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Lung, Tracheal and Bronchial Cancer in Nickel, Uranium and Gold Miners

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This medical discussion paper will be useful to those seeking general information about the medical issue involved. It is intended to provide a broad and general overview of a medical topic that is frequently considered in Tribunal appeals.

Each medical discussion paper is written by a recognized expert in the field, who has been recommended by the Tribunal's medical counsellors. Each author is asked to present a balanced view of the current medical knowledge on the topic. Discussion papers are not peer reviewed. They are written to be understood by lay individuals.

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Lung, Tracheal and Bronchial Cancer in Nickel, Uranium and Gold Miners

This paper will be presented in a question and answer format. The questions were posed by the WSIAT.

1. **Please review the scientific literature that has addressed the risk of lung, tracheal and bronchial cancers in Ontario nickel, uranium and gold, miners.**

    a. What is the level of excess risk in each of these groups of miners for these cancers?

    b. What is the role of arsenic, radon progeny, silica and dust in the excess risk of these cancers?

    c. Does the evidence of increased risk of lung cancer in any of the mining groups attribute this risk to specific exposure, or to the mining environment generally?

    The key studies to address these issues was carried out by Kusiak et al (1991, 1993). The study reported in 1991 was a large retrospective cohort study of a cohort of 54,128 men who had worked in Ontario mines. The mortality in the group between 1955 and 1986 was compared to the expected mortality in the cohort based on the age, sex and calendar year specific mortality rates in Ontario for carcinoma of the lung and the age and calendar year person years distribution of the members of the cohort.

    In the subcohort of 13, 603 Ontario gold miners, an excess of carcinoma of the lung was found with a standardized mortality ratio (SMR) of 129 and a 95% confidence interval of 115 to 145. The excess of lung cancer mortality was found to be associated with having started mining before 1946 (a proxy for high dust exposure), exposure to arsenic before 1946 and exposure to radon decay products.

    In the sub-cohort of nickel miners an excess of carcinoma of the lung was found in men who began to mine nickel before 1936 (SMR 141, 95% confidence interval of 105 to 184). No increase in the mortality from carcinoma of the lung was evident in men who began mining nickel after 1936 when the dust exposures were lower.

    A study of Ontario uranium miners was reported by Kusiak et al in 1993. The cohort had an SMR of 225 (152 lung cancers observed, 67.6 expected) and a 95% confidence interval of 191 to 264. Mortality for

lung cancer in this cohort was clearly related to exposure to short-lived radon progeny. The excess risk of lung cancer from the same degree of exposure to short-lived radon progeny was greatest from 5 to 14 years after exposure. It was also greater in men under the age of 55 years and lower in older men. The prevalence of smoking in this cohort of uranium miners was greater than the general population and this might explain some of the increased risk but the authors felt that it would not explain the whole excess. As well, miners are an itinerant group and part of the excess of lung cancer mortality in uranium miners was probably due to arsenic exposure that had occurred earlier when they worked in gold mines.

These studies by Kusiak et al did not address the contribution of silica or silicosis to the risk of lung cancer in the various types of mines. Another study by Finkelstein (1999) did examine the relationship between lung cancer and silicosis and exposure to radon in Ontario miners. In this case control study both radon progeny (measured as working level months) and the presence of silicosis were found to be predictive of lung cancer. Therefore some of the risk of lung cancer in miners attributed to specific exposure such as radon and arsenic might also be due to silicosis.

2. What is the significance of the above exposures if the worker has silicosis?

As indicated in the above study by Finkelstein and also by a number of other studies summarized by Steenland et al (1996), silicosis is associated with increased risk of lung cancer. As well, the review by Steenland et al indicated that silica exposure itself in the absence of silicosis may be associated with an increased risk of lung cancer but the risk appears lower than that associated with silicosis. A recent review by Pelucchi et al (2006) of epidemiological studies published in 1996-2005 reached similar conclusions with a clear risk of lung cancer identified for silicosis (1.69 for retrospective cohort studies; 3.27 for case control studies) and a lower and less evident risk for silica.

Therefore if a worker has lung cancer and silicosis, the silicosis may have contributed to the development of lung cancer, but this does not preclude other exposures such as arsenic and radon progeny from also being independent risk factors for the development of the lung cancer.

3. **Please explain the terms SMR and SIR. How are they calculated? What is being measured?**

The term SMR refers to Standardized Mortality Ratio and the term SIR refers to Standardized Incidence Ratio. In studies of cancer, the SMR

would refer to the standardized mortality ratio for a particular type of cancer and the SIR would refer to the standardized incidence ratio for a particular type of cancer. For the SMR the outcome is mortality from cancer and for the SIR the outcome is the occurrence of cancer.

These are both calculated by dividing the observed number of outcomes by the expected number and then multiplying the ratio by 100. The expected number is based on the rates for the outcome in the reference population (in this case from the Ontario male population). These reference rates are obtained for specific age and calendar year periods (because cancer rates vary according to age and calendar year) and are multiplied by the number of person years of the cohort in the corresponding age and calendar year periods to generate the expected numbers. The effect of this calculation for expected numbers is to determine the number of outcomes in the cohort of miners that would be expected if the miners had the same age and calendar year specific rates for the outcome as the reference population.

The SMR or SIR is an estimate of the relative risk and tells us how much more likely the health effect is in a particular exposed group in comparison to the reference population. In other words, an SMR of 200 could indicate that there is a two-fold increased risk in the exposed group in comparison to the reference group. A 95% confidence interval can be calculated for the SMR and from this a test of statistical significance can be carried out. If the lower confidence limit for the SMR or SIR exceeds 100 then the SMR or SIR is statistically significant.

4. Please explain the significance of an SMR of 200 or above.

a. Will that establish that the exposure was the likely cause of death in the cohort being studied?

An SMR of 200 indicates that there is a two-fold increase in the risk of the outcome in the exposed group in comparison to the reference group.

b. What would be the probability that the death was due to the exposures in an individual?

The etiological fraction among the exposed (EFE) can be used to calculate the probability that the death of an individual exposed cohort member from the outcome of interest was due to the exposure.

The etiologic fraction among the exposed can be calculated as follows:

EFE = [(SMR - 100) / SMR] × 100 %

Therefore if the SMR was 200 the etiologic fraction among the exposed would be:

EFE = [(200 -100) / 200] × 100%
= 50%

This would indicate that in an exposed individual who developed the outcome of interest there was approximately a 50% likelihood that the outcome was due to that exposure. As the SMR increases above 200 this probability also increases above 50%.

5. **If the SMR is less that 200, (for instance 150), please explain how the probabilities are mathematically calculated, to establish whether the exposure is the cause of the death.**

The etiologic fraction among the exposed can be used to calculate this probability. When the SMRs drop below 200 the etiological fraction among the exposed drops below 50%. For example, an SMR of 150 would be associated with the following etiological fraction among the exposed:

EFE = [(150 - 100) / 150] × 100%
= 33%

When the etiologic fraction among the exposed is calculated, an attempt should be made to define exposure categories from the epidemiologic studies that match those of the individual being evaluated. However, when subgroups from the overall study group are obtained that match the exposure characteristics of the individual, the sample size is reduced (in comparison to the overall cohort) and the SMR estimates become less precise (e.g. the confidence intervals become wider) and the power is reduced to detect statistically significant results. As well in any study there may be sources of bias such as confounding, selection and measurement bias that affect the measurement and interpretation of risk. The issue of potential bias is especially relevant to the interpretation of small SMRs because such SMRs might be entirely explained by bias.

6. **If the SMR for a particular exposure (or exposures) in a cohort is 150, is it correct to say that each individual in that cohort is at a 50% increased risk of death from lung, tracheal, or bronchial cancer, as compared to someone in the control group?**

If the SMR for a particular exposure in a cohort is 150 it means that there is a 50% increased risk of the outcome in the exposed cohort in comparison to the reference group.

These results refer to the cohort as a whole. On an individual basis there likely is some variation in risk due to factors such as variation in the activity of DNA repair enzymes or metabolism or excretion of the chemical. As well co-morbidity and other risk factors (such as smoking) might influence individual risk.

a. Does this mean that one third of deaths from these cancers in the cohort would likely be caused by the exposure?

The etiologic fraction among the exposed for an SMR of 150 would be 33%. This means that in an individual with the exposure who developed the outcome of interest, there would be a 33% chance that the outcome was actually caused by the exposure. Applied to all the members of the cohort who developed the outcome of interest, it would mean that in one third of them their outcomes and subsequent deaths would be due to the exposure.

However the use of the etiologic fraction among the exposed to estimate individual etiologic probabilities can be problematic. The probability calculation assumes a precise estimate of risk that is free of bias. However this may not be the case as outlined in the response to question 5.

b. If calculated mathematically, would this mean that the work exposure constituted one third of the cause, or was a significant cause, in the death of an individual who died from one of these cancers in the cohort studied?

The etiologic fraction among the exposed indicates that one third of the outcomes in the exposed group were due to the exposure. It does not mean that in each individual case this exposure constituted one third of the overall cause of the condition. For example if 150 outcomes of interest occurred in the exposed group, 100 would be unrelated to exposure and 50 would be due to exposure. The problem is that for each case we do not know into which group they fall. However in each individual the probability that the exposure caused the outcome would be 33%.

The determination of significant cause is a legal issue which in this context would fall within the purview of civil law interpretation. Often a balance of probabilities criterion is taken to be a 50% probability and, given this assumption, the 33% probability cited above would not be interpreted as a significant cause.

7. **As a scientist, can you explain your understanding of the difference between epidemiological evidence, and what is established by it, and the determination of cause in an individual case?**

   Epidemiologic studies provide us with empirical information about the relationship between particular exposures and health outcomes. Each study should be evaluated for its methodological rigour and in particular sources of random error and bias should be evaluated. When a number of similar epidemiologic studies have been carried out, these can be evaluated collectively using specific criteria. For example the Bradford Hill criteria examine such factors as the strength of the association, dose response, consistency, specificity, temporality, biologic sense and overall coherence of the information. These are referred to by epidemiologists as criteria for causation but essentially they provide general rules for the evaluation of the epidemiologic evidence. When you examine these various criteria an overall decision about the totality of the evidence still has to be made.

   Within the context of compensation, the determination of cause in an individual case is essentially an administrative / legal issue. The epidemiologic evidence may be included in a particular decision and the evaluation of this evidence may be helped by using the Bradford Hill criteria. However a decision about causation is made after evaluating all of the available evidence and taking into consideration the overall context of the decision and the statutory framework for making such a decision.

8. **As a scientist, can you explain your understanding of how the Board addressed the issue of the excess risk indicated by the epidemiological evidence, when it established its gold miner policy? (See Operational Policy 04-040-08 and Board Minute # 5, August 29, 1991, Page 5471).**

   The study by Kusiak et al (1991) indicated that the main factors associated with the excess of lung cancer mortality in Ontario Gold miners were exposure to high dust concentrations before 1946, exposure to arsenic before 1946 and exposure to radon decay products. The association with high dust exposure prior to 1946 is a marker for such high exposure generally. As such, high dust exposure in a gold mining environment of sufficient duration would be associated with increased risk regardless of the calendar year period of exposure. The same would pertain to any high concentration of arsenic. These major risk factors are incorporated into the operational policy for lung cancer in gold miners. Gold miners are also potentially exposed to radon progeny and as such the findings from Kusiak et al (1993) in uranium miners would also be relevant to gold miners. In particular, the risk of lung

cancer from radon progeny is higher in younger men (given the same level of exposure) and also the latency is shorter for lung cancer from radon progeny than from other exposures. These factors related to age of onset of exposure and latency for radon progeny exposure are incorporated into the operational policy. Therefore the Operational Policy appears to have tried to incorporate the existing epidemiologic evidence of the risk of lung cancer associated with the various exposures of gold miners.

9. How was this addressed in the uranium policy? (See Operational Policy 04-04-10 and 16-02-14).

In uranium miners the key exposure is to radon progeny. The epidemiologic evidence indicates that the risk of lung cancer is higher in men under the age of 55. Therefore the Operational Policy requires a lower radiation index in younger men to qualify for compensation. Also in the calculation of the radiation index, greater weight is given to exposure in working level months sustained 5 to 14 years before the diagnosis of lung cancer and this is consistent with the epidemiologic evidence of the excess risk of lung cancer from the same degree of exposure to short lived radon progeny being greatest in the 5 to 14 year period after exposure starts. As well the policy mentions that a worker's non-smoking status can provide evidence of work relatedness and this is consistent with the epidemiologic evidence that smoking is strongly associated with lung cancer. Therefore the Operational Policy seems to be broadly connected with the epidemiologic evidence. As well, the Operational Policy 04-04-10 indicates that claims which fail to meet the stipulated criteria must be considered on their own merits having regard for all factors.

10. What does the scientific evidence indicate about the role of smoking in assessing the risk of these cancers in nickel miners? What about the risk in uranium miners? What about the risk in gold miners?

In the mining cohorts and often in industrial cohorts in general, the prevalence of smoking is greater than in the general population. Therefore, tobacco smoking which is a known risk factor for lung cancer may act as a confounder of the relationship between the particular type of mining or mining exposures and lung cancer. However, the effect of such confounding is unlikely to be large. Usually if the SMR is above approximately 150 to 200 the increased risk of lung cancer in the exposed cohort is unlikely to be accounted for by differences in the prevalence of smoking in the exposed cohort and the reference group.

An example will help to illustrate this statement. If the following assumptions are made:

a. the prevalence of smoking (Ps) is equal to 50% in the occupationally exposed group and 30% in the reference group

b. the prevalence of not smoking (Pns) is the complement of the prevalence of smoking (Pns = 100% - Ps)

c. the relative risk of lung cancer due to smoking (RRs) is 10,

d. the relative risk of lung cancer in nonsmokers (RRns) is 1.

The relative risk of lung cancer in the occupationally exposed group due only to confounding may be calculated as follows:

RR confounding = (RRs x Ps)+ (RRns x Pns) in the occupationally exposed group divided by the same calculation in the reference group.

In our example the calculation is as follows:

RR confounding = [(10 x 0.5) + (1 x 0.5)] ÷ [(10 x 0.3) + (1 x 0.7)]
= 5.5 ÷ 3.7
= 1.48.

Therefore in this example a fairly large difference of 20% in the prevalence of smoking between the reference population (30%) and the exposed group (50%) only resulted in an increase in the relative risk to 1.48. This would be equivalent to an SMR of 148.

a. Is the effect of smoking additive to mining exposures?

b. Is there a multiplicative or synergistic effect?

The effect of smoking probably should be considered additive to mining exposures. There is no good evidence of interaction between smoking and exposure to dust, arsenic or silica or the presence of silicosis in miners. There is some evidence of the combined effect of smoking and radon progeny exposure being greater than additive. However, this seems to fall short of a multiplicative effect.

11. The scientific evidence has established an increased risk for gold miners exposed to arsenic, radon progeny, silica and dust. The Board's gold miner and uranium miner polices address these risks either directly, or in the case of silica, by the rating code used in interpreting chest x-ray results. These miners were also exposed to other substances that may be carcinogenic. What is the implication, if any, of these additional exposures for the calculation of the SMR, or in considering the probability that the exposure(s) caused the deaths from cancer in this group?

The SMR's are calculated for the exposed cohorts and reflect the increased risk of lung cancer from a particular type of mining experience generally. As such, If there are additional carcinogens other than those referred to above, their effect would already be included in the calculation of the SMR for the overall exposed cohort. However the attribution of risk due to the unknown carcinogens would be unrecognized. As well the attribution of risk per unit exposure to the known carcinogens would be overestimated. The paper by Finklestein (1995) illustrates how the recognition of lung cancer risk due to the presence of silicosis in miners influences the interpretation of lung cancer risk per unit exposure due to radon.

12. How does one differentiate between the "usual" risk in a cohort and any any increased risk in a particular individual?

a. What factors should be considered?

The exposed cohort consists of individuals with varying levels of exposure. In some epidemiologic studies the overall cohort is broken down into high, medium and low exposure and the SMR's are calculated for these exposure categories. This allows some estimation of the gradient of risk associated with a particular level of exposure. The individual's particular exposure history could then be used to estimate what the associated risk might be. The main factors to consider would be the level and duration of exposure and the time since exposure began to ensure that sufficient latency had elapsed to put someone at risk of the outcome of interest. As well other factors such as the age at first exposure and temporal patterns of exposure could be examined as well as confounding factors such as smoking.

References

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