Risk of cancer in adults with primary immune thrombocytopenia: a binational population-based real-world cohort study from Denmark and France

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Abstract

Immune dysregulation and immunosuppression occur due to the pathophysiology and management of primary immune thrombocytopenia (ITP), which together may increase the risk of subsequent cancer. We investigated the cancer risk in ITP compared with the general population in a binational cohort study in Denmark and France. We identified 12,456 patients with ITP and 218,971 age- and sex-matched general population comparators from 1980-2018 in Danish and French health registries. All individuals were followed for solid and hematologic cancer. We estimated nation-specific five-year cumulative incidences, cause-specific [csHR], and combined meta-analysis csHR for cancer. We stratified analyses on age and sex. The five-year cumulative incidences of solid cancer in Denmark were 6.7% (95% confidence interval [CI]: 5.9-7.5) in ITP *versus* 6.1% (95% CI: 6.0-6.2) in comparators driven by differences in female, thorax and upper gastrointestinal cancers, and 8.4% (95% CI: 7.6-9.2) *versus* 6.0% (95% CI: 5.6-6.4) in France driven by skin and colorectal cancers. The corresponding numbers for hematologic cancer were 2.6% (95% CI: 2.2-3.2) *versus* 0.4% (95% CI: 0.4-0.5) in Denmark, and 7.6% (95% CI: 6.9-8.3) *versus* 1.1% (95% CI: 0.9-1.2) in France. Across both countries, differences were driven by leukemia, lymphoma, and other hematologic cancers. The five-year adjusted csHR for solid cancer were 1.3 (95% CI: 1.1-1.5) in Denmark, 1.3 (95% CI: 1.2-1.5) in France, and 1.3 (95% CI: 1.2-1.4) combined. CsHR for hematologic cancer were 7.4 (95% CI: 6.1-9.1) in Denmark, 9.0 (95% CI: 7.5-10.8) in France, and 8.2 (95% CI: 6.8-9.9) combined. Risks were highest during the first year after ITP diagnosis, and in younger and female patients. The risk of cancer following ITP increased, with risk of hematologic cancer in particular. This knowledge should influence treatment and follow-up.

Introduction

Primary immune thrombocytopenia (ITP) is characterized by autoimmune reactions directed against platelets and platelet production, and associated with adverse health outcomes.[1] To be characterized as primary, an ITP diagnosis requires exclusion of other causes of thrombocytopenia, including underlying cancer. Perception of the disease and treatment landscape of ITP has changed markedly over the past decades, and it is now considered to be a complex autoimmune disease with heterogeneous immune dysfunction, relapses and chronicity, associated with complications and poorer prognosis compared to the general population.[1-3] Novel treatments such as thrombopoietin-receptor agonists and fostamatinib have emerged, with a concomitant reduction in, e.g., splenectomy procedures and associated risks.[4-6] However, immunosuppressants and immunomodulating drugs remain the cornerstones of treatment,[7] but can increase the risk of lymphoproliferative cancers.[8] Solid cancer (e.g., breast cancer and lung cancer) and ITP may occur concomitantly, but the literature is sparse and mostly based on case reports.[9] In addition, ITP carries an increased risk of death from hematologic cancer, while, conversely, the risk of death from solid cancer is similar to that of the general population.[1,10] This could indicate an increased incidence of cancer following ITP, like in other types of autoimmune disorders.[11]

According to a previous study, there is a high risk of both solid and hematologic cancer following an ITP diagnosis, and risk estimates for hematologic cancers are particularly high.[12] Given the rapid emergence of other non-immunosuppressing treatments both now and in the future, these findings need to be supported and substantiated by similar studies from comparable populations, since this could potentially influence clinical decisions for the diagnostic work-up and management of ITP.

In this binational cohort study, we leveraged real-world data to investigate the risk of solid and hematologic cancer in patients with ITP compared with the general population in Denmark and France.

Methods

Data sources and study population

We identified adult patients with ITP, comparators, comorbidity co-variates, and cancer outcomes in Danish and French health registries. The first registration of the designated International Classification of Disease (ICD-10) registration (D69.3) (*Online Supplementary Tables S1, S2*) served as index date, and up to 40 age- and sex-matched comparators per patient in Denmark and up to 6 in France were allotted and followed from the same index date. The high number of comparators in Denmark allowed for precise estimation of the underlying general population risks, and the study of rare cancer events. We have previously used these validated identification approaches in similar studies,[13,14] and details can be found in the *Online Supplementary Appendix*.

We identified Danish patients and comparators in the period 1980-2016, and in 2011-2018 correspondingly in France. Patients with secondary ITP, Evans syndrome, genetic thrombocytopenias, and prevalent ITP were excluded (*Online Supplementary Table S1*). We excluded secondary ITP since cancer would often be considered a qualifying underlying disorder. All individuals with any type of prevalent hematologic cancer were also excluded, since there could have been multiple causes of thrombocytopenia in these cases.

Follow-up and outcomes

We followed patients and comparators in both countries until the first of: cancer, death, emigration, or end of country-specific study time. Cancer was divided in the following solid and hematologic subgroups: any solid, female, male, thorax, urological, upper gastrointestinal (GI), colorectal, skin, head-neck, central nervous system (CNS), other solid cancer, any hematologic, leukemia, lymphoma, myeloma, other hematologic cancer (*Online Supplementary Table S3*). The 'any' categories were defined as the first of any of the respective solid and hematologic subgroup cancers. Individuals registered with one type of cancer, remained in follow-up for the other types of cancer.

Co-variates

We adjusted our regressions for the following prevalent comorbidities with some serving as proxy measures for smoking or alcohol usage: liver disease, chronic pulmonary disease, diabetes mellitus, and any type of prevalent solid cancer (dichotomous variables) (*Online Supplementary Table S4*).[15] We also adjusted for: age, sex, and calendar decade of diagnosis, similar to previous studies.[1,16]

Statistical analysis

We calculated baseline characteristics as medians with interquartile range (IQR) for age, and percentages with 95% confidence intervals (95% CI) for distributions of sex, age-groups, prevalent comorbidities and cancers. Patients were stratified according to sex (male, female) and age (18-59 years, ≥60 years). In Denmark, patients were also stratified by period of diagnosis (1980-1993, 1994-2016).

We assessed the one-year, five-year, and end of study absolute risk of cancer using the Fine-Gray cumulative incidence function with death and emigration as competing events. Differences between patients and comparators were tested using Gray's test. The Danish population also included ten-year and twenty-year estimates.

Cox proportional hazard and Fine-Gray regression were used to estimate instantaneous risks of cancer in terms of five-year crude (univariate) and adjusted (multivariate) cause-specific hazard ratios (csHR) and subdistribution hazard ratios for cancer in patients with ITP compared with the general population. For the most frequent prevalent cancers, we also estimated time-split 1st year and the 2nd to the 5th year csHR and subdistribution hazard ratios. The proportional hazard assumption in the Cox models were tested and deemed sufficient using Schoenfeld and Cox-Snell residuals.

We used a random-effect model to perform a meta-analysis of selected Danish and French csHR estimates.

We performed a sensitivity analysis with a prior exclusion of all individuals registered with any type of prevalent solid cancer from the risk estimations of each of the subgroups of cancers; for example, individuals with a prevalent lung cancer would be excluded from the main incidence analysis of lung cancer, but not if they had prevalent upper GI cancer. In contrast, in the sensitivity analysis, all individuals with prevalent solid cancer were excluded independent of the type of cancer whose incidence was being measured. All analyses were done separately for each outcome for the set of patients with ITP and their respective general population comparators.

Data-storage, data-management, and statistical analyses in Denmark were performed at a secured server at Statistics Denmark using Stata 18.0 (StataCorp, College Station, TX, USA), and in a secured Health Data Hub using SAS Enterprise Guide™ Version 7.15 (SAS Institute Inc., Cary, NC, USA) in France.

Ethics approval statement

In Denmark, registry-based research without direct patient contact does not require ethics committee approval according to Danish law. In France, research for ITP in the SNDS was approved by the Institut des Données de Santé in March 2012 (n. 40) and the Commission Nationale de l'Informatique et des Libertés in July 2012 (DE-2012-076).

Results

Cohort characteristics

We included 4,768 patients with ITP and 189,662 age- and sex-matched general population comparators in Denmark, and correspondingly 7,688 patients and 29,309 comparators in France (Table 1). Total follow-up times were: in Denmark, 35,727 person-years (PY) for patients (median 8.7 years) and 1,673,404 PY (median 9.7 years) for comparators; in France, 27,444 PY for patients (median 3.5 years) and 109,894 PY (median 3.6) for comparators. Women comprised 2,670 individuals (56%) in Denmark and 4,217 (55%) in France. Median age at inclusion for patients were 58 years (IQR 38-54) in Denmark, and 62 years (IQR 41-77) in France. The prevalence of comorbidities (chronic pulmonary disease, diabetes, liver disease, and any solid cancer) were all more pronounced in patients compared with the general population in both Denmark and France (Table 1).

Cumulative incidences of cancer

In Denmark, the five-year cumulative incidences of any solid cancer were 6.7% (95% CI: 5.9-7.5) in patients and 6.1% (95% CI: 6.0-6.2) in comparators (Table 2, Figure 1). This was mainly driven by differences in the occurrence of upper GI cancer, with relatively more cases of liver and pancreatic cancer, and more cases of lung cancer in patients (*Online Supplementary Table S5*). In France, the five-year cumulative incidences of any solid cancer were 8.4% (95% CI: 7.6-9.2) in patients and 6.0% (95% CI: 5.6-6.4) in comparators (Table 2, Figure 1, *Online Supplementary Figure S1*). This was driven by relatively more frequent occurrences of skin cancer (melanoma, non-melanoma skin cancer) and colorectal cancer in the patients. The risk was most pronounced during the first year after ITP diagnosis in both countries.

In Denmark, the five-year cumulative incidences of any hematologic cancer were 2.6% (95% CI: 2.2-3.2) in patients and 0.45% (95% CI: 0.42-0.48) in comparators (Table 2, Figure 1, *Online Supplementary Figure S2*). Corresponding French estimates were 7.6% (95% CI: 6.9-8.3) and 1.05% (95% CI: 0.91-1.20). The underlying drivers were an increased occurrence in patients of lymphoma, leukemia, and other hematologic cancers in both countries, though lymphoma and other hematologic cancer risks differed across countries. The risk across both countries was most pronounced during the first year after ITP diagnosis (*Online Supplementary Table S6*).

In general, differences between patients and comparators levelled out with time for solid cancer but persisted for hematologic cancer. This finding was substantiated by Danish 20-year estimates showing that risk of solid cancer diminished to that of the general population after about eight years (*Online Supplementary Figure S3*) but persisted for most hematologic cancers (*Online Supplementary Figure S4*).

Incident risk of cancer

We found an elevated instantaneous risk of solid cancer following ITP compared to the general population. The five-year adjusted csHR for any solid cancer was 1.3 (95% CI: 1.12-1.5) in Denmark, 1.3 (95% CI: 1.2-1.5) in France, and 1.3 (95% CI: 1.2-1.5) in the combined meta-analysis (Figure 2, *Online Supplementary Table S7*). This was mainly driven by an increased first-year risk of 1.7 (95% CI: 1.3-2.1) in Denmark and 1.8 (95% CI: 1.5-2.5) in France. Underlying drivers were an increased occurrence of female (mainly breast), thoracic (mainly lung), and upper GI (mainly liver, pancreas) cancer in Denmark, and skin (mainly melanoma, not-specified skin cancer), CNS, colorectal cancer, and head-neck cancer in France (*Online Supplementary Table S5*).

The five-year adjusted csHR for any hematologic cancer was 7.4 (95% CI: 6.1-9.1) in Denmark, 9.0 (95% CI: 7.5-10.8) in France, and 8.2 (95% CI: 6.8-9.9) in the meta-analysis (Figure 2, *Online Supplementary Table S7*). The first-year risk was 13.1 (95% CI: 9.3-18.4) in Denmark and 17.9 (95% CI: 12.9-24.9) in France. Leukemia, lymphoma, and other hematologic cancers were the underlying drivers with csHR ranging from 4.2-12.4 (Figure 2, *Online Supplementary Table S7).*

The instantaneous risk diminished over time for most types of cancers (*Online Supplementary Table S7*). Subdistribution hazard ratios generally lowered estimates for solid cancers towards the null-association. Starting follow-up at +6 months and +12 months instead of +30 days from ITP diagnosis lowered risk estimates in Denmark. The adjusted 'any solid cancer' risk was 1.2 (95% CI: 1.1-1.4) and 1.2 (95% CI: 1.1-1.4) at +6 and +12 months, respectively (*Online Supplementary Table S7*). Corresponding numbers for any hematologic cancer were 6.1 (95% CI: 4.9-7.6) and 5.8 (95% CI: 4.6-7.3), respectively.

Our sensitivity analysis did not change the overall results compared to the main analysis (*Online Supplementary Table S8*).

Risk across age, sex and time

The risk of any solid cancer in ITP compared with the general population was elevated, but did not differ across countries for age groups. The combined meta-analysis five-year csHR for patients aged 18-59 years was 1.6 (95% CI: 1.3-1.9) (Figure 2, *Online Supplementary Table S7*). The corresponding estimate for patients aged >60 years was 1.2 (95% CI: 1.1-1.4). The risk estimates were slightly higher for women compared to men, and comparable across countries, with a binational combined csHR for women of 1.4 (95% CI: 1.2-1.6) and 1.2 (95% CI: 1.1-1.4) for men.

For any hematologic cancer, the adjusted five-year csHR for patients with ITP aged 18-59 years were 11.3 (95% CI:

7.5-16.9) in Denmark and 28.1 (95% CI: 16.0-49.6) in France (meta-analysis: 17.4 [95% CI: 7.1-42.6]). The corresponding csHR for patients aged >60 years were more closely aligned across countries, with a binational combined csHR of 6.9 (95% CI: 6.0-8.1) (Figure 2, *Online Supplementary Table S7*). These findings were also found in the cumulative incidences of cancer in both age groups, where differences between patients and comparators were generally higher in France

Table 1. Baseline characteristics of adult patients with primary immune thrombocytopenia and age- and sex-matched general population comparators in Denmark and France.

Characteristics	Country	Primary ITP	General population comparators
Total number of individuals included	DK	4,768	189,662
	FR	7,688	29,309
Women, % [95% CI] (N)	DK	56 [55-57] (2,670)	56 [56-56] (106,404)
	FR	55 [54-56] (4,217)	56 [56-57] (16,467)
Age in years, median (IQR)	DK	58.4 (37.9-73.0)	58.3 (37.7-73.0)
	FR	62.1 (41.1-76.5)	59.9 (39.7-73.9)
Age at death in years, mean (95% CI)	DK	76.7 (76.1-77.4)	82.3 (82.2-82.4)
	FR	80.8 (80.2-81.5)	82.6 (82.1-83.0)
30-day mortality after ITP, % [95% CI] (N)	DK	1.87 [1.50-2.29] (89)	0.01 [0.01-0.02] (21)
	FR	0.70 [0.53-0.92] (54)	0.09 [0.06-0.13] (27)
Age groups, % [95% CI] (N)			
18-59 years	DK	52.3 [50.9-53.8] (2,496)	52.5 [52.3-52.8] (99,637)
	FR	46.5 [45.4-47.6] (3,576)	50.1 [49.5-50.7] (14,696)
≥60 years	DK	47.7 [46.2-49.1] (2,272)	47.5 [47.2-47.7] (90,025)
	FR	53.5 [52.4-54.6] (4,112)	50.0 [49.3-50.5] (14,613)
Prevalent comorbidities, % [95% CI] (N)			
Chronic pulmonary disease	DK	7.19 [6.48-7.96] (343)	5.18 [5.08-5.28] (9,821)
	FR	7.52 [6.94-8.13] (578)	4.02 [3.80-4.25] (1,179)
Diabetes	DK	7.24 [6.52-8.01] (345)	3.76 [3.68-3.85] (7,139)
	FR	12.71 [11.97-13.47] (977)	5.24 [4.99-5.50] (1,536)
Liver disease	DK	3.21 [2.73-3.75] (153)	0.68 [0.64-0.71] (1,284)
	FR	3.39 [3.00-3.82] (261)	0.68 [0.58-0.78] (198)
Prevalent cancers, % [95% CI] (N)			
Overall	DK	5.87 [5.22-6.58] (280)	3.58 [3.49-3.66] (6,783)
	FR	13.37 [12.62-14.15] (1,028)	8.76 [8.44-9.09] (2,567)
Female	DK	2.02 [1.52-2.63] (54)	1.35 [1.28-1.42] (1,284)
	FR	6.10 [5.39-6.86] (257)	4.26 [3.95-4.58] (701)
Male	DK	1.53 [1.05-2.15] (32)	1.22 [1.15-1.30] (1,284)
	FR	6.17 [5.39-7.02] (214)	4.74 [4.37-5.12] (608)
Thorax	DK	0.69 [0.48-0.97] (33)	0.13 [0.12-0.15] (252)
	FR	1.09 [0.87-1.35] (84)	0.48 [0.40-0.56] (140)
Urological	DK	0.48 [0.31-0.72] (23)	0.29 [0.27-0.32] (557)
	FR	1.59 [1.32-1.89] (122)	0.91 [0.81-1.03] (267)
Upper gastrointestinal	DK	0.42 [0.26-0.65] (20)	0.06 [0.05-0.07] (115)
	FR	0.96 [0.76-1.21] (74)	0.37 [0.31-0.45] (109)
Colorectal	DK	0.78 [0.55-1.07] (37)	0.46 [0.43-0.49] (875)
	FR	2.00 [1.70-2.34] (154)	1.54 [1.40-1.68] (450)
Skin	DK	1.80 [1.45-2.22] (86)	1.58 [1.53-1.64] (2,998)
	FR	1.69 [1.41-2.00] (130)	1.02 [0.91-1.14] (299)
Head-neck	DK	0.21 [0.10-0.39] (10)	0.15 [0.13-0.17] (286)
	FR	1.21 [0.98-1.48] (93)	0.76 [0.67-0.87] (224)
Central nervous system	DK	0.08 [0.02-0.21] (<5)	0.03 [0.02-0.04] (53)
	FR	0.53 [0.38-0.72] (41)	0.16 [0.12-0.22] (48)
Other	DK	0.15 [0.06-0.30] (7)	0.06 [0.05-0.08] (122)
	FR	2.13 [1.82-2.48] (164)	0.93 [0.82-1.05] (273)

Other solid cancers included all remaining types and generally unspecified rare types of solid cancers, e.g., bone and cartilage cancer, peripheral nerve cancer, and unspecified metastatic cancers. CI: confidence interval; DK: Denmark; FR: France; IQR: interquartile range; ITP: immune thrombocytopenia; N: number.

compared to Denmark for both solid and hematologic cancer (*Online Supplementary Figure S5*).

Though not pronounced, women also had a higher risk of hematologic cancer compared with men, with the largest risk found in French women with a csHR of 11.1 (95% CI: 8.3-15.0). Thus, there were no differences between men and women in the overall risk of both solid and hematologic cancer.

The one-year estimates were generally higher for all groups (*Online Supplementary Table S7*). Danish estimates across study periods indicated that absolute risk of solid and hematologic cancers seemed to increase over time for both patients and comparators. However, the median age at diagnosis of ITP also increased from 55 years (IQR: 34-73) in 1980-1993 to 59 years (IQR: 38-73) in 1994-2016 in Denmark (*Online Supplementary Figure S6*). Stratifying Danish instantaneous risk estimates by decades showed a stable solid cancer risk across the long study period, while hematologic cancer risk differed (although this was not statistically significant) with the lowest csHR of 3.5 (95% CI: 1.7-7.2) in 1990-1999 (*Online Supplementary Table S7*).

Discussion

This binational cohort study shows that the risk of cancer is elevated following a diagnosis of ITP compared with the

Table 2. Five-year cumulative incidences of cancer for patients with primary immune thrombocytopenia and age- and sex-matched general population comparators in Denmark and France.

Cumulative incidence of cancers, % [95% CI] (N)	Country	Primary ITP	General population comparators
Solid cancers			
Overall	DK	6.65 [5.87-7.49] (260)	6.12 [6.00-6.24] (9,267)
	FR	8.36 [7.58-9.18] (415)	5.99 [5.62-6.37] (996)
Female	DK	2.53 [1.90-3.30] (50)	1.90 [1.80-1.99] (1,641)
	FR	1.73 [1.29-2.28] (50)	1.67 [1.43-1.94] (178)
Male	DK	1.63 [1.12-2.31] (30)	1.68 [1.58-1.78] (1,171)
	FR	2.27 [1.71-2.95] (54)	2.24 [1.93-2.60] (182)
Thorax	DK	0.95 [0.69-1.29] (45)	0.70 [0.66-0.74] (1,146)
	FR	1.02 [0.78-1.32] (59)	0.84 [0.72-0.98] (172)
Urological	DK	0.49 [0.31-0.75] (23)	0.45 [0.41-0.48] (733)
	FR	0.92 [0.69-1.21] (53)	0.75 [0.63-0.88] (150)
Upper gastrointestinal	DK	0.78 [0.54-1.09] (35)	0.45 [0.42-0.48] (728)
	FR	1.13 [0.87-1.43] (66)	0.70 [0.58-0.83] (137)
Colorectal	DK	0.60 [0.39-0.88] (30)	0.83 [0.78-0.87] (1,367)
	FR	1.76 [1.44-2.13] (103)	1.30 [1.15-1.47] (259)
Skin	DK	1.97 [1.57-2.44] (76)	2.04 [1.97-2.11] (3,247)
	FR	1.86 [1.52-2.25] (104)	1.30 [1.14-1.47] (256)
Head-neck	DK	0.32 [0.18-0.54] (14)	0.25 [0.23-0.28] (416)
	FR	0.86 [0.63-1.15] (45)	0.45 [0.37-0.56] (95)
Central nervous system	DK	0.13 [0.05-0.29] (5)	0.09 [0.08-0.11] (148)
	FR	0.50 [0.34-0.72] (29)	0.13 [0.09-0.19] (27)
Other	DK	0.43 [0.27-0.67] (19)	0.28 [0.25-0.30] (450)
	FR	2.71 [2.30-3.16] (158)	2.10 [1.90-2.31] (417)
Hematologic malignancies			
Overall	DK	2.64 [2.19-3.16] (111)	0.45 [0.42-0.48] (734)
	FR	7.57 [6.90-8.27] (465)	1.05 [0.91-1.20] (208)
Leukemia	DK	1.11 [0.82-1.47] (46)	0.14 [0.12-0.16] (234)
	FR	1.57 [1.26-1.92] (92)	0.24 [0.18-0.31] (50)
Lymphoma	DK	0.42 [0.26-0.67] (17)	0.12 [0.11-0.14] (197)
	FR	1.77 [1.45-2.14] (108)	0.20 [0.14-0.27] (42)
Multiple myeloma	DK	<0.1 (<5)	0.06 [0.05-0.08] (104)
	FR	0.24 [0.13-0.40] (13)	0.11 [0.07-0.16] (20)
Other	DK	1.19 [0.89-1.55] (51)	0.12 [0.11-0.14] (202)
	FR	5.08 [4.53-5.66] (313)	0.66 [0.55-0.79] (125)

Overall solid cancers and hematologic malignancies represent the first of any solid or hematologic cancer, respectively. Competing events were death or emigration. For corresponding graphic illustration, see Figures 1 and 2. Due to Danish rules for sharing microdata, some estimates are not provided in detail. CI: confidence interval; DK: Denmark; FR: France; ITP: immune thrombocytopenia; N: number.

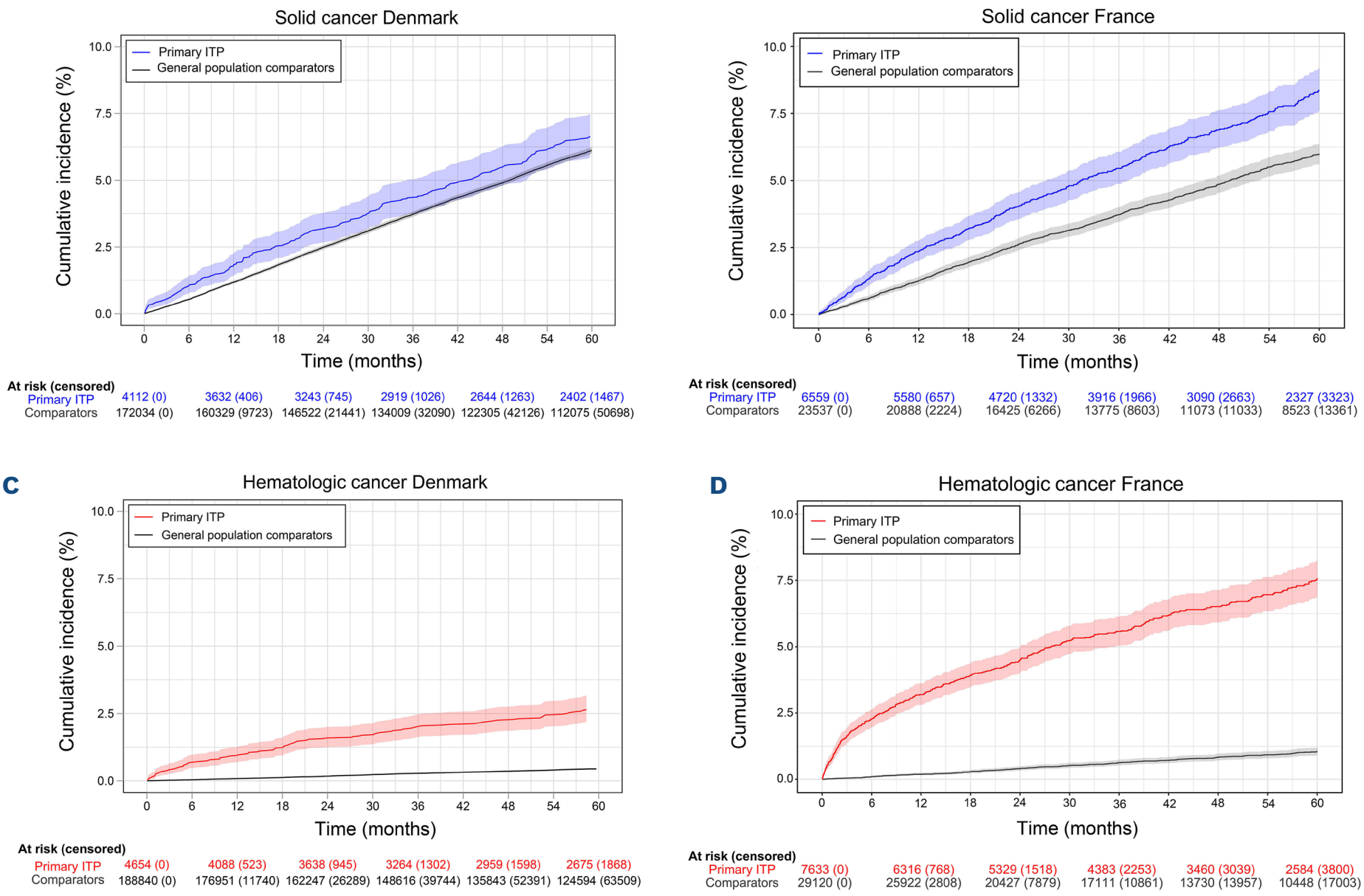
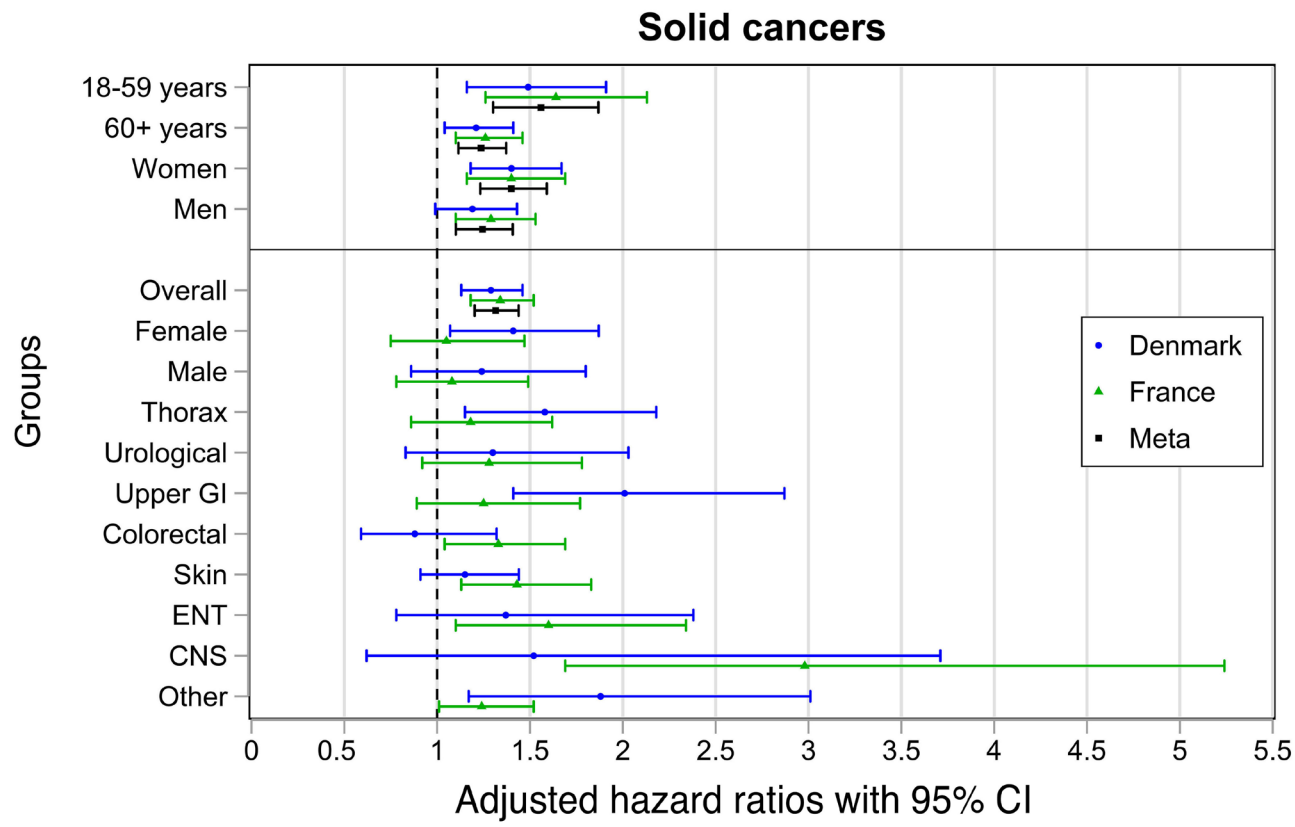


Figure 1. Five-year cumulative incidences of cancers in primary immune thrombocytopenia and general population comparators. Solid cancer (A) in Denmark and (B) in France. Hematologic cancer (C) in Denmark and (D) in France. Colored lines represent patients; the gray lines represent comparators. Cumulative incidences were calculated as the first-ever of any type of either solid or hematologic cancer in the respective countries. ITP: immune thrombocytopenia.

general population, and of hematologic cancer in particular. This applies generally across the two Western populations, despite differences in specific cancer subgroups and sizes of the individual risk estimates likely attributable to other factors. Patients aged 18-59 years and women had the highest instantaneous risks. In both countries, the instantaneous risk of solid cancer was elevated, but competing risks were more prominent in the elderly. The subgroups of solid cancers driving the elevated solid cancer risk differed across countries, while the instantaneous risk of lymphoma, leukemia and other hematologic cancers were elevated in both countries although with variances in the individual subgroup estimates. The instantaneous risks were highest for most cancers during the first year after ITP, but diminished thereafter.

Though Denmark and France have comparable populations, the two cohorts differed on some points. Patients with ITP and comparators had a higher median age in France than in Denmark, and more comorbidity at baseline, prevalent solid cancer included. The French cohort was established in 2010, and France has screening programs, for example, for prostate cancer. Screening programs for colorectal cancer were established in both countries in 2015, and could explain the higher incidence in France since follow-up ended in 2018 in France, in contrast to 2016 in Denmark. In addition, cancer risk increases considerably with age and there has also been a general increase in cancer incidence over recent decades.[17] Taken together, these national differences in data from routine databases could partly explain some of the differences in the Danish and French estimates. However, a time-stratified analysis of the Danish cohort did not show any differences, but rather a generally unchanged risk of cancer across decades. This could indicate potential differences between the cohorts that were not captured or adjusted for (e.g., diet). In general, the strength of the Danish cohort was the long follow-up, while the French cohort included more patients. Our estimates of solid cancer risk aligned with a recent Swedish



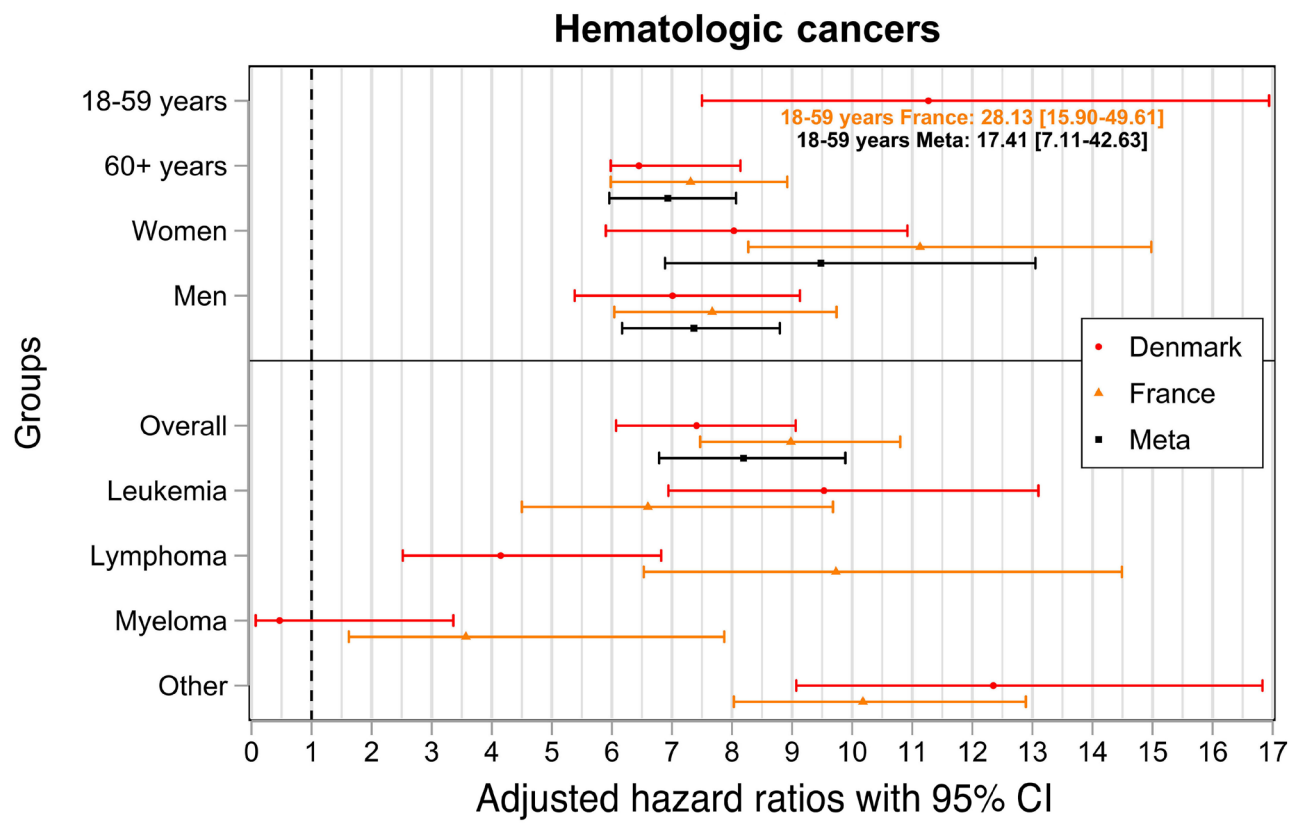


Figure 2. Graphic illustrations of the five-year risk of cancer in primary immune thrombocytopenia compared with the general population. Some estimates are provided written and with numbers to avoid pronounced right-shifted x-axis. Random-effect models were used to assess the meta-estimates (see *Online Supplementary Table S7*). CI: confidence interval(s); CNS: central nervous system; ENT: ear-nose-throat (head and neck); GI: gastrointestinal.

study that reported a csHR for any cancer of 1.4 among 6,740 patients with ITP and 59,394 age- and sex-matched comparators.[12] However, this estimate included both solid and hematologic cancer. With a slightly younger study population, the Swedish study found an elevated risk of liver, digestive and skin cancer, similar to the findings in Denmark and France combined. The elevated risk of skin cancer in France could be due to the higher median age of patients, the increasing incidence of cancer in general, or the immunosuppressive treatment of ITP;[18,19] a higher exposure to ultraviolet sun radiation in France compared to Denmark could also be a contributing factor. Bleeding symptoms from the digestive tract due to ITP could trigger endoscopic examinations revealing an incident colorectal or head-neck cancer in France. In Denmark, the elevated risk of upper GI cancer was mainly driven by liver cancer, similar to the Swedish study. The risks of thoracic cancer, mainly lung cancer, and female cancer were increased in

Denmark in contrast to both Sweden and France. Paraneoplastic associations between small cell lung cancer, breast, and ovarian cancers and ITP have been reported.[9,20] The absolute numbers of solid cancers were higher in both patients and comparators in France compared to Denmark. Reasons for this could be the general increase in the incidence of cancer and the more recent French study period, but also differences in demographics (the ethnic composition of France differs from that of Denmark), culture, and lifestyle, e.g., the higher proportion of smokers in France compared with Denmark.[21] The instantaneous risk of solid cancer was elevated across both age groups in both countries, but competing events partly mitigated the effect in the elderly population.

Our estimates of hematologic cancer risk in Denmark are in line with Nørgaard *et al.*, estimating a five-year cumulative incidence of hematologic malignancy of 1.8% in 407 patients with chronic ITP, and 0.4% in 4,069 age- and sex-matched comparators.[22] The corresponding numbers for patients in France were higher (7.6%), but this was also the case for comparators (1.1%). This could indicate a higher use of bone marrow smears and detection of hematologic cancers in the general French population as well, while the instantaneous five-year risks of hematologic cancer were the same in both countries. The cumulative risk seemed to increase in Denmark as well, both for patients and comparators, when analyses were stratified across decades. A study from the US including 3,131 patients with chronic ITP and 9,392 age- and sex-matched comparators also found an elevated risk of hematologic malignancies.[23] The study found an increased instantaneous risk of lymphoma with a factor 4 in line with the Danish estimate, but a higher (i.e., 20-fold higher) risk of leukemia. Reasons for this difference could be differences across national health systems. The US study was based on an insurance database with 30 million health plans including mainly younger individuals since most health plans were linked to employment, and 64% of the population were aged 18-59 years. In addition, the ethnic composition of the American population differs from the European. The French risk estimates on hematologic cancer subgroups were generally higher than the corresponding Danish risk estimates. This could be explained by improved diagnostics over time, as well as the emergence of new diagnoses and the continuous update of disease definitions, e.g., the revision and recognition of several myeloid neoplasms as independent disease entities in 2001.[24] Furthermore, the French cohort was more recent, and could, therefore, be more likely to have bone marrow smears performed routinely as part of both the diagnostic work-up (recommended in French ITP guidelines for all patients aged >60 years) and in the follow up of the ITP course.

While the higher instantaneous risk of lymphoma could be associated with the immunosuppressive treatment in ITP,[25] the risk of other hematologic malignancies in both countries was mainly driven by an increased incidence of myeloproliferative and myelodysplastic neoplasms. Combined with the high risk of leukemia, the risk of myeloid malignancies was, therefore, higher than lymphoid malignancies. Distinguishing between ITP and typically early-stage myeloid neoplasms can be challenging. For example, patients first classified as ITP may later develop overt chronic myelomonocytic leukemia or myelodysplastic neoplasms.[26,27] The gradual implementation over time of next-generation sequencing in bone marrow diagnostics and the emergence of new disease entities such as idiopathic cytopenia of unspecified significance could reveal underlying and new causes of thrombocytopenia other than ITP in more recent study periods.[28,29] Recently published data also suggest that isolated thrombocytopenia in itself associates with an elevated risk of hematologic malignancy in the population >60 years of age.[30]

The instantaneous risk of solid cancer was highest during the first year after ITP but persisted throughout the 2nd to the 5th year for younger patients and women. ITP remains a diagnosis of exclusion, and this persisting risk underlines the necessity for sufficient and timely diagnostics for potential cancers in selected groups of patients with ITP, despite the absolute risk of most cancers remaining low. Young patients with ITP have long life expectancy, and a persisting risk of hematologic cancer beyond 20 years was found in Denmark. However, while one study did not find any differences in up-front bone marrow biopsies in younger *versus* older patients with ITP, our results indicate that ITP can precede hematologic neoplasms in particular, and remind clinicians of this risk in the clinical follow-up program.[31] This could influence future clinical practice and decision making in ITP, and lower the threshold for cancer diagnostics in specific groups such as refractory ITP failing multiple lines of treatment, or patients presenting with underlying cancer suspect symptoms.

Strengths and limitations

The mains strengths of this study are the binational approach, the large size of the cohorts that facilitate precise estimates of rare events, and the data retrieval from public and continuously updated nationwide health registries with long follow-up. The cohorts are demographically and ethnically comparable Western populations, include large age- and sex-matched general population comparators, and are thoroughly characterized with regards to comorbidity allowing adjustment for potential confounders.

Despite this, our study has limitations. We excluded secondary ITP since this is a poorly defined entity associated with increased comorbidity and mortality.[1] The run-in period for secondary defining diseases ended 30 days after index date, and the emergence of underlying causes beyond this time would potentially increase risk estimates. A previous US study counteracted misclassification by excluding early onset hematologic malignancies after ITP, and still found a factor

10 elevated risk of leukemia.[23] Even though an ITP diagnosis registration is highly valid in Denmark and France,[13,14] the impact of ITP being a diagnosis of exclusion on our results is unknown. An extended run-in period of +6 and +12 months lowered risk estimates for both solid and hematologic cancer, but they remained statistically significant and did not, therefore, change the overall conclusion. However, this also increases immortal time bias and conditions results on future events, and the influence of these possibly opposite effects on our results are unknown.

The diagnostic program for the associated benign blood disorder autoimmune hemolytic anemia usually includes a CT scan to exclude underlying cancer, but this is not general practice for ITP. This could introduce a detection bias underestimating the true incidence of co-incident cancer cases. Vice versa, surveillance bias could also influence the results, as a patient with ITP could be more likely to be diagnosed with cancer while attending regular hospital follow-up. The overall risk of solid cancer was mainly driven by an early effect reverting to baseline over time. This could indicate that solid cancer following ITP could be co-incidental and attributable to surveillance bias, and not necessarily a biological link. However, the risk persisted for, for example, younger patients. We used co-variates like a COPD diagnosis to adjust for confounding but lacked granular data on treatment- and cancer-associated risk factors such as smoking, obesity, and genetics. Hematologic cancer risk decreased but remained elevated over time. This could indicate that ITP may be an early proxy measure for bone marrow or immune dysfunctions, or elevated future risk of hematologic neoplasms. Our follow-up spanned long time periods with changes in registration practices, treatments, diagnostics, and the definition and disease perception of ITP, which may also have influenced our results.

Conclusion

We have shown that the risk of cancer is increased following a diagnosis of ITP compared with the general population. This applies particularly to the first years following ITP diagnosis, for hematologic cancer, and in younger and female patients. The absolute risk increments are small but may promote clinical awareness. Our binational registry findings substantiate the existing knowledge and could help clinicians in their future clinical decisions regarding not only diagnostics and best choice of treatment for ITP, but also in the information given to the patients at the time of ITP diagnosis. Future clinical studies should seek to identify high-risk patient groups that could benefit from intensified front-line diagnostics, individualized follow-up programs and interventions, and further elucidate the influence of immunosuppressants on cancer risk.

Disclosures

NM has received financial support from Novartis Healthcare for this work, received conference fees from AbbVie and Swedish Orphan Biovitrum (SOBI), guest speaker fees from Novartis and SOBI, and served as Advisory Board member for SOBI outside this work. DLH has received research grants from Alexion and Novartis (over 5 years ago), served as Advisory Board member for Janssen and Takeda, and received conference fees from EUSA Pharma and Alexion outside this work. GM received meeting attendance grants from Amgen, Grifols and Novartis. He is co-ordinator of research studies granted by Amgen, CSL Behring, Grifols, Novartis and Sanofi. He participated in educational sessions funded by Amgen, Grifols and Novartis, on boards for Amgen, Argenx, Novartis, Sanofi, Alpine and SOBI, and research grants from Bayer, BMS/Pfizer, Argenx and UCB, all outside this work. AP has participated in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Novo Nordisk, Servier and LEO Pharma, all regulator-mandated phase IV-studies, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the work reported in this paper. HF received research support from SOBI outside this work. All of the other authors have no conflicts of interest to disclose. None of the authors report any other conflicts of interest related to this work.

Contributions

NM, DLH, GM and HF are responsible for the study concept. NM, DLH, GM, AP and HF designed the study. NM, GM and HF applied for funding. NM, YZ, DLH, JM and ML performed data curation and formal analyses. NM wrote the first draft. All authors read and approved the final version of the manuscript.

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Data-sharing statement

The authors are prohibited from sharing Danish and French national health data or grant access to the data according to Danish and French law. All analyses were performed without access to detailed patient medical files. Access to data can be granted upon request through applications and contacts to the designated national authorities. A statistical analysis plan and study protocol can be shared upon request.

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