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Biliary tract cancer in male printers and typesetters in the European rare cancer case-control study

Kumagai et al recently observed a striking increase in mortality from cholangiocarcinoma (CC) among workers in a colour Occup Environ Med August 2014 Vol 71 No 8 591 proof-printing shop in Japan, based on six deaths among 11 CC cases in a group of 62 workers employed between 1991 and 2006. Exposure to 1,2-dichloropropane and dichloromethane was reported.¹ Kubo et al extended the observation including 111 workers employed from 1981 to 2012, and reported 17 CC cases.² The Nordic Occupational Cancer Study (NOCCA) was used to explore the generalisability of the Japanese cluster findings to the printing industry and related occupations at large.³ An overall standardised incidence ratio (SIR) of 2.34 (95% CI 1.45 to 3.57) was found for intrahepatic CC, based on 21 cases in men. Women had an SIR of 1.95 (95% CI 0.84 to 3.85) with eight cases. Printers and lithographers had the highest SIRs and both occupations were recognised as entailing exposures to cleaning agents and being possibly related with the use of chlorinated solvents. A European multicentric case-control study was conducted between 1995 and 1997 on rare cancers of unknown aetiology, including gallbladder and extrahepatic tract cancers (ECC). We used the study dataset to assess the association of ECC with printing jobs in men. The study design has been fully reported.⁴ In brief, nine countries were involved. In six of them population-based cases and controls were recruited, while centres from three countries recruited hospital case-series and hospital recruitment-area controls. Study subjects were administered a standard questionnaire during face-to-face or telephone interviews. Surrogate interviews with a next-of kin (NoK) were performed if the index subject was too ill or had died before contact was established. All jobs lasting at least 6 months were recorded with the start and end years, working hours, materials handled, and chemical exposures. Jobs were coded according to the 1968 International Standard Classifications of Occupations (ISCO) on a four-digit level.⁵ Analyses were restricted to the pooled European dataset with available population controls, using 153 cases considered as definite or possible after pathological review and 1421 population controls. Printers were defined as individuals ever employed in an occupation corresponding to the ISCO code 92*** (ie, the first two ISCO digits), and typesetters as ISCO code 921**. The reference group was formed by all participants who were never employed as printers or typesetters. Results are presented as ORs with 95% CIs (95%-CI). Risk estimates were calculated by unconditional logistic regression models. Logistic regression models included country (one dummy variable for each country) and year of birth as a continuous variable (OR₁). Further models adjusted for history of gallstones (self-reported as being confirmed or treated by a physician) and NoK status (OR₂). Analyses were performed with SAS (V.8.2). As shown in table 1, ORs were increased for both printers and typesetters. CIs were wide due to the rarity of the cancers and occupations of interest, but our results lend support to the hypothesis of an increased risk for ECC in printing occupations, and are in agreement with the fact that cases of extrahepatic CC were observed along with those of intrahepatic CC in Japanese printers. ^{1 2} Out of five cases among printing workers, two were from Sweden—the only Nordic country involved in our casecontrol study—and both were typesetters. We were unable to identify candidate agents to explain this association because no information on specific chemicals used in the printing industry was available in our study, differently from other exposures.^{6–8} It is clear, however, that if the association is causal in nature, the causative agent(s) must have been present in printing rooms for a long time.

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Table 1 Number of printers and typesetters among cases and controls and corresponding ORs in the European case-control study of rare cancers

Job category	Controls n (%)	Cases n (%)	OR ₁ (95% CI)	OR ₂ (95% CI)
Printing worker (ISCO 92***)				
No	1396 (98.2)	148 (96.7)	1.00 (–)	1.00 (–)
Yes	25 (1.8)	5 (3.3)	1.88 (0.69 to 5.17)	2.42 (0.81 to 7.24)
Typesetter (ISCO 921**)				
No	1411 (99.3)	150 (98.0)	1.00 (–)	1.00 (–)
Yes	10 (0.7)	3 (2.0)	3.26 (0.82 to 12.99)	5.78 (1.43 to 23.29)