Evaluating the Association Between Selected Cancers

And

Occupation as a Fire fighter

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Executive Summary

Certain types of cancer present unique issues and methodological problems with interpreting epidemiological data. Recently, the British Columbia Professional Fire Fighters' Association requested our assistance in evaluating the association of specific types of cancer with fire fighting: brain, bladder, kidney, testicular, non-Hodgkins lymphoma (often referred to as "lymphatic cancer") together with myeloma and leukemia (often referred to as "haematopoietic cancer") and lung. 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, testicular cancer, non-Hodgkins lymphoma (lymphatic cancer) and leukemia (haematopoietic cancer) for claims associated with occupation as a fire fighter. Collateral evidence and a close analysis of the problem suggests that it is reasonable to establish a presumption for lung cancer among fire fighters who do not smoke cigarettes. It is acknowledged that such a presumption based on smoking status presents practical problems in adjudication. Colon cancer among fire fighters is also worth considering for addition to a presumption list.

The presumption for bladder cancer, kidney cancer and testicular cancer are based firmly on evidence for an excess in the literature. The presumption for brain cancer, non-Hodgkins lymphomas and 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. The presumption for lung cancer is limited to non-smokers and presents a particularly difficult problem in disentangling the attributable risk from fire fighting from the strongly confounding effect of cigarette smoking. The evidence does not support a presumption that lung cancer in fire fighters who smoke cigarettes arises out of occupation more often than not. However, there is evidence that occupation as a fire fighter is associated with some attributable risk and that in non-smoking fire fighter this risk is sufficiently elevated to justify a presumption. General guidelines for latency and elapsed time are also discussed.

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Introduction

The occupational health problems of fire fighters have been extensively studied, to the point that the world epidemiological literature on this topic is among the most complete and detailed available for any occupation. Despite this detail, intense interest and relative completeness, there are many unresolved issues. Whether fire fighters are at increased risk for cancer, in particular, has been an active topic of investigation.

Past efforts at meta-analysis did not successfully identify several cancers for which later cohort studies provided strong evidence for a probable increased risk, such as kidney and bladder (Howe and Burch, 1990). Pooled studies with large populations but limited resolution have not fully resolved these issues, either (Burnett, 1994). Since the rate of publication of studies on fire fighters appears to be slowing from a peak in the early 1990's, these issues are highly unlikely to be resolved by more data in the near term (Guidotti, 2000). Indeed, further studies using existing databases and the same methodology are likely to replicate the pattern of past studies of fire fighters, which are among the most complete, detailed and comprehensive studies available on any occupation.

We suggest that these issues represent a class of problem in occupational epidemiology that is best approached rigorously by examining the structure of the problem outcome by outcome. In this report we make an initial effort to do so.

Background

Because of their occupational exposure to a variety of toxic agents, fire fighters may be at risk for a number of exposure-related diseases (Guidotti, ed., 1998). A major unproven hypothesis is that risk increased following the introduction in the 1950's of combustible plastic furnishing and building materials known to generate toxic combustion products (Guidotti, 1992). Collateral toxicological evidence suggests that certain cancers are likely to be associated with fire fighting because of the exposures that fire fighters sustain, specifically lung cancer and genitourinary cancers. However, to date there has not been an unequivocally clear and consistent demonstration of excess risk due to occupational exposure for the most anticipated outcomes, including lung cancer, and for certain uncommon cancers, including leukemias, lymphomas and myeloma.

In 1994, the Industrial Disease Standards Panel of Ontario (ISDP, 1994) produced a widely-quoted report designed to identify candidate conditions for occupational disease presumptions in workers' compensation.

We published a similar analysis in 1995 (Guidotti, 1995). We concluded the following for various cancers of concern:

- Lung cancer: There is evidence for an association but not of sufficient magnitude for a general presumption of risk. We suggested that a presumption be considered for non-smoking fire fighters.

- Cancers of the genitourinary tract, including kidney, ureter, and bladder: The evidence is strong for both an association and for a general presumption of risk.

- Cancer of brain: Incomplete evidence strongly suggests a possible association at a magnitude consistent with a general presumption of risk.

- Cancer of lymphatic and haematopoietic tissue: As a group, there is some evidence for both an association and a general presumption or risk. However, the aggregation is medically meaningless. We therefore recommended a case-by-case approach.

- Cancer of the colon and rectum: There is sufficient evidence to conclude that there is an association but not that there is a general presumption of risk.

In 2002 we prepared a report on the health risks to fire fighters for the Government of Manitoba at the request of the Minister for Labour and Immigration, who is also responsible for the Workers' Compensation Act, The Hon. Becky Barrett. Based on that report, Bill 5 was introduced into the Manitoba Legislature to facilitate claims for certain chronic diseases (stated as cancers of bladder and kidney, cancer of the brain, haematopoietic cancers and lymphatic cancers) and was passed into law. The report was also mentioned by the Lieutenant Governor of Manitoba, The Honourable Peter Liba, in his Speech from the Throne in November. This report has garnered much attention in the press and from other governments. The Workers Compensation Board of Manitoba later requested guidance on the adjudication of claims involving certain types of cancer. This guidance was intended to support proposals for the amendment of the Workers' Compensation Act with respect to establishing presumption for occupational disease among fire fighters. We here present the evidence and rationale for our recommendations.

There were three parts to the review. The first was to identify evidence for an association that was sufficient in magnitude and circumstances to be causal and not appreciably confounded. The second was to evaluate whether the magnitude of the association, in context, was consistent with equal odds, or a doubled risk compared to an unexposed reference population. The third was to advise on latency periods that would be deemed plausible for work-related cancers. For fire fighters, as for most occupations, the only practical basis for such a criterion is duration of employment. We did not advise on criteria for specific job assignments or cumulative number of alarms for fire stations to which fire fighters were assigned, as these are generally not well documented.

This report also draws on evidence submitted to the workers' compensation boards and tribunals in Alberta and British Columbia for some of the same selected cancers and for lung cancer.

The present report was prepared for the British Columbia Professional Fire Fighters' Association, with special reference to the *Protocol for the Assessment of Medical/Scientific Information* of the Workers' Compensation Board of British Columbia, 1993. There is no accepted, appropriate and transparent forum for obtaining open peer review and discussion of methodology that applies to policies rather than research. Few peer-reviewed scientific journals are interested in receiving such papers. The next best option is to present the concept at an open scientific meeting to obtain reaction and feedback. The rationale described below for approaching haematopoeitic cancers, cancer of the brain, and lung cancer in non-smoking fire fighters was described in full before an international audience of approximately 50 peer occupational epidemiologists on 25 February 2003, at the International Congress on Occupational Health (Iguassu Falls, Brazil), where an abstract describing the general problem (but not the specifics of methodology) was peer-reviewed and accepted. No objections were expressed, the general approach was considered sound and a delegate from Germany indicated in open discussion that a similar proposal was under active consideration by the national workers' compensation system, die Berufgenosschaften.

The Rationale of Adjudication

The *Protocol for the Assessment of Medical/Scientific Information* is a carefully constructed and reasonable general guide to evaluating the epidemiological literature for purposes of weighing adjudication. In the sections below on specific cancer type, we generally adhere closely to its provisions. However, there are a few areas that the Protocol does not address that are fundamental to the issue of establishing presumption, for fire fighters or for any other occupation. These are discussed in this section, which assumes familiarity with the *Protocol*. For a more detailed, basic, theoretical and systematic treatment of each topic, readers are referred to our recent book *Science on the Witness Stand: Evaluating Scientific Evidence in Law, Adjudication and Policy* (Guidotti and Rose, eds., 2001).

Logic of Assessing Causation

Strict causation is one of several types of association that are important in workers' compensation but not the only form of association that merits recognition. Aggravation (a form of causation), contribution (where the exposure is necessary but not sufficient), multifactoral disease and confounding (in which a second hazard is associated with both the occupation and the outcome and is therefore work-related but not measured as a primary effect) all represent forms of association that qualify a condition as arising out of work although a strict cause-effect relationship may be lacking. The *Protocol* does not make this clear because it is focussed on a more traditional "strict causation" model more appropriate for epidemiological research.

As a consequence, there is an important component missing from the *Protocol* and that is guidance on how to frame the problem in the first place. For example, the difficult problem of brain cancer is inappropriately framed in several extant discussions of the problem. Unlike bladder cancer (which itself is not strictly homogeneous as a category but can be treated as such to a first approximation), brain cancer is not a sensible aggregation of outcomes: it consists of several ICD-9 codes and several different types of cancers, each with different risk factors. As will be demonstrated below, the problem with brain cancer is not whether the risk for the diagnostic group is elevated but whether there is evidence of an elevation in risk for a biological

relevant tumour within the overall group. This issue will be explored in much greater detail in subsequent sections of this report.

The essential issue in workers' compensation is not whether an attributable risk is strong enough to justify the presumption of a group risk but on the question of whether the group risk applies to the individual and informs the adjudication of the individual claim, since all claims must be adjudicated on their individual merit. For this reason epidemiology is a very valuable guide to identify and to characterize an association, but ultimately the facts of the individual case determine whether the information gained from epidemiological research can be applied and is useful. The *Protocols* are silent on the critical issue of interpreting epidemiological data for the individual case.

The logic of assessing causality in adjudication is also not the same as for concluding causation in a scientific investigation. The near-universal standard of certainty is "more likely than not", rather than the conventional 95% level of certainty (the meaning of the standard alpha probability for Type I error, commonly expressed as $p < 0.05$, for a scientific finding or study). Thus, one obstacle to applying the results of epidemiology to adjudication practice is learning to abandon the conventional notion of certainty one learns as a scientist and which creates a highly conservative, and therefore reassuring, standard of certainty. In evaluating a claim or as an expert for purposes of litigation, one is working within a framework in which individual studies may be so judged but the weight of evidence is evaluated as odds, with greater than equal odds favouring one conclusion over another. The *Protocol* is silent on this.

The relationship between risk and the decision to accept a claim or to adjudicate in favour of a claimant or plaintiff is therefore not simple. Merely demonstrating that there is an elevated risk of a particular outcome among members of an occupational group is not enough. It is also necessary to demonstrate that the individual circumstances of the claimant are consistent with the premise that the condition arose out of work. The weight of the available evidence, which is usually incomplete, must then support a decision that it is more likely than not (with the benefit of the doubt going to the claimant if the odds are even) that the claimant's condition did indeed arise out of work. The factor causing the outcome could be a job-related hazard or circumstances intimately associated with work (such as passive cigarette smoking) but would not normally be a voluntary activity that is not required by the job (such as active cigarette smoking).

It is important to realize that the application of epidemiology "as if" the standard of certainty were 50+% does not represent a distortion of scientific standards. Rather, it represents a legal requirement. Expert witnesses must follow the rules of the court.

Measuring Risk

Critical to assessing the strength of an association is a measure of risk. The magnitude of risk is expressed in epidemiology in one of two general forms. Studies that observe the experience of a population over time (i.e. cohort or prospective studies) use a ratio of the observed number of cases to the expected number of cases or relative risk. This may be expressed as a ratio but in occupational cohort studies is often expressed multiplied by 100, as if a percentage. When referring to the frequency deaths, this ratio times 100 is called the standardized mortality ratio (SMR) and when referring to the fraction of all deaths represented by the particular outcome it is called the proportionate mortality ratio (PMR). (Confusingly, some authors, such as Baris et al (2001) express SMRs as relative risks without the conventional normalization to 100.) The alternative term for describing magnitude of risk is used in study designs that compare how often a risk factor was present in the past among those who have developed the outcome and compares that with those who did not (case-referent or retrospective studies) in the form of a ratio. This is called an odds ratio (OR or, if specifying associations with mortality, sometimes MOR). The odds ratio is closely related to a relative risk mathematically but generally has more uncertainty.

In this paper, the risk estimates will be presented as they were reported in the original paper. SMRs are given to three places, without decimals, or expressed as relative risks as in Baris et al 2001). Relative risks are given as decimals, with no qualification. Odds ratios are given as decimals and identified as such.

Presumption

One situation in which attributable risk can be directly applied to individual claims, rather than treated only as supporting evidence, is in a rebuttable presumption.

Presumption is, simply, the doctrine that claims should be accepted without opposition when, all other things being equal, a claim received from a worker in a certain occupation is demonstrably more likely than not to have arisen out of work, whether or not it is possible to

prove the association in the individual case. An SMR of 200 is equal to an attributable risk of 100% of expected, and represents a high degree of association. It implies that the attributable risk due to work as a fire fighter is equal to the shared risk from other factors in life, including environmental factors associated with living as a member of the community. As a practical matter, in workers' compensation and tort litigation an SMR of 200 implies that, all other things being equal, the risk of a fire fighter developing a cancer (such as bladder) from work-related exposure is approximately equal to that of the risk of the same cancer in everyday life. Therefore, that the cancer arose from work and that it did not are equal odds and it is as or "more likely than not" (giving the benefit of the doubt to the worker) that the condition arose out of work. This constitutes the basis for a "rebuttable presumption" under which such cases would normally be considered work-related unless there is evidence to the contrary (Industrial Disease Standards Panel, 1992; Guidotti, 1995).

A presumption assumes that, all other things being equal, most cases of a certain type are associated with occupational exposure, even though it is not possible to determine which. Presumption is a way of being inclusive in the acceptance of such claims given that it is not possible to distinguish among them. Presumption is usually based on demonstration that the relative risk exceeds two because this statistical measure corresponds to even odds, but in practice, it is impossible to make such a fine distinction. A relative risk of 1.7 or 1.8 (SMR of 170 or 180) is usually indistinguishable statistically from one of 2 (200) with any confidence. Presumption is most 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 (Guidotti, 1998).

It would be desirable from a scientific basis to establish the subgroups in which the risk is concentrated, to identify the specific types of cancer in the aggregate categories most likely to be associated with elevated risk and to determine the threshold level associated with significant risk. However, to do so is not feasible, any more than it is now practical to identify the specific carcinogen that is responsible for the risk. To reject all such claims or to apply criteria that are arbitrary, such as restricting compensation to non-smokers, will predictably deny benefits to persons whose disorders did in fact arise from occupation but who cannot demonstrate the association. To accept all such claims will predictably include all such cases in which the disorder did not arise from occupation as well. To apply criteria that are liberal, i.e. that include

almost all workers with a plausible claim and exclude those who do not fit the criteria, inevitably raises issues regarding the adequacy, specificity and validity of the criteria and is likely to exclude some few individuals whose condition did arise out of work but may not have fit the inexact criteria precisely. To avoid this problem, presumption is sometimes applied as a means of ensuring that persons whose disorder did arise from their occupation are compensated, recognizing the expense of accepting some claims in which it did not.

Latency

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.

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 for the tumour to become manifest. 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.

The *Protocol* does not discuss latency other than in the context of temporal relationships.

Positive and Negative Findings

An epidemiological approach based on a standard of "more likely than not" accepts the preponderance of evidence for an association even when that evidence does not achieve a scientific standard of certainty. 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. Statistical "error" and low power predict that many replicate studies are not likely to show a true excess. Evidence for an elevation should rightly, therefore, be weighted more heavily than evidence for a negative finding in a similar study, all other things being equal. When they are

not, the validity of study design and power of the more substantial positive and negative studies are more persuasive than a meta-analysis.

All epidemiological risk estimates are just that – estimates – and represent the experience reflected in the populations being studied. Uncommon events, such as lung cancer, are subject to chance variation. This is precisely why we derive confidence intervals for our estimates. The power of a study is its ability to detect an elevated risk when there actually is one. One likes to have a power of at least 80% but few studies can achieve even 50% for lung cancer, because it is not common enough. This means that a large fraction of studies might well miss the true association. This is not controversial. What to do about negative studies when there are strong positive studies addressing an association is highly controversial. This is the case with lung cancer among fire fighters.

If one believes that power considerations and inherent bias make it more likely that an association will be missed than that one will be revealed, then one places greater weight on positive studies. This uncertainty over power means that studies that do show an excess risk should carry more weight in adjudication than the evidence of studies that have not demonstrated an excess risk. Studies that show no elevation in risk may simply have missed the excess and convey no information. Studies that show an excess risk, especially if they are consistent and show a dose-response relationship (one important criterion of a true association) are likely to be more useful in assessing the probable magnitude of the true excess risk. A meta-analysis, in this view, is not likely to be very helpful because the true risk will merely be diluted by the low risk estimates of studies that failed to detect the elevation.

Meta-analysis is often used to interpret the epidemiological evidence and indeed is a useful tool for doing so, but only one tool. Meta-analysis, even properly conducted under near-ideal conditions, has failed to predict the outcome of larger and more complete studies. For example, in the 1990's, meta-analysis of several small retrospective studies strongly suggested that great benefits could be made in the management of patients following a heart attack by giving them a certain type of drug that reduced demands on the heart muscle. A randomized clinical trial intended to validate this finding had to be stopped early because the results were opposite: patients died more often when they received the drug. Such clinical studies represent a near ideal application for meta-analysis because dosage (exposure) is accurately quantified and consistent and subjects are randomized, leading to similar populations within statistical limits. Studies in occupational epidemiology are

much less standardized and present much greater uncertainty. If meta-analysis was so far off in an ideal application, why should it be given undue weight in a less certain situation? Indeed, the premiere, but now dated meta-analysis conducted on studies of fire fighters (Howe and Burch, 1990) did not successfully predict elevated rates for some cancers, such as colon and genitourinary cancers, in studies over the next decade.

Criteria for Assessing Causation

Much has been made of the traditional Bradford Hill criteria (temporal sequence, exposure-response, strength of association, biological plausibility, consistency, specificity, coherence) applied to adjudication (Bradford Hill, 1995). However, these criteria are not clearly valid for the purpose. The Bradford Hill criteria (commonly called the "Hill criteria") are powerful tools but to prevent their misuse it is important to appreciate their limitations (Guidotti, 1992).

First, they exist to be a guide (and no more than that: Bradford Hill himself took the position that they do not constitute proof) to concluding that an association is causal once an association has been demonstrated. In other words, the criteria are not intended to be applied to the question of whether an association exists but to that of whether an association, once demonstrated, is causal. Thus, where there is a question about the certainty or magnitude of an association in the first place, the criteria do not apply.

Second, when an association exists, its interpretation is different in workers' compensation than in other arenas. An association that coexists with an occupational exposure but does not arise from it may still arise from work. A confounding risk factor, which by definition is associated with the occupation in some way, is equally valid as a causal determinant in relationship to work. For example, if a fire fighter develops asthma after exposure to floor wax polishing the floor of the fire station, it does not matter that the relevant exposure was not to the characteristic exposure of fire fighting - products of combustion. The condition is still work-related. If many fire fighters develop asthma for this reason (unlikely, of course) it would not matter if the Hill criteria applied or not – the condition would still be work-related.

Third, the individual criteria do not fit the problem of adjudication and the Hill criteria, individually or together, were never designed to be applied to adjudication. Several criteria require a complete database that is rarely available (fire fighters are here the exception): exposure-response relationship, consistency, specificity, coherence. Several of the criteria require corollary evidence

that is seldom available or relevant: coherence, biological plausibility. The criterion for strength of association is redundant, since this criterion is taken into account when an association is first identified and, if taken as a doubling or greater for the group as a whole, is overly stringent for individuals who may belong to an identifiable subgroup. Both the criterion for coherence taken alone and the other Hill criteria taken together require a vastly greater standard of certainty than "more likely than not" and are therefore highly prejudicial to individual cases where the database is incomplete or some part of the evidence is equivocal.

Finally, the Hill criteria can never be applied to an individual case, only to a body of evidence.

As useful as the Hill criteria are in epidemiology, they do not replace sound and informed judgement with appreciation of the particulars of the individual case.

The Evidentiary Base

In 1995, we reviewed the current literature on disease risk among fire fighters in order to compare findings and to infer magnitude of risk (Guidotti, 1995). Since 1995, there have been three major studies that have contributed to the world literature on fire fighters. They are summarized below.

Burnett et al (1994), which was actually not available until 1995, conducted a very large proportionate mortality study on fire fighters in 27 American states from 1984 through 1990, using data from the National Occupational Mortality Surveillance system. Limitations of these data are partially overcome by the sheer size of the database, which, with 5744 deaths among white male fire fighters, is beyond what may be achieved in any one cohort study. This system is an example of population surveillance for occupational disease we have advocated elsewhere (Guidotti, 1999).

Deschamp et al (1995) studied the recent experience of relatively small number of fire fighters in Paris from 1977, as a prelude to a longer-term cohort study. An elevated SMR was found for respiratory cancers (1.12), gastrointestinal cancers (1.14) and genitourinary cancers (3.29) among other findings. However, the study is anomalous in several ways, uniquely demonstrating an elevated mortality from stroke (1.19) and a very low overall mortality (0.52), the lowest reported to date among fire fighters. Further experience with this cohort is required to interpret the findings.

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 the Burnett et

al., as its purpose was different, but it is much smaller and covers a heavily overlapping population. For this study, the NOMS database was extended by three years to 1993 but 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 fire fighters and 66 deaths of black fire fighters. 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 fire fighters.

Bates et al (2001) reported a study on fire fighters in New Zealand from 1977 to 1996, conducted to investigate the observation of a cluster of testicular cancer. This elevation was confirmed as finding independent of the cluster. This study is unusual in reporting both cancer incidence and mortality. It reports one of the lowest mortality ratios reported for fire fighters (0.58), suggesting a strong healthy worker effect. Bates et al. observed no significant elevation except for testicular cancer. The authors caution that matching to mortality data and cancer registration data may be incomplete prior to 1990 and suggest that they have greater confidence for findings after this date. Among cancers of interest in this paper, they found a marked increase in testicular cancer and nonsignificant elevations in incidence in the 1977 – 1996 cohort of cancers of interest: lung (1.14, 95% 0.7 – 1.8), which showed a modest increase with duration of service, bladder (1.14, 95% CI 0.4 – 2.7), brain (1.27, 95% CI 0.4 – 3.0), and "myeloleukemia" (1.81, 95% 0.5 – 4.6), but not kidney (0.57, 95% CI 0.1 – 2.1). Limiting the analysis to the 1990 – 1996 subcohort, however, they found the increase in testicular cancer and a deficit in the same cancers, except for brain (1.59, 95% CI 0.3 – 4.6), and no kidney or "myeloleukemia" cases. A strikingly different picture is observed in the pattern of deaths, however. Mortality among fire fighters in the 1977 – 1996 cohort is elevated for bladder cancer (2.73, 95% CI 0.3 – 9.8) but less than expected for lung (0.86, 95% CI 0.4 – 1.6), brain (0.68, 95% CI 0.1 – 2.4) and "hematopoietic cancer" (0.72, 95% CI 0.2 – 1.8), and no deaths from testicular cancer. The discrepancy between incidence and mortality in cancers with a high case mortality, such as lung, is an anomaly. However, all numbers are small and the authors are candid in describing limitations of the database outside their control.

Baris et al (2001) conducted an exemplary cohort mortality study. This study should be accorded great weight because among recent studies it has exceptional power, spans most of the 20th century, and has the most complete follow-up. The study therefore merits description in detail.

The cohort consisted of 7789 Philadelphia fire fighters employed from 1925 to 1986 compared to US white male rates, comprising 204,821 person years of follow-up. The men were hired in their late 20s (on average) and worked for approximately 18 years, with an average of 26 years follow up. Baris et al (2001) examined their cohort by age, duration of employment, job assignment and by number of runs to fight fires (enumeration of responses from the firehall) in three broad ordinal categories.

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). Nonsignificant excesses were reported for cancers of the buccal cavity and pharynx (1.36; 95% CI=0.97, 2.14); for non-Hodgkin's lymphoma (1.41; 95% CI=0.91,2.19); for multiple myeloma (1.68; 95% CI=0.90-3.11) and for lung cancer (1.13; 95% CI 0.97-1.32). With >20 years of fire fighting, the following cancer sites showed elevated risks: colon cancer (1.68; 95% CI 1.17-240); kidney cancer (2.20; 95% CI 1.18-4.08); non-Hodgkins lymphoma (1.72; 95% CI 0.90-3.31); multiple myeloma (2.31; 95% CI 1.04-5.16); and benign neoplasms (2.54; 95% CI 1.06-6.11).

Baris et al developed a direct index of exposure by assessing risk by three categories of fire fighting 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 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 (1.00) to high exposure, several cancer sites demonstrated increasing risk: stomach, 1.20; pancreas, 1.42; leukemia, 1.22; and benign neoplasms, 2.06. The authors also compared lifetime runs with diesel exposures, including a category of nonexposed. 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 also an apparent dose-response for assessment of low, medium and high exposure related to diesel exhaust for mortality from respiratory diseases (but not for any cancer). The risk rises from 1.00 (nonexposed) 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 fire fighter (regardless of diesel exposure).

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

From the Baris et al study, some tentative conclusions emerge from an overview of the epidemiology data. There were no significantly *reduced* SMRs for any of the a priori tumour sites plausibly linked with fire fighting: brain, bladder, kidney, and lymphatic malignancies. Further, the Baris study adds weight to linkages between fire fighting and cancers of lymphatic system and with kidney, and suggests associations with colon, pancreas and prostate cancers.

Most recently, Stang et al (2003) have published a focused case-control of testicular carcinoma among firefighters in north Germany, showing an odds ratio of 4.5 (0.7 – 30.5). This was interpreted as consistent with the results from New Zealand by Bates et al (2001) described above.

Brain

Cancers of the brain arising from brain tissue (i.e. primary malignancies of the brain, rather than metastatic brain tumours) are relatively rare and may include twenty or more individual types. Epidemiological studies do not distinguish among them because they most are individually rare and subject to miscoding and aggregated coding when reported. In all probability there are different environmental causes for the different types, when and if environmental factors play a role in causation.

The most common type of "brain" tumour is glioma, followed by meningioma, which is not obviously associated with environmental or occupational exposures. A serious nosological problem faced by cancer epidemiologists is that tumour registries continue to record meningiomas, which are usually benign, in overall statistics for brain cancer. This tends to dilute any risk estimate specific for gliomas. Gliomas (astrocytomas) are the primary type of malignancy and these tumours 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 (and, in the case of most

meningiomas, benign tumours) 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 fire fighting. 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 and require large populations. Unless more specific studies are conducted on individual types of brain cancer among fire fighters, which is not likely, this problem cannot be resolved and the risk within the class must be inferred from the available data.

Burnett (1994) did not observe an elevation for cancer of the brain. The PMR was 85 for fire fighters 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. Ma et al reported that no elevation was observed for brain cancer among white fire fighters but a very large elevation, with a mortality odds ratio (MOR) of 6.9 (95% CI 3.0 – 16.0) was observed for black fire fighters.

Baris observed a relative deficit of brain cancer, with an SMR of 0.61 (95% CI 0.31-1.22). Risk did not appear to be concentrated in any subset of fire fighters by assignment, number of runs or duration, although the highest SMR (1.18) was observed among fire fighters with more than 729 runs in the first five years of duty. Because brain is an uncommon tumour site, statistical power is usually limited in epidemiological studies. This study therefore 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.

Brain cancers, 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) and was not so analyzed in Guidotti et al (1993) because of small numbers, so that 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 peaking at over a tripling (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.

Leukemia, Lymphoma, Myeloma

This is not a medically defensible aggregation of disease outcomes. Even so, many studies have aggregated deaths or incident cases in these three broad categories in order to achieve sufficient numbers for statistical analysis. The problem comes when these aggregations are taken at face value, as legitimate disease outcomes. They are not and elevations in one disease or a deficit in another can easily distort the aggregate risk estimate.

Non-Hodgkin's Lymphomas

Lymphatic cancers are generally known as lymphomas. Unfortunately, because they are not common they tend to contribute a small number of deaths in most studies and are difficult for epidemiologists to analyze. In smaller studies they are often aggregated with leukemias and myeloma into a residual category of cancers. This obscures differences among the groups. Because they are a collection of conditions and they tend to manifest themselves in older persons, their relationship to environmental factors is more difficult to determine.

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-Hodgkins lymphomas. Hodgkins 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-Hodgkins lymphomas are a larger, more heterogeneous category and have been associated, in the aggregate, with many environmental exposures and occupations. Non-Hodgkins lymphoma is further divided in many epidemiological studies into "lymphosarcomas" and "reticulum cell sarcomas". More commonly, all lymphomas are aggregated or lumped together with haematopoietic cancers and multiple myeloma.

This aggregation obscures the level of risk that may exist for certain critical types of lymphoma. There are over 30 types of lymphoma recognized in the current classification system (the WHO and R.E.A.L. system), at least nine of which were commonly observed in, for example, India (Naresh et al, 2000). New types are expected to be identified as immunological

and genomic methods become more sophisticated. Different types of lymphoma are known to be associated with different occupational risk factors, including follicular cell lymphoma with the meatpacking industry and small cell lymphoma with solvent exposure (Tatham et al, 1997). Multiple myeloma most closely resembles the lymphomas and is a tumour of B-lymphocytes, but appears to have different risk factors. Chronic lymphocytic leukemia, which is more accurately considered a lymphoma appearing in blood, was recently separately identified as a probable risk of Vietnam veterans exposed to herbicides on the basis of its characteristics and differences from leukemias in general, which are not so recognized (NAS, 2003).

If, as seems plausible, different environmental exposures may be associated with different cell types of non-Hodgkins 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 fire fighting. 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. Unless more specific studies are conducted using molecular markers on lymphoma cases arising among fire fighters, 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.

Lymphatic cancers were separately addressed in the Burnett et al (1994) study, which revealed an elevation for non-Hodgkins lymphoma. The PMR was 161 for fire fighters 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. These cancers were also separately identified by Ma, who found a statistically significant elevation of lymphatic cancer was observed among white fire fighters, with a MOR of 1.4. Ma found no elevation was observed among black fire fighters, based on a single case.

Baris observed a not-quite significant overall elevation for non-Hodgkins lymphoma, with an SMR of 1.41. While not achieving statistical significance, this rose to 1.72 for fire

fighters 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 associations do achieve statistical significance, their lower bounds are greater than 1.0. This suggests the possibility that these are true elevations in these subgroups. Baris et al found that among those employed more than 20 years, the SMR was 2.20 (95% CI=0.90,3.31).

Leukemias

Haematopoietic cancers (which affect the blood-forming organs, most particularly bone marrow) are generally known as leukemias. There are about a dozen well-recognized forms of leukemia, of which five or six predominate. Acute myeologenous leukemia 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 fire fighting. 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 fire fighters, which is not likely to occur, this problem cannot be resolved and the risk within the class must be inferred from the available data.

Haematopoietic cancers were separately addressed in the study by Burnett et al (1994), which revealed an elevation for the class as a whole. The PMR was 171 for fire fighters 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 observed no apparent elevation for haematopoietic cancers, with a MOR of 1.1. There were no cases among black fire fighters. This is unusual but probably reflects the small numbers of black fire fighters in the population.

L'Abbé and Tomlinson (1992), in a study of fire fighters in Toronto, uniquely reported risk for general types of leukemia. They observed an excess of "lymphatic" [lymphocytic] leukemia at 190 (42 – 485). This was highly influential in the IDSP report, however the finding is surprising. Acute myelogenous leukemia (AML) is the type to be expected in circumstances in which benzene is a hazard, not lymphocytic, presumably the acute form which is more common than chronic.

Baris found no overall elevation was observed for the leukemias (SMR 83, 95% CI 0.50-1.37), not specified as acute or chronic or by type. A statistically significant elevation in SMR of 275 (95% CI 1.03-7.33) was observed for fire fighters 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 (95% CI 0.70-8.54) and with medium (but not high) levels of runs over a lifetime, with SMR of 2.50 (95% CI 0.56-11.10). These data are not compelling evidence for a true association in this population but do not rule it out. Because of power considerations, this study also does not contradict others that have demonstrated a higher overall risk. However, the study by Baris et al (2001) does not really clarify this issue, either.

The apparent association with "lymphatic cancer" is an anomaly, from these points of view. However, in its totality the evidence suggests (again, at the level of "more likely than not") that one cannot choose among the types of leukemia on the basis of current evidence. It cannot, for example, be convincingly argued that only one form of acute leukemia, either myelogenous or lymphocytic, should be recognized. One is suggested by the empirical data, the other by the known toxicological profile of exposures experienced by fire fighters. Although Ontario now recognizes lymphocyctic leukemia, the evidence presented by L'Abbé and Tomlinson (1992) is not definitive and because of power considerations 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, ALL or, for that matter, only acute and not chronic leukemias.

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.

Myeloma

Myelomas are B-cell lymphomas and malignant plasma cell dyscrasias. 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 fire fighting and lymphatic cancers—Non-Hodgkins and leukemia, specifically. These authors found that 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, with some suggestion of correlation with medium and high diesel exposures (latter based on small numbers of deaths).

Genitourinary Cancers

Bladder cancer

Burnett et al (1994) found no elevation for bladder cancer but the authors imply that they expected a deficit due to the healthy worker effect. The PMR was 101 for fire fighters 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. Using the same database, Ma (1998) reported a not-quite statistically significant elevation of 1.2 was observed for bladder cancer among white fire fighters and an elevation (but based on a single case) for black fire fighters.

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 1940's and 1950's 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 fire fighters, where exposure tends to be much less and highly intermittent. The exposure of fire fighters 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 employed (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 fire fighter 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 fire fighters to be on the order of 15 years.

Kidney cancer

Burnett et al (1994) found a marked elevation for cancer of the kidney. The PMR was 141 for fire fighters 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. Using the same database, Ma (1998) reported a borderline statistically significant elevation of 1.3 was observed for cancer of the kidney among white fire fighters. No cases were observed for black fire fighters.

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 fire fighters, 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, but latency periods less than 20 but greater than 15 would not be unreasonable.

The standard cancer epidemiology text 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. Fire

fighters are not exposed to the same intensity of exposure but are exposed to the same or similar 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 and co-workers (2001) reported a doubling of risk with an SMR=2.20, 95% CI=1.18, 4.08 among those employed for 20 or more years.

Testicular Cancer

Bates et al (2001) found a standardized incidence ration of 3.0 (1.3 – 5.90) for firefighters in the New Zealand city of Wellington. The findings of Stang et al (2003) from northern Germany were consistent with this finding, although their odds ratio of 4.3 (0.7 – 30.5) was not statistically significant. Such high risks are unlikely to be confounded by differences in the prevalence of cryptorchism (the major known risk factor), smoking (not known to be associated with testicular carcinoma) or other plausible alternative risk factors. In their community-based study of testicular carcinoma, only four firefighters and three controls were firefighters out of 269 and 797, respectively, making the power of their study very limited. Stang et al (2003) also reported on duration of employment. Of the four cases, two had been employed as firefighters more than 20 years and two for less than 4.

There are five basic tissue types of testicular cancer, the most common by far being seminoma (about 95%). Bates et al (2001) does not specify the histology of the tumour. Stang et al (2003) reports that of the four, two were embryomas, an unusually high frequency, which suggests, but does not prove, and that this type (which is also found in mixed germ cell types) may be associated with occupational risk. The evidence is too weak to rely on, however.

Biological credibility for the association, however, comes from the observation by Olshan et al (1990) that the offspring of male firefighters (the vast majority are male) are at significant and (for atrial septal defects, with an odds ratio of almost 6) substantial elevated risk for birth defects, specifically common cardiac anomalies. Such a finding, implying a congenital birth defect mediated by a male factor, points to an effect mediated by the testes or, less plausibly, seminal fluid.

Given the totality of the evidence, it is reasonable to establish a presumption for testicular carcinoma on the basis of current evidence. However, given the methodological limitations of

Bates et al (2001) and the lack of available evidence on exposure, tissue type of the tumours and latency, no further guidance can be recommended.

Evaluation in Light of Recent Evidence

Overall

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-Hodgkins lymphomas) and haematopoietic cancers.

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 fire fighters, but these subgroups cannot be readily identified by usable criteria in adjudication. The inconsistency in the literature cannot be explained by current data but given power considerations, the demonstration of an excess in past studies appears more convincing as evidence of a confounded or obscured association than the inconsistency is convincing as evidence of no association.

The weight of evidence for lymphatic cancer of the non-Hodgkins type and haematopoietic cancer suggests that the elevation in risk reflects a true risk in certain subgroups but these subgroups cannot be readily identified by usable criteria in adjudication. The more recent evidence is consistent with an elevation for lymphoma and does not contradict the finding in other studies of an increased risk for haematopoietic cancers (leukemias). The L'Abbé/Aronson and Tomlinson (1992) and Demers et al (1992) studies, for example, provide strong evidence suggesting an elevated risk notwithstanding the variation in risk estimates in other studies. Baris et al (2001) present a confusing picture for non-Hodgkins because employment for 20 or more years produces an SMR of 1.72, with elevated risk for those hired after 1935, but there was an inverse of risk for cumulative number of runs. 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.

Lung Cancer

Lung cancer has been the most difficult cancer site to evaluate in epidemiologic studies of fire fighters. Despite the obvious exposure to carcinogens inhaled in smoke, it has been difficult to document an excess in mortality from lung cancer of a magnitude and consistency compatible with occupational exposure. Documentation of an association between lung cancer and occupational exposure as a fire fighter remains elusive; many investigators, including this author, continue to believe that an association exists that is confounded by cigarette smoking. An effect probably does exist but it is likely to be heavily obscured by confounding factors and may not be as strong as would be suggested by the toxicological literature (Guidotti and Clough, 1992).

Without question, cigarette smoking is a confounding exposure that complicates the analysis, but the prevalence of smoking among fire fighters does not appear to be excessive compared to other blue collar occupations. Respiratory protection has probably reduced individual exposure levels since the 1970's, although it was not optimally used for many years in most fire departments. This may be the reason that studies rich in recent person-years of observation, such as Baris et al (2001), do not observe elevations. A major issue is whether the large-scale introduction of synthetic polymers into building materials and furnishings after about 1950 has increased the risk of cancer among fire fighters because of exposure to the combustion products. Studies we conducted in Alberta on fire fighters entering the fire service from 1927 to 1987 show evidence for such an increase in risk (Guidotti, 1993).

What is the Unconfounded Risk Attributable to Fire fighting?

Many studies have shown an excess of lung cancer on the order of 20 to 80% (i.e. SMRs around 120 or 180), a magnitude not uncommon in studies of other blue collar occupations with less plausible exposure levels (Guidotti, 1987). However, the empirical findings on lung cancer from recent, well-designed epidemiological studies have been inconsistent. One study from Denmark in which the comparison population is unusual reported a standardized mortality ratio of 317 for older fire fighters, while studies on cohorts from San Francisco and Buffalo showed no excess and even suggest a deficit. The possibility of an association that is obscured in comparison to the general population by the healthy worker effect is probably less likely for this cause of death than for other chronic diseases; over the long periods of observation typical for these studies the mortality

experience of initially selected workers can be expected to approach that of the general population more closely, especially for noncardiovascular causes of death.

In 1995, we proposed that the true risk for lung cancer associated with fire fighting was probably on the order of 150 (Guidotti, 1995). This figure has been disputed. We suggest that there are contextual reasons for thinking that the true risk has been underestimated in career fire fighters and both diluted and confounded by the effect of cigarette smoking, which is a much greater risk factor. One may examine virtually all extant studies in the literature (Guidotti, 1995, and above) and observe that those studies that are positive, relevant, close to the primary data, large and well done seem to cluster in a band from an excess of 30% (Rosenstock, 1990) to 68% (Petersen and Milham, 1977).

The principal exceptions are Baris et al (2001) and Vena and Fiedler (1987). Baris et al, despite a low overall risk (1.13, 95% 0.97 – 1.32) does report suggestive elevations in certain subgroups, notably fire fighters with less than 9 years of service (1.52, 95% CI 1.16 – 2.01), those assigned to engine companies (1.18, 95% CI 0.93 – 1.51), and those hired before 1935 (1.30, 95% CI 0.97 – 1.73). Vena and Fiedler (1987) present one of the lower overall risks in the fire fighting literature (0.94, 95% CI 0.62 – 1.36) but their data show a possible exposure-response relationship with duration of employment (a near-monotonic increase of 0.14 relative risk for each of five decade of fire service, nonparametric $p < 0.07$) and a statistically significant excess (at $p < 0.01$) for fire fighters with more than 40 years of fire service (1.29). Heyer et al (1990) reported an overall risk of only 97 (95% CI 65-139) but observed an elevated risk among fire fighters aged 65 years or more, an age when the incidence of lung cancer tends to peak. Thus, even in so-called "negative" studies there are hints of a possible association.

Among those studies that appear to be unequivocal in reporting low risk, Beaumont et al (1991), which shows the lowest risk (0.84, 95% CI 0.64 – 1.08), also shows the largest healthy worker effect (i.e. the lowest overall mortality from all causes (0.90) and from cancer (0.95) among the major studies) and is also atypical in age and the high rate of cirrhosis.

At the other extreme is one study in which an overall risk of 163 (95% CI 75 – 310) was accompanied by a tripling of risk (317) for fire fighters aged 60 to 74 (Hansen, 1990). This is an imaginative Danish study that aggregated other occupational groups into a synthetic reference group. The artificiality of this construct makes the study difficult to interpret.

In our study of urban fire fighters in Alberta (Guidotti, 1993), we found trends that we believe suggest a true SMR on the order of 150 in that population. Individually, these trends are not definitive but together they are highly suggestive. The overall SMR for lung cancer was 142 (95% confidence interval 91, 211), statistically not significant, and statistically indistinguishable from 150. However, lung cancer was elevated to an SMR of 167 among fire fighters entering the fire service in the 1960's, the most recent cohort which at the time of the study was surviving as a group beyond the expected latency period. This is not strong evidence, because it is based on only two cases, but the following cohort of fire fighters entering in the 1970's showed an even greater risk, 261 (but based on a single case). The risk of lung cancer also showed an exposure-response relationship in our data, with groups of fire fighters who had higher exposure opportunities and duration showing elevations on the order of 200. By duration of employment, an initially high risk for those with less exposure declined with duration of employment but achieved a doubling for those working 40 or more years (but only two fire fighters were in that group). More persuasively, when duration of employment was corrected for exposure opportunity in job classification, the exposure-response relationship changed to suggest an initially high risk among probationary fire fighters or those unfit for duty, a more or less consistent but low elevation for the middling exposed varying around 150 (range 32 to 258), and a significantly elevated risk (408, $p < 0.05$) for those with more than 35 exposure opportunity-weighted years of employment. Baris et al (2001), although negative overall, appears to show the same effect in the first 9 years. Unfortunately, the data from other studies cannot be disaggregated on the same basis as the Alberta cohort.

An important factor in the Alberta study, which was not appreciated at the time of initial publication, is that cigarette smoking is historically less of a confounding factor in Alberta than it has been in other populations. Subsequent studies of smoking-related lung disease outcomes suggest that smoking rates have been historically low in the province compared to the rest of the country and this is reflected in lower mortality from chronic obstructive pulmonary disease. In recent years mortality rates for smoking-related disorders appear to have converged with the rest of Canada as smoking rates in the rest of the country have gone down and those in Alberta have changed less dramatically (Guidotti, 1995b). Again, this suggests, but does not prove, that the Alberta experience is less confounded by cigarette smoking than elsewhere.

An anomaly of the Alberta data is that the excess was seen in one city (Edmonton) and not another (Calgary). This represents a valuable internal replication because the same study team

collected data from both cities, matched against death certificates concurrently and analyzed both datasets simultaneously. Were Edmonton to have been studied separately, the risk would be 201, the highest overall risk for lung cancer reported.

Taken together, and supported by the methodologically stronger studies in the literature, 150 seems to be a reasonable estimate of the true (unconfounded) risk. The attributable risk fraction would therefore be on the order of 50% for fire fighters. Population attributable risks are used as crude, best estimates in estimating the risks for an individual. For the average fire fighter, therefore, the most likely estimate of the risk of working as a fire fighters would be about half that of the actual risk of lung cancer associated with living in the community, or as a member of the population as a whole.

The Non-Smoking Fire fighter

The findings of epidemiological studies are best estimates for the individual, but they are not necessarily applicable to the circumstances of an individual case. Claims under workers' compensation and other adjudication systems are generally required to be based on individual circumstances, not on broad generalizations, unless there is a relevant presumption. One of the individual factors of greatest practical importance is smoking. When lung cancer occurs in a fire fighter who does not smoke, the relevant comparison is to the risk of other nonsmokers, not the population as a whole, which includes many smokers. For a non-smoking fire fighter, the a priori risk for lung cancer is low. Is the additional risk attributable to fire fighting sufficient to achieve a doubling, the threshold for presumption? There is evidence that it is but some reasonable assumptions are required.

There is no study available that describes the experience of non-smoking fire fighters. This is not unusual: it is difficult to identify or to partition out the risk of non-smokers in most epidemiological studies of occupational risk factors. The smoking effect is so strong that it makes it difficult to isolate other factors in epidemiological studies. Lung cancer in a non-smoker is rare. Although lung cancer is rare in people who do not smoke, when it occurs it is usually adenocarcinoma. However, adenocarcinoma is also increased among smokers, so tissue type does not help as an indicator in the individual case.

In calculating the SMR or relative risk, both the numerator and the denominator include smokers. Smokers among the fire fighters contribute the majority of cases of lung cancer, as they

do in the general population. Although their risk may be increased compared to similar smokers who do not fight fires, the increase is probably small in absolute terms given their already increased risk, which is in the range of 5 to 10 times that of nonsmokers (Schottenfeld and Fraumini). In the 1980's, perhaps 30 to 40% of fire fighters smoked; the data available are sketchy but seem to be more or less in line with the general population (Gerace, 1990). The question therefore is how to attribute risk to nonsmoking fire fighters when most of the cases are already coming from smokers.

One may assume that, within a reasonable range of exposure, the magnitude of increase in risk for lung cancer associated with a given exposure to combustion products, such as polycyclic aromatic hydrocarbons, is the same for smoking and non-smoking fire fighters. For smoking fire fighters, this risk is added onto the existing risk from cigarette smoking, which is associated with at about ten times the risk as for nonsmokers. Thus, if the risk is increased by 50% for smoking fire fighters, the proportionate increase in risk for non-smokers would be much greater, by as much as tenfold, because the same attributable risk is added to a much smaller baseline risk.

One approach to quantifying the risk of nonsmoking fire fighters is to estimate that 40% ($f = 0.4$) of fire fighters smoke and that 60% do not ($1 - f$), that the relative risk of lung cancer for smokers is 10 times that of nonsmokers ($R = 10.0$), and that the relative risk (r) of lung cancer for fire fighters overall is 1.5. If x represents the attributable risk fraction, $0.4(10+x) + 0.6(1+x)/0.4(10) + 0.6(1.0) = 1.5$. Solving for x yields an attributable risk fraction of 2.3. This translates to a relative risk for nonsmoking fire fighters of 3.3, comfortably above a doubling. The exact value is unimportant because of the compounded uncertainties; that it exceeds a doubling is what matters.

Another way to approach the problem is to determine, based on the same assumptions, what the minimum relative risk for the population as a whole would have to be to reflect a true doubling of risk for nonsmoking fire fighters. The calculations are similar and yield $r = 1.22$, which is comfortably supported by the world literature whether or not the true risk is 1.5, as has been argued above. How sensitive is this model to underlying assumptions? Reducing the estimate of the proportion of the fire fighting population that smokes to 30% barely changes the overall relative risk required to support the presumption, to 1.27. Reducing the estimate of the relative risk associated with smoking from 10 to 5, which is a low estimate and intentionally

biases the model against nonsmokers, increases the overall relative risk required to support the presumption to 1.38, still in line with the world literature and below the 1.5 level that probably represents the "true" risk. Again, the exact number is unimportant; what matters is that the overall risks that would be associated with a doubling in the subgroup of nonsmoking fire fighters falls into an area entirely consistent with the literature and therefore best evidence.

Thus, it seems apparent that the available evidence supports the conclusion that the risk for lung cancer among nonsmoking fire fighters is at least doubled compared to the general population.

However, the most relevant comparison of all is to the nonsmoking population. If a nonsmoking fire fighter were compared to a similar population of people who also do not smoke, the expression would be $0.6(1 + x)/0.6(1.0) = 1 + x = 3.3$, which is the relative risk given above. (This is not coincidence, just the result of a mathematical identity. The group risk of people who do not smoke is defined as unity.) In other words, compared to nonsmokers as a group, smoking fire fighters have much more than a doubling of risk. Again, the exact value is unimportant because of the compounded uncertainties; that it clearly exceeds a doubling is what matters most.

Thus, properly framed it is clear that the risk for lung cancer among non-smoking fire fighters more likely than not exceeds a doubling, based on the best available evidence.

Other Sites

Because of the large power in the study of Baris et al (2001), and because there is some past evidence of an association, colon cancer is worth considering to be added to presumption list. Overall, Baris and co-workers found a 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 an excess of colon cancer risk was reported by Guidotti, 1993; Howe and Burch, 1990; Schwartz and Grady, 1986; and Vena and Fiedler, 1987, who reported a significant SMR of 1.83. Thus, two studies, one in two out of three subgroups and the other in the population as a whole, have demonstrated relative risks close or equal to a doubling. There may now be sufficient evidence to consider colon cancer to be added to the presumption list for claims related to fire fighting.

As well, a similar case to that made above for nonsmoking fire fighters may be made for fire fighters with a low personal risk of colon cancer, such as vegetarians with no family history of polyps. If the risk is assumed to be 1.50 (as suggested in Guidotti, 1995), a similar but simplified calculation could be made depending on the magnitude of risk reduction that is assumed.

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, testicular cancer, non-Hodgkins lymphoma (lymphatic cancer) and leukemia (haematopoietic cancer) for claims associated with occupation as a fire fighter, and for lung cancer among fire fighters who do not smoke. Colon cancer among fire fighters is also worth considering for addition to a presumption list. The presumption for brain cancer, bladder cancer, kidney cancer and testicular cancer are based firmly on a strong suggestion of an excess in the literature. The presumption for non-Hodgkins lymphomas and 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. The presumption for lung cancer among fire fighters who do not smoke is derived from a mathematical restatement of the problem which takes into account robust best estimates of risks for this subgroup.

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