for industry but at disadvantage to human health and environment. In fact, the ICNIRP guidelines have never been challenged by industry in peer-reviewed articles, which must be taken as a green card for acceptance by industry.

Attributable fraction

The attributable fraction (AF), sometimes also called the etiologic fraction, is the number of cases in which exposure played an etiologic role. This is the preventable fraction if exposure would not be present. In Belpomme et al. [73] we published meta-analyses for longest cumulative use of mobile phones with odds ratio (OR) and 95% confidence interval (CI), both for total and for ipsilateral wireless phone use. Note that only the Hardell group assessed also use of cordless phones (DECT). We present here AF based on statistically significant increased risks in the meta-analyses. AF is the proportion of cases that can be attributed to the particular exposure. This is calculated as the exposed case fraction multiplied by [(OR-1)/OR].

As displayed in Table 1 the AF for glioma was calculated to 4.88%, 95% CI = 2.44–6.57%, corresponding to 211 preventable cases, 95% CI = 105–284 cases in the longest time for all cumulative use of wireless phones. Regarding ipsilateral use of the wireless phone AF was 6.03%, 95% CI = 4.51–7.12%, yielding 150 cases; 95% CI 112–177 to be preventable.

For meningioma AF = 1.75%, 95% CI = 0.39–2.73 corresponded to 39 cases, 95% CI = 9–61 cases for ipsilateral use of the wireless phone was calculated. Calculation of AF for acoustic neuroma yielded 4.63%, 95% CI = 3.07–5.63% corresponding to 42 cases, 95% CI = 28–51 cases for ipsilateral use of the phone.

Table 1: Attributable fraction (AF) based on meta-analyses of case-controls studies on use of wireless phones with statistically significant increased risk. For details see Belpomme et al. [73]. Odds ratio (OR), 95% confidence interval (CI), and numbers (n) are given.

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Meta-analysis</th>
<th>AF</th>
<th>AF, corresponding cases</th>
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<tbody>
<tr>
<td></td>
<td>Total n</td>
<td>Exposed n</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Glioma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longest cumulative use ≥ 1640 h</td>
<td>4,319</td>
<td>445</td>
<td>1.90</td>
<td>1.31–2.76</td>
</tr>
<tr>
<td>Longest cumulative use, ipsilateral ≥ 1640 h</td>
<td>2,484</td>
<td>247</td>
<td>2.54</td>
<td>1.83–3.52</td>
</tr>
<tr>
<td><strong>Meningioma</strong></td>
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<tr>
<td>Longest cumulative use, ipsilateral ≥ 1640 h</td>
<td>2,241</td>
<td>119</td>
<td>1.49</td>
<td>1.08–2.06</td>
</tr>
<tr>
<td><strong>Acoustic neuroma</strong></td>
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<tr>
<td>Longest cumulative use, ipsilateral ≥ 1640 h</td>
<td>899</td>
<td>66</td>
<td>2.71</td>
<td>1.72–4.28</td>
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</table>

*Based on Interphone [67], Coureau et al. [101], Hardell and Carlberg [104], Carlberg and Hardell [102]. *Based on Interphone [68], Hardell et al. [108].
Rates of brain tumors in the Swedish National Inpatient Register ICD-code D43

Rates of brain tumors of unknown type, D43, were studied using the Swedish Inpatient Register (IPR) without any personal identification information [94]. It was established in 1964 and has complete national coverage since 1987 [95]. Register data on D43 are available from 1998. Currently more than 99% of hospital discharges are registered. For outpatients the data are less reliable due to missing information. The reporting of outpatients has increased during more recent years so these time trends may give spurious results, thus we omitted outpatients from the analysis.

Data were analyzed for the time period 1998–2019. Age-standardized rates are not available in the register. Instead numbers of patients per 100,000 inhabitants are reported. The Joinpoint Regression Analysis program version 4.1.1.1 was used to examine numbers of patients per 100,000 in inpatient care and incidence per 100,000 person-years in the Swedish Inpatient Register, by fitting a model of 0–3 joinpoints using permutation tests with Bonferroni correction for multiple testing to calculate the number of joinpoints that best fits the material [96]. When joinpoints were detected annual percentage changes (APC) and 95% CIs were calculated for each linear segment. Average annual percentage changes (AAPC) were also calculated for the whole time period using the average of the APCs weighted by the length of the segment. To be able to calculate APC and AAPC the data was log-transformed prior to analysis. Thus, it was not possible to perform joinpoint regression analysis when there were years with no cases during that time period. Since the data do not include any personal identification no ethical approval was needed.

In men AAPC increased during 1998–2019 with +1.77%, 95% confidence interval (CI) –0.02, +3.58%, Table 2; Figure 1. The increase was highest in the age group 20–39 years, +2.90%, 95% CI +1.66, +4.16 %, Figure 2. AAPC increased statistically significant in all age groups, except 0–19 years.

Similar results were found in women with AAPC +1.70%, 95% CI +0.38, +3.05% during 1998–2019, Table 3; Figure 3. Also in women the highest increase of AAPC was found in the age group 20–39 years, +2.89%, 95% CI +1.54, +4.27%, Figure 4. AAPC increased statistically significant in all age groups except 0–19 years and 80+ years. Especially high increase of APC was seen in women aged 60–79 years during 2005–2019, and women aged 80+ years during 2010–2019.

Table 2: Joinpoint regression analysis of brain tumor rates (numbers per 100,000) in men in the Swedish Inpatient Register 1998–2019, ICD-10 code D43 (https://sdb.socialstyrelsen.se/if_par/val.aspx).

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>Joinpoint location</th>
<th>APC 1 (95% CI)</th>
<th>APC 2 (95% CI)</th>
<th>APC 3 (95% CI)</th>
<th>AAPC (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>D43</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All men</td>
<td>2008; n=10,540</td>
<td>+0.13 (–0.85, 8.95)</td>
<td>+1.22 (–3.99, 0.16, 2.63)</td>
<td>+1.77 (–0.02, 3.58)</td>
<td></td>
</tr>
<tr>
<td>0–19 years</td>
<td>no joinpoint detected</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+1.83 (–0.13, 3.82)</td>
</tr>
<tr>
<td>20–39 years</td>
<td>no joinpoint detected</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+2.90 (+1.66, 4.16)</td>
</tr>
<tr>
<td>40–59 years</td>
<td>no joinpoint detected</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+1.61 (+0.88, 2.36)</td>
</tr>
<tr>
<td>60–79 years</td>
<td>no joinpoint detected</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+1.67 (+0.99, 2.36)</td>
</tr>
<tr>
<td>80+ years</td>
<td>no joinpoint detected</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+1.40 (+0.11, 2.70)</td>
</tr>
</tbody>
</table>

APC, annual percentage change (APC 1, time from 1998 to first joinpoint; APC 2, time from first joinpoint to 2019 or to second joinpoint; APC 3, time from second joinpoint to 2019); AAPC, average annual percentage change

Discussion

No doubt there are historical examples of late lessons from early warnings on health risks whereby preventive measurements have been neglected. Some of the examples here clearly show that if the scientific evidence on cancer risks had been taken seriously lives could have been saved.

Tobacco is a good example of cancer risks that were disregarded for decades since clear evidence of increased risk. It was not until 1986 that IARC classified tobacco as a human carcinogen, Group 1 [25]. The strategies by the tobacco industry to sow doubt on the risks include e.g., to fund research that supports their position, to hide their involvement, to promote ‘no risk’ studies, to criticize research that shows risk, and to disseminate data and their interpretation of the results to the press and layman, for further details see Bero [98].

In fact, these strategies by the tobacco industry to obscure scientific facts seem to be textbook examples on product defense that may be used by different industries.
One current controversy is cancer risks from RF radiation. No lessons on prevention of cancer risks seem to have been learned in spite of decades of publications on adverse health risks. In fact, early prevention is usually very cost effective [2, 99]. The issue on RF radiation risks is on-going and in fact increasing despite decades of research showing adverse effects on human health, plants, insects and birds. It seems as if the industry view of no risk dominates on national level [84], among many countries [85], also at EU level (www.5gappeal.eu), and even within WHO [88]. Notably such industry organizations and nations have the power and economic resources to suppress scientific evidence on risks and have access to mainstream media to propagate their views, may it be for political or economic reasons.

RF radiation is a current controversy regarding cancer risks. The 2011 IARC evaluation on carcinogenesis [62, 63] has been downplayed and detracted by industry and captured agencies from the very beginning in spite of increasing evidence on harmful effects. However, IARC has decided that a new evaluation of cancer risks is top priority within a few years [100].

Figure 1: Joinpoint regression analysis of number of patients per 100,000 inhabitants. According to the Swedish National Inpatient Register for men, all ages during 1998–2019 diagnosed with D43 = tumour of unknown type in the brain or CNS. Note that in Sweden 1G (NMT, Nordic mobile telephone System) operated during 1981–2007. 2G (GSM) started 1991, 3G UMTS) started 2003, 4G started 2015, and DECT started 1988 [97].

Figure 2: Joinpoint regression analysis of number of patients per 100,000 inhabitants. According to the Swedish National Inpatient Register for men aged 20–39 years during 1998–2019 diagnosed with D43 = tumour of unknown type in the brain or CNS.
Table 3: Joinpoint regression analysis of brain tumour rates (numbers per 100,000) in women in the Swedish Inpatient Register 1998–2019, ICD-10 code D43 (https://sdb.socialstyrelsen.se/if_par/val.aspx).

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>Joinpoint location</th>
<th>APC 1 (95% CI)</th>
<th>APC 2 (95% CI)</th>
<th>APC 3 (95% CI)</th>
<th>AAAPC (95% CI)</th>
</tr>
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<tr>
<td>D43</td>
<td></td>
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<tr>
<td>All women</td>
<td>2008; n=9,611</td>
<td>+0.24, +4.77, -4.35, +1.70</td>
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<tr>
<td>0–19 years</td>
<td>2017; (n=2,509)</td>
<td>-0.75, -3.32, -15.82, +0.38, +1.24, +6.24, +8.68, +3.05</td>
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</tr>
<tr>
<td>20–59 years</td>
<td>2005; (n=1,318)</td>
<td>-0.95, +3.45, -3.21</td>
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<tr>
<td>60+ years</td>
<td>2010; (n=1,318)</td>
<td>-0.66, +5.49, -1.93</td>
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<td></td>
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</tbody>
</table>

APC, annual percentage change (APC 1, time from 1998 to first joinpoint; APC 2, time from first joinpoint to 2019 or to second joinpoint; APC 3, time from second joinpoint to 2019); AAAPC, average annual percentage change.

In this article we give some further data on the RF carcinogenesis. The attributable fraction gives the number of cases that could have been prevented if no risk exists for a specific exposure. Based on results in case-control studies from three study groups that have shown statistically significant increased risk for glioma and acoustic neuroma 211 glioma cases (all exposure) and 42 acoustic neuroma cases (ipsilateral exposure) would have been preventable in the longest cumulative exposure group. The preventable fraction was 4.88 and 4.63%, respectively. Highest preventable fraction was found for glioma with ipsilateral wireless phone use, 6.03% corresponding to 150 cases. Lower AF was calculated for meningioma, 1.75%, yielding 39 preventable cases (ipsilateral exposure). As displayed in Belpomme et al. [73] these results were based on Interphone [67], Coureau et al. [101], and Carlberg, Hardell [102], each without statistically significant increased risk. However, meta-analysis of these studies yielded, OR = 1.49, 95% CI = 1.08–2.06.

We have previously published results on increasing rates of tumors of unknown type in the brain or CNS both in the Swedish Inpatient Register and Causes of Death Register during 1998–2013 [103]. There was a clear increasing trend in both genders during that time period, especially during more recent years with AAPC +1.78 %, 95% CI +0.76, 2.81% for both genders combined. A joinpoint was found in men in 2007; time period 2007–2013 AAPC +4.95%, 95% CI +1.59, +8.42%. Similarly, in women a joinpoint was detected in 2008; time period 2008–2013 AAPC +4.08%, 95% CI +1.80, +6.41%.

We have now extended the time period up to 2019. Thus, we report increasing AAPC in both genders during 1998–2019 of similar magnitude as previously. In men the result was of borderline significance although the AAPC
overlapped previous findings. Lower APC was found during more recent years in both men and women, see Figures 1 and 3. This may reflect a better diagnostic procedure and thus decreasing numbers of unknown brain tumor type. A delay in reporting to the register during recent years may also have an impact on the results.

It is noteworthy that we found highest AAPC in the age group 20–39 years in both men and women, Tables 2 and 3. We found in our case-control study on glioma a median latency period for use of mobile phone of 9.0 years (mean 10.1 years). The corresponding results for cordless phones (DECT) were 7.0 and 8.0 years, respectively [104]. In a population-based study during 2005–2006 on use of mobile and cordless phones among Swedish children aged 7–14 years 79.1% reported access to mobile phone and use of cordless phone was reported by 83.8% [105]. Thus, our current findings with increasing numbers of brain tumors in the age group 20–39 years may be consistent with use of wireless phones taking a reasonable latency period. Moreover, our previous results showed highest risk for subjects that started the use of mobile or cordless phone before 20 years of age [104]. That age groups would also be more vulnerable to RF radiation [106]. In legends to Figures 1 and 3 we report the history for wireless phone use in Sweden. Figure 5 displays the number of out-going mobile phone minutes in millions during 2000–2019 in Sweden according to post-och Telestyrelsen [The Swedish post and telecom Authority (PTS)]. Available from: https://statistik.pts.se/svensk-telekommarknad/tabeller/mobila-samtals-och-datatjanster/tabell-13-trafikminuter-utgaende/.
Sweden. The major increase is since early 21st century and may be associated with our findings of increasing numbers of brain tumors of unknown type considering a reasonable latency time.

As we have discussed elsewhere the Swedish Cancer Register is not reliable to study the incidence of brain tumors [103, 107]. The register is mainly based on reporting of cases with histopathological diagnosis. Now diagnosis may be based on CT and/or MRI without further investigations especially of patients with poor outcome. Biopsy or operation may be difficult to perform due to tumor location, age and co-morbidity. In the Swedish Cancer Register about 90% of the cases are diagnosed with cytology or histology, a number that has increased somewhat during recent years [107]. This fact indicates that brain tumors of unknown type are under-reported to the Cancer Register.

This review gives insight into missed opportunities for cancer prevention exemplified by asbestos, tobacco, certain pesticides and now RF radiation. No doubt economic considerations are favored instead of cancer prevention. The cancer victim is the loser in terms of suffering, life quality and shorter life expectancy. Also the life for the next-of-kin is affected. A strategy to sow doubt on cancer risks was established decades ago and is now adopted and implemented in more sophisticated way by the telecom industry regarding RF-EMF risks to human beings and the environment. Industry has the economic power, access to politicians and media whereas concerned people are unheard.

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