Chemical Substances and Biological Agents

Studies and Research Projects

REPORT **R-520**

Risk of Non-Hodgkin Lymphoma in Firemen

Douglas McGregor

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Legal Deposit
Bibliothèque et Archives nationales
2007
ISBN: 978-2-89631-175-2 (print format)
ISBN: 978-2-89631-176-7 (PDF)
Original Edition : ISBN: 978-2-89631-173-6
ISSN: 0820-8395

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Institut de recherche Robert-Sauvé
en santé et en sécurité du travail,
September 2007

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This study was financed by the IRSST. The conclusions and recommendations are those of the author.

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Non-Hodgkin Lymphoma

The term, "lymphoma," is widely used to describe a diverse group of neoplasms arising most often in lymphoid tissue. Apart from a very few neoplasms of uncertain malignant potential, all lymphomas are malignant and without treatment they usually limit the lifespan of the subject. Historically, lymphomas have been divided into Hodgkin disease (of which there are different types and are characterised by the presence of giant, mononuclear Hodgkin cells and giant, multinuclear Reed-Sternberg cells) and non-Hodgkin lymphoma (NHL). Within the category NHL, there are a large number of distinct diseases that have distinctive epidemiology, aetiology, clinical features and responses to therapy. The most recent, World Health Organisation (WHO, 2001), classification of haematological malignancies recognises three major categories of lymphoid neoplasms. These are: B cell neoplasms, T and NK cell neoplasms and Hodgkin lymphoma (Table 1). Both lymphoid leukaemia and lymphomas are included in this classification, the distinction between circulating and solid forms or phases of these neoplasms being considered artificial. In this classification, the peripheral T/NK cell and B-cell neoplasms are grouped according to their most typical clinical presentations: predominantly disseminated, leukaemic, primary extranodal lymphomas and predominantly nodal lymphomas (WHO, 2001).

Mature B-cell neoplasms comprise worldwide over 90% of lymphoid neoplasms and approximately 4% of new cancers each year. They are more common in developed countries, but particularly in Australia, Europe, New Zealand and North America. Of this group of neoplasms, the two most common are diffuse large B-cell lymphoma (incidence code 9680/3)[1], which comprises 30 – 40% of adult NHL in western countries (the proportion being even higher in developing countries) and follicular lymphoma (9690/3), which comprises about 35% of adult NHL in the USA and 22% worldwide (WHO, 2001). Both of these neoplasms arise predominantly in lymph nodes, but about one-third of diffuse large B-cell lymphomas arise almost anywhere (e.g., gastrointestinal tract, skin, brain, bone). Although follicular lymphoma may also be found in non-haematopoietic extra-nodal sites, this is usually in the context of widespread nodal disease. In epidemiological studies, however, these differences in diagnosis are seldom made, all of the subtypes being classified as NHL. At one extreme, some epidemiological publications refer to neoplasms of the lymphoid and haematopoietic system, with no attempt at a distinction, even at this level; others refer to lymphomas, which include both Hodgkin's disease and NHL, while others refer to NHL, which includes all types of lymphoma with the exclusion of Hodgkin's disease. This corresponds to the International Classification of Diseases, 8th or 9th editions (ICD-8 or ICD-9) mortality codes 200.0-200.8, 202.0-202.2, 202.8 and 202.9. Yet other publications make the distinction between lymphosarcoma or reticulum cell sarcoma (reticulosarcomas) and other lymphomas. This was the cytological division of NHL used before the Rappaport classification system (Rappaport, 1966) became the standard. While the pathology has progressed in the hands of experts through a succession of classification schemes (including Kiel, Lukes-Collins, Working Formulation, REAL[2] and FAB) right up to that of the WHO (WHO, 2001), the information available to the epidemiologists appears to be locked in an earlier era:

[1] These are the morphology codes of the International Classification of Diseases (ICD-O), third edition. Behaviour is coded /3 for malignant tumours and /1 for lesions of low or uncertain malignant potential

[2] REAL: Revised European-American Classification of Lymphoid Neoplasms. FAB: French-American-British morphological classification.

few publications in the epidemiological literature can make the distinctions described even in the earliest classification.

The incidence of NHL is increasing worldwide, with more than 280,000 new cases occurring annually, predominantly in more developed countries (52% of world total cases) where it is the seventh most common cancer (Stewart & Kleihues, 2003). There have been dramatic rises in the incidence since the 1970s, particularly in Western Europe, North America and Australia. The increases may have been partly reflecting better diagnosis or changing classification systems. Nevertheless, increases in NHL rates continue to occur worldwide and do not seem to have reached a maximum, according to trend predictions made on reliable data for 1973-1992 and assuming that the effect of environmental agents determining the trends will remain stable during the subsequent projection period (Bray et al., 2001). In contrast, mortality rates have, in general been declining as a consequence of improvements in therapy (Stewart & Kleihues, 2003).

Incidence of NHL rises steadily with age, especially after age 40 years. Although diffuse large B-cell lymphomas are the most common overall and can occur at any age, the median age of diagnosis is 65 years; 90% of new patients are aged > 50 years. Small lymphocytic (9823/3, 9670/3) and follicular lymphomas also are most commonly diagnosed over age 60 years, being extremely rare in children, whereas Burkitt's lymphoma (9687/3, 9826/3), and diffuse large B-cell lymphoma are the more common lymphomas in children.

There is a slight male-to-female preponderance and a higher incidence in white than in African-Americans. Similarly, in Canada, NHL is slightly more common in males than in females (age-standardised rate, on a world basis, 14.6/100,000 males and 10.5/100,000 females, Globocan 2000). The trend and incidence in Quebec follow closely those of Canada as a whole (Figure 1).

NHL has been associated with infectious agents including, most prominently, Epstein-Barr virus (Burkitt's lymphoma and NK and NK-like T-cell lymphomas that involve the upper aerodigestive tract as well as extranodal sites), HIV-1 (including follicular lymphoma and diffuse large B-cell lymphomas) and the bacterium, *Helicobacter pylori*, which predisposes to gastric (mostly MALT) lymphoma. Exposure to immunosuppressive drugs such as azathioprine and ciclosporin used in organ transplant recipients is associated with both Kaposi's sarcoma and lymphoma, although there has been well-documented regression of lymphoma following withdrawal of ciclosporin. In addition, there are associations with a family history of haematological cancers and with autoimmune diseases, such as Sjögren's syndrome and rheumatoid arthritis (Freedman & Nadler, 2001).

There have been suggestions of association of NHL with agricultural work and working in particular with chlorophenoxy herbicides such as 2,4-D, with exposure to chlorophenols and occupational exposure to solvents (trichloroethylene, tetrachloroethylene) and with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (IARC 1987, 1995, 1997, 1999). The evidence is, however, confusing for at least some of these examples. Thus, although there is evidence from some studies suggesting a link between increased risk of NHL and exposure of farmers to pesticides including chlorophenoxy herbicides, there appear to be geographical differences (IARC, 1987; Zahm et al., 1990; Asp et al., 1994) and the risks found in agriculture are generally not confirmed within manufacturing facilities (IARC, 1987; Bloemen et al., 1993; Burns et al., 2001). Furthermore, some studies have found increased risk of NHL

amongst farmers associated with exposure to a number of chemically and toxicologically diverse pesticides (McDuffie et al., 2001). This finding (and the decreased risks during manufacture) might suggest other risk factors not identified in these studies. On the other hand, a very large, multicentre, international collaborative study found an association between chlorophenol exposure and NHL (Kogevinas et al., 1995). Odds ratios for NHL, not adjusted for exposure to any other agents, were 1.3 (95% CL 0.5 – 3.1) for any chlorophenol, 2.8 (0.5 – 17.0) for pentachlorophenol and 1.0 (0.3 – 3.1) for 2,4-dichlorophenol. This same large study has been used to examine the effects of polychlorinated dibenzo-*para*-dioxins during employment in the manufacture of chlorophenoxy herbicides or chlorophenols and found mortality was elevated from NHL (24 deaths; Standardised Mortality Ratio, 1.3; 0.9 – 2.1), but workers not exposed to 2,3,7,8-TCDD or higher chlorinated congeners had SMRs of 1.0 (Kogevinas et al., 1997). Nevertheless, a detailed evaluation of the dioxin data for NHL concluded that increased risks were found in most populations studied, although the relative risks were mostly non-significant and below 2.0. Furthermore, although it is plausible that other chemicals cause NHL, strong confounding factors are not known. The lack of complete consistency among the studies and the weak effect detected in most of the positive ones caution against a causal interpretation of the findings (IARC, 1997).

Firemen: General Characteristics and Exposures

The task of fire fighting consists of two phases: (1) *knockdown*, during which the fire is brought under control, and (2) *overhaul*, when the fire is extinguished and clean up begins. Approximately 90% of structural fires are either extinguished or abandoned and fought from outside within 5 – 10 min., the average duration of heavy physical activity being 10 min. (Gilman & Davis, 1993). Although self-contained breathing apparatuses (SCBA)s are available, these are seldom worn from the time the firemen arrive at the scene until the time that they leave. In a study of exposures in the City of Montréal fire department, Austin et al., 2001a, found that SCBAs were worn about 50% of the time at structural fires, but they were worn for only 6% of the total time spent at all types of fires. Masks are generally put on when the firemen enter a fire or "see smoke," but it is difficult for them to judge when the mask can be safely removed and they are rarely worn during the smouldering phase of a fire or during mop-up operations. Furthermore, communication is essential and this is difficult with the mask in place. The largest category of non-fatal fire fighter injuries associated with fires has been reported to be contact with flames and smoke (39%) and the leading cause of non-fatal injury among younger firemen is related to smoke inhalation (FEMA, 1990).

In a study of municipal structural fires, Austin et al., 2001b found that just 14 different compounds accounted for about 75% of the total volatile organic materials measured (Table 2). These same compounds constituted approximately 65% of all volatile organic compounds in experimental fires burning various materials commonly found in structural fires (Austin et al., 2001c). The spectra of volatile organic compounds were dominated by benzene along with toluene and naphthalene. They also found that propylene and 1,3-butadiene were present in all of the fires and that styrene and other alkylated benzenes were frequently identified. Other materials that have quantified with some regularity include acrolein, carbon monoxide, formaldehyde, glutaraldehyde, hydrogen chloride, hydrogen cyanide and nitrogen

dioxide (Bolstad-Johnson et al., 2000; Caux et al., 2002). There may also be exposure to asbestos and various metals, such as cadmium, chromium and lead. In addition, there is almost certainly exposure to diesel exhaust and fumes and to polycyclic aromatic hydrocarbons (PAHs).

During overhaul, recommended ceiling or short-term exposure levels can often be exceeded, e.g., for acrolein, benzene, carbon monoxide, formaldehyde, glutaraldehyde, nitrogen dioxide and sulphur dioxide (Bolstad-Johnson et al., 2000) and several of these, e.g., carbon monoxide and benzene, were found to be present at appreciable concentrations in the atmosphere at real fire scenes when SCBAs were only used part of the time or not at all, owing to the impression that there was low smoke intensity (Brandt-Rauf et al., 1988, 1989).

Possible risk factors for NHL associated with fighting fires.

Certain exposures to possibly carcinogenic materials, such as polycyclic aromatic hydrocarbons (PAH), benzene, 1,3-butadiene and diesel exhaust, are associated with fighting fires, and it has been assumed in some publications that these chemicals may be involved in the development of NHL. The evidence for their involvement will be briefly summarised, as will consideration of the effect of tobacco smoke, because it has components in common with those encountered by firemen in their work, and it could also act as a confounder.

1,3-Butadiene. Among four particularly informative studies of occupational cohorts with exposure to 1,3-butadiene evaluated by the IARC (IARC, 1999), three studied NHL independently of leukaemia. All were based in the U.S.A. or the U.S.A. and Canada. In a cohort manufacturing 1,3-butadiene monomer, there were 42 deaths from lymphohaematopoietic cancers (ICD-8 codes 200-209), 9 of which were deaths from lymphosarcoma and reticulosarcoma (ICD-8 code 200; SMR = 1.9 (95%CI 0.9-3.6). Sub-cohort analyses were made for groups with background, low and varied exposure, based on industrial hygiene sampling. For this particular cancer coding there were 2 deaths (SMR = 1.1, 95%CI 0.1-4.0) and 7 deaths (SMR = 2.5, 95%CI 1.0-5.1) in the low and varied exposure groups, respectively (Divine & Hartman, 1996). In a relatively small cohort mortality study of three production units in which 1,3-butadiene was a primary product and neither benzene nor ethylene oxide was present, there were 4 cases of lymphosarcoma and reticulosarcoma (SMR = 5.8, 95% CI 1.6-14.8 with the population of the U.S.A. as the reference). The four cases all had duration of employment of ≥ 2 years (SMR = 8.3; $p < 0.05$) (Ward et al., 1995, 1996). The largest of these more informative studies (Delzell et al., 1996) evaluated the mortality experience of 15649 men employed for at least one year in styrene-butadiene rubber plants. Overall cancer mortality was lower than expected, with 950 deaths (SMR = 0.93, 95% CI 0.87-0.99). These deaths included 11 from lymphosarcoma (SMR = 0.8, 95% CI 0.4-1.4). Thus, the IARC evaluation of *limited evidence* for 1,3-butadiene carcinogenicity rests largely upon 48 cases of leukaemia in this cohort (SMR = 1.3 95% CI 1.0-1.7), the support from NHL being inconsistent in the three studies.

Benzene. Results from individual studies of petroleum workers, as well as from a very large pooled analysis, indicated that petroleum workers were not at an increased risk of NHL as a result of their exposure to benzene or other benzene-containing petroleum products in their work environment. This conclusion was

supported by cohort studies of workers in other industries who were exposed to benzene as well as by population-based case-control studies of NHL and occupational exposures (Wong & Raabe, 2000). However, benzene is an established risk for acute myeloid leukaemia (AML), therefore, if an increase in NHL were to be observed and benzene implicated, then it is to be expected that the incidence of AML would also increase.

PAHs. A study involving 3730 cancer cases of the possible association between occupational exposure to PAHs and 14 different kinds of cancer was conducted in Montréal (Nadon et al., 1995). Among the PAH exposures considered were benzo(a)pyrene and five categories of PAHs defined on the basis of the source material, which were wood, petroleum, coal, other sources and any source. Each PAH source was subdivided into unexposed, low and high exposure sub-groups (based on duration, concentration and frequency of exposure). In the study of NHL, no analysis resulted in an odds ratio greater than 1.0.

Diesel exhausts and fumes. An authoritative evaluation of possible carcinogenic effects of diesel exhausts and fumes did not identify such exposures as risk factors for NHL (IARC, 1989).

Tobacco smoke. Among six cohort studies of the association between NHL and tobacco smoking, no increased risk was observed in five of them. In one prospective study, men who had ever smoked cigarettes had a two-fold increase in risk for NHL and the risk was higher among the heaviest smokers. Data from case-control studies also fail to support a large effect of smoking on the incidence of NHL (IARC,2004).

Epidemiological Studies Reviewed.

In the epidemiological literature on risk of cancer among firemen that has been reviewed, 10 publications were suitable for examination of NHL specifically (Table 3).

Sama et al. (1990) examined associations between fire fighting and cancer incidence in Massachusetts, NHL being one of nine malignancies that were studied. Subjects were identified through the state cancer registry files for 1982-86. Disease classification was made on the basis of primary site and histology according to the International Classification of Diseases for Oncology (ICD-O) system (WHO, 1976). Occupation and industry were coded according to the 1980 U.S. Bureau of the Consensus (BC) system (U.S. Bureau of the Consensus, 1982). Male cancer cases included were fire fighter (BC code 417) and fire chief (BC code 413). Two "unexposed" reference populations were used: Massachusetts policemen and white Massachusetts men. Police were selected as a reference group because of their probable similarity to firemen with regard to socio-economic factors. Standardised morbidity odds ratios (SMOR) were statistically significantly increased for NHL among firemen, based on 14 cases, compared with police referents, SMORp = 3.27 (CI 1.19-8.98) and were substantially reduced and no longer significant when Massachusetts white men were used as the reference population, SMORp = 1.59 (CI 0.89-2.84). Incidence data (as used in this study) have the advantage over mortality data in that cancer registry information provides better diagnostic information than

death certificates. Over 96% of the cases were pathologically confirmed. Limitations of the study were that occupational information was available for only about 50% of the cases and misclassification of occupation in the cancer registry records could have occurred. Both of these limitations, however, are likely to be random. Another issue is that there was no sub-classification of firemen according to their actual duties, so no assessment of likely exposures is possible. This is likely to dilute effects of exposure and bias risk estimates towards the null, in this study. Thus, the finding of an increased risk in this study is particularly indicative of a possible effect.

Beaumont et al. (1991) calculated mortality rates for 3066 firemen who had been employed in San Francisco, CA between 1940 and 1970. Vital status was ascertained until 1982 and rate ratios calculated using USA death rates for comparison. Amongst 1186 deaths there were 236 cancer deaths, approximately as expected, RR = 0.95 (0.84-1.08). For NHL (lymphosarcomas and reticulosarcomas), the rate ratio was lower than expected, but not significantly so, RR = 0.89 (CI 0.24-2.29) based on 4 deaths.

Demers et al. (1992a) studied the mortality of 4546 men employed as firemen in Seattle and Tacoma, WA, and Portland, OR, USA for at least one year between 1944 and 1979. The standardised mortality ratios (SMRs) were calculated using reference rates for the USA as a whole and incidence density ratios (IDRs) were calculated for firemen relative to police in the same cities with standardisation by five-year age groups and time periods. Between 1945 and 1989, there were 1169 deaths in the study population, 291 being cancer deaths. There was no excess risk of overall cancer mortality: IDRp = 0.97 (CI 0.67-1.33), SMRm = 0.91 (CI 0.85-1.07). Whereas there was a non-significant higher risk of NHL (lymphosarcomas and reticulosarcomas) when compared with U.S.A. national rates for men: SMRm = 1.42 (CI 0.57-2.93), based on 7 deaths, there was not when compared with policemen from the same cities, IDRp = 0.81 (CI 0.30-2.22). The latter comparison is likely to be the better comparison, in terms of socio-economic factors that could influence risk. This study, like most others on firemen, relied upon death certificates for cause of death information.

Giles et al. (1993) studied the cancer incidence in a cohort of 2865 firemen employed in Melbourne, Victoria between 1980 and 1989. The cancer incidence in the cohort was compared with that of men in the state of Victoria. There were 20853 person-years of follow-up. The incidence of all cancers combined was not elevated, SIR = 1.13 (CI 0.84-1.48), based on 50 cases, whereas the incidence of NHL was elevated, although not significantly, SIR = 1.85 (CI 0.50-4.74).

Aronson et al. (1994) conducted a cohort study in metropolitan Toronto, Ontario on all 5414 employees who had worked as firemen for at least 6 months at any time between 1950 and 1989. Deaths and causes of deaths were obtained by computerised record linkage. There were 114008 person-years of follow-up. The average years of follow-up and years of employment were 21 and 20, respectively. The incidence of all cancers combined was not elevated, SMR = 1.05 (CI 0.91-1.20) based on 199 cases. The SMR for NHL (lymphosarcomas, ICD-9 code 200) was 2.04 (CI 0.42-5.96) based on 3 cases.

Demers et al. (1994) studied cancer in 2447 firemen in Seattle and Tacoma, WA, USA, with reference to tumour registry data. Incident cancer cases were identified through the population-based registry of the Cancer Surveillance System (CSS) of the Fred Hutchinson Cancer Research Center. Death certificates were not used as a

source of cancer information. Duration of active duty was assignable for Seattle firemen and used as a surrogate measure of cumulative exposure to combustion products from fires; no exposure was assigned for years spent in administrative duties or support services. Total years of employment had to be used for Tacoma firemen because records identifying the start and end dates of specific duties were not available for all of them. The study population was followed for 16 years (1974-89) and the cancer incidence compared with that among 1878 policemen from the same cities. There were 244 cancer cases in the study population. There was no excess risk of overall cancer: SIRp = 1.0 (CI 0.8-1.3), SIRm = 1.1 (CI 0.9-1.2) nor was there a statistically significant excess risk of NHL (codes 200 – 202) in particular: SIRp = 1.8 (CI 0.4-1.3), SIRm = 0.9 (CI 0.4-1.9), based on 7 cases. SIRs were also calculated according to duration of exposed employment, but in neither active duty as a fireman (Seattle) nor total employment (Tacoma) was there any underlying relationship of risk with increasing surrogate for exposure. Duration of active fire fighting employment (Seattle) represents an improvement over total duration of employment (Tacoma) as a surrogate index of exposure to specific agents. Thus, there was almost certainly misclassification of exposure in the Tacoma segment, which is likely to bias risk estimates towards the null (as in the Sama et al., 1990 study).

Burnett et al. (1994) conducted a particularly large investigation into the occurrence of cancer death in firemen that was reported as a brief communication (although full details are available from the authors). This was a proportionate mortality study of white firemen in 27 states of the USA from 1984 through 1990, using data collected from the National Occupational Mortality Surveillance system. There were 5744 deaths, 1636 being due to cancer. The proportionate mortality ratio (PMR) was statistically significantly increased for all cancers combined, PMR = 1.10 (1.06-1.14) and for that portion of the cases who died at < 65 years of age, PMR = 1.12 (1.04-1.21). Deaths from NHL significantly increased amongst firemen of any age, PMR = 1.32 (1.02-1.67) based on 66 deaths and for those that died at age <65 years, PMR = 1.61 (1.12-2.24) based on 35 deaths. The strength of this study is its very large numbers of cancer deaths. Its weaknesses (shared by other studies of this type) are its reliance on death certificate information, which may be inaccurate, especially for occupation, and give no information on duration of occupation and possible exposures involved, or on possible confounders. In addition, the PMR method of estimating risk will over estimate risk if the overall death rate for the occupational group is low, as might be the case among firemen (DeCouflé et al., 1980).

Ma et al. (1998) used a database overlapping that of Burnett et al. (1994) to examine possible racial differences in susceptibility to cancer mortality. Although the database was extended by three years to 1993, some data were lost because three states were removed from consideration (Alaska, New York and Pennsylvania). There were 6607 deaths, 1817 being due to cancer. Although the stated objective was a racial comparison, there was a large numerical imbalance of deaths between the races. For all cancers combined amongst whites, the mortality odds ratio (MOR) = 1.1 (CI 1.1-1.2) based on 1817 deaths, while amongst blacks the MOR = 1.2 (CI 0.9-1.5) based on 66 deaths. For NHL deaths amongst whites, the MOR = 1.4 (CI 1.1-1.7) based on 76 deaths, while amongst blacks the MOR = 0.8, based on a single death. The likely large degree of overlap with the Burnett et al., 1994 study indicates that these cannot be considered as completely independent investigations of NHL in the white population. This study is subject to the same limitations as described for Burnett et al., 1994.

Figgs et al. (1995) conducted a case-control analysis of 23890 death certificates indicating NHL as the cause of death in 24 states within the U.S.A. for 1984-1989. The reference group was people who died for reasons other than cancer, from other occupations. There were 5 controls for each case, matched for age, sex and race. There were 12 firemen for whom NHL was indicated as the cause of death. The mortality odds ratio (MOR) was 5.6 (CI 2.5-12.3), indication that being a fireman is a risk factor for NHL in this study.

Baris et al., 2001 studied an historical cohort of firemen in Philadelphia, 1925 to 1986. From the point of view of measures of exposure, length of the historical cohort and length of follow-up, this was a particularly interesting study, although the small numbers of cases in the sub-categories reduces the value of any interpretation of the results. Comparison was made against the general white male population of the USA. The 7789 firemen were normally employed in their late 20s and worked for an average of 18 years, with an average of 26 years follow-up. This provided 204821 person-years of follow-up in which there were 2220 deaths, of which 500 were due to cancer. The measures of exposure that were used were:

1. duration of employment (≤ 9 years; 10 – 19 years; ≥ 20 years);
2. type of company employment (engine only; ladder only; engine and ladder);
3. year of hiring (before 1935; 1935-1944; after 1944);
4. cumulative number of fire runs (low, ≤ 3323; medium, ≥ 3323 & ≤ 5099; high, > 5099, i.e., less than the median, ≥ median and ≤ 75^{th} percentile, and ≥ 75^{th} percentile);
5. accumulation of fire runs (low, ≤ 3191; high, > 3191);
6. fire runs during first 5 years as a fireman (low, ≤ 729; high, > 729), and
7. lifetime fire runs with diesel exposure (non-exposed; low exposed, 1 – 259 runs; medium exposed, 260 – 1423 runs; high, ≥ 1423 runs).

The overall risk of mortality from NHL was increased among firemen, with SMR = 1.41 (CI 0.91-2.19) based on 20 deaths. Mortality from NHL was significantly increased among firemen with 20 years or more duration of employment (SMR = 1.72, 0.9-3.31, 9 cases) and among firemen hired between 1935 and 1944 (SMR = 2.19, 1.18-4.07, 10 cases). On the other hand, excess risk was not associated with high cumulative number of lifetime runs (SMR = 0.73, 0.18-2.94, 2 cases) or high number of runs during the first five years as a fireman (SMR = 0.52, 0.18-1.53, 6 cases). Indeed, the SMR was highest among those in the low category of cumulative lifetime runs (SMR = 2.36, 1.31-4.26, 11 cases). Thus, no consistent pattern of increased risk in relation to duration or intensity of exposure was evident. However, since there were only 20 cases of NHL, there was limited possibility for sub-group analysis

Related epidemiological studies

In addition to the studies listed in Table 3, there were three groups of other publications on cancer epidemiology of firemen that were examined. Of these, 9 publications did not report NHL (ICD-9 codes 200 - 202) separately from other lymphoid tissue neoplasms (Table 4), 4 did not mention these neoplasms at all (Mastromatteo, 1959; Williams et al., 1977; Feuer & Rosenman, 1986; Hansen, 1990; Ide, 1998) and 5 were studies of other types of neoplasm (Morton & Marjanovic,

1984; Bates & Lane, 1995; Delahunt et al., 1995; Finkelstein, 1995; Bates et al., 2001).

In none of the studies listed in Table 4 was risk of cancer incidence or mortality significantly increased. The risk ratio was greater than unity in 3 cases, about unity in two and less than unity in 6 cases (Demers et al., 1992b counted twice). Most of these studies, however, had less than 5 cases of lymphoid or lymphoid and haematopoietic neoplasms.

Discussion

1. *Problems in the interpretation of epidemiological data.*

a. Healthy worker effect.

Fighting fires is a mentally and physically demanding occupation in which burns, falls and crush injuries are commonplace and exposure to smoke and other airborne organic and inorganic substances is part of the job (Gochfeld, 1995). Nevertheless, firemen tend to have a lower mortality rate than the general population, at least during the earlier years of employment. It may be, therefore, that front line firemen are a work population particularly prone to a healthy worker effect, since it appears that many firemen who develop symptoms early in their careers may be moved to other, non-fire-fighting roles (Guidotti & Clough, 1992). This suggestion is supported by the higher prevalence of non-specific respiratory disease amongst firemen who do not actually fight fires (Peters et al., 1974). The healthy worker effect is important during the earlier years of employment, due in large part to a reduction in cardiovascular disease, but the effect tends to disappear with longer employment (Guidotti, 1995). Any effect in late employment could be due to the removal of workers (because they become unfit) from exposure to risk factors predisposing them to early mortality. Bias of this kind, should it occur, is more likely to affect disease categories other than cancer. In the study of Baris et al. (2001) the SMR for all causes of death was significantly reduced during the first 9 years and after 20 years of employment, but not in the employment range 10 – 19 years. These changes seemed to be largely due to changes in SMRs for circulatory disease and ischaemic heart disease and so they are consistent with the suggestions made by Guidotti (1995).

b. Study size

Most of the studies reviewed here are based on small numbers of NHL cases. While the two largest studies (Ma et al., 1998 and the overlapping Burnett et al., 1994) had 76 and 66 cases, respectively, the remainder relied upon 20 or fewer cases. Thus, most of the studies lacked sufficient statistical power to detect a possible moderate association (e.g., a 2-fold increase in risk). Nevertheless, most of the studies showed a tendency for an increased risk, which, if not due to chance, could be indicative of a real underlying association between employment as a fireman and risk of NHL.

c. Occupational classification

There have also been concerns in several studies based on cancer registry data that information about occupation was missing or that misclassification of the reported occupation could have occurred. The probability of such misclassification is even higher for studies based on death certificates. This is because firemen belong to an occupational group that routinely retires early and then pursues another occupation

and it is the last occupation that is recorded; however, it was judged that the effect of such misclassification would be to reduce the strength of the observed association, because it is expected that the misclassification would be non-differential, i.e., it is independent of the cancer diagnosis.

d. Exposure assessment

Few studies could address the issue of actual fire-fighting experience among workers employed as firemen, because a fireman might have been fighting fires, or he might have been assigned purely administrative tasks. Such a lack of sub-classification could influence risk ratios, biasing them towards the null. In addition, the small numbers of cases available in most studies precluded meaningful analysis according to a fireman's actual or likely exposure.

A general problem affecting studies with firemen is that reliance by the investigators upon the number of years employed as a surrogate for actual exposures at fires, which probably resulted in misclassification and might not form a sound basis for describing dose-response relationships. Austin et al., 2001a provide such evidence, as only 66% of fire department personnel were in fact 1st line combat fire fighters and many of these combat firemen moved into non-exposed jobs before the end of their careers. In the same study there was a good correlation between the number of runs to fires and the time spent at fires, and they concluded that the number of runs would be a better surrogate for exposure than years worked as a fireman. However, it was also found that the number of runs may seriously over- or under-estimate the time spent at fires for individual crews, so that time spent at fires is the preferred surrogate. In one example, two crews had almost identical numbers of fire runs, but one spent 1.72 times longer at fires than the other. These results are contrary to the opinion of Guidotti & Goldsmith (2002) who specifically do not advise that job assignments or cumulative number of fire alarms to which firemen were assigned be used as measures of exposure (the only practical basis being, in their estimation, duration of employment). Within the studies reviewed here, Demers et al. (1994) used duration of active duty fighting fires and Baris et al. (2001) used not only duration of employment, but also estimated cumulative number of runs and number of runs during the first 5 years as a fireman. The last estimate of exposure was divided into two groups, low and high and the relative risk was greater in the high number of runs category. Year of first employment as a fireman, which was used in several of the studies, is more a measure of latency than exposure, since job categories are likely to have changed over the years. Interpretation of dose-response associations between fire fighting and NHL is, however, difficult, taking into account the very small numbers of cases available in sub-group analyses, even when only two categories of exposure were compared.

e. Adjustment for confounders

Most of the studies relied on death certificates as the main source of information and consequently no information about possible confounders (e.g., tobacco smoking and alcohol consumption) was available. An interesting observation is that in two of the three studies (Sama et al., 1990 and Demers et al., 1994) where both policemen and general population males were used as comparison groups, the risk was substantially stronger when policemen were used as the reference population. Policemen would be expected to share many socio-economic factors with firemen and this proximity could make for a more sensitive comparison. Should this be so, it would suggest that these

same socio-economic factors are associated with a reduced risk of NHL in comparison with the more general population. It is not known what factors might contribute to this difference.

f. Design weaknesses

Proportional measures can be misleading because their denominator is the total number of cases or deaths from all causes within the same population. The PMR method of estimating risk, as used by Burnett et al. (1994), will overestimate risk if the overall death rate for the occupational group is low, as might be the case for firemen (DeCouflé et al., 1980). To obtain Mortality Odds Ratios (MOR), as used by Ma et al. (1998), the expected numbers were calculated using all causes of death except cancers from the same occupational mortality database from which the firemen's deaths were obtained. As noted for PMRs, this measure relies on death certificate information and is therefore prone to bias because of misclassification of both the cause of death and the exposure. These two studies are interesting, however, because their study populations are overlapping (which would detract from their significance) and have used different analytical methods - which would add to the significance of their common conclusion.

Generally speaking, incidence data obtained from cancer registries form a more reliable and more detailed source of information on which to base analyses (Demers et al., 1992b). In any of these analyses, the characteristics of the reference population is important; it being an advantage to select a reference population as close to the study population as possible. This advantage was maximised in those studies (Sama et al. (1990); Demers et al. 1992a; 1994) that selected police as a reference group in addition to a more general population. Comparison of the data in the Demers et al. (1992a) and (1994) publications allows the effect of cancer registry data versus death certificates to be evaluated when using local police as the reference population. For the neoplasms of interest and based on the same number of cases (7), use of registry data resulted in a higher risk estimate, although it was not statistically significant, whereas death certificate data showed no increased risk.

2. General Discussion

Consistency and the strength of the observed associations are important factors in the identification of causality. No single study can provide definitive evidence for a relationship and the strength of the association (the size of the relative risk) must be taken into consideration.

In most of the 10 studies listed in Table 3, there was some indication of increased risk, but risks were significantly increased in only four studies (Sama et al., 1990; Figgs et al., 1995; Burnett et al., 1994; Ma et al., 1998) and the latter two were not independent with regard to study populations. Furthermore, the Burnett et al. (1994) study was based on proportional mortality. The strength of the association is generally low in these studies, except in the case of Sama et al. (1990), where the standardised mortality odds ratio was 3.27, using police as referents, and Figgs et al. (1995), where the mortality odds ratio was 5.6. The significant finding in the Sama et al. (1990) study was obtained with reference to police in the same State, the risk ratio being markedly lower (1.59) when the general, white, male population of the State was the reference populations. Although they were not statistically significant, similar results were obtained in Demers et al. (1994) with reference to the local

police. These effects of the police reference population add weight to the conclusions regarding firemen. Other non-significantly increased relative risks of NHL were found in four studies, the risk ratios being in the range1.5 – 2 in Giles et al. (1993) and Aronson et al. (1994) and < 1.5 in Baris et al. (2001) and that portion of Demers et al. (1992a) using mortality analysis with reference to the general, local male population.

Non-significantly reduced relative risks of NHL were observed in two studies, that of Beaumont et al. (1991) and that portion of Demers et al. (1992a) using cancer registry data with reference to the local male general population.

Other important factors in establishing causality are the existence of a biologically plausible mechanism and the demonstration of a dose-response relationship. Currently, there is a lack of a mechanistic basis that could link NHL with fighting fires. The common, identified exposures (e.g., the 14 volatile organic chemicals, including benzene and 1,3-butadiene, and PAHs in general) do not seem to be risk factors for NHL. Although other risk factors have been suggested and there is suggestive, if not conclusive, evidence for some, e.g., 2,3,7,8-TCDD, the association of these chemicals with structural fires has not been established. Because of the generally low numbers of cases the examination of dose-response relationships was not usually possible, although attempts were sometimes made. Baris et al. (2001) examined dose-response relationships, but there was no consistency in their results: duration of employment showed no relationship, a high number of runs during the first 5 years of employment reduced the risk and cumulative number of runs was associated with a significantly increased risk only in the low number category. Both of the latter findings are the reverse of what might be expected if NHL was an occupational risk for firemen, but the numbers were small in the high number of run categories.

Conclusion

The available epidemiological data are relatively consistent with there being either an increased risk or no effect on the incidence of NHL amongst firemen. While most of the elevated risk ratios were non-significant, small numbers of cases would have contributed to this result. In all but three studies, the risk ratio was equal to or less than 2.0 and the few attempts to examine dose-response relationships were not informative, because of the small numbers of cases involved. The absence of any clearly defined mechanistic factor also imposes some difficulties. Known or suspected risk factors for NHL are not especially to be found in firemen. On the other hand, it did appear that the risk ratios could sometimes be greater if bias was reduced by choosing a reference population with closer demographic similarities to firemen (e.g., police from the same area) than if the reference was the general population. Firm conclusions cannot currently be derived; therefore, although it is possible that a fireman presenting with NHL may have developed the disease as a consequence of his employment, this conclusion cannot be assumed. Unfortunately, it is not clear what characteristics of a particular patient and his exposures should be examined to determine whether his disease is related to his occupation.

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Figure 1. Age-specific rates (per 100,000) for neoplasms of lymphoid and haematopoietic tissues and for non-Hodgkin lymphoma amongst males in Canada and Quebec, 1993-1997 (Ferlay et al., 2002).

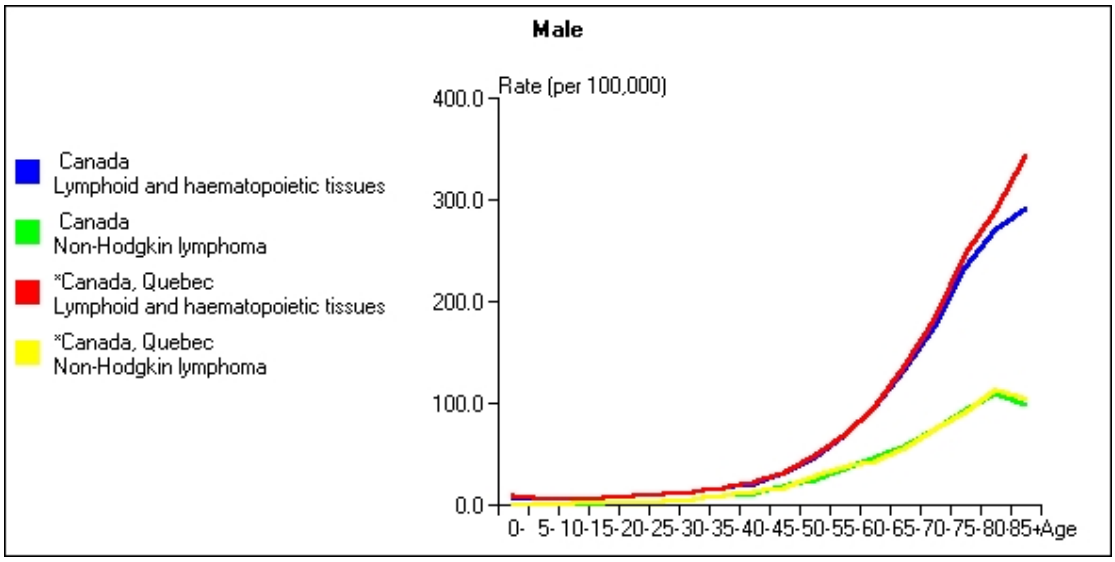

Table 1. WHO Classification of lymphoid neoplasms (WHO, 2001).

LYMPHOID NEOPLASM	ICD-O MORPHOLOGY CODE[3]
B-CELL NEOPLSMS	
Precursor B-cell neoplsm	
Precursor B lymphoblastic leukaemia/ lymphoma	9835/3 9728/3
Mature B-cell neoplsm	
Chronic lymphocytic leukaemia/ small lymphocytic lymphoma	9823/3 9670/3
B-cell prolymphocytic leukaemia	9833/3
Lymphoplasmacytic lymphoma	9671/3
Splenic marginal zone lymphoma	9689/3
Hairy cell leukaemia	9940/3
Plasma cell lymphoma	9732/3
Solitary plasmacytoma of bone	9731/3
Extraosseous plasmacytoma	9734/3
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma)	9699/3
Nodal marginal zone B-cell lymphoma	9699/3
Follicular lymphoma	9690/3
Mantle cell lymphoma	9673/3
Diffuse large B-cell lymphoma	9680/3
Mediastinal (thymic) large B-cell lymphoma	9679/3
Intravascular large B-cell lymphoma	9680/3
Primary effusion lymphoma	9678/3
Burkitt lymphoma/ leukaemia	9687/3 9826/3
B-cell proliferations of uncertain malignant potential	
Lymphomatoid granulomatosis	9766/1
Post-transplant lymphoproliferative disorder, polymorphic	9970/1
T-CELL AND NK-CELL NEOPLASMS	
Precursor T-cell neoplasms	
Precursor T lymphoblastic leukaemia/ lymphoma	9837/3 9729/3
Blastic NK cell lymphoma	9727/3
Mature T-cell and NK-cell neoplasms	
T-cell prolymphocytic leukaemia	9834/3
T-cell large granular lymphocytic leukaemia	9831/3
Aggressive NK cell leukaemia	9948/3
Adult T-cell leukaemia/lymphoma	9827/3
Extranodal NK/T cell lymphoma, nasal type	9719/3
Enteropathy-type T-cell lymphoma	9717/3

[3] These are the morphology codes of the International Classification of Diseases (ICD-O), third edition. Behaviour is coded /3 for malignant tumours and /1 for lesions of low or uncertain malignant potential

Hepatosplenic T-cell lymphoma	9716/3
Suncutaneous panniculitis-like T-cell lymphoma	9708/3
Mycosis fungoides	9700/3
Sezary syndrome	9701/3
Primary cutaneous anaplastic large cell lymphoma	9718/3
Peripheral T-cell lymphoma, unspecified	9702/3
Angioimmunoblastic T-cell lymphoma	9705/3
Anaplastic large cell lymphoma	9714/3
T-cell proliferation of uncertain ma;ignant potential	
Lymphomatoid papulosis	9718/1
HODGKIN LYMPHOMA	
Nodular lymphocyte predominant Hodgkin lymphoma	9659/3
Classical Hodgkin lymphoma	9650/3
Nodular sclerosis classical Hodgkin lymphoma	9663/3
Lymphocyte-rich classical Hodgkin lymphoma	9651/3
Mixed cellularity classical Hodgkin lymphoma	9652/3
Lymphocyte-depleted classical Hodgkin lymphoma	9653/3

Table 2. Volatile Organic Compounds Consistently found in 9 Municipal Structural Fires.

Chemical	**Concentration Range Found (ppm)**
Propene	0.22 – 21.64
Benzene	0.12 – 10.76
Xylenes (*o*-, *m*-, *p*-)	0.06 – 9.19
1-Butene/2-methyl propene	0.03 – 4.08
Toluene	0.05 – 5.52
Propane	0.03 – 3.63
1,3-Butadiene	0.03 – 4.84
2-Methylbutane	0.004 – 0.43
Ethylbenzene	0.01 – 5.97
Naphthalene	0.01 – 2.14
Styrene	0.003 – 2.01
Cyclopentene	0.002 – 3.29
1-Methylcyclopentene	0.001 – 1.79
Isopropylbenzene	0.0004 – 0.55

*Table 3. Summary characteristics and results of studies on the relation between occupational exposure as a fireman and risk of non-Hodgkin lymphoma.

Reference	Study base	Reference group	Study size	Risk* (95% C.I. or significance level)	Adjustments & Comments
Sama et al., 1990	Firemen in Massachusetts, 1982-86	MA police (p) White MA men (m)	315 cancer deaths	All cancers, not recorded NHL, 14, SMORp = 3.27 (1.19-8.98) SMORm = 1.59 (0.89-2.84)	Cancer registry incidence data.
Beaumont et al., 1991	Firemen in SanFrancisco, California, 1940-82.	White USA men	3066 firemen with 236 cancer deaths	All cancers, RR = 0.95 (0.84-1.08) Lymphosarcoma + reticulosarcoma, 4 RR = 0.89 (0.24-2.29)	Analysis of dose-response inconclusive. Number of person years not stated.
Giles et al., 1993	Firemen in Melbourne, Australia, 1980-89	Men in Victoria	2865 firemen, 50 cancer cases	All cancers, SIR = 1.13 (0.84-1.48) NHL, SIR = 1.85 (0.5-4.74)	20853 person-years of observation. Dose-response analysis non-significant
Aronson et al., 1994	Firemen in Toronto, Ontario, 1959-89	Men in Ontario	5414 firemen with 199 cancer deaths	All cancers, 199, SMR = 1.05 (0.91-1.20) Lymphosarcoma + reticulosarcoma 3, SMR = 2.04 (0.42-5.96)	114008 person-years of follow-up. Increasing risk with years since first employment.
Demers et al., 1992a	Firemen in Seattle, Tacoma WA & Portland, OR USA, 1945-89	Police in the same cities (p). White USA men (m)	4401 firemen with 291 cancer deaths	All cancers, 291, IDRp = 0.97 (0.80-1.17) SMRm = 0.95 (0.85-1.07) Lymphosarcoma + reticulosarcoma 7, IDRp = 0.81 (0.30-2.22) SMRm = 1.42 (0.57-2.93)	122852 person-years for the 3 cities Death certificate data (compare with Demers et al., 1994). NB SMR for police v USA men = 1.72 (0.56-4.02), 5 cases
Demers et al., 1994	Firemen in Seattle & Tacoma, NW USA, 1974-89.	Police in the same cities (p) Men in the same counties (m)	2447 firemen with 244 cancer deaths	All cancers, 224, SIRp = 1.0 (0.8-1.3) SIRm = 1.1 (0.9-1.2) NHL, 7, SIRp = 1.8 (0.4-13) SIRm = 0.9 (0.4-1.9)	Tumour registry data
Figgs et al., 1995	Case-control analysis of death certificates of firemen in 24 states of USA, 1984-89	People who died for other reasons, in from other occupations	12 firemen out 23890 who died of NHL.	NHL, MOR = 5.6 (2.5-12.3)	5 controls per case, selected for age, sex and race, but who died for reasons other than cancer. Multiple analyses
Burnett et al., 1994	Firemen in 27 states of the USA, 1984-90	Men who died in the same 27 states of USA	Number of firemen not stated. 1636 cancer deaths	All cancers, 1636, PMR = 1.10 (1.06-1.14) < 65 years age, 663, PMR = 1.12 (1.04-1.21) NHL, 66, PMR = 1.32 (1.02-1.67) <65 years age, 35, PMR = 1.61 (1.12-2.24)	Proportionality study. Large number of cases, but no information on possible confounders, length of employment or occupational exposures.
Ma et al., 1998	Firemen in 24 states of	Men who died	6607 deaths	**WHITE**:	Small numbers for some cancers in whites, small

	USA Mortality odds ratio study of death certificates for race-specific cancer risk, 1984-93	from causes other than cancer	of firemen with 1883 cancer deaths (1817 white, 66 black)	All cancers, 1817, MOR = 1.1 (1.1-1.2) NHL, 76, MOR = 1.4 (1.1-1.7) **BLACK** All cancers, 66, MOR = 1.2 (0.9-1.5) NHL, 1, MOR = 0.8	numbers for most cancers in blacks, leading to instability of the MORs.
Baris et al., 2001	Historical cohort mortality study of Philadelphia firemen employed 1925-86	Men in the general USA population	7789 firemen with 2220 deaths	All cancers, 500, SMR = 1.10 (1.00-1.20) NHL, 20, SMR = 1.41 (0.91-2.19) **Duration of employment:** ≤ 9 years NHL, 6, SMR = 1.47 (0.66-3.26) 10 – 19 years NHL, 5, SMR = 1.03 (0.43-2.47) ≥ 20 years NHL, 9, SMR = 1.72 (0.90-3.31) **Year of hiring (1925-1986)** Before 1935 NHL, 3, SMR = 0.72 (0.23-2.22) 1935-1944 NHL, 10, SMR = 2.19 (1.18-4.07) After 1944 NHL, 7, SMR = 1.29 (0.62-2.70) **Cumulative number of runs** Low (<3323 runs) NHL, 11, SMR = 2.36 (1.31-4.26) Medium (≥3323 & <5099 runs) NHL, 4, SMR = 1.55 (0.58-4.13) High (≥5099 runs) NHL, 2, SMR = 0.73 (0.18-2.94) **Runs during first 5 years as fireman** Low (≤729 runs) All cancers, 171, RR = 1.00 NHL, 11, RR = 1.00 High (>729 runs) All cancers, 169, RR = 1.05 NHL, 6, RR = 0.52 (0.18-1.53)	204821 person-years of follow-up. Thus, the largest study available to date. Reliance on death certificates for cause. Best estimates of exposure because, in addition to duration of employment, the cohort was analysed according to job assignment and – most importantly – number of runs.

*C.I. Confidence Interval

IDR = incidence density ratio; MOR = mortality odds ratio; PMR = proportional mortality ratio; RR = rate ratio; SIR = standardised incidence ratio; SMR = standardised mortality ratio; SMOR = standardised morbidity odds ratio; Subscripts: m = men; p = police

Table 4. Studies in which NHL was not separated from other neoplasms of lymphoid or lymphohaematopoietic neoplasms.

Reference	Disease classification (authors' definition)	Observed no. of cases	Risk Ratio
Musk et al. (1978).	Lymphoid and haematopoietic cancers	-	SMR 0.63 not significant
Eliopulos et al. (1984)	Lymphohaematopoietic cancer	3	SPMR* = 1.88 (95% CI 0.39-5.50)
Vena & Fiedler (1987	ICD-9 codes 200-209 combined	5	SMR = 0.55 (95% CI 0.18-1.29)
Heyer et al. (1990).	Other lymphatic/haematopoietic cancers	3	SMR = 2.25 (95% CI 0.47-6.60). PMR 0.95 (CI 0.36-2.50)
Grimes et al. (1991).	Lymphoid and haematopoietic cancers	-	
Demers et al. (1992b)	ICD-9 codes 200-209 combined. Incidence	12	SIR 0.64 (CI 0.34-1.12);.
" "	" " Mortality	11	SMR 1.07 (CI 0.53-1.92)
Guidotti (1993)	ICD-9 codes 200-208 combined	10	SMR = 1.27 (95% CI 0.61-2.33)
Tornling et al. (1994)	ICD-9 codes 200-209 combined	3	SMR = 0.32 (95% CI 0.06-0.92).
Bates et al. (2001)	ICD-9 codes 200-208 combined	4	SMR = 0.72 (95% CI 0.2-1.8)

*SPMR, Standardised proportional mortality ratios.