Risk of gastrointestinal cancers in patients with cystic fibrosis: a systematic review and meta-analysis

Akihiro Yamada, Yuga Komaki, Fukiko Komaki, Dejan Micic, Samantha Zullow, Atsushi Sakuraba

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Section of Gastroenterology, Hepatology and Nutrition, Department of Medicine, The University of Chicago, Chicago, IL, USA (A Yamada MD, Y Komaki MD, F Komaki MD, D Micic MD, A Sakuraba MD); **Department of Internal Medicine, Boston Medical Center, Boston, MA, USA** (S Zullow MD); **Section of Gastroenterology, Department of Internal Medicine, Toho University, Sakura Medical Center, Sakura, Japan** (A Yamada); **Section of Gastroenterology, Fujimoto General Hospital, Miyakonojo, Japan** (Y Komaki); **and Digestive and Life-style Diseases, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan** (F Komaki)

Correspondence to:
Dr Atsushi Sakuraba, Section of Gastroenterology, Hepatology and Nutrition, Department of Medicine, The University of Chicago, Chicago, IL 60637, USA
asakurab@medicine.bsd.uchicago.edu

Summary

Background The management and life expectancy of patients with cystic fibrosis have improved substantially in the past three decades, which has resulted in an increased number of these patients being diagnosed with malignancies. Our aim was to assess the risk of gastrointestinal cancers in patients with cystic fibrosis.

Methods In this systematic review and meta-analysis, we searched PubMed, MEDLINE, Google Scholar, Scopus, Embase, and Cochrane databases with no language restrictions for studies published from inception of the databases to Aug 1, 2017, assessing the risk of gastrointestinal cancers in patients with cystic fibrosis. We also searched abstracts from scientific meetings and the bibliographies of identified articles for additional references. Studies were included if they reported the standardised incidence ratio (SIR) or incidence ratio per person-years. No exclusion criteria with regard to patient characteristics (age, sex, comorbidities, cystic fibrosis mutation type), study setting (location and time period), or method of reporting cancer diagnoses were applied. The primary outcome was risk of gastrointestinal cancer and site-specific gastrointestinal cancers in patients with cystic fibrosis compared with the general population. Pooled summary estimates were calculated using a random-effects model, and subgroup analyses were done to establish whether risk of gastrointestinal cancer varied according to patient lung transplant status. The study is registered with PROSPERO, number CRD42017075396.

Findings Our search identified 95 681 records, of which six cohort studies including 99 925 patients (544 695 person-years) were eligible for the meta-analysis. The overall risk of gastrointestinal cancer was significantly higher in patients with cystic fibrosis than in the general population (pooled SIR 8·13, 95% CI 6·48–10·21; p<0·0001; log SIR 2·10, 95% CI 1·87–2·32; p<0·0001, I^2=93·93%). Subgroup analyses showed that the risk of gastrointestinal cancer among patients with cystic fibrosis who had a lung transplant was increased compared with that of patients who did not receive a transplant (pooled SIR 21·13, 95% CI 14·82–30·14; p<0·0001; log SIR 3·05, 95% CI 2·70–3·41; p<0·0001, I^2=28·52% *vs* pooled SIR 4·18, 3·10–5·62; p<0·0001; log SIR 1·43, 1·13–1·73; p<0·0001, I^2=22·66%). The risk for the following site-specific cancers was also significantly increased in patients with cystic fibrosis compared with the general population: small bowel cancer (pooled SIR 18·94, 95% CI 9·37–38·27; p<0·0001; log SIR 2·94, 95% CI 2·24–3·64; p<0·0001, I^2=38·61%), colon cancer (10·91, 8·42–14·11; p<0·0001; log SIR 2·39, 2·13–2·65; p<0·0001, I^2=88·09%), biliary tract cancer (17·87, 8·55–37·36; p<0·0001; log SIR 2·88, 2·15–3·62; p<0·0001, I^2=10·16%), and pancreatic cancer (6·18, 1·31–29·27; p=0·022; log SIR 1·82, 0·27–3·38; p<0·0001, I^2=62·57%).

Interpretation Our study suggests that patients with cystic fibrosis had a significantly increased risk of gastrointestinal cancer compared with the general population, including small bowel, colon, biliary tract, and pancreatic cancers. These findings highlight the need to develop individualised screening strategies for site-specific gastrointestinal cancers in patients with cystic fibrosis.

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Introduction

Cystic fibrosis is an autosomal recessive genetic disease, with an incidence of around 1 in 2500 livebirths in white populations, that is caused by mutations in both copies of the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR).[1] The resultant non-functional CFTR protein leads to restricted transport of chloride ions across epithelial cells of the respiratory, hepatobiliary, gastrointestinal, and reproductive tracts, and the pancreas.[2,3] This abnormal chloride transport is accompanied by decreased transport of sodium and water across the epithelial membrane of the target tissues, resulting in dehydrated and viscous secretions, which lead to luminal damage and obstructions in the affected organs.[2,3] Morbidity and mortality of the disease are predominantly caused by progressive respiratory complications.[3] Improvements in therapies through multidisciplinary care during the past three decades directed at airway clearance, management of infections, and nutritional supplementation, and the introduction of lung transplantation for some patients, have increased the life expectancy of patients with cystic

Research in context

Evidence before this study

Before 1980, most patients with cystic fibrosis died during infancy. As a result of multidisciplinary management, including treatment with pancreatic enzymes, antipseudomonal antibiotics, and lung transplant, the life expectancy of patients with cystic fibrosis has improved substantially, reaching age 50 years and older in some developed countries. Because an increasing number of patients with cystic fibrosis are surviving into adulthood, the number of patients being diagnosed with gastrointestinal malignancies has increased. We searched PubMed on April 28, 2014, for studies investigating the risk of gastrointestinal cancer in patients with cystic fibrosis using the search terms "cystic fibrosis[title]" and "cancer[title]", with no langauge or date restrictions, which yielded more than 40 case reports and eight cohort studies, but no systematic reviews or meta-analyses.

Added value of this study

To the best of our knowledge, this meta-analysis is the first to report the risk of gastrointestinal cancers in patients with cystic fibrosis. In January, 2018, a guideline was published recommending screening for colorectal cancer in patients with cystic fibrosis. However, no recommendations have been made regarding other gastrointestinal cancers because comprehensive data is scarce. We report that the overall risk of gastrointestinal cancer and site-specific cancers, including small bowel, colon, biliary tract, and pancreatic cancer, is significantly higher in patients with cystic fibrosis than in the general population. Furthermore, we found that the risk of gastrointestinal cancer is further increased in patients with cystic fibrosis who had an organ transplant compared with those who did not.

Implications of all the available evidence

The results of our meta-analysis support the recently published guidelines recommending screening for colorectal cancer in patients with cystic fibrosis. Considering the continuous improvement in life expectancy observed in patients with cystic fibrosis, we propose that screening strategies for other gastrointestinal cancers need to be developed urgently for these patients.

fibrosis to age 50 years and older in some developed countries.[2–7]

By 2025, the number of patients with cystic fibrosis reaching adulthood in developed countries is expected to increase by 70%,[2] thus the diagnosis of concomitant disorders will create new clinical needs for these patients. The number of patients with cystic fibrosis diagnosed with malignancies has increased since the 1980s.[8] Several cohort studies have assessed the risk of gastrointestinal cancer in patients with cystic fibrosis. In a study published in 1991, Neglia and colleagues[9] found no increased risk of gastrointestinal cancers in a cohort of 712 patients with cystic fibrosis when compared with an age-matched and sex-matched national database. However, in 1993, Sheldon and colleagues[10] reported that the incidence of malignant tumours was four times higher in a cohort of 412 patients with cystic fibrosis than in the general population. Because small, individual cohort studies might be underpowered to identify the incidence of gastrointestinal cancer in patients with cystic fibrosis, a comprehensive study is required to clarify the risk of site-specific gastrointestinal malignancies in this population, and to assess whether risk of gastrointestinal cancer increases with age. Therefore, we did a systematic review and meta-analysis to investigate the risk of gastrointestinal cancers in patients with cystic fibrosis compared with the general population.

Methods

Search strategy and selection criteria

We did this systematic review and meta-analysis according to prespecified criteria,[11] and followed the PRISMA[12] and MOOSE[13] guidelines for the reporting of meta-analyses.

We searched PubMed, MEDLINE, Google Scholar, Scopus, Embase, and the Cochrane electronic database for studies published from each database's inception to Aug 1, 2017, assessing the risk of gastrointestinal cancer in patients with cystic fibrosis, using the following search terms: "cystic fibrosis", "cancer", "malignancy", "esophageal cancer", "gastric cancer"', "pancreatic cancer", "liver cancer", "small bowel cancer", "colon cancer", and "rectal cancer". The full search strategies used for each database are described in the appendix (pp 1,2). For Google Scholar, only 1000 articles were reviewed at each search because this is the maximum number of results provided by the database. We supplemented database searching by screening all available abstracts from the following conferences: Digestive Disease Week, American College of Gastroenterology, United European Gastroenterology week, Amercian Society of Clinical Oncology Annual Meeting, North American Cystic Fibrosis Conference Annual Meeting, European Cystic Fibrosis Conference, and the American Thoracic Society International Conference. We also searched the bibliographies of identified articles or abstracts for additional references.

See Online for appendix

Articles were eligible for inclusion if they reported the risk of gastrointestinal cancer in patients with cystic fibrosis, in terms of standardised incidence ratio (SIR) or incidence ratio per person-years. We included only incidence rates and SIR in our analyses as an indirect method of adjustment for age and sex. No restrictions

regarding age, sex, comorbidities, cystic fibrosis gene mutation type, duration or location of the study, or method of reporting cancer diagnosis were applied. Our search had no language restrictions. Articles in languages other than English were translated if necessary.

Two authors (SZ and AS) independently screened the title and abstract of potentially eligible articles according to this eligibility criteria and any duplicates were excluded. Areas of disagreement or uncertainty were resolved by consensus. When the eligibility criteria were met on the basis of title and abstract screening, the full text was retrieved for data extraction. At this stage, we excluded studies that did not include patients with cystic fibrosis or did not report the SIR or incidence ratio per person-years.

Data extraction

Two authors (SZ and AS) independently extracted the following data in duplicate from all eligible studies using a predefined data extraction form: study characteristics (study design, year of publication, and corresponding author), study setting (location and period), study population characteristics (sample size, age of the patients, comorbidities, transplant status), and outcomes (duration of follow-up and cancer incidence per cancer type). Diagnosis and confirmation of cystic fibrosis and gastrointestinal cancer were done according to the criteria of each study. The corresponding authors of the studies, or the national registry databases used as a data source in the original studies, were consulted for additional information if required.

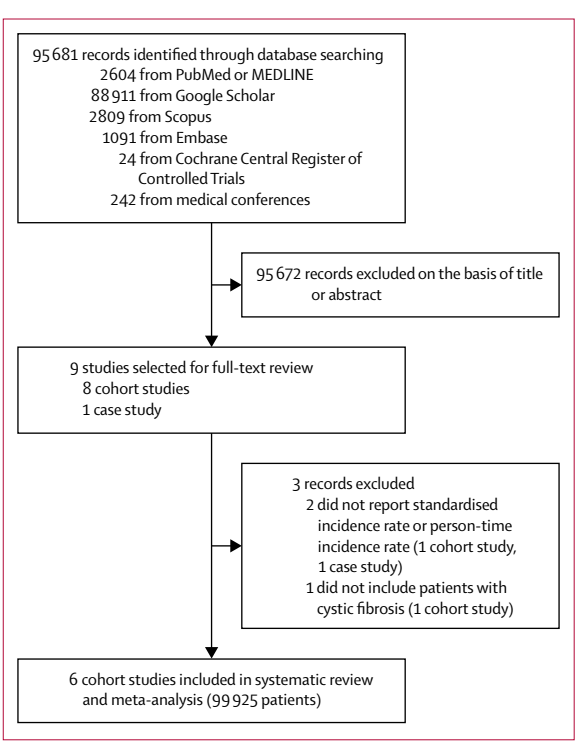

Figure 1: **Flow chart of study selection**

Outcomes

The primary outcome measure was the incidence of gastrointestinal cancer and site-specific cancers in patients with cystic fibrosis, reported as SIRs. The SIR for each study was defined as the reported number of patients diagnosed with cancer compared with the expected number of patients with cancer. The expected number of patients with cancer was determined using age-specific, sex-specific, and race-specific incidence rates from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute,[14,15] age and sex adjusted risk in the general population of each inlcuded country,[16] age and sex matched incidence rates for the general Swedish population,[17] and age, sex, and race adjusted risk from the US regional registry.[18]

Additional outcomes were the incidence per person-years of overall gastrointestinal and site-specific cancers, and the gastrointestinal cancer risk in patients with who had a transplant versus those who did not. Incidence per person-years was calculated from the number of people with cancer and person-year follow-up period when the value was not provided in the study. Person-years were calculated from the number of patients and overall follow-up period of the study for all patients when the value was not provided.[19] Subgroup analyses by lung transplant status were done separately for cohorts that included only transplanted patients and mixed cohorts including both non-transplant and transplant patients. If transplant status was not specified in the study (ie, a mixed cohort), these patients were considered to have not received a transplant for the purposes of analysis.

Statistical analysis

We used random-effects meta-analysis to assess the risk and incidence of gastrointestinal cancers in patients with cystic fibrosis. To calculate the pooled SIR of gastrointestinal cancers, we combined the extracted study-specific estimates and 95% CIs using the DerSimonian and Laird random-effects model.[20] We did mixed-effects subgroup meta-analyses on the basis of patient transplant status. A random-effects model[20] was first used to combine studies in defined subgroups by lung transplant status (transplant patients, non-transplant patients, and mixed cohorts [transplant and non-transplant patients]), assigning a relative weight to each study within the subgroup that summed to 100%. The relative weight of each study was calculated by inverse-variance weighting.[21] Subsequently, the Mantel-Haenzel method in a fixed-effects model was used to combine subgroups and estimate the overall effect.[22] Forest plots presented $\log_{10}$ SIRs.

For the calculation of the pooled incidence rate of gastrointestinal cancers per patient-year, the number of reported patients with gastrointestinal cancer and the number of person-years were extracted from each study. The incidence rate per person-years was transformed into a logit incident rate as previously described.[23,24] The logit values were converted back to incidence rate and 95% CI for forest plot presentation.[24]

The Newcastle-Ottawa Scale[25] was used to assess the risk of bias of the included studies. Studies with a rating of 6 or higher were considered high quality.[26,27]

We assessed heterogeneity across studies using the I^2 statistic (I^2 0–25%, mild heterogeneity; I^2 25–50%, moderate heterogeneity; I^2 >50%, large heterogeneity[28,29]). We also assessed heterogeneity across studies using Cochran's Q statistic with a significance level of $p<0\cdot10$.[30] We used Begg's and Egger's tests to assess the potential for small-study effects (publication bias), and represented the data in funnel plots to visualise possible asymmetry when three or more studies were available.[31,32] We also did cumulative meta-analyses ranked by year and influence analysis to assess the influence of each individual study in the pooled analysis results.

We did all statistical analyses using the Comprehensive Meta-Analysis Software (version 2.0; Biostat, Englewood, NJ, USA). All statistical tests, with the exception of the Q statistic, used a two-sided α value of 0·05 for significance.

This study is registered with PROSPERO, number CRD42017075396.

Role of the funding source

There was no funding source for this study. AY, SZ, and AS had full access to the raw data of the study and the corresponding author had final responsibility to submit for publication.

Results

Our literature search identified 95 681 records, of which 95 672 were excluded after initial screening of titles and abstracts. Nine full-text articles were assessed for eligibility (figure 1). Six studies, published between Nov 1, 1993, and Jan 16, 2017, including 99 925 patients (544 695 person-years) with cystic fibrosis that reported gastrointestinal cancer incidence, were included in the meta-analysis.[10,14–18] There was no inter-rater disagreement for the extracted data. The median Newcastle-Ottawa rating for the six studies included was 9 (IQR 7·8–9·0; appendix p 3). The population characteristics and outcomes of the included studies are summarised in table 1.

One[10] (17%) of six studies reported cancer incidence but not the SIR. Thus, the study was excluded from analyses of SIR, but was included in analyses of incidence ratio per person-years.

Four[15–17] (80%) of five studies that reported transplantation status included cohorts of non-transplant and transplant patients with cystic fibrosis, of which one

	Study period	Study location	Registry used	Age at enrollment, years*	Men	Women	Patients (patient-years)	Transplant patients	Mean age at gastrointestinal cancer diagnosis, years (SD)	Mean follow-up, years*	Observed cases of gastrointestinal cancer	Expected cases of gastrointestinal cancer	Gastrointestinal cancer SIR (95% CI)	Newcastle-Ottawa scale rating
Neglia et al (1995)[14]	1985–92	USA, Canada	CFF, CCFFR	Median 7 (range 0–64)	15 161 (53%)	13 350 (47%)	28 511 (164 764)	..	32·2 (12·6)	5·7	13	2·0	6·5 (3·5–11·1)	9
Schöni et al (1996)[16]	1982–94	Europe	Survey	0–63	..	..	24 500 (NA)	..	35·1 (15·1)	..	11	2·92	3·7 (2·1–6·8)	8
Johannesson et al (2009)[17]	1968–2003	Sweden	NIR	Mean 24·2	462 (52%)	422 (48%)	884 (18 564)	33	52·5†	21·4	4	0·71	5·6 (1·5–14·4)	9
Maisonneuve et al (2013)[15]	1990–2009	USA	CFF	Mean 19·0	..	..	43 937 (352 349)	2749	..	8·0	64	13·9	‡	9
Fink et al (2017)[18]	1987–2011	USA	USTR	Most patients <35 at transplant	846 (50%)	835 (50%)	1681 (6220)	1681	..	3·7	23	0·93	24·7 (16·4–34·9)	9
Sheldon et al (1993)[10]	1961–89	UK	RBH	Most patients 15–24	226 (55%)	186 (45%)	412 (2708)	..	..	6·6	2	..	..	7

Data are n, n (%), range, mean (SD), or median, unless otherwise stated. SIR=standardised incidence ratio. CFF=Cystic Fibrosis Foundation. CCFFR=Canadian Cystic Fibrosis Foundation Registry. NA=not applicable. NIR=National Inpatient Register. USTR=US Transplant Registry. RBH=Royal Brompton Hospital. *None of the studies reported SD. †SD not reported. ‡Overall SIR cannot be calculated because original study data was presented separately for each subgroup.

Table 1: **Population and study characteristics**

study[15] reported outcomes for transplant and non-transplant patients separately, and three studies[14,16,17] reported outcomes of mixed cohorts, which included both transplant and non-transplant patients. The remaining study[18] included only transplanted patients. Of the three studies reporting mixed cohorts in terms of transplantation status, two studies[14,16] included only a small number of transplant patients because the participants were recruited before 1994, and one study[17] included a cohort in which only 33 (4%) of 884 patients with cystic fibrosis had lung transplantation. Therefore, for the subgroup analyses by transplantion status the outcomes of the studies reporting mixed cohorts were combined with those of the non-transplant patients reported by Maisonneuve and colleagues[15] (non-transplant group) and these were compared with patients who received transplants reported by Fink and colleagues[18] and Maisonneuve and colleagues[15] (transplant group).

The overall risk of gastrointestinal cancer among the five studies reporting SIR,[14–16,18] with a median follow-up

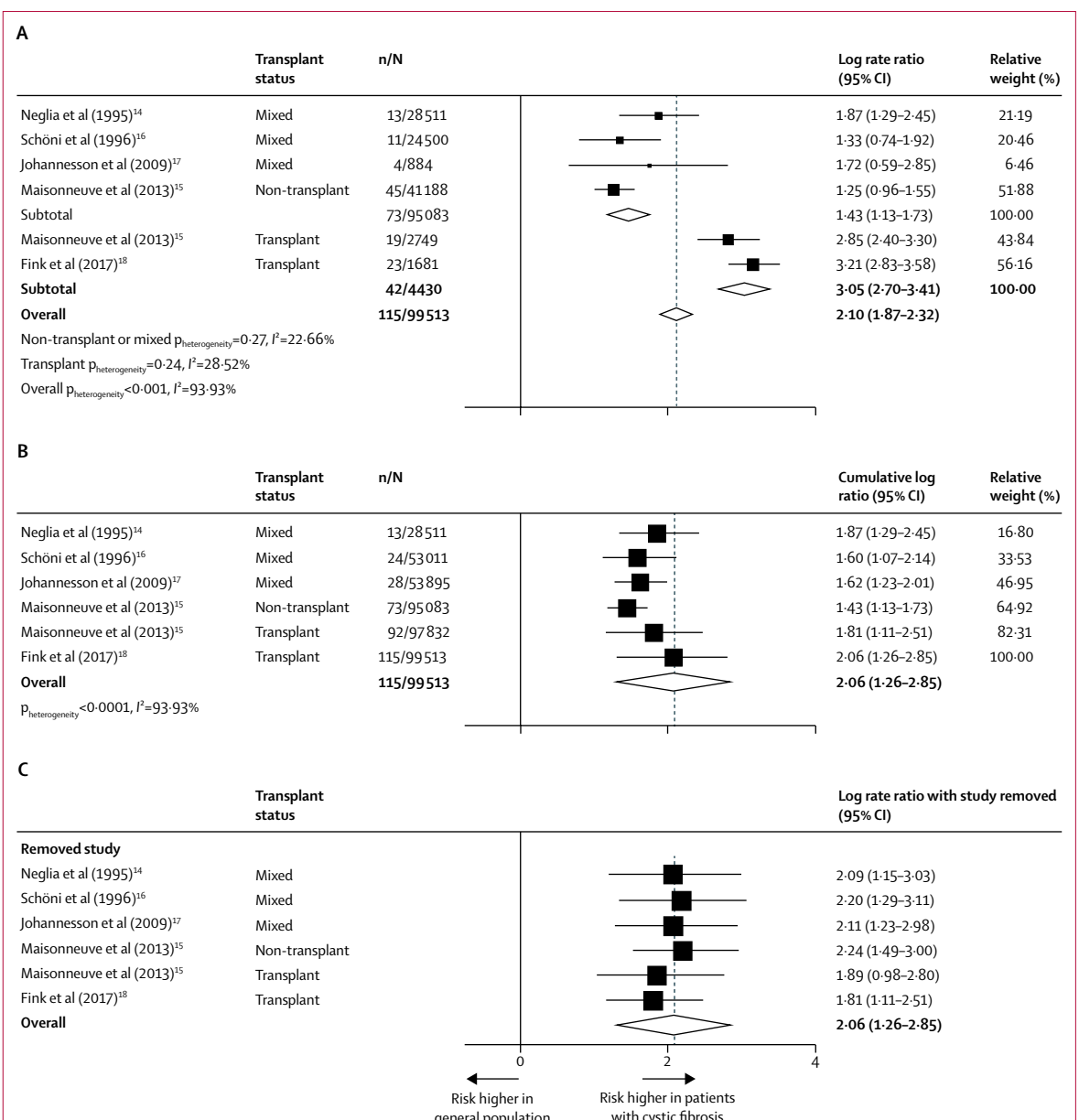

Figure 2: **Standardised incidence ratios for gastrointestinal cancer in patients with cystic fibrosis by transplant status**
(A) Risk of gastrointestinal cancer stratified by transplant status. Cumulative (B) and influence (C) analysis of gastrointestinal cancer risk. Data are presented as $\log_{10}$ standardised incidence ratio. The markers vary in size according to the weight assigned to each study. Diamonds show the pooled effect. n=number of events. N=number of patients.

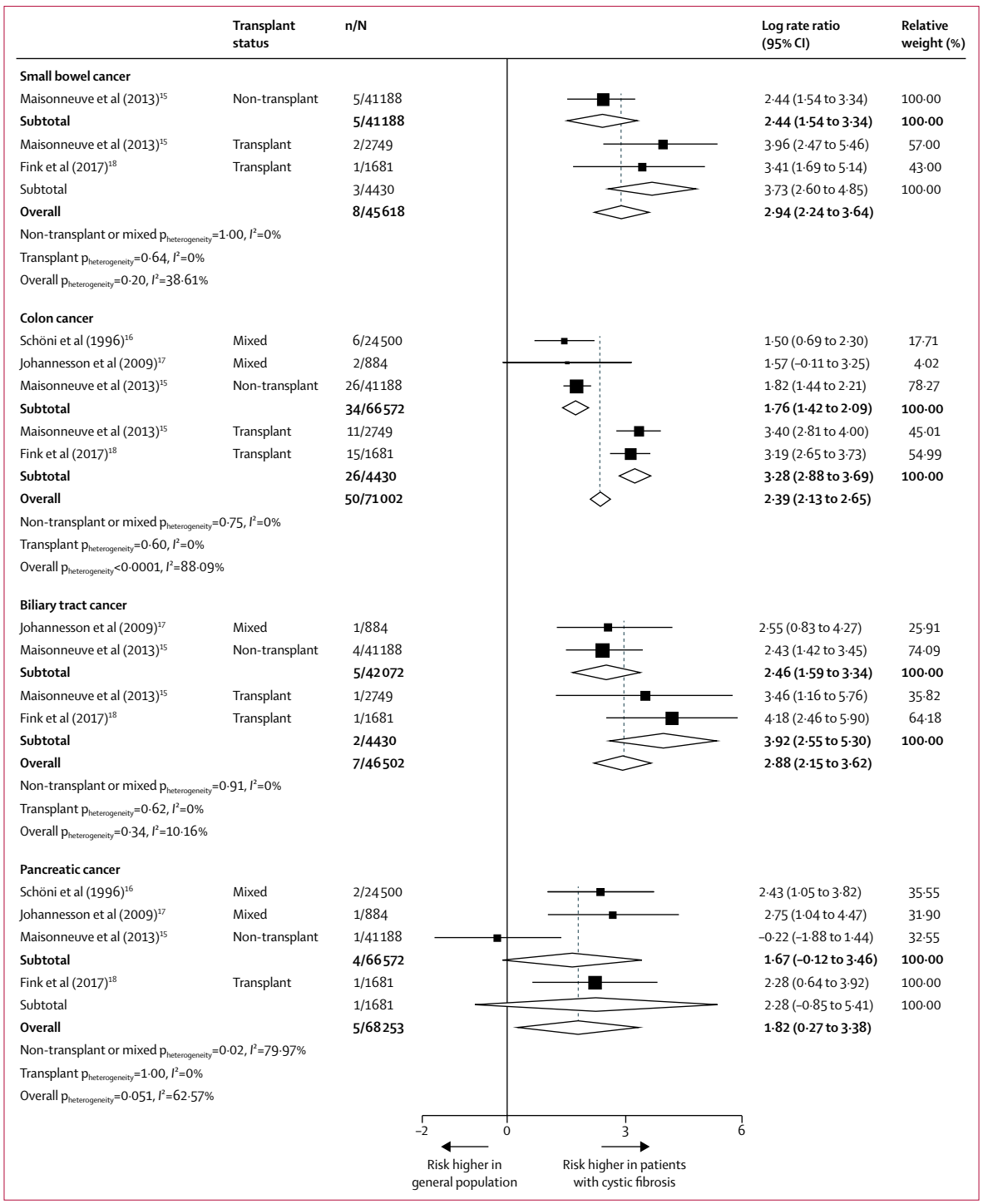

Figure 3: **Standardised incidence ratios for site-specific gastrointestinal cancers in patients with cystic fibrosis by transplant status**
Data are presented as $\log_{10}$ standardised incidence ratio. The markers vary in size according to the weight assigned to each study. Diamonds show the pooled effect. n=number of events. N=number of patients.

of 6·9 years (IQR 4·2–18·1), was significantly higher in patients with cystic fibrosis than the general population (pooled SIR 8·13, 95% CI 6·48–10·21; p<0·0001; log SIR 2·10, 95% CI 1·87–2·32; p<0·0001, I^2=93·93%; figure 2A). Heterogeneity was high when studies were pooled together; however, the funnel plot showed no asymmetry, and no small-study effects or publication bias as assessed by Begg's test (p=0·85) and Egger's test

(p=0·89) were observed (appendix p 4). Cumulative analysis showed that individuals with cystic fibrosis had an elevated risk of gastrointestinal cancers compared with the general population regardless of the study year (figure 2B). However, the registry periods of most included studies overlapped. Influence analysis showed that the random-effects estimate was not influenced by any one particular study (figure 2C).

We next analysed the risk of site-specific gastrointestinal cancers among patients with cystic fibrosis. Two studies[15,18] with a median follow-up of 3·7 years (IQR 3·3–6·3) were assessed for risk of small bowel cancer, four studies[15–18] with a median follow-up of 6·3 years (IQR 3·5–12·0) for risk of colon cancer, three studies[15,17,18] with a median follow-up of 6·3 years (IQR 3·5–12·0) for risk of biliary tract cancer, and four studies[15–18] with a median follow-up of 8·9 years (IQR 6·3–15·1) for risk of pancreatic cancer (figure 3).

The risk of small bowel cancer, colon cancer, biliary tract cancer, and pancreatic cancer was significantly increased in patients with cystic fibrosis compared with the general population (pooled SIR 18·94 [95% CI 9·37–38·27; p<0·0001] for small bowel cancer; 10·91 [8·42–14·11; p<0·0001] for colon cancer; 17·87 [8·55–37·36; p<0·0001] for biliary tract cancer; and 6·18 [1·31–29·27; p=0·022] for pancreatic cancer; figure 3).

Heterogeneity was high among the studies investigating the incidence of colon and pancreatic cancer, which is likely to be because of the difference in risk between transplanted patients and patients in the mixed cohorts, and among patients in the mixed cohorts. Visual inspection of the funnel plots for each site-specific analysis showed no asymmetry, and no small-study effects or publication biases according to Begg's test and Egger's test (appendix p 5). Cumulative analyses showed that the incidence of all site-specific cancers was higher in patients with cystic fibrosis than the general population, and influence analyses showed that the random-effects estimate was not influenced by any particular study for each cancer type, with the exception of pancreatic cancer, whereby an increased risk was found only when the study by Maisonneuve and colleagues[15] was removed (appendix p 6).

In the subgroup analysis by transplantation status, the pooled SIR of gastrointestinal cancer among transplanted patients with cystic fibrosis (median follow-up 8·9 years [IQR 7·3–15·1]) was five times higher than in those who did not receive a transplant (pooled SIR 21·13, 95% CI 14·82–30·14; p<0·0001; log SIR 3·05 [95% CI 2·70–3·41]; p<0·0001, I^2=28·52% *vs* pooled SIR 4·18, 3·10–5·62; p<0·0001; log SIR 1·43 [1·13–1·73]; p<0·0001, I^2=22·66%; figure 2A). The subgroup analysis for site-specific gastrointestinal cancers showed that the risk of small bowel cancer, colon cancer, biliary tract cancer, and pancreatic cancer was two to five times higher in transplanted patients than in those who did not receive a transplant (figure 3).

The pooled incidence rate of gastrointestinal cancers per person-years was 0·79 per 1000 person-years (95% CI 0·20–3·15; appendix p 7). The incidence rates for small bowel, colon, biliary tract, and pancreatic cancer were 0·13 per 1000 person-years (95% CI 0·027–0·43), 0·39 per 1000 person-years (0·072–2·08), 0·051 per 1000 person-years (0·012–0·19), and 0·058 per 1000 person-years (0·0064–0·37), respectively (appendix p 7).

Discussion

The findings of this systematic review and meta-analysis suggest that patients with cystic fibrosis have a significantly higher risk of gastrointestinal cancer than the general population, including cancers of the small bowel, colon, biliary tract, and pancreas. The risk seems to be higher in patients who had lung transplantation than in those who did not.

The risk of small bowel cancer was substantially higher than that of the other site-specific cancers, with a risk that was almost 20 times higher in patients with cystic fibrosis than in the general population. No formal guidelines or recommended screening methods have been established for small bowel cancer, but a substantial proportion of tumours are identified in the terminal ileum,[33] which indicates the need for terminal ileal assessment during colonoscopy (table 2). Capsule endoscopy and balloon-assisted endoscopy enable the exploration of the entire small bowel. Capsule endoscopy is less invasive than balloon-assisted endoscopy, thus this method warrants further investigation as a screening tool.[38]

Compared with the general population, the risk of colon cancer was ten times higher in patients with cystic fibrosis with an incidence rate of 0·39 per 1000 person-years (95% CI 0·072–2·08). Our results support the Cystic Fibrosis Foundation Task Force recommendation[34] to initiate colon cancer screening at age 40 years, with repeat screening every 5 years thereafter and 3-year surveillance intervals (or on the basis of individual findings; table 2). The proportion of individuals older than 40 years with cystic fibrosis who are diagnosed with polyps has been reported to be as

	Screening method	Screening period*
Small bowel cancer	Terminal ileal intubation at the time of colonoscopy (efficacy and safety of capsule endoscopy or balloon endoscopy need to be determined)	Every 5 years for non-transplant patients, every 3 years after transplant
Colon cancer	Colonoscopy[34]	Every 5 years for non-transplant patients, every 3 years after transplant
Biliary tract and pancreatic cancers	Abdominal ultrasound, magnetic resonance cholangiopancreatography, or endoscopic ultrasonography,[35–37] and measurement of cancer antigen 19-9	Every 2–3 years for non-transplant patients, every 1–2 years after transplant

*Proposed age to start screenings for all site-specific gastrointestinal cancer in patients with cystic fibrosis is 40 years or immediately after transplant.

Table 2: **Proposed screening strategy for site-specific gastrointestinal cancer in patients with cystic fibrosis**

high as 50% for adenomatous polyps and 25% for advanced adenomas,[39] providing further evidence to support individualised treatment decisions for cancer prevention within the cystic fibrosis population.

Our results showed that the risk of biliary tract and pancreatic cancers were also increased in patients with cystic fibrosis compared with the general population. We propose a screening strategy for pancreatobiliary cancer that includes magnetic resonance cholangiopancreatography, endoscopic ultrasound, or abdominal ultrasound and measurement of cancer antigen 19–9 (table 2). This screening method has been used for cholangiocarcinoma in patients with primary sclerosing cholangitis and pancreatic cancer in individuals with a history of hereditary pancreatic cancer,[35,37,40] starting at age 40 years with 2–3 year screening intervals (table 2). However, such recommendations need to be validated and the cost-effectiveness of these approaches requires investigation before implementation.[41] The optimum age to initiate screening also needs further assessment since a previous study[14] reported that the mean age of onset of gastrointestinal cancer was 32·2 years (SD 12·6).

Our results indicate that the risk of gastrointestinal cancer is between two and five times higher in patients with cystic fibrosis who had a lung transplant compared with those who did not have a transplant, which could be associated with the increase in life expectancy and use of immunosuppressive therapies by transplanted patients.[19] Reduced immune surveillance has been suggested to increase cancer risk, but other factors associated with damaged epithelial cells might contribute to the gastrointestinal cancer risk for patients with cystic fibrosis.[18] Regarding lung transplant status, our findings support the recommendations of the Cystic Fibrosis Foundation Task Force, which specify that screening for colorectal cancer should start within 2 years of transplant,[34] or even before transplant, to ensure no additional surgical comorbidities are present. The risks of biliary tract and pancreatic cancer were also higher in patients with cystic fibrosis who had a lung transplant than those who did not, therefore we propose that screening should also be initiated after lung transplant in these organs (table 2). The pathogenesis of cancer in patients with cystic fibrosis remains unclear, but multiple hypotheses exist. Previous studies[42,43] have reported evidence of chronic increased gastrointestinal epithelial cell turnover beginning in infancy and early childhood in cystic fibrosis, which might explain the increasing number of young adults with cystic fibrosis who are diagnosed with gastrointestinal cancer. Impairments in the CFTR lead to an increase in viscosity of luminal secretions and impaired mucociliary clearance, which results in mucosal obstruction and inflammation primarily driven by neutrophils.[44] Chronic inflammation in this setting has been suggested to cause direct damage of epithelial cells or bacterial dysbiosis, which can play a role in tumour initiation.[45] Evidence of chronic gastrointestinal mucosal inflammation was found in a population with cystic fibrosis using capsule endoscopy of the small bowel,[46] and the role of cystic fibrosis transmembrane conductance regulator protein in colon cancer development has been investigated using murine models. *CFTR*-knockout mice have an increased incidence of colon cancer compared with wild-type mice, and dysregulation of genes associated with immune responses and intestinal stem cells regulation.[47] Frequent exposure to radiation (ie, x-rays and CT scans) might also contribute to the increased risk of cancer in patients with cystic fibrosis.

Our study had several limitations. Because short follow-up study periods can prevent the detection of cancers, we only considered in our analyses incidence rates and standardised incidence ratio, as an indirect method of adjustment for age and sex. Heterogeneity between the studies was high in the combined analysis, and decreased in the subgroup analysis, suggesting that the overall heterogeneity is due to the difference between subgroups regarding transplant status. Additionally, this meta-analysis only included retrospective observational studies, including data from multicentre and national registries, and differences in the reporting of cancer incidence could have affected the quality of the reported data. Drugs that reverse abnormalities in chloride transport have been developed, and the management and life expectancy of patients with cystic fibrosis are expected to improve further;[48] however, all the studies included in this meta-analysis were done before these drugs were used in clinical practice. The paucity of data regarding the age at which patients were diagnosed with gastrointestinal cancer is another limitation; however, patient level meta-analysis would be extremely difficult to do since the range of included study periods is extremely wide. Furthermore, the cancer incidence rate per person-years does not control for increasing risk with age. Another limitation of this meta-analysis is that the number of reported cases of cancer is small, which might decrease the robustness of our results. However, all of the studies included a large number of participants and studies of larger cohorts are unlikely to be reported in this setting.

In conclusion, this systematic review and meta-analysis suggests that patients with cystic fibrosis have an increased risk of gastrointestinal cancer compared with the general population, including site-specific cancers of the small bowel, colon, biliary tract, and pancreas. Additionally, our findings suggest that patients who had an organ transplant have a higher risk of developing gastrointestinal cancer than those who did not. Although further studies are needed to monitor gastrointestinal cancer incidence over time in patients with cystic fibrosis, the development of a screening strategy for gastrointestinal cancer in these patients is warranted.

Contributors

AS conceived and designed the study. All authors analysed data and contributed to drafting the manuscript.

Declaration of interests

We declare no competing interests.

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