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THE INDUSTRIAL INJURIES ADVISORY COUNCIL

POSITION PAPER 22

LARYNGEAL CANCER
AND
ASBESTOS EXPOSURE

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Laryngeal Cancer and Asbestos Exposure
Position paper 22

Summary

1. The possible association between laryngeal cancer and asbestos exposure was last considered by the Council in 1989 when it was concluded that the evidence was insufficient to support prescription. The matter was recently brought to the Council's attention again by the Manchester Asbestos Victims' Support Group. It was noted that a number of new studies on the subject had been published since 1989, and it was agreed that the position should be reviewed.

2. Laryngeal cancer is a relatively uncommon disease. Alcohol and smoking are important risk factors for disease occurrence, particularly in combination. This makes it difficult to establish the independent effect of occupational factors and allowance for the effects of alcohol and smoking is important in the interpretation of studies on this topic.

3. A number of reviews of the evidence carried out since 1989 were identified. These have reached differing conclusions, reflecting the fact that the link between asbestos exposure and laryngeal cancer remains unclear. A comprehensive high quality review carried out by the US National Academy of Sciences (NAS) was published in 2006. This considered the evidence from 47 studies (29 cohort studies and 18 case-control studies) published since 1979 and provided a basis for the Council's own evaluation of the evidence. In addition, the Council's Research Working Group carried out its own literature search and as a consequence evaluated a further three cohort studies and one further case-control study.

4. Although a number of studies indicated an increased risk in relation to asbestos exposure, relatively few studies indicated a risk which was more than doubled (the threshold the Council normally requires before recommending prescription). Analyses carried out by the authors of the NAS review indicated that the combined relative risk (RR), derived from all the cohort studies, was 1.40 and that from case-control studies was 1.43. Further, meta-analyses carried out by other authors yielded a combined RR for 18 cohort studies of 1.57 and a combined RR for nine case-control studies of 1.37.

5. The Council considered carefully those studies which investigated whether risks were higher in workers with very high or very long duration of exposure. Data from a minority of cohort studies suggested that the risk might be doubled in those with at least 20 years of exposure. However, where increased risks were demonstrated, these tended to occur in historical cohorts and included workers whose first exposure had occurred more than 40 years previously. Combined analysis of those in the highest exposure groups (defined in a variety of ways), carried out by the NAS reviewers, yielded an RR greater than 2.0. However, confidence in the data from the cohort studies is weakened by the absence of a full adjustment for smoking and alcohol consumption.

6. While case-control studies mostly allowed for these important confounding factors, exposure assessment in this type of study is generally considered to be less reliable. Moreover, case-control studies which included a dose-response analysis did not find a doubling of risks in high exposure groups or a markedly increased risk by level or duration of exposure.

7. The Council has concluded that the current literature does not provide strong, consistent evidence of a doubling of risk associated with asbestos exposure and is therefore not sufficiently robust to recommend prescription. The Council will however keep this matter under review and will monitor the emerging literature on the subject, including a proposed review, in 2009, by the international Agency for Research on Cancer, of cancers associated with asbestos exposure.

Background

8. The possible association between asbestos exposure and an increased
    risk of laryngeal cancer was considered by the Council in 1989. At that
    time it was concluded that the evidence for an association was
    insufficient to support the case for prescription. In March 2007 the
    subject was once more brought to the attention of the Council by a
    member of the Greater Manchester Asbestos Victims' Support Group.
    The Council noted that further evidence had emerged since 1989 and
    agreed to consider the matter again.

9. The larynx, commonly known as the voice box, comprises the glottis
    which includes the vocal chords, and the tissue above (supraglottis)
    and below (subglottis) this area. The supraglottis includes the
    epiglottis, a fold which closes the larynx during swallowing to prevent
    food inhalation. Carcinoma of the larynx is a relatively uncommon
    disease. It is more common in men than in women and its incidence
    increases after the age of 45.[1]

10. Most cancers of the larynx are squamous cell carcinomas that arise in
    the upper airway. Vocal symptoms, such as hoarseness, and easily
    visible signs of the disease, such as tiny tumour masses on the vocal
    chords, occur at a relatively early stage so that early diagnosis is
    common and survival rates are high.

11. The relationship between asbestos exposure and laryngeal cancer is
    regarded as biologically plausible since the larynx, like the lung, is in
    the direct path of inhaled asbestos fibres. In addition, squamous cell
    carcinomas of the lung and larynx exhibit certain histological
    similarities. Asbestos exposure is an established cause of lung cancer.
    However, there is an absence of clinical data which documents the
    accumulation and persistence of asbestos fibres in the larynx in
    exposed workers, while animal experiments involving inhalation of
    asbestos fibres at levels sufficient to cause lung cancer and
    mesothelioma have failed to induce laryngeal cancer, (McConnell *et al*
    1999).

12. Two strong risk factors for laryngeal cancer in the general population
    are tobacco smoking and alcohol consumption, particularly when

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[1]Age standardised incidence rates per 100,000 population per year for the UK, 2002-4, for
men and women were 5.4 and 0.3 respectively. Office of National Statistics, HMSO, London.
www.statistics.gov.uk/statbase

occurring in combination.[2] The effect of smoking increases markedly with the number of cigarettes smoked per day and the total duration of smoking, and relative risks can increase by as much as 9-44-fold in some studies (e.g. Bosetti *et al*, 2002; Menveille *et al,* 2004; Shapiro *et al*, 2000). Among heavy drinkers risks may be increased some 6-fold, even after allowing for smoking (e.g. Menveille *et al,* 2004; Zang *et al*, 2001).

The Industrial Injuries Disablement Benefit Scheme

13. The Industrial Injuries Advisory Council (IIAC) is an independent statutory body set up in 1946 to advise the Secretary of State for Social Security on matters relating to the Industrial Injuries Scheme. The major part of the Council's time is spent considering whether the list of prescribed diseases for which benefit may be paid should be enlarged or amended.

14. The Industrial Injuries Disablement Benefit (IIDB) Scheme provides a benefit that can be paid to an employed earner because of an industrial accident or Prescribed Disease.

The legal requirements for prescription

15. The Social Security Contributions and Benefits Act 1992 states that the Secretary of State may prescribe a disease where he is satisfied that the disease:

    i. ought to be treated, having regard to its causes and incidence and any other relevant considerations, as a risk of the occupation and not as a risk common to all persons; and

    ii. is such that, in the absence of special circumstances, the attribution of particular cases to the nature of the employment can be established or presumed with reasonable certainty.

16. In other words, a disease may only be prescribed if there is a recognised risk to workers in an occupation, and the link between disease and occupation can be established or reasonably presumed in individual cases.

17. In seeking to address the question of prescription for any particular condition, the Council first looks for a workable definition of the disease. It then searches for a practical way to demonstrate in the individual case that the disease can be attributed to occupational exposure with reasonable confidence. For this purpose, reasonable

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[2] IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol.44 (1988) Alcohol Drinking; Vol. 83 (2004) Tobacco Smoke. Lyon, France, WHO.

confidence is interpreted as being based on the balance of probabilities according to available scientific evidence.

18. Within the legal requirements of prescription it may be possible to ascribe a disease to a particular occupational exposure in two ways – from specific clinical features of the disease or from epidemiological evidence that the risk of disease is at least doubled by the relevant occupational exposure.

Clinical features

19. For some diseases attribution to occupation may be possible from specific clinical features of the individual case. For example, the proof that an individual's dermatitis is caused by his/her occupation may lie in its improvement when s/he is on holiday and regression when s/he returns to work, and in the demonstration that s/he is allergic to a specific substance with which s/he comes into contact only at work. It can be that the disease *only* occurs as a result of an occupational hazard (e.g. coal workers' pneumoconiosis).

Doubling of risk

20. Other diseases are not uniquely occupational, and when caused by occupation, are indistinguishable from the same disease occurring in someone who has not been exposed to a hazard at work. In these circumstances, attribution to occupation on the balance of probabilities depends on epidemiological evidence that work in the prescribed job, or with the prescribed occupational exposure, increases the risk of developing the disease by a factor of two or more.

21. The requirement for, at least, a doubling of risk is not arbitrary. It follows from the fact that if a hazardous exposure doubles risk, for every 50 cases that would normally occur in an unexposed population, an additional 50 would be expected if the population were exposed to the hazard. Thus, out of every 100 cases that occurred in an exposed population, 50 would do so only as a consequence of their exposure while the other 50 would have been expected to develop the disease, even in the absence of the exposure. Therefore, for any individual case occurring in the exposed population, there would be a 50% chance that the disease resulted from exposure to the hazard, and a 50% chance that it would have occurred even without the exposure. Below the threshold of a doubling of risk only a minority of cases in an exposed population would be caused by the hazard whereas above it individual cases can be attributed to exposure on the balance of probabilities.

22. The epidemiological evidence required should ideally be drawn from several independent studies, and be sufficiently robust that further research at a later date would be unlikely to overturn it. The excess risk should arise from the occupational exposure or work in question and not simply as a result of other factors in the general population that happen to be associated with exposure (e.g. smoking).

Availability of evidence

23. Laryngeal cancer is not a uniquely occupational disease. The strong relationship between the disease and the common exposures of smoking and alcohol consumption means that the case for prescription must rest on reliable evidence that asbestos exposure results in a more than doubling of risk of cancer of the larynx after taking into account the influence of these non-occupational factors.

24. A number of studies have been published since the Council last considered the matter in 1989 and there is now a large research literature on the subject. Despite this, the association between laryngeal cancer and asbestos exposure has remained unclear, and successive reviews on the subject since 1989, (Smith *et al* 1990; Kraus *et al* 1995; Brown & Gee 2000; Griffiths & Malony 2003.) have reached differing conclusions. Most recently a comprehensive, high quality review was published by the US National Academy of Sciences (NAS) in 2006.[3] This review provided a detailed evaluation of the evidence from 47 studies published since 1979 and formed the basis for the considerations of the Council. In addition, the Council's Research Working Group carried out its own literature search and identified four further studies.

Consideration of the evidence

25. The epidemiological evidence identified relates to two types of study, cohort studies and case-control studies, each of which has certain advantages and disadvantages. In cohort studies a group of individuals with exposure to a particular agent, in this case asbestos, are identified, and their incidence of disease or death is compared with that of unexposed comparison populations. This allows the calculation of a direct estimate of relative risk (RR) or of relative mortality (Standardised Mortality Ratio, SMR). Cohort studies often focus on specific workforces in which exposures tend to be relatively high and of long duration, often with supporting exposure measurements. Cohort studies of cancer in the occupational setting typically overcome the practical problem of long latency (the many years an investigator has to wait between exposure and cancer onset) by studying populations in

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[3] National Academy of Sciences. Committee on Asbestos. Selected Health Effects. Asbestos: Selected Cancers. Ch 8. Laryngeal Cancer and Asbestos.
http://www.nas.edu/catalog/11665.html

retrospect using records of employment and exposure, linked with databases of cancer registry or more usually death certification. Most of the cohort studies located in this review were of mortality. As survival rates from laryngeal cancer are high, these studies may have underestimated the incidence of the disease. Moreover, retrospective studies often lack information on the smoking and drinking habits of the workforces studied. Finally, even large cohort studies may accumulate few cases if the disease in question is very rare.

26. In case-control studies patients who have been diagnosed with a disease, in this case laryngeal cancer, are identified, and their past exposure to possible causal agents, including asbestos, is compared with that of non-cases who do not have the disease. From this an odds ratio (OR) is calculated which, for rare outcomes, is similar to an RR. This design overcomes the problem of latency, as the starting point is a collection of established cases. Cases are also plentiful (often coming from special hospital clinics), but typically these are drawn from all walks of life, rather than a particular highly exposed industry. Exposure assessment in case-control studies is made retrospectively (by asking the patient) and is potentially subject to reporting bias. For example, those suffering from disease may be more likely to recall certain exposures than those without disease. However, the opportunity exists to ask also about drinking and smoking habits and so to allow for these factors in analysis.

Cohort Studies

27. The NAS review identified 29 published studies which included 35 cohorts[4]. Of these, five were incidence studies and the remainder were mortality studies. In addition, the Council identified two further mortality studies and one further incidence study. The studies covered a range of occupations, including mining, textiles and insulation work and thus involved exposure to different forms of asbestos. The cohorts varied considerably in size, and three studies each reported only one case, the largest number of cases identified being 36.

28. An analysis from the NAS review combined data from all of the individual cohort studies, and this estimated a RR of 1.40 (95% Confidence Interval,[5] CI, 1.19-1.64). In keeping with this, a meta-analysis by Goodman *et al* (1999) of 18 asbestos exposed cohorts reporting on morbidity and mortality yielded combined RRs for laryngeal cancer of between 1.33 and 1.57 (under differing assumptions about the time course of disease onset).

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[4] Some studies provided separate analyses of male and female workers.
[5] A 95% confidence interval (CI) represents a plausible range in which the true population value lies, given the extent of statistical uncertainty in the data. A lower confidence limit >1 suggests a positive association that is unlikely to arise simply by chance (less than 1 chance in 20).

29. Eleven studies from the NAS review, and the three further studies identified by the Council, assessed dose-response relationships, and some of these provided evidence of higher risks among those with a greater intensity or longer duration of exposure to asbestos. Indeed, in certain subsets risks were substantially increased – for example, by 11.9-fold in men who worked for more than 20 years with brake linings containing chrysotile (Finkelstein *et al*, 1989), by 5.5-fold in cement workers with high intensity exposure prior to 1940 (Raffn *et al*, 1989), and by 8.5-fold in insulation workers with heavy exposure to asbestos in shipyard work (Puntoni *et al*, 2001).

30. The NAS reviewers calculated aggregate RRs (based on 11 studies) for those in the highest vs. lowest exposure categories, first for the strongest associations reported across studies and then for the weakest associations reported. These were respectively 2.57 (CI 1.47-4.49), and 2.02 (CI 1.64-2.47). However, a wide range of measures of 'dose' were included in these studies and the authors note that subjects were included if they fell in the highest exposure category 'by any definition'. This causes a problem for prescription purposes in defining the actual level at which risks may have been doubled.

31. Moreover, nine of the 14 studies which assessed dose-response relationships did not demonstrate a statistically significant increased risk in any exposure group, and in several studies trends were not clear cut. Thus, for example, in studies by Peto *et al* (1985), Liddell *et al* (1997), Pira *et al* (2005) and Purdue *et al* (2006), increased risks were seen in the intermediate but not in the highest bands of exposure intensity or duration. In a study of chrysotile miners that attempted to quantify exposure intensity, Piolatto *et al* (1990) reported a statistically significant trend of increasing risk with exposure from <100 fibre-years to >400 fibre-years, and in the two highest exposure groups the RRs were raised two- to almost four-fold, but in a study of cancer incidence from the construction industry, which employed a semi-quantitative scale, the RR for high exposures was 0.8 while that for intermediate exposures was 2.3 (Purdue *et al*, 2006).

32. In general, studies that reported significant dose-response relationships involved historical cohorts whose first exposures occurred more than 40 years previously, whereas cohort studies of more recently exposed workers did not demonstrate significant associations with asbestos exposure.

33. In principle, the associations described above could have been exaggerated if the blue-collar cohorts under investigation had smoked or drank more and for longer than the comparison populations. Only a few studies in this dataset controlled directly for alcohol consumption (Putoni *et al*) or smoking (Purdue *et al*, 2006; Liddell *et al,* 1997), and none controlled for both. Several other studies employed surrogate measures, such as the incidence of alcohol- and smoking-related diseases (e.g. liver cirrhosis, coronary heart disease), to argue against

confounding by these factors, but in practice smoking and alcohol are such strong risk factors for laryngeal cancer as to justify a cautious interpretation of the cohort data.

Case-control studies

34. The NAS review identified 18 case-control studies and one further study was identified by the Council. The studies involved from 20 cases to 940 cases, with seven studies having 200 or more. All studies had attempted to control for the effects of smoking and alcohol consumption.

35. Fifteen of the 18 studies presented RRs for 'any exposure' to asbestos as compared with 'no exposure'. All these studies reported an RR greater than 1.0, but only two studies (Burch *et al* 1981*;* Zheng *et al* 1992) reported a risk which was (slightly) more than doubled.

36. The combined OR for these 15 studies was 1.43 (95% CI 1.15-1.78). When only those (10) studies considered to have higher quality exposure data were included, with adjustment for alcohol consumption and smoking, the OR fell to 1.18 (95% CI 1.01-1.37). The study identified by the Council, and therefore not included in these analyses (Shangini *et al*), did not identify an increased risk. A further meta-analysis of 9 case-control studies by Dr Leslie Rushton and colleagues at Imperial College, London, yielded a combined OR of 1.37 (L Rushton, Personal Communication).

37. Eight of the studies distinguished subjects by intensity or duration of exposure. Among these, two studies found statistically significant increased risks with longer duration of exposure. Brown *et al* reported an RR of 2.2 following 5-14 years exposure, compared to 1.3 following <5 years exposure. However, the trend was inconsistent in that, for those with > 15 years exposure, the RR was only 1.4. De Stefani *et al* reported an RR of 2.4 after 21+ years exposure versus 0.9 for those with fewer than 21 years exposure.

38. One study (Marchand *et al*) reported an increased risk in those with 'high' exposure (RR 2.22) as opposed to those with 'intermediate' (RR 1.69) or low exposure (RR 1.45). However, here the risk was confined only to cancer of the epilarynx (the tube above the vocal folds). Overall, therefore, only two of the case-control studies reported a doubling of risk and those which investigated dose-response relationships did not provide strong consistent evidence of an increased risk at longer or higher levels of exposure.

Prevention

39. Asbestos diseases can be prevented by ensuring that workers who come into contact with asbestos containing materials are not exposed to the asbestos fibres which may be released when these materials are handled. The importation, supply and use of asbestos has now been banned but asbestos was extensively used as a building material from the 1950s through to the late 1970s. Those currently at risk from exposure to asbestos fibres include those who remove asbestos containing materials and building and maintenance workers who may unknowingly be exposed during the course of their work. To deal with the risks of exposure, there is a requirement in the Control of Asbestos Regulations 2006 to carry out a risk assessment and to take a series of actions depending on the assessment to prevent exposure to asbestos fibres so far as is reasonably practicable. This includes a requirement for training and medical surveillance in certain circumstances. Since May 2004, there has been a duty on those who have maintenance and repair responsibilities for nondomestic premises to assess those premises for the presence of asbestos and the condition of that asbestos and, again, to take a series of preventive actions depending on the assessment.

Conclusions

40. The relationship between asbestos and laryngeal cancer has been investigated in a large number of epidemiological studies. Although a number of these have indicated an increased risk in asbestos exposed workers, in general risks have not been more than doubled, and have typically been less than 1.5.

41. Higher risks may exist in subsets of workers with higher or longer exposures, and a few cohort studies suggest a doubling of risk following exposure exceeding 20 years, in workers who were first employed more than 40 years ago. Meta-analyses of those groups considered to fall in the highest exposure categories indicated a more than doubling of risk, albeit by pooling data with dissimilar definitions of high exposure. However, confidence in the data from the cohort studies is seriously weakened by an absence of control for two major common risk factors for this disease, smoking and alcohol consumption.

42. While case-control studies allowed for these factors, exposure assessment in this type of study is generally considered to be less reliable. Moreover, case-control studies which included a dose-response analysis did not find a doubling of risks in highly exposed groups or a markedly increased risk by level or duration of exposure.

43. Thus, while the data suggest there may be an association between laryngeal cancer and asbestos exposure, they do not provide strong, consistent evidence of a doubling of risk, particularly given the possibility of confounding by smoking and alcohol.

Recommendations

44. The Council concludes that the data are not sufficiently robust to support prescription. However, the Council will keep the matter under review and will monitor future research findings on this subject. In particular, it has been noted that the WHO International Agency for Research on Cancer (IARC) proposes to conduct a review of cancers related to asbestos exposure in 2009, the findings from which the Council will scrutinise.

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