Annals of Oncology 23: 2173–2178, 2012
doi:10.1093/annonc/mdr581
Published online 9 January 2012

History of cholelithiasis and cancer risk in a network of case–control studies

A. Tavani[1*], V. Rosato[1], F. Di Palma[1], C. Bosetti[1], R. Talamini[2], L. Dal Maso[2,3], A. Zucchetto[2], F. Levi[4], M. Montella[5], E. Negri[1], S. Franceschi[6] & C. La Vecchia[1,3,7]

[1]Department of Epidemiology, Istituto di Ricerche Farmacologiche "Mario Negri", Milan; [2]Unit of Epidemiology and Biostatistics, Centro di Riferimento Oncologico, Aviano; [3]Department of Occupational Health, University of Milan, Milan, Italy; [4]Cancer Epidemiology Unit and Registre Vaudois des Tumeurs, Institut universitaire de médecine sociale et préventive, Lausanne, Switzerland; [5]Unit of Epidemiology, Istituto Tumori "Fondazione Pascale", Naples, Italy; [6]International Agency for Research on Cancer, Lyon; [7]International Prevention Research Institute, Lyon, France

Received 30 September 2011; revised 15 November 2011; accepted 15 November 2011

Background: We analyzed the relationship between cholelithiasis and cancer risk in a network of case–control studies conducted in Italy and Switzerland in 1982–2009.

Methods: The analyses included 1997 oropharyngeal, 917 esophageal, 999 gastric, 23 small intestinal, 3726 colorectal, 684 liver, 688 pancreatic, 1240 laryngeal, 6447 breast, 1458 endometrial, 2002 ovarian, 1582 prostate, 1125 renal cell, 741 bladder cancers, and 21 284 controls. The odds ratios (ORs) were estimated by multiple logistic regression models.

Results: The ORs for subjects with history of cholelithiasis compared with those without were significantly elevated for small intestinal (OR = 3.96), prostate (OR = 1.36), and kidney cancers (OR = 1.57). These positive associations were observed ≥10 years after diagnosis of cholelithiasis and were consistent across strata of age, sex, and body mass index. No relation was found with the other selected cancers. A meta-analysis including this and three other studies on the relation of cholelithiasis with small intestinal cancer gave a pooled relative risk of 2.35 [95% confidence interval (CI) 1.82–3.03].

Conclusion: In subjects with cholelithiasis, we showed an appreciably increased risk of small intestinal cancer and suggested a moderate increased risk of prostate and kidney cancers. We found no material association with the other cancers considered.

Key words: case–control study, cholelithiasis, kidney cancer, prostate cancer, small intestinal cancer

introduction

Cholelithiasis (i.e. the presence of gallstones) is a common disease that implies changes in bile release and hence may modulate the risk of digestive tract neoplasms. Consequently, a possible relation between cholelithiasis and cancer risk has been focused on cancers of the digestive tract [1–10]. Cholelithiasis is the major risk factor for gallbladder and perhaps for bile duct cancers [3, 8, 9]. Its role on small intestinal cancerogenesis is less clear, and the information is based on four small studies [1, 2, 4, 5], on account of the rarity of the disease.

Data are scanty and inconsistent with reference to other cancer sites. The Oxford record linkage study, comparing a cohort of patients who had undergone cholecystectomy with a reference cohort, observed 2921 cases of cancer overall, compared with 2966 expected, after the exclusion of cancer cases diagnosed up to 2 years after cholecystectomy [relative risk (RR) of 0.98, 95% confidence interval (CI) 0.95–1.02], but found a short-term significant increase of cancer incidence at colon, pancreas, liver, and stomach [11]. In a Danish cohort of patients with gallstones (72% had also undergone cholecystectomy), including 3940 cancer cases, a 7%increased risk of cancer was found [2]. The excess risk was, however, restricted to selected cancers of the digestive tract and kidney [2]. In the third USA National Health and Nutrition Examination Survey, gallstone disease was associated with an increased risk of cancer overall (651 deaths), with a RR of 1.4 (95% CI 1.1–1.8), while the RR for cholecystectomy was 1.2 (95% CI 0.79–1.7) [12]. Most record linkage studies, however, had limited information on covariates and were hence unable to provide adequately adjusted RRs.

We analyzed the relation between cholelithiasis and the risk of cancers at selected sites using data from a network of case–control studies, conducted in Italy and Switzerland, where allowance for a large number of covariates was possible. Moreover, we combined all published data using a

*Correspondence to: Dr A. Tavani, Department of Epidemiology, ''Mario Negri'' Institute for Pharmacological Research, Via G. La Masa 19, 20156 Milan, Italy. Tel: +39-02-3901-4722; Fax: +39-02-33200231; E-mail: alessandra.tavani@marionegri.it

meta-analytic approach to provide an overall quantitative estimate of the association between cholelithiasis and small intestinal cancer.

methods

Between 1982 and 2009, we conducted an integrated series of case–control studies on several neoplasms in various areas of northern (the greater Milan area; the provinces of Pordenone, Padua, Udine, Gorizia, and Forlì; the urban area of Genoa), central (the provinces of Rome and Latina), and southern Italy (the urban area of Naples). We also conducted companion studies on cancers of the oral cavity/pharynx, esophagus, colorectum, larynx, breast, and endometrium in the Canton of Vaud, Switzerland. The present analysis includes a total of 1997 cases of cancer of the oral cavity and pharynx [13,14,15], 917 of the esophagus [15,16,17], 999 of the stomach [18, 19], 23 of the small intestine [20], 3726 of the colorectum [21,22,23], 684 of the liver [24, 25], 688 of the pancreas [26], 1240 of the larynx [15, 27], 6447 of the breast [28, 29], 1458 of the endometrium [30], 2002 of the ovary [31, 32], 1582 of the prostate [33, 34], 1125 of the kidney [33, 35], 741 of the bladder [33], and a total of 21 284 controls (Table 1).

All studies included incident cases, identified in the major teaching and general hospitals of the study areas. Controls were subjects admitted to the same network of hospitals as cases for a wide spectrum of acute non-neoplastic conditions, unrelated to known risk factors for the corresponding cancer site. Overall, 17% of controls were admitted for traumatic conditions, 24% for nontraumatic orthopedic conditions, 29% for acute surgical conditions, and 30% for miscellaneous other illnesses.

Refusal of subjects approached was <5% in Italy and ∼15% in Switzerland. The study protocols were revised and approved by the ethical committees of the hospitals involved according to the regulations at the time of each study conduction, and all participants gave informed consent.

Trained staff interviewed cases and controls during their hospital stay using similar structured questionnaires, including information on sociodemographic characteristics, anthropometric measures, lifestyle habits (e.g. tobacco smoking and alcohol drinking), dietary habits, personal medical history, family history of cancer and, for women, menstrual and reproductive factors, and use of oral contraceptives and hormone replacement therapy. History of cholelithiasis and selected other medical conditions were self-reported and included age at first diagnosis.

statistical analysis

Odds ratios (ORs) of various cancers according to history of cholelithiasis and the corresponding 95%CI were estimated by unconditional multiple logistic regression models [36]. All models included terms for sex (when appropriate), *quinquennia* of age, study center, year of interview, education (<7, 7–11, ≥12 years), alcohol drinking (<14, 14–27, ≥28 drinks per week), tobacco smoking (never, ex-smokers, current smokers of <15, current smokers of 15–24, or current smokers of ≥25 cigarettes per day), and body mass index (<20, 20–24, 25–29, ≥30 kg/m^2). For breast, ovarian, and endometrial cancers, models further included terms for parity, menopausal status, age at menopause, and use of oral contraceptives and menopausal hormone replacement therapy; for breast cancer, a further term for age at first birth was also included.

results

Table 2 gives the distribution of cancer cases and controls according to history of cholelithiasis and the corresponding OR. The ORs for subjects with history of cholelithiasis compared with those without were significantly elevated for

Table 1. Number of cases of selected cancer sites and controls by sex and corresponding median age. Italy and Switzerland, 1982–2009

Cancer site	Cases (men/women)	Median age (years)	Controls[a] (men/women)	Median age (years)
Oral cavity and pharynx	1640/357	58	4369/1799	57
Esophagus	783/134	60	2735/931	58
Stomach	612/387	61	1506/1122	56
Small intestine	10/13	66	100/130	60
Colorectum	2115/1611	62	3806/3218	57
Colon	1258/1033	62	3806/3218	57
Rectum	857/578	62	3806/3218	57
Liver	525/159	62	1419/537	58
Pancreas	403/285	61	1489/715	58
Larynx	1139/101	61	3380/997	59
Breast	−/6447	54	−/6459	55
Endometrium	−/1458	61	−/3822	57
Ovary	−/2002	55	−/5478	55
Prostate	1582/−	66	2231/−	63
Kidney	737/388	61	1768/851	61
Bladder	627/114	64	780/305	60

[a]In some instances, the same controls were used for different cancer sites.

Table 2. Distribution of cases of selected cancer sites and controls and corresponding odds ratios (ORs) and 95% confidence intervals (CIs), according to history of cholelithiasis. Italy and Switzerland, 1982–2009

Cancer site	History of cholelithiasis				OR[a] (95% CI)
	No		Yes		
	Cases	Controls	Cases	Controls	
Oral cavity and pharynx	1910	5761	87	407	0.88 (0.66–1.16)
Esophagus	858	3421	59	245	1.15 (0.80–1.65)
Stomach	897	2415	102	213	1.29 (0.99–1.67)
Small intestine	18	210	5	20	3.96 (1.10–14.3)
Colorectum	3365	6431	361	593	1.05 (0.91–1.21)
Colon	2058	6431	233	593	1.10 (0.93–1.30)
Rectum	1307	6431	128	593	0.99 (0.81–1.22)
Liver	625	1809	59	147	1.17 (0.83–1.65)
Pancreas	624	2013	64	191	0.94 (0.69–1.29)
Larynx	1158	4063	82	314	1.11 (0.82–1.50)
Breast[b]	5722	5724	725	735	1.02 (0.91–1.14)
Endometrium[c]	1272	3380	186	442	0.92 (0.76–1.12)
Ovary[c]	1795	4858	207	620	0.89 (0.75–1.06)
Prostate	1444	2097	138	134	1.36 (1.04–1.78)
Kidney	992	2418	133	201	1.57 (1.23–1.99)
Bladder	681	1010	60	75	1.22 (0.84–1.79)

[a]Estimates from multiple logistic regression models adjusted for sex (when appropriate), age, study center, year of interview, study period, education, alcohol drinking, tobacco smoking, and body mass index. Reference category: no history of cholelithiasis.
[b]Further adjusted for parity, age at first birth, menopausal status, age at menopause, and oral contraceptives and hormone replacement therapy use.
[c]Further adjusted for parity, menopausal status, age at menopause, and oral contraceptives and hormone replacement therapy use.

Table 3. Distribution of cases of selected cancer sites and controls and corresponding odds ratios (ORs) and 95%confidence intervals (CIs), according to time since diagnosis of cholelithiasis. Italy and Switzerland, 1982–2009

Cancer site	Time since diagnosis of cholelithiasis					
	<2 years		2–9 years		≥10 years	
	N^a	OR^b (95% CI)	N^a	OR^b (95%CI)	N^a	OR^b (95%CI)
Stomach	11/8	3.67 (1.43–9.43)	30/70	1.23 (0.79–1.93)	61/133	1.19 (0.86–1.65)
Small intestine	–	–	2/7	5.37 (0.82–35.20)	3/13	3.28 (0.67–15.98)
Prostate	9/10	1.91 (0.73–4.99)	38/44	1.14 (0.70–1.84)	91/80	1.42 (1.02–1.98)
Kidney	12/14	2.21 (1.00–4.87)	43/55	1.78 (1.17–2.70)	77/131	1.40 (1.04–1.89)

[a]Number of cases/controls with a diagnosis of cholelithiasis. The sum does not add up to the total because of some missing values.
[b]Estimates from logistic regression model adjusted for sex (when appropriate), age, study center, year of interview, study period, education, alcohol drinking, tobacco smoking, and body mass index. Reference category: no history of cholelithiasis.

Table 4. Distribution of cases of prostate and kidney cancers and corresponding odds ratios (ORs) and 95%confidence intervals (CIs), according to history of cholelithiasis, by selected covariates. Italy and Switzerland, 1982–2009

	Prostate cancer		Kidney cancer	
	N^a	OR^b (95%CI)	N^a	OR^b (95%CI)
Sex				
Men	138	1.36 (1.04–1.78)	66	1.66 (1.19–2.32)
Women	–	–	67	1.43 (1.01–2.03)
Age at diagnosis of cancer/interview				
<60 years	17	1.22 (0.62–2.40)	41	1.48 (0.97–2.25)
≥60 years	121	1.42 (1.06–1.91)	92	1.62 (1.21–2.18)
Body mass index				
<25 kg/m^2	48	1.62 (1.02–2.59)	47	1.80 (1.20–2.72)
≥25 kg/m^2	90	1.24 (0.89–1.73)	86	1.42 (1.05–1.91)

[a]Number of cases with a diagnosis of cholelithiasis. The sum does not add up to the total because of some missing values.
[b]Estimates from multiple logistic regression models adjusted for sex, age, study center, year of interview, study period, education, alcohol drinking, tobacco smoking, and body mass index. Reference category: no history of cholelithiasis.

cancers of the small intestine (OR = 3.96), prostate (OR = 1.36), and kidney (OR = 1.57). The association with stomach cancer was of borderline statistical significance (OR = 1.29). No relationship was found between history of cholelithiasis and the risk of cancers of the oral cavity/pharynx (OR = 0.88), esophagus (OR = 1.15), colorectum (OR = 1.05), liver (OR = 1.17), pancreas (OR = 0.94), larynx (OR = 1.11), breast (OR = 1.02), endometrium (OR = 0.92), ovary (OR = 0.89), and bladder (OR = 1.22).

The relationship with selected cancer sites according to time since diagnosis of cholelithiasis is reported in Table 3. For small intestinal, prostate, and kidney cancers, the increased risk persisted even ≥10 years after the diagnosis of cholelithiasis. For stomach cancer, a positive association was observed only when cholelithiasis was diagnosed <2 years before cancer diagnosis.

There was no heterogeneity in the risk of prostate and kidney cancer across strata of sex, age at diagnosis of cancer/interview, and body mass index (Table 4).

discussion

The present findings confirm that the risk of small intestinal cancer is appreciably elevated in subjects with a history of cholelithiasis. The excess risk persisted after adjustment for body mass index and ≥10 years after the diagnosis of cholelithiasis. There was also a suggestion of a possible moderate excess risk of cancers of prostate and kidney. No association was found between the history of cholelithiasis and the risk of cancer at the other considered sites.

Our results on cancer of the small intestine are in agreement with previous evidence and provide a quantitative evidence of a positive association with cholelithiasis. In an American record linkage study, 3 out of 23 patients with adenocarcinoma of the small bowel, and 3 out of 17 patients with carcinoids of the small bowel had a history of cholecystectomy, while none of the 52 controls reported history of cholecystectomy [1]. A Danish cohort study of 42 098 patients discharged with a diagnosis of gallstones found a RR of 2.6 (95% CI 1.6–3.9), based on 23 cases of small intestinal cancer [2]. In a Swedish cohort study of 278 460 patients with cholecystectomy, the standardized incidence ratio in patients with proximal small bowel adenocarcinomas was 3.14 (95% CI 1.95–4.80), based on 68 cases, and the standardized incidence ratio in patients with distal small bowel carcinoids was 1.50 (95% CI 0.84–2.48), based on 98 cases [5]. In a case–control study of small bowel adenocarcinoma conducted in Denmark, Sweden, France, Germany, and Italy, the OR for patients with gallstone ultrasound/X-ray verified was 1.4 (95% CI 0.6–3.2) based on 8 cases [4]. Excluding the American record linkage study [1] for which no risk estimate was available, we pooled the RR of the other three studies [2, 4, 5] and the present one, using a meta-analytic approach and the fixed-effects model [37] (Figure 1). The meta-analysis was based on 72 cancer cases with cholelithiasis. The pooled RR of the association between cholelithiasis and small intestinal cancer risk was 2.35 (95% CI 1.82–3.03) for the four studies, 2.42 (95% CI 1.84–3.18) for the two cohort [2, 5], and 1.91 (95% CI 0.95–3.85) for the two case–control studies [4] and the present study. The RR was 2.62 (95% CI 1.76–3.89) for adenocarcinomas of the small intestine only [4, 5]. Although based on small number of subjects due to the rarity of the disease, these findings, together with the observation that adenocarcinomas of the small intestine occur more frequently near the ampulla of Vater in

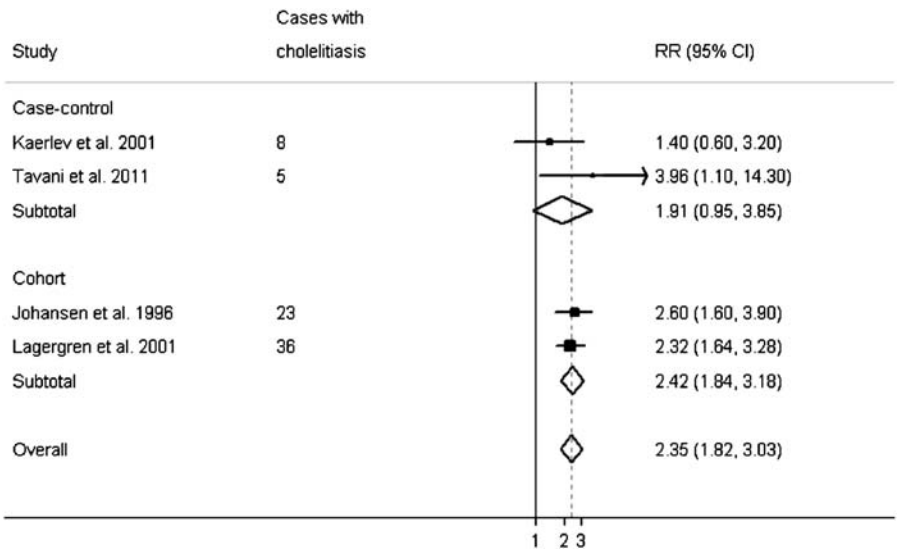

Figure 1. Meta-analysis of studies of the relation between history of cholelithiasis and small intestinal cancer risk. The center projection of the black square indicates the relative risk (RR) in each study, with its square size proportional to the inverse of the log RR variance, and the horizontal lines represent 95% confidence intervals (CIs). A diamond is used to plot the summary RR (from fixed-effects model) whose center represents the RR and its extremes the 95%CI.

the duodenum [38], support the hypothesis that bile is a carcinogen for the small intestine especially in proximity with the site where bile is excreted. Biliary constituents were reported to be genotoxic and to cause local cellular damage and consequent increased mitotic activity of damaged tissue [38].

A possible association between cholelithiasis and prostate cancer was first suggested by an ecological study [39]. Subsequently, a record linkage study of subjects with cholecystectomy [11] and a prospective study of subjects hospitalized for gallstones [2] found no significant relationships, although the risk estimates were above unity. An increased risk (hazard ratio = 1.72, 95%CI 1.12–2.66) was found in the Ohsaki cohort [40], especially for advanced prostate cancer. Prostate cancer has been associated with hypercholesterolemia [34, 41] and inversely related with the use of statins [42,43,44]. Hypercholesterolemia is the strongest known risk factor for cholelithiasis and cholesterol the main component of the commonest type of gallstones. There is, therefore, a plausible biological explanation for the association between gallstones and prostate cancer risk, although it needs to be confirmed.

Subjects who had undergone cholecystectomy had a RR of kidney cancer of 1.13 (95% CI 0.86--1.45) in the Oxford record linkage study [11], and those hospitalized for gallstones had a RR of 1.2 (95% CI 1.0–1.5) in a prospective study from Denmark [2]. As overweight, obesity, and related conditions (such as hypertension, insulin resistance, diabetes, hyperlipidemia, and high estrogen levels) have been related to kidney cancer [45, 46], it is difficult to assess whether cholelithiasis is an independent risk factor. However, in our study, the excess risk for kidney cancer persisted after adjustment for body mass index.

A meta-analysis on cholecystectomy and colorectal cancer suggested a moderate increased risk in 33 case–control studies (RR = 1.34, 95% CI 1.14–1.57), stronger in the proximal colon (RR = 1.88), but not in six prospective studies (RR = 0.97) [47]. Another meta-analysis of 35 studies found an overall modest positive association (RR = 1.11, 95% CI 1.02–1.21), slightly stronger among women and for right-sided cancer [48]. A positive association of cholecystectomy with cancer of the proximal colon, which diminishes in the distant colon and the rectum, has been reported in some [5, 49], but not in all studies [11, 23]. A similar gradient of association was found for gallstone disease [2], while another study of colorectal cancer found a positive association with biliary tract, but not with gallbladder inflammation [50].

The relationship of cholecystectomy with pancreatic cancer has been considered in at least 24 studies, 15 of which showed a positive association [6, 51], which appeared stronger among subjects with a diagnosis of pancreatic cancer close in time to that of cholelithiasis, suggesting a possible reverse causation, i.e. a cancer-related diagnosis of cholelithiasis [6, 51].

In the third USA National Health and Nutrition Examination Survey, total and cancer mortality were positively associated with both ultrasound-diagnosed gallstones and cholecystectomy [12]. However, subjects with ultrasound-documented gallstones compared with those with cholecystectomy had a slightly higher elevated risk of cancer mortality.

The present data support a lack of association of cholelithiasis with other considered cancer sites. Among previous studies, one showed a positive [2] and one showed no association [10] of gallstone disease with cancer of the oral cavity and esophagus, and a few studies found no relation of cholecystectomy with squamous cell carcinoma [10, 11, 52, 53] and adenocarcinoma of the esophagus and gastric cardia [52, 53]. No relation was found for cancer of the stomach [2, 11, 54], larynx [2, 10], breast [2, 3, 11, 55, 56], ovary [2, 11], and bladder [2, 11]. Data are inconsistent for cancers of the liver [2, 11, 57] and endometrium [2, 11, 58].

In this study, cholelithiasis was self-reported. Abdominal ultrasonography for the diagnosis of cholelithiasis has became more frequent, leading to a more accurate diagnosis of the disease also for less severe cases. However, an analysis stratified for period of diagnosis of cholelithiasis found no difference in the association of cholelithiasis and the risk of cancer of the prostate, and the association was apparently stronger for more recent diagnosis (OR 2.00, 95%CI 1.17–3.41 for subjects diagnosed in 1985 or later compared with those diagnosed before 1985). However, we cannot exclude that the apparent association with prostate and kidney cancers may be attributable to multiple testing since we combined different cancer sites. With reference to strength of the present study, the hospital setting should reduce differences in recalling diseases between cases and controls who were matched for year at cancer diagnosis or interview. Recall bias is unlikely, as both cases and controls were unaware of the possible relation between cholelithiasis and cancer. Reliability of data on medical conditions was satisfactory in our study and the kappa coefficient for reproducibility of information on cholelithiasis was 0.91 [59]. Possible sources of selection bias should also be limited since participation was high, and cases and controls were selected in the same catchment areas. A major strength of our study, besides its large dataset, was the possibility to allow for several confounding factors.

In conclusion, our data strongly support a positive association of cholelithiasis with the risk of small intestinal cancer and provide quantitative estimates of the overall association. A moderate positive association with prostate and kidney cancer is also suggested, while a role of cholelithiasis on the risk of the other considered cancer sites can be excluded.

acknowledgements

The authors thank Mrs. I Garimoldi for editorial assistance.

funding

The Italian Association for Cancer Research, Milan, Italy (10068); and the Swiss League and Research against Cancer/ Oncosuisse (KFS-700, OCS-1633).

disclosure

The authors declare no conflicts of interest.

references

1. Chen CC, Neugut AI, Rotterdam H. Risk factors for adenocarcinomas and malignant carcinoids of the small intestine: preliminary findings. Cancer Epidemiol Biomarkers Prev 1994; 3: 205–207.
2. Johansen C, Chow WH, Jorgensen T et al. Risk of colorectal cancer and other cancers in patients with gall stones. Gut 1996; 39: 439–443.
3. Zatonski WA, Lowenfels AB, Boyle p et al. Epidemiologic aspects of gallbladder cancer: a case-control study of the SEARCH Program of the International Agency for Research on Cancer. J Natl Cancer Inst 1997; 89(15): 1132–1138.
4. Kaerlev L, Teglbjaerg PS, Sabroe S et al. Medical risk factors for small-bowel adenocarcinoma with focus on Crohn disease: a European population-based case-control study. Scand J Gastroenterol 2001; 36: 641–646.
5. Lagergren J, Ye W, Ekbom A. Intestinal cancer after cholecystectomy: is bile involved in carcinogenesis?. Gastroenterology 2001; 121: 542–547.
6. Anderson KE, Mack TM, Silverman DT. Pancreatic cancer. In Schottenfeld D, Fraumeni JF, Jr, Cancer Epidemiology and Prevention, 3rd edition. New York: Oxford University Press 2006; 721–762.
7. Giovannucci E, Wu K. Schottenfeld D, Fraumeni JF, Jr. Cancers of the colon and rectum. Cancer Epidemiology and Prevention 3rd edition. New York: Oxford University Press 2006; 809–829.
8. Hsing AW, Rashid A, Devesa SS, Fraumeni JF, Jr. Biliary tract cancer. In Schottenfeld D, Fraumeni JF, Jr, Cancer Epidemiology and Prevention, 3rd edition. New York: Oxford University Press 2006; 787–800.
9. Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. Int J Cancer 2006; 118: 1591–1602.
10. Lagergren J, Mattsson F. Cholecystectomy and risk of laryngeal and pharyngeal cancer. Int J Cancer 2011 June 29 [epub ahead of print], .
11. Goldacre MJ, Abisgold JD, Seagroatt V, Yeates D. Cancer after cholecystectomy: record-linkage cohort study. Br J Cancer 2005; 92: 1307–1309.
12. Ruhl CE, Everhart JE. Gallstone disease is associated with increased mortality in the United States. Gastroenterology 2011; 140: 508–516.
13. Garavello W, Foschi R, Talamini R et al. Family history and the risk of oral and pharyngeal cancer. Int J Cancer 2008; 122: 1827–1831.
14. Levi F, Pasche C, La Vecchia C et al. Food groups and risk of oral and pharyngeal cancer. Int J Cancer 1998; 77: 705–709.
15. D'Avanzo B, La Vecchia C, Talamini R, Franceschi S. Anthropometric measures and risk of cancers of the upper digestive and respiratory tract. Nutr Cancer 1996; 26: 219–227.
16. Bosetti C, La Vecchia C, Talamini R et al. Food groups and risk of squamous cell esophageal cancer in northern Italy. Int J Cancer 2000; 87: 289–294.
17. Levi F, Pasche C, Lucchini F et al. Food groups and oesophageal cancer risk in Vaud, Switzerland. Eur J Cancer Prev 2000; 9: 257–263.
18. La Vecchia C, D'Avanzo B, Negri E et al. Attributable risks for stomach cancer in northern Italy. Int J Cancer 1995; 60: 748–752.
19. Lucenteforte E, Scita V, Bosetti C et al. Food groups and alcoholic beverages and the risk of stomach cancer: a case-control study in Italy. Nutr Cancer 2008; 60: 577–584.
20. Negri E, Bosetti C, La Vecchia C et al. Risk factors for adenocarcinoma of the small intestine. Int J Cancer 1999; 82: 171–174.
21. La Vecchia C, D'Avanzo B, Negri E, Franceschi S. History of selected diseases and the risk of colorectal cancer. Eur J Cancer 1991; 27: 582–586.
22. Negri E, Bosetti C, La Vecchia C et al. Allergy and other selected diseases and risk of colorectal cancer. Eur J Cancer 1999; 35: 1838–1841.
23. Altieri A, Pelucchi C, Talamini R et al. Cholecystectomy and the risk of colorectal cancer in Italy. Br J Cancer 2004; 90: 1753–1755.
24. La Vecchia C, Negri E, Cavalieri d'Oro L, Franceschi S. Liver cirrhosis and the risk of primary liver cancer. Eur J Cancer Prev 1998; 7: 315–320.
25. Polesel J, Zucchetto A, Montella M et al. The impact of obesity and diabetes mellitus on the risk of hepatocellular carcinoma. Ann Oncol 2009; 20: 353–357.
26. Lipworth L, Zucchetto A, Bosetti C et al. Diabetes mellitus, other medical conditions and pancreatic cancer: a case-control study. Diabetes Metab Res Rev 2011; 27: 255–261.
27. Bosetti C, La Vecchia C, Talamini R et al. Food groups and laryngeal cancer risk: a case-control study from Italy and Switzerland. Int J Cancer 2002; 100: 355–360.
28. Franceschi S, la Vecchia C, Negri E et al. Breast cancer risk and history of selected medical conditions linked with female hormones. Eur J Cancer 1990; 26: 781–785.
29. Talamini R, Franceschi S, Favero A et al. Selected medical conditions and risk of breast cancer. Br J Cancer 1997; 75: 1699–1703.
30. Lucenteforte E, Bosetti C, Talamini R et al. Diabetes and endometrial cancer: effect modification by body weight, physical activity and hypertension. Br J Cancer 2007; 97: 995–998.
31. Parazzini F, Moroni S, La Vecchia C et al. Ovarian cancer risk and history of selected medical conditions linked with female hormones. Eur J Cancer 1997; 33: 1634–1637.
32. Tavani A, Gallus S, La Vecchia C et al. Aspirin and ovarian cancer: an Italian case-control study. Ann Oncol 2000; 11: 1171–1173.

33. Talamini R, Franceschi S, Dal Bo V, Monfardini S. Pattern and determinants of diagnostic interval in cancers of the prostate, bladder and kidney. Tumori 1991; 77: 350–354.
34. Bravi F, Scotti L, Bosetti C et al. Self-reported history of hypercholesterolaemia and gallstones and the risk of prostate cancer. Ann Oncol 2006; 17: 1014–1017.
35. Zucchetto A, Dal Maso L, Tavani A et al. History of treated hypertension and diabetes mellitus and risk of renal cell cancer. Ann Oncol 2007; 18: 596–600.
36. Breslow NE, Day NE. The analysis of case-control studies. In Statistical Methods in Cancer Research, Vol. 1, Lyon, France: IARC Science Publications 1980.
37. Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008–2012.
38. Ross RK, Hartnett NM, Bernstein L, Henderson BE. Epidemiology of adenocarcinomas of the small intestine: is bile a small bowel carcinogen?. Br J Cancer 1991; 63: 143–145.
39. Lowenfels AB. Gallstones and the risk of cancer. Gut 1980; 21: 1090–1092.
40. Li Q, Kuriyama S, Kakizaki M et al. History of cholelithiasis and the risk of prostate cancer: the Ohsaki Cohort Study. Int J Cancer 2011; 128: 185–191.
41. Freeman MR, Solomon KR. Cholesterol and prostate cancer. J Cell Biochem 2004; 91: 54–69.
42. Cyrus-David MS, Weinberg A, Thompson T, Kadmon D. The effect of statins on serum prostate specific antigen levels in a cohort of airline pilots: a preliminary report. J Urol 2005; 173: 1923–1925.
43. Moyad MA, Merrick GS, Butler WM et al. Statins, especially atorvastatin, may favorably influence clinical presentation and biochemical progression-free survival after brachytherapy for clinically localized prostate cancer. Urology 2005; 66: 1150–1154.
44. Shannon J, Tewoderos S, Garzotto M et al. Statins and prostate cancer risk: a case-control study. Am J Epidemiol 2005; 162: 318–325.
45. Bergstrom A, Hsieh CC, Lindblad P et al. Obesity and renal cell cancer—a quantitative review. Br J Cancer 2001; 85: 984–990.
46. Dal Maso L, Zucchetto A, Tavani A et al. Renal cell cancer and body size at different ages: an Italian multicenter case-control study. Am J Epidemiol 2007; 166: 582–591.
47. Giovannucci E, Colditz GA, Stampfer MJ. A meta-analysis of cholecystectomy and risk of colorectal cancer. Gastroenterology 1993; 105: 130–141.
48. Reid FD, Mercer PM, Harrison M, Bates T. Cholecystectomy as a risk factor for colorectal cancer: a meta-analysis. Scand J Gastroenterol 1996; 31: 160–169.
49. Shao T, Yang YX. Cholecystectomy and the risk of colorectal cancer. Am J Gastroenterol 2005; 100: 1813–1820.
50. Lin HL, Lin HC, Lin CC. Increased risk of colorectal cancer among patients with biliary tract inflammation: a 5-year follow-up study. Int J Cancer 2011; 128: 447–452.
51. Ko AH, Wang F, Holly EA. Pancreatic cancer and medical history in a population-based case-control study in the San Francisco Bay Area, California. Cancer Causes Control 2007; 18: 809–819.
52. Freedman J, Lagergren J, Bergstrom R et al. Cholecystectomy, peptic ulcer disease and the risk of adenocarcinoma of the oesophagus and gastric cardia. Br J Surg 2000; 87: 1087–1093.
53. Freedman J, Ye W, Naslund E, Lagergren J. Association between cholecystectomy and adenocarcinoma of the esophagus. Gastroenterology 2001; 121: 548–553.
54. Fall K, Ye W, Nyren O. Risk for gastric cancer after cholecystectomy. Am J Gastroenterol 2007; 102: 1180–1184.
55. Adami HO, Meirik O, Gustavsson S et al. Cholecystectomy and the incidence of breast cancer: a cohort study. Br J Cancer 1984; 49: 235–239.
56. Lagergren J, Ye W, Ekbom A. No increased risk of breast cancer after cholecystectomy. Int J Cancer 2000; 88: 679–681.
57. Shibata A, Ogimoto I, Kurozawa Y et al. Past medical history and risk of death due to hepatocellular carcinoma, univariate analysis of JACC study data. Kurume Med J 2003; 50: 109–119.
58. Morimoto LM, Newcomb PA, Hampton JM, Trentham-Dietz A. Cholecystectomy and endometrial cancer: a marker of long-term elevated estrogen exposure?. Int J Gynecol Cancer 2006; 16: 1348–1353.
59. Bosetti C, Tavani A, Negri E et al. Reliability of data on medical conditions, menstrual and reproductive history provided by hospital controls. J Clin Epidemiol 2001; 54: 902–906.