

Gallstones and incident colorectal cancer in a large pan-European cohort study

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Abbreviations used: BMI: body mass index; CRC: colorectal cancer; EPIC: European Prospective Investigation into Cancer and Nutrition; HR: hazard ratio; CI: confidence interval; HRT: hormone replacement therapy; SEER: Surveillance, Epidemiology and End Results

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Abstract

Gallstones, a common gastrointestinal condition, can lead to several digestive complications and can result in inflammation. Risk factors for gallstones include obesity, diabetes, smoking and physical inactivity, all of which are known risk factors for colorectal cancer (CRC), as is inflammation. However, it is unclear whether gallstones are a risk factor for CRC. We examined the association between history of gallstones and CRC in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, a prospective cohort of over half a million participants from ten European countries. History of gallstones was assessed at baseline using a self-reported questionnaire. The analytic cohort included 334,986 participants; a history of gallstones was reported by 3,917 men and 19,836 women, and incident CRC was diagnosed among 1,832 men and 2,178 women (mean follow-up: 13.6 years). Hazard ratios (HR) and 95% confidence intervals (CI) for the association between gallstones and CRC were estimated using Cox proportional hazards regression models, stratified by sex, study centre, and age at recruitment. The models were adjusted for body mass index, diabetes, alcohol intake, and physical activity. A positive, marginally significant association was detected between gallstones and CRC among women in multivariable analyses (HR=1.14, 95%CI 0.99–1.31, $p=0.077$). The relationship between gallstones and CRC among men was inverse but not significant (HR=0.81, 95%CI 0.63–1.04, $p=0.10$). Additional adjustment for details of reproductive history or waist circumference yielded minimal changes to the observed associations. Further research is required to confirm the nature of the association between gallstones and CRC by sex.

1 Introduction

2 Gallstone disease is one of the most common gastrointestinal diseases. Within Europe, the
3 estimated prevalence of gallstone disease ranges from 5.9% in Italy to 21.9% of all adults in Norway.¹
4 Gallstones are formed of cholesterol, bilirubin, and calcium salts, with smaller amounts of protein
5 and other materials.² Women are at greater risk of gallstones than men: exposure to higher levels of
6 oestrogen, through pregnancy, hormone therapy, or oestrogen-containing hormonal contraception,
7 may increase biliary cholesterol levels and decrease gallbladder movement, resulting in gallstone
8 formation.² Additional risk factors for gallstones include increasing age, family history of gallstones,
9 ethnicity, high serum cholesterol levels, obesity, physical inactivity, smoking, and high energy intake,
10 whereas lower risk has been found for higher intakes of dietary fibre and calcium, and moderate
11 consumption of coffee and alcohol.^{3,4} The majority of gallstones are asymptomatic; a prospective
12 study of Danish adults estimated only 20% of gallstones were of clinical significance.⁵ However, the
13 complications associated with gallstones include biliary colic, cholecystitis, cholangitis, biliary
14 pancreatitis, and gallbladder cancer;^{6,7} the inflammation associated with these conditions may also
15 be associated with greater risk of colorectal cancer (CRC).⁸ Altered bile flow may be due to either
16 gallstones themselves⁷ or gallstone treatment (cholecystectomy).⁹ A meta-analysis of case-control
17 and cohort studies reported that higher faecal levels of chenodeoxycholic acid were measured
18 among CRC cases, although no such differences for total bile acids or other bile acid subtypes were
19 detected.¹⁰ Gallstones have also been associated with incident diabetes¹¹, a risk factor for
20 developing CRC.¹²

21 Current epidemiologic evidence on the association between gallstones and CRC is inconclusive, with
22 results indicating either no association,¹³ a positive association^{14,15} or inconsistent associations by CRC
23 subsite.^{16,17} The available studies differ notably in sample size and adjustment for covariates: large
24 population-based cohorts had high numbers of gallstone cases (e.g. 42,000)¹⁵ but were limited to
25 clinical covariate data, whereas studies with more extensive data on potential confounders (e.g. diet,

alcohol, anthropometry, serum lipids) had fewer gallstone cases (e.g. <600).¹⁶ Additionally, differences in the relationship between gallstones and CRC by sex require further study, as women are at higher risk of both gallstones³ and developing more aggressive right-sided (proximal) colon cancer¹⁸ than men. Furthermore, previous case-control studies have reported differences in the association between gallstones and CRC by sex.¹⁹ Therefore, the aim of this research was to examine gallstones and CRC risk in the large European Prospective Investigation into Cancer and Nutrition (EPIC) study, with information on a wide range of potentially confounding variables collected at baseline.

Methods

Study participants

From 1992-2000, the EPIC study recruited 521,324 adults (aged 25-70 years) from Denmark, France, Germany, Greece, Italy, Norway, the Netherlands, Spain, Sweden, and the United Kingdom.²⁰ Questionnaires on demographics, diet and other lifestyle factors were completed by participants at baseline. All EPIC centres measured height, weight, waist, and hip circumference except France, Norway, and Oxford, where they were self-reported. Dietary intake over the past year was assessed at baseline through country-specific questionnaires.²⁰ Self-reported history of diagnosed gallstones (categorical: yes, no or unknown) and age at diagnosis (continuous) of gallstones were obtained from the health and lifestyle questionnaire administered at recruitment.

Each participant was followed from baseline to cancer diagnosis, emigration, loss to follow-up, death, or end of study follow-up (which varied by centre from June 2008-December 2013), whichever came first.

The study was approved by the review board of the International Agency for Research on Cancer and national review boards, and all participants provided consent for the retention of acquired data and follow-up for incidence of cancer and death.²⁰

Identification of CRC cases

Cancer registries were used to identify cancer cases in seven of the countries participating in EPIC (Denmark, Italy, The Netherlands, Norway, Spain, Sweden and the UK). In the three remaining countries (France, Germany and Greece), a combination of methods was used including health insurance records, cancer and pathology registries, and active follow-up of the study subjects and their next of kin relatives.

The site of the tumour was coded using the 'International Statistical Classification of Diseases and Related Health Problems 10th Revision' (ICD-10). For this analysis, we examined incident CRCs, defined as: colon cancers (C18), rectosigmoid junction cancers (C19) and rectal cancers (C20). When looking at colon and rectal cancer separately, the definition of rectal cancer included cancers in the rectosigmoid junction and the rectum. Proximal colon cancer included tumours of the caecum, appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure (C18.0–18.5). Distal colon cancer included tumours in the descending and sigmoid colon (C18.6–18.7). Overlapping lesions of the colon (C18.8) and colon NOS (not otherwise specified, C18.9) were not classified as either proximal or distal.

Exclusions

Data related to gallstones were not collected in Sweden and Norway, therefore, participants from these countries were not included in the analysis (n= 91,022). Among the remaining eight countries, participants who were missing data on gallstones (n=74,744), and those who reported being unsure of gallstone diagnosis (n=1,275) were excluded from the analysis. Additionally, participants who were

missing data on length of follow-up (n=22,642) and/or potential confounders (diabetes, alcohol intake, and physical activity, n = 42,948) were also excluded; the selection of these covariates is described below. The present analysis included data from 334,986 participants.

Statistical Analyses

Cox proportional regression models were used to estimate hazards ratios (HRs) and 95% confidence intervals (CIs). Person years of follow-up since recruitment was the primary time variable in all models. All models included age at recruitment as a covariate, and with study centre, sex, and age at recruitment (one-year intervals) as stratum variables.

The proportional hazards assumption was examined using a time interaction model, with the consistency of the association between gallstones and CRC during follow-up estimated by splitting follow-up time in 5-year bands, and fitting interactions between the exposure and bands of follow-up time. Covariates for the multivariable model were evaluated individually to determine if they changed the beta value for the association between gallstones and CRC by greater than 10%, relative to a model without the covariate of interest. The evaluation of potential confounders was restricted to participants without missing data on covariates of interest. The variables tested included: education level (none, primary school completed, technical/professional school, secondary school, or tertiary education); body mass index (BMI, kg/m², continuous); smoking status (never, former, current smoker), alcohol intake (grams/day: 0, >0 – 6, >6-12, >12-24, >24-60, >60 – 96, >96), physical activity (Cambridge Index: inactive, moderately inactive, moderately active, active), family history of CRC (yes, no), diabetes (yes, no), hyperlipidaemia (yes, no), red meat intake (g/day, continuous), processed meat intake (g/day, continuous), total fibre intake (g/day, continuous), total fat intake (g/day, continuous), and total cholesterol intake (mg/day, continuous). Among women, variables reflecting reproductive history were also assessed: history of full term pregnancy (yes, no), ever use of oral contraceptive pill (yes, no), menopausal status (premenopausal, postmenopausal, perimenopausal, surgical

menopause), ever breastfeeding (yes, no), and ever used hormone replacement therapy (HRT, yes, no). Among these variables, BMI, alcohol intake, diabetes, and physical activity met the criteria for inclusion in the multivariable models. BMI may be related to CRC through multiple mechanisms, including factors related to gallstone development, therefore BMI was included as an additional adjustment (Model 3) separate to the other above-listed covariates (Model 2).

Among participants with a history of gallstones, the models were re-run to examine the effect of age at gallstone diagnosis (comparing above/below median age at diagnosis). A lag analysis was performed to investigate the possibility of reverse causation: the Cox regression models were re-run after excluding those who had less than two person-years of follow-up.

Tests for interaction were conducted using multiplicative model terms. For binary variables, the p-value for interactions was obtained from the analytic model; for categorical variables, p-values were obtained from likelihood ratio tests comparing nested models (with and without the interaction term). STATA (version 13) was used for all analyses.

Results

Baseline characteristics

Among the 334,986 participants, 23,753 (7.1%) had gallstones (3,917 in men and 19,836 in women). Compared to those without a history of gallstones, men and women with a history of gallstones were more likely to be older, have a higher BMI, have been diagnosed with diabetes, have been diagnosed with hyperlipidaemia, and were more likely to be classified as physically inactive (Table 1). Among women, those with a history of gallstones reported lower levels of tertiary education, less use of oral contraceptives, a higher proportion of full term pregnancies, and were more likely to be post-

menopausal than those without a history of gallstones. The median age at diagnosis of gallstones was 46 years among men and 39 years among women.

Incident CRC was diagnosed among 1,832 men [1102 colon (440 distal, 536 proximal), 730 rectal] and 2,178 women [1,485 colon (721 distal, 626 proximal), 693 rectal]. The mean follow-up time was 13.6 years (SD 3.9).

Gallstones and CRC risk

Preliminary analyses yielded evidence of an interaction between sex and gallstones in relation to CRC risk ($p=0.036$); therefore, subsequent analyses were conducted separately for men and women. Among women, gallstones were positively associated with the risk of CRC in the age- and centre-adjusted model (model 1: HR 1.15, 95%CI 1.00-1.33, $p=0.045$); further adjustment for BMI, diabetes, alcohol intake, and physical activity attenuated the significance of the association (model 3: HR 1.14, 95% CI 0.99 – 1.31, $p=0.077$). Among men, the relationship between gallstones and CRC was inverse but not statistically significant (Table 2).

Gallstones were associated with greater colon cancer risk among women (HR=1.20, 95%CI: 1.02-1.41; $p=0.032$); as with CRC, further adjustment attenuated the significance of the association (model 3: HR 1.18, 95%CI 1.00 – 1.39, $p=0.054$). There were no associations detected between gallstones and rectal cancer among women, nor between gallstones and colon cancer among men. Among men, the relationship between gallstones and rectal cancer was inverse but not significant (model 2: HR 0.69, 95% CI 0.44 – 1.07, $p=0.10$); further adjustment for BMI yielded marginal significance (model 3: HR 0.67, 95% CI 0.43 – 1.05, $p=0.078$).

Among women, no interactions were observed between gallstones, risk of colon cancer and ever use of HRT ($p=0.41$), ever use of oral contraceptives ($p=0.36$), menopausal status ($p=0.24$), history of full-term pregnancy ($p=0.81$), or history of breastfeeding ($p=0.13$). The associations between gallstones

and distal colon cancer [men, HR 0.85 (95% CI 0.53 – 1.38); women, HR 1.17 (95 %CI 0.93 – 1.49)] were similar to those observed for proximal colon cancer [men, HR 0.91 (95% CI 0.59 – 1.42); women HR 1.21 (95% CI 0.94 – 1.55)], adjusted for covariates, model 3. Adjusting for reproductive history among women yielded minimal changes to the observed associations for gallstones and CRC (HR 1.17, 95%CI 0.99-1.31), colon cancer (HR 1.18, 95% CI 1.00 – 1.39), and rectal cancer (HR 1.05, 95% CI 0.79 – 1.38). Similarly, a post-hoc sensitivity analysis to additionally adjust for waist circumference among female participants with these data available (n=186,198, including 1,290 colon cancer cases) yielded HR values within 10% of those from model 3, Table 2.

Tests for interaction by country or BMI yielded predominantly null results for CRC, colon cancer, and rectal cancer among men and women; as an exception, a marginally significant interaction was detected for rectal cancer and country among women (Table 2).

Comparison by median age at diagnosis, did not yield any significant associations with CRC, colon or rectal cancer risk (Table 2). Excluding participants with less than two years of follow-up [n=5,479 participants, including 322 CRC cases (144 men, 178 women)] yielded results comparable to those of the main analysis (models 1 and 2, Table 2) for CRC, colon cancer, and rectal cancer (data not shown). No significant variation was detected across 5-year bands of follow-up for CRC, colon cancer or rectal cancer (Supplementary Table 1).

Discussion

In this large multi-country European study, a history of gallstones was modestly associated with CRC in general and colon cancer specifically, in women but not in men. Adjustment for reproductive history did not account for the marginal association detected among women. Gallstones were not associated with rectal cancer among women; in contrast, effect sizes among men were suggestive of an inverse association between gallstones and rectal cancer.

1 There is a limited literature on gallstones and CRC for comparison with the present results. A necropsy
2 analysis found that there was a positive association between gallstones and CRC in females only,
3 particularly for right-sided CRC (odds ratio 6.79, 95%CI 1.14-46.46).²¹ Furthermore, an association
4 between gallstones and CRC was found only among women in a meta-analysis of 28 case-control
5 studies conducted in Chinese populations.¹⁹ In contrast, screen-detected gallstones were associated
6 with right-sided colon cancer in the general population of Copenhagen, but no interaction by sex was
7 found.¹⁶ In the large Surveillance, Epidemiology and End Results (SEER) database, gallstones were
8 inversely associated with rectal cancer, marginally associated with lower risk of distal colon cancer,
9 and not associated with CRC overall.¹⁷ However, sex-specific analyses or tests for interaction by sex
10 were not reported for SEER, and only age, sex, and diabetes were included as covariates.¹⁷ We are
11 not aware of studies reporting specifically on gallstones and rectal cancer among men. Although
12 speculative, a potential pathway for the inverse association between gallstones and rectal cancer
13 among men could be through bilirubin, which is typically higher among men, contributes to the
14 formation of gallstones and has been associated with lower risk of CRC in some²², but not all²³,
15 previous studies. Among women, the marginal association between gallstones and colon cancer may
16 reflect the influence sex hormones²⁴, which may not have been fully adjusted for with the available
17 covariates. Further research in large cohort studies with detailed covariate data is needed to confirm
18 the relationship between gallstones and CRC.

19
20 Strengths of the present analysis included the large size and prospective design of EPIC which
21 permitted stratification by sex and eliminated the potential for recall bias. To date, this is the largest
22 cohort study that has included anthropometric measurements and extensive health and lifestyle
23 questionnaire data, which permitted exploration of a wide range of potential causes of gallstones.
24 Multivariable models were presented with and without adjustment for BMI to examine the
25 relationship between gallstones and CRC risk independent of obesity, as gallstones may be on the

causal pathway between obesity and CRC. However, data on history of gallstones was missing from 17% of the EPIC participants, data on cholecystectomy and other treatment types was not collected, and data on age at diagnosis was limited. Data was collected only at baseline, therefore data on incident gallstones or treatment after baseline was not available. It has been estimated that only 18% of all gallstones will be clinically detected during long-term follow-up, ⁵ therefore those reporting a history of gallstones in EPIC were likely of greater clinical severity, and potentially represent a biased subset of potential gallstone cases. Additionally, those who experienced gallstones and were diagnosed with CRC prior to recruitment in EPIC would not have been included in the present analysis. The effect sizes detected were modest and the potential for residual confounding cannot be excluded. Lastly, self-reported gallstone history may have resulted in some misclassification, however this is more likely to have attenuated associations towards the null.

In conclusion, the current analysis suggests there may be an increased risk of colon cancer among women with a history of gallstones. These results suggest that gallstones may reflect pathways that are relevant for CRC such as bilirubin/bile acid metabolism, sex hormones and cholesterol. Future research should focus on confirming if such associations exist in other populations, and if so, identifying the underlying mechanisms that could account for such variation by CRC sub-site and sex.

Novelty and Impact (max 75 words)

Gallstones may be associated with colorectal cancer, but few longitudinal studies have been conducted. In our large European study, a marginally significant, positive association between gallstones and colorectal cancer among women was found. Further research is required to clarify the nature of this association.

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Data sharing statement: For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at <http://epic.iarc.fr/access/index.php> .

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