Report to the Workers Compensation Board of Manitoba on the Association Between Selected Cancers and the Occupation of Firefighter

Prepared by Tee L. Guidotti and David F. Goldsmith
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Executive Summary

Four organ systems and five specific types of cancer are the subject of this inquiry:

- Brain
- Genitourinary, which consists for the purposes of this report of:
    - Bladder
    - Kidney
- Non-Hodgkin's Lymphoma (referred to elsewhere as "lymphatic cancer")
- Leukemia (referred to elsewhere as "hematopoietic cancer")

Each has unique issues and methodological problems with interpreting epidemiological data.

The evidence available since 1994 suggests that it is reasonable, given the available scientific evidence, to adopt a policy of presumption for claims submitted by full-time urban firefighters for primary-site brain cancer, bladder cancer, kidney cancer, non-Hodgkin's lymphoma (lymphatic cancer) and leukemia (hematopoietic cancer). The presumption for brain cancer, bladder cancer and kidney cancer is based firmly on a strong suggestion in the scientific literature of an excess risk. The presumption for non-Hodgkin's lymphomas and leukemias is based on the inference within the literature that within the overall category there are specific disorders for which the evidence suggests an elevated risk, but it is not possible to discern which among several are in excess.

Guidelines for assessing substantial contribution and plausible latency were developed based on direct job exposure.

Background

The Workers Compensation Board of Manitoba has requested guidance on the adjudication of claims involving certain types of cancer. This guidance is intended to support proposals for the amendment of *The Workers Compensation Act* with respect to establishing presumption for occupational disease among firefighters.

Four (really five) types of cancer are the subject of this inquiry:

- Brain
- Genitourinary, which consists for the purposes of this report of:
  - Bladder
  - Kidney
- Lymphatic
- Hematopoietic

Each has unique issues and methodological problems with interpreting epidemiological data.

Cancers of the brain arising from brain tissue are relatively rare and in the aggregate may include twenty or more individual types. Epidemiological studies do not distinguish among them because they are individually rare and subject to miscoding and aggregated coding when reported. In all probability, there are different environmental causes for different types when and if environmental factors play a role in causation. The most common type of "brain" cancer is meningioma, which is not obviously associated with environmental or occupational exposures. Gliomas (astrocytomas) are the second major type and are more likely to be associated with environmental and occupational exposures. Thus, with brain cancer it is probably the case that a true excess in one or more types may be diluted by the inclusion in the category of cancers of all other types. This leads to an inherent bias to underestimate the risk for that subset of cancers that may have a true association with firefighting. An analysis by specific tumour type might identify which one, if any, is associated with the risks of firefighting, but these cancers are uncommon and such a study would be very difficult and require large populations. Unless more specific studies are conducted on brain cancer among firefighters, which is not likely to occur, this problem cannot be resolved and the risk within the class must be inferred from the available data.

Genitourinary cancers include cancers of the kidney, ureter, bladder and the common structures of the urethra and reproductive tracts. Prostate cancer is generally separated out. There is no current evidence to suggest that cancers of the reproductive tract are associated with firefighting. Urinary tract structures are potentially affected by carcinogens that occur in urine, as demonstrated historically by the association between this class of cancer and exposure in aniline dye workers. Bladder cancer is much more common than kidney cancer, and cancer of the ureter and renal pelvis is rare.

Lymphatic cancers are generally known as lymphomas. There are many of them and new types are regularly identified as immunological methods become more sophisticated. Epidemiological studies generally do not separate the various types, or, if they do, use an old classification system that divides lymphomas into Hodgkin's disease and non-Hodgkin's lymphomas. Hodgkin's disease is actually a class of apparently closely related lymphomas that tend to peak in young adulthood and again at older age and have not been associated with occupational or environmental exposures or occupational risks. Non-

Hodgkin's lymphomas are a larger, more heterogeneous category and have been associated, in the aggregate, with many environmental exposures and occupations. Non-Hodgkin's lymphoma is further divided in many epidemiological studies into "lymphosarcomas" and "reticulum cell sarcomas". However, it is more common in the epidemiological literature to aggregate or lump together all lymphomas with hematopoietic cancers and multiple myeloma. This obscures the level of risk that may exist for certain critical types of lymphoma. (Multiple myeloma most closely resembles the lymphomas and is a tumour of B-lymphocytes, but appears to have different risk factors.)

If, as seems plausible, different environmental exposures may be associated with different cell types of non-Hodgkin's lymphoma, a truly elevated risk that may, for example, arise from exposure to some constituent of combustion gases may be diluted by inclusion with all the other types of lymphoma, many of which may have no environmental association. This leads to an inherent bias to underestimate the risk for that subset of lymphomas that may have a true association with firefighting. An analysis by specific tumour type might identify which one, if any, is associated with the risk, but these cancers are uncommon and such a study would be very difficult, likely impossible for one occupation, and require huge populations. Such a study has been attempted with pooled data from North American and European cancer registries and failed to identify a pattern, primarily because of difficulties in reliably and consistently typing the cancers by type of lymphoma (Sheila Hoar-Zahm, personal communication, 5 December 2001). Unless more specific studies are conducted using molecular markers on lymphoma cases arising among firefighters, and pooling data from many fire services, this problem cannot be resolved. Such a study is not likely to occur, and so the risk within the class must be inferred from the available data.

Hematopoietic cancers are generally known as leukemias. There are about a dozen well-recognized forms of leukemia, of which five or six predominate. Acute myeologenous leukemia (AML) is known to be associated with benzene exposure. AML is the most common leukemia in adults and this leukemia has been the subject of several specific studies exploring this association. Individually, leukemias are relatively uncommon and in population-based epidemiological studies of occupational risk they are often aggregated with other diseases as "leukemia, lymphoma and multiple myeloma". This obscures the level of risk that may exist for certain critical types of leukemia. Different environmental exposures may be associated with different cell types and particularly AML. Thus, a truly elevated risk of AML that may arise from exposure to benzene in combustion gases, may be diluted by inclusion with all the other types of lymphoma, many of which may have no environmental association. This leads to an inherent bias to underestimate the risk for that subset of lymphomas that may have a true association with firefighting. An analysis by specific leukemia type might identify an elevated risk confined to one type, such as AML, but leukemias are uncommon and such a study would require large populations. Unless more specific studies are conducted on leukemia among firefighters, which is not likely to occur, this problem cannot be resolved and the risk within the class must be inferred from the available data.

A presumption assumes that, all other things being equal, most cases of a certain type of cancer will be associated with occupational exposure, even though it is not possible to determine which case is actually caused by the occupation. A presumption is a way of being inclusive in the acceptance of such claims given that it is not possible to distinguish among them. A presumption is usually based on the demonstration that the relative risk exceeds twice that of the general population, because this statistical measure corresponds to even odds, or the notion that the risk arising out of work equals or exceeds that in daily life. In practice, it is impossible to make such a fine distinction. A relative risk of 1.7 or 1.8 (standard mortality ratio, or SMR, of 170 or 180) is usually indistinguishable statistically from one of 2 (a SMR of 200) with any confidence. A presumption is also appropriate when the condition is rare and there is a pattern or strong suggestion of strong association with an occupation that may be concealed by other factors that complicate interpretation of the risk estimate.

Past Recommendations

The Industrial Disease Standards Panel of the Ontario Workers' Compensation Board (as it was then called) submitted a report reviewing the association between selected disease outcomes and the occupation of firefighter (IDSP, 1994). This diverse advisory body, which was supported by a team of trained investigators, developed internal criteria for selecting possible associations between illnesses and work:

- An SMR that is statistically significant,
- an SMR that achieves a level of 170 whether or not it is statistically significant,
- a lower end of the 95% confidence interval that falls between 90 and 100,
- a dose-response relationship or evidence from other sources and jurisdictions.

The IDSP applied these criteria to proritize and organize its analysis. This analysis examined the existing literature and Ontario data on selected causes of death. The IDSP concluded the following on the basis of the evidence available at that time:

- Brain cancer: A strong association, consistent among studies, was identified and provided sufficiently strong evidence to conclude that "a probable connection exists between firefighting and primary cancer of the brain." IDSP recommended that "primary cancer of the brain should be made a rebuttable presumption."
- Lymphatic and hematopoietic cancers: A strong association was identified in certain studies but it was not consistent among studies. (Hodgkin's disease was not at issue. The lymphomas suggested by the evidence for firefighters were of the non-Hodgkin's type.) Evidence for a dose-response relationship and the known presence of benzene in combustion gases provided sufficiently strong evidence to conclude that "a probable connection exists between firefighting and primary lymphatic and hematopoietic cancers." The IDSP recommended that cancers of the lymphatic and hematopoietic systems be made a rebuttable presumption. Because available studies rarely dis-aggregated the categories, the IDSP could not separate its recommendations by cell type.
- Genitourinary cancers, bladder: Driven by excesses reported for bladder limited evidence for a dose-reponse, but not cancer frequency at genital sites, the IDSP concluded that "a probable connection exists between primary bladder cancer and the occupation of firefighting." It submitted guidelines for adjudicators in assessing claims for bladder cancer.
- Genitourinary cancers, kidney: Driven by a strong excess reported in Guidotti (1993) in Alberta (SMR=414, 7 cases) and elevations found on

reanalysis of data on Chicago firefighters (Orris, 1992), the IDSP concluded that "a probable connection exists between kidney cancer and the occupation of firefighting." It submitted guidelines for adjudicators in assessing claims for kidney cancer.

As of 1995, Guidotti (1995) reviewed much of the same literature in the course of preparing a report on the evidence for presumption of risk among firefighters for compensation purposes. This paper, informed by his own experience conducting a large and relatively complete cohort mortality study, pointed out several methodological issues and interpreted the available literature somewhat differently from IDSP report. This report, which has been widely cited and frequently submitted in evidence, took the following positions on the cancers of concern:

- Brain cancer: Sufficient evidence existed to assume a general presumption of risk for brain cancer among firefighters.
- Bladder cancer: Sufficient evidence existed to assume a general presumption of risk for bladder cancer among firefighters.
- Kidney cancer: Sufficient evidence existed to assume a general presumption of risk for kidney cancer among firefighters.
- Lymphatic cancers (other than Hodgkin's disease): Insufficient evidence existed to justify a presumption or an association. Guidotti therefore recommended a case-by-case approach.
- Hematopoietic cancer: Insufficient evidence existed to justify a presumption, but strong evidence existed for an association with AML. Guidotti therefore recommended a case-by-case approach.

The IDSP relied in part on a study by L'Abbé and Tomlinson on firefighters in metropolitan Toronto, reported in 1992. At the time of its publication, this was one of the better and larger studies to have been conducted. This study appeared to have been more specific in its taxonomy of lymphoma and leukemia than other studies. An SMR of 190 (52 – 485) was reported for one type of leukemia, "lymphatic leukemia", using terminology which is not standard. We therefore reviewed it again to determine the basis for this apparent specificity. The authors make a clear distinction between lymphomas and leukemias in the text and do not count lymphomas with leukemias in the tables, although they do not report lymphomas separately as a category of malignancy in their tables. From the text of the original report, it appears that unless there was an error in terminology, all cases of leukemia observed which were coded (three out of four) and reported to the Ontario Cancer Treatment and Research Foundation were of lymphatic origin. This is unusual, as acute myelogenous leukemia is more common among adults than either acute or chronic lymphocytic leukemias. There are two anomalies in these anecdotal data: Firstly, the report does not specify whether the leukemias were acute or chronic, which is unusual. Secondly, only one case of lymphatic leukemia is described as "histologically confirmed". The diagnosis of leukemia, and cancer is general, demands histological confirmation. Finally, the profile of exposures in firefighting, which includes benzene, is more characteristically associated with acute myelogenous leukemia than either form of lymphocytic leukemia. One must conclude that although L'Abbé and Tomlinson may be correct in reporting an excess of one specific type of leukemia, their report is not incontrovertibly evidence of this. It is evidence, however, consistent with an increased risk for leukemia overall.

The data from L'Abbé and Tomlinson (1992) for non-Hodgkin's lymphomas is more straightforward to interpret. They make a conventional distinction between lymphosarcoma and reticulum cell sarcoma (see above), but aggregate both in the analysis in the text and both together with other malignancies in the tables. An excess risk of SMR 203 (42 – 592) was observed on the basis of numbers too small to achieve statistical significance. The fact that three of the four observed lymphomas were lymphosarcomas does not deviate from expected, given the usual distribution of these cancers, the lack of specificity in the groupings and the small numbers.

There is no evidence that Hodgkin's disease, which is a distinct class of lymphoma, is associated with occupational or environmental exposures in general and firefighting in particular.

Evidence Since These Recommendations for a Presumption

Additional relevant studies have been added to the literature on firefighting since these two contemporaneous reports.

Burnett *et al.* (1994) conducted a very large proportionate mortality study on firefighters in 27 American states from 1984 through 1990, using data from the National Occupational Mortality Surveillance (NOMS) system. Limitations of these data are partially overcome by the sheer size of the database, which, with 5744 deaths among white male firefighters, is beyond what may be achieved in any one cohort study. They reported the following:

- <u>Brain cancer:</u> No elevation was observed. The proportionate mortality ratio (PMR) was 85 for firefighters dying under the age of 65 and 103 for those dying at or over the age of 65. With 19 and 38 deaths, respectively, this is a large collection of deaths by brain cancer. Applying the IDSP criteria would not have flagged this cause of death as an outcome of concern.

- Bladder cancer: No elevation was observed but the authors imply that they expected a deficit due to the healthy worker effect. The PMR was 101 for firefighters dying under the age of 65 and 99 for those dying at or over the age of 65. With 9 and 37 deaths, respectively, this is a large collection of deaths by bladder cancer. Applying the IDSP criteria would not have flagged this cause of death as an outcome of concern.
- Kidney cancer: A marked elevation was observed. The PMR was 141 for firefighters dying under the age of 65 and 144 for those dying at or over the age of 65. With 24 and 53 deaths, respectively, this is a large collection of deaths by kidney cancer.
- Lymphatic cancers: These were separately addressed in the Burnett *et al.* study, which revealed an elevation for non-Hodgkin's lymphoma. The PMR was 161 for firefighters dying under the age of 65 and 130 for those dying at or over the age of 65. With 35 and 66 deaths, respectively, this is a large collection of deaths by lymphoma.
- Hematopoietic cancers: These were separately addressed in the Burnett *et al.* study, which revealed an elevation for the class as a whole. The PMR was 171 for firefighters dying under the age of 65 and 119 for those dying at or over the age of 65. With 33 and 61 deaths, respectively, this is a large collection of deaths by leukemia.

Ma *et al.* (1998) conducted a large study using the same database to explore race-specific disparities in cancer mortality. The study was not intended to replicate or overlap with Burnett *et al.*, as its purpose was different. It is much smaller and covers a heavily overlapping population. For this study, the NOMS database was extended by three years to 1993, but it lost data from three states that were removed. As expected, the results were similar. Race as coded on the death certificates yielded 1817 deaths of white firefighters and 66 deaths of black firefighters. Of greater interest is the pattern of race-specific elevations. If an environmental or occupational factor is the major risk factor for a type of cancer, one would expect elevations in both white and black firefighters. Ma *et al.* reported:

- Brain cancer: No elevation was observed for white firefighters, but a very large elevation, with a mortality odds ratio (MOR) of 6.9 (95% CI 3.0 – 16.0), was observed for black firefighters.
- Bladder cancer: A not-quite statistically significant elevation of 1.2 was observed for white firefighters and an elevation (but based on a single case) was observed for black firefighters.
- Kidney cancer: A borderline statistically significant elevation of 1.3 was observed for white firefighters. No cases were observed for black firefighters.
- Lymphatic cancer: These were identified separately, as in the study by Burnett *et al.* A statistically significant elevation was observed among white firefighters, with an MOR of 1.4, but no elevation was observed among black firefighters (but based on a single case).
- Hematopoietic cancers: No apparent elevation was observed, with an MOR of 1.1. There were no cases among black firefighters. This is unusual but probably reflects the small numbers of black firefighters in the population.

Baris *et al.* (2001) conducted a cohort mortality study of 7789 Philadelphia firefighters employed from 1925 to 1986. The authors used a retrospective cohort mortality study compared to US white male rates in order to calculate standardized mortality ratios. These men were hired in their late 20s (on average) and worked for approximately 18 years, with an average of 26 years follow-up. This cohort of firefighters had 204,821 person years of follow-up. This study should be accorded the most weight because it has the greatest firefighter follow-up (i.e., study power), spanning most of the 20th century, and thus best reflects the cancer and non-cancer associations related to this occupation. The investigators examined their cohort by age, duration of employment, job assignment and by number of runs (based on an enumeration of responses from the firehall) in three broad ordinal categories. This study is the best on the topic methodologically and least susceptible to bias to be published since the mid 1990s. It must be given the greatest weight.

There were 2220 deaths among the members of the cohort. All causes of death and all cancers were approximately equal to the expected rates for all U.S. white males. The authors did observe statistically significant excesses for colon cancer (SMR=1.51; 95% CI =1.18-1.93). Non-significant excesses were reported for cancers of the buccal cavity and pharynx (SMR=1.36; 95% CI=0.97, 2.14); for non-Hodgkin's lymphoma (SMR=1.41; 95% CI=0.91,2.19); for multiple myeloma (SMR=1.68; 95% CI=0.90-3.11) and for lung cancer (SMR=1.13; 95% CI 0.97-1.32). With >20 years of firefighting, the following cancer sites showed the following risks: colon cancer (SMR=1.68; 95% CI 1.17-240); kidney cancer (SMR=2.20; 95% CI 1.18-4.08); non-Hodgkin's lymphoma (SMR=1.72; 95% CI 0.90-3.31); multiple myeloma (SMR=2.31; 95% CI 1.04-5.16); and benign neoplasms (SMR=2.54; 95% CI 1.06-6.11).

Baris *et al.* developed a direct index of exposure by assessing risk by three categories of firefighting runs, with low exposure being less than 3322 runs; medium exposure being greater than or equal to 3323 and less than 5099 runs; and high exposure being greater than 5099 runs. Cancer of the pancreas showed a clear dose-response with SMRs that rose from 1.02 for low to 1.17 for medium to 1.61 for high exposure. Although there were no other tumour sites with exposure-response gradient, when comparing low exposure (SMR set to 1.00) to high exposure, several cancer sites demonstrated increasing risk: stomach, SMR=1.20; pancreas, SMR=1.42; leukemia, SMR=1.22; and benign neoplasms, SMR=2.06. The authors also compared lifetime runs with diesel exposures, including a category of non-exposed. Although there were no exposure-response gradients, several sites demonstrated increasing risks in the medium and high categories compared to unexposed: buccal cavity and pharynx, prostate, brain, multiple myeloma, and leukemia.

There is an apparent dose response for assessment of low, medium and high exposure related to diesel exhaust for respiratory diseases, but not for any cancer. The SMR rises from 1.00 (non-exposed) to 1.37 for low exposure to 1.45 for medium and finally to 1.49 among those in the high exposure group. Interestingly, there is no such exposure-response relationship for number of runs over the career of the firefighter (regardless of diesel exposure).

All of these excesses have relevance to toxicology and inhaled toxic hazards found in the firefighting profession, except the excesses for benign neoplasms. This is a "wastebasket", or residual category of diagnostic rubrics. It is not clear whether this represents a true elevation in some unusual class of tumour or (more likely) misclassification.

- Brain cancer: A relative deficit of brain cancer was observed, with an SMR of 0.61 (95% CI 0.31-1.22). Risk did not appear to be concentrated in any subset of firefighters by assignment, number of runs or duration, although the highest SMR (1.18) was observed among firefighters with more than 729 runs in the first five years of duty. Because brain is an uncommon cancer, statistical power is usually limited in epidemiological studies. Therefore, this study does not contradict the findings of other studies that suggest an elevation in risk (upper 95% CI was 1.22), but it does not support them either.
- Bladder cancer: A non-significant slight elevation in risk for bladder cancer was observed, with an overall SMR of 1.25 (95% CI 0.77-2.00). The elevations for bladder cancer are due largely to historical exposure among firefighters hired before 1935, among whom the SMR is 1.71 and not quite significant, compared to 1.17 for those hired between 1935 and 1944 and 0.35 for those hired after 1944. Risk was concentrated in firefighters who had been assigned to ladder companies (SMR 1.81) over engine companies (0.53), with those assigned to both having an intermediate risk of 1.70. Although there is a reverse dose-response relationship with employment overall and cumulative runs, there is an apparent exposure-response relationship with runs during the first 5 years as a firefighter. Compared to those with lower frequencies of runs, those with high frequencies (>729 runs) showed an SMR of 2.54 (95% CI 0.49-14.59). This could be interpreted as evidence that the intensity of exposure at the beginning of the latency period is the principal risk factor. This study does not contradict, and lends modest support to, other studies that suggest a higher risk.
- Kidney cancer: No elevation was observed overall, but significantly elevated risks occurred among firefighters who had been employed 20 years

or more (SMR 2.20, 95% CI 1.18-4.08), those hired between 1935 and 1944 (SMR 2.11, 95% CI 1.06-4.24) and those with medium levels of runs during their careers. Those with high levels of runs did not show an excess, but this might be explained by a survivor effect or competing mortality. There is a suggestion in these data that a true elevation, exceeding a doubling of risk, may exist in subgroups with longer duration of exposure. This is consistent with other studies that show higher risks.

- Lymphatic cancer: A not-quite significant overall elevation was observed for non-Hodgkin's lymphoma, with an SMR of 1.41. While not achieving statistical significance, this rose to 1.72 for firefighters with 20 years or more experience and 2.65 for those assigned to ladder companies. The subset hired between 1935 and 1944 did show a statistically significant elevation of SMR 2.19 (95% CI 1.18-4.07). A reverse dose-response relationship was observed by number of runs, with the group experiencing the lowest number showing a significant elevation, with an SMR of 2.36 (95% CI 1.31-4.26), but no relationship was found with runs during the first five years. These data may appear internally inconsistent. However, when the association does achieve statistical significance, their lower bounds are remarkably high (i.e., greater than 1.0). This suggests the possibility that these are true elevations in these subgroups.
- Hematopoietic cancers: No overall elevation was observed for the leukemias (SMR was 0.83). A statistically significant elevation in SMR of 2.75 (95% CI 1.03-7.33) was observed for firefighters assigned to ladder companies only, but not to those assigned to both ladder and engine companies. A non-significant elevation was observed for those with a high level of runs in the first five years, with an SMR of 2.44 (0.70-8.54), and with medium (but not high) levels of runs over a lifetime, with SMR 2.50

(0.56-11.10). These data are not compelling evidence for a true association in this population but does not rule it out. Because of power considerations, this study also does not contradict others that have demonstrated a higher overall risk.

From the Baris *et al.* study, some tentative conclusions emerge for all the epidemiology data. There are no significantly *reduced* SMRs for any of the prior tumor sites linked with firefighting: brain, bladder, kidney and lymphatic malignancies. Furthermore, the Baris study adds weight to linkages between firefighting and cancers of lymphatic system and with kidney, and suggests associations with colon, pancreas and prostate cancers.

Evidence for Adjudicative Criteria

In the previous section we examined evidence, taking methodological issues into consideration, for an association between firefighting and certain cancers of a magnitude approaching or consistent with equal odds. In this section we examine evidence for criteria necessary to presume that exposure was sufficient in magnitude to be causal and not coincidental. These criteria can then be used in adjudication. We do not advise specific job assignments or cumulative number of fire alarms to which firefighters were assigned. These are generally not well documented and are associated with statistical findings for populations that may not apply to individual firefighters. For firefighters, as for most occupations, the only practical basis for such a criterion is duration of employment.

Duration of employment is difficult to separate from latency. Latency is the elapsed time between first exposure to a carcinogen and the clinical manifestation of the disease. It reflects the time after the genetic constitution of the cell has been altered that the cell is dormant, then becomes cancerous and finally proliferates by dividing until a cancer appears that is visible, detectable on tests or interferes with function and is discovered.

Brain cancer, being a heterogeneous category, is not adequately described by a single latency. The excess reported for brain in other studies is not observable in either Baris *et al.* (2001) or Guidotti *et al.* (1993) because of small numbers. Neither study is available for the purpose of establishing the association between risk and occupational activity for this set of cancers. Demers *et al.* (1992) does document a doubling of risk (SMR 257) at less than ten years of employment and peaking at greater than a tripling of risk (SMR 353) up to 19 years. Heyer *et al.* (1990) also shows a near doubling of risk (184) at less than 15 years duration of exposure. On the limited available evidence, therefore, an elapsed period of less than ten years cannot be used to rule out an association in an individual. It is not clear what the minimum latency for a brain cancer might be, especially for rapidly growing astrocytoma. It would be reasonable to assume that for aggressive brain cancers, exposure periods plus latencies may be very short, perhaps as short as five years.

For bladder cancers, latencies tend to be shorter and more variable than for other solid tumours. It is generally held as a rule of thumb that the latency period for solid tumours is on the order of twenty years, but this should be understood as the modal latency, the time elapsed before an excess is observed, and not the minimum time required to elapse. Such rules of thumb do not readily apply to individuals. Cancers associated with occupational exposures can and do appear well before an arbitrary latency period, although there is usually a minimum imposed by the biology of the tumour and its rate of proliferation. For bladder cancer, evidence from aniline dye workers in the 1940s and 1950s provided strong evidence for a latency as short as seven years. Latency is responsive to dose for many tumours and the high, constant exposure of workers in the chemical industry in the early twentieth century may have compressed the latency period to its absolute minimum in a tissue that is susceptible to malignant degeneration. This is not plausibly the case for firefighters, where exposure tends to be much less and highly intermittent. The exposure of firefighters to potential bladder carcinogens is much less than for chemical workers in that era. In data from Alberta (Guidotti, 1993), bladder cancer did not appear before age 60 or before 20 years of service and showed a very long peak latency of 40 years. Baris *et al.* reported a slightly elevated SMR of 1.25 for bladder cancer, with greatest risk being among those hired before 1935 (SMR=1.71 95% CI=0.94,3.08), and among those with greater number of runs during their first 5 years of employment (SMR=2.59, 95% CI=0.64,9.84). It would be difficult to accept a latency under 10 years for bladder cancer in a firefighter but the literature does not rule out latencies under twenty years in other occupations. One might expect that the duration of service associated with risk among firefighters to be on the order of 15 years.

It is not clear that kidney cancer follows the same pattern as bladder cancer and latency has not been as intensively studied for kidney cancer. On the basis of current understanding and the literature on firefighters, it might be difficult to accept a latency under 15 years, just on the basis of the time required for a solid tumour to proliferate. However, latency periods of less than 20 but greater than 15 would not be unreasonable.

The standard cancer epidemiology text by Schottenfeld and Fraumeni (1996) cites several studies in which a near doubling of risk is associated with duration of employment less than ten years, among them aluminum workers exposed to polycyclic aromatic hydrocarbons. Firefighters are not exposed to the same intensity of exposure but are exposed to these carcinogens. In data from Alberta (Guidotti, 1993), a marked elevation in risk for kidney cancer was visible in the category 10–19 years of employment. Baris *et al.* (2001) reported a doubling of risk (SMR=2.20, 95% CI=1.18, 4.08) among those employed for 20 or more years.

Lymphomas (other than Hodgkin's disease) appear to have long latencies. However, they are a collection of conditions that tend to manifest themselves in older persons, and their relationship to environmental factors is more difficult to determine. As a result, it is difficult to generalize over the class. Baris *et al.* found that among those employed more than 20 years, the SMR was 2.20 (95% CI=0.90,3.31).

Leukemias tend to have short latencies, on the order of five years or so. Short latencies and, therefore, duration of employment for leukemia are reasonable, on the order of four years, to ensure that no errors of exclusion are likely. Baris *et al.* did not find consistent evidence of excesses of leukemia, though for those assigned to ladder companies the SMR was 2.75 (95% CI=1.03,7.33).

Interpretation

When a strong potential exists for misclassification or dilution of risk estimates, or when power considerations make the achievement of statistical significance unlikely because of small numbers, elevated risks take on added significance. In this analysis we have placed greatest weight on the magnitude and consistency of the association for bladder and kidney cancer, which are discreet and separable tumours, and on suggestions of an elevation in various subgroups for brain, lymphatic (non-Hodgkin's lymphomas) and hematopoietic cancers.

Brain Cancer

The weight of evidence to date suggests that the elevation in risk for brain cancer reflects a true risk in certain subgroups, as demonstrated in black firefighters, but these subgroups cannot be readily identified by usable criteria in adjudication. The inconsistency in the literature cannot be explained by current data. However, given power considerations, the demonstration of excess in brain cancer in past studies appears most likely as evidence of a confounded or obscured association than as evidence of no association with the occupation of firefighting.

Kidney and Bladder Cancer

The weight of evidence to date suggests that the elevation in risk for both bladder and kidney cancer reflects a true risk associated with occupation. The elevations are not entirely consistent but this may reflect employment history, the era covered by the study and possibly exposure during the first few years of service. It is noteworthy that the findings of the Baris *et al.* (2001) study support a doubling of risk for those employed for 20 years or more, or for those who began work in the 1930s or 1940s. The elevations reported in other studies suggest an association with exposure that may not rise to the level of a doubling of risk in recent data, but they are compatible with past recommendations for a presumption.

Lymphatic and Hematopoietic Cancers

The weight of evidence for lymphatic cancer of the non-Hodgkin's type and hematopoietic cancer suggests that the elevation in risk reflects a true risk in certain subgroups but these subgroups cannot be readily identified by criteria that would be useful for adjudication. The more recent evidence is consistent with an elevation for lymphoma and does not contradict the finding in other studies that found an increased risk for hematopoietic cancers (leukemias). For example, the L'Abbé and Tomlinson (1992) and Demers *et al.* (1992) studies provide strong evidence suggesting an elevated risk, notwithstanding the variation in risk estimates in other studies. Baris *et al.* (2001) presents a confusing picture for non-Hodgkin's lymphoma because employment for 20 or more years produces an SMR of 1.72, with an elevated risk for those hired after 1935, but there was an inverse of risk for cumulative number of runs. Because of power considerations with uncommon disease outcomes and the tendency for misclassification and ascertainment bias to lower the estimate of risk, it is entirely possible by chance alone to miss a true elevation in an uncommon disease. Evidence for an elevation should, therefore, be weighted more heavily than evidence for a negative finding in a similar study, all other things being equal. Thus, the earlier recommendations from IDSP (1994) for a presumption and by Guidotti (1995) for an implied presumption but with individual evaluation of each case are not contradicted by the new evidence.

Multiple myeloma (ICD-9= 203) is often lumped with lymphatic malignancies, and the results from Baris *et al.* (2001) lend weight to the prior assessment of firefighting and lymphatic cancers—non-Hodgkin's and leukemia, specifically. These authors found that multiple myeloma increased with duration of employment, with 20+ years having a statistically significant SMR of 2.31, and a statistically significant SMR of 2.54 for engine company employment only. There was some suggestion of correlation with medium and high diesel exposures (the latter based on small numbers of deaths).

In the case of hematopoietic cancer (leukemia) there is an additional issue. The L'Abbé and Tomlinson (1992) study would be unsurprising if the leukemia in question were acute myelogenous leukemia (AML), which is to be expected in circumstances in which benzene is a hazard. However, the leukemia reported to be in excess, on the basis of small numbers and scanty evidence, is "lymphatic" (lymphocytic) leukemia (LL), presumably the acute form, which is more common than chronic. Baris *et al.* (2001) does not help clarify this issue, nor is the SMR evidence clear. Leukemia mortality is not broken into AML or LL subtypes, and only those from ladder companies had a significant doubling of risk for an SMR of 2.75. This means that it cannot be argued convincingly that only one form of acute leukemia, either myelogenous or lymphocytic, should be recognized. Although Ontario recognizes lymphocyctic leukemia, the evidence presented by L'Abbé and Tomlinson (1992) is not definitive and cannot be used to rule out the possibility of an association with AML. Thus, it is not possible to recommend a selective criterion that only recognizes AML or LL or, for that matter, acute and not chronic leukemias.

Other Tumour Sites for Future Consideration

Because of the large study power of Baris *et al.* (2001), and because there is some past evidence of an association, colon cancer is worth considering for addition to the presumption list. Overall, Baris *et al.* found an SMR of 1.51 (95% CI 1.18,1.93), based on 64 deaths; there was no consistent dose-response for duration of employment nor for cumulative number of runs. However the risks were greater than 1.00 for all three levels: 1.93 for low; 2.22 for medium and 1.22 for high number of runs. It is worth noting that Guidotti (1993), Howe and Burch (1990) and Schwartz and Grady (1986) reported excess colon cancer risk. Also, Vena and Fiedler (1987) reported a significant SMR of 1.83. Thus, two studies, one examining two out of three subgroups and the other the population as a whole, have demonstrated relative risks close or equal to double. There is beginning to be sufficient evidence to consider adding colon cancer to the presumption list in the future for claims related to firefighting.

Conclusion

The evidence available since 1994 suggests that it is reasonable given the available scientific evidence to adopt a policy of presumption for brain cancer, bladder cancer, kidney cancer, non-Hodgkin's lymphoma (lymphatic cancer) and leukemia (hematopoietic cancer) for claims associated with occupation as a firefighter. The presumption for brain cancer, bladder cancer and kidney cancer are based firmly on a strong suggestion of an excess in the literature. The presumption for non-Hodgkin's lymphomas and the leukemias are based on the inference that within the overall category there are specific disorders for which the evidence suggests an elevated risk but it is not possible to discern which among several are in excess.

We suggest that non-Hodgkin's lymphomas and leukemias as categories be watched for possible revision of the scheduled presumption in the future in the unlikely event that one or more particular varieties are shown to be individually associated with occupational as a firefighter.

Colon cancer is another category to be watched for possible addition to the presumption list.

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