

Fever of unknown origin and cancer: a population-based study



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Summary

Background Fever of unknown origin is associated with cancer, but the tumour types most commonly involved and the prognostic implications of this relation have not been studied. We aimed to assess the risk of cancer and survival after hospital admission for fever of unknown origin in a nationwide Danish follow-up study.

Methods We linked the Danish national registry of patients and the nationwide cancer registry, and assessed cancer risk for 43 205 patients discharged for the first time from Danish hospitals after admission for fever of unknown origin during 1977–97. We compared cancer frequency with that expected on the basis of cancer incidence in the general population, and survival of patients with cancer who had had fever of unknown origin with that of controls (ie, patients with cancer matched for cancer site, age at time of cancer diagnosis, and year of cancer diagnosis).

Findings Median follow-up was 6.3 years (IQR 2.7–12.3). During the first year of follow-up, 399 cancers were diagnosed in those who had had fever of unknown origin (standardised incidence ratio 2.3 [95% CI 2.1–2.5]). These individuals had an increased risk of developing cancer—in particular haematological malignant disease; sarcoma; and cancers of the liver, brain, kidney, colon, and pancreas. After 1 year of follow-up, individuals had an increased risk of developing haematological malignant disease and cancers of the liver, brain, and kidney. A slightly higher proportion of people diagnosed with cancer within 1 year of hospital discharge after fever of unknown origin had distant metastases compared with controls (101 [34%] of 294 vs 819 [28%] of 2907; prevalence ratio 1.2 [95% CI 1.0–1.4], and had worse survival than did controls (mortality rate ratio 1.4 [95% CI 1.2–1.6]).

Interpretation Hospital admission for fever of unknown origin is a marker of occult cancer and is associated with a poor outlook.

Introduction

Fever of unknown origin was defined in 1961 by Petersdorf and Beeson as an illness characterised by fever of more than three weeks' duration, with temperatures of more than 38.3°C and a failure to identify the origin of the fever despite 1 week of hospital stay.^{1–3} In 2003, this definition was modified, and a hospital setting was not needed for assessment of this illness.⁴ However, the need for thorough assessment of these patients emphasises that the diagnosis of the underlying cause of fevers of unknown origin remains a difficult clinical problem. After work-up, fevers of unknown origin are generally a result of infections, neoplasms, collagen–vascular diseases, or various other disorders.^{1,5–18}

In previous case studies, neoplasms accounted for 17–30% of fevers of unknown origin.² However, since the 1980s, this proportion seems to have declined, probably because improved imaging has facilitated early diagnosis of cancer.⁹ Furthermore, studies of fever of unknown origin have been fairly small, based on 40–300 patients, and several reports based on referral centres lack controls.^{1,5–17} Although most fevers of unknown origin resolve spontaneously, the risk of occult cancer remains a concern. We therefore aimed to assess the association between fever of unknown origin and risk and prognosis of cancer in a follow-up study using population-based data from the Danish health system.

Methods

The Danish national registry of patients, established in 1977, records 99.4% of all discharges from Danish hospitals, since almost no private hospital treatment exists in Denmark.¹⁹ The recorded information includes: civil registration number, unique to every Danish citizen; dates of hospital admission and discharge; surgical procedures done; and up to 20 discharge diagnoses, classified according to the Danish version of the international classification of diseases, 8th revision (ICD-8) until Dec 31, 1993, and according to 10th version (ICD-10) thereafter. We included all people listed in this registry who were classified as having had at least one hospital-discharge diagnosis of fever of unknown origin (ie, ICD-8 788.89 or ICD-10 R50) between Jan 1, 1977, and Dec 31, 1997, during at least one admission to hospital.

By use of the civil registration number, all members of the study cohort were linked to the nationwide mortality registry, which records causes of death, and to the nationwide cancer registry, which has recorded data for incidence of cancer in Denmark since 1943.²⁰ Cancers are classified according to the modified Danish version of the international classification of diseases, 7th revision (ICD-7). Registration is based on notification forms completed by hospital departments, including departments of pathology and forensic medicine, and practising physicians when a person is

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	Number of patients with fever of unknown origin	All years*			Within first year		
		Number of cancers observed	Number of cancers expected	Standardised incidence ratio (95% CI)	Number of cancers observed	Number of cancers expected	Standardised incidence ratio (95% CI)
Overall							
All patients	43 205	1496	1151.1	1.3 (1.2–1.4)	399	173.3	2.3 (2.1–2.5)
Sex							
Men	22 964	757	560.2	1.4 (1.3–1.5)	220	91.6	2.4 (2.1–2.7)
Women	20 241	739	590.9	1.3 (1.2–1.3)	179	81.7	2.2 (1.9–2.5)
Age (years)†							
<5	17 990	36	27.3	1.3 (0.9–1.8)	10	3.4	2.9 (1.4–5.4)
5–59	15 283	441	310.3	1.4 (1.3–1.6)	91	22.7	4.0 (3.2–4.9)
≥60	9932	1019	813.5	1.3 (1.2–1.3)	298	147.2	2.0 (1.8–2.3)
Year of discharge							
1977–87	16 733	861	710.4	1.2 (1.1–1.3)	152	67.0	2.3 (1.9–2.7)
1988–97	26 472	635	440.7	1.4 (1.3–1.6)	247	106.3	2.3 (2.0–2.6)

*0–19 years' follow-up. †Age at time of admission to hospital for fever of unknown origin.

Table 1: Standardised incidence ratio for cancer after hospital admission for fever of unknown origin according to sex, age at the time of admission, and year of discharge

diagnosed with cancer, at autopsy, or when changes are made to an initial cancer diagnosis. Manually recorded cases are supplemented by unreported cases identified by computerised links to the death-certificate file and the national registry of patients. Comprehensive assessment has shown the registry to be 95–98% complete and valid.²⁰

Through links to the cancer registry, we excluded patients who had had fever of unknown origin and a previous diagnosis of cancer other than non-melanoma skin cancer. We followed up cases for the occurrence of cancer from the date of first hospital admission for fever of unknown origin until the date of death, emigration, or until Dec 31, 1998, whichever came first.

To assess the association between fever of unknown origin and prognosis after diagnosis of cancer, we selected a control group of ten patients with cancer, but who had not had fever of unknown origin, for every case diagnosed with cancer who had had fever of unknown origin. Controls were obtained from the cancer registry and were matched to cases on cancer site, sex, age at

time of cancer diagnosis in 10-year age groups, and year of diagnosis in 5-year periods. For two cases, we obtained only nine controls. Cases and controls were linked to the mortality registry, which provided continuously updated data for vital status. The study was approved by the Danish Registry Board.

Statistical analyses

We calculated the expected number of cases of cancer after a first hospital-discharge diagnosis of fever of unknown origin using national incidence rates of first-cancer diagnoses according to sex, age, and year of diagnosis in 5-year intervals. Multiplication of the number of person-years of follow-up by the incidence rates yielded the number of people with cancer that would be expected if patients with fever of unknown origin had the same risk of cancer as did the general population.²¹ We used the standardised incidence ratio—the ratio of observed number of cancers to expected number of cancers—to measure the association between fever of unknown origin and cancer, and calculated 95% CI on the basis of the assumption that the observed number of cancers in a specific category followed a Poisson distribution. Exact 95% CI were used when the observed number was less than ten, otherwise Byar's approximation was used. Data are not presented for cancer sites with fewer than five recorded diagnoses.

Through use of the Danish cancer registry, we obtained data for the extent of cancer spread in cases, which we classified as “no spread”, “regional spread”, and “distant metastases”. We calculated the prevalence ratio, with 95% CI, of distant metastases—ie, the proportion of cases with distant metastases divided by the proportion of controls with distant metastases.

We used Cox proportional-hazards regression analyses to compare death rates after cancer diagnosis in cases with that of controls; comparisons were based

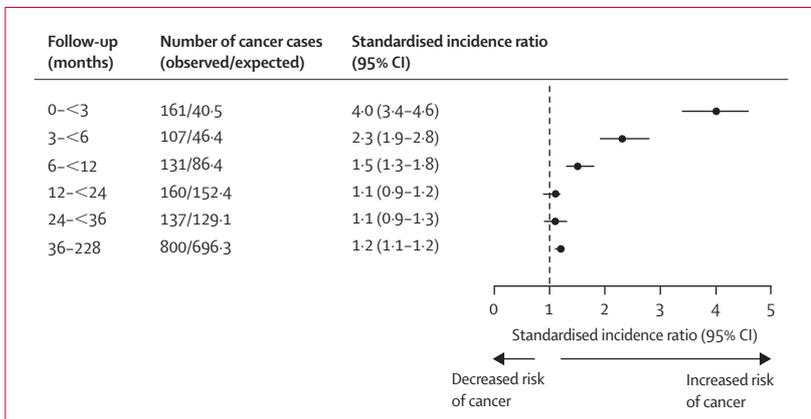


Figure 1: Standardised incidence ratio for overall cancer risk after hospital admission for fever of unknown origin

on estimation of mortality ratios and 95% CI. We estimated cumulative risks using the life-table method. All statistical analyses were done with SAS software version 8.2.

Role of the funding source

The sponsor of the study had no role in the study design; in the collection, analysis, or interpretation of the data; or in the writing of the report. The corresponding author had full access to all data in the study, and had the final responsibility to submit for publication.

Results

We identified 43 205 patients discharged with fever of unknown origin (table 1) of median age 9.7 years (IQR 1.5–56.8); median follow-up was 6.3 years (2.7–12.3). Overall, these patients were at increased risk of developing any type of cancer (table 1). Risk of cancer was much the same for those with fever of unknown origin listed as a first-discharge diagnosis (standardised incidence ratio 1.3 [95% CI 1.2–1.4]) and those listed with fever of unknown origin as a secondary diagnosis when the primary diagnosis was any disease (1.4 [1.3–1.5]). Table 1 also shows the standardised incidence ratio for patients admitted to hospital for fever of unknown origin according to sex, age at time of hospital admission, and year of discharge for all years and for within the first year of follow-up.

In the first year of follow-up after discharge with fever of unknown origin, those aged 5–59 years had the highest risk of developing cancer (table 1). Risk of

	Observed*	Expected	Standardised incidence ratio (95% CI)
All neoplasms (140–205)	1097	977.8	1.1 (1.1–1.2)
Sarcomas (140–205)	16	13.6	1.2 (0.7–2.0)
Buccal (140–148)	21	20.6	1.0 (0.6–1.6)
Oesophagus (150)	12	11.5	1.1 (0.5–1.8)
Stomach (151)	33	30.4	1.1 (0.8–1.5)
Colon (153)	113	99.4	1.1 (0.9–1.4)
Rectum (154)	44	49.6	0.9 (0.6–1.2)
Liver, primary (155)	19	10.2	1.9 (1.1–2.9)
Gall bladder (155.1)	9	9.8	0.9 (0.4–1.8)
Pancreas (157)	37	30.3	1.2 (0.9–1.7)
Lung, primary (162)	133	126.8	1.1 (0.9–1.2)
Breast (170)	110	119.1	0.9 (0.8–1.1)
Cervix uteri (171)	11	17.2	0.6 (0.3–1.2)
Corpus uteri (172)	20	24.9	0.8 (0.5–1.2)
Ovary (175)	21	22.4	0.9 (0.6–1.4)
Prostate (177)	76	70.9	1.1 (0.9–1.3)
Testis (178)	12	8.3	1.4 (0.7–2.5)
Kidney (180)	41	26.6	1.5 (1.1–2.1)
Urinary bladder (181)	70	65.7	1.1 (0.8–1.4)
Malignant melanoma (190)	22	26.3	0.8 (0.5–1.3)
Eye (192)	6	2.9	2.1 (0.8–4.5)
Brain (193)	49	34.7	1.4 (1.0–1.9)
Thyroid (194)	7	4.2	1.7 (0.7–3.4)
Non-Hodgkin lymphoma (200, 202)	38	27.2	1.4 (1.0–1.9)
Hodgkin's disease (201)	11	5.2	2.1 (1.1–3.8)
Multiple myeloma (203)	20	12.7	1.6 (1.0–2.4)
Leukaemia (204)	56	33.1	1.7 (1.3–2.2)

Numbers in parentheses after disease are sites and types of cancer from modified version of the International Classification of Diseases, 7th revision. *Sites with five or more recorded cancers.

Table 3: Standardised incidence ratio for cancers in patients followed up 1–19 years after hospital admission for fever of unknown origin

	Observed*	Expected	Standardised incidence ratio (95% CI)
All neoplasms (140–205)	399	173.3	2.3 (2.1–2.5)
Hodgkin's disease (201)	16	0.6	27.8 (15.9–45.1)
Non-Hodgkin lymphoma (200, 202)	43	4.4	9.9 (7.1–13.3)
Sarcomas (140–205)	14	2.1	6.6 (3.6–11.1)
Liver, primary (155)	12	2.0	6.1 (3.2–10.7)
Leukaemia (204)	35	6.2	5.6 (3.9–7.8)
Multiple myeloma (203)	10	2.3	4.4 (2.1–8.0)
Brain (193)	21	5.2	4.1 (2.5–6.2)
Pancreas (157)	21	5.7	3.7 (2.3–5.6)
Colon (153)	48	18.0	2.7 (2.0–3.5)
Gall bladder (155.1)	5	1.9	2.7 (0.9–6.3)
Kidney (180)	13	5.0	2.6 (1.4–4.5)
Ovary (175)	7	3.6	1.9 (0.8–4.0)
Buccal (140–148)	6	3.6	1.7 (0.6–3.6)
Lung, primary (162)	35	23.4	1.5 (1.0–2.1)
Prostate (177)	20	14.8	1.4 (0.8–2.1)
Urinary bladder (181)	16	12.5	1.3 (0.7–2.1)
Breast (170)	21	18.4	1.1 (0.7–1.7)
Stomach (151)	7	6.3	1.1 (0.5–2.3)
Rectum (154)	7	9.4	0.8 (0.3–1.5)

Numbers in parentheses after disease are sites and types of cancer from modified version of the International Classification of Diseases, 7th revision. *Sites with five or more recorded cancers.

Table 2: Standardised incidence ratio for cancers diagnosed within 1 year of hospital admission for fever of unknown origin

cancer in the first year after discharge was much the same for those discharged between 1977 and 1987, and those discharged between 1988 and 1997 (table 1). Figure 1 shows the risk of cancer by month of follow-up.

During the first year of follow-up, patients who had had fever of unknown origin had a raised risk of developing various types of cancer—in particular Hodgkin's disease; non-Hodgkin lymphoma; leukaemia; multiple myeloma; sarcoma; and tumours of the liver, brain, kidney, colon, and pancreas (table 2). Table 3 shows the risk of various cancers 1–19 years after discharge for fever of unknown origin; figure 1 shows the risk of cancer 12–<24 months, 24–<36 months, and 36–228 months after discharge. After the first year of follow-up, individuals were at increased risk of having haematological malignant disease and cancers of the liver, brain, and kidney: table 4 shows the risk for these cancers according to follow-up.

Data for the extent of cancer at the time of diagnosis was available for 1129 (75%) of 1496 cases and for 11 448 (77%) of 14 958 controls. In the first year of follow-up, a slightly higher proportion of cases had distant metastases than did controls (101 [34%] of 294 vs 819 [28%] of 2907; prevalence ratio 1.2 [95% CI 1.0–1.4]). For cases diagnosed more than 1 year after

	Follow-up (months)	Number of cancers observed	Numbers of cancers expected	Standardised incidence ratio (95% CI)
Liver, primary	12–24	4	1.7	2.3 (0.6–6.0)
	25–<36	4	1.4	2.8 (0.8–7.1)
	36–228	11	7.1	1.6 (0.8–2.8)
Kidney	12–24	4	4.4	0.9 (0.3–2.4)
	25–<36	6	3.7	1.6 (0.6–3.5)
	36–228	31	19.0	1.7 (1.1–2.4)
Brain	12–24	8	4.7	1.7 (0.7–3.4)
	25–<36	6	4.1	1.5 (0.5–3.2)
	36–228	35	25.9	1.4 (0.9–1.9)
Non-Hodgkin lymphoma	12–24	7	3.9	1.8 (0.7–3.7)
	25–<36	7	3.3	2.1 (0.8–4.3)
	36–228	24	20.0	1.2 (0.8–1.8)
Hodgkin’s disease	12–24	0	0.5	..
	25–<36	4	0.5	8.6 (2.3–21.9)
	36–228	7	4.2	1.7 (0.7–3.4)
Multiple myeloma	12–24	4	2.0	2.0 (0.5–5.1)
	25–<36	3	1.7	1.8 (0.4–5.2)
	36–228	13	9.0	1.5 (0.8–2.5)
Leukaemia	12–24	10	5.5	1.8 (0.9–3.3)
	25–<36	11	4.7	2.3 (1.2–4.2)
	36–228	35	1.5	1.5 (1.1–2.1)

Table 4: Standardised incidence ratios for haematological malignant disease and cancers of the liver, kidney, and brain after 1 year of follow-up

discharge for fever of unknown origin, the proportion of cases and controls with distant metastases was much the same (193 [23%] of 835 vs 2164 [25%] of 8541; 0.9 [0.8–1.4]).

Cases who were diagnosed within 1 year of discharge for fever of unknown origin had worse survival than did controls (mortality ratio 1.4 [95% CI 1.2–1.6]; figure 2). By contrast, survival for cases diagnosed more than 1 year after discharge from hospital was much the same as that for controls (1.1 [1.0–1.2]).

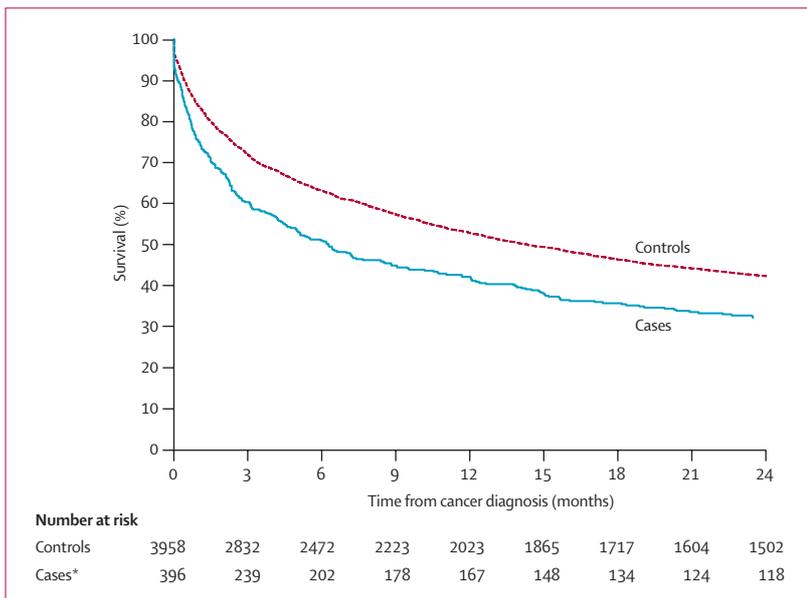


Figure 2: Survival of patients diagnosed with cancer within 1 year after hospital admission for fever of unknown origin and controls

*Complete follow-up data not available for three cases.

Discussion

We have shown that patients admitted to hospital with fever of unknown origin have an increased risk of developing cancer compared with the general population. In the first year of follow-up after discharge from hospital, individuals had a high risk of haematological cancer; sarcoma; and malignant disease of the liver, brain, kidney, colon, and pancreas. In subsequent years, there was only a small increase in overall cancer risk, but fever of unknown origin remained a weak indicator of long-term risk for haematological malignant disease and cancers of the liver, brain, and kidney. However, the risk of developing various cancers was low, and the overall risk during the first year of follow-up was lower than those reported previously.² Moreover, fever of unknown origin was also associated with more-advanced disease and a poor outlook.

Previous studies^{1,2,7,9,11,13,14} of patients with fever of unknown origin and subsequent cancer risk have included about 1200 people in total, and the recorded distribution of cancers was similar to that noted for the first year of follow-up in this study in that the most common malignant diseases were Hodgkin’s lymphoma and non-Hodgkin lymphoma. Nearly all common cancers have been noted in previously published case studies of fever of unknown origin, although lymphoma and kidney cancer are most frequently reported. Furthermore, our findings confirm those of a study of nine patients, which showed an association between fever of unknown origin and multiple myeloma.²²

The frequency of malignant disease in patients with fever of unknown origin seems to have decreased over time—from about 30% in the 1970s to 9–20% in the 1990s.² This trend may be due to improved diagnostic imaging (eg, CT and MRI), which has aided the detection of otherwise occult solid tumours.^{2,9,11,15,16} Likewise, the proportion of abdominal abscesses has decreased.²³ In our study, the frequency of malignant disease after fever of unknown origin was low, perhaps because the population-based design resulted in a large proportion of young patients. Furthermore, referral patterns might also affect the number of cancers recorded. We also note that we did not find a decrease in risk of cancer from 1977–87 to 1988–97.

Cancer might be associated with fever of unknown origin for several reasons. Heightened diagnostic effort could account for some of the association; however, after several years of follow-up, diagnostic bias should not be a major contributing factor to the number of cancers recorded, and a short-term association due to diagnostic bias alone would be followed by a later compensatory deficit (ie, cancer risk would be less than one during extended follow-up). However, we found the risk of cancer to be slightly above, or close to, one for most cancer types, which suggests that the association between fever of unknown origin and cancer cannot be explained by diagnostic bias, although some role for this

factor cannot be excluded completely. Furthermore, cancer can cause fever through several mechanisms, including occult infections, inflammation, vasculitis, and neutropenia.¹⁷

The large cohort we studied obtained nationwide, population-based registries that had complete follow-up data, which led to more statistical precision in our analyses compared with previous studies and which enabled us to assess risks of developing specific cancers. The use of 5-year age intervals in statistical analyses might have caused some residual confounding by age in children because of the low number of cancers noted in this age group. The use of population controls enabled us to estimate risks and relate the findings to a defined population.

Our data do not take into account the criteria used for the diagnosis of fever of unknown origin, which might have resulted in incorrect classification of the discharge diagnosis as fever or in missed diagnoses of fever.²⁴ Such lack of specificity would tend to weaken the strength of the associations we recorded. Moreover, the lack of clinical details prevents us from suggesting guidelines for the diagnostic care of patients admitted to hospital because of fever of unknown origin,²⁵ and whether patients admitted to hospital with fever of unknown origin differ over time is not known. With the administrative pressures to avoid hospital admission for assessment, cases from the past 15 years are, in particular, likely to be either ill or problematic to diagnose. Thus, a substantial proportion of more recent cases that previously would have been admitted for fever of unknown origin were not in our cohort because they were assessed as outpatients.

In conclusion, our data show that fever of unknown origin is a marker of occult cancer, although this association was much weaker than those previously reported. In particular, the risk of haematological cancers was increased within 1 year after discharge of patients with fever of unknown origin.

Contributors

H T Sørensen had the study idea. All co-authors participated in the design of the study. L Mellekjær obtained cancer data; H T Sørensen, L Mellekjær, and M V Skriver did data analyses; H T Sørensen, L Mellekjær, J H Olsen, and J A Baron organised and directed the statistical analyses; H T Sørensen wrote the first draft of the paper; and all authors participated in the writing of the paper.

Conflict of interest

We declare no conflicts of interest.

Acknowledgments

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