EVALUATING CAUSATION IN EPIDEMIOLOGICAL STUDIES OF FIREFIGHTERS

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Background: The evaluation of causation in cancers associated with firefighting presents problems in causality common to other applications of occupational epidemiology in adjudication of individual claims for workers' compensation. A global trend to establish legislated presumptions for compensation of firefighters has created an opportunity to reevaluate the literature applying standards of certainty based on the "weight of evidence" ("50% + 1") rather than elusive and, for many cancers, unattainable scientific certainty. Such standards are the norm and are *required* to be used in workers' compensation, which is also *required* to take into account individual factors.

Methods: We have exhaustively and repeatedly reviewed the epidemiological literature (to which we have also contributed) on cancer risk among firefighters based on the weight of evidence rather than scientific certainty.[1] Generalizable frameworks were formulated to define recurrent issues in assessing the evidence from epidemiological studies.

Results: We have identified four analytical frameworks describe the problems in analysis encountered:
1. Rare cancers. "Rare" (in biostatistical sense) cancers are prone to inadequate statistical power in individual studies (e.g. testicular). Misguided response is usually to aggregate cancers into biologically meaningless groups for analytical convenience (e.g. "non-Hodgkin lymphoma"). 2. Aggregation, one tumor type dominates. Dilution of the risk estimate by misclassification bias introduced by aggregation into rubrics (e.g. brain, when Grade 4 astrocytoma, "glioblastoma", is the tumor of interest at 34% of total). Elevation in tumor type of interest is easily missed. 3. Aggregation, no one type dominates. Epidemiological studies tend to promote illogical groups (e.g. "leukemia, lymphoma, myeloma"). Elevation in tumor type of interest is diluted and variable among studies. 4. Potential confounding by smoking. Fletcher(2) has provided a method for correcting for smoking prevalence. By this method, contribution to risk of lung cancer in a non-smoking firefighter could be backed out of the equation and estimated at approximately 2.0 or 3.0.

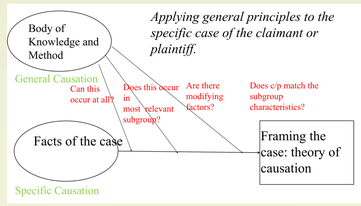
Conclusion: Epidemiological studies do not, by themselves, answer all the important questions about the etiology (cause) of occupational disease that are required to make a judgment for compensation. They inform conclusions about "general causation", which refers to evidence for an elevation of risk and the connection between disease and possible causes *in general*. Workers' compensation and other compensation systems require individualized evaluation of each case, called "specific causation", taking into account the individual circumstances, risk factors, and health risks for the claimant. Epidemiology can also inform specific causation by indicating whether risks are disproportionately elevated in certain job assignments, after a certain number of years of exposure, or against a background of other, non-occupational risks (such as cigarette smoking). This requires interpretation.

Methodological Issues Are Significant

- Firefighting is exacting and highly demanding.
- Ff's are in excellent shape, generally lower lifestyle risk factors for mortality from cancer and cardiovascular disease
  - Yet no deficit or healthy worker effect: evidence for offset by competing mortality
- Low smoking prevalence
  - But, mortality not much better than population
  - Cancer risks are *selectively* elevated.
- Years of svc a poor metric for risk
  - Covaries with age, latency, change in ff-ing

	Situation	Methodological problem	Sites
I	Uncommon, many confounders	Power, bias, and confounding	Kidney, bladder, testes
I I	Aggregation of tumor types by site for main type	Dilutes risk estimate	Brain
I I I	Aggregation of uncommon tumor types	Obscures risk signal	AML, lymphomas
I \	Confounder overwhelms risk factor	Confounding (smoking)	Lung cancer

Different Standards of Adjudication



- Scientific certainty is not reasonable in assessing risk.
- Applicable standard in "real world" is "weight of evidence." (reasonable medical or epidemiological certainty, latter applies *only* to general causation)
- In science, >95% ($p < 0.05$, Type I error): Not appropriate for decision making
- Seldom attainable, even in ideal situations
- Not particularly useful in court or compensation
- Contrary to civil standard of certainty "50+1%"
- In workers' compensation, 50% certainty + benefit of the doubt or (in most states) rebuttable presumption
- Meta-analysis, while useful, does not solve interpretation problem, esp. for rare outcomes in *etiological* studies: power, intrinsic bias, inadequate adjustment for exposure.

Documented Exposures Associated with Cancer Risk in Firefighting

Not Associated with FIRE Combustion

Antimony (constituent of flame retardant on turn-out gear)
Asbestos
Diesel exhaust (inc. PAHs, nitroarenes, fine particulate matter)
Cadmium
Lead
PFOA (perfluorooctanoic acid and its product polytetrafluoroethylene)
Pesticides (few)
Polybrominated biphenyl compounds (mixed, low)
Polychlorinated biphenyl compounds (mixed)
Shiftwork
Silica dust

IARC Group I carcinogens are in red.

We have insufficient exposure information on halogenated (chlorinated) short-chain alkanes.

Associated with FIRE combustion

Acetaldehyde
Acrolein
Aldehydes (mixed)
Alkanes, straight chain (inc. propane*)
Alkenes, straight chain (inc. propene* 1-butene*/2-methylpropene)
*Benzene**
Benzaldehyde
Brominated hydrocarbons (low)
*1,3-Butadiene**
Carbon dioxide*
Carbon monoxide*
Chlorinated alkanes (low)
Chlorobenzenes (low)
Cycloalkanes
Cyclopentenes
Dioxins and furans (including 2,3,7,8-dibenzodioxin and –furan*)
Dichlorofluoromethane
Ethylbenzene
Formaldehyde
Glutaraldehyde*
Hydrogen chloride
Hydrogen fluoride
Hydrogen cyanide
Hydrogen fluoride
Isopropylbenzene
Isovaleraldehyde
Methylene chloride
Naphthalene (a PAH)
Nitriles (mixed)
Nitroarenes (nitroso-substituted analogues of PAHs)
Nitrogen dioxide
Particulate matter (fine)
Phosgene
Polycyclic aromatic hydrocarbons (mixture, multiple carcinogens*)
Sulfur dioxide
Styrene*
Tetrachloroethylene
Toluene*
*Tricholoroethylene**
Vinyl chloride (pyrolysis of PVC)
Xylenes (including o-xylene*)

* Predominate in nonspecific urban structural fires.

Conclusions

- Firefighters are at risk for specific cancers.
- Studies of ff require interpretation.
- Individual cases *always* require individual review.
- Scientific certainty is not fair in adjudication.
- Risk profile is changing:
- need new studies for a new generation of ff.s!

Adapted for the 2019 State of the Science National Firefighter Symposium from previous presentations at the John P. Redmond Symposium and international meetings.

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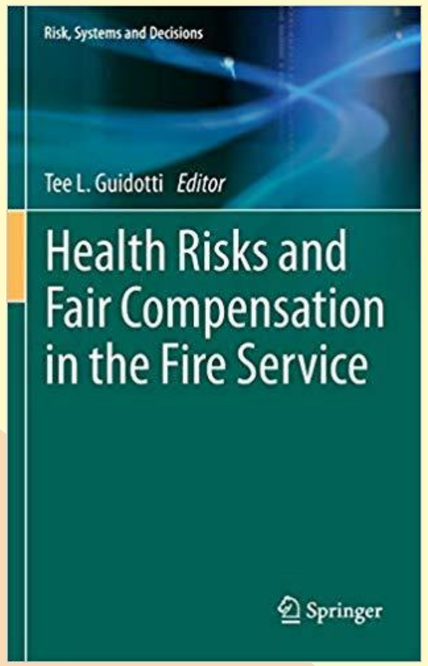

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