

Risk of Brain Tumours in Firemen

Douglas B. McGregor

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STUDIES AND RESEARCH PROJECTS REPORT





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| | |
|--|----|
| Brain tumours | 1 |
| Firemen: general characteristics and exposures | 3 |
| Studies reviewed | 4 |
| Studies not reviewed | 9 |
| Discussion | 9 |
| Conclusions | 13 |
| References | 14 |
| Table 1 | 20 |

Brain tumours

Tumours of the central nervous system (CNS) are uncommon. Worldwide, CNS tumours account for less than 2% of all malignancies. Geographical variation in incidence is less than for most other malignancies, but there has been an increase in both incidence and mortality of brain tumours in the elderly over recent decades, particularly in developed countries. In most European and North American countries, there are about 6-8 new cases annually per 100,000 of the population. The highest incidence rates occur in U.S.A. whites (e.g., in Los Angeles), Croatia, Iceland, Norway and Sweden, while the lowest rates occur in Asian populations (e.g., in Los Angeles Japanese). Within Canada, the age standardised incidence ratio (per 100,000) for cancers of the central nervous system was reported to be 7.73 for males and 5.97 for females (Parkin et al. 1997). However, malignant tumours occur more frequently in men, while the benign meningiomas are predominantly found in women. Also, within the same geographical areas of the U.S.A., blacks tend to have lower rates than do whites (Preston-Martin & Mack, 1996). Some of the racial differences vary according histological type of tumour, e.g., in blacks the rates for glioma are lower, while rates for meningioma are higher than in whites.

The age distribution is bimodal. After leukaemias, cancers of the CNS are the second most common childhood neoplasm. In both boys and girls the rates decline after 10 years of age, but increase again after age 25 years and stabilise after age 75 years. The average age of onset for all primary brain tumours is 53 years. Amongst 15-34 year-olds, CNS tumours are the leading cause of cancer deaths for males and the fourth leading cause for females in the U.S.A. (SEER).

Rather more than 50% CNS tumours are gliomas (over 80% of which are astrocytic gliomas and glioblastoma multiforme) and about 25% meningiomas. Cranial and spinal nerve tumours constitute about 7% of the total, the remainder being a variety of tumour types, including CNS lymphoma (about 4%) and germ cell tumours (about 1%) (Preston-Martin & Mack, 1996; Prados, 2000). The rising incidence of glioblastomas among the elderly in recent years may be due in part to the introduction of neuroimaging (WHO, 2003). Astrocytic tumours comprise a wide range of neoplasms that differ in their location within the CNS, age and sex distribution, growth potential, invasiveness and progression. It appears that these differences are reflections of the type and sequence of genetic alterations that are acquired during neoplastic transformation (Kleihues & Cavanee, 2000).

There is evidence for a causal involvement of *TP53* in glial tumourigenesis. Thus, expression of exogenous wild-type *TP53* activity in glioblastoma cell lines suppresses their growth (Mercer et al., 1990; Van Meir et al., 1995). Also, cortical astrocytes from mice that lack functional *TP53* (the protein product of a gene that normally suppresses tumour growth) appear to be immortalised when grown *in vitro* and rapidly acquire a transformed phenotype. Mouse cortical astrocytes with one functional copy of *TP53* (the gene that codes for *TP53*) resemble wild-type astrocytes and show signs of immortalisation and transformation only upon loss of their one functional copy of *TP53* (Bogler et al., 1995; Yahanda et al., 1995). Those cells without functional *TP53* become markedly aneuploid (Yahanda et al., 1995), in keeping with the observation that *TP53* loss results in genomic instability (Van Meyel et al., 1994). The pattern of *TP53* mutations in human astrocytic tumours is characterised by a high frequency of GC → AT mutations, of which more than 50% are located at CpG sites (i.e., parts of DNA that consist of sequential cytosine-guanosine bases that are linked by a phosphodiester chemical group on the same chain). This suggests a role of 5-methylcytosine deamination by endogenous processes rather than by exogenous genotoxic carcinogens (Kleihues et al., 1995).

Despite the intensive research into CNS tumours, identification of risk factors is elusive. No environmental causes of human CNS tumours have been unequivocally identified, except for ionising radiation. There have been suggestions in some studies of associations with certain occupations, but most of these have not been confirmed and neither have causative agents been identified (WHO, 2003). There have, however, been suggestions that exposure to acrylonitrile, formaldehyde, polycyclic aromatic hydrocarbons (PAH) or vinyl chloride may be risk factors for brain cancer. In the case of acrylonitrile, data from non-overlapping epidemiological studies of workers exposed to the chemical do not support the earlier hypothesis (IARC, 1999). There is some evidence that exposure to formaldehyde among pathologists and embalmers is associated with increased risk of brain cancers, particularly in proportionate mortality studies, but there is no suggestion of an effect among industrial workers (IARC, 1995). There have been reports that exposure to vinyl chloride increases risk of brain cancer (IARC 1987), but hepatic haemangiosarcomas is a much more common outcome, so it would be expected that this tumour would be increased amongst firemen if vinyl chloride was involved in risk of brain cancer in this occupation. Similarly, an involvement of PAHs in brain cancer should be accompanied by an elevated risk for cancers of the respiratory system (WHO, 1998). However, the studies reviewed here (which includes most of the publications on

cancers risk amongst firemen) do not suggest that there is any increased risk of either haemangiosarcomas or respiratory system cancers due to fighting fires.

Some chemicals have been identified as causing CNS tumours in rodents, particularly in rats. These substances are almost all organic chemicals of low molecular weight and include alkylating agents (e.g., methyl- and ethyl-nitrosoureas, *bis*-chloroethylnitrosourea, 1,3-propane sultone, 2-methylaziridine), certain substituted hydrazines and related compounds (e.g., diethylhydrazine, azoethane, azoxyethane, dacarbazine) and certain substituted alkenes (e.g., acrylonitrile, glycidol, vinyl chloride) (Rice & Wilbourn, 2000). Other than for the chemicals mentioned in the previous paragraph, in no case has the human CNS been identified as a target for any of these substances. Indeed, the IARC classification of acrylonitrile (2B, “downgraded” from 2A) reflects the total absence of carcinogenic effects in industrial workers exposed to the compound and the lack of any evidence that the mechanism of carcinogenic action of acrylonitrile in rats also applies to man (IARC, 1999).

Firemen: General Characteristics and Exposures

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 taken for granted (Gochfeld, 1995). 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). 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).

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. Although self-contained breathing apparatus (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.

It is recognised that 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). Several toxic materials, 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). In a study of municipal structural fires, Austin et al., 2001b found that the spectra of volatile organic compounds were similar and remarkable for their simplicity, being 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. Indeed, just 14 different compounds accounted for about 75% of the total volatile organic materials measured. 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). None of these compounds has been implicated as human brain or other CNS carcinogens. 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). However, neither PAHs (Nadon et al., 1995) nor diesel exhausts and fumes (IARC, 1987) have been implicated as risk factors for cancer of the human CNS.

Studies Reviewed.

A recent review of latent health effects, particularly cancers, in firemen (Haas et al., 2003) included many of the publications considered below. Some of the publications included here in the assessment of effects on brain or other CNS cancer were dismissed by Haas et al. (2003) on the grounds that proportionate mortality ratios - a concede weakness - were used in the analysis (Burnett et al., 1994; Grimes et al., 1991); they did not contain duration of employment data (Hansen, 1990, Baris et al., 2000; Deschamps et al., 1995); or they were over-lapping studies (Heyer et al., 1990 overlapping with Demers et al., 1992a). The conclusion of Haas et al. (2003) was that there was no convincing evidence that employment as a fireman is associated with all-cause, coronary artery disease, cancer or respiratory disease mortality. The review by Haas et al. (2003) unfortunately omitted the Baris et al. (2001) paper, a particularly informative publication, from consideration.

There have been many studies of mortality amongst firemen, some of which have specifically identified the brain or other parts of the CNS as a possible target for carcinogenesis. These studies are reviewed here, independently of the opinions expressed by Haas et al. (2003).

The mortality experience was studied of 1867 white male firemen employed by the City of Buffalo for a minimum of five years with at least one year as a fireman between January 1950 and October 1979 (Vena & Fiedler, 1987). At the end of this period, the vital status of 99% of the firemen was determined, resulting in 470 observed deaths. Death certificates were obtained for 94% of the observed deaths. There were 32858 person-years available for analysis. Person-years combined into five-year age-time categories and multiplied by the corresponding age-time specific USA mortality rates for white men yielded the expected number of deaths. Deaths from cancer, all causes, was not different from the expected, the Standardised Mortality Ratio (SMR) being 1.09 with 95% Confidence Intervals (CI) of 0.89-1.32, based on 102 cancer deaths. For brain cancer, however, there was a significant increase in mortality, with the SMR = 2.36 (CI 0.86-5.13) based on 6 deaths. All of these men had been employed before 1930 and the latency was at least 30 years (one death, 0.9 expected). The maximum number of brain deaths (three) occurred with latencies of 20-29 years when the expected rate was 0.8 (significant). The remaining

three deaths occurred with latencies of 10 – 19 years (2 deaths when 0.6 were expected) and 1 - 9 years (1 death when 0.5 was expected).

Case-control analyses were conducted in a surveillance study in Massachusetts to examine associations between fire fighting and cancer incidence, brain cancer being one of nine that were studied (Sama et al. 1990). Subjects were identified through the state cancer registry files for 1982-86. Two “unexposed” reference populations were used: policemen and state wide males. Standardised morbidity odds ratios (SMOR) were not statistically significantly increased for brain cancer among firemen compared with either the state-wide male referents, SMOR_m = 0.86 (CI 0.34-2.15) or police referents, SMOR_p = 1.52 (CI 0.39-5.92).

Heyer et al., 1990 studied the mortality of firemen employed for at least one year in Seattle, WA, U.S.A. from 1945 through 1980, with follow-up through 1983. The 92 deaths observed due to cancer of any kind was as expected in comparison with U.S.A. white men, the Standardised Mortality Ratio (SMR) being 0.96 (CI 0.77-1.18). Mortality due to brain/nervous system cancer was similar, SMR = 0.95 (CI 0.20-2.79), based on 3 deaths. Brain cancer deaths were, however, elevated during the first 15 years since first exposure, but occurred less often than expected thereafter.

In a proportionality study of cancer mortality among firemen in Honolulu employed between 1969 and 1988, Grimes et al. (1991) found three brain cancer cases in 205 deaths from cancer, Proportional Mortality Ratio (PMR) = 3.78 (1.22-11.71). There was no reported analysis based on a surrogate of exposure in this weak analysis, as stated above (p. 3).

Mortality rates were calculated for 3066 firemen who had been employed in San Francisco, CA between 1940 and 1970 (Beaumont et al., 1991). 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 brain cancers, the rate ratio was lower than expected, but not significantly so, RR = 0.81 (CI 0.26-1.90) based on 5 deaths.

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 was compared with the national mortality in the USA(m) and with police mortalities(p) in the same cities (Demers et al., 1992a). 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: IDR_p = 0.97 (CI 0.67-1.33), SMR_m = 0.91 (CI 0.85-1.07), whereas there was increased risk of brain cancer, which was significant when compared with U.S.A. national rates for men: IDR_p = 1.63 (CI 0.70-3.79), SMR_m = 2.07 (CI 1.23-3.28), but this was based on only 2 deaths. This study, like most others on firemen, relied upon death certificates for cause of death information.

Demers et al., 1992b used tumour registry and death certificate information to study a population of firemen and policemen employed for at least one year in Seattle or Tacoma cities in the state of Washington, U.S.A. between 1974, when the tumour registry was fully operational, and 1979. Follow-up of the mortality study was until 1989. It is clear that there was an overlap of this population with that in the study described above. The cohort size was 4528, 388 of whom were diagnosed with

cancer. For cancer of the brain, the Standardised Incidence Ratio (SIR) was 1.01 (CI 0.37-2.20), based on 6 cases, and the Standardised Mortality Ratio (SMR) was 1.00 (CI 0.37-2.18), also based on 6 cases.

A later study of cancer in firemen by the same group that conducted the previous study reduced the study size to Seattle and Tacoma, WA, USA, which allowed them to use tumour registry data, rather than death certificates, for 2447 firemen (Demers et al., 1994). 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 in 1878 policemen from the same cities. There were 244 cancer deaths in the study population. There was no excess risk of overall cancer mortality: SIR_p = 1.0 (CI 0.8-1.3), SIR_m = 1.1 (CI 0.9-1.2) nor was there a statistically significant excess risk of brain cancer in particular: SIR_p = 1.4 (CI 0.2-11), SIR_m = 1.1 (CI 0.3-2.9), based on 4 deaths. SIRs were also calculated according to duration of exposed employment, but this did not reveal any underlying relationship of risk with increasing surrogate for exposure.

A historical cohort was assembled of all firemen employed between 1927 and 1987 in Edmonton and Calgary, Alberta (Guidotti, 1993). Even short employment periods (< 1 year) were justified on the grounds that much of the first year is in training with considerable exposure to smoke and the use of breathing apparatus. An exposure opportunity index term, reflecting estimates of the relative time spent in close proximity to fires by job classification, was applied to refine exposure data based on years of service. The applied weightings were: fireman lieutenant and captain = 1.0; safety or training officer = 0.2; district chief or volunteer fireman = 0.1; desk job and other posts not involving active fire fighting = 0.0. The firemen were followed for 64983 person-years and the vital status determined for 3193 firemen, which included 370 deaths, 92 being due to cancer. This provided a significantly increased risk for all cancers, standardised mortality ratio (SMR) = 1.27 (CI 1.02-1.55) based on the 92 cases. For cancers of the brain, the SMR = 1.47 (CI 0.30-4.29) based on 3 cases.

A cohort study of 5414 firemen in metropolitan Toronto, Ontario was conducted on all employees who had worked for at least 6 months at any time between 1950 and 1989 (Aronson et al., 1994). 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 brain cancer was 2.01 (CI 1.10-3.37) based on 14 cases. Portions of the data were also analysed after stratification according to years since first exposure and years of employment, but the CNS cancer data were too meagre for this analysis to be performed.

Tornling et al., 1994, studied cancer incidence and mortality in firemen who had been working with fire fighting methods used in Sweden from the beginning of the 20th century onwards. Firemen employed for at least one year in the City of Stockholm during the period 1931 to 1983 were traced and an index of the number of fires fought

was calculated for each individual. Overall cancer incidence for 1958 to 1986 was equal to the expected, SIR = 1.00 (CI 0.83-1.19) based on 127 cases, while brain cancer was somewhat more frequent than expected, but not significantly so, SIR = 1.37 (CI 0.44-3.20), based on 5 cases. The overall cancer mortality for 1951 to 1986 also was close to expected, SMR = 1.02 (CI 0.88-1.25), based on 93 cases, while risk of brain cancer was increased, SMR = 2.79 (CI 0.91-6.51) based on 5 cases. Although the elevation in brain cancer deaths did not reach statistical significance overall, the most highly exposed subgroup did show a statistically significant increase (> 1000 fire runs, SMR = 4.96, CI 1.35-12.70), based on 4 cases. This was not the position, however, for brain cancer incidence (> 1000 fire runs, SMR = 2.01, CI 0.40-5.88) based on 3 cases. It is noted that, in this study, the category of high number of runs would be in the low runs category in the Philadelphia firemen study described below (Baris et al., 2001).

A particularly large investigation into the occurrence of cancer death in firemen was that of Burnett et al., 1994, which unfortunately was reported only 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 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 (CI 1.06-1.14) and for that portion of the cases who died at < 65 years of age, PMR = 1.12 (CI 1.04-1.21). For all CNS cancer deaths the PMR = 1.03 (CI 0.73-1.41) based on 38 deaths and for those that died at age <65 years, the PMR = 0.85 (CI 0.52-1.34) based on 19 cases. The strength of this study is its very large numbers of cancer deaths. Its weakness is that it was a proportionate mortality study (see p. 9).

A related study was that of Ma et al., 1998, who used a database overlapping that of Burnett et al., 1994, but their stated objective was to examine possible racial differences in susceptibility to cancer mortality. Furthermore, 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 CNS cancer deaths amongst whites, the MOR = 1.0 (CI 0.8-1.4) based on 41 deaths, while amongst blacks the MOR = 6.9 (CI 3.0-16.0), based on 5 deaths. The likely large degree of overlap with the Burnett et al., 1994 study indicates that these cannot be considered as completely independent investigations of CNS cancer in the white population.

Bates et al., 2001 made a historical cohort study of all paid firemen in New Zealand from 1977 to 1995. The data were obtained from a registry of all firemen maintained by the United Fire Brigades Association of New Zealand (UFBA), principally for confirming eligibility for long-service awards. The study cohort was defined as every person in the UFBA database who had worked as a fireman for at least one year and who had been paid for at least one day in the study period. Anonymous cancer and mortality data came from the New Zealand Health Information Service. General

population data, by age and sex, was obtained for 5-year periods of the census years between 1971 and 1996. The final cohort contained 4305 firemen (4221 male, 84 female). The cancer follow-up time for the cohort was 62366 male person-years and 691 female person-years. The standardised incidence ratio (SIR) for all male cancers combined was not elevated, SIR = 0.95 (CI 0.8-1.1) based on 118 cases. The incidence of male cancer of the brain was 1.27 (CI 0.4-3.0) based on five cases.

From the point of view of measures of exposure, length of the historical cohort and the length of follow-up, the study of firemen in Philadelphia, 1925 to 1986, conducted by Baris et al., 2001, is particularly valuable. 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. Thus, this study that is so strong from other points of view involved a cancer study population of about 30% the size of Burnett et al., 1994 or Ma et al., 1998. 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, \geq median and $\leq 75^{\text{th}}$ percentile, and $\geq 75^{\text{th}}$ 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 brain cancer was not increased among firemen, with SMR = 0.61 (CI 0.31-1.22) based on 8 deaths and showed no increase with duration of employment, year of first employment, type of company employment, cumulative number of fire runs in any position (fireman, lieutenant or captain), or the number of fire runs during the first 5 years of employment.

New adult cases of histologically diagnosed gliomas were studied in a case-control study in the bay area of San Francisco, CA, USA (Krishnan et al., 2003). The study comprised two temporal parts, 1991-1994 and 1997-1999 in which 476 and 403 cases, respectively, were identified. The controls (462 in series I and 402 in series II) were recruited by random number dialling and matched to cases by age, race and sex. Series I results had been reported earlier (Carozza et al., 2000) and its study limitations included small numbers for many of the occupational groups, a high percentage of proxy respondents among cases, and lack of specific exposure information. Some of these limitations were corrected in Series II, although the lack of specific exposure information remained (although 81% of the cases were interviewed). The two series were combined in the current analysis. The odds ratio was 5.93 (0.71 – 49.49) where employment as a fireman was the longest held occupation (based on 6 cases, 5 of which were astrocytic tumours).

Studies not reviewed

In addition to the studies listed in Table 1, there were two groups of other publications on cancer epidemiology of firemen that were examined. Of these, the following publications did not report brain cancer:

Mastromatteo, 1959, with 34 cancer deaths;
 Williams et al., 1977, with 58% interviews of 13179 cancer cases in 8 regions of USA;
 Feuer & Rosenman, 1986, with 23 cancer deaths;
 Hansen, 1990, with 21 cancer deaths;
 Ide, 1998, with 8 malignancies diagnosed.

And the following were case-control studies on firemen that examined cancers other than those of the CNS:

Morton & Marjanovic, 1984;
 Bates & Lane, 1995;
 Figgs et al., 1995;
 Finkelstein, 1995

Discussion

1. Problems in assessment.

a. Healthy worker effect.

Firemen tend to have a lower mortality rate than the general population, at least during the earlier years of employment. It may be 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). According to Guidotti, 1995, the healthy worker effect seems to be important during the first 20 years or so of employment, due in large part to a reduction in cardiovascular disease, but tends to disappear with longer employment. 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. Guidotti, 1995, has suggested that the healthy worker effect late in employment could be due to the removal of workers (because they become unfit) from exposure to risk factors predisposing them to early mortality.

b. Inter-study comparison of exposure

In reviewing the literature covering studies of firemen in different parts of the world, with the intention of applying the results to a particular region, it is as well to be aware that the definition of exposure categories may differ substantially between studies. Thus, in the Baris et al, 2001 study, a low cumulative number of runs in Philadelphia was defined as ≤ 3323 , whereas in Tornling et al., 1994, the highest cumulative run category in Stockholm was > 1000 . These are very different exposure experiences, yet the mean duration of employment in the Philadelphia study was 18

years, while 61% of firemen in the Stockholm study continued until retirement, 69% of the total having begun employment before the age of 25 years (mean duration of employment not given). This comparison also highlights the difficulty in using employment time as a surrogate for exposure.

c. Data presentation

Other important characteristics of the studies reviewed are the weaknesses of proportionate mortality studies. As recognised and listed by Burnett et al. (1994) these include: the information on the death certificate may be inaccurate, especially for an occupational group that routinely retires early and may pursue other jobs; there is no information on possible confounders such as tobacco smoking and alcohol consumption; and there is no information on length of employment or possible occupational exposures. Proportional measures can be misleading because their denominator is the total number of cases or deaths from all causes, not only that being studied. Furthermore, the PMR method of estimating risk 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). If this assumption is correct, then these reservations would apply to the studies of Grimes et al. (1991) and Burnett et al. (1994) in which data were reported as PMRs. To obtain the Mortality Odds Ratios (MOR) 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. 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). These authors compared the two methods and found that 20 (14%) of the cases identified by both methods did not agree as to the primary site of the malignancy. This is an important factor when considering brain cancer since many tumours found in the brain are secondaries. However, this possibility did not influence their particular study. Histological diagnoses were available in the only case-control study (Krishnan et al., 2003) and an elevated odds ratio, although statistically significant, was observed. The small number of cases (6 gliomas, 5 of which were astrocytic) is a factor to be considered in the evaluation of this result.

2. Criteria for causation

The database consisting of the reviewed studies was interpreted according to widely agreed criteria of causation. These are:

1. Consistency of the observed association;
2. Strength of association
3. Temporal sequence of events;
4. Dose-response relationship;
5. Specificity of the association;
6. Biological plausibility of the observed association;
7. Experimental evidence.

A consistent effect must be seen in several studies in different populations and at different times; no single study can provide definitive evidence for a relationship. The strength of the association (the size of the relative risk) is also important for

inference of causality, as is the correct time sequence of exposure and response, and dose-response relationship. Furthermore, the effect should show a specificity following a particular exposure and be biologically plausible; experimental evidence might be helpful in this respect.

Relative risk of brain cancer were increased in eight of the 19 studies (Heyer et al., 1990 & Ma et al., 1998 all being counted twice because of the multiple comparisons made):

Vena & Fiedler (1987), SMR 2.36 (CI 0.86-5.13);
 Grimes et al. (1991) PMR 3.78 (CI 1.22-11.71)
 Demers et al. (1992a), SIR_(men, general) 2.01 (CI 1.10-3.37); SIR_(police) 1.63 (CI 0.70-3.79);
 Aronson et al. (1994) SMR 2.01 (1.10-3.37);
 Tornling et al. (1994) SMR 2.79 (CI 0.91-6.51);
 Ma et al. (1998) MOR_(black men) 6.9 (CI 3.0-16.0);
 Krishnan et al., (2003) OR 5.93 (CI 0.71-49.49).

The remaining 11 studies (including the studies with race or comparison group differences) had risk ratios either below or close to unity:

Musk et al. (1978), SMR 1.03;
 Heyer et al. (1990), brain cancer SMR 0.95 (CI 0.20-2.79);
 Sama et al. (1990), SMOR_m 0.86 (CI 0.34-2.15);
 Beaumont et al. (1991) SMR 0.81 (CI 0.26-1.90);
 Demers et al. (1992b) SIR 1.01 (CI 0.37-2.20); SMR 1.00 (CI 0.37-2.18)*
 Guidotti (1993) SMR 1.47 (CI 0.30-4.29)
 Burnett et al. (1994) PMR 1.03 (CI 0.73-1.41)
 Demers et al. (1994) SIR_(police) 1.4 (CI 0.2-11); SIR_m 1.1 (CI 0.3-2.9)
 Ma et al. (1998) MOR_(white men) 1.0 (CI 0.8-1.4);
 Bates et al. (2001) SIR 1.27 (CI 0.4-3.0)
 Baris et al. (2001) SMR 0.61 (CI 0.31-1.22)

*Mixed population of firemen and policemen.

An important point to consider is that, generally, the numbers of cases were small. The three largest numbers of brain and other CNS cancer cases were in Ma et al. (1998) when 41 white men were analysed, but with no increase in risk (MOR = 1.0); in Burnett et al. (1994) when 38 men were analysed, but again with no increase in risk (PMR = 1.03); whereas in Aronson et al. (1994) with 14 cases analysed there was an increase in risk (SMR = 2.01). The numbers of cases in the remaining studies were less than 10.

Thus, there are a number of studies in which risks were elevated, but only in the smallest of the three studies with more than 10 cases was this observed. Also, with the exception of Aronson et al., 1994, the studies that appear to be the better conducted ones (irrespective of numbers of cases) in terms of exposure analysis and/or data collection and type of analysis (Demers et al., 1994; Baris et al, 2001) report risk ratios that are not elevated. It has already been emphasised that the number of cases in both of these latter studies are small.

The high risk found in the Ma et al. (1998) study of black firemen (MOR = 6.9, CI 3.0-16.0) and which was clearly significant is impressive, even though it was based on only 5 cases. None of the other studies attempted to study racial differences. This is a topic worthy of further investigation, particularly since the risks of cancer of the nervous system tend to be lower amongst black Americans than white Americans of the general population (Preston-Martin & Mack, 1996).

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 has most probably resulted in misclassification. Consequently, number of years employed 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 exposed employment 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. However, in neither study were there sufficient numbers of cases on which to draw any conclusions. 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.

3 *Routes towards a conclusion.*

The steps that are to be followed in arriving at a conclusion regarding the way that a particular disease should be handled by a compensation authority are:

1. hazard identification, based on an evaluation of the available studies;
2. judgment as to whether it is more likely than not that the exposure is the cause of the disease within that population;
3. consideration of the characteristics of a particular individual to see if that judgment can be applied without modification or whether it should be modified, in either direction.

a. *Nomenclature used by the International Agency for Research on Cancer*

The strongest (*sufficient*, in IARC terms) evidence for a causal relationship is when a positive relationship has been established between the exposure and human cancer in studies (note the use of the plural) in which chance, bias and confounding have been ruled out with reasonable confidence. Weaker (*limited*, in IARC terms) evidence for a causal relationship is when a causal relationship is considered to be credible, but chance bias and confounding cannot be ruled out with reasonable confidence. The evidence is considered *inadequate* when there are no data or the available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association. These terms are used in the context of hazard identification, not risk assessment.

b. Aetiological fraction

An alternative method of arriving at a judgment of “more likely than not” to be due to occupational exposure that has been suggested is the use of the “aetiological fraction,” this being the $(\text{Relative Risk} - 1)/\text{Relative Risk}$. If the relative risk (RR) is > 2.0 then the requirement for toxic torts is said to have been met (Muscat & Huncharek, 1989)¹. This criterion has been used more recently in relation to firemen (Guidotti, 1996), but less stringent conditions have also been applied (Guidotti & Goldsmith, 2002, who also quote the Industrial Disease Standards Panel of the Ontario Workers’ Compensation Board, 1994). The latter two publications seem to have settled on a Standardised Mortality Ratio of 1.7.

Conclusion

According to Guidotti & Goldsmith (2002) the elevation in risk for brain cancer reflects a true risk in certain subgroups. In support of this statement is the Ma et al., 1998 study finding of a large excess risk amongst black firemen. However, as mentioned here, this finding, although interesting, requires verification. Guidotti & Goldsmith (2002) were also concerned by the inconsistencies in the data, but they considered that the demonstration of an excess brain cancer in earlier studies appears most likely to be evidence of a confounded or obscured association, rather than no association with fire fighting. At the same time, these authors considered that the study by Baris et al. (2001) must be given the greatest weight. The current reviewer concurs with this last judgment, but also notes that this study gives no support to the suggestion that brain and other nervous system cancers in firemen are due their occupational exposures. Guidotti & Goldsmith (2002) were clearly uncertain about the relationship between fighting exposures and brain cancer. The current reviewer shares these uncertainties.

There is a tendency for risk of brain cancer to be higher than expected in firemen across the majority (10) of the 16 publications considered, although the excesses were frequently very small and reached statistical significance in only 4 studies, one of

¹ Questions that appear to be left unanswered are whether: (1) the RR itself should be > 2.0 , while the magnitude of the 95% confidence interval is of no interest; (2) the RR should have a lower confidence interval that is > 1 and a higher interval that includes 2.0; (3) the RR itself should be > 2.0 and the lower confidence interval should be > 1 ; or (4) the RR should have a lower confidence interval of > 2.0 . In the opinion of this reviewer, (1) is too lax and (4) is too stringent, while both (2) and (3) are consistent with the conventional requirement for statistical significance. Which of these is chosen has presumably been determined in the courts.

which was based on proportionate mortality. However, one of the remaining three (Aronson et al., 1994) was an SMR analysis that had more than 10 cases and therefore one of the larger available. The other two studies with more than 10 cases included a PMR analysis (Burnett et al., 1994). The overall conclusion reached is that there are some indications of an elevated risk. This increase can be very small, however, and conclusions from two of the three larger studies were based on the PMR method of analysis, which is normally used to generate hypotheses rather than to confirm a hypothesis. Therefore, use of the IARC term, *limited* evidence, in the light of the uncertainties is perhaps too strong and *inadequate* evidence is probably a better description of the currently insufficient evidence to lead to a presumption that a CNS tumour in a fireman is due to occupational exposures.

There are so many uncertainties in these small epidemiological studies that it is difficult to accept these results as indicating that exposure to exogenous carcinogens of any kind are responsible for the excesses reported. As described in the Introduction, there are many histological types of CNS tumours, each with its own characteristics. Thus, a true excess in incidence or mortality due to one histological type may be diluted by the inclusion in the analysis of other histological types that may be unaffected by the exposure. Almost all of the epidemiological studies described relied on death certificate information. This source seldom records a histological diagnosis, a weakness that can lead to misclassification, resulting in inflated risk estimates if death certificates indicate cause of death as due to a CNS tumour when it is actually due to a metastasis from another part of the body. The single case-control study described did not rely on death certificates (81% of the cases were interviewed and there was histological diagnoses), but 5 of the 6 relevant cases were astrocytic tumours. There is evidence (again, see the Introduction) that endogenous processes, rather than exogenous carcinogens can explain the transformation of astrocytes to a neoplastic phenotype. Astrocytes are the most common source of brain tumours.

Therefore, it is concluded that in the face of a lack of biological plausibility as well as the uncertainties regarding the status of the epidemiological studies, it cannot be either assumed or dismissed that a brain or other nervous system cancer developing in a fireman is the result of occupational exposure; however, a presumption of causality cannot be made.

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***Table 1. Summary characteristics and results of studies on the relation between occupational exposure as a fireman and cancer.**

| Reference | Study base & type | Reference group | Numbers | Risk* (95% C.L. or significance level) | Adjustments & Comments |
|-----------------------|--|---|--|---|--|
| Musk, et al., 1978 | Firemen in Boston, MA Cohort 1915-75 | Massachusetts men | 5655 firemen with 367 cancer deaths | All cancers not recorded CNS, 8, SMR = 1.03 (0.44-2.03). | No dose-response analysis. Based on death certificates. 104561 person-years actively working; 38414 person-years retirees |
| Vena & Fiedler, 1987 | Firemen in Buffalo, NY, 1950-1979 | White USA men | 102 cancer deaths | All cancers, SMR = 1.09 (0.89-1.32) Brain, 6, SMR = 2.36 (0.86-5.13) | Gradient in the SMR with years of service for all cancers, colon and urinary bladder. 32858 person-years |
| Heyer et al., 1990 | Firemen in Seattle, WA, 1945-83. | White USA men | 2289 firemen, 92 cancer deaths | All cancers, SMR = 0.96 (0.77-1.18) Brain, 3, SMR = 0.95 (0.20-2.79) | Small numbers of cancer cases, resulting in instability of the SMRs. Dose-response analysis inconclusive. 52914 person-years. |
| Sama et al., 1990 | Firemen in Massachusetts, 1982-86 | Massachusetts police (p); Massachusetts white men (m) | 315 cancer deaths | All cancers not recorded. Brain, SMORp = 1.52 (0.39-5.92) SMORm = 0.86 (0.34-2.15) | Cancer registry data |
| Grimes et al., 1991 | Firemen in Honolulu, Hawaii, 1969-88. | Hawaii men | 205 deaths, including 58 cancer deaths. | All cancers, PMR = 1.19 (0.96-1.49) Brain, 3, PMR = 3.78 (1.22-11.71) | Proportionality study. Analysis by person-years not reported |
| Beaumont et al., 1991 | Firemen in San Francisco, California, 1940-82. | White USA men | 3066 firemen with 236 cancer deaths | All cancers, RR = 0.95 (0.84-1.08) Brain + other CNS, 5, RR = 0.81 (0.26-1.90) | Analysis of dose-response inconclusive. Number of person years not stated. |
| 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) Brain, 18, IDRp = 1.63 (0.70-3.79) 18, SMRm = 2.07 (1.23-3.28) | 122852 person-years for the 3 cities Death certificate data (compare with Demers et al., 1992b & 1994). NB SMR for police v USA men = 1.36 (0.59-2.69), 8 cases |
| Demers et al., 1992b | Firemen and policemen in Seattle & Tacoma WA, U.S.A. 1974-1979 | For SIR, male rates for the urban counties of region For SMR, white WA, U.S.A. men | 4528 firemen & policemen with 338 cancer cases | Brain, 6, SIR = 1.01 (0.37-2.20) 6, SMR = 1.00 (0.37-2.18) | Comparison of cancer registries and death certificate data for reliability. Policemen & firemen not separated, but see Demers et al., 1992a |
| Guidotti, 1993 | Firemen in Edmonton & Calgary, Alberta, 1927-87 | Men in Alberta | 3328 firemen with 92 cancer deaths | All cancers, 92, SMR = 1.27 (1.02-1.55) Brain, 3, SMR = 1.47 (0.30-4.29) | Follow-up of 96% of the cohort for 64983 person-years. Weighting of years of service with job category time at fires estimates: fireman |

| | | | | | |
|-----------------------|---|---|--|--|---|
| | | | | | lieutenant, captain = 1; safety/training = 0.2; district chief = 0.1; desk job = 0.0. Dose-response analysis inconclusive |
| Aronson et al., 1994 | Firemen in Toronto, Ontario, 1959-89 | Men in Ontario | 5414 firemen with 199 cancer deaths 7 bladder | All cancers, 199, SMR = 1.05 (0.91-1.20) Brain, 14, SMR = 2.01 (1.10-3.37) | 114008 person-years of follow-up. Dose response analysis non-significant.. |
| 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) Brain + other CNS, 38, PMR = 1.03 (0.73-1.41) <65 years age, 19, PMR = 0.85 (0.52-1.34) | Proportionality study. Large number of cases, but no information on possible confounders, length of employment or occupational exposures. |
| Demers et al., 1994 | Firemen in Seattle & Tacoma, WA 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) Brain, 4, SIRp = 1.4 (0.2-11) SIRm = 1.1 (0.3-2.9) Duration of exposed employment < 10 years Brain, 1, SIRm = 1.6 (0.0-8.8) 10 – 19 years Brain, 0, SIRm = 0.0 (0.0-4.6) 20 – 29 years BRAIB, 3, SIRm = 1.6 (0.3-4.2) ≥ 30 years Brain, 0, SIRm = 0.0 (0.0-16) | Tumour registry data (compare Demers et al., 1992). |
| Tornling et al., 1994 | Firemen in Stockholm, Sweden, 1951-86 | Men in the Stockholm region | 1116 firemen with 93 cancer deaths | All cancers, 93, SMR = 1.02 (0.88-1.25) Brain, 5, SMR = 2.79 (0.91-6.51) Number of fire runs Brain cancer incidence <800, 0, SMR = 0 (0-2.53) 800 – 1000, 2, SMR = 2.82 (0.32-10.17) >1000, 3, SMR = 2.01 (0.40-5.88) Brain cancer mortality <800, 0, SMR = 0 (0.6-11) 800 – 1000, 1, SMR = 2.62 (0.07-14.62) >1000, 4, SMR = 4.96 (1.35-12.70) | Tendency for a dose-response relationship between duration of employment and number of fires attended for cancers of the brain. |
| Ma et al., 1998 | Mortality odds ratio study of death certificates of | Men who died from causes other | 6607 deaths of firemen | WHITE: All cancers, 1817, MOR = 1.1 (1.1-1.2) | Small numbers for some cancers in whites, small numbers for most cancers in blacks, |

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| | firemen for race-specific cancer risk in 24 states of USA, 1984-93 | than cancer | with 1883 cancer deaths (1817 white, 66 black) | Brain + CNS, 41, MOR = 1.0 (0.8-1.4) BLACK All cancers, 66, MOR = 1.2 (0.9-1.5) Brain + CNS, 5, MOR = 6.9 (3.0-16.0) | leading to instability of the MORs. Database similar to Burnett et al., 1994, but extended by 3 years and 3 states not included; similar strengths and weaknesses. |
| Bates et al., 2001 | Historical cohort study of all firemen in New Zealand, 1977-95 | Men who died from cancer in the same period throughout New Zealand | 4221 firemen | All cancers, 118, SIR = 0.95 (0.8-1.1) Brain, 5, SIR = 1.27 (0.4-3.0) | 58709 person-years. Data do <u>not</u> include 2/4 testicular cancer cases occurring in the Wellington cluster (Bates & Lane, 1995) Results (notably for testes) not changed by analysis for 1990-96 period (Cancer Registry database more complete from about 1990) |
| 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) Brain, 8, SMR = 0.61 (0.31-1.22)= Duration of employment: ≤ 9 years Brain, 2, SMR = 0.47 (0.12-1.89) 10 – 19 years Brain, 2, SMR = 0.44 (0.11-1.75) ≥ 20 years Brain, 4, SMR = 0.94 (0.35-2.49) Year of hiring (1925-1986) Before 1935 Brain, 1, SMR = 0.36 (0.05-2.57) 1935-1944 Brain, 3, SMR = 0.70 (0.23-2.17) After 1944 Brain, 4, SMR = 0.66 (0.25-1.77) Cumulative number of runs Low (<3323 runs) Brain, 3, SMR = 0.60 (0.19-2.85) Medium (≥3323 & <5099 runs) Brain, 2, SMR = 0.78 (0.20-3.11) High (≥5099 runs) Brain, 2, SMR = 0.73 (0.18-2.93) Runs during first 5 years as fireman Low (≤729 runs) All cancers, 171, RR = 1.00 Brain, 3, RR = 1.00 | 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. |

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| | | | | High (>729 runs) All cancers, 169, RR = 1.05 Brain, 4, RR = 1.18 (0.25-5.70) | |
| Krishnan et al., 2003 | Case-control study of all new adult glioma diagnoses in the San Francisco bay area, 1991-1994 (series I) and 1997-1999 (series II) | Men and women in the same area recruited by random digit telephoning | Series I: 476 cases, 462 controls. Series II: 403 cases, 402 controls | Longest held occupation Firefighters, men, gliomas, 6, OR = 5.93 (0.71-49.49). No women firefighters with gliomas. | Series I and II combined. Controls frequency matched to cases by age, race and sex. 5 of the 6 gliomas were astrocytic |

*I.D.R. = incidence density ratio; M.O.R. = mortality odds ratio; O.R. = odds ratio; R.R. = relative risk; S.I.R. = standardised incidence ratio; S.M.R. = standardised mortality ratio; S.P.M.R. = standardised proportional mortality ratio