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Malignancy rates in Crohn's disease patients with perianal fistula: A German retrospective cohort study

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Abstract

Background: Patients with inflammatory bowel disease are at increased risk of colorectal and extra-intestinal cancer. However, the overall cancer risk in patients with Crohn's disease (CD) with perianal fistulas (PF) (CPF) and those with CD without PF (non-PF CD) is unclear.

Objective: To describe the prevalence and incidence of cancer in patients with CPF and non-PF CD, and to estimate incidence rate ratio (IRR) of cancer between CPF and non-PF CD groups.

Methods: A retrospective cohort study was conducted using the German InGef (Institute for Applied Health Research Berlin) research database. Patients with a CD record and PF from 1 January 2013 to 31 December 2014 were identified and followed up from 1 January 2015 until the first occurrence of cancer, end of health insurance contributing data, death, or end of study period (31 December 2020). Prevalence of any type of cancer including patients with CD diagnosed with cancer in the selection period and incidence of cancer excluding patients with CD diagnosed with cancer in the selection period were calculated.

Results: In total, 10,208 patients with CD were identified. Of 824 patients with CPF (8.1%), 67 had had a malignancy (6-year period crude malignancy prevalence 8.13% [95% confidence interval (CI) 6.36%–10.21%]), which was lower than patients with non-PF CD (19.8% [95% CI 19%–20.6%]). Incidence (per 100,000 person-years) in patients with CPF was 1184 (95% CI 879–1561) and in non-PF CD was 2365 (95% CI 2219–2519). There was no significant difference in the adjusted IRR of cancer for the CPF group compared with the non-PF CD group (0.83 [95% CI 0.62–1.10]; $p = 0.219$).

Conclusion: There was no significant difference in the incidence of any cancer in patients with CPF compared with non-PF CD. However, patients with CPF had a higher numerical risk of cancer than the general German population.

KEYWORDS
cancer, Crohn's disease, IBD, inflammatory bowel disease, malignancy rate, perianal fistula

INTRODUCTION

Patients with Crohn's disease (CD) are at greater risk of some cancer types, particularly gastrointestinal cancer but also other site-specific cancers, than the general population.[1–4] Furthermore, the overall risk of developing cancer in patients with CD increases with disease duration and severity.[1,5]

A debilitating complication of CD is the occurrence of perianal fistulas (PF) and abscesses caused by inflammation. These manifestations can severely affect a patient's quality of life and are associated with higher morbidity and healthcare costs than in patients with CD without PF (non-PF CD).[6–8]

PFs rarely improve spontaneously, and patients ultimately require medical or surgical intervention.[9,10] However, medical therapies such as thiopurine immunomodulators, anti-tumor necrosis factor (anti-TNF), and other biologics for CD have also been linked to the development of cancer. Patients with CD and perianal fistulas (CPF) have been reported to be at a higher risk of skin cancer and lymphoma.[2,11–17] Furthermore, patients with CPF have a greater severity of inflammation compared with patients with non-PF CD, and given the increased risk of cancer associated with chronic inflammation it is reasonable to expect an elevation in site-specific cancers in the CPF population compared with the non-PF population.[18,19] More recently, owing to their regenerative properties, stem cells such as expanded allogeneic adipose-derived stem cells have been investigated for the treatment of patients with CPF.[20–24] Non-clinical studies suggest that the tumorigenicity risk with expanded allogeneic adipose-derived stem cells is low. However, the relevance of these data to humans is limited and there is concern that expanded allogeneic adipose-derived stem cells may retain differentiation potential in humans.[25]

Presently, there is a lack of population-based studies detailing the risk of any type of cancer and risk of site-specific cancers (e.g. perianal, lymphoma, or skin cancer), in patients with CPF. To contextualize the results from an ongoing Post Authorization Safety Study (PASS), it is important to first establish the background rates of cancer within the target population (individuals with CPF). The PASS study is investigating the risk of malignancies among patients treated with darvadstrocel. Therefore we designed this real-world evidence (RWE) study to estimate the prevalence and incidence of cancer in patients with CPF as well as those with non-PF CD in Germany. In addition, the study sought to estimate the incidence rate ratio (IRR) of cancer in patients with CPF versus non-PF CD and the standardized incidence ratio (SIR) of cancer diagnoses in patients with CPF versus the general German population.

Key summary

Summarize the established knowledge on this subject.

- Patients with inflammatory bowel disease, including those with Crohn's disease (CD), are at increased risk of developing colorectal and extra-intestinal cancers.
- However, the risk of any type of cancer in patients with CD and perianal fistulas (CPF) is not clearly defined.

What are the significant and/or new findings of this study?

- Overall, the prevalence and incidence of any cancer in patients with CPF was lower than in patients with CD without PF.
- The incidence rate ratio of any cancer to patients with CPF and patients with CD without PF was not significantly different (0.83, 95% confidence interval (CI) 0.62–1.10).

METHODS

Study design and data source

This retrospective cohort study (Figure 1) was conducted using the InGef (Institute for Applied Health Research Berlin) database, an anonymized German health claims database containing longitudinal data from across all federal states of Germany. The InGef research database comprises data from ~4.8 million insured members from approximately 60 German statutory health insurance (SHI) providers and is representative of the German population with regards to age and sex.[26,27] The database contains demographic data (quarter of birth, sex, quarter of death if applicable, region of residence on federal state level), inpatient care (diagnoses, operation and procedures (OPSs) and outpatient care (diagnoses, treatments, and specialties of physicians outside of hospital). In addition, information on dispensing of reimbursed drugs, dispensing of reimbursed remedies, devices and aids and sick leave and sickness allowance times are included. Costs from the SHI perspective are available for all healthcare sectors. Diagnoses are recorded using the International Classification of Diseases 10th revision German modification (ICD-10 GM) codes. Procedures are recorded using German Procedure Classification codes and German doctor fee's schedule codes. Prescriptions are recorded using the Anatomical Therapeutic Chemical classification.[26]

The study selection period was from 1 January 2013 to 31 December 2014, and the source population included all patients with a record of CD in the InGef database.

The index date for all patients entering this study was 1 January 2015, with patients followed from this point up to and including 31 December 2020.

The end of follow-up was defined as the earliest of the following outcomes: cancer record (not for prevalence analysis), an end of data collection (end of SHI providers contribution [which could indicate emigration, death or change to another healthcare provider], or end of study period), or death.

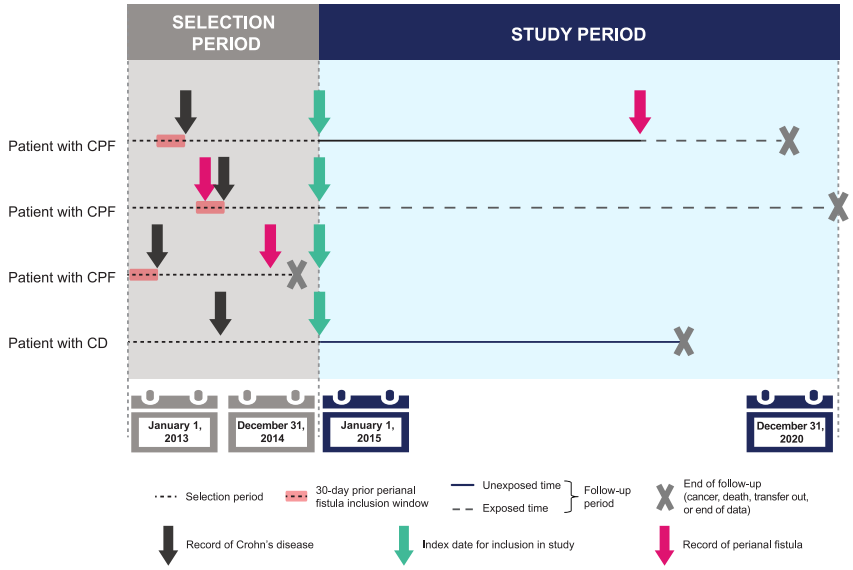

FIGURE 1 Study design. Source population: all individuals with a diagnosis of CD in the InGef research database from 1 January 2013 to 31 December 2014 (henceforth "selection period"). Follow-up start: The date at which an individual entered the study (index date) and begin to contribute time will be 1 January 2015 for all individuals in the study population. Perianal fistulas (PF) exposure: Individuals contribute time to the unexposed group up until a diagnosis of PF. For individuals with no history of PF in the selection period, individuals were considered "unexposed" up until the point they develop a PF (if ever) during follow-up, after which case they were considered "exposed". If an individual had a record of PF during the selection period, all their follow up was considered as "exposed" time. The individual has a diagnosis (or related procedure code) of perianal fistula within 30 days prior to the specified pre-CD diagnostic perianal fistula inclusion window. The end of follow-up: cancer, end of data collection (transfer out date, end of statutory health insurance (SHI) contribution, or end of study period), or death. CPF, Crohn's disease with perianal fistula; PF, perianal fistula.

Study population

Inclusion criteria

Individuals aged 18 years and older, with a minimum of 2 years continuous insurance in the InGef database during the selection period were eligible for inclusion. In addition, patients also had to have at least one ICD-10 GM CD diagnosis code (K50. x) between 1 January 2013 and 31 December 2014 as the main or secondary hospital discharge diagnosis and/or an ICD-10 CD GM diagnosis code recorded as an outpatient, to be eligible. A full list of diagnostic codes is in Supplementary Table 1.

Exclusion criteria

Patients were excluded from the analysis if they had a diagnosis (or related procedure code) of PF before the specified window for diagnosis of PF before CD (30 days prior to the first CD diagnosis in hospital records, or during the same quarter in outpatient records in which they received their first CD diagnosis), and of ulcerative colitis during the study period.

Patients with a diagnosis of cancer during the selection period were excluded from the incidence analyses to avoid categorizing previous cancers (present prior to 2015) as incident cancer during the study period. Patients having received major colorectal surgery were excluded.

Study groups

Two groups of patients were included in the analysis, a CPF group and a non-PF CD group. Patients in the non-PF CD group contributed to this group unless they had a record of PF during the selection period, in which case their follow-up was considered as contributing to the CPF group.

Study variables

Perianal fistula exposure

CPF was defined as ≥1 medical code for CD and one medical code for PF or an OPS code denoting surgery for PF within the hospital or in an outpatient setting (Supplementary Table 1).

The PF exposure was considered a time varying variable. An individual with no history of PF during the selection period could potentially provide both unexposed and exposed follow-up time.

Individuals with no history of PF in the selection period were considered "unexposed" up until the point they developed PF during follow-up, after which case they were considered "exposed". If an individual had a record of PF during the selection period, all their follow up was considered as "exposed" time.

Malignancy exposure

Malignancies were defined and determined using the ICD-10 GM code lists in a hospital or outpatient setting. Analyses were conducted for (1) any cancer, (2) digestive tract cancer (colorectal cancer, anal/perianal cancer, and other cancers of the upper-digestive system), and (3) extra-intestinal cancers (lung cancer, lymphomas, and skin cancer) (Supplementary Table 1).

Covariates

Variables which were identified as potential confounders of both CD and cancer included region, sex, and age (5-year age groups). For the overall study population, an individual's age was estimated at the index date. Additional baseline potential confounders, if present in the first two quarters after 1 January 2015 were major colorectal surgery (using Deutsches Institut fur Medizinische Dokumentation und Information OPS 2021 procedure codes), smoking, alcohol abuse (those with ICD-10 GM codes relating to problems with alcohol), obesity (those with ICD-10 GM code relating to obesity; body mass index measures were not available in German SHI data), comorbidities (primary sclerosing cholangitis, diabetes, autoimmune diseases (lupus, psoriasis, sarcoidosis, primary biliary cirrhosis, rheumatoid arthritis, and celiac disease), and CD treatment associated with an increased risk of lymphoma or skin cancer (thiopurines: azathioprine or mercaptopurine, anti-TNF (adalimumab or infliximab); other biologics (ustekinumab or vedolizumab) using relevant Anatomical Therapeutic Chemical and/or OPS codes.[11] Smoking was not collected as a specific variable in the InGef Database and a proxy algorithm was developed to identify smoking with the use of ICD-10 GM codes for Chronic Obstructive Pulmonary Disease (COPD) and nicotine abuse/dependence.

Analysis

Prevalence and incidence were calculated by calendar year and overall, for the complete study period, for the whole study population, and age subgroups among patients with CPF and those with non-PF CD. Categories with less than five patients were not reported due to data privacy regulations.

Crude and age-standardized cancer prevalence and incidence rate per 100,000 person-years were estimated. This was based on the direct standardization method using the German standard population at the end of 2017 obtained from the Federal Statistical Office of Germany.[28–30]

Prevalent study population and prevalence analysis

Patients with a cancer record within the follow-up period were classified as prevalent cancer cases. Prevalence was estimated as the number of patients with CPF or non-PF CD registered in the InGef database who developed cancer during the study period, divided by the number of patients in the InGef database reference population.

All patients categorized with PF exposure who developed cancer were considered as prevalent cases of cancer within their initial PF exposure category up until the end of the study period, regardless of whether or not their PF was resolved clinically following a record of cancer.

Incident study population and incidence analysis

Patients were classified as incident cancer cases if they had a record of cancer within the follow-up period, but not during the selection period. Incidence was estimated as the number of patients in each PF exposure category (CPF or non-PF CD) with a first record of cancer during the study period, divided by the number of person-years of follow-up corresponding to patients within the particular PF exposure category. Incidence rates and 95% confidence intervals (CIs) were reported by 100,000 person-years. Confidence intervals were calculated assuming a Poisson distribution. All cases diagnosed for cancer in 1 year and their person-time units were not considered for the study of incidence in the following years.

Incidence rate ratio

The IRR of cancer between CPF and non-CPF groups was estimated using Poisson regression using Generalized Linear Models in which study periods were treated as covariates. Covariates such as gender, age, time from CD record and CPF record, region, and other potential confounders (e.g. nicotine abuse, alcohol abuse, obesity, primary sclerosing cholangitis, diabetes, autoimmune disease, and CD treatment) were used for the adjustment. The crude and fully adjusted models were reported with the IRR, 95% CIs, and p values.

Standardized incidence rates

Standardized incidence rates (SIR) for cancer were calculated for patients with CPF and compared with the rates of all cancer types (including non-melanoma skin cancer) occuring in the general German population. The estimated number of new cases (for both sexes and all ages) in 2020 in Germany was obtained from the Global Cancer Observatory (International Agency for Research on Cancer).[31]

Sensitivity analysis

To eliminate the possible effect of varying disease duration in patients with CPF versus non-PF CD, a sensitivity analysis was conducted in a subgroup of newly diagnosed patients with CD (i.e., patients who had a CD record in 2014 but not 2013). Analyses included crude and age-standardized prevalence and incidence of malignancies in CPF and non-PF CD, and IRR of cancer among CPF versus non-PF CD.

RESULTS

Study population

Overall, 13,519 patients with a record of CD during the selection period were identified in the InGef database, of whom 10,208 met the inclusion criteria. Of these, 824 patients (8%) were included in the CPF group (354 patients developed PF during follow-up) (Supplementary Figure 1).

Approximately 11% of patients (n = 1117/10,208) had ≥1 record of cancer during the selection period and were excluded from the incidence analysis. The five most common cancers recorded during the selection period were non melanoma skin cancer (30%), breast cancer (11%), colon cancer (8%), prostate cancer (6%), and melanoma (6%).

Baseline demographics and characteristics (Table 1) were similar for CPF and non-PF CD groups for the incidence study population (n = 9091), with the exception of mean age. Age was higher in the non-PF CD group, and the use of thiopurines or anti-TNF treatments, both of which was higher in the CPF group.

At the end of the study period, 804 patients (8.8%) had CPF, comprising 4222 total years and 45,316 person-years (mean 5.3 years, standard deviation 1.6 years) of follow-up. The CPF and non-PF CD groups had a similar mean duration of follow-up and time from index date to cancer outcome (Table 2).

Prevalence

Crude prevalence of any type of cancer in the non-PF CD group was higher than in the CPF group (19.81% [95% CI 19.01%–20.63%] vs. 8.13% [95% CI 6.36%–10.21%], respectively), higher by age and across all cancer types and sites, with the exception of anal/perianal cancer (Figure 2a and Table 3). Details of the most common "other" cancers in the CPF and non-PF CD groups are shown in Supplementary Table 2.

TABLE 1 Characteristics of incidence study population at index date.

	CPF *N* = 804	Non-PF CD *N* = 8287
Age, years, mean (SD)	42.01 (14.29)	48.57 (16.21)
Sex, *n* (%)		
Female	418 (51.99)	4775 (57.62)
Male	386 (48.01)	3512 (42.38)
Nicotine abuse, *n* (%)	62 (7.71)	562 (6.78)
Alcohol abuse (problem drinker), *n* (%)	6 (0.75)	105 (1.27)
Comorbidities, *n* (%)		
Primary sclerosing cholangitis	0 (0.00)	34 (0.41)
Obesity	57 (7.09)	771 (9.30)
Diabetes	63 (7.84)	718 (8.66)
Autoimmune disease[a]	65 (8.08)	624 (7.53)
Major colorectal surgery	27 (3.36)	93 (1.12)
CD treatment, *n* (%)		
Thiopurines	176 (21.89)	1105 (13.33)
Methotrexate	<5 (–)	7 (0.08)
Anti-TNFs[b]	197 (24.50)	558 (6.73)
Other biologics: Ustekinumab and vedolizumab	20 (2.49)	43 (0.52)

Abbreviations: CD, Crohn's disease; CPF, Crohn's disease perianal fistula; PF, perianal fistula; SD, standard deviation; TNF, tumor necrosis factor.

[a]Autoimmune disease: lupus, psoriasis, sarcoidosis, primary biliary cirrhosis, rheumatoid arthritis, and celiac disease.

[b]Anti-TNFs: adalimumab and infliximab.

TABLE 2 Characteristics of study duration in the incidence study population.

	CPF N = 804	Non-PF CD N = 8287
Total duration of follow-up, person-years	4222	41,094
Duration of follow-up, years, mean (SD)	5.25 (1.61)	4.96 (1.84)
Time from index date to cancer outcome, years, mean (SD)	4.51 (1.93)	4.44 (1.78)
Reason for censoring follow-up, *n* (%)		
Cancer record	50 (6.22)	972 (11.73)
End of insurance (contributing data)	137 (17.04)	1528 (18.44)
Death (excluding cancer)	25 (3.11)	363 (4.38)

Abbreviations: CD, Crohn's disease; CPF, Crohn's disease perianal fistula; PF, perianal fistula; SD, standard deviation.

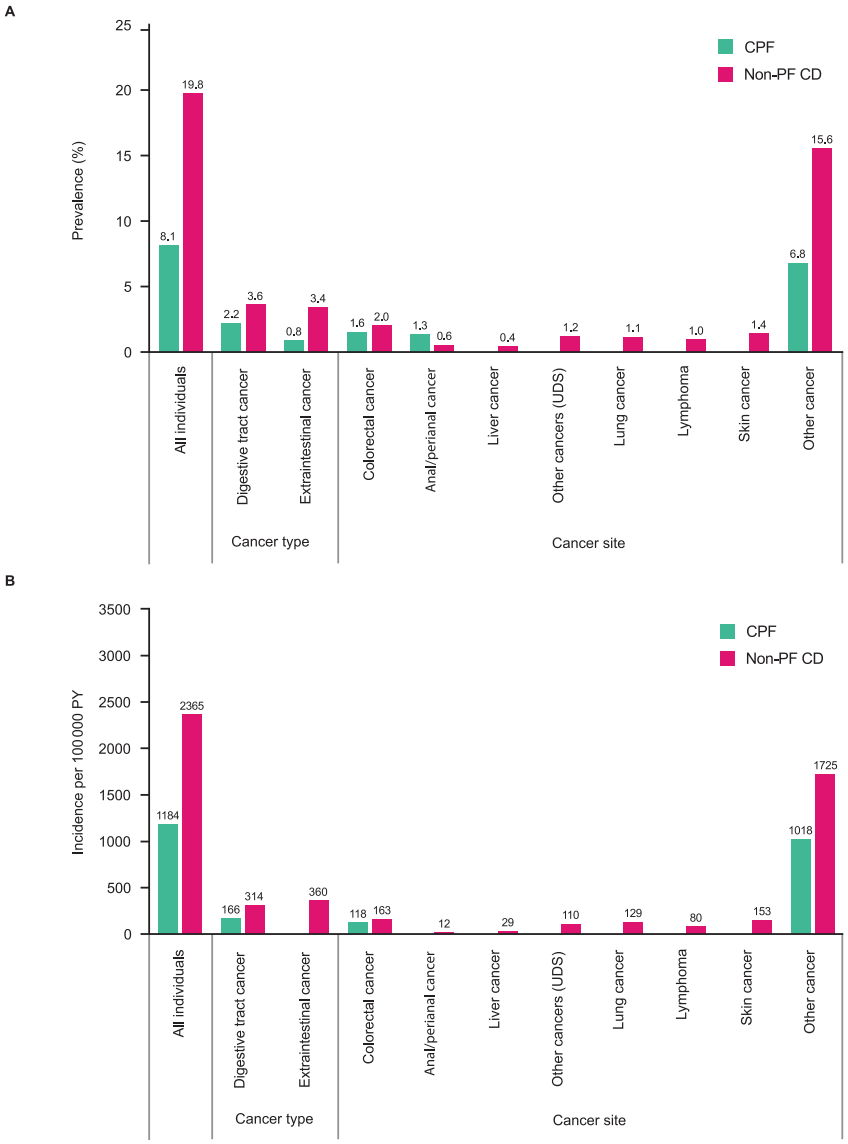

FIGURE 2 Crude cancer prevalence (a) and incidence (b) overall and by cancer type and site. CD, Crohn's disease; CI, confidence interval; CPF, Crohn's disease perianal fistula; PF, perianal fistula; PY, person-years; UDS, upper digestive system.

Over the duration of the study, the proportion of patients with a record of cancer ranged from 9.84% in 2015 to 11.92% in 2020, and a similar trend in crude prevalence of cancer was observed for both patient groups (Table 4).

The age-standardized (using 2017 German population) cancer prevalence in patients with CPF was 8.65% (95% CI 8.47%–8.82%). Standardized cancer prevalence was higher in males than females: 10.66% (95% CI 10.47%–10.85%) versus 7.03% (95% CI 6.88%–7.19%) respectively. The age-standardized prevalence for patients with non-PF CD was 17.32% (95% CI 17.09%–17.56%): 19.55% in males (95% CI 19.30%–19.79%) and 16.20% in females (95% CI 15.98%–16.43%).

Incidence

Similar to prevalence, the crude incidence of any cancer across all patients (2365/100,000 [95% CI 2219–2519] vs. 1184/100,000 [95% CI 879–1561] person-years, non-PF CD vs. CD and perianal fistulas, respectively), all cancer types and sites including anal/perianal cancer was higher in the non-PF CD group than in the CPF group (Figure 2b). The incidence of cancers classified as "other" in the CPF and non-PF CD groups was similar to the prevalence data (Supplementary Table 2), and there was also an increasing trend in the incidence of cancer with increasing age (Table 3).

TABLE 3 Crude cancer prevalence and incidence in the study population by age group.

	Prevalence				Incidence			
	CPF		Non-PF CD		CPF		Non-PF CD	
Age, years	*N*	Proportion, % (95% CI)	*n*	Proportion, % (95% CI)	*n*	Per 100,000 PY	*n*	Per 100,000 PY
18–20	<5	-	6	3.49 (1.29, 7.44)	<5	-	<5	-
20–24	<5	-	13	3.47 (1.86, 5.86)	<5	-	10	573.92
25–29	<5	-	32	4.73 (3.26, 6.61)	<5	-	22	674.01
30–34	<5	-	46	6.17 (4.55, 8.14)	<5	-	32	883.55
35–39	<5	-	62	8.56 (6.63, 10.84)	<5	-	41	1146.70
40–44	6	7.50 (2.80, 15.61)	88	10.93 (8.86, 13.29)	<5	-	57	1464.45
45–49	11	10.78 (5.51, 18.48)	148	14.86 (12.71, 17.22)	10	1826.81	95	1985.11
50–54	9	9.89 (4.62, 17.95)	196	17.00 (14.87, 19.29)	6	1240.91	109	2003.94
55–59	7	10.94 (4.51, 21.25)	236	23.30 (20.73, 26.03)	6	1822.15	128	2862.88
60–64	5	15.15 (5.11, 31.90)	777	29.60 (26.41, 32.95)	<5	-	138	4283.54
65–69	11	27.50 (14.6, 43.89)	591	35.19 (31.34, 39.20)	8	4508.89	95	4223.36
70–74	<5	-	538	42.19 (37.98, 46.49)	<5	-	105	5644.81
≥75	<5	-	817	45.92 (41.47, 48.41)	<5	-	136	6332.75

Abbreviations: CD, Crohn's disease; CI, confidence interval; CPF, Crohn's disease perianal fistula; PF, perianal fistula; PY, person-years.

TABLE 4 Crude cancer prevalence and incidence by study year.

	2015	2016	2017	2018	2019	2020	Overall percentage (2015–2020)
Prevalence, %							
Overall study population	9.84	10.24	10.64	11.11	11.45	11.92	18.87
CPF	3.16	3.64	2.49	3.51	4.07	3.91	8.13
Non-PF CD	10.42	10.82	11.38	11.80	12.12	12.65	19.81
Incidence, per 100,000 PY							
Overall study population	2464	2445	2131	2286	2034	2083	2255
CPF	1532	1479		1449	1219	1110	1184
Non-PF CD	2555	2542	2322	2374	2120	2187	2365

Abbreviations: CD, Crohn's disease; CPF, Crohn's disease perianal fistula; PF, perianal fistula; PY, person-years.

With regard to crude incidence of cancer, a slight decrease over the study period was observed for both groups, decreasing in patients with CPF from 1532 (95% CI 792–2676) at the index date to 1110 (95% CI 446–2288) by study end, and in patients with non-PF CD from 2555 (95% CI 2217–2931) to 2187 (95% CI 1826–2598) (Table 4).

The age-standardized cancer incidence in patients with CPF was 1378/100,000 (95% CI 1306–1452): 1457/100,000 (95% CI 1383–1534) in males and 1203/100,000 (95% CI 1136–1273) in females. In patients with non-PF CD, an age-standardized cancer incidence of 2311/100,000 (95% CI 2218–2407) was reported: 2929/100,000 in males (95% CI 2824–3037) and 2145/100,000 in females (95% CI 2055–2237).

Incidence rate ratio

When the IRR was evaluated using a crude model, age, nicotine abuse, alcohol abuse, obesity, diabetes, autoimmune disease, and the use of thiopurines were observed risk factors for cancer (Supplementary Table 3). The use of anti-TNF drugs (adalimumab or infliximab) and biologics (ustekinumab or vedolizumab) appeared to reduce the risk of cancer. However, when the model was adjusted for potential cofounders, only year, age, and use of thiopurines remained significant risk factors for cancer (Table 5), with no significant difference in the adjusted IRR of cancer for the CPF group compared with the non-PF CD group (0.83 [95% CI 0.62–1.10]; $p = 0.219$).

Standardized incidence rates

Over the duration of this study, 50 new cases of any cancer type in patients with CPF were identified (Table 2). Using the 2020 International Agency for Research on Cancer database, the expected number of any type of cancer in the general German population was 31.62; hence, the SIR for cancer in patients with CPF was 1.58 (95% CI 1.17–2.08)-fold greater than in the general German population. A similar SIR was noted for colorectal cancer (1.44 [95% CI 0.47–3.36], although the SIR for digestive tract cancers was in accordance with that of the general German population (0.99 [95% CI 0.40–2.03]). Standardized incidence ratio data for other cancer types (anal/perianal, liver upper-digestive, lung, and skin cancer, and lymphoma) could not be determined because the number of cases was below five.

TABLE 5 Adjusted incidence rate ratios in the study population.

	Adjusted IRR (95% CI)	*p* value
Time (year)	0.40 (0.38–0.41)	<0.001
Age	1.03 (1.02–1.03)	<0.001
Thiopurines (ref: no)		
Yes	1.44 (1.21–1.70)	<0.001
CD-PF (ref: no)		
Yes	0.83 (0.62–1.10)	0.219

Abbreviations: CD, Crohn's disease; CI, confidence interval; IRR, incidence rate ratio; PF, perianal fistula.

Sensitivity analysis

A sensitivity analysis was conducted to explore the impact of the duration of CD in a subgroup of patients who had a CD record in 2014 but not in 2013 in the selection period, thereby considering this subgroup as patients with possible newly diagnosed CD. The IRR for any cancer in newly diagnosed CPF versus non-PF CD (adjusted for the same factors as in the main analysis) was 0.82 (95% CI: 0.25–0.99).

DISCUSSION

This is the first RWE European study to compare the prevalence and incidence of any type of cancer in patients with CD with and without PF. This retrospective cohort study, using data from the German InGef research database between 2015 and 2020 showed that there were no statistically significant differences in the adjusted IRR for any type of cancer between the CPF and non-PF CD groups even after adjustment for potential cofounders. A similar result was found following a sensitivity analysis (included to control for the possible effect of varying disease duration) in a subgroup of newly diagnosed patients, demonstrating the robustness of the main study results.

We observed that the SIR of any type of cancer in patients with CPF was more than 1.5-times higher than in the general German population. These results are in line with previous literature comparing incidence of cancer in CD patients and the general population in Swedish Registers during the years 1964–2004 (1424 people developed cancer out of 21,788 patients hospitalised for the first time for CD, overall SIR of 1.54; 95% CI: 1.46–1.62). Similarly in Danish health care databases recorded from 1978 to 2010 (772 cases of invasive cancer among 13,756 patients with CD [SIR, 1.3; 95% CI: 1.2–1.4]).[32,33]

When crude rates were considered, we observed that the prevalence of any type of cancer was higher in the non-PF CD group, with the exception of anal/perianal cancer, which demonstrated marginally higher prevalence in patients with CPF. Similar to prevalence, the incidence of any cancer in patients with CPF was lower than in patients with non-PF CD. Previously, it has been reported that patients with CPF have a more active disease with a higher inflammatory component and greater exposure to treatments,[1,34] which is believed to increase the risk of cancer. In addition, the potential pathogenesis of anal and perianal cancers has been postulated to arise from chronic inflammation within the fistula triggering malignant transformation and/or a higher prevalence of anal human papilloma virus infection.[34–37] However, age-standardized prevalence and incidence rates of

cancers in this study were higher in patients with non-PF CD than with CPF. A potential explanation could be due to the age difference between the two groups, because patients with CPF were, on average, 7 years younger than those with non-PF CD. Age is a well-known risk factor for cancer, and indeed we have observed an increasing trend in prevalence and incidence of cancer with increasing age for both groups studied.[38] Another explanation is that CPF patients are more likely to have higher healthcare contacts as a result of their PF, such as the need for more colonoscopy and MRIs, and as such any diagnosis of precancerous lesions would likely be captured in timely manner.

Overall, our observations suggest no increased risk of any type of cancer in patients with CPF, and that it is likely any differences in rates of cancer between patients with CD with or without PF are driven by the presence of CD.

To our knowledge, there are no studies that have reported the risk of any type of cancer in patients with CPF compared with patients with non-PF CD. A similar study comparing cancer outcomes in patients with CPF and those without CPF was conducted in Israel and described a cohort of 12,905 patients with CD with a median follow-up of 6.6 years; however, this study focused only on inflammatory bowel disease (IBD)-related cancer. Nevertheless, similar to our observations, the risk of any IBD-related cancer was similar in patients with and without CPF.[15]

Our observational study has a number of notable strengths. Firstly, the InGef research database is a large RWE database, which has been utilized to demonstrate a good overall accordance with the general German population with regard to age, sex, morbidity, mortality, and drug prescriptions and dispensations.[27] In addition, the identification of the PF exposure through both ICD-10 GM and OPS codes, the use of a time window to determine that PF was related to the record of CD, and the consideration of PF as a time-dependent variable are all strengths of the approaches taken in this study.

Several limitations of this study should be acknowledged. Although 8 years was used for patient identification, follow-up was limited to the most recent 6 years. This may have affected the sample size and limited the number of events identified, with a consequent reduction in the power of the study to detect true differences, which could lead to misclassification of incident/prevalent exposure and limit the ability to determine duration and severity of CD. In addition, the small sample size, in particular the group of patients with PF, may limit the interpretation of the findings.

The data transferred to the SHI providers in general, and therefore the InGef database may also be a limitation because an immeasurable time bias may have been introduced, such as a lack of information on key cancer characteristics (e.g. stage or prognosis), and exact diagnosis dates being available. Similarly, treatment was evaluated only at the index date and not during the whole study period. Further studies are needed to analyze the possible link between treatment and cancer risk in a longitudinal way. Key confounders were not possible to capture such as smoking status (a proxy algorithm was developed with the use of codes for COPD and nicotine abuse/dependence), whether a patient's PF was active (considered to be PF with drainage, pain, abscess or other symptoms) or not, the PF was "simple" or "complex", and the severity of CD.

General limitations of studies using administrative data are that coding inaccuracies may have occurred leading to a misclassification bias and additional analysis on the potential impact of the early evaluation and diagnosis of precancerous lesions is not possible due to the information not being recorded in the database.

Finally, immortal time bias (a period of time where the outcome cannot occur) may also have affected this study, which was mitigated by considering PF as a time-updating variable with follow-up censored at death for all individuals and by censoring colorectal cancer outcomes follow-up at colorectal cancer surgery, to preclude the development of colorectal cancer.

In conclusion, although our study reported higher standardized incidence rates of any cancer in patients with CPF compared with the general German population, we did not observe any significant difference in the incidence of any type of cancer between patients with CD with or without PFs. This study suggests that the presence of PFs in patients with CD does not increase the risk of any type of cancer when compared against patients who do not have PFs. However, as this is the first real world study of any type of cancer in patients with CPF, these observations should be interpreted with appropriate caution given the limitations described. Additional observational studies conducted over longer follow-up periods and with a larger sample size are therefore needed to confirm the findings of this study.

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CONFLICT OF INTEREST STATEMENT

Bélène Podmore is an employee of OXON Epidemiology. OXON was contracted to design and conduct the study in collaboration with WIG2. Dominik Beier is employed by InGef, which acted as a subcontractor and received funding from WIG2. Johan Burisch has received grants and personal fees from AbbVie, Bristol Myers Squibb, Celgene, Janssen-Cilag, MSD, Takeda, and Tillots Pharma, personal fees from Ferring, Galapagos, Pharmacosmos, Pfizer, and Samsung Bioepis and grants from Novo Nordisk. Elisabeth Genestin is an employee of Takeda and Takeda Shareholder. Dennis Haeckl is an employee of WIG2 GmbH, which received funding from OXON Epidemiology for the conduct of the study. Oliver Nagel is employed by InGef, which acted as a subcontractor and received funding from WIG2. Nawab Qizilbash is an employee of OXON Epidemiology. OXON was contracted to design and conduct the study in

collaboration with WIG2. David A. Schwartz has been a consultant for Abbvie, UCB, Janssen, Takeda, Gilead, and Pfizer, and has served as a DSMB member with Tract. Stephan R. Vavricka has received consulting fees, speakers honorary, and unrestricted research grants from Abbott, Alfasigma, Amgen, Arenapharm, Falk Pharma GmbH, Ferring Pharmaceuticals, Gilead, iQuone, Janssen, MSD, Permamed, Pfizer Inc, Sanofi-Aventis, Takeda, Tillotts, UCB, and Vifor. Dimitri Bennett is an employee of Takeda. Axel Dignass has received fees for participation in clinical trials and for review activities, such as data monitoring boards, statistical analysis and endpoint committees from Abivax, AbbVie, Arena, Celgene/Bristol Myers Squibb, Falk, Gilead, Janssen and Pfizer; consultancy fees from AbbVie, Amgen, Biogen, Boehringer-Ingelheim, Celgene/Bristol Myers Squibb, Celltrion, Falk, Ferring, Fresenius Kabi, Galapagos, Gilead, Janssen, Lilly, MSD, Pfizer, Pharmacosmos, Roche/Genentech, Sandoz/Hexal, Takeda, Tillotts and Vifor; and payment for lectures including service on speaker bureaus from AbbVie, Amgen, Biogen, Celltrion, Falk Foundation, Ferring, Gilead/Galapagos, Janssen, Lilly, MSD, Pharmacosmos, Pfizer, Takeda, Tillotts and Vifor.

DATA AVAILABILITY STATEMENT

All data generated in this study is provided in the results and/or in the supplementary material file.

ETHICS APPROVAL

All patient-level data in the InGef research database are de-identified to comply with German data protection regulations. Use of the study database for health services research is therefore fully compliant with German federal law and, accordingly, institutional review board/ethical approval and informed consent of the patients were not needed.

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SUPPORTING INFORMATION

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