

THE RISK OF CANCER AMONG PATIENTS WITH CYSTIC FIBROSIS

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Abstract Background. Anecdotal reports suggest an increased frequency of certain cancers in patients with cystic fibrosis, the commonest genetic disorder of whites. One third of patients with cystic fibrosis now reach adulthood, when cancer is more frequent, implying that cancer rates in these patients will increase over time. We investigated the relation between cystic fibrosis and cancer in North American and European patients with cystic fibrosis.

Methods. We performed a retrospective cohort study of the occurrence of cancer in 28,511 patients with cystic fibrosis from 1985 through 1992 in the United States and Canada. The number of cases observed was compared with the number expected, calculated from population-based data on the incidence of cancer. We also analyzed proportional incidence ratios to assess the association between specific cancers and cystic fibrosis in Europe.

Results. Thirty-seven cancers were observed in the

North American cohort during 164,764 person-years of follow-up, as compared with an expected number of 45.6, yielding a ratio of observed to expected cancers of 0.8 (95 percent confidence interval, 0.6 to 1.1). Thirteen digestive tract tumors were observed, as compared with an expected number of two, for a ratio of observed to expected cancers of 6.5 (95 percent confidence interval, 3.5 to 11.1). In Europe, 11 of 39 cancers originated in the digestive tract, yielding a positive association between digestive tract tumors and cystic fibrosis (odds ratio, 6.4; 95 percent confidence interval, 2.9 to 14.0).

Conclusions. Although the overall risk of cancer in patients with cystic fibrosis is similar to that of the general population, there is an increased risk of digestive tract cancers. Persistent or unexplained gastrointestinal symptoms in these patients should be carefully investigated. (N Engl J Med 1995;332:494-9.)

CYSTIC FIBROSIS is the commonest recessive genetic disease of whites. About 2 to 4 percent of all white persons carry the gene for cystic fibrosis, and there are approximately 25,000 patients with this disease in the United States.¹ The disease has a broad range of symptoms, including meconium ileus, recurrent suppurative lung infection, sinusitis, and pancreatic insufficiency.

Because of improved care, the life span of patients with cystic fibrosis is increasing. In the United States, the median survival of these patients doubled between 1969 and 1990; one third of all patients now attain adulthood.¹ With increasing survival, a predisposition to cancer, previously obscured by the short life span of these patients, may become evident.

Previous reports suggested that patients with cystic fibrosis may have an increased risk of cancer, particularly digestive tract cancers and leukemia.²⁻¹⁵ To evaluate this risk, we conducted a retrospective cohort study of the occurrence of cancer in more than 25,000 patients with cystic fibrosis who were followed at centers in the United States or Canada, and we studied

the distribution of cancer in more than 18,000 patients with cystic fibrosis from 17 European countries.

METHODS

U.S. and Canadian Cohorts

Patients

The incidence of cancer in two cohorts of patients with cystic fibrosis was analyzed. The U.S. cohort consisted of all patients with cystic fibrosis who were registered and followed between 1985 and 1992 at any of 115 centers in the United States accredited by the Cystic Fibrosis National Foundation (see the Appendix). This registry currently includes nearly 20,000 living patients, representing 80 percent of the estimated 25,000 patients with cystic fibrosis in the United States.¹

The Canadian cohort was obtained from the Canadian Cystic Fibrosis Foundation Registry, which includes nearly 3000 patients in 33 centers, representing over 95 percent of Canadian patients with cystic fibrosis.

Reporting of Cancers

All U.S. and Canadian centers responded to a questionnaire requesting the number of incident cancers that had occurred between January 1, 1985, and December 31, 1992. Information supplied included the patient's date of birth, sex, and race; date of diagnosis of the cancer; type and location of tumor and histologic verification; and vital status.

Statistical Analysis

To calculate the number of cancers expected, the period during which patients were at risk was defined as the time from the organization of the cohort to death or to the end of the calendar year in which a patient visited a cystic fibrosis center. The time at risk for patients born after the establishment of the cohort began at that person's birth date. Two starting dates were chosen: January 1, 1985, and January 1, 1988. The first was chosen because the U.S. Cystic Fibrosis Registry was standardized as of that year. The second was chosen to exclude potential underreporting of cases in the earliest years of the study, while still allowing a five-year period of ascertainment. Data on all persons alive and actively followed were censored as of December 31, 1992. Data on persons reported as not seen during a calendar year or reported as lost to follow-up during that year were censored as of the end of the previous year.

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The number of cancers expected during both at-risk periods was determined by applying age-, sex-, and race-specific incidence rates from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute for 1984 to 1988 to the total person-years accumulated in the corresponding categories (five-year blocks).¹⁶ Because of the similarities of the cohorts and cancer rates in the United States and Canada, person-years accumulated by both the Canadian and U.S. cohorts were pooled. Ninety-five percent confidence intervals for the ratio of the number of cancers observed to the number expected were calculated on the basis of a Poisson model.¹⁷

For both periods, we calculated the expected number of all cancers as well as the expected numbers of three subgroups of cancer: digestive tract cancers, leukemias and lymphomas, and all other tumors. We also calculated the numbers of cancers expected for the following groups: 9 years of age and younger, 10 to 19 years, 20 to 29 years, 30 to 39 years, and 40 years and older.

Case-Control Study

We conducted an exploratory case-control study matching North American patients with cystic fibrosis who had cancer to a maximum of four patients with cystic fibrosis who were cancer-free. The patients were matched for age (within three years), sex, race, and center. Patients older than 40 years were matched for age within five years. The chi-square test was used to determine statistical significance.

European Cohorts

Patients

From data bases maintained by European cystic fibrosis organizations, we compiled a list of 377 centers or physicians who treat patients with cystic fibrosis in 17 European countries. The countries included in the study, and the estimated numbers of patients with cystic fibrosis in each country in 1992 as reported to the International Cystic Fibrosis Association, were as follows: Austria, 500; Belgium, 600; Denmark, 330; France, 5500; Germany, 3850; Hungary, 450; Iceland, 6; Ireland, 1000; Italy, 2400; the Netherlands, 800; Norway, 210; Romania, 120; Spain, 1510; Sweden, 350; Switzerland, 800; and the United Kingdom, 6000. For Finland, the estimated number of patients with cystic fibrosis was less than 100. The number of patients under treatment in these 17 countries was approximately 24,500.

The North American survey questionnaire was mailed to all identified physicians or treatment centers. Responses were received from physicians treating approximately two thirds of all patients with cystic fibrosis in the 17 study countries (see the Appendix). For the United Kingdom, Italy, Germany, Sweden, and Denmark, the overall rate of response was 88 percent. The study period extended from January 1, 1982, through March 1, 1994.

Statistical Analysis

Because there was no well-defined cohort of European patients with cystic fibrosis, we used proportional incidence ratios to measure the association between cystic fibrosis and any particular type of cancer. The data were analyzed as if arising from a case-control study in which the reference population included all patients with cancer, with cystic fibrosis as the exposure variable.¹⁸ Case patients with cystic fibrosis were defined as patients with tumors of the types under study; controls with cystic fibrosis were identified as patients with other types of cancer. Case patients and controls without cystic fibrosis were obtained from published data on the incidence of cancer according to age, sex, and country.¹⁹ If the odds ratio indicated an association between any particular type of cancer and cystic fibrosis, patients with that type of cancer were then excluded from both the group with cystic fibrosis and the referent group before an analysis was performed for other types of cancer. Logistic-regression analysis was used to calculate a summary odds ratio and 95 percent confidence interval for each type of cancer, adjusted for age (in five-year increments), sex, and country.

Since all cancers included in the final study occurred during or after 1982, recent country-specific data on the incidence of cancer in Europe were used to obtain the number of cases occurring in case pa-

tients and controls without cystic fibrosis.¹⁹ For Austria, we substituted data from Switzerland. Non-melanoma skin cancers were excluded from the comparison group without cystic fibrosis. For countries with more than one cancer registry, all reported cases of cancer from individual registries were combined.

For both Europe and North America, the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) was used to classify cancers into various groups.

RESULTS

North American Study

Characteristics of the Cohort

During the study period, 28,511 patients with cystic fibrosis were reported to the U.S. and Canadian cystic fibrosis registries. Of these, 15,161 were male (53.2 percent) and 13,350 were female (46.8 percent). Ninety-five percent of the cohort was described as white and 2.8 percent as black. The age at entry into the cohort ranged from birth to 64 years (median, 7).

From January 1, 1985, to December 31, 1992, a total of 164,764 person-years of follow-up was recorded. For the five-year period from January 1, 1988, to December 31, 1992, 24,869 persons contributed a total of 103,916 person-years of follow-up.

Reported Cancers

Between 1985 and 1992, 41 cancers were reported in the North American cohort. Four cancers that were not reportable on the basis of SEER data were excluded from the analysis: three carcinomas in situ and one basal-cell skin cancer. Thus, the study included 37 histologically confirmed cancers (32 in the United States and 5 in Canada) (Fig. 1). These consisted of 13 diges-

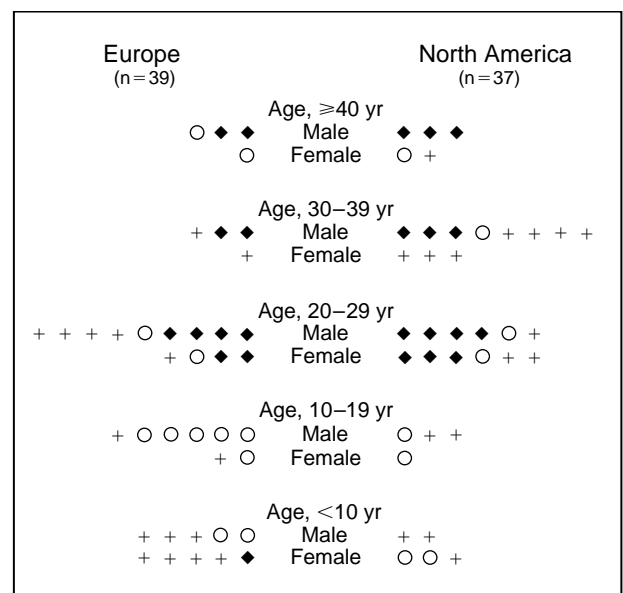


Figure 1. Cancers among 76 Patients with Cystic Fibrosis, According to the Patient's Age at Diagnosis of the Cancer, Sex, Type of Tumor, and Geographic Location.

The diamonds denote digestive tract cancers (ICD-9-CM codes 150 to 159), circles hematopoietic cancers (ICD-9-CM codes 200 to 208), and plus signs all other types of tumors.

tive tract cancers (esophagus, 1; stomach, 1; small intestine, 2; large intestine, 3; liver or biliary tract, 5; and pancreas, 1), 8 cases of leukemia and lymphoma (including 1 post-transplantation lymphoma), 5 central nervous system tumors, 4 testicular cancers, 2 cervical cancers, 2 breast cancers, 1 cancer of the tongue, 1 cancer of the thigh (rhabdomyosarcoma), and 1 malignant melanoma. All cancers occurred in white patients. Tables 1 and 2 and Figure 1 compare the demographic characteristics of the patients and the distribution of cancer among the North American and European groups.

Ratios of Observed to Expected Cases

From 1985 to 1992, a total of 45.6 cancers would have been expected in the North American cohorts with cystic fibrosis, on the basis of age-, sex-, and race-specific SEER rates (Table 3). Thirty-seven cancers were reported, yielding a ratio of observed to expected cases of 0.8 (95 percent confidence interval, 0.6 to 1.1). For digestive tract cancer, the ratio of observed to expected cases was 6.5 (95 percent confidence interval, 3.5 to 11.1). For leukemias and lymphomas, the ratio of observed to expected cases was 0.7 (95 percent confidence interval, 0.3 to 1.3). For all other tumors (after the exclusion of digestive tract cancers, leukemias, and lymphomas), the ratio of observed to expected cases was 0.5 (95 percent confidence interval, 0.3 to 0.8).

To determine whether the risk of cancer increases with age, the number of cases observed and the number expected in the North American cohort were calculated for five age groups (0 to 9 years, 10 to 19 years, 20 to 29 years, 30 to 39 years, and ≥ 40 years) for the full cohort (1985 to 1992). The age-specific ratios of observed to expected cases for all cancers were as follows: 0 to 9 years, 0.4 (95 percent confidence interval, 0.1 to 1.03); 10 to 19 years, 0.49 (95 percent confidence interval, 0.1 to 1.3); 20 to 29 years, 1.0 (95 percent confidence interval, 0.5 to 1.7); 30 to 39 years, 1.2 (95 percent confidence interval, 0.6 to 2.1); and ≥ 40 years, 0.9 (95 percent confidence interval, 0.3 to 2.1). A marked

Table 1. Comparison of North American and European Patients with Cystic Fibrosis and Cancer.

VARIABLE	NORTH AMERICA (N = 37)	EUROPE (N = 39)	TOTAL GROUP (N = 76)
Age at cancer diagnosis — yr*			
All cancers	26.9±13.4	21.5±15.9	24.2±14.9
Digestive tract	32.5±9	31.7±16	32.2±12.6
Hematopoietic	21.9±17.6	20.4±16.8	21.0±16.6
Other	24.7±13.1	15.3±11.9†	20.0±13.2
Sex — no. (%)			
Male	22 (59)	26 (67)	48 (63)
Female	15 (41)	13 (33)	28 (37)
Type of tumor — no. (%)			
Digestive tract	13 (35)	11 (28)	24 (32)
Hematopoietic	8 (22)	12 (31)	20 (26)
Other	16 (43)	16 (41)	32 (42)
Positive biopsy — no. (%)	37 (100)	37 (95)	74 (97)
Mortality rate — no. (%)	20 (54)	22 (56)	42 (55)

*Values are means ±SD.

†P=0.04 for the comparison with the North American group.

Table 2. Distribution of Cancer in 37 North American and 39 European Patients with Cystic Fibrosis, According to Age, Sex, and Type of Tumor.

TYPE OF TUMOR	AGE GROUP					TOTAL
	<10 YR	10-19 YR	20-29 YR	30-39 YR	40-49 YR	
Digestive tract						
Male	0	0	8	5	5	18
Female	1	0	5	0	0	6
Total	1	0	13	5	5	24
Hematopoietic						
Male	2	6	2	1	1	12
Female	2	2	2	0	2	8
Total	4	8	4	1	3	20
Other						
Male	5	3	5	5	0	18
Female	5	1	3	4	1	14
Total	10	4	8	9	1	32
All tumors						
Male	7	9	15	11	6	48
Female	8	3	10	4	3	28
Total	15	12	25	15	9	76

elevation of the risk ratio for digestive tract tumors was seen for the age range of 20 to 29 years (ratio of observed to expected cases, 23.2; 95 percent confidence interval, 10.6 to 44.0).

Because of possible underreporting of all cancers in the earliest years of the study, the number of cases observed and the number expected were also analyzed for the most recent five-year period for which data were available (January 1988 through December 1992). During this period, 29 cancers were observed and 29.8 were expected (ratio of observed to expected cases, 0.97; 95 percent confidence interval, 0.7 to 1.4). No change was seen in the ratio of observed to expected cases of digestive tract cancer: 9 were observed and 1.36 were expected, yielding a ratio of 6.6 (95 percent confidence interval, 3.0 to 12.6). The statistically significant deficit of other types of cancers observed in the full cohort disappeared. No significant difference was noted between sexes in the pattern of observed and expected cases of cancer.

Case-Control Study

Exploratory analysis of the 37 case patients and 131 matched controls in the North American cohort did not suggest any characteristics associated with an increased risk of cancer ($P>0.10$). The variables assessed included the age at diagnosis of cystic fibrosis; presenting signs and symptoms of cystic fibrosis, such as steatorrhea, malnutrition, meconium ileus, rectal prolapse, and liver disease; and subsequent clinical characteristics, such as malnutrition, decreased lung function, pancreatic insufficiency, cirrhosis, diabetes, distal bowel obstruction, rectal prolapse, and pancreatitis.

European Study

From January 1982 through March 1994, 41 patients with cystic fibrosis were given a diagnosis of cancer in the European centers (Fig. 1). Two patients were excluded: one with non-melanoma skin cancer and one with carcinoma in situ of the cervix. The following countries contributed 1 or more patients to the study:

Table 3. Number of Cancers Observed and the Number Expected among North American Patients with Cystic Fibrosis.

TYPE OF TUMOR* (ICD-9-CM CODE)	STUDY PERIOD	NO OBSERVED/ NO. EXPECTED	RISK RATIO (95% CI)†
Digestive tract (150–159)	1985–1992	13/2	6.5 (3.5–11.1)
	1988–1992	9/1.36	6.6 (3.0–12.6)
Hematopoietic (200–208)	1985–1988	8/11.85	0.7 (0.3–1.3)
	1988–1992	6/7.5	0.8 (0.3–1.7)
All other tumors	1985–1988	16/31.8	0.5 (0.3–0.8)
	1988–1992	14/20.1	0.7 (0.4–1.2)
Total	1985–1992	37/45.6	0.8 (0.6–1.1)
	1988–1992	29/29.8	1.0 (0.7–1.4)

*For the period 1985 to 1992, the specific tumors diagnosed consisted of 13 digestive tract cancers (esophagus, 1; stomach, 1; small intestine, 2; large intestine, 3; liver or biliary tract, 5; pancreas, 1), 8 hematopoietic cancers (lymphoma, 4; leukemia, 4), and 16 other types of tumors (tongue, 1; rhabdomyosarcoma, 1; malignant melanoma, 1; breast, 2; cervix, 2; testis, 4; brain, 5).

†CI denotes confidence interval.

the United Kingdom, 12; Italy, 10; Germany, 7; France, 3; Sweden, 2; Denmark, 2; and Austria, Hungary, and Spain, 1 each. The diagnosis of cancer was confirmed histologically in all but two patients, one with a clinical diagnosis of neuroblastoma and another with a diagnosis of a craniopharyngioma. Eleven of the 39 cancers (28 percent) originated in the digestive tract: 1 in the esophagus, 1 in the small intestine, 6 in the large intestine, 2 in the pancreas, and 1 in the retroperitoneum.

Analysis of the European data yielded findings similar to those of the North American study (Table 4). For digestive tract cancers the odds ratio was significantly elevated (odds ratio, 6.4; 95 percent confidence interval, 2.9 to 14.0). Significant associations were found for cancer of the esophagus, cancer of the small and large intestine, and cancer of the pancreas. For subjects who were 20 to 29 years of age, the odds ratio for all digestive tract cancers was 20.2 (95 percent confidence interval, 6.1 to 67). The single case of multiple myeloma and the three endocrine tumors were also statistically associated with cystic fibrosis. No significant association was found for the broader group of lymphatic and hematopoietic neoplasms (ICD-9-CM codes 200 to 208) or for the miscellaneous other tumors (odds ratio, 1.4 and 0.7, respectively).

Genotype Information

Genotype information was available for 21 patients (15 European and 6 North American). Fourteen patients (67 percent) were homozygous for the ΔF_{508} mutation.

DISCUSSION

In this study of more than 38,000 persons with cystic fibrosis, there is clear evidence of an excess of digestive tract cancers and no evidence of an increased risk of any other cancers. The digestive tract cancers included cancers of the esophagus, stomach, small and large intestine, colon, liver, biliary tract, pancreas, and rectum. Many of these patients were only in their third decade at the time of the diagnosis of cancer.

There have been only two other analyses of the risk of cancer in cystic fibrosis. One study of 712 patients

with cystic fibrosis did not show an excess risk,¹⁴ but another report involving 412 patients demonstrated a significant excess of pancreatic and small-intestine cancers.¹⁵

Our data show an excess of cancer in an organ system known to be disrupted by the cystic fibrosis disease process. Organ-specific risks of cancer may be associated with the differential localization and expression of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. High levels of *CFTR* expression, which are maintained throughout life, are found in many fetal and adult digestive tissues, such as pancreatic ducts, bile ducts, gallbladder epithelium, and intestinal crypts.^{20,21} In contrast, the expression of *CFTR* in respiratory tissue, although present in primordial lung epithelia, is greatly reduced at birth; in adult respiratory epithelia, the expression of *CFTR* is localized to the serous submucosal glands and a few cells in gland ducts, with little expression in other respiratory epithelia.^{22–25} Furthermore, the response of different organ systems to the absence of *CFTR* function appears to vary. Therefore, the differential risk of cancer in various organs may be partly explained by the level of *CFTR* expression and by varying sensitivities of individual organs.

Another possible explanation for our findings is that the excess risk of digestive tract cancer is caused by the effect of the cystic fibrosis disease process on digestive tract organs. Barrett's syndrome, a disease known to be associated with esophageal cancer, has been reported in patients with cystic fibrosis.²⁶ Hepatobiliary tract cancers often occur in patients with gallstones, and gallstones are frequently found in patients with cystic fibrosis.²⁷ Persistent pathologic alterations in digestive tract organs, leading to increased cell turnover, might

Table 4. Association between Cystic Fibrosis and Various Types of Cancer in European Patients.

TYPE OF TUMOR (ICD-9-CM CODE)	CASE PATIENTS	CONTROLS*	ODDS RATIO (95% CI)†
Digestive tract (150–158)	11	28	6.4 (2.9–14.0)
Esophagus (150)	1	28	14.3 (1.4–148)
Bowel (152–154)	7	28	9.3 (3.5–25)
Pancreas (157)	2	28	31.5 (4.8–205)
Retroperitoneum (158)	1	28	3.4 (0.4–29)
Lymphatic or hematopoietic (200–208)	12	16	1.4 (0.6–3.2)
Lymphoma (200–202)	5	23	1.1 (0.4–3.0)
Myeloma (203)	1	27	17.2 (1.9–159)
Leukemia (204–208)	6	22	1.3 (0.5–3.4)
All other sites	16	12	0.7 (0.3–1.6)
Oral cavity (140–149)	1	27	2.4 (0.3–19.5)
Lung (162)	1	27	1.4 (0.1–16.8)
Bone or soft tissue (170–171)	2	26	0.7 (0.2–3.1)
Ovary (183)	1	27	0.9 (0.1–7.9)
Testis (186)	2	26	0.7 (0.1–3.3)
Eye (190)	1	27	2.0 (0.2–16.6)
Brain or nervous system (191–192)	3	25	0.7 (0.2–2.5)
Thyroid (193)	2	26	2.6 (0.5–21.1)
Endocrine (194)	3	25	5.4 (1.5–19.8)

*For digestive tract, bowel, and pancreatic tumors, the controls are patients with cystic fibrosis and all other types of cancer. For tumors at other sites, the controls are patients with cystic fibrosis and all other types of non-digestive tract cancer.

†CI denotes confidence interval.

explain the excess risk of digestive tract cancer. Also, patients with cystic fibrosis frequently have steatorrhea, which has been linked to small-bowel cancer in patients with celiac disease.²⁸ Patients with cystic fibrosis and persistent malabsorption have also been found to have deficiencies of the antioxidants selenium and vitamin E, which may offer some protection from cancer.^{29,30}

Despite the excess number of digestive tract cancers, the total number of cancers was not increased. Warren and coworkers suggested that the cystic fibrosis gene may protect against some tumors, such as melanoma.³¹ However, even with the large numbers of patients and person-years included in the North American study, the small numbers of expected cancers limited our ability to detect minor age-specific or site-specific changes in the frequency of cancer. Prospective ascertainment of cancers over longer periods in these cohorts will be necessary to determine whether there are any other excesses or deficits.

Genetic data were only available for 21 of the 76 study patients with cancer. In this small group, the frequency of the ΔF_{508} mutation was similar to that in cancer-free patients with cystic fibrosis.³² More detailed genotypic analysis, including an examination of genes known to be associated with the risk of cancer, could yield potentially useful information.

There are several potential sources of bias in this study. The European study depended on the ability of physicians to report information about patients with cancer over a 12-year period. An apparent excess of digestive tract tumors would be observed if physicians were more likely to remember and report digestive tract tumors and to overlook non-digestive tract tumors. Such a differential bias seems unlikely, since the findings were nearly identical in the North American cohort. Five patients with cancer in the European series, including three with digestive tract tumors, were previously included in a cohort study. When these patients were excluded, the excess risk of digestive tract cancer persisted (odds ratio, 5.8; 95 percent confidence interval, 2.4 to 14.0).

The European study could be biased by an excess of non-digestive tract tumors in countries with a low response rate. Thirty-three of 39 cancers were reported from the United Kingdom, Italy, Germany, Sweden, and Denmark. When we restricted the analysis to these countries, where the overall rate of response was 88 percent, the excess risk of digestive cancer persisted (odds ratio, 6.7; 95 percent confidence interval, 2.9 to 15.4).

The risk of digestive tract cancers might have been overestimated in the North American cohort if cancer-free adult patients with cystic fibrosis were more likely to be lost to follow-up. Data from the U.S. Cystic Fibrosis Foundation show that approximately 600 persons are lost to follow-up each year at a median age of 16 years. Given this, the expected number of total cancers could be expected to increase by less than one case. It is also possible that occult cancers were missed in living patients because of the severity of cystic fibrosis

and the similarity of the gastrointestinal symptoms of cancer and cystic fibrosis; if so, our results are conservatively biased. Finally, for both the North American and European studies, increased surveillance might have led us to detect more cancers in the patients than are detected in the general population. This seems unlikely since the elevated risk of cancer was restricted to a single organ system, with no apparent overall increase in the risk of cancer.

Despite these possible biases, it appears that cystic fibrosis can be added to the growing list of genetic defects that are related to cancer. As the life span of patients with cystic fibrosis increases, more digestive tract cancers will occur. Although cancer will continue to be an uncommon diagnosis for patients with cystic fibrosis, the increased risk of digestive tract cancer in these patients suggests that persistent or unexplained gastrointestinal symptoms deserve careful investigation.

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APPENDIX

The following physicians contributed one or more cases to the study:

Canada — E.R. Ecclestone, Children's Hospital of Western Ontario, London, Ont.; and H. Levison, Hospital for Sick Children, Toronto.

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