

# Central nervous system lymphoma and radiofrequency radiation – A case report and incidence data in the Swedish Cancer Register on non-Hodgkin lymphoma



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## ABSTRACT

Earlier animal studies have provided evidence that non-Hodgkin lymphoma (NHL) may be caused by exposure to radiofrequency (RF) radiation. This was recently confirmed by the U.S. National Toxicology (NTP) study that showed an increased incidence of malignant lymphoma in female mice exposed to the GSM modulated or the CDMA modulated cell phone RF radiation. Primary central nervous system lymphoma (PCNSL) is a rare malignancy in humans with poor prognosis. An increasing incidence has been reported in recent years. Based on a case-report we present the hypothesis that use of the hand-held mobile phone may be a risk factor for PCNSL. The increasing incidence of non-Hodgkin lymphoma in Sweden is discussed in relation to etiologic factors.

## Introduction

Primary central nervous system lymphoma (PCNSL) is a rare malignancy with poor prognosis (survival usually < 1 year) [1]. The annual incidence rate has been reported to vary between 7 cases per 1,000,000 persons in USA [2] and 0.2 cases per 100,000 person-years in high income countries [3]. An increased lymphoma risk has been identified among severely immunodeficient patients such as HIV-infected or organ transplant individuals [4–6].

An increasing trend in PCNSL among HIV un-infected and non-transplant persons was reported from USA. In men and women aged + 65 years the incidence increased during 1992–2011 with 1.7% and 1.6%/year, respectively, which was statistically significant [7]. In other age groups the incidence was stable. In a Swedish study on PCNSL diagnosed 2000–2013 the average annual increase was 4%, 95% confidence interval (CI) = 1.01–1.06. It was more pronounced in subjects aged 70 + with average annual increase 6%, 95% CI = 1.02–1.10 [3].

## Hypothesis

The etiology of the increasing incidence of PCNSL among persons with no HIV or no organ transplantation is unknown. One factor that has not been discussed so far is exposure to radiofrequency (RF) fields

to the brain during use of the handheld mobile phones and cordless phones (DECT). We discuss it further based on a case report and we hypothesize that the increasing incidence of PCNSL may be caused by exposure to RF fields. We obtained informed consent by the patient to review the medical records.

## Methods

We analysed non-Hodgkin lymphoma (NHL) incidence per 100,000 person-years age-adjusted according to the World population for the time period 1970–2017. The database was updated until 2018, but the year 2018 was excluded due to missing cases according to the Swedish Cancer Register (note in the online database). We selected ICD-7 codes 200 + 202 for NHL in the register administered by the National Board of Health and Welfare ([https://sdb.socialstyrelsen.se/if\\_can/val.aspx](https://sdb.socialstyrelsen.se/if_can/val.aspx)).

## Statistical methods

The Joinpoint Regression Analysis program, version 4.7.0.0 was used to examine incidence per 100,000 person-years in the Swedish Cancer Register, by fitting a model of 0–5 joinpoints using permutation tests with Bonferroni correction for multiple testing to calculate the number of joinpoints that best fit the material [8]. When joinpoints

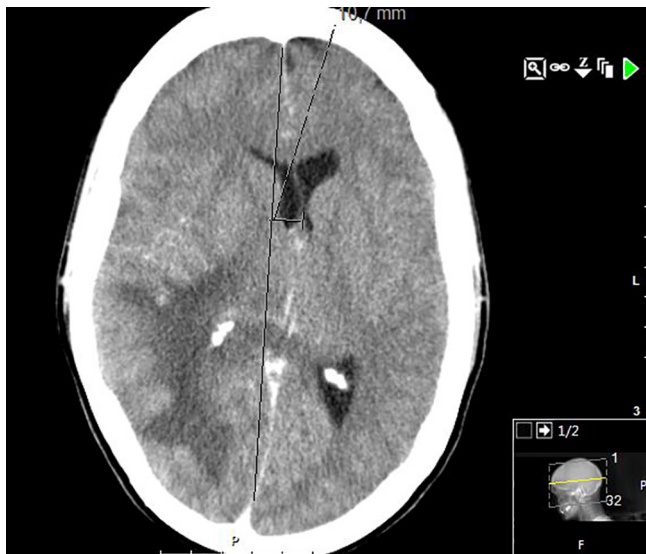
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**Fig. 1.** CAT scan of the brain shows a large 50 × 20 × 30 mm right sided tumour (dark area) with central necrosis located in the temporal, parietal and occipital lobes. Note the 10 mm deviation of the midline to the left with compression of the ventricular system. The small picture shows the lateral view of the sectional image.

were detected annual percentage changes (APC) and 95% confidence intervals (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.

## Results

### Case-report

A female case aged 53 years was in 2006 diagnosed with PCNSL of diffuse large B-cell type. According to CAT scan it was a multilobular tumour with central necrosis located in the right temporo-parieto-occipital region, see Fig. 1. There was a 10 mm deviation of the brain midline to the left with compression of the ventricular system. The patient was treated with primary surgery, chemotherapy, autologous bone marrow transplantation and local radiotherapy. She survived 5 years and 3 months.

The patient had since early 1990's used a GSM mobile phone (global system for mobile communication) in her administrative work. She used always her right hand and had no hands-free device. The mobile phone was provided by her employer and her cumulative use during working time was reported to be about 13,200 h (roughly 4 h per day). Fig. 2 shows the RF field superimposed on the CAT scan, based on calculations of depth of 900 MHz GSM mobile phone radiation [9, with courtesy].

### Incidence of NHL

In the Swedish Cancer Register the AAPC of the NHL incidence in men increased during 1970–2017 with 1.66%, 95% confidence interval (CI) + 1.40, +1.91%, with two joinpoints, in 1990 and 2005, Table 1 and Fig. 3. The corresponding result in women was +1.31%, 95% CI + 0.92, +1.70%, with two joinpoints, 1977 and 1988, Table 2 and Fig. 4. During the 1970's and 1980's a substantial statistically significant increase in the incidence was seen in both genders. In both men and women, the incidence increased statistically significant also during 2005–2017 and 1988–2017, respectively, but to a lower degree. Unfortunately, it is not possible to analyze the incidence of PCNSL using

the Swedish Cancer Register online database.

## Consequences of the hypothesis and discussion

This patient had a typical PCNSL of diffuse large B-cell type. She had no known risk factors such as HIV (tested HIV negative) or organ transplant. She underwent multidisciplinary treatment resulting in fairly long survival.

PCNLs in HIV-infected patients and organ transplant subjects are associated with Epstein-Barr virus (EBV) whereas interaction with EBV is uncommon in immunocompetent subjects [10]. Based on the questionnaire this patient did not report any pesticide exposure and she had no organ transplant or intake of immunosuppressive drugs.

The patient reported a reasonable amount of RF radiation exposure from a GSM hand-held mobile phone. She reported more than 13,000 h of total use, with a latency time (tumour induction period) of 15 years. She had worked all time at an employment office using a mobile phone provided by her employer as a working tool for about half time of the daily work. She used no protective measurements like a hands-free device or loudspeaker, and used the handheld phone the whole time at the same side of the brain where her PCNSL was diagnosed. About 50% of energy absorbed in the brain is within the temporal lobe and about 10% is absorbed in the parieto-occipital lobes from mobile phones marketed 2001 and later [11]. As seen in Fig. 2 her PCNSL developed in the most radiated area of the brain.

Pesticides and persistent organic pollutants are known risk factors for NHL, for overview see [12,13]. Some of these, like 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and polychlorinated biphenyls (PCBs), are immunosuppressive agents and an interaction with Epstein-Barr virus (EBV) has been shown for the risk of NHL [13–15].

### Biological aspects

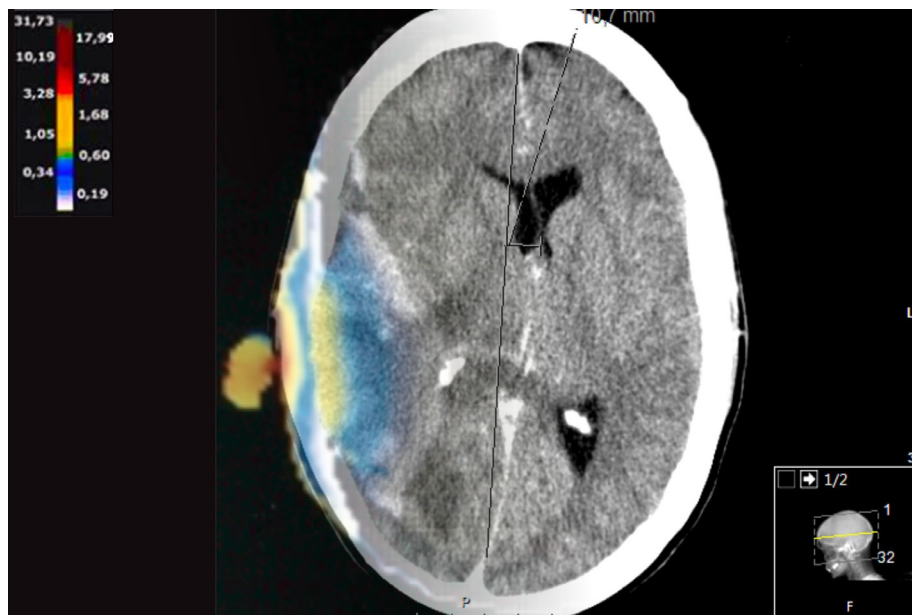
Exposure of glioma cells for 2 h to 27 or 2,450 MHz continuous-wave RF radiation in vitro modulated the rates of DNA and RNA synthesis. The alterations indicated effects on cell proliferation and were not caused by RF-induced cell heating. The dose response for either frequency of the radiation was biphasic. Exposure to specific absorption rate (SAR) of 50 W/kg or less stimulated whereas higher SAR suppressed DNA and RNA synthesis [16].

Whole human blood was exposed or sham-exposed in vitro for 2 h to 27 or 2,450 MHz RF radiation. Exposure to radiation at either frequency at specific absorption rates below 50 W/kg resulted in a dose-dependent, statistically significant increase of <sup>3</sup>H-TdR uptake, whereas exposure at 50 W/kg or higher suppressed <sup>3</sup>H-TdR uptake relative to that of sham-exposed cells. The biphasic, dose-dependent effects of the radiation on lymphocyte proliferation were not dependent on heating [17].

### Animal studies

Compared with 200 sham exposed rats a statistically significant increased incidence of primary malignant diseases combined at all sites ( $p = 0.005$ ) was found in exposed rats in the study by Chou et al [18]. Among the malignancies found in exposed rats were malignant lymphoma and thyroid cancer. SAR ranged from 0.144 W/kg to 0.4 W/kg depending on the rats' weight in this study on 200 rats exposed to 2,450 MHz pulsed RF radiation 21.5 h per day for 25 months. Thus, SAR was low compared to the International Commission on Non-Ionizing Radiation Protection (ICNIRP) guideline on SAR 2 W/kg to the brain for use of mobile phones [19].

In a study on mice carrying a lymphomagenic oncogene the lymphoma risk was statistically significantly higher in the exposed mice than in the controls [20]. The study included one hundred mice that were sham-exposed and 101 exposed for two 30-min periods per day for up to 18 months to 900 MHz pulsed RF radiation with power densities



**Fig. 2.** CAT scan of the brain with superimposed RF field (GSM 900 MHz) from a mobile phone held close to the right ear. Colour scale to the left shows SAR in Watts per kilogram (Om Gandhi with courtesy).

**Table 1**

Joinpoint regression analysis of age-standardized incidence rates per 100,000 in men, all ages, for NHL (ICD-7 codes 200 + 202) in the Swedish Cancer Register during 1970–2017. Two joinpoints detected (1990, 2005).

	Change/year (%)	95% CI
1970–2017*	+1.66	+1.40, +1.91
–1970–1990**	+3.40	+3.10, +3.70
–1990–2005**	–0.18	–0.68, +0.31
–2005–2017**	+1.10	+0.47, +1.73

\*AAPC (Average Annual Percent Change); \*\*APC (Annual Percent Change).

2.6–13 W/m<sup>2</sup> (SAR 0.008–4.2 W/kg, averaging 0.13–1.4 W/kg). These results were not replicated [21], but the latter study was criticized for using different study methods.

Mice were exposed to RF radiation; 0 (sham), 0.04, 0.4 and 2 W/kg SAR, and numbers of tumors of the lungs and livers in exposed animals were statistically significantly higher than in sham-exposed controls including numbers of malignant lymphoma [22]. A tumor-promoting effect by RF radiation was found at low to moderate levels (0.04 and 0.4 W/kg SAR), well below ICNIRP exposure limits for users of mobile phones [22].

#### National Toxicology program (NTP) study

In female mice exposed to GSM modulated cell phone RF radiation for 2 years there were increased incidences of malignant lymphoma in all exposed groups compared to the controls [23]. The increase was statistically significant in the 2.5 W/kg ( $p = 0.004$ ) and 5 W/kg groups ( $p = 0.035$ ). In the CDMA modulated cell phone RF radiation for 2 years the lymphoma incidence increased in female mice in all exposed groups compared to the controls, statistically significant in the 2.5 W/kg group ( $p = 0.035$ ).

No conclusive evidence of increased incidence of malignant lymphoma was reported in female rats in the NTP study [24];  $p$  trend = 0.537 for GSM modulated cell phone RF radiation and  $p$  trend = 0.339 for CDMA modulated cell phone RF radiation, see also a commentary on the results [25].

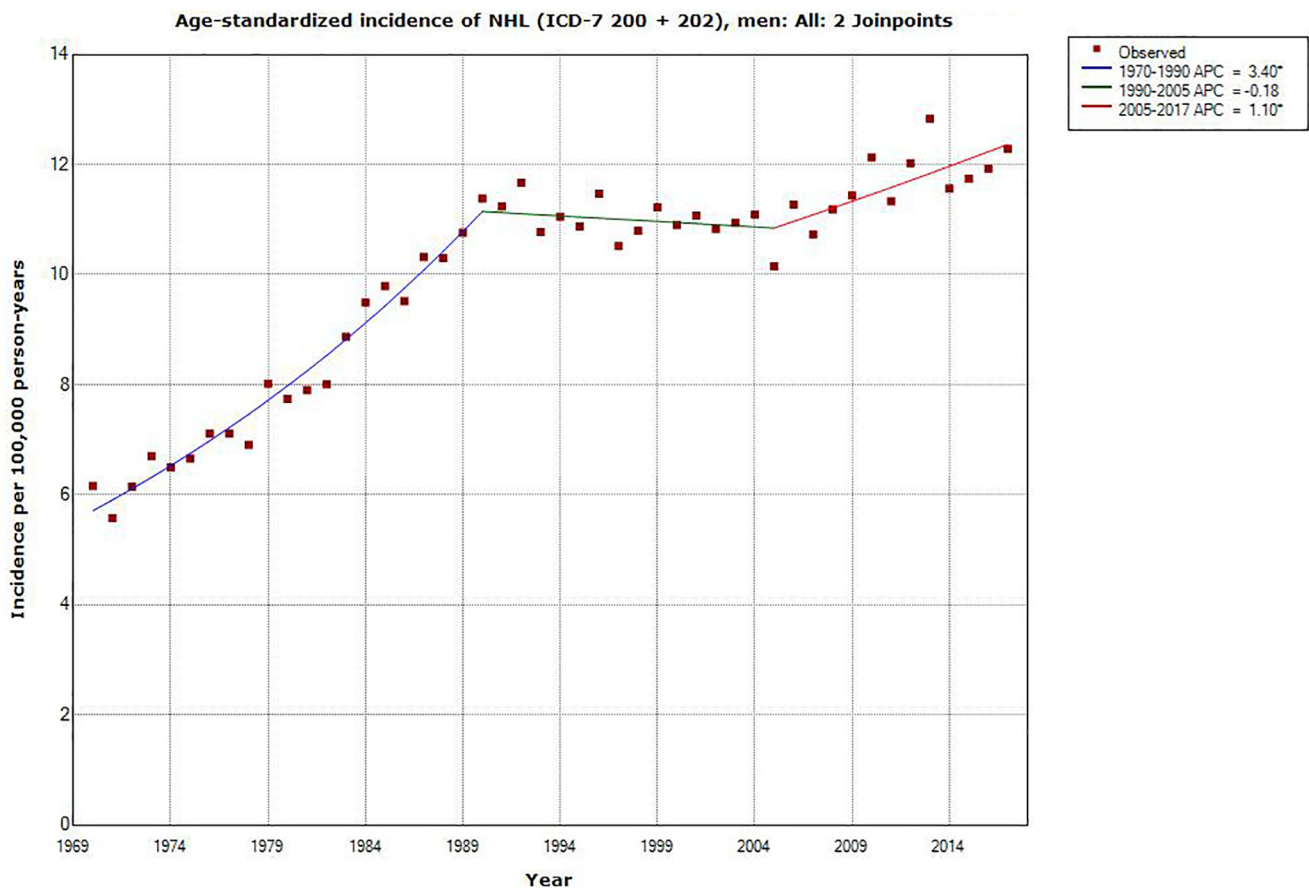
#### Human studies

No epidemiological studies on risk factors for PCNSL exists to our knowledge. Since it is a rare disease studies would be hampered by low numbers of cases. Few studies exist on malignant lymphoma overall and exposure to RF radiation. In a case-control study male and female subjects aged 18–74 years living in Sweden were included during a period from 1 December 1999 to 30 April 2002 [26]. Controls were selected from the national population registry. Exposure to different agents was assessed by questionnaire. In total, 910 (91%) cases and 1,016 (92%) controls participated.

NHL of the B-cell type was not associated with the use of cellular or cordless telephones. Regarding T-cell NHL and > 5 year latency period, the use of analogue cellular phones yielded: OR = 1.46, 95% CI = 0.58–3.70, digital: OR = 1.92, 95%; CI = 0.77–4.80 and cordless phones: OR = 2.47; 95% CI = 1.09–5.60.

The corresponding results for certain lymphoma, e.g. of the cutaneous and leukaemia T-cell types, were for analogue phones: OR = 3.41, 95%; CI = 0.78–15.0, digital: OR = 6.12, 95%; CI = 1.26–29.7 and cordless phones: OR = 5.48, 95%; CI = 1.26–23.9. The results indicated an association between T-cell NHL and the use of cellular and cordless telephones. The study was however based on low numbers and must be interpreted with caution. Regarding B-cell NHL no association was found [26].

A case-control study in USA used a questionnaire to assess cellular telephone use in 551 NHL cases and 462 frequency-matched population controls [27]. Compared to persons who had never used cellular telephones, the risk was not increased among regular users, OR = 0.9, 95% CI = 0.6–1.4. Among regular users compared to those who had never used hand-held cellular telephones, the risk of NHL was not statistically significantly associated with minutes per week, duration, cumulative lifetime or year of first use, although NHL was non-significantly higher in men who used cellular telephones for more than 8 years; OR = 2.4, 95% CI = 0.8–7.0. NHL not otherwise specified was statistically significantly increased in men using mobile phone with  $\geq 6$  years duration, OR = 4.4, 95% CI = 1.3–14.6. Little evidence linked use of cellular telephones with total, diffuse large B-cell lymphoma or follicular NHL. No results were presented for T-cell lymphoma.



\* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level. Final Selected Model: 2 Joinpoints.

**Fig. 3.** Jointpoint regression analysis of age-standardized incidence rates per 100,000 in men, all ages, for NHL (ICD-7 codes 200 + 202) in the Swedish Cancer Register during 1970–2017. ([https://sdb.socialstyrelsen.se/if\\_can/val.aspx](https://sdb.socialstyrelsen.se/if_can/val.aspx)).

**Table 2**  
Jointpoint regression analysis of age-standardized incidence rates per 100,000 in women, all ages, for NHL (ICD-7 codes 200 + 202) in the Swedish Cancer Register during 1970–2017. Two joinpoints detected (1977, 1988).

	Change/year (%)	95% CI
1970–2017*	+1.31	+0.92, +1.70
–1970–1977**	–0.11	–1.94, +1.75
–1977–1988**	+4.42	+3.30, +5.55
–1988–2017**	+0.49	+0.27, +0.71

\*AAPC (Average Annual Percent Change); \*\*APC (Annual Percent Change).

*Incidence of NHL in the Swedish Cancer Register*

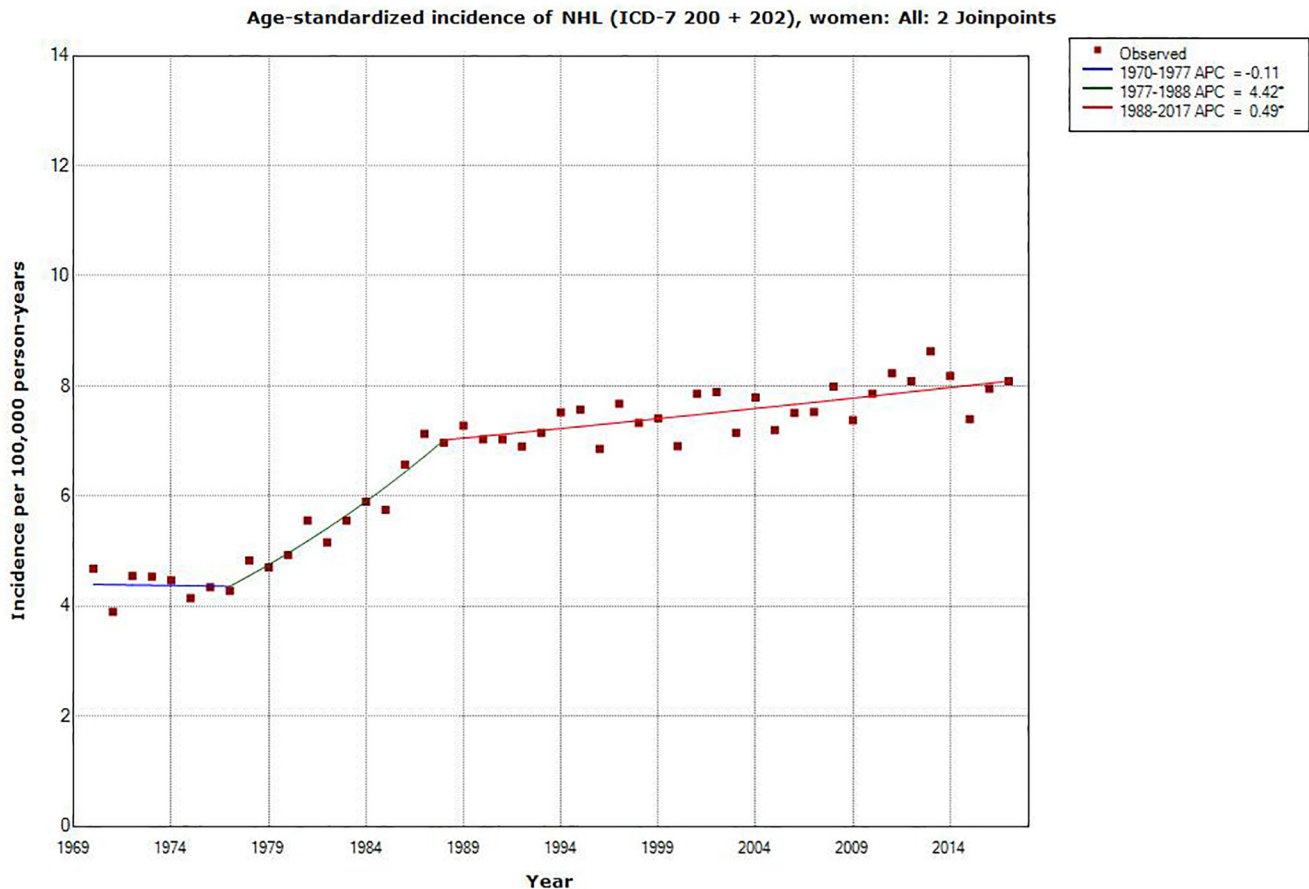
In men the incidence of NHL increased sharply during 1970–1990 with APC + 3.40, 95% CI + 3.10, +3.70%. In women the highest increase was seen during 1977–1988 with APC + 4.42%, 95% CI + 3.30, +5.55%. Thus, these results are similar in both genders. The high APC during these time periods may be explained by exposure to certain pesticides and persistent organic pollutants that were banned during the 1970’s [28]. Phenoxy herbicides (2,4,5-T) and chlorophenols that have been associated with NHL risk were banned on the Swedish market in 1977 and 1978, respectively [28]. Regulations of the use of some toxic persistent organic substances in the 1970’s has resulted in lower contamination of the food chain [29]. Thus, reduced exposure due to regulations to certain toxic chemicals may explain the lower increasing incidence during the last three decades.

The increasing incidence of NHL was lower in the last time period in

our study, although still statistically significant. The increase may partly be explained by exposure to other chemical agents such as the widely used herbicide glyphosate that has been indicated to increase the NHL risk [30,31]. Immunological impairment is a contributing risk factor to NHL. During the last three decades exposure to RF radiation has increased substantially which may have some detrimental effects on the immune system and thus contribute to the increasing incidence. Thus, it cannot be excluded that RF radiation is a risk factor for NHL. PCNSL is a rare disease and incidence data cannot be studied by using the Swedish Cancer Register. Instead the Swedish Lymphoma Register was used by Eloranta et al. [3].

RF radiation may suppress the immune system, for example through the human Vitamin-D receptor and its ligand, which is reported to be associated with many chronic inflammatory and autoimmune diseases [32]. Other studies report that long lasting low exposure to RF radiation in rats down to 2500 μW/m<sup>2</sup> and SAR-values as low as 600 μW/kg can induce oxidative stress, with lowered antioxidant levels and increased free radicals, an inflammatory response through increase in pro-inflammatory cytokines and DNA damage [33–35]. Of interest is a recent article that stated: “In conclusion, 900-, 1800-, and 2100-MHz RFR [radiofrequency radiation] emitted from mobile phones may cause oxidative damage, induce increase in lipid peroxidation, and increase oxidative DNA damage formation in the frontal lobe of the rat brain tissues. Furthermore, 2100-MHz RFR may cause formation of DNA single-strand breaks.” [36]. Thus, immunological impairment and oxidative damage from RF radiation may be of etiologic importance in NHL.

RF radiation from GSM 915 MHz and UMTS 1,947 MHz on human lymphocytes showed a long-lasting inhibition of DNA repair foci. The



**Fig. 4.** Joinpoint regression analysis of age-standardized incidence rates per 100,000 in women, all ages, for NHL (ICD-7 codes 200 + 202) in the Swedish Cancer Register during 1970–2017. ([https://sdb.socialstyrelsen.se/if\\_can/val.aspx](https://sdb.socialstyrelsen.se/if_can/val.aspx)).

exposure from UMTS had the highest effect [37]. Mesenchymal stem cells can be more sensible to RF radiation than differentiated cells and the capacity to repair DNA double-strand breaks was more affected in stem cells than in fibroblasts from humans [38].

A study on two groups of rats exposed to 1.4 mW/cm<sup>2</sup> RF radiation 1,800 MHz from a mobile phone base station positioned 8 m away for 5 weeks showed an increase in white blood cell counts where the lymphocytes increased 50–100% and the neutrophils decreased about 40% compared to a control group [39].

Three studies from India on people living near mobile phone base stations compared to people living further away showed a higher frequency of micronuclei, induced DNA damage and lowering of antioxidant levels in blood lymphocytes [40–42]. DNA unrepaired damage may lead to genomic instability and in the long run induction of cancer [40].

## Conclusions

No etiologic factor has clearly been defined to explain the increasing incidence of brain lymphoma. However, it has occurred during a time period when RF radiation to the brain from wireless phones has increased. Based on human epidemiology studies and laboratory studies there is evidence that malignant lymphoma may be related to exposure to RF radiation. This case-report stimulates the hypothesis that the increasing incidence of PCNSL may be caused by exposure to RF fields.

The effects from RF radiation through DNA damage and decreased DNA repair, by oxidative stress in the cells and increase in pro-inflammatory cytokines are some possible pathways that may influence

the immune system and the lymphocytes. RF radiation from a mobile phone held near the right ear during 4 h per working day during 15 years may have had an impact on the development of the PCNSL in this female case report.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Ethics approval and consent to participate

The study was approved by the ethics committee: Regional Ethics Committee, Uppsala University; Uppsala, Sweden. DNR 2005:367.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://>

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