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Evaluating causality for occupational cancers: the example of firefighters

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Background The evaluation of causality in cancers associated with firefighting presents problems common to other applications of occupational epidemiology in adjudication of individual claims for workers' compensation. A trend in Canada to establish legislated presumptions for compensation of firefighters created an opportunity to re-evaluate the literature applying medicolegal standards of certainty.

Objective To evaluate causality in selected cancer categories for firefighters using the criteria applied in tort litigation and workers' compensation, which is based on the weight of evidence and which is required to take into account individual factors.

Methods The epidemiological literature on cancer risk among firefighters was reviewed based on the weight of evidence rather than scientific certainty. Generalizable frameworks were formulated to define recurrent issues in assessing the evidence from epidemiological studies. The evidence for latency and for a threshold effect with duration of employment was also examined in order to provide practical guidelines.

Results Presumption is justified for the following cancers: bladder, kidney, testicular and brain, and lung cancer among non-smokers. Non-Hodgkin lymphoma, leukaemia and myeloma (each as a class) not only present particular problems in assessment but also merit an assumption of presumption. Four analytical frameworks describe the problems in analysis encountered.

Discussion The preponderance of evidence supports the presumption of causation for certain cancer, mostly rare. These frameworks are applicable to other problems of adjudication that rest on interpretation of epidemiological data. The named cancers, taking into account the special assessment issues described by each framework, are supported by sufficient evidence to conclude that a presumption is warranted but not necessarily sufficient evidence to accept as proof by a scientific standard.

Key words Adjudication; bladder cancer; brain cancer; epidemiology; firefighters; kidney cancer; leukaemia; lung cancer; lymphoma; myeloma; occupational cancer; presumption; testicular cancer; weight of evidence; workers'; compensation..

Introduction

Firefighters are exposed (as in Figure 1) to carcinogens associated with combustion, including polycyclic aromatic hydrocarbons [1]. However, the expected increase in risk of cancer that might result has been difficult to demonstrate, although not for lack of trying [2–5]. The epidemiological literature on firefighters is now among the most complete and detailed for any occupation. The general quality of epidemiological studies on firefighters since 1980 is high and the methods employed are generally similar for the prospective cohort studies, although no two studies are or can ever be identical. This makes firefighters nearly ideal as an occupation through which to explore evidentiary issues in causality.

In Canada, most provincial legislatures and the workers' compensation agencies of the remaining provinces have recently adopted statutory rebuttable presumptions or re-examined eligibility criteria for compensation for firefighters for designated cancers, including bladder, kidney, testes, non-Hodgkin lymphoma, brain, leukaemia, myeloma, and lung cancer in non-smokers. Rebuttable presumption means that one of these cancers arising in a firefighter is considered work-related unless there is compelling evidence to the contrary.

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The increasing attention to this issue as a matter of public policy has stimulated interest in approaches to assessment appropriate to applications in adjudication, where the relevant criterion in law is the weight of evidence rather than scientific certainty. In civil litigation and dispute resolution systems derived from it, such as workers' compensation, the relevant standard is the 'balance of probabilities'. The more familiar standard of scientific certainty is closer to the notion of 'beyond reasonable doubt', which is the relative standard for criminal prosecution and is too stringent for adjudication and dispute resolution [6]. Adherence to such a high standard would place an unacceptable burden of proof on the plaintiff, appellant or claimant, especially in cases where an association has not been studied or scientific evidence is difficult to obtain. Because claims or applications for compensation must be adjudicated in a timely manner, the evidence must be evaluated as it is at the time, taking into account whatever limitations there may be.

High-quality scientific evidence that reliably demonstrates aetiology is always preferable to reasoning by balance of probabilities. However, such evidence is often lacking. Scientific certainty requires replication and convergent lines of evidence, and normally requires a mechanistic explanation. Epidemiological associations that meet conventional or even more stringent standards of statistical inference (i.e. $P < 0.05$ or, say, $P < 0.001$) are not in themselves definitive proof of causality however suggestive they may be, because epidemiology cannot document mechanisms [6].

Decisions must be made in law courts and by adjudication bodies regardless of the sufficiency of the scientific data available. When a sound scientific basis exists for assigning causality, these decisions can be made with greater clarity and confidence, although interpretive problems still arise often. However, when scientific investigation has not resolved causality, these decisions must be made by interpretation, taking into account the direction and magnitude of uncertainties, judgement and the balance of probabilities. The unresolved issues associated with firefighting, where the available data and the quality of studies are unusually good, are characteristic examples of problems in assessing causality (or 'causation', as the term is used in North America). They are unlikely to be resolved by accumulating more data [3], especially for very rare outcomes where sufficient numbers are unlikely ever to be achieved, or by meta-analysis, which simply reassesses the data available [4–6]. Even so, certain problems may be untangled by logical analysis [6].

Methods

The epidemiological literature [5–12] on cancer risk among firefighters was reviewed, applying criteria consistent with principles of adjudication in workers' compensation and statutory presumption, in which the relevant criterion is weight of evidence rather than scientific certainty. Workers' compensation acts also specify, almost universally (the American state of Vermont is an exception), that in the event of even odds or balance, the benefit of the doubt must given to the claimant.

Heuristic frameworks were developed to describe recurring problems in assessment. Convergent evidence among studies for at least a doubling of risk among firefighters or compelling reasons was sought or reasons why an elevation of this magnitude might be obscured through bias or confounding. It is often difficult to identify a true underlying doubling of risk due to random error, low power for rare outcomes, misclassification bias and common study biases, which generally tend to result in underestimates of risk [2,6,7]. Confounding was examined by modelling for lung cancer among non-smokers and for other cancers by whether the risk estimate increased in the study with progressive refinement in exposure assessment or evidence of increased exposure to work-related hazards. Evidence for minimum latency and for a threshold effect with duration of employment was also examined, in order to derive practical guidelines.

Results

Four frameworks were devised to describe common problems encountered in the assessment. For consistency, standardized mortality ratios (SMR) and proportionate mortality ratios (PMR) are uniformly presented in the form (risk estimate, 95% confidence interval) as decimals, rather than the convention of using a percentage in which 100 represents unity.

Framework 1: conventional situation

Framework 1 describes the conventional situation, in which individual diseases are more or less satisfactorily classified, misclassification is unlikely and risk estimates probably do reflect the experience of the group for the specified cancer site (although not necessary specific histological types), as in the case of genitourinary cancers.

Bladder

Risk estimates for bladder cancer has been highly variable among studies, even those exploiting the same database [5,10]. In data from Alberta [13], the overall risk for bladder cancer was elevated overall above a doubling (SMR = 3.2, 0.9–8.1) but did not achieve statistical significance. Ma *et al.* [14] found among firefighters in Florida, a significant elevation for men (SIR = 1.29, 1.01–1.62) and suggestive elevation for women (10.0, 0.13–55.60) which was, however, based on a single case. Baris *et al.* [12] reported a slightly elevated SMR of 1.3

for bladder cancer, with greatest risk being among those hired before 1935 (1.7, 0.9–3.1), when exposures to combustion products were likely to have been higher, and among those with greater number of runs during their first 5 years employed (2.6, 0.5–14.6), which suggests a higher risk associated with greater individual exposure and more precise exposure assessment. Thus, the weight of evidence favours a presumption, given sufficient exposure.

Among Alberta firefighters, the elevation did not appear before age 60 or before 20 years of service and showed a very long peak latency of 40 years [13]. However, much more intensely exposed aniline dye workers in the 1940s and 1950s demonstrated latency periods as short as 7 years, which probably represents the biological limit [15]. One might expect a minimum latency on the order of 15 years for firefighters, shorter than is typical for solid tumours but not so extreme. There is not sufficient evidence to conclude that women in the fire service are uniquely susceptible, but the weight of evidence suggests that are not protected compared to men [14].

Kidney

Risk estimates for kidney cancer were markedly and significantly elevated among firefighters in Alberta (SMR = 4.1, 1.7, 8.5), which increased with application of a weighted exposure index to years of employment, and in Philadelphia [12] (SMR = 2.2, 1.2–4.1) among those employed for ≥20 years. The excess risk for the occupation has also been confirmed in large population-based studies [5,10]. Ma *et al.* [14] found a suggestive but not significant elevation for women (SIR = 4.2, 0.05–23.2) but not for men in Florida. Aluminium potroom workers, also exposed to polycyclic aromatic hydrocarbons, demonstrate a near doubling of urinary tract cancer risk after <10 years employment [15]. While it might be difficult to accept a latency <15 years for a solid tumour, latency periods <20 are not impossible for urinary tract cancers, as above.

Testes

Recently, Bates *et al.* [11] found a risk in excess of doubling (OR = 3.0, 1.3–5.9) for testicular cancer among firefighters in Wellington (New Zealand), but did not report the histological types. Stang *et al.* [16] reported similar findings from northern Germany, although their OR of 4.3 (0.7–30.5), based on four cases, two employed as firefighters >20 years and two for <4 years. Two cases were embryomas, an unusual finding. Ma *et al.* [14] showed a significant but lower elevation among firefighters in Florida (SIR = 1.6, 1.2–2.09) but did not report on tissue type. Given the totality of the evidence, it is reasonable to establish a presumption for testicular carcinoma on the basis of current evidence. However, there is insufficient evidence to characterize criteria for latency or exposure or to conclude that embryoma is the predominant outcome.

Framework 2: aggregated category, one disease predominates

In Framework 2, the nosological category aggregates cancers which are individually rare and which may be subject to miscoding, but one or more predominates. If one type of cancer is in excess, the aggregation leads to dilution and a misleading estimate of risk. Cancers of the brain are an example.

Brain

Cancers arising from brain tissue are relatively rare. Among the ≥20 individual types, gliomas (astrocytomas) constitute about half of the total and are more likely to be associated with environmental and occupational exposures [15]. The weight of evidence to date, predominantly from earlier studies, suggests that the elevation in risk for brain cancer reflects a true risk on the order of a doubling for firefighters with more than one decade of exposure, with variations among subgroups [8,17,18]. On the whole, therefore, the weight of evidence is sufficient to justify a presumption, at least for glioma.

The minimum latency for a brain cancer might be as short as 10 years for rapidly growing glioma (Stage IV astrocytoma).

Framework 3: aggregated category, no disorder predominates

In Framework 3 the nosological category aggregates cancers which are individually rare, but no one disease predominates. 'leukaemia, lymphoma, myeloma', for example, is a common aggregation in epidemiological studies. Although such aggregate categories compile sufficient numbers for statistical analysis, they are etiologically meaningless. If the individual disease risks cannot be separated, the benefit of the doubt should go to the claimant, as required by workers' compensation acts, unless reliable information is available on specific tissue types.

Non-Hodgkin lymphoma

Epidemiological studies may divide lymphomas into simply 'Hodgkin's disease' and non-Hodgkin lymphomas, with a further subdivision into 'lymphosarcomas' and 'reticulum cell sarcomas' in some older studies [15,19]. Hodgkin's disease, itself a set of diseases, has not been associated with occupational or environmental exposures and so aggregation may dilute the risk estimate for all lymphomas. Non-Hodgkin lymphomas include at least 30 recognized types, some of which are known [19,20] and others suspected [21] to be associated with environmental exposures and occupations.

'Lymphatic cancers' were separately addressed in Burnett *et al.* [5], which revealed a statistically significant elevation for non-Hodgkin lymphoma (PMR = 1.3, 1.0, 1.7) for all deaths from non-Hodgkin lymphoma and firefighters dying under the age of 65 (1.6, 1.1, 2.2) and, in another analysis of this large national dataset, white but not black firefighters [10]. The association increases in magnitude with improved exposure assessment. Baris *et al.* [12] observed an elevation for non-Hodgkin lymphoma (SMR = 1.4, 0.9–2.2) and a significant excess for the subset hired between 1935 and 1944 (2.2, 1.2–4.1), which rose (1.7, 0.9–3.3) for firefighters with ≥20 years experience and rose further (2.7, 0.7–8.2) for those assigned to ladder companies, and for those in the older subset employed >20 years (2.2, 0.9–3.3). Taken together, these observations suggest an underlying excess risk approaching or exceeding a doubling, which is diluted in the overall estimate.

Leukaemia

Burnett *et al.* [5] reported a statistically significant elevation in risk for all deaths in a large national collection of deaths by leukaemia (SMR = 1.2, 0.9–1.5) and for firefighters dying under the age of 65 (1.7, 1.2–2.4). Baris found no elevation for the leukaemias overall (0.8, 0.5–1.4) but a statistically significant excess (2.8, 1.0–7.3) for firefighters assigned to ladder companies only (although not for those assigned to both ladder and engine companies), and those with a high numbers of runs in the first 5 years (2.4, 0.7–8.5) and with medium but not high numbers of runs over a lifetime (2.5, 0.6–11.1).

Acute myelogenous leukaemia, the most common in adults, might plausibly be associated with exposure to benzene in combustion gases. Unexpectedly, the limited evidence suggests that firefighters may be at greater risk for other leukaemias. L'Abbé and Tomlinson [22], in a study of firefighters in Toronto, observed an (non-significant) excess of 'lymphatic' (lymphocytic) leukaemia (SMR = 1.9, 0.4–4.9). Ontario therefore now presumptively recognizes lymphocyctic leukaemia among firefighters.

Leukaemias tend to have short latencies, on the order of 5 years or so. Acceptance of short minimum latencies, and therefore duration of employment, on the order of 4 years, is reasonable to avoid errors of exclusion.

Myeloma

Myelomas are B-cell lymphomas and malignant plasma cell dyscrasias. Baris *et al.* [12] found an overall excess (SMR = 1.7, 0.9–3.1) which increased and became statistically significant with >20+ years duration of employment (2.3, 1.0–5.2) and for exclusive engine company employment (2.5, 1.2–5.7), with some suggestion of a correlation with medium and high diesel exposures (the latter based on small numbers of deaths). Insufficient data are available to address latency.

Framework 4: unitary category affected by a strong confounder

Framework 4 applies to well-defined outcomes with a strong confounding factor, usually smoking [6,23]. Lung cancer, especially, has been among the most difficult cancer sites to evaluate risk among firefighters. The weight of evidence suggests that the risk of lung cancer for non-smoking firefighters is elevated relative to other non-smoking adults but the demonstration is indirect and requires a mathematical derivation.

Workers' compensation acts require consideration of individual characteristics, such as smoking, in adjudicating a claim. Smokers among the population of firefighters would still contribute the great majority of cases of lung cancer, as they do in the general population. There is some evidence as well that firefighters smoke less than the general population [24], although there is no deficit of lung cancer for the group.

When lung cancer occurs in a firefighter who does not smoke, the relevant comparison is to the risk of other non-smokers, not to the population as a whole. There is no study available that describes the experience of non-smoking firefighters. Tissue type does not help as an indicator in the population or in the individual case because the risk of adenocarcinoma, which is the usual tissue type when non-smokers develop lung cancer, also increases with smoking [15].

The problem can be approached statistically, however, given a reasonable toxicological assumption: the risk is proportionate to the cumulative exposure to combustion products from both cigarette smoke and fire-related sources [2,6,8,25]. The first step in this analysis is to derive a rough estimate of the true relative risk of lung cancer among all firefighters [8, 26].

Taken together, and supported by the methodologically stronger studies in the literature, 1.5 seems to be a reasonable estimate of the true (unconfounded) relative risk for lung cancer among all firefighters. The attributable risk fraction would therefore be on the order of 33% for firefighting as an occupation. This magnitude of excess is also often found in studies of other blue-collar occupations, most of which have less plausible exposure to known carcinogens [23]. The estimate is based both on the totality of the literature and the findings of one study with relevant information.

Most extant studies that are positive, relevant, close to the primary data, large and methodologically sound seem to cluster reporting excess risk in a band from 30 to 68%, but there are also exceptional elevations in certain subgroups and specific sites within studies [13,15,19].

Exceptions have plausible explanations. Hansen [26] reported much a higher risk but used an unusual comparison populations. Studies by Vena and Fiedler [27] yielding lower risks showed a possible exposure–response relationship based on years of employment and association with age at first employment. Studies exceptionally rich in recent person years, such as Baris *et al.* [12] may report lower risks because respiratory protection has reduced exposure levels to combustion products since the 1970s. Beaumont *et al.* [28] which showed an unusually low risk, was also characterized by an atypical age distribution and a much larger healthy worker effect than is normally found for this population [3].

Studies of urban firefighters in Alberta also suggested a true SMR on the order of 1.50 when analysed by era of entry, duration of employment and a unique cumulative index of exposure opportunity. Cigarette smoking has also been documented to be less of a confounding factor in Alberta historically than in other populations [29]. The overall risk estimate was (SMR = 1.4, 0.9, 2.1) increased (to ≥2.0) in subgroups with higher exposure opportunities and duration and showed an exposure–response relationship. A higher risk was found for the middling-exposed, and a significantly elevated risk (4.1, $P < 0.05$) was found for those with >35 exposure opportunity-weighted years of employment [13].

One approach to quantifying the risk of non-smoking firefighters is to assume the following:

(i) The prevalence of smoking among firefighters during the era in which studies were conducted was roughly 40% ($f = 0.4$), similar to other blue-collar workers, and so 60% ($1 - f$) did not smoke.
(ii) The relative risk of lung cancer for smokers is 10 compared to non-smokers [15].
(iii) The relative risk (R_{ff}) of lung cancer for fire fighters overall is 1.5 (corresponding to an SIR of 1.50).

Consider x to represent the attributable risk fraction normalized by the expected risk for non-smokers, only, in the general population, which represents the proportionate additional risk arising solely from occupation as a firefighter. $R_{ff} = 0.4(10 + x) + 0.6(1 + x)/0.4(10) + 0.6(1.0) = 1.5$. Solving for x yields $x = 2.3$, which represents an estimate of the risk of lung cancer arising from the occupation alone, normalized by the risk of non-smokers in the general population. The relative risk for non-smoking firefighters, compared only to non-smokers in the general population, would be $(1.0 + x)/1.0$ or 3.3. The relative risk for non-smoking firefighters, compared to the general population, would be $R_{ns,ff} = [3.3/0.4(10.0) + 0.6(1.0)]$, or 0.72, indicating that non-smoking firefighters still would have a lower risk of lung cancer than would be expected in the general population, but that the deficit would be less than for other non-smokers.

Another way to approach the problem is to determine, based on the same assumptions, what the minimum relative risk calculated for firefighters as a whole would have to be to reflect a true doubling of risk for non-smoking firefighters. The calculation is similar and yields $R_{ff} = 1.2$, which is comfortably supported by the world literature and less than the 1.5 stipulated in the model.

However calculated, therefore, non-smoking firefighters demonstrate much greater than a doubling of risk when compared to other non-smokers, although the exact value cannot be known because of compounded uncertainties. This model is not sensitive to underlying assumptions. Reducing the estimate of the smoking prevalence among firefighters 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 increases the overall relative risk required to support the presumption only to 1.38.

Notwithstanding this demonstration, the personal risk of lung cancer among non-smokers remains less than that for smokers.

Discussion

The presumption for genitourinary cancers, including kidney, bladder and testes, are based firmly on a strong suggestion of excess in the literature by conventional criteria. These findings generally converge with a recent meta-analysis conducted by LeMasters *et al.*, which was unconnected with the presumption work. Using conventional methods of meta-analysis and standards of inference applied to 32 studies, they found an elevated 'metarelative' risk among firefighters for myeloma a probable association with non-Hodgkin lymphoma, prostate and testicular cancer, a 'possible' risk for brain, melanoma, colon and rectum, oral and leukaemia and 'unlikely' elevations for bladder and kidney, although the lower limit of the confidence interval for bladder was just below unity and they noted heterogeneity among studies. They did not disaggregate categories or conduct an analysis similar to the present study and did not evaluate the strength of individual studies [30].

Interpreted by criteria relevant to workers' compensation, the evidence available suggests that it is reasonable to adopt a policy of presumption for brain cancer, non-Hodgkin lymphoma (lymphatic cancer) and leukaemia for claims associated with occupation as a firefighter. A presumption is also reasonable for lung cancer in firefighters who do not smoke based on derived estimates risk. These presumptions are based on the weight of evidence, as required by adjudication, not on scientific certainty, but reflect a legitimate and necessary interpretation of the data for the intended purpose.

More generally, the frameworks applied in this study are generally applicable to the analysis of common problems in adjudication when data sufficient to provide a definitive conclusion are not available. The approach taken in this analysis rests on legal and adjudication criteria applied to the resolution of medicolegal cases and compensation claims, where decisions must be made on uncertain evidence. Such assessments for medicolegal and adjudicatory purposes are not intended to replace the standards of scientific certainty that are the foundation of etiologic investigation [6]. They are social constructs required to resolve disputes in the absence of scientific certainty.

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Conflicts of interest

None declared. The author frequently serves as a consultant or an expert witness in cases involving firefighters.

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