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Short Communication

Cystic fibrosis gene mutations and gastrointestinal diseases

Shahram Bahmanyar [a,b,*], Anders Ekbom [a], Johan Askling [a], Marie Johannesson [c], Scott M. Montgomery [a,d,e]

[a] *Clinical Epidemiology Unit, Department of Medicine, Karolinska Hospital, Stockholm, Sweden*
[b] *Faculty of Medicine, Golestan University of Medical Sciences, Gorgan, Iran*
[c] *Department, Paediatrics and Child Health, University of Otago, Wellington, New Zealand*
[d] *Clinical Epidemiology and Biostatistics Unit, Örebro University Hospital, Örebro, Sweden*
[e] *Department of Primary Care and Social Medicine, Charing Cross Hospital, Imperial College, London, UK*

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Abstract

Background: This study examined if CF mutation heterozygosity is associated with diseases of gastrointestinal epithelial barrier function.
Design and methods: Swedish registers identified 865 patients with a diagnosis of CF between 1968 and 2003 and matched with 8101 individuals without CF. Gastrointestinal disease risk was examined among 1534 biological parents and 1396 siblings of CF patients, compared with 15,526 parents and 15,542 siblings of individuals without CF.
Results: First-degree relatives of CF patients were not at lower risk of the gastrointestinal diseases, in contrast with a raised risk among CF patients.
Conclusion: Heterozygosity for CF gene mutations does not protect against gastrointestinal diseases where impaired barrier function may be relevant.

Keywords: Cystic fibrosis; Gene mutation; Gastrointestinal diseases; Barrier function

1. Introduction

While there is little evidence that increased fertility [2] accounts for the relatively high frequency of CF gene mutations among Caucasians, [1] there may be some protection from gastrointestinal and other infections [3,4]. The entry of infectious agents into epithelial cells is impaired in animals heterozygous for CF polymorphisms [4]. Despite normal intestinal chloride secretion in humans [5], improved gastrointestinal barrier function may theoretically contribute to protection, including against diseases involving an immune response against luminal contents (such as bacteria) including peptic ulcer [6], coeliac disease, ulcerative colitis and Crohn's disease [7]. We examined the risk of these diseases in first-degree relatives of CF patients as the majority would be heterozygous for CF mutations and compared them with relatives of a matched cohort without CF. To examine the specific role of likely barrier function, diseases where barrier function is less relevant were also investigated: pancreatic diseases, cholelithiasis, diverticulitis, appendectomy, cholecystitis, and fibrosis and cirrhosis of liver. The risks for the gastrointestinal diseases were also estimated among the CF patients.

2. Subjects and methods

The Swedish Inpatient Register [8] identified Swedish patients with a diagnosis of CF between 1968 and 2003 (ICD-8 code 273.0; ICD-9 code 277.0; and ICD-10 code E84), age 60 or less at follow-up as CF patients rarely live beyond 60 years of age [9]. The 865 patients were matched with 10 individuals

* Corresponding author. Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Karolinska Hospital, SE-171 76 Stockholm, Sweden. Tel.: +46 8 517 79323; fax: +46 8 517 79304.
E-mail address: Shahram.Bahmanyar@ki.se (S. Bahmanyar).

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(fewer in a small minority) without the disease by year of birth, sex, vital status at diagnosis and region of residence ($n=8101$). The Multi-Generation Register [10] identified 759 and 7707 biological fathers, 775 and 7819 biological mothers of subjects with and without CF, respectively. Failure to identify parents was mainly due to births before 1932, pre-dating inclusion in the register [10]. Some 1396 and 15,542 siblings of subjects were identified with and without CF, respectively. The Inpatient Register was used to identify diagnoses of gastrointestinal diseases. This study was approved by Karolinska Institutet regional ethics committee.

3. Statistical analysis

Cox regression (SAS software) was used to estimate the risk of the gastrointestinal diseases. Parents and siblings of patients with a diagnosis of CF were compared with parents and siblings of the cohort without CF. We excluded 114 siblings who also had a CF diagnosis. Follow-up was from 1964, when the Inpatient Register was established, or from birth or immigration if this occurred subsequently; and continued until emigration, death, or 31st December 2003. The underlying time scale for all models was attained age, and adjustment was for the matching characteristics used to define risk-sets. The Cox regression was internally stratified by calendar period (in ten-year intervals).

4. Results

The average follow-up time for parents of CF patients and the comparison parents was over 36.0 years. Siblings of patients with CF and comparison siblings were followed for an average of 23.0 years. The index subjects with and without CF were followed for averages of 21.0 and 23.5 years, respectively.

4.1. First-degree relatives

There was no notable risk reduction for any of the diseases among parents (Table 1) and siblings (Table 2) of patients with CF. In stratified analyses there was no increased or decreased risk of the gastrointestinal diseases among mothers of those with CF. The risks for gastric ulcer and ulcerative colitis were statistically significantly increased among fathers of patients with CF. There were no statistically significant associations in siblings (Table 2). Stratification by sex did not reveal notable associations.

Stratification by calendar year of CF diagnosis, to tackle possible variation in diagnostic accuracy and differences in follow-up time, did not alter any of the results notably.

4.2. Cystic fibrosis patients

Among patients with CF, we observed statistically significant increased risks for peptic ulcer, ulcerative colitis, Crohn's disease, coeliac disease, pancreatic diseases, cholelithiasis, appendectomy, cholecystitis, and fibrosis and cirrhosis of the liver, compared with individuals without CF (Table 3).

5. Discussion

Contrary to our hypothesis, there was no evidence of reduced risk for any of the diseases among first-degree relatives of CF patients and we identified statistically significant excess risks for gastric ulcer and ulcerative colitis among fathers. This was similar to our previous finding of no protective effect against cancer in relatives of CF patients [11]. As expected, the patients with CF in this study were at a higher risk of having a range of gastrointestinal diseases.

The relative risks for some of the gastrointestinal diseases in relatives were close to unity, consistent with an earlier study of

Table 1
Gastrointestinal disease risk among parents of patients with cystic fibrosis (759 fathers and 775 mothers) compared with parents of the comparison group without cystic fibrosis (7707 fathers and 7819 mothers).

	Mothers		Fathers	
	Events exposed/unexposed	HR 95% CI	Events exposed/unexposed	HR 95% CI
Diseases of impaired barrier function				
Peptic ulcer	10/93	1.03 (0.54–1.99)	21/168	1.14 (0.72–1.80)
Gastric ulcer	3/47	0.64 (0.20–2.07)	15/57	2.39 (1.35–4.25)
Duodenal ulcer	4/35	1. 12 (0.40–3.17)	5/76	0.62 (0.25–1.54)
Ulcerative colitis	3/30	1.02 (0.31–3.36)	8/33	2.48 (1.14–5.40)
Crohn's disease	2/28	0.75 (0.18–3.14)	1/17	0.60 (0.08–4.54)
Coeliac disease	2/11	1.91 (0.42–8.72)	0/4	–
Other diseases				
Acute pancreatitis	5/36	1.47 (0.57–3.74)	7/65	1.08 (0.49–2.35)
Other diseases of pancreas	2/7	3.07 (0.63–14.9)	4/18	2.11 (0.71–6.27)
Cholelithiasis	56/476	1.20 (0.91–1.58)	21/182	1.11 (0.71–1.75)
Diverticulitis	12/89	1.33 (0.73–2.45)	8/73	1.07 (0.52–2.23)
Appendectomy	57/482	1.20 (0.91–1.58)	29/372	0.81 (0.55–1.18)
Only appendicitis	17/242	0.70 (0.43–1.14)	23/242	0.98 (0.64–1.51)
Cholecystitis	4/61	0.66 (0.24–1.83)	3/41	0.62 (0.19–2.02)
Fibrosis and cirrhosis of liver	2/17	1.18 (0.27–5.10)	3/47	0.64 (0.20–2.06)

HR 95% CI — hazard ratio and 95% confidence interval.

Table 2
Gastrointestinal disease risk among siblings of patients with cystic fibrosis (n=1396) compared with siblings of the comparison group without cystic fibrosis (n=15,542).

	Events exposed/unexposed	HR, 95% CI
Diseases of impaired barrier function		
Peptic ulcer	7/46	1.48 (0.66–3.34)
Only gastric ulcer	3/20	1.49 (0.43–5.13)
Only duodenal ulcer	4/20	1.97 (0.65–5.97)
Ulcerative colitis	1/36	0.34 (0.05–2.53)
Crohn's disease	4/29	1.51 (0.53–4.32)
Coeliac disease	3/31	1.08 (0.33–3.53)
Other diseases		
Acute pancreatitis	4/27	1.54 (0.53–4.44)
Other diseases of pancreas	2/8	2.13 (0.43–10.55)
Cholelithiasis	16/182	0.89 (0.53–1.49)
Diverticulitis	3/30	1.04 (0.31–3.51)
Appendectomy	69/768	0.99 (0.77–1.26)
Only appendicitis	42/544	0.86 (0.63–1.17)
Cholecystitis	3/23	1.16 (0.33–4.02)
Fibrosis and cirrhosis of liver	1/14	1.03 (0.13–7.98)

HR 95% CI — hazard ratio and 95% confidence interval.

associations with cholelithiasis and liver cirrhosis in carriers of CF gene mutations [12]. However, we cannot rule out the possibility that a protective effect is masked by our use of a cohort of first-degree relatives of patients with a diagnosis of CF (rather than identifying heterozygosity through screening). It is possible that a proportion of such individuals are compound heterozygous for CF, and also carry a second mutation on the other chromosome resulting in a sub-clinical or variant form of CF [13] themselves, thus increasing gastrointestinal disease risk as observed in patients with CF. The statistically significant risks for gastric ulcer and ulcerative colitis among fathers who were CF gene mutation carriers are not consistent with our hypothesis, and may represent a chance finding.

Consistent with results from previous studies [13–15], the patients with CF were at a higher risk of Crohn's disease, celiac disease, pancreatic diseases, cholelithiasis, cholecystitis, and fibrosis and cirrhosis of liver. In contrast with earlier reports of lower risk of appendectomy among patients with CF [16,17] we observed a higher risk of appendectomy among CF patients. When we restricted the analysis to appendectomy *due only to acute appendicitis* (data not shown), the raised risk was no longer observed. The frequent examinations experienced by CF patients may have resulted in an over-estimation of associations with some diseases.

This study had some potential limitations. Although we had information on all inpatients diagnosed with CF in Sweden over a long period, the number of patients with CF remained small. Although the DF508 mutation is the most common in CF, we did not have information on mutation-type and could not investigate specific associations. Diseases were identified using the Swedish Inpatient Register, the validity of which is generally high [18] and bias due to diagnostic misclassification, if any, is likely to move relative risks toward the null thus potentially masking any protective effect among first-degree relatives.

In conclusion, we did not observe any significant risk reduction for the gastrointestinal diseases among people identified as likely heterozygous CF gene mutation carriers. Patients with CF are at higher risk of hospital admission for a variety of gastrointestinal diseases.

Table 3
Gastrointestinal disease risk among patients with cystic fibrosis (n=865) compared with the comparison group without cystic fibrosis (n=8101).

	Events among subjects with CF	Events among subjects without CF	HR.95% CI
Diseases of impaired barrier function			
Peptic ulcer	14	14	16.97 (7.83–36.81)
Ulcerative colitis	6	16	4.98 (1.92–12.88)
Crohn's disease	6	17	4.69 (1.83–12.03)
Coeliac disease	30	15	21.21 (11.36–39.60)
Other diseases			
Acute pancreatitis	12	9	23.50 (8.73–63.25)
Other diseases of pancreas	19	5	48.49 (17.81–132.06)
Cholelithiasis	28	83	5.57 (3.56–8.69)
Diverticulitis	2	13	2.64 (0.57–12.17)
Appendectomy	47	364	1.70 (1.25–2.30)
Cholecystitis	10	8	20.41 (7.63–54.59)
Fibrosis and cirrhosis of liver	42	10	62.14 (29.08–132.80)

HR 95% CI — hazard ratio and 95% confidence interval.

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