Cancer risk in patients with cystic fibrosis: the European data

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INTRODUCTION

Some recent reports suggest that there may be an association between cystic fibrosis (CF) and cancer, particularly digestive tract cancer[1,2]. One-third of all patients now attain adulthood. With increased survival, it is possible that a predisposition to malignancy, previously obscured by the short life-span of these patients, will become evident. However, in a large international survey we could demonstrate that the overall risk of cancer in patients with cystic fibrosis is similar to that in the general population and that there is about a 6 fold excess of digestive tract tumours[3].

In the present paper we report the European data, which were collected during January 1985 through July 1992 in 17 European countries, which were included in part in the previous report[3].

METHODS

To study the frequency of cancer in patients with CF, we requested information about the occurrence of cancer from 377 centres or physicians who treat patients with CF in 17 European countries. Additional cancer information was received directly from the UK CF Survey. The countries responding to our requests included all those shown below.

Austria	500	Belgium	600
Denmark	330	France	5500
Germany	3850	Hungary	450
Iceland	6	Ireland	1000
Italy	2400	Netherlands	800
Norway	210	Romania	120
Spain	1510	Sweden	350
Switzerland	800	UK	6000
Finland	Not reported		

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The numbers of CF patients in these countries were based on reported incidence data of the national CF associations. In the questionnaire, the following questions were asked: (1) number of patients currently under treatment in the specialized centre; (2) length of the observation period of the patients reported; (3) number of cases with cancer; and (4) cancer patients' data as age, sex, race, vital status, date of diagnosis, type of cancer and confirmation by histology or autopsy and if available the determined genotype.

The ninth revision of the International Classification of Diseases (ICD) was used to classify cancers into five major groups: digestive (ICD Nos 150–159); brain (ICD Nos 191–192); lymphoma (ICD Nos 200–202); leukaemia (ICD Nos 204–208); all others.

Several statistical models were used to analyse data[4].

(1) Comparison was made between the observed distribution of different types of cancer in the CF patients with the expected distribution of cancer in the background population of each country, after adjusting for sex and age. Furthermore, the ratio of observed cases of specific types of cancer divided by the expected number of cancers multiplied by 100 defines the proportional incidence ratio (PIR)—the measure of risk reported; 5 year age-bands were used to adjust for age.

(2) The PIR can be expressed as $PIR=(R/E)\times 100$ where R=observed number of cancer cases in the CF group of interest and E=expected number of cancer cases in the CF group of interest. The expected number of cancer cases (E) is obtained as follows:

$$E = \sum_i t_i (r_i^*/t_i^*)$$

r_i^*=number of cases of the cancer group of interest in the age group i in the standard population

t_i^*=number of cases of cancer (all sites) in the age group of the CF study group

t_i^*=total number of cases of cancer in age group i of the CF group

For the estimation of the standard error of the PIR the conservative method by Breslow and Day was used: $SE(\log PIR)=1/R^{0.5}$

Since we could not define a consistent cohort in Europe, the data were also analysed with the method of a case control study, where the referent population included all cancer patients, and the exposure variable being CF. The calculated odds ratio then expressed the strength of the association between CF and any type of cancer.

RESULTS

In the 17 countries approximately 24 500 patients were included. The overall response rate to the questionnaire was 66%; for UK, Italy, Germany, Sweden and Denmark it was 88%.

The final group consisted of 39 patients (13 females, 26 males) with cancer diagnosed during the years 1982–1993. Mean age of the patients at the time of diagnosis of cancer was 21.5 ± 15.9 years (standard deviation, range 0.5–63 years). Twenty-two patients (56%) died during the study period. The number of cancers reported by country were:

UK	12	Italy	10
Germany	7	France	3
Sweden	2	Denmark	2
Austria	1	Hungary	1
Spain	1		

The distribution of tumours was as follows: digestive tract=11 (oesophagus=1, small intestine=1, large bowel=6, pancreas=2, intestinal tract, other=1); lymphoma=5; leukaemia=6, brain=3; other=14 (oral cavity=1, lung=1, soft tissues=2, female reproductive=1, testis=2, eye=1, thyroid=2, endocrine=3, myeloma=1). The data of location of the tumours and their association with CF is shown in Table 1. In this table comparisons for digestive tract cancers were made to controls including all patients with CF and all other types of cancer: for tumours at other sites, the controls were patients with CF and all other types of non-digestive tract cancer. If age and sex standardized proportion ratios were used the highly significant proportional incidence ratios for digestive tumours, even in subsites, were obvious (see Table 2). Of the 39 tumours, 37 (95%) were histologically verified: the final pathological diagnosis, the city and country from where the cancer was reported, the age, sex and whether the patients died or are still alive, are given in Table 3. Three cancer patients were excluded from the analysis, since they were diagnosed before 1977 and two unclear cases were omitted due to unclear histological and clinical diagnosis. Table 4 depicts the distribution of identified cancer cases by age, sex and tumour type, and Figure 1 shows the geographical distribution of cancers found in Europe.

DISCUSSION

As in the USA survey we observed a strong association between digestive tract cancers and CF: odds ratio=6.4 (95% confidence limit: 2.9–14). In the CF population in Europe the excess of digestive cancer was similar to that reported in the North American CF population with an odds ratio of 6.5. One previous cohort study based on data from the National Cystic Fibrosis Registries in the USA[1] and another from a single hospital in the UK have examined the risk of cancer in patients with CF[2]. In both studies an increased risk of digestive tract cancer was found. In the present study, which is a part of an international collaborative study between Europe and US/Canada CF centres[3], based on data from the majority of CF patients in 17 European countries, there is also a definite increased risk of gastrointestinal cancers.

PIR, obtained by dividing observed by expected cancer cases, was significantly elevated for all digestive tumours with a PIR of 377% (95% confidence limit: 209–680%). The highest proportional incidence ratio, 1132% was observed for pancreatic cancer. Furthermore, an excess of endocrine tumours (n=3) and myeloma (n=1) was observed (P=0.01), but these findings were based upon very small numbers.

In fact there are now three conclusive studies reporting an excess of cancer in one of the major organ systems known

Table 1 **Association between cystic fibrosis and cancer in Europe**

Type of tumour	n	*Controls*	*Odds ratio (95% CI)*
Digestive tract*	11	28	6.4 (2.9–14.0)
Lymphatic or blood	12	16	1.4 (0.6–3.2)
All other	16	12	0.7 (0.3–1.6)
Total	39		

*Digestive tract tumours include (n): Oesophagus (1); bowel (7); pancreas (2); retroperitoneal (1)

Table 2 **Observed and expected tumours in European cystic fibrosis patients**

Cancer site	*Observed*	*Expected*	*PIR (%)*	*PIR (95%CI)*
Digestive tumours	11	2.92	377	209–680
Bowel, colon, rectum	6	1.35	446	200–993
Pancreas	2	0.17	1144	286–4574
Soft tissues	2	3.32	60	15–241
Testis	2	4.84	41	10–165
Thyroid	2	1.15	174	44–696
Brain tumours	3	4.82	62	20–193
Lymphomas	6	6.16	97	44–217
Leukaemias	5	5.49	91	38–219
Other tumours	8	10.29		

PIR=Proportional incidence ratio; CI=confidence interval

Table 3 **Cystic fibrosis and cancer in Europe: summary of the findings**

City	Country	Birth (year)	Alive/year of death	Cancer	Age	ICD	Sex	Year diagnosed	Group*	Histology
Innsbruck	Austria	1969	a	Adrenocortical carcinoma	23	194	f	1992	OTH	Yes
Copenhagen	Denmark	1968	1989 (d)	Myeloid leukaemia	21	205	f	1989	LEU	Yes
Copenhagen	Denmark	1976	1985 (d)	Abdominal B-lymphoma	10	205	m	1986	LYM	Yes
Sevilla	Spain	1975	1987 (d)	NHL Burkitt-Type Stadium I	11	200	m	1986	LYM	Yes
Vandoeuvre	France	1982	a	Retinoblastoma	2	190	m	1984	OTH	Yes
Camiers	France	1976	1993 (d)	Chondrosarcoma	17	170	m	1993	OTH	Yes
Dunkerque	France	1963	1989 (d)	Digestive carcinoma (glandular type)	25	159	f	1988	DIG	Yes
Kreefeld	Germany	1976	1993 (d)	AML	17	205	f	1993	LEU	Yes
Essen	Germany	1964	1992 (d)	ACD	28	153	m	1992	DIG	Yes
Mechernich	Germany	1966	a	Seminoma Stadium I	25	186	m	1991	OTH	Yes
Frankfurt	Germany	1982	a	Neuroblastoma	1		m	1982	OTH	No
Giessen	Germany	1971	1990 (d)	Non-Hodgkin lymphoma	17	200	m	1988	LYM	Yes
Homburg	Germany	1967	1990 (d)	Teratoma (retroper. intermed. type)	22	158	m	1989	DIG	Yes
Böblingen	Germany	1967	1993 (d)	Chronic myeloid leukaemia	19	205	m	1986	LEU	Yes
Parma	Italy	1963	a	Pharyngeal undiff. lymphoma UL	28	149	m	1991	OTH	Yes
Firenze	Italy	1971	a	Thyroid papillary carcinoma	22	193	m	1993	OTH	Yes
Genova	Italy	1991	a	Neuroblastoma	1		f	1992	OTH	Yes
Messina	Italy	1959	a	Colorectal adenocarcinoma	25	153	m	1984	DIG	Yes
Roma	Italy	1986	a	Acute lymphoblastic leukaemia	2	204	m	1988	LEU	Yes
Roma	Italy	1966	1990 (d)	Hodgkin's lymphoma	21	201	m	1987	LYM	Yes
Verona	Italy	1978	1982 (d)	Craniopharyngioma	4	192	f	1982	BRA	No
Verona	Italy	1973	a	Cystadenocarcinoma right ovary	19	183	f	1992	OTH	Yes
Huddinge	Sweden	1919	1991 (d)	Colonic cancer (recto-sigmoid)	63	153	m	1982	DIG	Yes
Huddinge	Sweden	1961	1993 (d)	Liver with myeloproliferative disease	32	155	m	1993	OTH	Yes
Lund	Sweden	1948	a	Papillary carcinoma of thyroidea	37	193	f	1985	OTH	Yes
Manchester	UK	1980	a	Ependymoma of posterior fossae	2	191	f	1982	BRA	Yes

Glasgow	UK	1949	1983 (d)	Adenocarcinoma of bowel	34	153	m	1983	DIG	Yes
Norfolk	UK	1958	a	Oesophageal adenocarcinoma metastatic	35	150	m	1993	DIG	Yes
CF-Survey	UK	1956	1987 (d)	Teratoma testicle right	30	186	m	1986	OTH	Yes
CF-Survey	UK	1955	1984 (d)	Carcinoma of ileo-caecal junction	29	152	m	1984	DIG	Yes
CF-Survey	UK	1923	a	B-cell lymphoma/lymphatic leukaemia	63	204	m	1986	LEU	Yes
CF-Survey	UK	1933	1991 (d)	Pancreatic carcinoma	58	157	m	1991	DIG	Yes
CF-Survey	UK	1960	1984 (d)	Adenocarcinoma of pancreas	24	157	f	1984	DIG	Yes
CF-Survey	UK	1974	a	Fibrosarcoma of foot	9	171	m	1983	OTH	Yes
CF-Survey	UK	1973	1992 (d)	Lymphoproliferative disorder spleen/neck	19	203	m	1992	LYM	No
CF-Survey	UK	1985	a	Haemangioendothelioma of colon	6	153	f	1991	DIG	Yes
CF-Survey	UK	1987	1993 (d)	Glioblastoma of brain	6	191	f	1993	BRA	Yes
CF-Survey	UK	1974	a	Hodgkin's lymphoma	17	201	m	1991	LYM	Yes
Mosdos	Hungary	1971	1991 (d)	Pulmonary carcinoma	20	162	m	1991	OTH	Yes
Exclusions										
Diagnosed before 1977										
Uppsala	Sweden	1961	a	Wilms's tumour	4	189	m	1965	OTH	Yes
CF-Survey	UK	1965	a	Lymphoma right tonsil	21	200	m	1976	LYM	Yes
Nottingham	UK	1974	1986 (d)	Pontine glioma	2	191	f	1976	BRA	Yes
Unclear cases										
CF-Survey	UK	1949	a	Non-melanoma skin cancer	44		m	1993	OTH	No
Halle	Germany	1960	a	Carcinoma *in situ* of cervix	29		f	1989	OTH	Yes

NHL=Non-Hodgkin lymphomas; AML=Acute myeloblastic leukaemia; ACD=adenocarcinoma colon discendens; Tera=teratoma; UL=undifferentiated lymphoepithelioma; DIG=digestive tumours ICD 150–159; BRA=brain tumours ICD 191–192; LYM=lymphomas ICD 200–202; LEU=leukaemias ICD 204–208; OTH=all other malignant tumours

Table 4 **Distribution of cancer cases by age, sex and tumour type**

Females		*Males*
✱✣✣	0–4	■✱✱
✣●	5–9	✱
	10–14	◆◆
✱■	15–19	■◆◆◆✱
✱■●	20–24	●◆◆✱✱
●	25–29	●●●✱✱
	30–34	●✱✱
✱	35–39	●
	40–44	
	45–49	
	50–54	
	55–59	●
	60–64	●■
	65+	

●-Digestive tract (ICD9 150-9)
■-Leukaemias (ICD9 204-8)
◆-Lymphomas (ICD9 200-2)
✣-Brain tumours (ICD9 191-2)
✱-Other tumours

to be disrupted by the disease process. Interestingly, this excess is confined to the gastrointestinal tract, whereas only one tumour originated from the lung was found. If the CF gene was itself responsible for cancer in these patients, then one would have expected to see a more uniform increase in the risk of cancer in various organ systems. It seems much more likely that the excess risk of gastrointestinal cancer in these patients is caused by a secondary effect of the CF disease process on the digestive organs. Some degree of pancreatic insufficiency and disturbed intestinal motility is common in the majority of CF patients. Persistent pathologic alterations in digestive tract organs, perhaps associated with increased cell turnover, might well be the mechanism eventually leading to excess cancer.

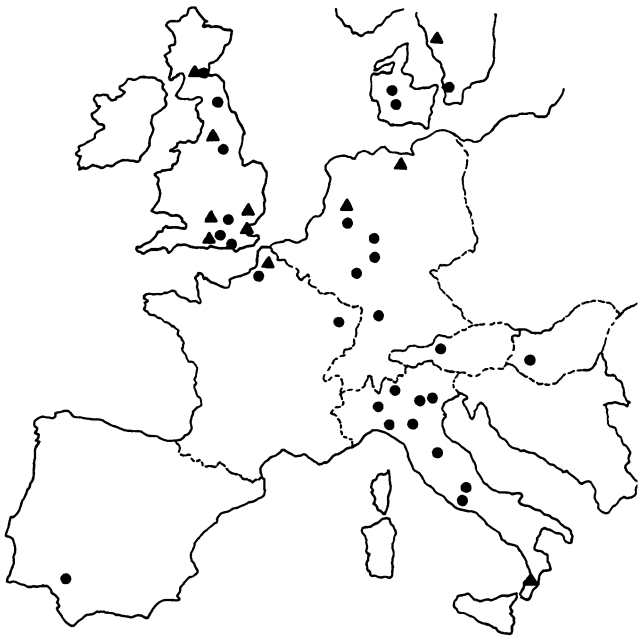

Figure 1 **Geographic distribution of cancer cases in European cystic fibrosis patients. ▲=Digestive; ●=non-digestive**

There could be other possible explanations for our findings. In particular, this study relied upon the ability of physicians to report information about patients with cancer over a 12 year period. An apparent excess of digestive cancers would be observed if physicians were more likely to remember and report digestive tumours and to overlook non-digestive tumours. Such a differential bias seems unlikely, since the findings of the two previous studies were unknown well after data collection was initiated for this study.

Finding an excess of digestive cancer in this proportional incidence study would result if cystic fibrosis selectively protects against non-digestive tract tumours. Under this unlikely circumstance, digestive tract tumours would appear to be increased. The study could also be biased if there were a large excess of non-digestive tract tumours in those countries with low response rate. However, when we restricted the analysis to those countries with a high response rate—UK, Scandinavia, Italy and Germany—the excess risk was still present (PIR 374%; 201%–696%CI). Five cancers in this study, including three digestive tract tumours, have been previously included in a cohort study from the UK[2]. When we removed these cases to restrict the analysis to previous unreported cases, the excess of digestive tract cancer remains (PIR 385%; 193%–770%CI).

One hundred and eighty-three centres supplied demographic data about the average number of patients under observation, sex, age distribution and length of observation period. For these centres we could calculate an approximate estimate of the incidence of cancer in patients with CF, based upon age and sex-specific person-years data. For these centres a total of 27 cancers were observed compared to 25.1 expected. For digestive cancers seven tumours were observed versus 1.16 expected (P=0.007). This analysis suggests that the overall risk of cancer in patients with CF is not increased and confirms the excess of gastrointestinal tumours.

It appears that CF must be added to the growing list of genetic disorders that are linked to cancer. Despite the fact that genotype information was available in only 27.6% of the patients and the homozygous delta F508 genotype was present in 67% one must assume that the linkage of cancer to the digestive tract is indirect and could be explained by organ damage induced by CF.

It has been suggested that generally adopted cancer screening methods such as determination of blood in stool

might be helpful. If one takes all reported cancers of the gastrointestinal tract in CF patients in North America and Europe into consideration, the actual number was small—only about 2–3 tumours per year. Only a single tumour each year would arise in the small or large bowel where examining the stool for blood, and, because false positive tests are common, testing for occult blood in CF patients seems not a valid option at this time. The risk of cancer, however, is likely to persist or even increase since longevity under improved therapy conditions or even under lung–gene therapy will increase.

We conclude that the risk of digestive cancer is significantly elevated in patients with CF and we anticipate that the frequency of cancer, and particularly digestive cancer, will increase as the life span of CF patients increases.

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