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Is lung cancer associated with asbestos exposure when there are no small opacities on the chest radiograph?

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Summary

This study was designed to test the hypothesis that the risk of lung cancer from asbestos exposure is confined to persons with radiographic evidence of pulmonary fibrosis.

Occupational and smoking histories were obtained from 274 patients with a confirmed diagnosis of primary lung cancer and 678 referents (279 with other respiratory disease and 399 with cardiac disease). Histories were reviewed blind to assess the timing, duration, and probability of exposure to asbestos. To allow for a lag between asbestos exposure and the development of lung cancer, subjects were classified by the time they had spent in an occupation entailing definite or probable exposure more than 15 years before diagnosis. The presence and extent of fibrosis was assessed blindly from chest radiographs by three readers and scored for small opacities with the ILO 1989 International Classification of Radiographs of the Pneumoconioses. 93 (34.3%) cases had worked in an occupation with definite or probable asbestos exposure compared with 176 (25.8%) referents (crude odds ratio for lung cancer 1.49, 95% CI 1.09-2.04). After adjustment for age, sex, smoking history, and area of referral, the odds ratio (95% CI) was 2.03 (1.00-4.13) in the subgroup of 211 with a median ILO score for small parenchymal opacities of 1/0 or more, and 1.56 (1.02-2.39) in the 738 with a score of 0/1 or less (ie, those without radiological evidence of pulmonary fibrosis).

These results suggest that asbestos is associated with lung cancer even in the absence of radiologically apparent pulmonary fibrosis.

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Introduction

Asbestos exposure increases the risk of lung cancer, but it is unclear whether such exposure does so in the absence of radiological evidence of pulmonary fibrosis. In the UK and several other countries, compensation for asbestos-related disease recognises lung cancer as asbestos related only if there is radiological or pathological evidence of lung fibrosis or diffuse pleural thickening. In other countries, compensation is based on duration of exposure in relevant occupations.

Cohort studies show that the excess of lung cancer in asbestos-exposed workers is at least as great as the number of cases of mesothelioma.¹ De Vos Irvine and colleagues estimated that 5.7% of lung cancers in Glasgow and the west of Scotland were asbestos related.² This is in line with estimates from the USA.³ There are around 35 000 new lung cancers each year in England and Wales,⁴ of which 2000 or so may be asbestos related. Data from the SWORD surveillance scheme⁵ suggest that comparatively few such cases are recognised, possibly because once the patient is identified as a tobacco smoker, the physician does not inquire into asbestos exposure. But another factor may be the prevailing view that pulmonary fibrosis is a necessary prerequisite.

Small opacities on the chest radiograph are a useful, if imperfect, marker of pulmonary fibrosis. They can be objectively assessed with the ILO 1989 International Classification of Radiographs of Pneumoconioses.⁶ With this system, a score of 1/0 or more for small, characteristically irregular opacities is usually considered evidence of fibrosis, whereas a score of 0/1 or less indicates no radiological evidence of fibrosis. We used this score in a hospital-based case-referent study to examine whether pulmonary fibrosis is a prerequisite of asbestos-related lung cancer.

Patients and methods

Subjects were selected from routine adult admissions to the London Chest Hospital between September, 1992, and March, 1993. Cases were consecutive patients with a histologically or cytologically confirmed diagnosis of primary bronchial carcinoma; referents were consecutive patients with respiratory diseases other than lung cancer and a random sample (averaging one in three) of admissions with cardiac disease (table 1). A patient was excluded if he or she had first been admitted with the

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Results

96 (35.4%) lung cancer cases, 106 (38.0%) respiratory referents, and 92 (23.1%) cardiac referents were women (table 3). Lung cancer cases were on average older and had smoked more heavily. 56% of cases came from the local population; the proportion was higher for respiratory referents (71%) than cardiac referents (41%). A high proportion of male cases (51.4%) had worked in a job with some degree of asbestos exposure, as had 35.6% of male referents. Very few women had any exposure.

There was little difference between lung cancer cases and respiratory referents in their ILO scores for small opacities, but few cardiac referents had a profusion score of 1/0 or above. 2 of the 4 respiratory referents with profusion scores of 3/2 or above had cryptogenic fibrosing alveolitis, 1 had pulmonary tuberculosis, and 1 had sarcoidosis. Agreement about ILO scores was unanimous in 563 (76.3%) of the 738 patients with a median score of 0/1 or less (no radiological evidence of pulmonary fibrosis) (table 4). Overall agreement was similar to that found in previous studies in which chest radiographs have been scored by multiple readers with the ILO system.^{1,2}

In the study group as a whole, 93 (34.3%) cases had worked in an occupation with definite or probable asbestos exposure compared with 176 (25.8%) referents (OR 1.49, 95% CI 1.09-2.04). Table 5 shows the results of a logistic model which adjusts for age, sex, smoking, and origin of the patient (local or tertiary referral), and includes exposure categorised by duration. Type of referral had only a small effect on the association between asbestos exposure and lung cancer, and led to a statistically insignificant improvement in model fit. However, it was considered a potential confounding factor, and was retained in the model. Each of the other variables had a larger influence on the observed association between asbestos and lung cancer, and led to significant improvement in model fit.

The logistic model showed that ORs for lung cancer increased with pack-years of smoking and with age, and that patients who had worked in a job with definite or

Median score	All readers agreed (%)	One reader differed by one category (%)	One reader differed by two categories (%)	Readers recorded three different categories (%)
0	563 (76.3)	166 (17.5)	9 (0.9)	0
1	47 (5.7)	113 (11.9)	0	14 (1.5)
2	13 (1.6)	15 (2.0)	1 (0.1)	0
3	2 (0.2)	2 (0.2)	0	0

Table 4: Agreement between the 3 readers on ILO score for small opacities in 949 radiographs

probable asbestos exposure more than 15 years before diagnosis had a higher risk of lung cancer than those who had not. With a simple classification of exposure—any relevant job against none—the OR for lung cancer adjusted for age, sex, smoking, and type of referral was 1.66 (1.15-2.38). The corresponding OR with respiratory referents only was 2.02 (1.26-3.24), and with cardiac referents only 1.44 (0.96-2.16).

In the subgroup of 211 with a median ILO score of 1/0 or more, the OR was 2.03 (1.00-4.13), and in the 738 with a score of 0/1 or less, it was 1.56 (1.02-2.39), suggesting an association between asbestos exposure and lung cancer in the absence of fibrosis. The corresponding ORs from separate analyses of the referent groups were also similar: 1.08 (1.13-3.45) for respiratory referents, and 1.41 (0.88-2.26) for cardiac referents.

In the subgroup of 655 patients with a median ILO score of 0/0 or less (those for whom at least two readers agreed about the absence of small opacities) the adjusted OR for lung cancer was 1.48 (0.93-2.35); for respiratory referents, 2.09 (1.12-3.89); for cardiac referents, 1.35 (0.82-2.22); and 1.44 (0.89-2.32) when the 37 patients with any form of pleural thickening were also excluded. The results for the separate referent groups, including several not tabulated here, were taken as sufficiently similar to justify combining respiratory and cardiac referents for the main analysis.

Tests for exposure-response are shown in table 6. The point estimates of the OR were not higher in the category of less than 5 years' exposure, although the CIs were wide. There was evidence that ORs increased with duration of exposure both in patients with ILO scores of

Characteristic	Men			Women		
	Cases (n=175)	Respiratory controls (n=173)	Cardiac controls (n=307)	Cases (n=96)	Respiratory controls (n=106)	Cardiac controls (n=92)
Age (yr)						
<50	24 (13.7)	56 (37.3)	75 (24.4)	13 (13.5)	33 (31.1)	17 (18.5)
50-59	36 (20.6)	34 (19.7)	81 (29.6)	11 (11.5)	24 (22.6)	21 (22.8)
60-69	69 (39.4)	40 (23.1)	112 (36.5)	33 (34.4)	29 (27.4)	26 (30.1)
≥70	46 (26.3)	43 (24.9)	28 (9.5)	39 (40.6)	20 (18.9)	18 (19.6)
Pack-years of cigarette smoking						
None	2 (1.1)	41 (23.7)	87 (21.8)	12 (12.5)	50 (47.2)	39 (42.4)
<15	19 (10.9)	25 (14.5)	45 (14.7)	5 (5.2)	18 (15.1)	16 (17.4)
15-29	42 (24.0)	31 (17.9)	80 (26.1)	29 (30.2)	16 (15.1)	22 (23.9)
30-44	44 (25.1)	34 (19.7)	66 (21.5)	28 (29.2)	12 (11.3)	9 (9.8)
≥45	68 (38.9)	42 (24.3)	49 (16.0)	22 (22.9)	12 (12.3)	8 (8.5)
Local referral	103 (58.9)	121 (69.9)	119 (38.8)	49 (51.0)	78 (73.6)	46 (50.0)
Years of exposure*						
None	85 (48.6)	121 (69.9)	188 (61.2)	93 (96.0)	104 (98.1)	88 (95.7)
<5	23 (13.1)	15 (8.7)	34 (11.1)	1 (1.0)	1 (0.9)	0
5-9	18 (10.8)	6 (3.5)	19 (6.2)	1 (1.0)	1 (0.9)	2 (2.2)
≥10	48 (27.4)	31 (17.9)	66 (21.5)	1 (1.0)	0	1 (1.1)
Median ILO score for small opacities						
0	118 (67.4)	121 (69.9)	260 (84.7)	80 (83.3)	74 (69.8)	85 (92.4)
1	48 (27.4)	39 (22.5)	43 (14.0)	15 (15.6)	23 (21.7)	8 (8.5)
2	9 (5.1)	11 (6.4)	4 (1.3)	1 (1.0)	7 (6.6)	1 (1.1)
3	0	2 (1.2)	0	0	2 (1.9)	0

*Years in job classified as entailing definite or probable asbestos exposure at least 15 years before diagnosis.

Table 3: Patients' characteristics

Lung cancers (n=272)	
Non-small cell	24
Squamous cell	99
Large cell	34
Adenocarcinoma	39
Small cell	58
Alveolar	3
Mixed/undetermined	14
Respiratory controls (n=279)	
Chronic airways disease	73
Bronchiectasis	21
Obstructive sleep apnoea	21
Tuberculosis	33
Respiratory infections	18
Connective tissue disease	14
Miscellaneous other	99
Cardiac controls (n=329)	
Ischaemic heart disease	347
Valvular heart disease	27
Rhythm disturbances	11
Other	14

Table 1: Histological type of lung cancers and diagnosis of controls

relevant disease more than 9 months before, or if no chest radiograph was available. 4 patients were excluded because their original referral letters suggested they had been referred because of possible asbestos exposure, 23 because they did not wish to be interviewed or would not complete the interview, 29 because the chest radiograph was technically unsatisfactory or unavailable, and 7 because full case notes could not be traced.

Diagnosis and reason for and source of referral were obtained from case notes, and occupational and smoking histories by interview during admission by a research nurse who was not informed of the patient's diagnosis and did not know the study hypothesis. Since bias might be introduced by informing patients of the purpose of the research, the hospital ethics committee agreed that subjects could only be asked whether they would be willing to participate in a study of occupational factors in illness.

Patients were asked to list, with dates, every job since leaving school of more than 6 months' duration, the name of employers, to describe the work, and whether the work had entailed exposure to dust from wood, copper, asbestos, silica, or cement.

At the end of the study a list, based on a previously published study of mesothelioma,¹ was drawn up of thirty-one occupations possibly associated with asbestos exposure. Occupational histories were blindly reviewed and each job placed in one of these occupational categories or classified as entailing no asbestos exposure. The categories were subsequently grouped by their probability of exposure (table 2). Information on smoking habit included an estimate of the average daily cigarette consumption during each decade of life, the sum of which gave the total pack-years of consumption.

The presence and extent of small opacities and pleural changes were assessed from the chest radiograph taken nearest to the time of first diagnosis. Three readers independently scored each film with the ILO system.⁶ As nearly all cases and many controls had radiological changes which suggested the disease for which they had been admitted to hospital, each radiograph was first reviewed by a radiologist not participating in the scoring who blacked out changes such as a tumour mass or lymphadenopathy with an opaque silhouette over the affected quadrant; no more than two quadrants per film were obscured. 6 cases and 9 referents were rejected because the film was of poor quality or because diagnostic features could not be disguised by covering two quadrants. Films were processed in batches of fifty and within each batch each quadrant was covered with similar frequency in films from cases and referents, to achieve a similar distribution of blacked-out areas in the two groups, even if there was no abnormality. Under the ILO system, a profusion score for small opacities is given by reference to a set of standard films. Scores comprise two numbers. The first is the reader's best assessment of the appropriate category, the second is whichever adjacent category had also to be considered. They form the following 12-

Probability of asbestos exposure (occupational group)	No of cases (%)	No of referents (%)
Definite exposure		
Asbestos production	1 (0.4)	5 (0.7)
Heating trades	13 (4.8)	35 (5.2)
Insulation work	2 (0.7)	6 (0.9)
Probable exposure		
Construction	51 (18.6)	88 (13.0)
Electrical work	7 (2.6)	15 (2.2)
Foundry work	7 (2.6)	16 (2.4)
Fireman (steam locomotive)	1 (0.4)	4 (0.6)
Rail-engine fitter	3 (1.1)	4 (0.6)
Sheet-metal worker	3 (1.1)	7 (1.0)
Shipyard/dock work	21 (7.8)	41 (6.1)
Possible exposure		
Alcohol fitter	2 (0.7)	10 (1.5)
Firefighter	4 (1.5)	3 (0.4)
Lathe operator	16 (5.9)	48 (7.1)
General maintenance/maintenance engineer	6 (2.2)	10 (1.5)
Oil/chemical refinery work	3 (1.1)	9 (1.3)
Paint factory	2 (0.7)	5 (0.7)
Paper factory	3 (1.1)	8 (1.2)
Railtrack engineer	2 (0.7)	3 (0.4)
Seaman	24 (8.9)	46 (6.8)
Transport worker	17 (6.3)	48 (6.8)
Exposure unlikely		
Carpentry (not on building sites)	6 (2.2)	14 (2.1)
Civil engineering	3 (1.1)	12 (1.8)
Dry cleaning	1 (0.4)	1 (0.2)
Electrical engineering	1 (0.4)	1 (0.2)
Electronics manufacture	1 (0.4)	2 (0.3)
Garage mechanic	7 (2.6)	28 (4.1)
Handling building supplies	2 (0.7)	9 (1.3)
Rubber/plastic manufacture	14 (5.2)	19 (2.8)
Scrap-metal work	9 (3.1)	10 (1.5)
Surveyor/site supervisor	0	5 (0.7)
Telephone-cabling engineer	2 (0.7)	3 (0.4)

Only jobs which started 15 years or more before diagnosis are shown; 125 (48.1%) cases and 357 (52.7%) referents had not been employed in any of these occupational groups in the relevant period. Individual workers may have contributed to more than one occupational group. Mean number of relevant jobs per person was 0.65 in cases and 0.76 in referents, with range in both groups of 0 to 5.

Table 2: Probability of asbestos exposure in occupational groups

point scale of increasing profusion: 0/-, 0/0, 0/1, 1/0, 1/1, 1/2, 2/1, 2/2, 2/3, 3/2, 3/3, 3/4.

Jobs were divided into those associated with definite or probable asbestos exposure, and those with possible, unlikely, or definitely no exposure. Patients who had worked in jobs with definite or probable exposure were further subdivided by the length of time in these jobs: 0 years, less than 5 years, 5 to 9 years, 10 years or more. Because of the lag between exposure and the development of cancer, only time spent in jobs more than 15 years before diagnosis was considered relevant.

Crude and adjusted odds ratios for lung cancer were calculated for all subjects and subgroups defined by the median ILO score for small opacities. The main study hypothesis related to the group with a median score of 0/1 or less since these patients may be considered to have no radiological evidence of fibrosis. Although small opacities may be due to pathological changes other than fibrosis, their absence suggests that the patient is unlikely to have relevant fibrosis. Respiratory and cardiac referents were combined for the main analyses, but analyses were also carried out separately for each set of referents. Their results were broadly similar.

The influence of potential confounding factors (sex, age-group, pack-years of smoking, and type of referral) on the disease-exposure relation was assessed by multivariate logistic modelling. Improvements in model fit were assessed from the likelihood ratio statistic, although confounding variables were included in the model because of their observed or potential influence on the association between asbestos exposure and lung cancer; they did not need to meet specified criteria for improvement in model fit. All quoted likelihood ratio statistics are those obtained by fitting the relevant variable last. Odds ratios (OR) are shown with 95% CIs.

Characteristic	No. of patients	OR	95% CI	LRS	df	p
Sex						
Men	655	1				
Women	294	2.23	1.53-3.25	17.7	1	<0.001
Age-group (years)						
<50	238	1				
50-59	217	0.86	0.57-1.40	18.5	3	<0.001
60-69	319	1.49	0.83-2.39			
≥70	195	2.97	1.43-3.93			
Pack-years of cigarette smoking						
None	211	1				
<15	126	3.87	1.89-7.94	90.2	4	<0.001
15-29	220	7.57	4.40-14.2			
30-44	193	8.92	4.70-16.9			
≥45	199	12.0	8.27-22.8			
Referral						
Local	516	1				
Tertiary	433	1.09	0.79-2.79	0.26	1	0.61
Years of exposure						
0	680	1				
<5	74	1.58	0.90-2.79	8.51	3	0.037
5-9	48	2.22	1.18-4.29			
≥10	147	1.52	0.97-2.37			

*LRS=likelihood ratio statistic, df=degrees of freedom.

Table 5: Results of logistic model

0/1 or less and in those with scores of 0/0. Only 8 women had any relevant asbestos exposure. Lung cancer was rare below the age of 40, and few younger patients had sufficient time to accumulate significant exposure given the 15-year lag. Construction and electrical work contributed most to excess of asbestos exposure in lung cancer cases, although insulation and foundry work were also important.

Patients were inaccurate in assessing their asbestos exposure; only 121 (44.9%) of the 269 patients classified as asbestos exposed on the basis of their occupation reported that they had worked with asbestos, and 42 (15.5%) reported exposure, although their jobs suggested they had none. In the subgroup with ILO scores of 0/1 or less, the adjusted OR for self-reported exposure was 1.19 (0.73-1.91), which was lower than the estimate based on objective assessment.

One participating physician in the study (RMR) had a special interest in asbestos-related disease, but exclusion of patients first admitted under his care made little difference to the point estimate (OR in the subgroup with ILO scores of 0/1 or less was 1.61 [0.86-2.99]).

Of the 127 patients occupationally exposed less than 15 years before first diagnosis, all but 20 had also been exposed more than 15 years before diagnosis. The independent effect of recent exposure could not therefore be determined with precision but, in the study group overall, exposure within 15 years of diagnosis and not before had an OR of 1.11 (0.34-3.59). This point

Years of exposure	All subjects (n=738)	Men ≥40 years (n=449)
ILO score <1/0		
0	1	1
<5	0.98 (0.47-2.06)	0.90 (0.41-1.96)
<10	2.56 (1.24-5.20)	3.33 (1.51-7.32)
≥10	1.55 (0.91-2.65)	1.46 (0.84-2.54)
ILO score ≥1/0		
0	1	1
<5	0.83 (0.37-1.85)	0.78 (0.38-1.78)
<10	2.42 (1.14-5.12)	3.23 (1.44-7.43)
≥10	1.55 (0.88-2.83)	1.42 (0.76-2.64)

Table 6: Adjusted ORs for lung cancer in relation to radiological score and years of exposure

estimate is lower than the corresponding figure for pre-lag exposure (OR 1.66 [1.15-2.38]).

Discussion

Our results do not suggest that radiological evidence of fibrosis is a prerequisite for asbestos-related lung cancer. In patients without parenchymal opacities, there was a 56% excess of lung cancer in those who had a high probability of occupational asbestos exposure at least 15 years before with some, albeit weak, evidence of a relation with duration of exposure.

Two issues affect interpretation of our findings: the adequacy of occupational histories in reflecting asbestos exposure, and the sensitivity of chest radiography in detecting pulmonary fibrosis. The occupational classification we used discriminated well between mesothelioma cases and controls in a survey in the USA and Canada,⁷ and we have no reason to think that it would not have done so adequately for lung cancer in our study. The sensitivity of the chest radiograph for detecting pulmonary fibrosis is about 80% of cases with histological evidence.^{10,11} However, sensitivity estimates will depend on the specificity and sensitivity achieved by radiologists and histologists, and selection of cases. Staples and colleagues have shown that high-resolution computed tomography may reveal abnormalities in around a third of asbestos-exposed workers without small opacities on the chest radiograph.¹² This method may thus be a more sensitive indicator of asbestos-related fibrosis than radiography.

In this, as in most case-referent studies, it is impossible to eliminate all bias. But patient interviews and exposure assessments were carried out without knowledge of the underlying diagnosis, and we believe that the use of opaque silhouettes on the chest radiograph was successful in disguising the underlying diagnosis, although on some occasions an area of fibrosis might have been obscured. Although patients may be selective in their recall of asbestos-exposed jobs, the systematic way in which jobs were recorded and classified, and the fact that patients themselves were inaccurate at assessing their own exposure, make it unlikely that this was a significant source of bias. Since allocating jobs to particular occupational categories was carried out blind to diagnosis, this is likely to have led to random misclassification of exposure and thus a conservative bias, 36% of male referents had some asbestos exposure. However, in the area of London where the study was made, exposure is known to be high.

Our findings must be considered with evidence from other epidemiological work. In a longitudinal study of male asbestos-cement workers in Louisiana, USA, Hughes and Weill found no excess of lung cancer in workers without small opacities on the chest radiograph, even among long-term workers,¹³ although the power of the study was limited. In workers without small opacities followed for at least 20 years from first exposure, only 10 developed respiratory cancers, whereas 9.5 were expected. Sluis-Cremer and Bezuidenhout, in a necropsy series of 339 amphibole-asbestos miners in South Africa, found the proportional mortality ratio for lung cancer was raised in those with histological evidence of pulmonary fibrosis but not otherwise.¹⁴

Evidence that fibrosis may not be necessary for asbestos-related lung cancer comes from a longitudinal study of Quebec asbestos miners and millers.¹⁵ The investigators concluded that most, but not all, lung

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cancers attributable to asbestos showed radiological abnormalities, most of which were small opacities. However, the chest radiographs used in this analysis were often taken many years before death and some workers may subsequently have developed fibrosis. Our results are consistent with a hospital-based case-control study in which an excess risk of lung cancer was observed in patients with an occupational history of asbestos exposure but no pulmonary fibrosis.¹⁴

If there is an association between asbestos and lung cancer without fibrosis, it is of interest for both scientific and practical reasons. From a scientific standpoint, it may suggest that asbestos is not carcinogenic solely because it is fibrogenic, although the absence of small opacities on the chest radiograph does not exclude fibrotic change at a microscopic level. More importantly, from a practical point of view, it indicates that asbestos exposures which do not cause small opacities on the chest radiograph may nonetheless increase the risk of lung cancer, and this needs to be considered by those responsible for industrial hygiene and compensation of workers with asbestos-related lung disease.

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HIV-1 subtypes and male-to-female transmission in Thailand

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Summary

We examined the risk factors for heterosexual transmission of HIV in a case-control study of couples in Thailand. 90 HIV-positive men and their regular sex partners were enrolled at the Immune clinic, Chulalongkorn Hospital, where 92% of male index cases had HIV-1 serotype A (subtype E). Most index cases had acquired HIV through sexual intercourse. 95 couples were enrolled at 15 detoxification clinics, where 79% of them had HIV-1 serotype B (subtype B). Most men had acquired HIV through injecting drug use (IDU).

The HIV seroconcordance rate was higher in the immune clinic (69%) than in the IDU clinics (48% overall, and 27% after excluding female partners who were IDUs) ($p < 0.01$). The rate was also higher among couples in whom the male index case was infected with serotype A (subtype E) compared with serotype B (subtype B) (70% vs 52%, OR 2.1, 95% CI 1.2-4.2). When we excluded couples in whom the female was also an IDU, the difference in concordance rates was even more pronounced (70% vs 26%, OR 6.8, 95% CI 2.7-17.6). Viral factors or subjects' characteristics may have contributed to the concordance rates. In a multivariate logistic regression analysis, HIV-1 serotype A (subtype E) of male partners (adjusted OR 3.1, 95% CI 1.1-9.0) and history of IDU in female partners (adjusted OR 4.8, 95% CI 1.4-15.9) remained independently associated with HIV seroconcordance.

This study suggests that HIV-1 subtype E may be associated with higher risk of heterosexual transmission than subtype B. If so, the predominance of subtype E in Thailand may have contributed to the rapid spread of the HIV epidemic.

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