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Cancer risk among patients with cystic fibrosis and their first-degree relatives

Marie Johannesson[1,2], Johan Askling[3], Scott M. Montgomery[3,4,5], Anders Ekbom[3] and Shahram Bahmanyar[3,6]*

[1]*Department of Public Health and Caring Sciences, Family Medicine and Clinical Epidemiology Section, Uppsala University, Uppsala, Sweden*
[2]*School of Health and Medical Sciences, Örebro University, University Hospital, Örebro, Sweden*
[3]*Clinical Epidemiology Unit, Department of Medicine, Karolinska Hospital, Stockholm, Sweden*
[4]*Clinical Research Centre, Örebro University Hospital, Örebro, Sweden*
[5]*Department of Primary Care and Social Medicine, Charing Cross Hospital, Imperial College, London, United Kingdom*
[6]*Golestan University of Medical Sciences, Gorgan, Iran*

Patients with cystic fibrosis (CF) are at increased risk of some cancers. Little is known about the cancer risks among carriers heterozygous for the CF mutation and it is hypothesized this may be associated with reduced cancer risk. Using Swedish general population-based registers, we identified 884 patients with CF from 1968 to 2003 and 3,033 of their first-degree relatives The subjects were followed from birth of index persons or 1958, whichever came later, until death, emigration or 2003, whichever came first. Cancer risks were compared with the general Swedish population using standardized incidence ratios (SIR) with 95% confidence intervals (CI). Patients, followed for an average of 21 years, were at a higher overall risk of cancer. Some 26 cancer diagnoses, after excluding multiple diagnoses of nonmelanoma skin cancer in one man, produced an overall SIR of 3.2 (95% CI 2.1–4.6). We found statistically significantly increased risks for kidney, thyroid, endocrine, lymphoma and nonmelanoma skin cancer. There was no modification of cancer risk among parents and siblings, with an average of 21 years of follow-up. This study did not identify a heterozygote advantage for CF gene mutations in relation to cancer risk.

Key words: cystic fibrosis; gene mutation; cancer; risk

Improvements in the management of cystic fibrosis (CF), over the last 3 decades, have resulted in markedly improved survival and the number of patients surviving to adulthood is increasing. Few studies have indicated an increased risk of certain cancers among these patients, although some of these studies may be limited by short follow-up time and concerns about selection bias.[1–6]

With an estimated prevalence of 1/25–1/40 heterozygosity for CF gene mutations is common, yet little studied. Compared with those, who do not carry a mutation, heterozygosity is associated with reduced expression of the CF transmembrane conductance regulator (CFTR) gene product,[7] but not with clinical symptoms of CF. The reason for the high prevalence of CF gene mutations worldwide is unclear. It has been hypothesized that heterozygosity for CF gene mutations would offer an advantage through improved protection against infectious disease. Support for this theory has come from *in vitro* studies of gastrointestinal infectious agents.[8,9] Since the etiology of many gastrointestinal tumors is thought to involve an infectious agent,[10] or as a late consequence of chronic inflammatory activity,[11] it is plausible that CF heterozygosity could also confer some degree of cancer protection, particularly gastrointestinal tract cancers. Indeed, in a gene-study of cancer patients in Wales, patients with colorectal cancer had a lower than expected prevalence of CF gene mutations.[12] Increased fertility is another suggested heterozygote advantage that could account for the high prevalence of CF gene mutations. However, there are no epidemiological data to support this hypothesis.[13]

Due to autosomal recessive inheritance, all parents and two-third of nondiseased siblings of patients with CF are heterozygous for a CF mutation. To our knowledge, no previous general population-based study has investigated cancer risk among first-degree relatives of patients with CF. In this general population-based study, with long follow-up time, we investigated overall and site-specific cancer risk in a cohort of patients with CF, as well as cancer risk among their parents and siblings.

Material and methods

We used the National Inpatient Register,[14] which records information on date of discharge and diagnoses according to the ICD codes, to identify patients with a diagnosis of CF in Sweden between 1968 and 2003 (ICD-8 code 273.0; ICD-9 code 277.0; and ICD-10 code E84). As, CF patients rarely live beyond 60 years of age,[15] we included only those who were aged 60 years or less at follow-up, to improve the specificity of a CF diagnosis from this register, although the effect of excluding such patients was investigated. In Sweden, all inpatient care is public and tax-funded, private practice in this area is almost nonexistent. The Multi-Generation Register allows linkage between parents and children born in Sweden from 1932 or later and alive in 1961. The coverage that mainly depends on the year of birth of the index-individual is on average close to 90% of all parents.[16] This register was used to identify both biological parents, as well as siblings of the patients. The Swedish Migration and Death registers provided information on date of migration or death among index subjects, their parents and siblings. The National Swedish Cancer Register, established in 1958 and reportedly more than 98% complete,[17] was used to identify the date and diagnosis of cancer among index subjects, their parents and siblings. All data were linked using the unique personal identity number issued to all Swedish residents alive in 1947 or subsequently.

Using the Swedish Inpatient Register, 884 CF patients were diagnosed between 1968 and 2003 (Table I). Through register linkage, we identified 761 biological fathers and 777 biological mothers corresponding to some 86% of the total number of potentially eligible parents. Failure to identify parents was mainly because patients or their parents were born before 1932.[16] We also obtained data on 1,495 siblings of CF patients.

This study was approved by the Karolinska Institutet regional ethics committee.

Statistical analysis

The standardized incidence ratio (SIR), the ratio of the observed to the expected number of cancers in the cohort, was used as a measure of relative risk. The expected number of cancer diagnoses was calculated by adding all person-years accumulated in the cohort divided into strata defined by sex, age (in 5-year groups) and calendar year of observation (in 5-year intervals) and then multiplying the stratum-specific person-time by the corresponding stratum-specific incidence rates for the entire Swedish population. In the calculation of these incidence rates the denominator was estimated as the number of individuals in the mid-year population

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***Correspondence to:** Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Karolinska Hospital, SE-171 76 Stockholm, Sweden. Fax: +46 (0)8 517 79304. E-mail: Shahram.Bahmanyar@ki.se

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TABLE I – CHARACTERISTICS OF STUDY POPULATION

	CF patients	Fathers	Mothers	Siblings
Total number	884	761	777	1,495
Sex				
Male %	52.3	–	–	49.9
Mean follow-up, years	21.4	21.1	22.2	21.8
Mean year of entry/Exit	1979/2000	1979/2000	1979/2001	1980/2002
Mean age at exit, years	24.2	55.3	52.7	26.2
Mean age at diagnosis of cancer, years				
All cancers	40.4	64.2	54.8	35.9
Digestive cancers	52.5	63.7	65.8	–
Others	39.1	64.5	53.1	35.9

TABLE II – RELATIVE RISK OF CANCER, OVERALL AND BY TYPE, AMONG 884 SWEDISH PATIENTS WITH CYSTIC FIBROSIS 1968–2003, COMPARED WITH SWEDISH GENERAL POPULATION

Cancer type	ICD7	Obs./Exp.	SIR (95% CI)
Cancer in any site[1]	140–209	26/8.21	3.2 (2.1–4.6)
Digestive Cancer	150–159	4/0.71	5.6 (1.5–14.4)
Colorectal Cancer	153–154	2/0.42	4.8 (0.6–17.3)
Biliary passage and liver cancer	155	1/0.08	12.8 (0.3–71.2)
Pancreatic cancer	157	1/0.06	15.7 (0.4–87.5)
Trachea, bronchus, lung cancer	162	1/0.23	4.3 (0.1–24.0)
Testis cancer	178	1/0.39	2.6 (0.07–14.5)
Kidney cancer	180	3/0.21	14.0 (2.9–40.9)
Urinary organ cancer excluding kidney	181	1/0.14	7.0 (0.2–39.2)
Thyroid cancer	194	2/0.2	9.8 (1.2–35.5)
Endocrine cancer	195	3/0.25	12.0 (2.5–35.0)
Lymphoma	200–202,205	5/0.68	7.3 (2.4–17.11)
Nonmelanoma skin cancer[1]	191	3/0.13	23.3 (4.8–68.2)

[1]One of the patients had multiple diagnoses of nonmelanoma skin cancer and we included only the first diagnosis of nonmelanoma skin cancer for this patient.

without previously reported cancer. The 95% confidence intervals (CI) were calculated assuming that the observed events followed a Poisson distribution.

The cohorts were followed from 1958, when the Cancer Register was established, or from birth of index persons, or immigration if this occurred subsequently until the date of emigration, death or until December 31, 2003, whichever occurred first. Follow-up for the younger siblings started from their birth date, immigration or 1958, whichever occurred last. We excluded all benign tumors and cancers found incidentally at autopsy.

In an additional analysis, we restricted our data to those patients who received a diagnosis of cystic fibrosis ($n = 664$) as hospital inpatients on 2 separate occasions to ensure diagnostic accuracy. We also performed stratified analyses for CF patients where the age at follow-up was below age 20 years, 20–39 years or over age 39 years. Another stratified analysis was by calendar year of hospital admission (before or after 1989). We also investigated the effect of excluding patients who lived beyond age 60 years, by reanalyzing the data without age restriction.

All analyses were conducted using SAS statistical software.

Results

Cystic fibrosis patients

The 884 patients with CF were followed for an average of 21.4 years. During the follow-up period, 41 cancers were observed in 24 individuals compared with 8.22 expected, corresponding to a SIR of 5.0 (95% CI 3.6–6.8). However, 1 patient had multiple diagnoses of nonmelanoma skin cancer, and to prevent a disproportionate influence on the results, we repeated the analysis including only the first nonmelanoma skin cancer diagnosis; and the risk estimate for overall cancers was somewhat reduced to 3.2 (95% CI 2.1–4.6), but remained statistically significant (Table II). There was an increased risk for cancers of the digestive system (SIR = 5.6; 95% CI 1.5–14.4, $n = 4$). There were statistically significant increased risks for cancers of the kidney, thyroid, endocrine (3 adrenal malignancies), lymphoma and nonmelanoma skin cancers.

A total of 33 patients with CF underwent lung transplantation and 3 of them developed cancer (1 lymphoma, 1 nonmelanoma skin cancer and 1 thyroid cancer) compared with 0.39 expected, corresponding to a SIR of 7.6 (95% CI 1.6–22.3). Among the patients without lung transplantation, 23 cancers were observed compared with 7.75 expected, corresponding to a SIR of 3.0 (95% CI 1.9–4.5). The mean age at diagnosis of cancer was 40.4 years (with a range from 2.3 to 59.8 years). We observed 4 childhood cancers including 2 patients with lymphoma and 2 with cancers of the kidney.

Analysis restricted to those who received a diagnosis of cystic fibrosis on at least 2 separate occasions as hospital inpatients resulted in a SIR of 3.8 (95% CI 2.2–6.1). Stratification by age at follow-up found a consistently increased cancer risk among all strata compared with the general population rate, with SIRs (and 95% CI) of 5.1 (1.4–13.0), 2.3 (0.8–4.9), and 3.0 (1.7–5.0) for follow-up at ages under 20, 20–39, and over 39 years, respectively. In stratified analysis by calendar year of hospital admission (before or after 1989), we observed a statistically significant increased overall cancer risk in both periods: for 1968–1988 SIR = 3.3 (95% CI 1.8–5.5) and for 1989–2003 SIR = 2.8 (95% CI 1.4–5.0). When we included those who lived beyond age 60 years, the risk estimate for overall cancer was 1.7 (1.3–2.0).

First-degree relatives

The 761 biological fathers and 777 biological mothers of CF patients were followed for an average of 21 years. During the follow-up period, 133 cancers were observed in 119 individuals, compared with 137.44 expected (SIR = 1.0, 95% CI 0.8–1.2) (Table III). Thus, there was no association with cancer risk among parents. In the site-specific analyses, the only statistically significant association was an increased risk of esophageal cancer (SIR = 4.7, 95% CI 1.5–10.9, $n = 5$), all in fathers, 2 of squamous cell type and 3 with unspecified histology).

TABLE III – RELATIVE RISK OF CANCER, OVERALL AND BY TYPE, AMONG 1,538 PARENTS AND 1,495 SIBLINGS OF PATIENTS WITH CYSTIC FIBROSIS 1968–2003, COMPARED WITH SWEDISH GENERAL POPULATION

Cancer type	Parents		Siblings	
	Obs./Exp.	SIR (95% CI)	Obs./Exp.	SIR (95% CI)
Cancer in any site	133/137.44	1.0 (0.8–1.2)	21/19.59	1.1 (0.7–1.6)
Digestive cancer	26/25.57	1.0 (0.7–1.5)	0/2.01	0 (0–1.8)
Esophageal cancer	5/1.07	4.7 (1.5–10.9)	0/0.07	0 (0–50.0)
Stomach cancer	3/4.05	0.7 (0.2–2.2)	0/0.25	0 (0–14.7)
Colorectal cancer	14/13.79	1.0 (0.6–1.7)	0/1.19	0 (0–3.1)
Biliary passage and liver cancer	1/2.55	0.4 (0.01–2.2)	0/0.20	0 (0–18.7)
Pancreatic cancer	2/3.04	0.7 (0.1–2.4)	0/0.20	0 (0–18.7)
Trachea, bronchus, lung cancer	11/9. 68	1.1 (0.6–2.0)	2/0.75	2.7 (0.3–9.6)
Breast cancer	23/22.48	1.0 (0.7–1.5)	3/3.50	0.9 (0.2–2.5)
Cervix uteri cancer	3/3.17	1.0 (0.2–2.8)	2/0.75	2.7 (0.3–9.6)
Corpus uteri cancer	3/3.77	0.8 (0.2–2.3)	0/0.33	0 (0–11.1)
Ovarian cancer	2/3.85	0.5 (0.1–1.9)	2/0.61	3.3 (0.4–11.9)
Prostate cancer	15/15.82	1.0 (0.5–1.6)	1/0.67	1.5 (0.04–8.3)
Testis cancer	0/1.03	0 (0 – 3.6)	3/0.76	4.0 (0.8–11.6)
Kidney cancer	1/3.84	0.3 (0.01–1.5)	0/0.43	0 (0–8.6)
Urinary organ cancer excluding kidney	5/5.99	0.8 (0.3–2.0)	0/0.42	0 (0–8.7)
Brain cancer	6/5.3	1.1 (0.4–2.5)	5/1.98	2.5 (0.8–5.9)
Thyroid cancer	2/1.46	1.4 (0.2–5.0)	0/0.46	0 (0–8.1)
Endocrine cancer	1/2.81	0.4 (0.01–2.0)	0/0.57	0 (0–6.5)
Lymphoma	4/5.28	0.8 (0.2–1.9)	0/1.37	0 (0–2.7)
Melanoma skin cancer	9/6.30	1.4 (0.7–2.7)	1/1.51	0.7 (0.02–3.7)
Non melanoma skin cancer	4/4.78	0.8 (0.2–2.1)	0/0.38	0 (0–9.8)

Among the 1,495 siblings of CF patients, who were followed for an average of 21 years, 21 cancers were observed while 19.59 were expected (SIR = 1.1, 95% CI 0.7–1.6) (Table III). Again indicating a lack of association with cancer in first-degree relatives of those with CF. We did not find any statistically significant cancer risks among the site-specific cancers studied in siblings of CF patients.

Analysis restricted to first-degree relatives of those patients who received a CF diagnosis on at least 2 separate occasions, to ensure diagnostic accuracy, showed no conspicuous variation in the results (data not shown).

Discussion

This general population-based study with essentially unbiased long-term follow-up suggests that patients with CF are at an elevated overall risk of cancer. We also confirmed the previously reported higher risk of digestive tract cancers. In this study, we also investigated the risk of cancer among first-degree relatives likely to be heterozygous for CF polymorphisms and did not find any significant increased or decreased overall cancer risk.

The increased occurrence of gastrointestinal cancer among patients with CF, in our study, is consistent with results from previous studies.[1–6] We also observed statistically significant increased risks of cancers of the kidney, thyroid, endocrine, lymphoma and nonmelanoma skin cancer. Patients with CF are exposed to X-ray examinations repeatedly at an early age. This is one potential explanation for higher risk of cancers of the thyroid,[18] kidney[19] and bone.[20] Studies of individuals exposed to radiation for treatment and of Japanese atomic bomb survivors suggested a causal association between ionizing radiation and cancers of thyroid and kidney. The thyroid gland is highly sensitive to ionizing radiation especially at younger ages.[18] The increased risk of lymphoma could be secondary to post-transplant immune-suppression.[2] However, only one of the patients with lymphoma had a report of lung transplantation. It is also worth emphasizing that CF patients have a substantial exposure to antibiotics over their life, especially aminoglycosides. Surveillance bias, due to the intensive medical follow-up of CF patients, could also be responsible for the observed higher risk of some site-specific cancers such as the thyroid cancer. As the number of site-specific cancers was small, chance could be other explanation for these findings. It has been shown that the increased risk of cancer might be more pronounced in CF patients who underwent lung transplantation.[2] In our study, we observed a higher relative risk among those who had lung transplantation, although this finding was based on small numbers. A significant excess cancer risk remained among those who were not transplant recipients.

It has been argued that the high prevalence of heterozygosity for CF gene mutations could be explained by some advantages that this confers, such as improved defense against infections, particularly in the gastrointestinal tract.[8,9] Credence for this hypothesis has been lent by results from *in vitro* studies showing that the entry of infectious agents into epithelial cells is impaired in animals heterozygous for CF polymorphisms.[9] Due to the autonomic recessive inheritance of CF, both parents of an affected child are heterozygous (or homozygous) for a CF gene mutation. In this study, we did not find any significant change in the risk of cancer among individuals heterozygous for CF gene mutations. Lowenfels *et al*.[21] estimated cancer risk among relatives of CF patients using self-reported information. They found a 50% reduction in smoking-related cancers among parents of cystic fibrosis patients, but they did not observe any increase or decrease in overall cancer risk, which is consistent with the results of this study. However, we did not confirm the reduced risks for smoking-related cancers. Our finding of a significant excess risk of esophageal cancer is not consistent with our a priori hypothesis and may represent a chance finding. Padua *et al*.[12] investigated the rate of the DF508 mutation among 1,765 patients with a diagnosis of malignant melanoma, myelodysplasia, acute myeloid leukemia, lymphoma, colon or breast cancer and compared it with the DF508 mutation rate among 301 hospital-based controls. The results indicated a lower than expected prevalence of heterozygosity among patients with colorectal cancer and malignant melanoma.[12] In our study, these reduced risks were not confirmed. In contrast with earlier reports,[22,23] we observed that the risk of breast cancer in mothers and sisters was close to unity, suggesting that heterozygosity for CF is unrelated to breast cancer risk.

Strengths of this study include its general population-based setting with a study population encompassing virtually all known CF cases in Sweden from 1968 to 2003, and the complete and long follow-up using Swedish registries such as the Swedish Cancer Registry. Information from the Swedish Multi-Generation register made it possible to identify and follow first-degree relatives of CF patients. The Swedish Cancer Register with more than 98% completeness[17] ensured the validity of the outcome.

Our study had some limitations. Although we used information on all individuals diagnosed with CF in Sweden over a long period of time, the number of diagnosed patients per year was relatively small and for those that were young at the end of the study period, the statistical power to estimate risk was limited. We were able to identify only 86% of the parents of index subjects. In our study, the assumption that first-degree relative status indicates heterozygosity is valid for the vast majority of parents, but might be subject to misclassification among siblings, moving any association toward the null. Therefore, the results of cancer risk among siblings should be interpreted with greater caution as they may underestimate an association, if it exists. Although the DF508 mutation is by far the most common in CF, we did not have individual information on mutation-type, so some type-specific effects may not have been identified here. Patients with CF were identified through diagnoses recorded in medical registers, the validity of which is generally high. Error from diagnostic misclassification, if any, is likely to move relative risks toward unity thus potentially underestimating the magnitude of associations. Another possibility is that some non-CF patients, such as polycystic kidney disease or cystic thyroid nodules, who may be misclassified as having CF might have excess cancer risk which could explain the observed increased overall cancer risk. However, to increase diagnostic specificity, we also restricted the analyses to those who received at a diagnosis of CF on at least 2 separate hospital admissions. The results from these subanalyses of patients with greater diagnostic certainty suggest that our findings are not due to diagnostic inaccuracy.

In conclusion, patients with CF are at an overall excess risk of cancer and particularly for cancers of the digestive tract, kidney, thyroid, endocrine, lymphoma and nonmelanoma skin cancer. We did not observe a statistically significant risk reduction among heterozygous gene mutation carriers.

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