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Vinyl chloride exposure and cirrhosis: A systematic review and meta-analysis

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ABSTRACT

Background: It has been proposed that vinyl chloride exposure is associated with increased risk of death from cirrhosis, although epidemiologic evidence is limited.
Methods: We analyzed the risk of death from cirrhosis by occupational vinyl chloride exposure by conducting a meta-analysis on seven available studies, including more than 40,000 workers exposed to vinyl chloride mostly in North America and Europe, with a total of 203 deaths from cirrhosis.
Results: All epidemiological studies on vinyl chloride exposure and risk of death from cirrhosis resulted in an overall relative risk of 0.73 (95% confidence interval 0.61–0.87). Thus, the epidemiologic evidence does not suggest an excess mortality from cirrhosis in vinyl chloride-exposed workers; this is consistent with histopathological observations in livers of angiosarcoma patients and of vinyl chloride-exposed rodents revealing no signs of cirrhosis.
Conclusion: Overall, our findings indicate the absence of increased risk of death from cirrhosis in vinyl chloride-exposed workers.

1. Introduction

Liver cirrhosis is caused by chronic liver diseases and it is characterized by hepatocyte islands surrounded by fibrotic septa devoid of a central vein, resulting in impaired exchange between hepatic sinusoids and adjacent liver parenchyma. Death and compensatory proliferation of hepatocytes occur, resulting in progressive replacement of liver tissue by fibrosis and regenerative nodules, leading to a loss of liver function [1].

Cirrhosis is a leading cause of death in the world. In Europe, 95,609 males and 53,123 females died of cirrhosis in 2002, with large differences in age-adjusted death rates among the different European geographical areas [2].

Alcoholic liver disease, hepatitis C virus infection, and non-alcoholic steatohepatitis (NASH) are the most common causes of cirrhosis in Europe and North America, whereas hepatitis B virus infection is the prevailing cause in most parts of Asia and sub-Saharan Africa [1,3,4]. Increased risk of cirrhosis is also associated with several monogenic disorders, such as alpha1-antitrypsin deficiency, hemochromatosis, porphyrias, and tyrosinemia type I, and with several conditions modulated by complex genetics, such as autoimmune hepatitis, diabetes mellitus and NASH [5].

Cirrhosis confers a high risk of hepatocellular carcinoma (HCC), with relative risk (RR) up to 27.5 and with more than 70% of HCC cases developing in cirrhotic livers [6,7].

Exposure to high levels of vinyl chloride (VC) has been implicated in the development of liver angiosarcoma, a rare tumor originating from endothelial cells in the liver [8], whereas the association between VC exposure and risk of HCC has remained controversial [9–11].

An argument put forth for an association between VC exposure and HCC is the presence of an association between VC exposure and liver cirrhosis [12]: such an association was suggested by results reported in exposure–response analyses (internal analyses) conducted by Ward [9] and Pirastu [13].

To clarify the possible association between VC and liver cirrhosis, we reviewed and conducted a meta-analysis of the available literature on VC and liver cirrhosis.

2. Methods

2.1. Search strategy, inclusion criteria and data collection

Two authors (E.F. and C.Z.) conducted an independent search in the PubMed, Medline, Embase and Web of Science databases up to

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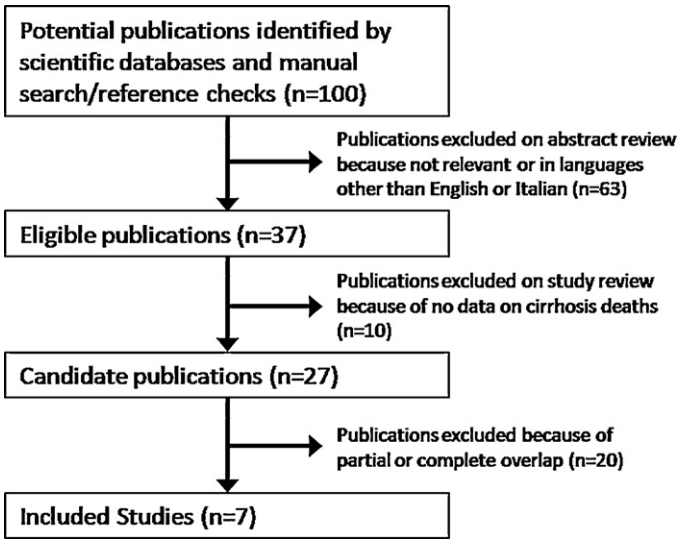

Fig. 1. Selection of studies included in the meta-analysis.

January 2011 for all epidemiological studies that investigated the risk of death from cirrhosis in relation to occupational exposure to VC, using different combinations of the keywords "liver cirrhosis"; "cirrhosis"; and "vinyl chloride". Publications were evaluated by checking their titles and abstracts; references of all computer-identified publications were also checked for additional studies that might have been missed in the initial search. Publications were checked for overlapping worker populations and; in the case of overlapping datasets; only the largest or most recent study was included. In case of doubt about overlap between studies; the authors were contacted to clarify this issue.

The inclusion criterion was evaluation of mortality from cirrhosis in workers exposed to VC. Information collected from all eligible studies included authors' name, journal and publication date, country of study location, number and type of plants included, number of workers observed, number of deaths from cirrhosis in exposed individuals and number of expected deaths in the non-exposed/reference population, and person-years. In the original papers, the numbers of expected deaths were calculated using the standardized mortality ratios (SMR) or the proportionate mortality rate (PMR). Fig. 1 summarizes the systematic literature search.

2.2. Statistical analyses

The meta-analysis was carried out using the Review Manager statistical package (Rev-Man version 5.0, provided by The Cochrane Collaboration, Oxford, England). A random-effects model, fitted via the general linear (mixed-effects) model, was used for all comparisons, since it can reduce the effect of larger studies and minimize the possible heterogeneity among studies. Homogeneity of study results in different groupings was assessed using Q and I^2 statistics. Publication bias was estimated by visual inspection of funnel plots, in which each standard error of log(RR) of each study was plotted versus the corresponding risk ratio (RR).

3. Results

All seven studies investigating causes of death among workers employed in VC plants were considered eligible for the meta-analysis. Among these, two large multicentric collaborative re-analyses, one of which was from North America [14] and one from Europe [9], included several previous investigations (detailed results of the European multicenter study are available in a separate publication [15] (Table 1). Four additional smaller independent cohort studies [13,16–18] and one additional sample cohort study [19] were included in our meta-analysis. Because the population described in an Italian cohort [13] did not completely overlap with those in the corresponding multicenter study [9] and because the follow-up in the former [13] was more extended than in the collaborative report [9], we included that study in the meta-analysis but subtracted the corresponding figures [13] (Porto Marghera plant) from the collaboration report [9] (Table 1). A case–control study [20] was not included in the present meta-analysis because of its partial overlapping with the Pirastu 2003 cohort study [13] and since the controls in that study were selected from a population of claimants in a lawsuit, and were not a representative sample of the cohort of exposed workers from which the cases were identified [12]. No evidence of publication bias was found in the funnel plot (Fig. 2).

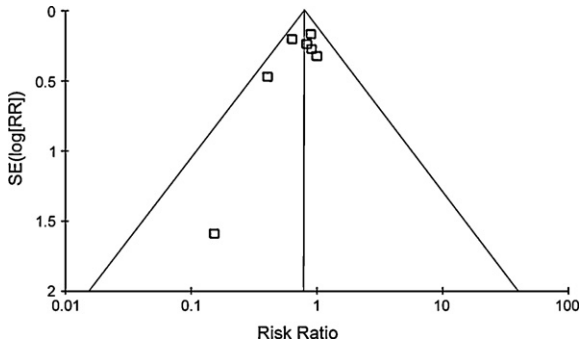

Fig. 2. Funnel plot of the risk ratio (RR) for studies used in the meta-analysis. Standard error of log(RR) of each study is plotted versus the corresponding RR.

For cohort studies, we extracted number of observed and expected deaths from cirrhosis, whereas for the sample cohort study, we extracted the number of deaths from cirrhosis in exposed and unexposed workers, respectively.

Overall, our meta-analysis comprised a total of more than 40,000 workers exposed to VC, with 203 deaths from cirrhosis among 10,721 deaths from all causes combined (Fig. 3). However, the population included in the US study by Chiazze et al. [16] reporting 3847 deaths from 1964 to 1973 in 17 plants partially overlapped with that contained in the study by Mundt et al. [14] reporting 3191 deaths by December 31, 1995 in 37 plants. Since it was not possible to define the number of overlapping individuals among the two studies, we carried out a first analysis excluding the study of Chiazze et al. [16], obtaining a summary RR of 0.77 (95% confidence interval (CI) 0.63–0.95; $P = 0.01$; Fig. 3). Inclusion of the study by Chiazze et al. (1981) resulted in a RR of 0.60 (95% CI 0.42–0.87, $P = 0.006$ (Fig. 3). The overall meta-analysis including the study of Chiazze et al. (1981) revealed a statistically significant decreased risk of death from liver cirrhosis upon VC exposure (RR = 0.73, 95% CI 0.61–0.87; $P = 0.0005$), in the absence of heterogeneity (Q statistics P value = 0.62; I^2 =0%; Fig. 3).

The event rates were similar among studies, suggesting comparable follow-up periods (Table 1).

4. Discussion

The results of our meta-analysis on VC exposure and risk of death from cirrhosis in exposed workers indicate no association between VC exposure and increased risk of liver cirrhosis, a finding that did not change whether or not we included the study of Chiazze et al. [16] in the meta-analysis. The reduced risk of deaths from cirrhosis herein detected in VC-exposed workers (RR = 0.73) as compared to the general population might be attributed to a decreased prevalence of heavy drinkers among the workers, i.e.,