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Use of cellular or cordless telephones and the risk for non-Hodgkin's lymphoma

Received: 25 October 2004 / Accepted: 13 April 2005
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Abstract *Objectives:* To evaluate the use of cellular and cordless telephones as the risk factor for non-Hodgkin's lymphoma (NHL). *Methods:* Male and female subjects aged 18–74 years living in Sweden were included during a period from 1 December 1999 to 30 April 2002. Controls were selected from the national population registry. Exposure to different agents was assessed by questionnaire. *Results:* In total, 910 (91%) cases and 1016 (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: odds ratio (OR) = 1.46, 95%; confidence interval (CI) = 0.58–3.70, digital: OR = 1.92, 95%; CI = 0.77–4.80 and cordless phones: OR = 2.47; CI = 1.09–5.60. The corresponding results for certain, e.g. cutaneous and leukaemia, T-cell lymphoma for analogue phones were: 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. *Conclusions:* The results indicate an association between T-cell NHL and the use of cellular and cordless telephones, however based on low numbers and must be interpreted with caution. Regarding B-cell NHL no association was found.

Keywords T-cell · B-cell lymphoma · Microwaves · Risk factors · Cellular · Cordless phones

Introduction

Non-Hodgkin's lymphoma (NHL) is a heterogeneous group of lymphoid malignancies, where new classification systems based on immunohistochemistry, cytogenetics and evolving knowledge in clinical presentation and course has led to modern classification systems (Jaffe et al. 2001). Today, it is therefore more adequate to discuss NHL as many different diseases that share some features but also differ in several aspects.

Interest in the etiology of NHL has been strengthened by an observed substantial increase in the incidence of the disease from the 1960s to the 1990s reported from most countries with reliable cancer registries. The established risk factors for development of NHL include different immunosuppressive states, e.g. HIV, autoimmune diseases as Sjögren's syndrome and SLE, immunodepressants used after organ transplantation and some inherited conditions (Hardell and Axelson 1998). Exposure to certain persistent organic pollutants, pesticides and organic solvents has been implicated to be of etiologic significance (Hardell and Eriksson 1999; Hardell et al. 2001). An interaction between Epstein-Barr virus (EBV) and pesticides has been shown in some studies (Rothman et al. 1997; Nordström et al. 1999; Nordström et al. 2000).

The increasing incidence of NHL has clearly levelled off in many countries since the early 1990s, i.e. in Sweden, Denmark and the USA (Hardell and Eriksson

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2003). This may be explained by the decreasing exposure to certain risk factors such as PCB and dioxins in the population since the 1980s (Hardell and Eriksson 2003).

An increased incidence of lymphoma was found in genetically engineered mice exposed to pulsed 900 MHz RF radiation (Repacholi et al. 1997). However, these results were not replicated in a more recent study (Uteridge et al. 2002). Induction of micronuclei in human lymphocytes exposed in vitro to microwave radiation has been reported (Zotti-Martelli et al. 2000; Tice et al. 2002). In a recent study, 900 MHz continuous wave induced DNA breaks and activation of apoptotic pathways, and genes involved in pro-survival signalling in T-lymphoblastoid leukaemia cells (Marinelli et al. 2004). Several studies have shown that exposure to electromagnetic fields (EMF) may induce chromosomal aberrations in human lymphocytes (Garaj-Vrhovac et al. 1992; Maes et al. 1993; Gadhia et al. 2003; Mashevich et al. 2003).

The increasing use of cellular telephones has caused concern of an increased risk for different diseases, e.g. brain tumours. Certainly the lymphoma findings in experimental studies warrant further studies regarding human beings.

Radio frequency (RF) signals are transmitted and received in the range of 400–2000 MHz during cellular phone calls. In Sweden, the analogue (Nordic Mobile Telephone; NMT) system was introduced in 1981 which operated at 450 MHz. Typically in the beginning, these phones were used in a car with external antenna, but from 1984 the first portable analogue phones were available. In Sweden, the analogue 900 MHz system started in 1986, but was closed down in 2000.

The digital system (Global System for Mobile Communication; GSM) started in 1991 and grew commercially from 1992 to be the most common phone at the end of the 1990s, in Sweden.

Use of cordless phones started in Sweden in 1988. Initially, the analogue system in the 800–900 MHz RF range was used. From 1991 digital cordless telephones (DECT) that operate at 1 900 MHz were available.

We have performed a new case-control study to further evaluate the relation between exposure to pesticides and other chemicals and NHL. Similar questions regarding the use of cellular and cordless telephones as in our previous study on brain tumours (Hardell et al. 2003a) were included in the questionnaire. This paper describes the results for use of cellular or cordless telephones.

Materials and methods

The study covered four (Umeå, Örebro, Linköping, Lund) out of seven health service regions in Sweden and data were collected during a period from 1 December 1999 to 30 April 2002. Regarding recruitment of cases and controls administrative collaboration was established

with another research group, which ran a parallel study on NHL during the same time in Sweden and Denmark.

Cases

All consecutive patients aged 18–74 years with newly diagnosed NHL, identified through physicians treating lymphoma and through pathologists diagnosing the disease, were approached. On their acceptance to participate, they were included as preliminary cases, and went through the data assessment procedure described below. All of the diagnostic pathological specimens were scrutinised by a panel of five Swedish expert lymphoma-reference pathologists, if they were not initially judged by one of these five. Therefore, some preliminary cases could later be excluded if a NHL diagnosis was not verified, and in those occasions all collected exposure information was disregarded. The pathologists also subdivided all NHL cases according to the WHO classification (Jaffe et al. 2001), to enable etiological analyses also for the different diagnostic NHL entities.

Controls

From registries covering the whole Swedish population, randomly chosen controls living in the same health service regions as of the cases were recruited during several occasions within the study period. The controls were frequency-matched to the cases and chosen within 10 years age groups to approximately mirror the age and sex distribution of the included cases, as to increase efficacy in the adjusted analyses. On their acceptance to participate, they were included as controls.

Assessment of exposure

The study was approved by the ethics committees and was performed in accordance with the ethical standards laid down by the Helsinki Declaration. All included persons had the possibility to refuse participation. All who gave their consent to participate received a comprehensive questionnaire by mail, which was sent out shortly after the subjects had been telephone-interviewed by the other research group with which we had administrative collaboration as stated above. Their interview, however, was a separate one from ours and did not focus on the questions relevant in our study such as work environment, chemical exposure or use of cellular and cordless phones, but rather dealt with other life style factors and diseases. Thus, the aims of these studies did not overlap each other. Specially trained interviewers scrutinised the answers and collected additional exposure information by phone if important data were lacking, incomplete or unclear. These interviewers were blinded with regard to case or control status. Telephone

interviews related to the whole questionnaire were performed for 12 cases and 13 controls who disagreed to fill in the questionnaire but still agreed to participate.

Regarding cellular telephones, questions were asked on type of phone and years of use. Also, the first part of the phone number (prefix) was asked for so as to check if it was an analogue (010) or digital (07) phone. Mean number of daily calls and minutes were asked for and after that cumulative use in hours for all years was calculated. Data were also collected on use in a car with fixed external antenna or a hands-free device with an earpiece outside a car, both taken as no exposure to microwaves. One of the questions was about the ear most frequently used during cellular phone calls or whether both the ears were equally used.

Regarding cordless phones the years of use, mean number of minutes per day and the ear used were asked for in the same way.

Subjects who started their use of a mobile or cordless phone within one year prior to diagnosis were regarded as unexposed. Thereby, the year for recruitment to the study was used for the controls. Cumulative exposure was calculated in hours from the first year of use up to the year before diagnosis. If the first year was apparently incorrect, i.e. before the use of respective phone was on the market, this was corrected during the interviews and coding of exposure.

Statistical methods

Unconditional logistic regression analysis was used to calculate odds ratios (OR) and 95% confidence intervals (CI), (Stata/SE 8.2 for Windows; StataCorp, College Station, TX). The material was divided into two groups, exposed and unexposed regarding the use of cellular and cordless telephones. The exposed cases and controls were further divided according to phone type: analogue,

digital and cordless. It is to be noted that a person may have been using more than one type of telephone. The unexposed group consisted of cases and controls without exposure to cellular or cordless telephones. Adjustment was made for age, sex and year of diagnosis (cases) or enrolment (controls). When analysing the material separately for B-cell NHL and T-cell NHL, all controls were used in both groups. In the dose-response calculations, median number of hours of use among controls was used as the cut-off. By grouping the use of the different phones into three categories of latency, >1–5 years, >5–10 years and >10 years, trend test for latency period was performed.

Results

In total, 1163 cases were reported from the participating clinics. Of these, 46 could not participate due to medical conditions, 88 died before they could be interviewed, 3 were not diagnosed during the study period, 1 lived outside the study area and 30 were excluded not being NHL (Hodgkin's disease: 20, acute lymphoblastic leukaemia: 1, other malignancy: 7 and unclear diagnosis: 2).

Of the finally included 995 cases with NHL, 910 participated in the study (91%). Of these, 819 were B-cell NHL, 53 T-cell and 38 unspecified. Among the 1108 initially enrolled controls, 92 did not respond to the mailed questionnaire, resulting in 1016 (92%) controls to be included in the analyses. The medium and median age in cases were 60 and 62 years and in controls it was 58 and 60 years, respectively. Of the cases, 534 were male and 376 female compared with 592 male and 424 female controls.

Use of cellular and cordless telephones is displayed in Table 1. Cases with T-cell lymphoma had used these phone types more frequently than the controls whereas this was not found for B-cell and unspecified NHL.

Table 1 Use of cellular and cordless telephones among cases and controls. Unexposed did not use any of these phone types. Numbers and percentage are given for all NHL and some subtypes

Diagnosis	Number	Analogue	Digital	Cordless	Unexposed
Cases, all NHL	910	159 (17.5%)	471 (51.8%)	353 (38.8%)	303 (33.3%)
B-cell NHL	819	141 (17.2%)	422 (51.5%)	313 (38.2%)	278 (33.9%)
Other not specified	38	4 (10.5%)	18 (47.4%)	15 (39.5%)	12 (31.6%)
T-cell NHL	53	14 (26.4%)	31 (58.5%)	25 (47.2%)	13 (24.5%)
Lymphoblastic lymphoma	6	2 (33.3%)	4 (66.7%)	3 (50.0%)	0 (0%)
Large granular lymphocytic leukemia	1	0 (0%)	1 (100%)	0 (0%)	0 (0%)
Mycosis fungoides/Sézary syndrome	5	1 (20.0%)	2 (40.0%)	3 (60.0%)	1 (20.0%)
Peripheral T-cell lymphoma not specified	5	3 (60.0%)	2 (40.0%)	2 (40.0%)	1 (20.0%)
Angioimmunoblastic lymphoma	4	1 (25.0%)	2 (50.0%)	2 (50.0%)	2 (50.0%)
Nasal type T/NK-cell lymphoma	2	0 (0%)	2 (100%)	1 (50.0%)	0 (0%)
Intestinal T-cell lymphoma	4	1 (25.0%)	2 (50.0%)	0 (0%)	2 (50.0%)
Anaplastic large T-cell lymphoma	14	4 (28.6%)	10 (71.4%)	9 (64.3%)	3 (21.4%)
Subcutaneous panniculitic T-cell lymphoma	2	0 (0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)
Primary skin CD30-positive T-cell lymphoproliferation	2	1 (50.0%)	2 (100%)	2 (100%)	0 (0%)
Unspecified low-grade T-cell lymphoma	2	0 (0%)	1 (50.0%)	0 (0%)	1 (50.0%)
Unspecified high-grade T-cell lymphoma	2	1 (50.0%)	1 (50.0%)	1 (50.0%)	0 (0%)
Unspecified T-cell lymphoma	4	0 (0%)	1 (25.0%)	1 (25.0%)	2 (50.0%)
Controls	1,016	178 (17.5%)	559 (55.0%)	420 (41.3%)	321 (31.6%)

Table 2 Odds ratio (OR) and 95% confidence interval (CI) for use of cellular and cordless telephones and the risk of B-cell non-Hodgkin's lymphoma ($n=819$ cases). Numbers of exposed cases (Ca) and controls (Co) are given. Dose-effect calculations were

made with median number of use in hours among controls as the cut-off. Unconditional logistic regression analysis adjusted for age, sex and year of diagnosis (cases) or enrolment (controls)

	> 1 year latency period			> 5 year latency period			> 10 year latency period		
	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI
Analogue									
450 MHz	72/103	0.81	0.55–1.18	68/93	0.85	0.57–1.25	48/62	0.93	0.60–1.47
900 MHz	97/113	1.08	0.75–1.56	86/96	1.16	0.79–1.71	40/52	0.96	0.59–1.56
all	141/178	0.94	0.68–1.30	131/156	1.02	0.73–1.43	74/95	0.96	0.65–1.42
≤ 198 h	61/89	0.82	0.56–1.22	54/68	0.97	0.64–1.48	21/29	0.89	0.49–1.64
> 198 h	80/89	1.08	0.73–1.59	77/88	1.07	0.72–1.59	53/66	0.99	0.64–1.55
Digital	422/559	1.02	0.81–1.28	133/184	0.92	0.66–1.27	7/8	1.13	0.38–3.35
≤ 91 h	223/298	0.98	0.76–1.26	28/51	0.68	0.41–1.12	1/1	1.34	0.08–22.1
> 91 h	199/261	1.09	0.82–1.45	105/133	1.05	0.73–1.50	6/7	1.10	0.35–3.50
Cordless	313/420	1.01	0.80–1.28	121/157	0.96	0.70–1.32	34/39	1.07	0.64–1.78
≤ 243 h	135/211	0.85	0.64–1.13	28/53	0.62	0.37–1.03	4/7	0.68	0.19–2.40
> 243 h	178/209	1.19	0.90–1.58	93/104	1.15	0.81–1.63	30/32	1.15	0.67–1.99

In Table 2 OR and CI are given for B-cell NHL. No significantly increased or decreased risks were found. Further statistical analysis was performed on different subtypes of B-cell lymphoma with similar results (data not shown). Also for unspecified NHL ($n=38$) OR was close to unity in the different calculations.

Regarding T-cell NHL increased risk was found for analogue phones, OR = 1.56, 95%; CI = 0.64–3.81, however with no effect of different latency periods, P for trend = 0.93, and without a dose-effect response effect (Table 3). Also for digital telephones a somewhat increased OR was found with a tendency to influence latency period, P for trend = 0.29, and number of hours for use. Thus, for > 5 year latency period and > 91 h cumulative use, OR was calculated to 2.47, 95%; CI = 0.90–6.75. These findings were based on low numbers, especially regarding > 10 year latency period. Cordless telephones yielded OR = 1.36, 95%; CI = 0.65–2.86 increasing to OR = 3.15, 95%; CI = 1.05–9.48 for

> 10 year latency period, with a significant trend test, $P=0.01$.

It was of interest to further study certain T-cell NHL, e.g. of the cutaneous and leukaemia type, Table 4. This yielded increased OR for the studied phone types, highest for digital cellular telephones and cordless with an effect of latency period and dose-response. A latency period of more than 5 years yielded for digital cellular telephones: OR = 6.12, 95%; CI = 1.26–29.7 and for cordless telephones: OR = 5.48, 95%; CI = 1.26–23.9. As can be seen from Table 4 the ORs were further increased when the exposure time to the phones was taken into account. A dose-effect connection was seen when the median number of use in hours for controls was used as the cut-point. The OR for digital phone use and five year latency was then found to be at 8.73, 95%; CI = 1.55–49.1, and the corresponding values for cellular phone was: OR = 8.42, 95%; CI = 1.81–39.2.

Table 3 Odds ratio (OR) and 95% confidence interval (CI) for use of cellular and cordless telephones and the risk of T-cell non-Hodgkin's lymphoma ($n=53$). Numbers of exposed cases (Ca) and controls (Co) are given. Dose-effect calculations were made with

median number of use in hours among controls as the cut-off. Unconditional logistic regression analysis adjusted for age, sex and year of diagnosis (cases) or enrolment (controls)

	> 1 year latency period			> 5 year latency period			> 10 year latency period		
	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI
Analogue									
450 MHz	5/103	0.95	0.30–2.99	5/93	1.04	0.33–3.28	3/62	0.99	0.25–3.95
900 MHz	9/113	1.48	0.53–4.14	7/96	1.33	0.44–3.99	4/52	1.36	0.37–4.95
all	14/178	1.56	0.64–3.81	12/156	1.46	0.58–3.70	7/95	1.47	0.50–4.33
≤ 198 h	8/89	1.81	0.66–4.95	6/68	1.74	0.58–5.25	3/29	2.24	0.54–9.31
> 198 h	6/89	1.30	0.43–3.90	6/88	1.26	0.42–3.76	4/66	1.17	0.33–4.13
Digital	31/559	1.41	0.68–2.92	14/184	1.92	0.77–4.80	1/8	3.00	0.26–34.1
≤ 91 h	16/298	1.37	0.63–3.00	2/51	1.02	0.22–4.81	0/1	–	–
> 91 h	15/261	1.48	0.62–3.54	12/133	2.47	0.90–6.75	1/7	3.30	0.29–38.0
Cordless	25/420	1.36	0.65–2.86	17/157	2.47	1.09–5.60	6/39	3.15	1.05–9.48
≤ 243 h	12/211	1.30	0.56–3.04	6/53	2.36	0.81–6.93	2/7	4.98	0.87–28.7
> 243 h	13/209	1.43	0.61–3.32	11/104	2.53	1.03–6.21	4/32	2.68	0.77–9.34

Table 4 Odds ratio (OR) and 95% confidence interval (CI) for use of cellular and cordless telephones and the risk for certain T-cell non-Hodgkin's lymphoma ($n=23$). Numbers of exposed cases (Ca) and controls (Co) are given. Dose-effect calculations were made with median number of use in hours among controls as the cut-off. Unconditional logistic regression analysis adjusted for age, sex and year of diagnosis (cases) or enrolment (controls). The studied types

were lymphoblastic lymphoma/leukemia ($n=6$), large granular lymphocytic leukemia ($n=1$), mycosis fungoides/Sézary syndrome ($n=5$), peripheral T-cell lymphoma not specified ($n=5$), nasal type T/NK-cell lymphoma ($n=2$), subcutaneous panniculitic T-cell lymphoma ($n=2$), primary skin CD30-positive T-cell lymphoproliferation ($n=2$)

	> 1 year latency period			> 5 year latency period			> 10 year latency period		
	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI
Analogue									
450 MHz	3/103	2.57	0.43–15.3	3/93	2.77	0.47–16.4	2/62	3.83	0.49–29.9
900 MHz	4/113	2.43	0.45–13.1	4/96	3.05	0.55–16.8	1/52	1.62	0.14–19.1
all	7/178	3.03	0.69–13.3	7/156	3.41	0.78–15.0	3/95	3.34	0.55–20.2
≤ 198 h	2/89	1.94	0.29–13.0	2/68	2.56	0.38–17.3	0/29	–	–
> 198 h	5/89	3.88	0.82–18.4	5/88	3.92	0.83–18.6	3/66	4.53	0.72–28.3
Digital	14/559	3.21	0.84–12.3	7/184	6.12	1.26–29.7	0/8	–	–
≤ 91 h	7/298	3.03	0.74–12.4	1/51	3.00	0.29–31.4	0/1	–	–
> 91 h	7/261	3.59	0.78–16.6	6/133	8.73	1.55–49.1	0/7	–	–
Cordless	12/420	3.40	0.88–13.1	7/157	5.48	1.26–23.9	3/39	8.55	1.38–52.8
≤ 243 h	6/211	3.33	0.78–14.3	1/53	1.86	0.18–19.3	1/7	12.6	0.95–168
> 243 h	6/209	3.47	0.80–15.1	6/104	8.42	1.81–39.2	2/32	7.44	1.02–54.5

Table 5 Odds ratio (OR) and 95% confidence interval (CI) for different combinations of use of cellular and cordless telephones and the risk of non-Hodgkin's lymphoma, total, B-cell and T-cell.

Numbers of exposed cases (Ca) and controls (Co) are given. Unconditional logistic regression analysis adjusted for age, sex and year of diagnosis (cases) or enrolment (controls)

	> 1 year latency period			> 5 year latency period			> 10 year latency period		
	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI
Total									
Analogue only	18/21	0.90	0.46–1.75	14/14	1.05	0.49–2.25	9/6	1.54	0.54–4.42
Digital only	174/196	1.04	0.79–1.38	36/47	0.85	0.52–1.39	2/1	2.32	0.20–26.4
Cordless only	107/99	1.20	0.87–1.65	32/35	0.99	0.60–1.65	9/5	2.05	0.67–6.25
Analogue + digital	130/141	1.02	0.73–1.44	123/131	1.04	0.73–1.46	70/85	0.91	0.61–1.36
Analogue + cordless	79/99	0.86	0.59–1.26	72/94	0.84	0.57–1.24	42/64	0.72	0.45–1.13
Digital + cordless	235/305	0.97	0.74–1.26	139/177	0.92	0.67–1.26	36/37	1.04	0.62–1.75
Analogue + digital + cordless	68/83	0.91	0.60–1.37	62/81	0.85	0.56–1.30	39/58	0.74	0.46–1.19
Total, any combination	607/695	1.06	0.87–1.31	306/359	0.95	0.74–1.22	116/125	1.01	0.72–1.42
B-cell									
Analogue only	16/21	0.89	0.45–1.77	12/14	1.00	0.45–2.22	9/6	1.72	0.60–4.96
Digital only	155/196	1.01	0.76–1.35	32/47	0.84	0.51–1.39	1/1	1.32	0.08–21.8
Cordless only	95/99	1.15	0.83–1.60	29/35	0.98	0.58–1.65	7/5	1.75	0.54–5.65
Analogue + digital	117/141	1.03	0.72–1.46	112/131	1.06	0.74–1.51	64/85	0.93	0.62–1.41
Analogue + cordless	68/99	0.82	0.55–1.23	64/94	0.83	0.55–1.24	36/64	0.69	0.43–1.11
Digital + cordless	210/305	0.96	0.73–1.26	124/177	0.90	0.65–1.25	30/37	0.97	0.57–1.66
Analogue + digital + cordless	60/83	0.90	0.59–1.37	56/81	0.86	0.56–1.32	34/58	0.73	0.44–1.19
Total, any combination	541/695	1.03	0.83–1.27	275/359	0.95	0.73–1.22	102/125	0.99	0.70–1.40
T-cell									
Analogue only	1/21	0.89	0.11–7.48	1/14	1.32	0.15–11.3	0/6	–	–
Digital only	10/196	1.46	0.58–3.64	2/47	0.95	0.19–4.69	0/1	–	–
Cordless only	6/99	1.55	0.56–4.28	3/35	2.03	0.54–7.62	2/5	8.72	1.43–53.3
Analogue + digital	11/141	1.54	0.58–4.13	9/131	1.27	0.46–3.51	6/85	1.41	0.45–4.41
Analogue + cordless	9/99	1.83	0.67–5.05	7/94	1.49	0.51–4.39	6/64	1.81	0.58–5.61
Digital + cordless	17/305	1.14	0.49–2.66	13/177	1.68	0.67–4.21	5/37	2.50	0.76–8.22
Analogue + digital + cordless	7/83	1.65	0.54–5.03	5/81	1.18	0.35–3.95	5/58	1.60	0.48–5.34
Total, any combination	40/695	1.47	0.74–2.90	25/359	1.58	0.74–3.38	12/125	2.05	0.81–5.17
T-cell, certain, e.g. cutaneous/leukaemia types									
Analogue only	1/21	2.39	0.22–26.2	1/14	3.23	0.28–36.7	0/6	–	–
Digital only	5/196	4.67	0.90–24.1	2/47	8.40	0.85–83.4	0/1	–	–
Cordless only	3/99	3.23	0.61–17.2	0/35	–	–	0/5	–	–
Analogue + digital	4/141	2.21	0.41–11.7	4/131	2.28	0.43–12.0	2/85	2.86	0.36–22.6
Analogue + cordless	4/99	4.07	0.74–22.4	4/94	4.27	0.77–23.6	3/64	5.39	0.83–34.9
Digital + cordless	7/305	2.43	0.53–11.1	5/177	3.77	0.72–19.6	3/37	10.7	1.61–70.7
Analogue + digital + cordless	2/83	2.34	0.31–17.7	2/81	2.35	0.31–17.7	2/58	3.65	0.46–28.7
Total, any combination	20/695	3.71	1.04–13.2	12/359	3.58	0.91–14.1	6/125	4.85	0.999–23.5

In Table 5, the results for different combinations of use of cellular and cordless telephones are displayed. Except for the use of analogue (NMT) phones only, increased OR was found for T-cell NHL, although not significantly so. Several of the calculations were based on low numbers. Use of cellular and cordless phones in any combination yielded for T-cell NHL for >1 year latency period: OR = 1.47, 95%; CI = 0.74–2.90, and for >10 year latency period increasing to: OR = 2.05, 95%; CI = 0.81–5.17. For certain T-cell lymphoma, e.g. cutaneous/leukaemia, the >1 year latency period use of any phone type yielded: OR = 3.71, 95%; CI = 1.04–13.2 and for >10 year latency period: OR = 4.85, 95%; CI = 0.999–23.5.

In several publications, exposure to herbicides has been reported to be a risk factor for NHL (Hardell et al. 2003b). We analysed a potential interaction between herbicide exposure and use of cellular or cordless phones, however without any tendency for that (data not shown).

Discussion

In this study, cases were consecutively recruited from the participating clinics and pathology departments as soon as histopathological diagnosis was obtained. Thus, it was possible to include the cases soon after diagnosis. This is of advantage since, patients with a rapid progress of the disease could also be included. In spite of this, 134 cases were excluded since they were too ill or had died before interview. However, excluding the 134 cases would bias any risk increase towards unity since it is unlikely that a risk factor is preventive in a subgroup of patients with bad prognosis. A panel of pathologists reviewed all available diagnostic tissue specimens so as to have the cases classified according to modern diagnostic criteria. Thus in the analysis, we could make calculations for different entities of NHL.

All case-control studies may be limited by different kinds of bias. The study was designed to minimise this problem. Thus, using population controls recruited from the national population registry makes selection bias less likely. Blinding of case/control status in all data collection and coding of exposure avoided observation bias. Furthermore, the subtypes of NHL were not included until the statistical analysis. Recall bias may be introduced in a study if cases and controls have a different reason to remember certain types of exposure. In this study, the questionnaire contained a lot of other questions on, e.g. different jobs, chemical exposures, smoking habits etc. with no specific focus on cellular and cordless telephones. Furthermore, an association between these phone types and NHL has not at all been discussed in the society, and the risk of any recall bias seems to be minor.

B-cell neoplasms represent clonal proliferation of B-cells at various stages of differentiation, ranging from naïve B-cells to mature plasma cells. The anatomical sites vary at various stages, e.g. bone marrow, blood and germinal centres. T-cell lymphomas are derived from

mature or post-thymic T-cells. They have a more unfavourable course than B-cell NHL. Several subtypes are related to virus, i.e. EBV and human T-cell leukaemia virus (HTLV-1). T-cell lymphomas are uncommon and constituted 5.8% of the cases in this study. Thus, low numbers hampered statistical analyses in that group.

One result of this study was an increased risk for T-cell NHL in subjects who reported use of digital cellular or cordless telephones. With more than 5 year latency period the result was significant for cordless phones with a significant trend for increasing latency period. Also for digital phones, OR increased with latency period indicating some biological relevance of the finding. However, it should be noted that several of these calculations were based on low numbers and these results must be regarded as preliminary. Thus, they need to be confirmed in larger studies. The recruitment of cases was from 1 December 1999 until 30 April 2002. Further studies will give a longer period for use of both cellular and cordless phones yielding more subjects with longer tumour induction period. Regarding analogue phones a somewhat increased risk was found for T-cell lymphoma. No dose-response effect was seen and the result was similar for different latency periods.

Analysing e.g. cutaneous/leukaemia T-cell lymphoma increased the risk further. All cases except for one subject had used GSM cellular or cordless phones. Hence, they had used digital phones. The highest risk was found for use of GSM and cordless phones with >10 year latency period yielding OR = 10.7, 95%; CI = 1.61–70.7. Excluding peripheral T-cell lymphoma (n = 5) gave similar results. Four of these were located in the head and neck area (data not shown).

During calls with cellular or cordless phones, exposure to microwaves occurs mainly in the same area on the side of the head used for calls. An increased risk for brain tumours within that area has been indicated (Hardell et al. 2003a; Hansson Mild et al. 2003; Kundi et al. 2004). However, an increased risk for NHL is for biological reasons obscure. In this study, we found some association with T-cell NHL but not with the B-cell type. However, these types of NHL represent different disease entities. Furthermore, T-cell lymphomas are initiated from mature or post-thymic circulating T-cells. Thus, exposure to microwaves may occur in the circulating blood during phone calls. During a phone call about 30% of the microwaves are absorbed by the skin and subcutaneous tissue with highest exposure in the head and neck region, especially the area of the external ear. Naïve B-cells are small resting lymphocytes that circulate in the blood and occupy primary lymphoid follicles. However, we did not find any association between the use of cellular and cordless telephones and chronic lymphocytic leukaemia (data not shown) of interest is a potential association between EMF and leukaemia. Of course, interaction with other factors such as virus would be of interest to study.

It is important to note that several studies have shown chromosomal aberrations in human lymphocytes (Garaj-Vrhovac et al. 1992; Maes et al. 1993; Gadhia et al. 2003;

Mashevich et al. 2003). Genetic instability or increased proliferation of the stem cell population may be caused by exposure to microwaves as one hypothesis (Marinelli et al. 2004). However, there are also studies that do not support these findings although the recent REFLEX-studies give additional support for non-thermal biological effects from microwaves (REFLEX final report 2005). The risk increase would be lower for more differentiated clones such as nodular lymphoma. Our findings may give some support for that hypothesis regarding T-cell lymphoma. However, for different subtypes of B-cell lymphoma no increased risk was found. Furthermore, the results may have been confounded if use of cordless or cellular telephones is associated with another risk factor such as herbicides, i.e. more common in farmers. We have no information that farmers use these phone types more often than other groups in the society. In one analysis, we studied potential interaction between cellular and cordless phones and herbicide exposure without any such effect indicating no confounding.

We also analysed the risk for persons living in urban or rural area with the same method as in our case-control study on brain tumours (Hardell et al. 2005). This did not significantly change the results as presented above, neither for B-cell nor for T-cell lymphoma (data not shown). Thus, it is unlikely that occupations related to urban and rural living could explain the results.

A few animal studies exist in this area. A significantly increased incidence of lymphoma in mice exposed to 900 MHz pulsed microwaves was reported (Repacholi et al. 1997). These findings were however not replicated in a later study on mice exposed to 898.4 MHz pulsed microwaves (Utteridge et al. 2002). However, these findings have been criticised due to different experimental strategies (Hansson Mild et al. 2003; Kundi et al. 2004). A study on rats which were exposed to pulsed 2,450 MHz microwaves showed a statistically significant increase of primary malignancies with some excess of haematopoietic malignancies in the exposed group combining primary and metastatic disease (Chou et al. 1992).

Our main result was no increased risk for B-cell NHL associated with the use of cellular or cordless phones. However, the results regarding T-cell lymphoma are intriguing and deserve further studies. It should be noted that the same method was used for all studied subtypes of NHL. The results are not easily explained by bias or confounding and clearly not from a biological standpoint, and must be regarded as preliminary. Since T-cell lymphoma constituted only 5.8% of all NHL and widespread use of both cellular and cordless telephones dates to recent years an increased risk associated with the use of these phone types would not be detected as an increasing incidence of NHL at the present time.

Acknowledgements Supported by grant no 2001–0224 from FAS, Cancer-och Allergifonden, Nyckelfonden, Örebro University Hospital Cancer Fund. Ms Iréne Larsson participated in the data collection and Matz Eriksson performed interviews. We thank cytologist Edneia Tani and pathologists Måns Åkerman, Göran

Roos, Anna Porwit-MacDonald and Åke Öst for extensive review of the tumour material.

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