Letter to the Editor

Reply: Gallstones, cholecystectomy, and the risk for developing pancreatic cancer

Sir

In a combined analysis of the Nurses’ Health Study and the Health Professional Follow-up Study, on a total of 206 women and 143 men with cancer of the pancreas, Schernhammer et al (2002) did not find an increased risk of pancreatic cancer in relation to history of gallstones or cholecystectomy after adjusting for potential confounding factors. The issue of a possible association between gallstones or cholecystectomy and cancer of the pancreas is, however, still open to discussion, because several investigations reported an excess pancreatic risk in patients with gallstones. Apart from the papers quoted in Schernhammer et al (2002), some excess risks were found in cohort studies from the United States (Bansal and Sonnenberg, 1996), Denmark (Johansen et al, 1996), and Sweden (Ye et al, 2001), and case–control studies from the United Kingdom (Cuzick and Babiker, 1989), Greece (Kalapothaki et al, 1993), and Israel (Schattner et al, 1997). The strength of the association, however, was variable across studies, and different potential confounding factors were not always taken into account.

In order to provide further information on the issue, we updated the analysis of a case–control study conducted in Italy between 1983 and 1992 (La Vecchia et al, 1990). Briefly, the study included 362 patients from the major teaching and general hospitals in Greater Milan with incident, histologically confirmed pancreatic cancer (229 men, 133 women, median age 59 years), and 1552 controls (1141 men, 411 women, median age 55 years) admitted to the same network of hospitals for acute, non-neoplastic conditions, unrelated to alcohol or tobacco consumption (33% traumas, 17% nontraumatic orthopedic conditions, 36% acute surgical diseases, and 14% other miscellaneous disorders). Less than 3% of cases and controls approached refused the interview.

Trained interviewers identified and questioned cases and controls using a structured questionnaire, including information on education and other socioeconomic factors, anthropometric measures, general lifestyle habits, such as tobacco and alcohol consumption, and a few selected indicator foods. The patients were also asked if they had a diagnosis of selected medical conditions, and the age at first diagnosis was recorded.

Odds ratios (OR) and corresponding 95% confidence intervals (CI) were estimated using unconditional multiple logistic regression models, including terms for age, education, tobacco consumption, body mass index, and history of diabetes.

Table 1 gives the distribution of pancreatic cancer cases and controls, and the corresponding ORs, according to history of cholelithiasis. Subjects with a history of cholelithiasis showed no increased risk of cancer of the pancreas (OR = 1.03, 95% CI = 0.67 – 1.59). The OR was 1.33 (95% CI = 0.74 – 2.40) for subjects with a diagnosis of cholelithiasis less than 10 years before interview, and 0.80 (95% CI = 0.43 – 1.50) for diagnosis 10 or more years before.

Thus, our findings are consistent with those of the Nurses’ Health Study and the Health Professional Follow-up Studies (Schernhammer et al, 2002), and indicate that cholelithiasis is not materially associated with pancreatic cancer risk after major identified confounding factors have been considered. A modestly increased risk was observed 10 years after a diagnosis of cholelithiasis, but no greater excess risk can be found 10 or more years after. Thus, if any association exists, it is unlikely to be causal. The apparent association reported from several case–control studies can at least in part be because of a more accurate recall of gallbladder disease by pancreatic cancer patients. In our study, however, information on medical history proved satisfactorily reproducible (Bosetti et al, 2001), indicating that recall bias is unlikely to have played a major role. Other potential biases of this study should be limited, given the almost complete response rate, the administration of a standard questionnaire under similar conditions, and the same catchment area for cases and controls.

Table 1  Relation between pancreatic cancer and history of cholelithiasis among 362 cases and 1552 controls (Milan, Italy, 1983–1992)

| History of cholelithiasis | Cases | Controls | OR* (95% CI) |
|--------------------------|-------|----------|--------------|
| No                       | 330   | 1430     | 1.03 (0.67 – 1.59) |
| Yes                      | 32    | 122      | 1.33 (0.74 – 2.40) |

Time since diagnosis (years)

| Time since diagnosis (years) | Cases | Controls | OR* (95% CI) |
|-----------------------------|-------|----------|--------------|
| < 10                        | 18    | 54       | 1.33 (0.74 – 2.40) |
| ≥ 10                        | 14    | 67       | 0.80 (0.43 – 1.50) |

*Correspondence: C Bosetti; E-mail: bosetti@marionegri.it

---

1Istituto di Ricerche Farmacologiche ‘Mario Negri’, Via Eritrea 62, 20157 Milan, Italy; 2Field and Intervention Studies Unit, International Agency for Research on Cancer, 150 Cours Albert-Thomas, F-69372 Lyon Cédex 08, France; 3Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, Via Venezian 1, 20133 Milan, Italy
ACKNOWLEDGEMENTS

This work was conducted with the contribution of the Italian Association for Cancer Research and the Italian League Against Cancer of Milan. The authors thank Ms MP Bonifacino for editorial assistance.

REFERENCES

Bansal P, Sonnenberg A (1996) Comorbid occurrence of cholelithiasis and gastrointestinal cancer. *Eur J Gastroenterol Hepatol* 8: 985 – 988

Bosetti C, Tavani A, Negri E, Trichopoulos D, La Vecchia C (2001) Reliability of data medical conditions, menstrual and reproductive history provided by hospital controls. *J Clin Epidemiol* 54: 902 – 906

Cuzick J, Babiker AG (1989) Pancreatic cancer, alcohol, diabetes mellitus and gall-bladder disease. *Int J Cancer* 43: 415 – 421

Johansen C, Chow WH, Jorgensen T, Mellemkjaer L, Engholm G, Olsen JH (1996) Risk of colorectal cancer and other cancers in patients with gall stones. *Gut* 39: 439 – 443

Kalapothaki V, Tzonou A, Hsieh CC, Toupadaki N, Karakatsani A, Trichopoulos D (1993) Tobacco, ethanol, coffee, pancreatitis, diabetes mellitus, and cholelithiasis as risk factors for pancreatic carcinoma. *Cancer Causes Control* 4: 375 – 382

La Vecchia C, Negri E, D’Avanzo B, Ferraroni M, Gramenzi A, Savoldelli R, Boyle P, Franceschi S (1990) Medical history, diet and pancreatic cancer. *Oncology* 47: 463 – 436

Schattner A, Fenakel G, Malnick SD (1997) Cholelithiasis and pancreatic cancer. A case – control study. *J Clin Gastroenterol* 25: 602 – 604

Schernhammer ES, Michaud DS, Leitzmann MF, Giovannucci E, Colditz GA, Fuchs CS (2002) Gallstones, cholecystectomy, and the risk for developing pancreatic cancer. *Br J Cancer* 86: 1081 – 1104

Ye W, Lagergren J, Nyren O, Ekbom A (2001) Risk of pancreatic cancer after cholecystectomy: a cohort study in Sweden. *Gut* 49: 678 – 681