Mesothelioma

Tuesday, 12 August 1997 **10:30–12:30**

ORAL SESSION

Mesothelioma

920* Environmental exposure to crocidolite and lung cancer

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Objectives: To determine the contribution of low dose crocidolite exposure to the risk of lung cancer among environmentally exposed subjects.

Methods: All cases of lung cancer among subjects with environmental (non-occupational) exposure to crocidolite at Wittenoom, Western Australia (WA), were each matched by age, sex and calendar-period to up to 4 controls selected from the Wittenoom residents' cohort. Personal details were collected for each subject, as well as their smoking and Wittenoom residential histories.

Results: The rate of lung cancer was higher than in age-, sex- and calendar-period-matched WA population controls (SMR = 2.3 95% CI: 1.6–3.2). When compared to controls from within the cohort, however, cases had shorter residence at Wittenoom, lower average intensity of crocidolite exposure and hence lower cumulative exposure. Cases smoked more than controls. The relative risk of lung cancer was increased to 11.4 (95% CI: 2.47–52.01) in subjects who had smoked over 50 pack-years, when compared to non-smokers. Adjusted logistic regression showed that duration of Wittenoom residence and asbestos exposure had no effect on lung cancer risk.

Conclusions: Low dose crocidolite exposure was not associated with an increased risk of lung cancer. Lung cancer arising in the Wittenoom residents' cohort appeared to be due mainly to smoking.

921* Soluble E-cadherin levels in benign and malignant pleural effusions

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E-cadherin is a Ca^{++} dependent adhesion molecule found in epithelial cells and mediates homophilic cell-cell adhesion. It has been reported that soluble form of E-cadherin (sE-cad) levels in serum from cancer patients were significantly elevated when compared with those from healthy controls. We measured sE-cad levels in benign and malignant pleural elusions using a sE-cad ELISA kit. Results were as follows:

Group	n	sE-cadherin (μg/ml)
Transudates	11	2.52 ± 0.88
Pleurisies	10	3.33 ± 2.18
Lung cancer	29	$4.86 \pm 3.04^{*}$
Adenocarcinoma	12	$4.86 \pm 2.80^{*}$
Squamous cell carcinoma	10	$5.45 \pm 3.57^{*}$
Small cell carcinoma	7	4.24 ± 3.17
Malignant mesothelioma	5	1.84 ± 0.96

(Data were mean $\pm$ SD; * $p < 0.05$ vs. transudates)

There was no significant difference in sE-cad levels between transudates and pleurisies. However, sE-cad levels were significantly higher in malignant effusions due to lung cancer in transudates and effusions due to malignant mesothelioma. These results indicated that the measurement of sE-cad in pleural effusion is useful for the diagnosis of malignant pleural effusion due to epithelium-derived tumor. It also may be helpful for distinguishing lung adenocarcinoma and malignant mesothelioma.

922* CT and MRI staging of malignant pleural mesothelioma: Correlation with surgical/pathologic results

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Cross-sectional imaging methods for evaluation of malignant pleural mesothelioma (MPM) are in common use but their accuracy has not been determined due to the rarity of the tumor, as well as a multiplicity of staging systems. Recently the International Mesothelioma Interest Group (IMIG) proposed a TNM staging system which hopefully will supersede previous staging systems. We have entered 82 patients into this study in which prospective surgical candidates with strongly suspected or proven malignant pleural mesothelioma received CT and MRI examination for preoperative staging. Fifty-five of these patients had various invasive surgical procedures for staging/therapy (excluding needle biopsies). The following Table indicates accuracies for various sites.

	No. of Sites Evaluated	CT Accuracy	MRI Accuracy
Invasion of diaphragm	34	0.471	0.412
Extension to peritoneum	9	0.667	0.667
Invasion of lung parenchyma	31	0.677	0.452
Solitary site of chest wall invasion	30	0.567	0.667
Mediastinal soft tissue Invasion	29	0.552	0.655
Pericardium	36	0.645	0.640
Regional lmph nodes; N1, N2	28; 29	0.643; 0.448	0.571; 0.414

Despite considerable inaccuracy in MPM staging, CT remains useful in demonstrating unexpected evidence of extensive local spread precluding resection.

923* Asbestos content of lung tissue in patients with malignant peritoneal mesothelioma: A study of 40 cases

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From a database including 160 cases of peritoneal mesothelioma, lung tissue was available for analysis of asbestos content in 40 cases. Analyses were performed by digesting tissue in sodium hypochlorite solution and counting asbestos bodies by light microscopy. Total asbestos fiber content was determined by using a scanning electron microscope (SEM) equipped with an energy dispersive spectrometer.

There were 36 men and 4 women with a mean age of 62 ± 9 years. The histologic subtypes were epithelial (24 cases), biphasic (13 cases), and sarcomatoid (2 cases). Eighteen of 40 cases (45%) had histologically confirmed asbestosis, and 21 of 33 (64%) had parietal pleural plaques (unknown in 7 cases). The median asbestos body count for the entire series was 840 AB/gm of wet lung tissue (range: <1–684,000). The asbestos body count exceeded our normal range in 31 of 40 cases (78%).

Cases were further divided into those with asbestosis (Group I, n = 18), parietal pleural plaques without asbestosis (Group II, n = 7), and neither plaques nor asbestosis (Group III, n = 9). The median asbestos body count in these three groups was 24,000 for Group I (range: 370–684,000); 5130 for Group II (range: 6.3–171,000); and 24 for Group III (range: 1–590). Fiber analysis by SEM was performed in 15 cases (8 from Group I, 2 from Group II, and 5 from Group III). The median total asbestos fiber count per gram of wet lung tissue for fibers 5 μ or greater in length was 604,000 for Group I (range: 38,600–1,960,000); 122,000 for Group II (range: 260–244,000); and 680 for Group III (range: 490–10,100). The vast majority of these fibers were commercial amphiboles (mostly amosite with lesser amounts of crocidolite). Tremolite and chrysotile were present at concentrations above background in one case each.

We compared these findings with lung fiber analyses in 170 patients with pleural mesothelioma. Peritoneal cases with asbestosis or plaques had higher median asbestos body counts than pleural cases with asbestosis (15,900 AB/gm) or plaques (900 AB/gm). These findings suggest that,

on average, more asbestos exposure is needed to induce peritoneal as compared to pleural mesotheliomas. The fiber types involved are mostly commercial amphiboles, predominantly amosite in the U.S. These findings are in agreement with previously published epidemiologic observations.

924* Malignant mesothelioma in women

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While most malignant mesotheliomas occur in men, two large series reported that women accounted for 21–22% of cases. Since relatively little detailed information has been published concerning mesotheliomas in women, we report clinicopathologic features, data regarding asbestos exposure, and asbestos concentration in lung tissue of 103 pathologically confirmed cases. The 103 women ranged in age from 28 to 89 with a mean of 62 years and a median of 63 years. 25 had a history of occupational exposure to asbestos and 43 had a history of bystander exposure to asbestos. 4 women had a history of smoking cigarettes whose filter contained crocidolite asbestos. Of the 103 cases, 92 were pleural, 12 were peritoneal and 1 was primary in the pericardium. Histologically, 62 were epithelial 22 were biphasic, 13 were sarcomatoid or desmoplastic, and 6 showed variable differentiation. Pleural plaques were identified in 22 of 57 cases with asbestos exposure and 9 of 53 cases showed pathologic asbestosis. An increased lung tissue concentration of asbestos was identified in 23 of 30 (76%) of cases analyzed. The asbestos fiber most commonly identified in lung tissue was amosite, followed by tremolite and chrysotile.

Our findings indicate that most cases of mesothelioma in women occur in those who have been exposed to asbestos, usually in a bystander situation.

925* Contrasting associations of exposure to asbestos and silica with subsequent lung cancer

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Background: Asbestos and crystalline silica are now classified as human carcinogens and both cause parenchymal fibrosis.

Objectives: To compare exposure-response relationships between crocidolite and incidence of lung cancer and between silica and mortality from lung cancer.

Methods: From a cohort of 6910 former crocidolite workers, cases of lung cancer and up to 25 controls per case matched on age and year, had radiographs scored according to the ILO Classification. Duration and intensity of exposure were obtained from employment records and dust surveys. Conditional logistic regression analyses modelled lung cancer incidence in relation to exposure, smoking category, years from x-ray, and level of profusion of small opacities. A second cohort of 2297 goldminers exposed to silica had data collected on respiratory symptoms and smoking in 1961. Subjects were followed up to the end of 1993. Survival analyses for lung cancer mortality were performed using age and year matched conditional logistic regression analyses.

Results: Among asbestos workers the prevalence of profusion of small opacities >1/0 on the ILO scale was around 30% for all selected control films. After adjustment for smoking, the presence of asbestosis on the x-ray increased the risk of lung cancer by 2.5 (95%CI 1.4–4.6) and exposure increased the risk by 1.3 per log (fibres/ml year) (95%CI 1.1–1.5) with both variables modelled together. The interaction between fibrosis and exposure was not significant ($p = 0.36$), although there was some evidence that, while lower, the exposure-response slope was steeper in the absence of fibrosis.

There were 138 lung cancers among 1386 deaths in the goldminers. There was no significant effect of any measure of silica exposure on lung cancer mortality but the risk of mortality from lung cancer increased after compensation for silicosis.

Conclusions: Radiographic asbestosis did not appear to be a pre-requisite of asbestos-associated lung cancer. In contrast, while the incidence of silicosis was clearly related to exposure to silica and the onset of silicosis conferred a significant increase in risk for subsequent death from lung cancer, there was no evidence that exposure to silica caused lung cancer in the absence of silicosis.

926* Intralesional vaccinia virus-interleukin 2 (VV-IL2) gene therapy in malignant mesothelioma (MM)

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MM is an aggressive tumor which is resistant to all conventional treatment modalities. We have *in vitro* evidence that MM may be recognised by the host immune system and that intratumoral IL2 in murine MM augments the anti-tumor immune response.

Aims: (1) To determine whether there is a risk of viral infection to hospital staff and family members from intralesional VV-IL2 administration;
(2) To ascertain whether VV-IL2 and IL2 can be detected in tumor tissue;
(3) To observe significant toxicity associated with VV-IL2 administration.

Methods: 4 patients (3 males/1 female) with subcutaneous MM tumor deposits received a total of 13 injections of intralesional VV-IL2 (each dose 1×10^7 pfu). Tumor biopsies, sputum, urine and blood samples were obtained on Days 0, 1 to 3 and 6 to 8 of each cycle and tested for the presence of vaccinia virus and IL2. VV-IL2 mRNA was detected in tumor biopsies by PCR (50 cycles) using VV-IL2 specific primers. Close family members, hospital staff involved in the trial and subject 1 received vaccinia vaccination prior to involvement in the trial.

Results: No infection of hospital staff or family members was observed. Levels of VV-IL2 mRNA were highest on Days 1 to 3 postinjection and fell to preinjection levels by Day 8. VV-IL2 was not cultured from sputum, urine or blood in any subject. VV-IL2 was cultured from tumor biopsies taken from the only subject who had never received vaccinia vaccination. Vaccinia virus IgG levels increased with treatment in all subjects compared to pretreatment levels. No significant toxicities were observed. No tumor regression was observed. Final results at completion of this trial will be presented.

Conclusion: Intralesional administration of VV-IL2 to subcutaneous MM deposits is safe, associated with minimal toxicity and results in a modest intratumoral expression of VV-IL2 for approximately one week post injection.

927* Mechanism of action of thymidine kinase suicide gene therapy in rat mesothelioma

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Administration of a recombinant adenovirus harboring the lacZ reporter gene (IG.Ad.CMV.LacZ) into the pleural cavity of Fischer rats with established mesothelioma results in transduction of a relatively small proportion of tumor cells. We confirmed the strong tumor growth inhibition following treatment with IG.Ad.CMV.TK recombinant adenovirus and ganciclovir (GCV) previously reported by Elshami et al, 1996 Human Gene Therapy 7:141. The anti-tumor effect dramatically exceeds the effects expected from the small fraction of transduced tumor cells as seen after IG.Ad.CMV.LacZ gene transfer. Such discrepancy is generally ascribed to a bystander effect. With a 14 days course of GCV treatment after injection of recombinant adenovirus into the pleural cavity at 9 days after inoculation of 10^5 tumor cells at the same site, symptom free survival time was 33 days as compared to 19 days in the controls. In an otherwise similar experiment the animals were sacrified after 4 days of treatment with GCV and the amount of tumor tissue was estimated. Calculation of tumor cell kill using conventional tumor growth kinetics, a large difference was found between the 4 and the 14 days treatment with GCV (2 and 7 log respectively). The prolonged symptom free survival is related to the duration of GCV treatment, which suggests that during that whole period tk expression was sufficient to maintain cytotoxic levels of phosphorylated GCV. We have excluded the mesothelium which is slowly dividing and shows a high transduction efficiency as a significant source of tk activity. As transduced tumor cells are bound to die during division, prolonged expression of tk can only be expected to proceed in dorment cells. Experiments are under way to test this hypothesis.