Incidence and risk factors of cancer in individuals with cystic fibrosis in the UK; a case-control study

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Abstract

To assess cancer incidence in the UK cystic fibrosis (CF) population and determine the associated risk factors, we undertook a nested case-control study of patients with CF, registered with the UK CF Registry. Each case with a first reported cancer between 1999 and 2017 was matched with up to 4 controls: by age (±2-years) and year of cancer diagnosis. Conditional logistic regressions were adjusted for sex, lung function (FEV_1%), CF related diabetes (CFRD), *F508del* status, transplant status, DIOS, gastro-oesophageal reflux disease, meconium ileus, Pseudomonas aeruginosa infection, pancreatic insufficiency, proton pump inhibitor (PPI) use, IV antibiotic days and BMI. **Results**: From 12,886 registered patients, 146 (1.1%) cases of malignancy were identified with 14.3% of cases occurring post solid organ transplant. Site of primary cancer was available for 98 patients: 22% were gastro-intestinal in origin (77% lower, 23% upper GI), 13% skin, 13% breast and 11% lymphomas/leukaemia. In univariable analysis, transplantation increased the odds of reporting any cancer by 2.4 times (95%CI: 1.3-4.6). An increased risk of reporting any cancer was found for CFRD (OR 2.35; 95% CI: 1.37-4.00) and PPI use (OR 2.0; 1.28-3.19). In the multivariable model significant associations with CFRD and transplant remained, while PA infection, PPI use and being overweight showed increased, but statistically insignificant risks. The incidence of GI cancer was strongly associated with CFRD (OR=4.04; 1.30-12.0). **Conclusions**: We observed a high incidence of lower GI cancers in our cohort which was significantly affected by the presence of CFRD. Screening for gastrointestinal cancers could benefit patients at higher risk.

- What is the key question?

Which are the most common cancers in the UK cystic fibrosis population and what factors are associated with the incidence of all cancers and in particular gastrointestinal malignancies?

- What is the bottom line?

The types of cancer in people with CF are varied but reflect those found in the general population. Any cancer and particularly GI cancer appear to be peaking at a younger age, while CFRD is confirmed as a risk factor alongside transplantation.

- Why read on?

This is the largest study conducted in the UK CF population exploring patterns of cancer incidence and factors associated with it. We observed a high incidence of GI cancers, skin and breast cancers compared to other cancer types. Screening for gastrointestinal cancers could benefit patients at higher risk.

Background

Individuals with cystic fibrosis (CF) are known to develop complications in multiple organ systems, including respiratory, gastrointestinal, and reproductive tracts. Early detection, improvements in nutrition, airway clearance therapy, and organ transplantation have led to a marked increase in life expectancy over the past 30 years.[1] Consequently, as the proportion of individuals surviving into adulthood increases, non-respiratory complications such as cancer are more common. In 1993, Sheldon et al. conducted the first cohort study of the association of CF with malignancy[2] and observed a possible association of CF with adenocarcinoma of the pancreas and terminal ileum, but only a single case was observed in each organ.

Previous studies have suggested that people with CF did not have elevated overall cancer risk, but did demonstrate a 3–6 fold increased risks for cancers of the digestive tract.[3-6] A recent systematic review with meta-analysis of 6 cohort studies that included a total of 99,925 individuals, confirmed that people with CF have a significantly higher risk of gastrointestinal cancer than the general population, including cancers of the small bowel, colon, biliary tract, and pancreas.[7] Initial studies focused on transplanted CF populations in whom there is an increased risk of malignancy due to immunosuppression. Maisonneuve et al. in the US reported an elevated cancer risk among people with CF who received a lung transplant, with nearly a 3-fold increased risk for cancer overall and 17-fold increased risk for digestive tract cancers. The authors reported a 6-fold increased risk of colon cancer among people with CF without a transplant and a 30-fold increase following lung transplant[6].

The risk factors for developing cancer in the general population have been extensively examined, with obesity and type 2 diabetes being well recognized risk factors[8]. There are few published data investigating potential risk factors for developing cancer in the CF population. The aim of this study was to describe the patterns and types of cancer reported in the UK CF population, using data obtained over a 17-year period from the UK Cystic Fibrosis Registry. An additional aim was to determine factors that affect the incidence of cancer in people with CF and in particular gastrointestinal types of cancer. Such information could identify those individuals at higher risk of developing cancer who might benefit from screening.

Methods

Study subjects and design

This is a nested case-control study of people with CF registered with the UK CF Registry. These individuals are seen in one of 60 specialist CF centres (comprising 27 adult and 33 paediatric clinics) for a comprehensive annual review, including evaluation of clinical status and use of major CF related therapies. This dataset captures information on all major complications including cancer. Other variables include demographics, diagnostic and laboratory data, nutrition, pulmonary function, respiratory and microbiology. The UK Cystic Fibrosis Registry is believed to include 99% of people with CF in the UK; further details about the registry can be found in its data resource profile.[9]

Identification of cases

The study population included people with CF whose details were recorded in the Registry between 1999 (first cancer case identified) and 2017, whether alive or deceased. The total

number of individuals with data recorded was 12,886, ranging in age from 0-82 years. Cancer cases are recorded as a yes/no variable, from 2016 a variable for type of cancer variable was available. The free text variable for 'complications' was also searched for mention of cancer and specific cancer names and sites. In addition, the free text field for 'cause of death' was also searched with the same strategy to attempt to capture all cancer cases. Gastrointestinal (GI) cancer cases were defined as those that reported colon, rectal, bowel, ileum, or oesophagus cancers.

Selection of controls

For each case (n=146), four controls with no history of cancer (n=575) were selected from the UK CF Registry database matched by age (within a 2-year window), pancreatic insufficiency status and by the year cancer was first recorded for the cases. They were not matched by sex.

Statistical analysis

Data are summarized using mean ± standard deviation (SD) or median (IQR) for continuous variables and number (%) for categorical variables. T-tests were performed to assess the mean differences in continuous normally distributed variables, Wilcoxon rank sum tests for skewed data and chi-square tests for categorical. To estimate the risk of cancer compared to controls, conditional logistic regression models were applied adjusted for sex, lung function (forced expiratory volume in 1 second recorded as % predicted according to GLI reference equations (FEV_1%), smoking, cystic fibrosis related diabetes (CFRD), F508del mutation status, past transplant status, Distal Intestinal Obstructive Syndrome (DIOS), gastro-oesophageal reflux disease (GORD), meconium ileus (MI), pancreatic insufficiency, iv antibiotics (home and

hospital) and BMI; the results are expressed as odds ratios (OR) with 95% confidence intervals (CI) . To assess the shape of the association between age and cancer, and estimate hazard ratios we used restricted cubic splines with 5 knots and the reference value of 25 years of age.

Results

A hundred and forty-six cases of cancer were reported as occurring for the first time in the year prior to an annual review; 98 of them had information regarding the type of cancer. Types of cancer and age of acquisition are shown in Table 1. Of the 98 cancer types identified, 22% were cancers of the gastro-intestinal tract (n=22), reproductive organ cancers across both sexes accounted for 18% (n=18, with 6 being testicular). Overall 13 cases of skin cancer were recorded with melanoma (n=5) and basal cell carcinoma (n=2) mentioned independently. Breast cancer was recorded across the adult age groups, peaking in the 26-35 year olds (n=13). One patient reported a second type of cancer within four years of the first (melanoma in 2012 and caecal cancer in 2016). Cancers in children were rare (n=8, 5% of the total cancers) and consisted of those known to occur in childhood such as leukaemia and brain tumours. Fifty percent of the identified cancers were observed between the ages of 26-45 years.

The 146 cancer cases were matched with 575 controls. Of the cases, 135 were perfectly matched with 4 controls each by year of diagnosis and age, the remaining were matched with a minimum of two controls and 6 needed to be matched to within 2 years of diagnosis rather than 1. The groups were well matched for age and year of annual review with the mean age being 40.6 years (41 years for cases, 40.3 for controls). Table 2 shows characteristics in the year of diagnosis of cancer. The groups showed no differences in gender, genotype, or smoking.

Risk of all cancers

In univariable analysis, having received a previous lung transplant increased the odds of reporting any cancer by 2.4 times (95%CI: 1.31-4.62). An increased odds of reporting any cancer was also found in those with CFRD (OR=2.3, 95% CI: 1.37-4.0) and for those using a proton pump inhibitor (OR=2.02, 95%CI 1.28-3.19). When these common risk factors were added into the model, backward stepwise selection showed that only CFRD and past transplant remained as important risk factors for developing any cancer (OR=1.9; 95%CI: 1.1-3.4 and OR=2.2; 95%CI: 1.1-4.6, respectively) (Table 3).

The hazard ratio for developing any cancer increased with age, this is shown graphically in the cubic spline figure 1. We observed a non-linear relationship between age and risk of cancer; specifically cancer incidence increased with age after the age of 25, peaked at the age of 40, decreased by the age of 50 and then started to rise again, with wide confidence intervals in the older age range reflecting smaller numbers.

Risk of GI cancers

In univariable analysis, the strongest risk factors for GI cancers were past transplant, CFRD, and GORD. (Table 3) The multivariable model showed previous transplant, GORD, DIOS, MI, chronic *Pseudomonas* and higher BMI were associated with an increased risk of GI cancers, however these associations were found to be statistically insignificant, leaving only the association with CFRD remaining (OR= 3.83; 95%CI: 1.29-11.3).

Discussion

We observed a high incidence of GI cancers, skin and breast cancers compared to other cancer types in our cohort. These occurred in young age groups with a median age at diagnosis of 40 years (IQR=32-50).

Gastro-intestinal tract cancers

Gastro-intestinal complications are common in CF and may be implicated in the increased risk of gastro-intestinal cancer. Gastro-oesophageal reflux, for example, is common and is linked to oesophageal cancers. This may explain the univariable association with proton pump inhibitors in our study. Pro-inflammatory states are also linked to GI cancer and an association with CF is not surprising as it is a disease of exuberant inflammation; there is direct evidence of increased inflammation in the CF gut with studies showing increased levels of the inflammatory biomarker calprotectin in CF stool samples.[10] It has also been postulated that the risk for developing colon cancer post lung transplant may be related to masking of symptoms of GI cancers in this group because of the side effects of the immunosuppression drugs that can mimic warning signs of GI cancer.[11] A study of the US Transplant registry has shown a 24 fold increase in colorectal cancer for individuals with CF post lung transplant.[12]

A single centre study prospectively performed colonoscopies in 88 people with CF, age ≥ 40 between 2008-2015. Adenomas, which can be a precursor to cancer were identified in 43 (49%) at initial screening colonoscopies, CFRD and the homozygous *F508del* genotype were statistically significant risk factors, and there was a trend toward significance with lung transplantation. Three were diagnosed with colonic malignancy, all homozygous *F508del* with documented CFRD.[13]

Other cancer types

In 2016, the year with the highest skin cancer incidence in our cohort there were four new cases representing 41 cases per 100,000, this appears to be higher than the general population with data from 2012 showing 21.6 new cases per year per 100,000 in the US and 13.2 new cases per year, per 100,000 in Europe.[14,15] We know that some commonly used drugs in CF such as azole antifungals and ciprofloxacin cause photosensitivity and there is a link to squamous cell carcinoma with long term use.[16] The thirteen cases of breast cancer reported in our cohort, indicates a rate of 46.5 cases per 100,000 of the population, compared to 14.5 cases reported by the UK Office of National Statistics (ONS) in 2017 for the general population, again suggesting there may be a higher incidence than in the general population, although there needs to be caution in this interpretation because of the small numbers in our cohort.

Twelve percent of the identified cases were lymphomas and leukaemia cancers which are frequent post lung transplant. These numbers appear high when compared to the study by Maisonneuve et. al. who found the absolute increase remained very low (approximately 2 per 100,000); the authors suggested that this might be due to the life-threatening nature of CF itself, that gave their study a low incidence.[6] There are concerns about the possible risk of radiation-induced cancer in CF with a lifetime of multiple radiological examinations from childhood including radiographs and computed tomography. In particular, exposure to postnatal diagnostic x-rays has been associated with an increased risk of childhood acute lymphoblastic leukaemia[17,18]. Apart from lymphoblastic cancers, it is also possible that some of the colon tumours in CF might be associated with excess radiation because in people with inflammatory bowel disease, repeated exposure to x-ray (small bowel radiographs or barium enemas) has been shown to potentially increase the risk of colorectal neoplasia[19]. However,

our analysis does not confirm that DIOS or neonatal MI are independent risk factors for GI cancers, and it would be this group that were most likely to have multiple abdominal x-rays leading to increased abdominal radiation exposure.

There was a low incidence of cancer of the respiratory tract and renal cancers (Table 1), possibly attributable to the low prevalence of smoking reported in the CF population at only 2.79%.

Common cancer risk factors

We found an increased association between CFRD and cancer. Associations between type II diabetes and cancer in the general population have been established through past epidemiological studies such as The National Health and Nutrition Examination Survey I (NHANES I) where it was reported that men with diabetes had a 39% increased risk of developing cancer overall, specifically colorectal and prostate cancer.[20] The Nurses' Health Study reported a 17% increased risk of breast cancer (HR 1.17, CI 1.01–1.35) in women with diabetes.[21] This association remained after adjustment for multiple factors and was found to be independent of age and obesity. One of the largest cohorts with the longest duration of follow up is the CPS II cohort.[22] After following these group for 26 years, an increased risk of death from liver, pancreatic, colon, and breast cancer was observed in both men and women with diabetes. Many other studies and meta-analyses have shown increased cancer incidence and mortality in people with diabetes, compared with the general population.[8]

We found no increase in risk of cancer in association with homozygosity for *F508del* mutation. This is in line with a Swedish registry study that assessed 884 people with CF from 1968 to 2003 and 3,033 of their first-degree relatives which did not find a heterozygote advantage for CF gene mutations in relation to cancer risk.[23]

There are multiple potential metabolic abnormalities that occur in diabetes that may explain the associated increased cancer risk. Developing fields of research include the role of the insulin receptor signalling and, interestingly, how changes in the intestinal microbiome may lead to obesity, diabetes, and cancer. The abnormalities of the gut microbiome are now becoming better understood in CF and this needs to be an area of further research in CF to establish if there is a link with the increased bowel cancer seen.[24-26]

Potential mechanisms

The underlying mechanism that drives GI or colon carcinogenesis remain speculative, Assis et al.[27] suggested it may be related to persistent inflammation generated or exacerbated by the absence or reduced function of CFTR protein in epithelial tissues. The malignancies reported in CF seem to originate in locations where CFTR is highly expressed, a PI children with CF have been shown to have increased intestinal cell turnover, raising the possibility that this contributes to malignancy later in life.[28] This is in line with findings of studies identifying apoptosis as a prognostic risk factor of various cancer types in the general population.[29,30]

CFTR has been identified as a potential driver of colorectal carcinoma, the dysfunction of CFTR affects the hydration of the mucus layer, changes the composition of microbiota, and can then affect epithelial function further. There are dysregulated genes that act as tumour suppressors (such as Kcnq1) and are associated with gastrointestinal malignancies these are thought to be linked to CFTR deficiency.[31] Further, CFTR participates in maintenance of tight junctions, and may contribute to epithelial cell polarization.[32,33] Another suggested mechanism is the increase in oxygen free radical generation from activated neutrophils, which is increased in CF populations[34] and has been linked with the development of cancer in the general population.[35]

Public health implications

The finding of high levels of potentially pre-cancerous adenomas in the single centre US study[13] has led the Cystic Fibrosis Foundation Task Force there to recommend initiating colon cancer screening at age 40 years, with repeat screening every 5 years thereafter, or 3 yearly surveillance endoscopies if pre-cancerous changes are found. Some UK CF centres have already started colon cancer screening although this is not yet a national requirement. There are 15 cases of known lower GI bowel cancer reported in the over 40 age group in this study. There are 1037 adults with CF above 40 years of age reported in the 2017 UK CF Registry.[36] Yearly there are between 15 and 20 new cancers of all types reported for the 10,500 active individuals within the UK CF Registry. The implications for individuals and health services in repeated colonoscopies and the financial costs of implementing this type of programme will need careful consideration. Targeted surveillance programmes may be a more viable option, for example the early introduction of colonoscopies for those at high risk such as those diagnosed with CFRD or even those with poor diabetic control. Implementation of the nationwide faecal occult blood (FOB) or faecal immunochemical test (FIT) screening may be a better, more cost effective approach although, again, more research is needed: the rates of FOB or FIT positive samples in people with CF in general is not known and this needs to be established before widespread screening should start.

Limitations

All 146 cases of cancer were used for the nested case control study to ascertain risk factors for all types of cancer in people with CF, however, we cannot ignore the fact that one third of the cases did not have the type of cancer recorded. This is in part due to early versions of the

Registry capturing cancer as a yes/no variable, despite this there were 41 cancer types were picked up from the free text fields. It is reasonable to assume that the proportions of cancers identified in the remaining 98 people are likely to be representative of the whole cohort and that 25% fairly reflects the proportion of GI cancers. Eight of the GI cancers were listed as "bowel" cancer, which as a colloquialism usually refers to the lower GI tract, but may not differentiate between rectal and colonic. It is possible that some cases of cancer were never reported to the CF Registry. This is particularly true for those post-transplant who may be followed-up at transplant centres rather than returning to the CF care centres, meaning there maybe some under-reporting of cases; further links with the UK Cancer Registry would be helpful in clarifying the numbers, although it is known that the UK registry has good data completeness.[36] This is a UK population study and therefore rates in other countries may vary.

Conclusions

This study adds to the literature by showing that the types of cancer in people with CF are varied and have a prevalence of 1.1%. They appear to peak at a younger age than the general population. Although GI cancer is the most prevalent, it still only accounts for 22% of the total cancers. CFRD has been confirmed as a risk factor alongside being post transplantation. As survival improves cancer is likely to become a more prevalent complication of CF.

Funding

The study was undertaken through the CF-EpiNet Strategic Research Centre supported by a grant from the Cystic Fibrosis Trust. OA was funded by the UK CF Trust research grant: SRC #4 CF-EpiNet: Harnessing data to improve lives.

Ethics approval

NHS research ethics approval (Huntingdon Research Ethics Committee 07/Q0104/2) was granted for the collection of data into the UK database. The Cystic Fibrosis Trust database committee approved the use of anonymised data in this study.

Acknowledgments

We thank people with cystic fibrosis and their families for consenting to their data being held in the UK CF Registry, and NHS teams in CF centres and clinics for the input of data into the Registry. The UK cystic fibrosis registry is supported and coordinated by the UK Cystic Fibrosis Trust.

Conflicts of Interest

None of the authors have any direct conflicts of interest to declare in relation to this study. OA was funded by the CF Trust research grant: SRC #4 CF-EpiNet: Harnessing data to improve lives. Outside of the submitted work SC, DB and NS are or have recently been principal investigators (PI) for CF Trust Registry-based pharmacovigilance studies: Pharmaxis (SC), Vertex, Teva (DB) and Chiesi (NS). SC and NS have received personal fees from Vertex, Chiesi, Zambon, NS has also received personal fees from Gilead and Teva outside of the submitted work.

References

1. Stephenson AL, Tom M, Berthiaume Y, Singer LG, Aaron SD, Whitmore GA, Stanojevic S. A contemporary survival analysis of individuals with cystic fibrosis: A cohort study. *European Respiratory Journal*. 2015;45:670
2. C. D. **Sheldon**, M. E. Hodson, L. M. Carpenter, A. J. Swerdlow. A cohort study of cystic fibrosis and malignancy. Br J Cancer. 1993;68(5): 1025-1028
3. Neglia JP, FitzSimmons SC, Maisonneuve P, Schöni MH, Schöni-Affolter F, Corey M, Lowenfels AB. The risk of cancer among patients with cystic fibrosis. *New England Journal of Medicine*. 1995;332:494-499
4. Neglia JP, Wielinski CL, Warwick WJ. Cancer risk among patients with cystic fibrosis. *The Journal of Pediatrics*. 1991;119:764-766
5. Maisonneuve P, FitzSimmons SC, Neglia JP, Campbell PW, Lowenfels AB. Cancer risk in nontransplanted and transplanted cystic fibrosis patients: A 10-year study. *Journal of the National Cancer Institute*. 2003;95:381-387
6. Maisonneuve P, Marshall BC, Knapp EA, Lowenfels AB. Cancer risk in cystic fibrosis: A 20-year nationwide study from the united states. *Journal of the National Cancer Institute*. 2012
7. Yamada A, Komaki Y, Komaki F, Micic D, Zullow S, Sakuraba A. Risk of gastrointestinal cancers in patients with cystic fibrosis: A systematic review and meta-analysis. *The Lancet Oncology*. 2018;19:758-767
8. Gallagher EJ, LeRoith D. Obesity and diabetes: The increased risk of cancer and cancer-related mortality. *Physiological Reviews*. 2015;95:727-748
9. Taylor-Robinson D, Archangelidi O, Carr SB, Cosgriff R, Gunn E, Keogh RH, MacDougall A, Newsome S, Schlüter DK, Stanojevic S. Data resource profile: The uk cystic fibrosis registry. *International journal of epidemiology*. 2017;47:9-10e
10. Bruzzese E, Raia V, Gaudiello G, Polito G, Buccigrossi V, Formicola V, Guarino A. Intestinal inflammation is a frequent feature of cystic fibrosis and is reduced by probiotic administration. *Alimentary Pharmacology & Therapeutics*. 2004;20:813-819
11. Meyer KC, Francois ML, Thomas HK, Radford KL, Hawes DS, Mack TL, Cornwell RD, Maloney JD, De Oliveira NC. Colon cancer in lung transplant recipients with cf: Increased risk and results of screening. *Journal of Cystic Fibrosis*. 2011;10:366-369
12. Aliza K. Fink, Elizabeth L. Yanik, Bruce C. Marshall, Michael Wilschanski, Charles F. Lynch, April A. Austin, Glenn Copeland, Mahboobeh Safaeian, Eric A. Engels. Cancer Risk amoung lung transplant recipients with CF. J Cyst Fibros. 2017 Jan; 16(1): 91–97.
13. Niccum DE, Billings JL, Dunitz JM, Khoruts A. Colonoscopic screening shows increased early incidence and progression of adenomas in cystic fibrosis. *Journal of Cystic Fibrosis*. 2016;15:548-553
14. European Cancer Observatory http://eco.iarc.fr/eucan. National cancer institute, surveillance epidemiology, and end results program. Http://seer.Cancer.Gov/. Accessed june 3, 2019.
15. Monshi B, Vujic M, Kivaranovic D, Sesti A, Oberaigner W, Vujic I, Ortiz-Urda S, Posch C, Feichtinger H, Hackl M. The burden of malignant melanoma–lessons to be learned from austria. *European Journal of Cancer*. 2016;56:45-53.
16. Cowen EW, Nguyen JC, Miller DD, McShane D, Arron ST, Prose NS, et al. Chronic phototoxicity and aggressive squamous cell carcinoma of the skin in children and adults during treatment with voriconazole. J Am Acad Dermatol 2010;62(1):31–7.

17. O'Reilly R, Ryan S, Donoghue V, Saidlear C, Twomey E, Slattery D. Cumulative radiation exposure in children with cystic fibrosis. *Irish medical journal*. 2010
18. Ron E. Ionizing radiation and cancer risk: Evidence from epidemiology. *Radiation research*. 1998;150:S30-S41
19. Jess T, Loftus Jr EV, Velayos FS, Winther KV, Tremaine WJ, Zinsmeister AR, Harmsen WS, Langholz E, Binder V, Munkholm P. Risk factors for colorectal neoplasia in inflammatory bowel disease: A nested case–control study from copenhagen county, denmark and olmsted county, minnesota. *The American journal of gastroenterology*. 2007;102:829
20. Steenland K, Nowlin S, Palu S. Cancer incidence in the national health and nutrition survey i. Follow-up data: Diabetes, cholesterol, pulse and physical activity. *Cancer Epidemiology and Prevention Biomarkers*. 1995 4:807-811
21. Michels KB, Solomon CG, Hu FB, Rosner BA, Hankinson SE, Colditz GA, Manson JE. Type 2 diabetes and subsequent incidence of breast cancer in the nurses' health study. *Diabetes care*. 2003;26:1752-1758
22. Calle EE, Rodriquez C, Walker-Thurmond K, Thun MJ. Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults. N Engl J Med 2003; 348:1625-1638
23. Johannesson M, Askling J, Montgomery SM, Ekbom A, Bahmanyar S. Cancer risk among patients with cystic fibrosis and their first-degree relatives. *International journal of cancer*. 2009;125:2953-2956
24. De Lisle RC, Borowitz D. The cystic fibrosis intestine. *Cold Spring Harbor Perspectives in Medicine*. 2013;3
25. Louis P, Hold GL, Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. *Nature Reviews Microbiology*. 2014;12:661
26. Ooi CY, Durie PR. Cystic fibrosis from the gastroenterologist's perspective. *Nature reviews. Gastroenterology & hepatology*. 2016;13:175
27. Assis DN, Freedman SD. Gastrointestinal disorders in cystic fibrosis. *Clinics in Chest Medicine*. 2016;37:109-118
28. Pang T, Leach ST, Katz T, Jaffe A, Day AS, Ooi CY. Elevated fecal m2-pyruvate kinase in children with cystic fibrosis: A clue to the increased risk of intestinal malignancy in adulthood? *Journal of Gastroenterology and Hepatology*. 2015;30:866-871
29. Sugamura K, Makino M, Kaibara N. Apoptosis as a prognostic factor in colorectal carcinoma. *Surgery today*. 1998;28:145-150
30. Heatley M. Association between the apoptotic index and established prognostic parameters in endometrial adenocarcinoma. *Histopathology*. 1995;27:469-472
31. Than BLN, Goos JACM, Sarver AL, O'Sullivan MG, Rod A, Starr TK, Fijneman RJA, Meijer GA, Zhao L, Zhang Y, Largaespada DA, Scott PM, Cormier RT. The role of kcnq1 in mouse and human gastrointestinal cancers. *Oncogene*. 2013;33:3861
32. Mehta A. Cystic fibrosis as a bowel cancer syndrome and the potential role of ck2. *Molecular and Cellular Biochemistry*. 2008;316:169-175
33. Sun TT, Wang Y, Cheng H, Zhang XH, Xiang JJ, Zhang JT, Yu SBS, Martin TA, Ye L, Tsang LL. Disrupted interaction between cftr and af-6/afadin aggravates malignant phenotypes of colon cancer. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research*. 2014;1843:618-628
34. Winklhofer-Roob BM. Oxygen free radicals and antioxidants in cystic fibrosis: The concept of an oxidant-antioxidant imbalance. *Acta Paediatrica*. 1994;83:49-57
35. Dreher D, Junod AF. Role of oxygen free radicals in cancer development. *European Journal of Cancer*. 1996;32:30-38
36. Cystic Fibrosis Trust. UK Cystic fibrosis registry report. Https://www.Cysticfibrosis.Org.Uk/the-work-we-do/uk-cf-registry/reporting-and-resources, accessed date: 16th March 2021

Table 1. Cases (n) of cancer by type and age group

Type of Cancer	Age groups						Total
	<16	16-25	26-35	36-45	46-55	>55	
Colon	0	0	0	2	5	0	7
Rectal	0	0	1	0	0	0	1
Bowel	0	0	3	1	1	3	8
Ileum	0	0	1	0	0	0	1
Oesophagus	0	0	0	3	2	0	5
Liver	0	0	0	0	2	0	2
Pancreas	0	0	3	1	1	0	5
Renal	0	0	0	0	0	2	2
Gallblader	0	0	0	0	1	1	2
Lymphoma	0	0	3	1	1	2	7
Leukaemia	1	1	0	1	0	1	4
Breast	0	1	1	6	1	4	13
Testicular	1	1	1	3	0	0	6
Prostate	0	0	0	0	0	4	4
Ovarian	0	0	0	2	0	0	2
Cervical	0	1	3	2	0	0	6
Lung	0	0	3	0	0	2	5
Skin	0	1	2	4	3	3	13
Brain	1	0	0	1	0	0	2
Haemangioendothelioma	0	0	1	0	0	0	1
Sarcoma	0	0	1	0	0	0	1
Teratoma	0	1	0	0	0	0	1
Other (unrecorded type)	5	2	7	16	14	4	48
Total	8	8	30	41	30	26	146

Table 2. Baseline characteristics of people with CF reported to have cancer and their matched controls who had no history of cancer

	Cancer (N=146)		Matched controls (N=575)		p-value
Variables	N recorded	N (%)	N recorded	N (%)	
Demographics*					-
Gender*	146		575		0.49
Males (%)		81 (55)		337 (58)	
Age†(matching variable) (mean, sd)	146	41.4 (16)	575	40 (16)	-
Ethnicity*	132		518		0.58
Caucasian (%)		129 (97)		499 (98)	
Smoking status*	105		368		0.11
Current/ex-smoker (%)		3 (2.8)		13 (3.5)	
CF-related diabetes (%)*	125	75 (60)	457	205 (45)	0.003
BMI continuous, median (IQR)	141	22.6 (20-25)	551	23 (20-26)	0.08
Clinical characteristics					
FEV predicted (%) (mean, sd)	133	61 (24)	529	60 (25)	0.6
*F508del**	143		571		0.99
Homozygous		52 (36)		208(36)	
Other		39 (27)		157 (27)	
Pancreatic insufficiency* (matching variable)	140	115 (82)	551	453 (82)	-
Meconium Ileus*	146	13 (9)	575	60 (10)	0.58
GORD (%)*	146	34 (23)	575	106(18)	0.18
DIOS (%)*	141	26(18)	568	115 (20)	0.63
Pseudomonas (%)*	138	91 (66)	536	359 (67)	0.05
Pseudomonas status*	70		300		0.03
Chronic (%)		57 (81)		247 (82)	
Intermittent (%)		13 (18)		53 (17)	
Medication/Therapy					

Transplants	146	21 (14.3)	575	37(6.4)	<0.00
Hospital IV days (mean, sd)	145	18 (35)	556	9.5 (21)	<0.00
Home IV days (mean, sd)	142	10 (20)	553	9 (18)	0.44
PPI (%)*	146	84 (57)	575	248 (43)	0.002

*Categorical variables are presented as frequencies and percentages (%)

-Reference categories: smoking (), Ethnicity (Caucasians), Gender (Males)

T-tests performed for continuous and normally distributed variables, Wilcoxon ranksum test for asymmetrical distributions*, chi2 tests for categorical variables

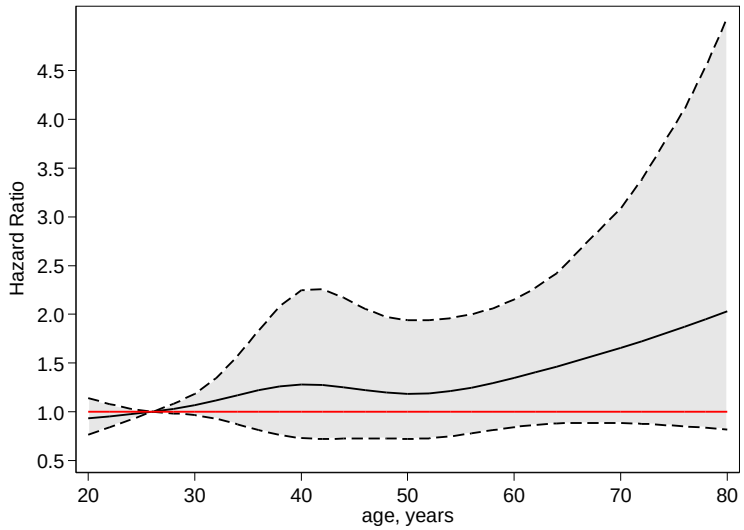
-CF related diabetes; CFRD, Gastro-oesophageal reflux disease; GORD, Distal Intestinal Obstruction Syndrome; DIOS, DF508, Proton Pump Inhibitor; PPI, meconium ileus; MI, pseudomonas presence, Home IV days and Hospital IV days

Table 3. Univariable and fully adjusted models of risk factors and the risk of total and GI cancers in people with CF

Risk factors	OR (95%CI)	
All cancers	Univariable analysis	Multivariable*
Female	1.15 (0.77-1.70)	-
BMI	0.95 (0.91-0.99)	-
FEV1	1.00 (0.99-1.00)	-
F508del Homozygous	0.95 (0.58-1.55)	-
GORD	1.43 (0.90-2.26)	-
DIOS	0.99 (0.47-2.08)	-
MI	0 .87 (0.43-1.76)	-
Pseudomonas	0 .95 (0.63-1.41)	-
CFRD	2.35 (1.37-4.00)	1.9 (1.1-3.4)
PPI	2.02 (1.28-3.19)	-
Home IV days	1.00 (0.99-1.01)	-
Hospital IV days	1.01 (1.00-1.01)	1.0 (1.0-1.0)
Previous transplant	2.46 (1.31-4.62)	2.2 (1.1-4.6)
GI cancers		
Female	1.59 (0.87-2.89)	-
BMI	0.95 (0.88-1.03)	-
FEV1	1.00 (0.99-1.01)	-
F508del Homozygous	1.27 (0.61-2.68)	-
GORD	2.40 (1.22-4.70)	-
DIOS	1.60 (0.65-3.94)	-
MI	1.13 (0.45-2.81)	-
Pseudomonas	1.25 (0.66-2.34)	-
CFRD	4.04 (1.47-11.1)	4.04 (1.3-12)
PPI	2.09 (1.01-4.36)	-
Home IV days	1.00 (0.99-1.01)	-
Hospital IV days	1.01 (1.00-1.02)	1.01 (1.01-1.02)
Previous transplant	2.88 (1.09-7.64)	-

*Backward stepwise selection results; Models adjusted for: previous transplants, sex, bmi, CF related diabetes (CFRD), gastro-oesophageal reflux disease (GORD), distal intestinal obstruction syndrome (DIOS), F508del, proton pump inhibitor (PPI) therapy, meconium ileus (MI), pseudomonas presence, home IV days and hospital IV days

Figure 1. Restricted cubic splines showing the increase in cancer risk across years of age



Solid line: Hazard ratio over age. Dashed line 95% CI