Original Investigation

Association Between Tumor Necrosis Factor-α Antagonists and Risk of Cancer in Patients With Inflammatory Bowel Disease

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IMPORTANCE A Cochrane review and network meta-analysis concluded that there is need for more research on adverse effects, including cancer, after treatment with tumor necrosis factor α (TNF-α) antagonists and that national registries and large databases would provide relevant sources of data to evaluate these effects.

OBJECTIVE To investigate whether patients with inflammatory bowel disease (IBD) exposed to TNF-α antagonists were at increased risk of developing cancer.

DESIGN, SETTING, AND PARTICIPANTS Nationwide register-based cohort study in Denmark, 1999-2012. Participants were 56 146 patients 15 years or older with IBD identified in the National Patient Registry, of whom 4553 (8.1%) were exposed to TNF-α antagonists. Cancer cases were identified in the Danish Cancer Registry.

MAIN OUTCOMES AND MEASURES Rate ratios (RRs) for incident cancer (overall and site-specific) comparing TNF-α antagonist users and nonusers, estimated using Poisson regression adjusted for age, calendar year, disease duration, propensity scores, and use of other IBD medications.

RESULTS During 489 433 person-years of follow-up (median, 9.3 years [interquartile range, 4.2-14.0]), 81 of 4553 patients exposed to TNF-α antagonists (1.8%) (median follow-up, 3.7 years [interquartile range, 1.8-6.0]) and 3465 of 51 593 unexposed patients (6.7%) developed cancer, yielding a fully adjusted RR of 1.07 (95% CI, 0.85-1.36). There was no significantly increased risk of cancer by TNF-α antagonist exposure. No site-specific cancers were in significant excess in fully adjusted models.

TNF-α Antagonist Exposure	Person-years	Cases, No.	Adjusted Rate Ratio (95% CI)
Accumulated doses, No.			
1-3	6694	31	1.02 (0.71-1.47)
4-7	4664	18	0.89 (0.55-1.42)
≥8	7083	32	1.29 (0.90-1.85)
Time since first exposure, y			
<1	3115	16	1.10 (0.67-1.81)
1-<2	3591	19	1.22 (0.77-1.93)
2-<5	7190	23	0.82 (0.54-1.24)
≥5	4545	23	1.33 (0.88-2.03)

CONCLUSIONS AND RELEVANCE In this Danish nationwide study, exposure to TNF-α antagonists among patients with IBD was not associated with an increased risk of cancer over a median follow-up of 3.7 years among those exposed. An increased risk associated with longer-term accumulated doses and follow-up cannot be excluded.

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The tumor necrosis factor α (TNF-α) antagonists infliximab, adalimumab, and certolizumab pegol are highly effective in the treatment of inflammatory bowel disease (IBD), with all 3 agents approved for Crohn disease and infliximab and adalimumab approved for ulcerative colitis.[1-6]

The efficacy of TNF-α antagonists must be weighed against the potential for adverse effects, and the treatment-induced immunosuppression has been suspected to lead to an increased risk of cancer.[7] In patients with rheumatoid arthritis, a meta-analysis of randomized clinical trials (RCTs) of TNF-α antagonists reported a more than 3-fold increased risk of malignancy that was dose-dependent,[8] but an increased risk of overall cancer was not confirmed in 3 later meta-analyses of RCTs.[9-11]

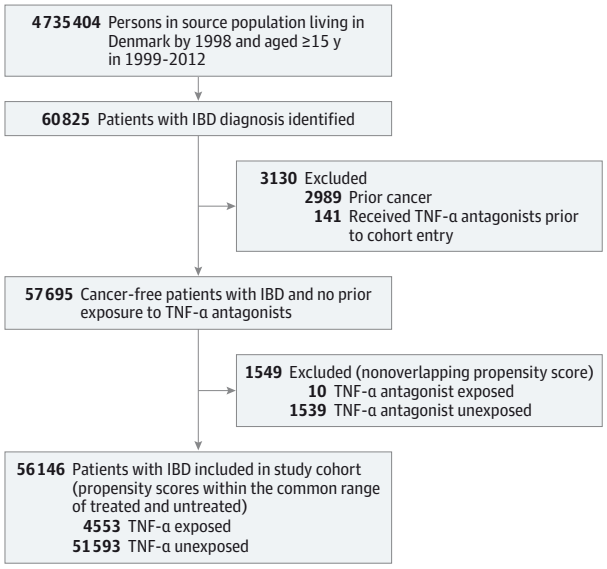
In patients with IBD, only 3 larger studies of cancer risk have been published.[12-14] An observational study of 6357 patients with IBD exposed or not exposed to TNF-α antagonists found no excess risk of cancer related to exposure, but mean follow-up time was only approximately 1 year.[12] Likewise, a study of 10 trials and a recent meta-analysis of 22 RCTs comparing TNF-α antagonist treatment vs placebo among patients with IBD reported no increased risk of cancer in exposed patients; however, duration of exposure and follow-up in the included trials in both of these studies were between 2 and 56 weeks, and the meta-analysis was based on only 16 TNF-α antagonist–exposed cancer cases.[13,14] Therefore, long-term observational studies of consequences of treatment with TNF-α antagonists are needed.[7]

In the present nationwide cohort study in Denmark, we studied rates of overall and site-specific cancer in patients with IBD exposed to TNF-α antagonists, as compared with patients with IBD not exposed to these drugs.

Methods

The source population consisted of all individuals 15 years or older and living in Denmark between 1999 and 2012 according to the Danish Civil Registration System[15] (**Figure 1**). By use of the unique personal identification number given to each Danish citizen at birth, the population was linked to the National Patient Registry (NPR),[16] which contains information on all hospitalizations in Denmark since 1977 and all outpatient visits and emergency department contacts since 1995. In the NPR, we identified patients with IBD using *International Classification of Diseases* (*ICD*) codes (*ICD-8* codes 56300-02 and 56308-09 and *ICD-10* code K50 for Crohn disease; *ICD-8* codes 56319 and 56904 and *ICD-10* code K51 for ulcerative colitis). Using a pathology database as reference, an assessment of nearly 800 patients estimated the completeness of registration of IBD in the NPR to be 94%, whereas the estimated validity, expressed as the proportion of confirmed diagnoses in the registry, was 97% for Crohn disease and 90% for ulcerative colitis.[17] Patients with IBD and a prior history of cancer (information available back to 1978) and those with use of TNF-α antagonists prior to 1999 or prior to IBD diagnosis were excluded.

Figure 1. Formation of Study Cohort



IBD indicates inflammatory bowel disease; TNF, tumor necrosis factor.

Incident cancers were identified through linkage to the Danish Cancer Registry,[18] which contains detailed information (including type, anatomical location, and date of diagnosis) on all incident cancers occurring in Denmark. In the study period, cancers were classified according to *ICD-10*. Based on this classification, we defined 11 categories for subtypes of cancer for preplanned subanalyses (eTable 1 in Supplement); in addition, a separate subanalysis of malignant melanoma was conducted because of previous findings of an increased risk for this particular cancer related to therapy using biologic agents.[19]

The study was approved by the Danish Data Protection Agency. Ethics approval is not required for registry-based research in Denmark.

Drug Exposure

Information on exposure to TNF-α antagonists was obtained from 4 sources to ensure completeness. Source 1 manually collected data on a nationwide cohort of all Danish patients with IBD treated with TNF-α antagonists (all infliximab) between their introduction in 1999 and 2005.[20] Source 2 collected data from the Danish Ministry of Health, which after year 2005 has kept track of treatment with biologic agents in all Danish hospital settings through the NPR (recording date of infusion and type of drug). Source 3 collected information on treatment with TNF-α antagonists reported in the period 1999-2010 to the Danish Crohn Colitis Database, which contains voluntary reports of detailed clinical data for patients with IBD from Danish hospitals. Source 4 collected information from the Danish Drug Prescription Registry (established in 1995 and containing individual-level information on all prescriptions filled at all Danish pharmacies)[21] on prescribed treatment with adalimumab and certolizumab pegol during the study period. Patients were

categorized as exposed to TNF-α-antagonists from the date of first dose and onward.

Propensity Scores and Covariates

To limit confounding effects, we used propensity scores that incorporated a range of baseline covariates. Propensity scores were estimated by logistic regression models as the predicted probability of initiating treatment with TNF-α antagonists conditional on year of birth; calendar year; sex; socioeconomic status; degree of urbanization; comorbidities; comedication use (not related to IBD); subtype of IBD; history of gastrointestinal or anal fistula, abscess, or fissure; and gastrointestinal surgery. After calculating propensity scores, individuals with nonoverlapping probability of TNF-α antagonist exposure were excluded to limit unmeasured confounding from patients at the extreme ends of the propensity score[22] (characteristics of patients excluded because of nonoverlapping propensity score are shown in eTable 2 in Supplement).

From the Danish Crohn Colitis Database, data on smoking (current, past, or never) and body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) were available for a subpopulation; the distribution of these variables was compared between patients exposed and unexposed to TNF-α antagonists, but they were not included in the propensity score because they were available for only a small proportion of the cohort. Data on alcohol consumption and exercise were not available.

Statistical Analyses

Individuals underwent follow-up from cohort entry until date of first cancer diagnosis, emigration, death, or end of study (December 31, 2012), whichever event occurred first. In all analyses, a 3-month lag period from first TNF-α antagonist dose was introduced to avoid including incipient cancers (unlikely to be caused by the recently initiated treatment); during this 3-month lag period, exposed patients did not contribute person-time to the user group but were categorized as a distinct group. Rate ratios (RRs) with 95% CIs of incident cancer in TNF-α antagonist users vs nonusers were estimated using Poisson regression.

We first performed crude analyses adjusted only for age in 10-year intervals. Next, we adjusted for baseline propensity scores categorized in quintiles and the following time-varying covariates, which may influence cancer risk or represent proxies for disease activity: age in 10-year intervals, calendar year in 2-year intervals, disease duration in 4-year intervals, and exposure to 5-aminosalicylates (6 months' use per prescription), local corticosteroids (1 months' use per prescription), oral corticosteroids (1 months' use per prescription) and methotrexate/cyclosporine/cyclophosphamide (6 months' use per prescription). A third analysis that additionally included adjustment for azathioprine use (6 months' use per prescription), which may be associated with an increased risk of cancer,[23] was regarded as the final fully adjusted model (see eTable 1 in Supplement for Anatomic Therapeutic Chemical Classification System codes). Statistical model information is provided in eTable 3 in Supplement.

To evaluate whether selection bias could influence the association between exposure to TNF-α antagonists and cancer, an analysis based on the fully adjusted model comparing the mortality rate among exposed and unexposed participants was performed. In this analysis patients were censored at first cancer diagnosis. Further, to validate our findings, stratified analyses of overall cancer risk (based on the fully adjusted model) were performed for sex, age at first TNF-α antagonist exposure (categorized arbitrarily as 15-49, 50-74, and ≥75 years), cumulative number of TNF-α antagonist doses (categorized arbitrarily as 1-3, 4-7, and ≥8 doses), and years since first exposure (categorized arbitrarily as <1, 1-<2, 2-<5, and ≥5 years). For the subset with available data on smoking status and BMI, comparisons between unexposed and exposed patients were performed by χ^2 test.

Analyses were performed using SAS version 9.3 (SAS Institute Inc). Differences were considered statistically significant when the 95% CIs did not overlap 1.0 or when the *P* value was <.05 (all tests were 2-sided).

Results

From the source population of 4 735 404 individuals, we identified 60 825 patients with IBD. A total of 4679 (7.7%) were excluded because of a history of prior cancer, TNF-α antagonist exposure prior to study entry, or nonoverlapping propensity score; this left 56 146 patients included in the study cohort (Figure 1) and undergoing follow-up for 489 433 person-years (median, 9.3 years [interquartile range {IQR}, 4.2-14.0]). Of these, 4553 (8.1%) were exposed to TNF-α antagonists after study entry (source 1, n = 651; source 2, additional n = 3821; source 3, additional n = 75; source 4, additional n = 6), contributing 19 559 person-years (median, 3.7 years [IQR, 1.8-6.0]) after exposure. The median number of TNF-α antagonist doses was 8 (IQR, 3-17). Exposed patients had a mean age of 33.7 (SD, 13.9) years at IBD diagnosis, 56% were female, and 54% had Crohn disease. The majority of exposed patients also received other IBD medications at some time during follow-up (5-aminosalicylates [80%], oral corticosteroids [91%], and azathioprine [85%]) (**Table 1**).

Overall Cancer

In total, 3465 patients with IBD unexposed to TNF-α antagonists (6.7%) and 81 exposed to TNF-α antagonists (1.8%) developed cancer (**Table 2**). Five cases of cancer were diagnosed during the 3-month lag period and were therefore excluded. Exposure to TNF-α antagonists was not associated with an increased overall cancer risk in the crude analysis (RR, 1.07 [95% CI, 0.86-1.33]), whereas the risk was significantly increased with adjustment for age, calendar year, disease duration, propensity scores, and use of IBD medications except for azathioprine (RR, 1.25 [95% CI, 1.00-1.58]). However, additional adjustment for azathioprine use in the final fully adjusted analysis attenuated the estimate markedly, leaving no significant association (RR, 1.07 [95% CI, 0.85-1.36]) (Table 2). Similar estimate patterns were observed for female and male patients separately (Table 2). In analyses stratified according to age group,

Table 1. Characteristics of Patients Exposed and Unexposed to TNF-α Antagonists[a]

Characteristic	TNF-α Antagonist Exposure, No. (%)	
	Exposed (n = 4553)	Unexposed (n = 51 593)
Sex		
Male	1993 (44)	23 321 (45)
Female	2560 (56)	28 272 (55)
IBD subtype		
Crohn disease	2459 (54)	15 390 (30)
Ulcerative colitis	2094 (46)	36 203 (70)
Age at IBD diagnosis, mean (SD)	33.7 (13.9)	44.5 (18.3)
Socioeconomic status		
Employment		
Unknown, basic, or no qualifications	1971 (43)	18 123 (35)
Medium-level qualifications	488 (11)	5445 (11)
High-level qualifications	345 (8)	4504 (9)
Self-employed/coworking spouse	163 (4)	2237 (4)
Outside labor market	1265 (28)	10 250 (20)
Pensioned	317 (7)	11 021 (21)
Degree of urbanization		
Population density, inhabitants per km^2		
≤49	335 (7)	3462 (7)
50-99	1358 (30)	15 183 (29)
100-199	1007 (22)	11 238 (22)
≥200	496 (11)	5430 (11)
Copenhagen suburbs	925 (20)	11 207 (22)
Copenhagen	432 (9)	5073 (10)
Comorbidities[b]		
Intestinal surgery[c]	333 (7)	2129 (4)
Intestinal/anal/rectal fissure, fistula, or abscess	268 (6)	840 (2)
Connective tissue disease/rheumatic disease	131 (3)	684 (1)
Cardiovascular disease	46 (1)	1738 (3)
Chronic pulmonary disease	61 (1)	1246 (2)
Diabetes	36 (1)	1042 (2)
Peptic ulcer disease	36 (1)	649 (1)
Renal or liver disease	22 (<1)	616 (1)
Dementia or paraplegia/hemiplegia	4 (<1)	154 (<1)
HIV/AIDS	0	0
Non-IBD medications[b]		
Cardiovascular drugs	613 (13)	13 347 (26)
Anemia treatment	578 (13)	4393 (9)
Antiobstructive pulmonary drugs	534 (12)	6673 (13)
Anticoagulants	147 (3)	5318 (10)
Antidiabetics	72 (2)	1768 (3)
Immunosupressives	8 (<1)	12 (<1)
IBD medications during follow-up[d]		
Oral corticosteroids	4147 (91)	26 822 (52)
Azathioprine	3860 (85)	8427 (16)
5-ASA/sulfasalazine	3627 (80)	30 058 (58)
Intestinal corticosteroids	2900 (64)	19 373 (38)
Methotrexate/cyclosporine/cyclophosphamide	823 (18)	1455 (3)
Smoking status[d,e]		
Current	489 (34)	880 (25)
Past	279 (19)	784 (23)
Never	674 (47)	1828 (52)
Body mass index, mean (SD)[d,f]	23.8 (5.0)	23.6 (4.3)

Abbreviations: HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; TNF-α, tumor necrosis factor α; 5-ASA, 5-aminosalicylates.

[a] All characteristics are as current at cohort entry unless stated otherwise.

[b] As registered within 2 years prior to cohort entry.

[c] As registered with 1 year prior to cohort entry.

[d] Not included in propensity score.

[e] Available for a subcohort of 1442 TNF-α antagonist–exposed patients and 3492 unexposed patients.

[f] Calculated as weight in kilograms divided by height in meters squared. Available for a subcohort of 1026 TNF-α antagonist-exposed patients and 3253 unexposed patients.

Table 2. Rate Ratios for Incident Overall Cancer Among 56146 Patients With Inflammatory Bowel Disease Exposed and Unexposed to TNF-α Antagonists[a]

	TNF-α Antagonist Exposure				Rate Ratio (95% CI)		
	Exposed		Unexposed				
	Person-years	Cases	Person-years	Cases	Crude[b]	Adjusted[c]	Adjusted[d]
Total	18 440	81	469 874	3465	1.07 (0.86-1.33)	1.25 (1.00-1.58)	1.07 (0.85-1.36)
Female	10 665	43	258 706	1803	1.01 (0.75-1.37)	1.12 (0.82-1.54)	0.96 (0.69-1.33)
Male	7776	38	211 168	1662	1.12 (0.82-1.85)	1.40 (1.00-1.96)	1.20 (0.85-1.69)

Abbreviation: TNF-α, tumor necrosis factor α.

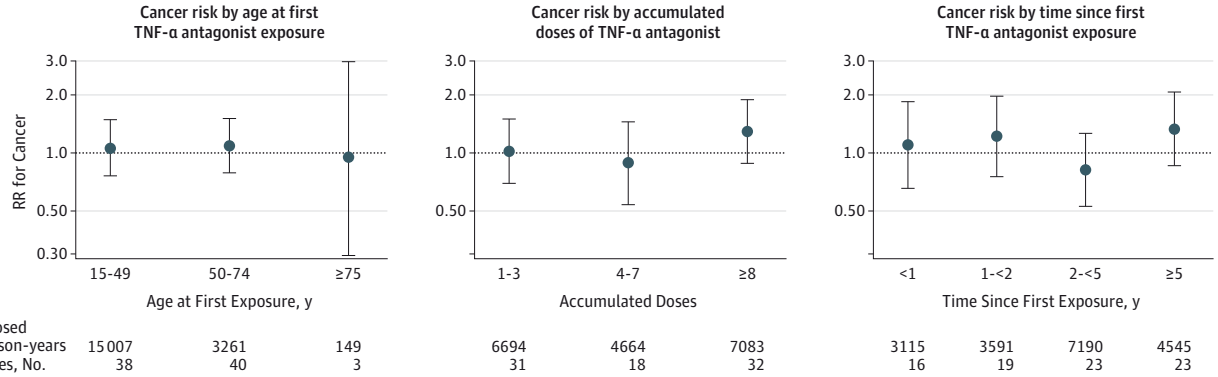
[a] Analyses were restricted to 3 months or more following first TNF-α antagonist exposure.

[b] Adjusted for age.

[c] Adjusted for age, calendar year, disease duration, baseline propensity scores, and use of 5-aminosalicylates/sulphasalazine, local and systemic corticosteroids, and methotrexate/cyclosporine/cyclophosphamide.

[d] Additionally adjusted for use of azathioprine.

Figure 2. Risk of Cancer According to Age at First Exposure to a TNF-α Antagonist, Accumulated Doses of TNF-α Antagonists, and Time Since First Dose of a TNF-α Antagonist, Comparing Exposed and Unexposed Patients With Inflammatory Bowel Disease



For each age category, patients exposed to tumor necrosis factor α (TNF-α) antagonists were compared with unexposed patients (469 874 person-years and 3465 cases). RR indicates rate ratio; error bars indicate 95% CIs. Analyses were adjusted for age, calendar year, disease duration, baseline propensity scores, and use of 5-aminosalicylates/sulphasalazine, local and systemic corticosteroids, methotrexate/cyclosporine/cyclophosphamide, and azathioprine.

cumulative number of TNF-α antagonist doses, and time since first TNF-α antagonist dose, there was no significantly increased risk of overall cancer associated with TNF-α antagonist exposure in any subgroup (**Figure 2**). There were no significant interactions between age and time since first TNF-α dose (P = .96) and age and number of doses (P = .89), respectively.

Site-Specific Cancer

There were no significant associations between TNF-α antagonist exposure and any of the cancer subgroups investigated, although these analyses were based on a small number of exposed cases (**Table 3**). For the majority of site-specific cancer subgroups, multivariable RRs decreased when additionally adjusting for azathioprine exposure.

With respect to site-specific cancers of previous concern in relation to TNF-α antagonist treatment in patients with IBD, 12 patients exposed to TNF-α antagonists developed skin cancer (9 malignant melanoma, 3 unspecified skin cancer) (eTable 4 in Supplement), resulting in a crude RR of 1.43 (95% CI, 0.80-2.56). In the adjusted (except for azathioprine) analysis, the RR was nearly unchanged at 1.45 (95% CI, 0.79-2.67), but further adjustment for azathioprine exposure resulted in an RR of 1.02 (95% CI, 0.55-1.89). In a subanalysis of malignant melanoma, the fully adjusted (including azathioprine) RR was 1.31 (95% CI, 0.63-2.74). The RR for hematopoietic cancers including lymphoma (8 exposed cases: 1 non-Hodgkin lymphoma; 2 Hodgkin lymphoma [1 nodular sclerosing and 1 mixed cellularity]; 1 T-cell lymphoma; 1 diffuse large B-cell lymphoma; 1 extramedullary plasmacytoma; 1 lymphoblastic lymphoma; 1 acute myelomonocytic leukemia) (eTable 4 in Supplement) decreased from 1.36 (95% CI, 0.67-2.76) in the crude model to 0.90 (95% CI, 0.42-1.91) in the fully adjusted (including azathioprine) model. In the analysis of colorectal cancer (8 TNF-α antagonist-exposed participants), the RR decreased from 1.32 (95% CI, 0.64-2.73) in the adjusted model to 1.00 (95% CI, 0.48-2.08) when further adjusting for azathioprine exposure.

Sensitivity Analyses

A sensitivity analysis restricted to incident IBD cases (diagnosed during the study period) produced estimates similar to those from the main analysis (adjusted [except for azathioprine] RR, 1.41 [95% CI, 1.04-1.91]; fully adjusted [including azathioprine] RR, 1.23 [95% CI, 0.90-1.69]), as did a sensitivity analysis with a 1-year lag period (fully adjusted [including azathioprine] RR, 1.07 [95% CI, 0.82-1.38]).

Table 3. Rate Ratios For Site-Specific Cancer Occurrence Among 56 146 IBD Patients Exposed and Unexposed to TNF-α Antagonists[a]

	TNF-α Antagonist Exposure						
	Exposed		Unexposed		Rate Ratio (95% CI)		
Cancer Site	Person-years	Cases	Person-years	Cases	Crude[b]	Adjusted[c]	Adjusted[d]
Lip, oral cavity, and pharynx	18 440	3	469 874	92	1.24 (0.39-3.93)	1.47 (0.43-5.00)	1.08 (0.31-3.70)
Digestive organs	18 440	10	469 874	341	1.52 (0.81-2.86)	1.71 (0.87-3.35)	1.36 (0.69-2.69)
Colorectal	18 440	8	469 874	487	0.74 (0.37-1.50)	1.32 (0.64-2.73)	1.00 (0.48-2.08)
Respiratory and intrathoracic	18 440	10	469 874	464	1.24 (0.66-2.33)	1.32 (0.69-2.54)	1.16 (0.59-2.25)
Skin[e]	18 440	12	469 874	315	1.43 (0.80-2.56)	1.45 (0.79-2.67)	1.02 (0.55-1.89)
Malignant melanoma	18 440	9	469 874	176	1.51 (0.77-2.97)	1.56 (0.76-3.18)	1.31 (0.63-2.74)
Breast	10 665	8	258 706	502	0.62 (0.31-1.24)	0.77 (0.38-1.59)	0.85 (0.40-1.78)
Genital organs							
Female	10 665	6	258 706	180	1.19 (0.53-2.71)	1.10 (0.46-2.61)	0.89 (0.37-2.15)
Male	7776	6	211 168	397	0.83 (0.37-1.86)	1.12 (0.49-2.55)	1.17 (0.50-2.73)
Urinary tract	18 440	5	469 874	162	1.71 (0.70-4.19)	2.11 (0.82-5.42)	1.60 (0.61-4.19)
Hematopoietic and lymphoid tissue	18 440	8	469 874	260	1.36 (0.67-2.76)	1.06 (0.50-2.22)	0.90 (0.42-1.91)
Other	18 440	5	469 874	260	0.83 (0.34-2.02)	1.42 (0.56-3.58)	1.28 (0.50-3.31)

Abbreviations: IBD, inflammatory bowel disease; TNF-α, tumor necrosis factor α.

[a] Analyses were restricted to 3 months or more following first TNF-α antagonist exposure.

[b] Adjusted for age.

[c] Adjusted for age, calendar year, disease duration, baseline propensity scores, and use of 5-aminosalicylates/sulphasalazine, local and systemic corticosteroids, and methotrexate/cyclosporine/cyclophosphamide.

[d] Additionally adjusted for use of azathioprine.

[e] Excludes basel cell carcinomas.

During follow-up, TNF-α antagonist-exposed patients had a median of 18 (IQR, 10-31) hospital contacts (inpatient admissions or outpatients visits), compared with 10 (IQR, 4-18) for unexposed patients. In an analysis of mortality, in which follow-up was censored at the date of a cancer diagnosis, the risk of mortality was not significantly increased in exposed patients compared with unexposed patients (RR, 1.01 [95% CI, 0.80-1.21]).

Data on smoking status and BMI were available for a subpopulation (Table 1). There was a significantly higher prevalence of current smokers ($P < .001$) and a significantly lower percentage of past smokers ($P < .001$) among TNF-α antagonist-exposed patients as compared with unexposed patients. No significant difference in BMI was observed between exposed and unexposed patients ($P = .28$).

Discussion

The present study provides nationwide Danish data on the long-term safety of TNF-α antagonist use among patients with IBD, finding that TNF-α antagonists were not associated with an increased risk of cancer in this group of patients. Given the upper limit of the confidence intervals, this study could rule out a more than 36% relative increase in the risk of overall cancer over a median follow-up of 3.7 years among patients exposed to TNF-α antagonists (with 25% of these undergoing follow-up for ≥6 years). This confirms and expands on previous work, which has had follow-up times of approximately 1 year, and confirms the most recent meta-analysis of RCTs based on 16 TNF-α antagonist-exposed cancer cases.[12-14] However, it should be noted that because of the relatively small sample size and the small number of cancer cases in our study, statistical power was limited in subgroup analyses of site-specific cancer and analyses stratified according to, for example, duration of follow-up. For instance, on the basis of the upper limits of the confidence intervals the study was not powered to rule out more than a 2-fold increase in the risk of skin cancer or cancer of hematopoietic and lymphoid tissue, nor could more than a 2-fold increase in overall cancer risk be excluded for the subset of patients who underwent follow-up for 5 years or more. Therefore, although no significant associations were observed in any of the fully adjusted analyses, all analyses should be interpreted considering their precision.

The primary strength of the study is the nationwide historically prospective cohort design enabling assessment of long-term safety of treatment in an unselected and well-defined IBD population. The registration of IBD diagnoses in the NPR has been evaluated and found to be nearly complete and highly valid for both Crohn disease and ulcerative colitis.[17] A complete history could be obtained for all patients exposed to TNF-α antagonists, hence avoiding prevalent user bias.[24]

The study also had limitations that should be considered. By adjusting for propensity scores and proxies of disease activity, such as hospitalizations and concomitant medications for IBD, we sought to limit the potential for confounding by indication. However, residual confounding related to disease severity may exist. This would potentially bias our results toward a falsely high risk of cancer in exposed patients related to systemic inflammation rather than treatment. However, no overall excess risk of cancer among exposed patients was observed. Although data on smoking, which may influence both IBD severity and risk of cancer, were not available for the full cohort and were thus not adjusted for, there was a significantly higher percentage of current smokers among TNF-α antagonist-exposed patients than among unexposed patients in

a subpopulation. However, because no increased risk of cancer associated with exposure to TNF-α antagonists was observed, smoking is unlikely to represent a major unmeasured confounder. Furthermore, despite our combination of data from 4 national registers, we cannot exclude that a minor proportion of exposed patients could have been missed, thereby potentially biasing results toward the null. Additionally, patients using TNF-α antagonists could have a higher disease burden and hence an increased risk of death; therefore, competing mortality could mask a true increased risk of cancer. However, our analysis of mortality (in which patients were censored at first diagnosis of cancer) was neutral, implying that the risk of death from causes other than cancer was similar in TNF-α antagonist–exposed and unexposed patients. Last, we were unable to analyze the 3 approved agents (infliximab, adalimumab, and certolizumab pegol) separately.

Our analyses of cumulative number of TNF-α antagonist doses could only exclude more than a 85% relative increase in overall cancer risk after 8 doses or more. This should be interpreted in the context of a previous meta-analysis of TNF-α antagonist treatment in patients with rheumatoid arthritis that suggested a dose-dependent increased risk of cancer.[8] Stratifying for cancer risk according to years since first exposure, no specific time-dependent pattern was observed in our study. However, considering the often protracted progression of cancer, an increased risk in the long term cannot be excluded and future studies with longer follow-up are needed.

We observed a significant association between TNF-α antagonist exposure and overall cancer in an analysis adjusted for propensity scores and all time-varying covariates apart from concomitant azathioprine use. However, when azathioprine use was also adjusted for, there was no evidence of an increased cancer risk associated with TNF-α antagonist exposure. Thus, the significant association initially observed among TNF-α antagonist users was almost fully explained by concomitant use of azathioprine. These observations are in accordance with those from previous RCTs.[7] A pooled analysis of 10 trials comprising 2385 patients with IBD found no increased risk of malignancy in infliximab-exposed patients, whereas a significantly higher incidence of malignancies was observed in patients with Crohn disease receiving immunomodulators vs no immunomodulators.[13] However, patients underwent follow-up for only 54 weeks, and only 13 cancer cases (excluding nonmelanoma skin cancers) were observed. In line with these findings, a recent study with pooled clinical trial data from 1594 patients with Crohn disease evaluated the risk of cancer among patients treated with adalimumab monotherapy and those treated with a combination of adalimumab and azathioprine and found that the risk of cancer (nonmelanoma skin cancer excluded) was increased among patients who received the combination therapy (standardized incidence ratio, 5.05 [95% CI, 2.61-8.82]) but not in those receiving adalimumab monotherapy (standardized incidence ratio, 1.2 [95% CI, 0.39-2.80]).[25] A nationwide Danish cohort study reported an increased overall risk of malignancies in patients with IBD receiving azathioprine (RR, 1.41 [95% CI, 1.15-1.74]),[23] with increased risks of lymphoid tissue cancer (RR, 2.40 [95% CI, 1.13-5.11]) and urinary tract cancer (RR, 2.84 [95% CI, 1.24-6.51]) in subgroup analyses. These observations are consistent with our finding of an increased risk of cancer seemingly related to azathioprine use rather than to exposure to TNF-α antagonists. In a single-center retrospective cohort study from Belgium, the risk of malignancies was compared in 743 patients with IBD treated with infliximab (median follow-up, 5.1 years) and in 666 patients with IBD not treated with biologic agents.[26] In accordance with the present findings, no increased risk of malignancies was observed.

The risk of lymphoid tissue cancer in IBD and its relation to medical treatment is debated. In the present study, 8 cases of lymphoid or hematopoietic cancer were observed in the TNF-α antagonist–exposed group, corresponding to a crude RR of 1.36 that decreased to 0.90 after adjusting for all potential confounders including azathioprine use. The risk of lymphoproliferative disorders associated with azathioprine exposure has been elucidated in a French clinic-based study of nearly 20 000 patients with IBD who underwent follow-up for a median of 35 months and revealed a 5 times higher risk in patients exposed to thiopurines compared with unexposed patients.[27] Also, in analyses of skin cancer, we observed confounding by azathioprine use. This is partly in accordance with previous studies suggesting an increased risk of nonmelanoma skin cancer in patients treated with thiopurines,[25,28-30] although not all published work supports this conclusion.[31] Treatment with biologic agents has been suggested to be associated with increased risk of melanoma,[19] but our results did not reveal any significant association.

Conclusions

This population-based cohort study of more than 56 000 patients with IBD found no increased risk of cancer associated with TNF-α antagonist exposure. Although a small increase in the risk of overall cancer may be observed in patients exposed to TNF-α antagonists, this increase in risk might be attributable to concomitant use of azathioprine. An increased risk of malignancy in the long term or with increasing number of cumulative doses of TNF-α antagonists cannot be excluded, and continuous follow-up of exposed patients is needed.

ARTICLE INFORMATION

Author Contributions: Dr Nyboe Andersen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Nyboe Andersen, Pasternak, Svanström, Hviid, Jess.
Acquisition, analysis, or interpretation of data: Nyboe Andersen, Pasternak, Basit, Andersson, Caspersen, Munkholm, Jess.
Drafting of the manuscript: Nyboe Andersen, Jess.
Critical revision of the manuscript for important intellectual content: Pasternak, Basit, Andersson, Svanström, Caspersen, Munkholm, Hviid, Jess.
Statistical analysis: Nyboe Andersen, Basit, Andersson.
Obtained funding: Nyboe Andersen, Jess.
Administrative, technical, or material support: Nyboe Andersen, Munkholm, Jess.
Study supervision: Jess.

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REFERENCES

1. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007;132(1):52-65.

2. Colombel JF, Sandborn WJ, Reinisch W, et al; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. 2010;362(15):1383-1395.

3. Hanauer SB, Feagan BG, Lichtenstein GR, et al; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002;359(9317):1541-1549.

4. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005;353(23):2462-2476.

5. Sandborn WJ, Feagan BG, Stoinov S, et al; PRECISE 1 Study Investigators. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med*. 2007;357(3):228-238.

6. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2012;142(2):257-265.

7. Singh JA, Wells GA, Christensen R, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev*. 2011;(2):CD008794.

8. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA*. 2006;295(19):2275-2285.

9. Askling J, van Vollenhoven RF, Granath F, et al. Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: does the risk change with the time since start of treatment? *Arthritis Rheum*. 2009;60(11):3180-3189.

10. Lopez-Olivo MA, Tayar JH, Martinez-Lopez JA, et al. Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: a meta-analysis. *JAMA*. 2012;308(9):898-908.

11. Moulis G, Sommet A, Béné J, et al. Cancer risk of anti-TNF-α at recommended doses in adult rheumatoid arthritis: a meta-analysis with intention to treat and per protocol analyses. *PLoS One*. 2012;7(11):e48991.

12. Haynes K, Beukelman T, Curtis JR, et al; SABER Collaboration. Tumor necrosis factor α inhibitor therapy and cancer risk in chronic immune-mediated diseases. *Arthritis Rheum*. 2013;65(1):48-58.

13. Lichtenstein GR, Rutgeerts P, Sandborn WJ, et al. A pooled analysis of infections, malignancy, and mortality in infliximab- and immunomodulator-treated adult patients with inflammatory bowel disease. *Am J Gastroenterol*. 2012;107(7):1051-1063.

14. Williams CJ, Peyrin-Biroulet L, Ford AC. Systematic review with meta-analysis: malignancies with anti-tumour necrosis factor-α therapy in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2014;39(5):447-458.

15. Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The Danish Civil Registration System: a cohort of eight million persons. *Dan Med Bull*. 2006;53(4):441-449.

16. Andersen TF, Madsen M, Jørgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register: a valuable source of data for modern health sciences. *Dan Med Bull*. 1999;46(3):263-268.

17. Fonager K, Sørensen HT, Rasmussen SN, Møller-Petersen J, Vyberg M. Assessment of the diagnoses of Crohn's disease and ulcerative colitis in a Danish hospital information system. *Scand J Gastroenterol*. 1996;31(2):154-159.

18. Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry—history, content, quality and use. *Dan Med Bull*. 1997;44(5):535-539.

19. Long MD, Martin CF, Pipkin CA, Herfarth HH, Sandler RS, Kappelman MD. Risk of melanoma and nonmelanoma skin cancer among patients with inflammatory bowel disease. *Gastroenterology*. 2012;143(2):390-399.

20. Caspersen S, Elkjaer M, Riis L, et al; Danish Crohn Colitis Database. Infliximab for inflammatory bowel disease in Denmark 1999-2005: clinical outcome and follow-up evaluation of malignancy and mortality. *Clin Gastroenterol Hepatol*. 2008;6(11):1212-1217.

21. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health*. 2011;39(7)(suppl):38-41.

22. Stürmer T, Rothman KJ, Avorn J, Glynn RJ. Treatment effects in the presence of unmeasured confounding: dealing with observations in the tails of the propensity score distribution—a simulation study. *Am J Epidemiol*. 2010;172(7):843-854.

23. Pasternak B, Svanström H, Schmiegelow K, Jess T, Hviid A. Use of azathioprine and the risk of cancer in inflammatory bowel disease. *Am J Epidemiol*. 2013;177(11):1296-1305.

24. Schneeweiss S. A basic study design for expedited safety signal evaluation based on electronic healthcare data. *Pharmacoepidemiol Drug Saf*. 2010;19(8):858-868.

25. Osterman MT, Sandborn WJ, Colombel JF, et al. Increased risk of malignancy with adalimumab combination therapy, compared with monotherapy, for Crohn's disease. *Gastroenterology*. 2014;146(4):941-949.

26. Fidder H, Schnitzler F, Ferrante M, et al. Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. *Gut*. 2009;58(4):501-508.

27. Beaugerie L, Brousse N, Bouvier AM, et al; CESAME Study Group. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet*. 2009;374(9701):1617-1625.

28. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, et al; Cesame Study Group. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. *Gastroenterology*. 2011;141(5):1621-1628.

29. Setshedi M, Epstein D, Winter TA, Myer L, Watermeyer G, Hift R. Use of thiopurines in the treatment of inflammatory bowel disease is associated with an increased risk of non-melanoma skin cancer in an at-risk population: a cohort study. *J Gastroenterol Hepatol*. 2012;27(2):385-389.

30. Singh H, Nugent Z, Demers AA, Bernstein CN. Increased risk of nonmelanoma skin cancers among individuals with inflammatory bowel disease. *Gastroenterology*. 2011;141(5):1612-1620.

31. van Schaik FD, van Oijen MG, Smeets HM, van der Heijden GJ, Siersema PD, Oldenburg B. Risk of nonmelanoma skin cancer in patients with inflammatory bowel disease who use thiopurines is not increased. *Clin Gastroenterol Hepatol*. 2011;9(5):449-450.