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SHORT COMMUNICATION

Smoking and biliary tract cancers in a cohort of US veterans

W-H Chow, JK McLaughlin*, Z Hrubec and JF Fraumeni Jr

Epidemiology and Biostatistics Program, Division of Cancer Etiology, National Cancer Institute, Bethesda, MD, USA.

Summary Except for gallstones, the risk factors for cancers of the biliary tract (CBTs) are poorly understood. Recent case-control studies have suggested cigarette smoking as a potential risk factor. In a cohort study of nearly 250 000 US veterans whose mortality was followed for up to 26 years, we evaluated the risk of CBT associated with tobacco use. Relative risks (RRs) and corresponding 95% confidence intervals (CIs) were calculated. A total of 303 CBT deaths were observed during the follow-up period. Compared with those who had never used any tobacco, current cigarette smokers at entry to the cohort had a 50% excess risk of CBT (RR = 1.5, CI = 1.1-2.0). A nearly 2-fold risk was observed among those who smoked more than 20 cigarettes per day and among those who started smoking under age 20. Non-significant increases in risk occurred among smokers of other forms of tobacco. This cohort study is consistent with reports that smoking is a risk factor for CBT, but further studies are needed to clarify whether the effect is specific for certain subsites and whether it reflects an association with pre-existent gallstones.

Keywords: biliary tract neoplasm; cigarette smoking; cohort study

Cancers of the biliary tract (CBT) encompass malignant tumours arising from the gallbladder, extrahepatic bile ducts and ampulla of Vater. These tumours are relatively uncommon, accounting for less than 1% of all incident cancers in the US (Ries *et al.*, 1994). Because of their rarity, risk factors have not been well examined. However, an association with antecedent gallstones is clearly established (Diehl, 1983; Lowenfels *et al.*, 1985; Maringhini *et al.*, 1987), along with obesity and high parity among women (Yen *et al.*, 1987; Zatonski *et al.*, 1992; Chow *et al.*, 1994; Moerman *et al.*, 1994*a*). An increased risk of CBT has been associated with cigarette smoking in a few recent case-control studies (Ghadirian *et al.*, 1993; Chow *et al.*, 1994; Moerman *et al.*, 1994*b*), but not in another study of cancer of the extrahepatic bile duct (Yen *et al.*, 1987). To examine further the role of cigarette smoking on CBT risk, we evaluated CBT mortality in a cohort of US veterans followed for up to 26 years.

Materials and methods

Details of the cohort and methods of follow-up have been reported elsewhere (Dorn, 1959; Kahn, 1966; Rogot and Murray, 1980; McLaughlin *et al.*, 1990). Briefly, the cohort comprised over 290 thousand US veterans who served in the Armed Forces between 1917 and 1940, and held active US Government life insurance policies in 1953. Over 99.5% of policy holders were men, and nearly all were white. Information on tobacco use, including current and past smoking status, type of tobacco used, amount of current tobacco use, and age at starting to smoke, was obtained from mailed questionnaires in 1954, and in 1957 for non-respondents to the first mailings. Duration of smoking was estimated by the difference between age at 1954 or 1957 and age started smoking. No additional information on tobacco use has been collected since the initial mailings; hence, categories of smokers are based solely on information obtained in 1954/1957.

Included in the analysis were 248 046 veterans (84% of the cohort) who responded to the questionnaires. The mortality of cohort members was ascertained until September 30, 1980, with about 96% completeness of ascertainment. Death certificates were obtained for 95% of the deceased veterans.

Causes of death were coded using the Seventh Revision of the International Statistical Classification of Diseases (ICD7) (WHO, 1957). In earlier reports on this cohort, CBT (ICD7 code 155.1) was not examined separately (Dorn, 1959; Kahn, 1966; Rogot and Murray, 1980). In the present analysis, the associations between CBT and tobacco use were assessed by relative risks (RRs) and corresponding 95% confidence intervals (CIs), using a Poisson regression program for modelling hazard functions with grouped data (Preston *et al.*, 1985). RRs were adjusted for age and calendar time periods in 5 year intervals.

Results

A total of 303 CBT deaths among cohort respondents was reported during the study period. Current smokers (in 1954 or 1957) had a significant 50% excess risk of CBT (RR = 1.5, CI = 1.1-2.0) compared with those who had never used any tobacco (Table I). In addition, non-significant excess risks were observed among former cigarette smokers (RR = 1.2, CI = 0.8-1.8), smokers of pipes/cigars only (RR = 1.4, CI = 0.9-2.2), and 'other' smokers (RR = 1.4, CI = 0.9-2.0), most of whom were former cigarette smokers who currently smoked cigars/pipes (Table I).

Among current cigarette smokers, a nearly 2-fold risk of CBT (RR = 1.8, CI = 1.2-2.7) was associated with smoking more than 20 cigarettes per day, although the dose-response trend ($P < 0.05$) with amount of cigarette consumption was not smooth (Table II). After adjustment for age, calendar time period, and number of cigarettes smoked per day, a consistent inverse association was found with age at starting smoking ($P < 0.05$). Risk increased from 1.4 (CI = 0.8-2.7) among those who started smoking at age 25 or older to 1.8 (CI = 1.1-3.1) among those who started under age 20. No clear association with duration of smoking was observed.

Correspondence: W-H Chow, National Cancer Institute, 6130 Executive Blvd, EPN 415, Bethesda, MD 20852, USA.
*Present address: International Epidemiology Institute, Rockville, MD, USA.
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Table I Relative risks (RRs) and 95% confidence intervals (CIs) of biliary tract cancers and tobacco use among US veterans, 1954–80

Smoking categories	*Number of deaths*	*Person-years*	*RR*[a]	*95% CI*
Total number of cases	303			
Never any tobacco	60	1 064 337	1.0	–
Cigars/pipes only	35	407 625	1.4	0.9–2.2
Other smokers[b]	51	658 478	1.4	0.9–2.0
Former cigarette smokers	49	743 281	1.2	0.8–1.8
Current cigarette smokers[c]	108	1 657 270	1.5	1.1–2.0

[a]Adjusted for age and calendar time period. [b]Smokers who did not fit into one of the other categories, mostly former cigarette smokers who currently smoked cigars/pipes. [c]Included cigarette smokers who also used cigars or pipes.

Table II Relative risks (RRs) and 95% confidence intervals (CIs) of biliary tract cancers in relation to amount and duration of smoking and age at starting smoking among current smokers

Smoking variables	*Number of deaths*	*Person-years*	*RR*	*95% CI*
Never any tobacco	60	1 064 337	1.0	–
Number of cigarettes per day[a]				
<10	21	238 834	1.6	1.0–2.6
10–20	45	834 010	1.2	0.8–1.8
21+	42	584 423	1.8	1.2–2.7
Age at starting smoking (years)[b]				
<20	58	930 203	1.8	1.1–3.1
20–24	32	474 893	1.6	0.9–2.9
>24	18	243 276	1.4	0.8–2.7
Duration of smoking (years)[b]				
<30	16	569 418	1.6	0.8–3.3
30–39	41	544 485	1.7	0.9–2.9
40+	51	534 483	1.7	1.0–2.9

[a]RR adjusted for age and calendar time period. [b]RR adjusted for age, calendar time period, and number of cigarettes smoked per day.

Discussion

The relation of tobacco smoking to CBT has been examined in a few small case–control studies. Among the findings are an excess risk of CBT among smokers who did not drink alcohol (Moerman *et al.*, 1994*b*), a 3-fold risk of extrahepatic bile duct cancers among heavy smokers (Chow *et al.*, 1994), a small excess risk of gallbladder cancer and a nearly 3-fold risk of extrahepatic bile duct cancer among smokers of non-filtered cigarettes (Ghadirian *et al.*, 1993). However, an inverse association between cigarette smoking and risk of CBT was reported in an earlier hospital-based study (Yen *et al.*, 1987), in which controls might be more likely to have smoked than the general population.

In this attempt to examine the association between tobacco use and CBT employing a cohort study design, we found a small excess risk among cigarette smokers and a suggestive dose–response relationship with amount of smoking and age started smoking. Our results provide further evidence linking smoking and CBT, although the risk estimates are lower than those reported in recent case–control studies (Ghadirian *et al.*, 1993; Chow *et al.*, 1994; Moerman *et al.*, 1994*b*).

A limitation of our study is that information on smoking habits was available only for 1954/1957. If the smoking patterns in this cohort of veterans resemble those of American men in general, over 40% of those smoking then may have stopped smoking during the 26 years of follow-up (US Surgeon General, 1989). Therefore, the risks of CBT associated with cigarette smoking may be underestimated in our study, as a result of the misclassification of ex-smokers as current smokers. The misclassification in duration of smoking also may have precluded the detection of a dose–response relation with risks.

Another limitation is that medical records were not obtained for cases in this study. However, in a previous study conducted to examine the accuracy of US cancer mortality data, 86.5% of CBT reported on death certificates was confirmed by hospital records (Percy *et al.*, 1981). In addition, we could not evaluate risk of CBT by anatomic subsite since these tumours were not coded separately in ICD7, so more detailed studies are needed. It is also important to evaluate information on other risk factors, including gallstones, which have been linked to smoking in some studies (McMichael *et al.*, 1992; Grodstein *et al.*, 1994). Excess gallstone risks of 30% to 2-fold have been observed among smokers, particularly among women (Baron and Logan, 1990; McMichael *et al.*, 1992; Grodstein *et al.*, 1994). Future studies should examine whether smoking affects CBT risks directly by a carcinogenic effect or indirectly by an association with gallstones.

In summary, this cohort study suggests that cigarette smoking is a weak risk factor for CBT. Additional studies of CBT are needed to clarify the effects of smoking on subsites of the biliary tract and to identify the mechanisms by which smoking may be related to CBT.

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