The exposure metric: does including time since exposure in the calculation of working lifetime exposure provide a better understanding of disease risk than the cumulative exposure?

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Exposure assessment; silica; pulmonary disease

SUMMARY

Background: *When exposure measurements are available for occupational epidemiology studies, the cumulative exposure (the sum of the products of duration and exposure intensity at all jobs) is generally selected as the summary metric for chronic diseases. For silica exposures, a metric that weights each exposure by the number of years since it occurred has been suggested as more biologically relevant. Comparative reports of analyses using both metrics have not been found in the literature, however.* **Methods:** *We calculated both metrics for silica exposure, and evaluated exposure-response relations for lung cancer and silicosis in two separate case-control studies.* **Results:** *Generally the results were consistent, due to the high correlation between the two metrics and the fact that the rate of time away from work during the employment years was low.* **Conclusion:** *The significant relation between exposure and silicosis using the weighted metric provides additional point estimates of risk, adding to the understanding of exposure-response.*

RIASSUNTO

«La dose cumulativa di esposizione a silice: è possibile una descrizione più accurata del rischio associato inserendo gli anni trascorsi dall'esposizione nel calcolo dell'esposizione cumulativa?». *Negli studi di epidemiologia occupazionale, per i quali sono disponibili dati di monitoraggio delle esposizioni nei luoghi di lavoro, si utilizza solitamente l'esposizione cumulativa, ossia la somma dei prodotti della durata per l'intensità di esposizione in ciascuna mansione o attività svolta nella storia lavorativa, quale indicatore di rischio per malattie cronico-degenerative. E' stato suggerito che, nel caso dell'esposizione a silice, sarebbe più rilevante dal punto di vista biologico il ricorso ad*

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un indicatore, che risulti dal pesare l'esposizione cumulativa in ciascuna mansione o attività lavorativa per il numero di anni trascorsi dall'epoca nella quale tale esposizione si verificò. Tuttavia, la letteratura scientifica non riporta esempi di confronti dei risultati ottenuti da analisi condotte utilizzando i due metodi. In questo lavoro, abbiamo calcolato le due stime di esposizione cumulativa a silice, ossia quella semplice e quella pesata per il numero di anni trascorsi dal verificarsi dell'esposizione, in due studi: lo studio caso controllo sul tumore polmonare interno alla coorte di 68285 lavoratori di cinque province Cinesi esposti a silice in 29 diversi tipi di attività industriale, e lo studio caso-controllo scaturito dal programma di sorveglianza delle attività industriali caratterizzate da esposizione a polveri nella Carolina del Nord, Stati Uniti d'America. Sulla base di ciascuna stima di esposizione, abbiamo quindi esaminato la relazione dose-risposta per il rischio di tumore polmonare e per quello di silicosi. Il confronto dei risultati ottenuti con i due metodi di calcolo ha mostrato la loro sostanziale sovrapponibilità, in ragione dell'elevata correlazione esistente tra i due indicatori e del fatto che il valore del rapporto tra gli anni trascorsi dal termine dell'esposizione e la durata totale dell'anzianità lavorativa è risultato piuttosto basso. La relazione significativa esistente tra esposizione cumulativa pesata e rischio di silicosi fornisce ulteriori elementi per la comprensione della relazione esistente tra l'esposizione a silice e le sue conseguenze patologiche.

Introduction

Workplace silica exposures have been known to cause disease for centuries (11). Despite documented successes in reducing exposures (1, 9, 10, 22, 23) silicosis continues to develop among workers in a number of industries (13, 15, 20). For more than 20 years, the potential relation between silica exposure and development of lung cancer has been of interest in silica-related epidemiology (7, 8). For much of this work, the cumulative exposure, the sum across all jobs of the product of exposure duration and intensity, has been the summary metric of choice in describing working life-time exposures. By this metric, the contribution of an exposure at years 1 and 30 during employment would be equal, if the intensity of exposure was the same. In a recent review, NIOSH (15) presents a summary of incidence estimates using the cumulative metric over a 45-year working lifetime. Jahr (12) proposed an alternative since the residence time of dust in the lung was thought to be related to risk of developing silicosis. For this metric, each exposure intensity is multiplied by the duration since it occurred (rather than the duration of exposure as in the calculation of cumulative exposure). Periods of time away from dust exposure change the overall calculation of this metric, depending upon when in the work history these occur; in the cumulative exposure, the placement of time away from exposure does not affect the final value. While it has been considered by others (6), no reports were found comparing the results of epidemiologic analyses using the cumulative and weighted metrics.

In this paper, we present an application of this weighted metric in two populations: a study of lung cancer among Chinese miners and pottery workers and a study of silicosis among North Carolina Dusty trades workers. These results are compared with the previous reports from these populations using the cumulative metric.

Methods

Both these of study populations have been described in detail. Briefly, the study of Chinese workers involved employees at 29 facilities in five provinces (2, 4, 5, 14, 21). Twenty-one of the operations were mines (10 tungsten, 1 clay, six iron/copper, 4 tin); the remaining 8 were pottery factories. The total cohort included 68,285 workers and was followed through December 31, 1989. A nested case-control study of lung cancer mortality included 316 male cases and 1352 male controls employed in the metal mines or pottery factories. Controls had survived to at least the age at which the case was diagnosed. Tobacco use, medical history and demographics were obtained on a questionnaire completed by the subject or next of kin. Quantitative estimates of exposures to dust, respirable silica, inorganic arsenic, polycyclic aromatic hydrocarbons and radon were developed for the years 1950 through 1988, using historical industrial hygiene measurements. Using cumulative respirable silica exposure in an exposure-response analysis, no consistent trends in lung cancer risk were associated with increasing exposure in the different industries. The odds ratios for lung cancer, by increasing cumulative exposure to arsenic, polycyclic aromatic hydrocarbons and radon, were not significant. Additional analyses failed to identify an exposure-response relation, despite the relatively high silica exposures in this population (3).

The North Carolina Dusty Trades surveillance program was initiated in 1935 (19). The analysis included 216 men diagnosed with silicosis and 762 controls (18). The controls were matched on years (within 5) of birth and hire, race and had to have been in the surveillance program for at least as many years as the case at his diagnosis. Subjects had been employed in a wide range of mineral industries, including granite (for dimension stone and crushing); the mining and milling of talc, pyrophyllite, mica, feldspar, quartz and kaolin; hard rock mining and drilling; foundry work; or in a group of other miscellaneous work activities with exposure to silica. Occupational histories and the results of x-ray evaluations were available. Exposure measurements collected throughout the program had been retained and were used to estimate exposure to silica (17). The trend in exposure-response across groups formed from the cumulative silica exposures was statistically significant. A matched pairs analysis was also conducted for the grouped data. For the groups exposed on average to 98 and 368 million particle years (mpy), or approximately 2.5 and 9 million particles per cubic foot (mppcf) respectively over a 40-year working lifetime, the odds ratios were 1.72 and 5.04, significantly greater than unity. The odds ratio for the group with mean annual exposure of approximately 1 mppcf over a 40-year working lifetime was 0.76 and not statistically significant.

Calculation of the exposure metrics

The job- and calendar-time-specific exposure estimates developed for the calculation of cumulative exposure were used for the calculation of the weighted metric for each study subject in the China and North Carolina case-control studies.

The weighted metric is expressed as:

$$E = \Sigma C_j[t_{j+1} - t_j]\,[T-(t_{j+1}+t_j)/2],\ j=1, 2, \ldots, n,$$

where n is the number of jobs held by the subject in the work history, C_j is silica concentration, t_j is the employment time at the j^{th} job, and T is the time interval between initial exposure and diagnosis, or the period of follow-up.

As an example, consider a worker with the following exposure levels: 1921-1925, 2 mg/m^3; 1926-1930, 1 mg/m^3; 1931-1935, 0 mg/m^3; 1936-1945, 0.5 mg/m^3; 1946-1955, 1 mg/m^3. The cumulative exposure is 30 mg/m^3; the weighted metric is 587.5 mg-yr/m^3. The cumulative and the weighted metrics for this example are contrasted in figure 1. The value of the weighted metric is affected by the placement of periods of no exposure in the work history. If exposure during 1931-35 had been 0.5

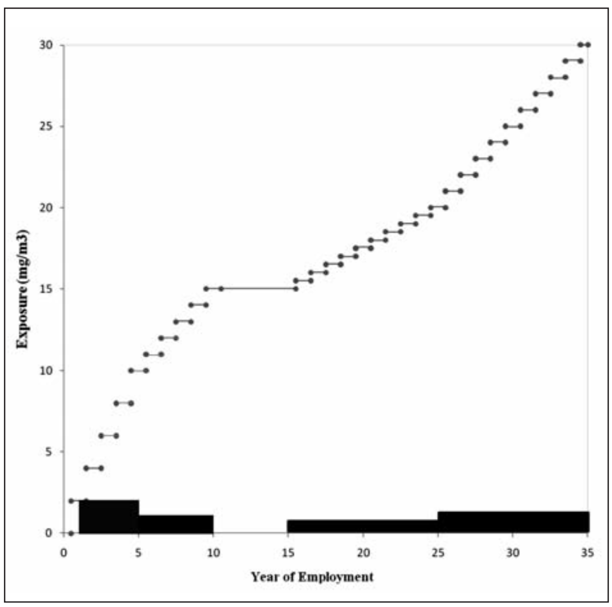

Figure 1 - Comparison of the cumulative and weighted metrics for a person having the following exposure during a 35-year time period: 1921-25, 2 mg/m^3; 1926-1930, 1 mg/m^3; 1931-1935, no exposure; 1936-1945, 0.5 mg/m^3; 1946-1955, 1 mg/m^3. The solid black area represents the cumulative exposure; the area under the rising curve represents the weighted metric

mg/m³ and the 5 years of no exposure had been in 1941-1945, the exposure estimate would have been 612.5 mg/m³, reflecting the weighting of the 0.5 mg/m³ exposure during the earlier time period. The cumulative exposure is unchanged.

Case-control analysis

Odds ratios (OR) were calculated to evaluate the association between exposure and disease, using the two metrics. For the China data set ORs were calculated using conditional logistic regression for matched pairs (21). The possible effects of other risk factors such as smoking were investigated using the same model. A variable case-control study software program was to calculate ORs for the North Carolina analysis (16).

Other exposures

Cumulative exposure to cadmium, nickel and polycyclic aromatic hydrocarbons and lifetime packs of cigarettes were available for the analysis of lung cancer risk.

Results

China

The weighted metric for respirable silica in the China data set was divided into quartiles based on equal numbers of exposed workers in each group. The groups were: >0-39,222; >39,222-137,519; >137,519-417,499; >417,499 mg-yr/m³. 167 cases and 374 controls were in the referent group with no exposure. Consistent with the previous analysis, odds ratios were calculated separately for each of the employment sectors, adjusting for cigarette smoking and age. The results are shown in table 1. Only one odds ratio was statistically significant (Pottery group 3 vs. referent). There was no pattern of increasing odds ratios, with increasing exposure group. When adjustment was also made for cadmium, nickel, PAH and silicosis status, respirable silica was related to lung cancer risk in several strata in iron-copper and tin; however, the estimated odds ratios did not increase monotonically.

North Carolina

The weighted metric for silica exposure in the Dusty Trades data set was divided into quartiles, based on statistically significant differences between the means of the exposure groups. The groups were: <250; 250-749.9; 750-2249.9; 2250 mpy and greater. The estimated odds ratios for silicosis are shown in table 2. There is a trend in the odds ratios,

Table 2 - Odds ratios for silicosis among North Carolina dusty trades workers by exposure group. The exposure (million particle years, mpy) was calculated using the weighted metric formula

Exposure			Odds Ratio (95% CI)
Group*	Range	Mean	
1	250-749.9	449	0.83 (0.53-1.31)
2	750-2249.9	1225	1.24 (0.71-2.17)
3	>=2250	4970	3.59 (1.91-6.73)

*referent group was exposed to <250 (mpy)

Table 1 - Odds ratios for lung cancer for four Chinese employment sectors by exposure group. The exposure (mg/m³) was calculated using the weighted metric formula

Exposure		Odds Ratio* (95% CI)			
Group**	Range	Tungsten	Pottery	Iron-Copper	Tin
1	1-39,222	0.77 (0.30-1.94)	1.58 (0.57-4.33)	0.91 (0.42-1.97)	1.84 (0.70-4.85)
2	>39,222-137,159	1.10 (0.52-2.34)	1.61 (0.67-3.88)	1.32 (0.53-3.27)	1.29 (0.55-3.06)
3	>137,519-417,499	0.56 (0.25-1.25)	4.13 (1.53-11.17)	2.21 (0.91-5.36)	1.42 (0.62-3.23)
4	>417,999	0.53 (0.24-1.17)	2.56 (0.38-17.38)	0.45 (0.08-2.50)	2.15 (0.93-4.99)

* adjusted for age and smoking
** referent group was not known to be exposed

with increasing exposure group ($p<0.0005$). The 95% Confidence Interval (CI) for the odds ratio for Exposure group 3 did not include unity. The trend in exposure-response was significant, $p<0.0001$.

Discussion

The two diseases chosen for this work have been studied in relation to long-term silica exposure using the cumulative metric. Silicosis is uniquely associated with exposure to silica, while lung cancer has been associated with a number of workplace and non-workplace exposures. The weighted model was proposed for use in the study of silicosis, because it incorporated a number of features of biological relevance (e.g., residence time in the lung and placement in the work history of periods of no exposure). We undertook this comparison to evaluate, in two previously investigated populations, if the metric provided additional insights, compared with the cumulative exposure. Moreover, previous analyses of the China miners and pottery workers found no consistent association between cumulative silica exposure and lung cancer, although substantial airborne concentrations had been measured (5).

Despite the biological plausibility of the weighted model, no marked difference in interpretation of exposure-response was identified in this analysis. That is, there is little evidence of exposure-response for lung cancer in the China group using this metric, similar to the original study; there is a strong exposure-response for silicosis in the North Carolina dusty trades workers, as seen using cumulative exposure. In order to better understand the consistency of results, the correlation between the two exposure metrics was evaluated. Overall, the Spearman rank correlation coefficient between the two metrics in the China data set was 0.93 and in the North Carolina data set was 0.96. Both were statistically significant ($p<0.0001$). Some variability in categorization was noted, however. In the China data, of the 625 persons in the lowest exposure group by at least one metric, 352 (56%) were not in the lowest exposure group by both metrics; similarly, of the 371 subjects in the highest exposure group for at least one metric, 156 (42%) were not in the highest category by both methods. In the North Carolina data, of the 533 subjects categorized in the lowest exposure group for at least one metric, 82 (15%) were not in the lowest category by both methods; similarly, among the 72 subjects in the highest exposure group for at least one metric, 21 (29%) were not in the highest category by both methods. These differences were not large enough to alter the exposure-response results.

The weighted metric is affected by periods away from exposure. The consistent results from the analyses using the two metrics indicate that this is not a factor in these populations. These workers either had no extended periods away from silica-exposure jobs, or cases and controls were away from these jobs at about the same times during the work history. In China, persons were generally employed at the same location from an early age until retirement or death/disability; thus, this aspect of the weighted metric would provide little discrimination in the Chinese workers. In North Carolina, cases spent an average of 2.7 years or 13% of their work time in non-dusty trades employment after entering the program. Controls spent 1.1 years away from dusty trades workplaces or 5% of their average employment time. These periods of time away from dusty employment may have been roughly at the same time, if they resulted from down-turns in the economy. No data are readily available to further evaluate this issue.

The estimates of risk from the weighted and cumulative metrics in the North Carolina data can be combined, if the average exposure of each group is divided by the appropriate duration for a working lifetime. Using the cumulative metric, ORs were calculated for groups with average exposure of 37, 98 and 368 mpy. The average exposure over a 40-year working life for these groups is approximately 1 (37/40), 2.5 (98/40) and 9 (368/40) mppcf, respectively. The average exposure for the weighted metric is calculated by dividing by 820, the sum of the weighting factors over a 40-year working lifetime, $1 + 2 + \ldots + 39 + 40$, and results in 0.5 (449/820), 1.5 (1235/820) and 6 mppcf (4970/820), respectively. The ORs are 0.76, 0.83, 1.24, 1.72, 3.59 and 5.04 for average exposures of 0.5, 1, 1.5, 2.5, 6 and 9 mppcf, respectively. The groups exposed on average to 6 (weighted metric) and 2.5 and 9 (cumulative metric) are at significantly increased risk of developing silicosis over a 40-year working lifetime. Using the weighted metric, no excess risk was identified at 0.5 or 1.5 mppcf; no significant risk at 1.0 from the cumulative metric has been reported previously (18).

To summarize, we presented exposure-response analyses for case-control studies of lung cancer and silicosis using a time-weighted exposure metric. For lung cancer among the China workers studied, we did not find a consistent association, while we observed a strong exposure-response relation for silicosis among North Carolina dusty trades workers. These results are generally consistent with earlier analyses using the cumulative metric. This is likely due in part to the high correlation between the two metrics. Periods of time away from work either did not occur, or occurred at similar times for cases and controls in these two groups. The interpretation of the level of exposure associated with the development of silicosis is enhanced from this analysis, however, as we have shown no statistically significant risk of silicosis at 1.5 mppcf. Larger differences than reported between cases and controls in the duration away from work and the timing of those periods of no exposure during the work history are needed if the weighted metric is to provide more information than the cumulative exposure. Simulations may be useful in better defining the magnitude of differences that are required.

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