Research Article

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Cancer Risk and Prognosis after a Hospital Contact for an Elevated Erythrocyte Sedimentation Rate

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Abstract

Background: An elevated erythrocyte sedimentation rate (ESR) may be a marker of occult cancer.

Methods: We linked Danish medical databases to examine cancer incidence in patients with a first-time hospital contact for elevated ESR during 1980 to 2013. We calculated standardized incidence ratios (SIR) of cancer compared with the general population, and comorbidity-adjusted HRs (aHR) versus matched population comparisons without elevated ESR. We also compared survival among patients with cancer with elevated ESR with that among patients with cancer without elevated ESR.

Results: During median follow-up of 4.9 years, we observed 3,926 cancers among 18,540 patients with a first-time hospital contact for elevated ESR. The risk for any cancer diagnosed during the first year following the contact for elevated ESR was 8.5% [95% confidence interval (CI), 8.1%–8.9%]. The overall 1-year cancer incidence was markedly elevated [SIR 5.3 (95% CI, 5.1–5.6); aHR 5.8 (95% CI, 5.4–6.3)] and was more than 3-fold elevated for most hematologic cancers and for cancers of the peritoneum and connective tissue in the abdominal wall, kidney, and adrenal glands. After the first year, patients were at increased risk of developing especially hematologic cancers. Patients diagnosed with cancer within 1 year after a contact for elevated ESR had poorer survival compared with matched cancer comparisons [adjusted mortality rate ratio 1.2 (95% CI, 1.1–1.3)].

Conclusions: Elevated ESR is a strong marker of undiagnosed cancer and is associated with poorer survival.

Impact: Our findings may help clinicians in assessing absolute risk, common sites, and prognosis of cancers discovered after hospital contact with elevated ERS.

Introduction

The erythrocyte sedimentation rate (ESR) is a frequently performed laboratory test, which measures the rate at which erythrocytes suspended in plasma settle when placed in a vertical tube (1). An elevated rate does not indicate a specific disease, but it is a marker that underlying disease may be present. The main determinants of elevated ESR are the degree of red blood cell aggregation and the hematocrit (packed cell volume; ref. 2). Red blood cell aggregation, in turn, is influenced mainly by the level of fibrinogen and other acute-phase proteins. The ESR may therefore be increased in association with infectious disease, other inflammatory processes, and collagen-vascular disease (1, 3). In addition to acute-phase proteins, red blood cell aggregation is increased by immunoglobulins. Presence of cancer cells in the body may stimulate an immune response from the host, thereby increasing the level of acute-phase proteins and immunoglobulins (4). Moreover, some hematologic cancer cells themselves may produce immunoglobulins that are excreted in the blood; that is, in multiple myeloma and Waldenstrom's macroglobulinemia.

At times physicians encounter patients with elevated ESR of unknown origin. It has been reported that malignancy develops infrequently in patients whose increased ESR cannot be explained (5), but evidence is sparse (6–8). In clinic-based cohorts from Kiel and Stockholm and in a population study of Swedish asymptomatic women, less than 6% of individuals with unexplained elevated ESR had cancer diagnosed during 5, 10, and 6 years of follow-up, respectively (6–8). However, these studies lacked comparison cohorts and follow-up was based on only 38 to 42 patients, precluding identification of specific cancer sites associated with elevated ERS. An additional issue is that little is known about the prognosis of patients with cancer discovered after a hospital contact for elevated ESR of unknown origin.

To address these questions, we conducted a nationwide Danish follow-up study to examine cancer occurrence and prognosis following a hospital contact for ESR.

Materials and Methods

Denmark has 5,748,769 inhabitants (January 1, 2017) and the Danish healthcare system provides tax-supported health care to all residents, guaranteeing free access to hospitals and primary medical care. The civil registration number, a unique identifier assigned to every Danish resident, allowed for valid linkage among the databases used in this study (9).

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Identification of patients with a hospital contact for elevated ESR

The Danish National Patient Registry (DNPR) has collected data on all nonpsychiatric hospital stays in Denmark since 1977 and on all hospital outpatient visits since 1995 (10). Data include dates of hospital admission and discharge, outpatient visit dates, and up to 20 discharge diagnoses coded by physicians according to the Danish version of the International Classification of Diseases, Eighth Revision (ICD-8) until the end of 1993, and Tenth Revision (ICD-10) thereafter. Our study population included all people born in Denmark with a record in the DNPR of a first-time inpatient hospitalization or hospital outpatient clinic visit with a diagnosis of elevated ESR (see Supplementary Table S1 for codes) between January 1, 1980 and November 30, 2013. People with previously elevated ESR between January 1, 1977 and January 1, 1980 were excluded. Both primary (i.e., the main reason for the hospitalization or hospital outpatient visit) and secondary diagnoses were included. The DNPR did not include data on the exact magnitude of ESR elevation.

Validation of hospital diagnoses of elevated ESR

We validated the hospital diagnosis of elevated ESR among a subpopulation of patients with ESR living in Central Denmark ($n = 2275$) and Northern Denmark ($n = 801$) through linkage with the Laboratory Information Systems (LABKA; ref. 11). This database stores ESR and other test results for all blood samples taken in hospital or by any general practitioner and submitted to any hospital laboratory in Central and Northern Denmark, including the exact time of blood sample collection. However, LABKA does not contain data on ESR tests performed and analyzed with rapid point-of-care devices by general practitioners in their own clinics. Laboratory data were available between 2000 and 2013 in Central Denmark and between 1997 and 2013 in Northern Denmark.

Data on autoimmune diseases and infections

Risk of cancer among patients with an elevated ESR may vary according to presence of autoimmune diseases and infections. We therefore used the DNPR to identify patients with an autoimmune disease (see Supplementary Table S2 for codes) diagnosed before or at the same time as the diagnosis of elevated ESR. We also used the DNPR to identify persons with an infection (see Supplementary Table S3 for codes) diagnosed within 3 months before or simultaneously with the first-time hospital contact for an elevated ESR.

Identification of cancer

We obtained information on all cancer diagnoses from the Danish Cancer Registry (DCR). This registry has maintained data on cancer incidence throughout Denmark since 1943 and is 95%–98% complete and valid (12). Cancers are classified according to ICD-10. Registration is based on notification of new cancer diagnoses by hospital departments (including departments of pathology and forensic medicine), general practitioners, and practicing specialists at the time of cancer diagnosis, at autopsy, or when changes are made to an initial cancer diagnosis. We excluded patients with a cancer diagnosis preceding the first hospital contact with elevated ESR.

Elevated ESR and survival after cancer diagnosis

To assess the association between elevated ESR and prognosis after a later diagnosis of cancer, we constructed a comparison cohort by matching 10 patients with cancer without a preceding hospital contact for elevated ESR to every case diagnosed with cancer who did have a preceding hospital contact with this indication. Members of the cancer comparison cohort were identified from the DCR. Matching was based on cancer site, sex, age in 5-year age groups, and calendar year of cancer diagnosis in 5-year periods. To adjust for comorbidity, we used the Charlson Comorbidity Index (CCI; ref. 13). We computed a CCI score for each study patient based on all available hospital diagnoses recorded in the DNPR before the date of cancer diagnosis. Three comorbidity levels were defined: low (score of 0), medium (scores of 1–2), and high (scores ≥ 3). Cancer diagnoses were excluded from the Index, as they defined our cancer cohort.

Vital status

Date of death or emigration was obtained through record linkage with the Civil Registration System (CRS). The CRS has kept electronic records of all changes in vital status since 1968 (14).

Statistical analysis

Cancer risk. We followed patients to detect any cancer diagnosis from the date of the first hospital contact with elevated ESR until date of death, emigration, or November 30, 2013, whichever came first.

The standardized incidence ratio (SIR) of cancer was computed as the observed number of cancers divided by the expected number of cancers. The expected number was obtained by multiplying the number of person-years at risk in our ESR cohort by national cancer incidence rates according to sex, age, and year of diagnosis in 5-year intervals. In a second analysis using Cox regression, for each person with elevated ESR, we selected five population comparisons without any elevated ESR history on the person's elevated ESR date. Comparison cohort members were matched to the elevated ESR patients on sex and year of birth, using matching with replacement. Comparison cohort members who developed elevated ESR were censored at this time and changed cohort contributing with follow-up time in the ESR-exposed cohort. Cox regression was used to compute adjusted hazard ratios (aHR) of cancer by total follow-up time after elevated ESR/index date, adjusting for recent infection, autoimmune disease, and overall level of comorbidity assessed by the CCI score.

Because a hospital contact for elevated ESR may be related to undiagnosed cancer, we computed SIRs and aHRs separately for early (first year) and longer-term (subsequent years) follow-up. SIRs and aHRs were computed for any cancer and for site-specific cancers. We computed risk estimates for cancer separately for hospital inpatient and outpatient diagnoses of elevated ESR, stratified by sex and age group (0–29, 30–49, 50–69, and 70+ years) and by calendar time periods. We also computed risk estimates for cancer separately for hypersedimentation patients with and without an autoimmune disease and with and without a recent infection. In an additional analysis, follow-up time after hospitalization for elevated ESR was divided into the following periods: 0 to 3 months, >3 to 6 months, >6 to 12 months, >1 to 2 years, >2 to 5 years, >5 to 10 years, and >10 years. Finally, to summarize time-to-events, we calculated the cumulative incidence of cancer, treating death as a competing risk.

Table 1. SIR for cancers diagnosed after a hospital contact for an elevated ESR, according to sex, age, year of diagnosis, contact type (in-/outpatient status), type of diagnosis (primary/secondary), recent infection, and autoimmune disease, and aHRs versus matched population comparisons without elevated ESR, according to year of diagnosis, contact type, type of diagnosis (primary/secondary), recent infection, and autoimmune disease

		All years		During first year of follow-up			During subsequent years of follow-up		
All cancers	**Number of patients with elevated ESR**	**Cancers observed/ expected**	**SIR (95% CI)**	**Cancers observed/ expected**	**SIR (95% CI)**	**aHR[b] (95% CI)**	**Cancers observed/ expected**	**SIR (95% CI)**	**aHR[b] (95% CI)**
Overall									
All patients	18,540	3,926/2,403.6	1.6 (1.6–1.7)	1,569/294.0	5.3 (5.1–5.6)	5.8 (5.4–6.3)	2,357/2,109.7	1.1 (1.1–1.2)	1.1 (1.0–1.1)
Sex									
Women	11,198	2,151/1,430.3	1.5 (1.4–1.6)	760/156.7	4.9 (4.5–5.2)	5.5 (4.9–6.1)	1,391/1,273.6	1.1 (1.0–1.2)	1.1 (1.0–1.1)
Men	7,342	1,775/973.3	1.8 (1.7–1.9)	809/137.3	5.9 (5.5–6.3)	6.2 (5.6–6.9)	966/836.1	1.2 (1.1–1.2)	1.1 (1.1–1.2)
Age (years)[a]									
0–29	703	44/20.1	2.2 (1.6–2.9)	20/0.2	83.7 (51.1–129.3)	43.6 (10.1–188.1)	24/19.8	1.2 (0.8–1.8)	1.3 (0.8–2.1)
30–49	1,290	231/134.9	1.7 (1.5–2.0)	64/3.9	16.6 (12.8–21.2)	13.2 (7.9–21.8)	167/131.1	1.3 (1.1–1.5)	1.2 (1.0–1.5)
50–69	6,326	1,635/992.2	1.7 (1.6–1.7)	580/75.8	7.7 (7.0–8.3)	7.9 (6.9–9.1)	1,055/916.4	1.2 (1.1–1.2)	1.1 (1.0–1.2)
≥70	10,221	2,016/1,256.4	1.6 (1.5–1.7)	905/214.0	4.2 (4.0–4.5)	4.7 (4.3–5.2)	1,111/1,042.4	1.1 (1.0–1.1)	1.1 (1.0–1.1)
Year of diagnosis									
1980–1984	2,482	541/358.3	1.5 (1.4–1.6)	151/30.3	5.0 (4.2–5.8)	6.1 (4.7–7.8)	390/328.0	1.2 (1.1–1.3)	1.2 (1.1–1.4)
1985–1989	3,016	613/435.2	1.4 (1.3–1.5)	210/40.2	5.2 (4.5–6.0)	5.7 (4.6–7.1)	403/395.0	1.0 (0.9–1.1)	1.0 (0.8–1.1)
1990–1994	3,200	666/442.6	1.5 (1.4–1.6)	208/48.4	4.3 (3.7–4.9)	4.0 (3.3–4.8)	458/394.2	1.2 (1.1–1.3)	1.3 (1.1–1.4)
1995–1999	3,060	739/459.2	1.6 (1.5–1.7)	277/48.0	5.8 (5.1–6.5)	6.7 (5.5–8.1)	462/411.2	1.1 (1.0–1.2)	1.1 (1.0–1.2)
2000–2004	2,767	682/389.0	1.8 (1.6–1.9)	303/48.0	6.3 (5.6–7.1)	7.0 (5.8–8.4)	379/341.0	1.1 (1.0–1.2)	1.0 (0.9–1.2)
2005–2009	2,425	500/255.3	2.0 (1.8–2.1)	268/49.6	5.4 (4.8–6.1)	6.9 (5.7–8.5)	232/205.7	1.1 (1.0–1.3)	1.1 (0.9–1.2)
2010–2013	1,590	185/64.0	2.9 (2.5–3.3)	152/29.5	5.2 (4.4–6.0)	5.1 (4.0–6.5)	33/34.5	1.0 (0.7–1.3)	0.9 (0.6–1.3)
Contact type									
Outpatient (first contact)	4,546	928/549.4	1.7 (1.6–1.8)	413/80.2	5.2 (4.7–5.7)	5.6 (4.8–6.5)	515/469.1	1.1 (1.0–1.2)	1.0 (0.9–1.1)
Inpatient (first contact)	13,994	2,998/1854.2	1.6 (1.6–1.7)	1,156/213.7	5.4 (5.1–5.7)	6.0 (5.4–6.5)	1,842/1,640.5	1.1 (1.1–1.2)	1.1 (1.1–1.2)
Type of elevated ESR diagnosis									
Primary diagnosis	9,579	2,067/1,313.6	1.6 (1.5–1.6)	829/155.1	5.3 (5.0–5.7)	5.6 (5.0–6.2)	1,238/1,158.5	1.1 (1.0–1.1)	1.0 (1.0–1.1)
Secondary diagnosis	8,961	1,859/1,090.0	1.7 (1.6–1.8)	740/138.8	5.3 (5.0–5.7)	6.3 (5.6–7.1)	1,119/951.2	1.2 (1.1–1.3)	1.2 (1.1–1.3)
Recent infection									
Yes	2,437	418/272.2	1.5 (1.4–1.7)	158/38.3	4.1 (3.5–4.8)	3.0 (2.0–4.7)	260/233.9	1.1 (1.0–1.3)	0.9 (0.7–1.1)
No	16,103	3,508/2,131.4	1.7 (1.6–1.7)	1,411/255.7	5.5 (5.2–5.8)	5.6 (5.2–6.0)	2,097/1,875.8	1.1 (1.1–1.2)	1.1 (1.0–1.1)
Autoimmune disease									
Yes	2,034	389/250.9	1.6 (1.4–1.7)	146/36.4	4.0 (3.4–4.7)	3.7 (2.8–5.0)	243/214.6	1.1 (1.0–1.3)	1.0 (0.8–1.2)
No	16,506	3,537/2,152.7	1.6 (1.6–1.7)	1,423/257.6	5.5 (5.2–5.8)	5.7 (5.3–6.1)	2,114/1,895.1	1.1 (1.1–1.2)	1.1 (1.0–1.1)

[a]Age at time of first hospital contact with ESR.

[b]In the case of stratification on contact type and type of diagnosis, elevated ESR patients within the relevant strata are compared with their sex- and age-matched population comparisons without elevated ESR, while adjusting for overall level of comorbidity, recent infection, and autoimmune disease. In the case of stratification on recent infection and autoimmune disease, elevated ESR patients within the relevant strata are compared with comparison members within the same strata, while adjusting for all the variables above except the stratification variable.

Survival after cancer diagnosis

We constructed survival curves for patients with cancer with and without a preceding hospital contact for elevated ESR, with follow-up starting on the date of the first cancer diagnosis. To compare death rates after cancer diagnosis according to ESR status, we used Cox regression to compute mortality rate ratios with 95% confidence intervals (95% CI), while controlling for level of comorbidity. We used SAS software (version 9.4, SAS Institute). The Danish Registry Board approved the study (Record no. 1-16-02-1-08).

Results

We identified 18,540 individuals (11,198 women and 7,342 men) discharged from a hospital or a hospital outpatient clinic visit with a diagnosis of elevated ESR between 1980 and 2013. Median age at study entry was 71.6 years [interquartile range (IQR): 61.4–78.8 years] and median follow-up was 4.9 years (IQR: 1.4–10.3 years).

Validation of diagnoses of elevated ESR

Among the 2,275 patients with a diagnosis of elevated ESR who were living in Central Denmark during 2000 to 2013, 1,805 (79%) had ESR measurements available in LABKA during the index hospitalization or 30 days before admission. Among those patients with a diagnosis of elevated ESR and with available ESR measurements, 1,670 had at least one ESR value above 30, corresponding to a positive predictive value of 93%. Among the 801 patients with a diagnosis of elevated ESR who were living in Northern Denmark during 1997 to 2013, 594 (74%) had ESR measurements available in LABKA and 576 had at least one ESR value above 30, corresponding to a positive predictive value of 97%.

Cancer risk

Cumulative risks for any cancer in the cohort with elevated ESR were 8.5% (95% CI, 8.1%–8.9%) after 1 year and 14.3% (95% CI, 13.8%–14.8%) after 5 years. Corresponding risks for hematologic cancers were 2.5% (95% CI, 2.3%–2.8%) after 1 year and 3.3% (95% CI, 3.0%–3.5%) after 5 years.

Patients with elevated ESR were more likely to be diagnosed with a subsequent cancer than persons in the general population. During the first year of follow-up, 1,569 cancers were identified in patients with elevated ESR, yielding a SIR for any cancer of 5.3 (95% CI, 5.1–5.6) and an aHR of 5.8 (95% CI, 5.4–6.3; Table 1), while the SIRs were 4.9 (95% CI, 4.5–5.2) for women and 5.9 (95% CI, 5.5–6.3) for men. Individuals younger than 30 years had the highest relative risk of a subsequent diagnosis of any cancer

Table 2. SIR for cancers diagnosed within 1 year of a hospital contact for an elevated ESR compared with the general population, and aHRs versus sex- and age-matched population comparisons without elevated ESR

Cancer site	Cancers observed[a]/ expected	SIR (95% CI)	aHR[b] (95% CI)
All cancers	1,569/294.0	5.3 (5.1–5.6)	5.8 (5.4–6.3)
Esophagus	6/2.9	2.0 (0.8–4.5)	1.5 (1.0–2.2)
Stomach	31/6.4	4.9 (3.3–6.9)	1.3 (1.0–1.7)
Small intestine	5/0.6	8.0 (2.6–18.7)	1.2 (0.5–2.5)
Colon	156/25.6	6.1 (5.2–7.1)	1.3 (1.2–1.5)
Rectum	18/12.2	1.5 (0.9–2.3)	0.8 (0.7–1.0)
Liver	25/2.5	9.9 (6.4–14.7)	2.1 (1.5–2.9)
Gallbladder and biliary tract	8/2.3	3.5 (1.5–6.9)	1.1 (0.7–1.7)
Pancreas	35/7.8	4.5 (3.1–6.3)	1.2 (0.9–1.5)
Second, poorly specified location in digestive organs	5/0.2	20.8 (6.7–48.3)	2.6 (0.9–7.3)
Lung, bronchi, and trachea	256/32.4	7.9 (7.0–9.0)	1.8 (1.6–1.9)
Pleura	9/0.7	12.3 (5.6–23.3)	2.8 (1.4–5.4)
Peritoneum and connective tissue in the abdominal wall	9/0.4	23.7 (10.9–45.0)	3.8 (1.8–8.1)
Other connective tissue	10/0.8	12.8 (6.1–23.6)	2.2 (1.1–4.2)
Breast	43/28.8	1.5 (1.1–2.0)	0.7 (0.6–0.9)
Cervix of uterus	6/2.7	2.2 (0.8–4.8)	1.0 (0.6–1.6)
Uterus	16/6.7	2.4 (1.4–3.9)	0.8 (0.6–1.1)
Ovary	20/5.1	3.9 (2.4–6.1)	1.0 (0.7–1.3)
Prostate	92/24.1	3.8 (3.1–4.7)	1.1 (0.9–1.3)
Kidney	107/4.5	23.7 (19.4–28.7)	3.5 (2.8–4.4)
Renal pelvis	8/1.0	8.1 (3.5–16.0)	1.9 (1.1–3.5)
Urinary bladder	28/16.2	1.7 (1.2–2.5)	1.0 (0.8–1.2)
Brain	9/4.3	2.1 (1.0–4.0)	0.8 (0.6–1.1)
Thyroid gland	5/0.8	6.6 (2.1–15.3)	1.3 (0.6–2.8)
Adrenal gland	8/0.1	117.7 (50.7–231.9)	8.7 (2.9–26.0)
Hodgkin's disease	41/0.5	91.2 (65.4–123.7)	11.1 (6.5–18.8)
Non-Hodgkin lymphoma	122/6.3	19.3 (16.0–23.1)	3.4 (2.8–4.1)
Malignant immunoproliferative disease	34/0.3	119.8 (83.0–167.5)	19.8 (10.5–37.1)
Lymphoid leukemia	28/3.7	7.6 (5.1–11.0)	1.5 (1.1–2.1)
Myeloid leukemia	37/2.4	15.3 (10.7–21.0)	3.2 (2.3–4.4)
Multiple myeloma	201/2.9	68.7 (59.5–78.9)	10.2 (8.1–12.8)
Squamous cell carcinoma of skin	10/10.4	1.0 (0.5–1.8)	0.9 (0.7–1.1)
Basal cell carcinoma of skin	37/48.3	0.8 (0.5–1.1)	0.8 (0.7–0.9)
Metastases and nonspecified cancer in lymph nodes	63/7.2	8.8 (6.8–11.3)	1.7 (1.4–2.1)
Other cancer with poorly specified site and nonspecified cancer	37/3.8	9.8 (6.9–13.5)	1.5 (1.1–2.1)

[a]Sites with five or more recorded cancers.
[b]Adjusted for overall level of comorbidity, recent infection, and autoimmune disease.

[SIR 83.7 (95% CI, 51.1–129.3)], although the relative risk was elevated in all age groups. SIRs varied between 4.3 and 6.3 within different calendar time periods in the first year after an elevated ESR diagnosis.

The relative risk of cancer also was similar among patients with an elevated ESR whose first hospital contact for this indication was as an outpatient [5.2 (95% CI, 4.7–5.7)] and among those whose first contact was as an inpatient [5.4 (95% CI, 5.1–5.7)]. Presence of a recent infection or an autoimmune disease decreased the relative cancer risk [SIR 4.1 (95% CI, 3.5–4.8) and 4.0 (95% CI, 3.4–4.7), respectively].

During the first year of follow-up, we found particularly high SIRs for all hematologic cancers [Hodgkin's disease: SIR 91.2 (95% CI, 65.40–123.7), non-Hodgkin's lymphoma: SIR 19.3 (95% CI, 16.0–23.1), malignant immunoproliferative diseases: SIR 119.8 (95% CI, 83.0–167.5), lymphoid leukemia: SIR 7.6 (95% CI, 5.1–11.0), myeloid leukemia: SIR 15.3 (95% CI, 10.7–21.0), and multiple myeloma: 68.7 (95% CI, 59.5–78.9; Table 2)]. In addition, SIRs exceeded 10 for cancers of the pleura, peritoneum and connective tissue in the abdominal wall, other connective tissue, kidney, adrenal glands, and poorly specified second locations in digestive organs (Table 2).

After the first year of follow-up, 2,357 cancers were diagnosed among patients with elevated ESR [SIR 1.1 (95% CI, 1.1–1.2) and aHR 1.1 (95% CI, 1.0–1.1; Table 1)]. The SIR was almost identical in men and women. After the first year of follow-up, individuals aged 30 to 49 years had the highest relative risk of being diagnosed with cancer [SIR 1.3 (95% CI, 1.1–1.5)]. SIRs were stable (around 1.0) within different calendar time periods and among patients with versus without a recent infection and with versus without an autoimmune disease. Table 3 presents the risk of different cancers after one year of follow-up. Risks were increased for hematologic cancers (except lymphoid leukemia), with SIRs ranging between 1.9 and 10.6, as well as for cancers of the oral cavity, salivary glands, pharyngeal cavity and tonsils, esophagus, liver, lung, bronchus and trachea, and skin cancer, with SIRs ranging between 1.3 and 3.5. The corresponding aHRs are shown

Table 3. SIR for cancers diagnosed in patients >1 to 33.9 years following a hospital contact for an elevated ESR compared with the general population, and aHRs versus sex- and age-matched population comparisons without elevated ESR

Cancer site	Cancers observed[a]/ expected	SIR (95% CI)	aHR[b] (95% CI)
All cancers	2,357/2,109.7	1.1 (1.1–1.2)	1.1 (1.0–1.1)
Lip	9/4.7	1.9 (0.9–3.7)	4.2 (1.3–12.9)
Tongue	5/4.5	1.1 (0.4–2.6)	0.9 (0.3–2.9)
Oral cavity	17/9.1	1.9 (1.1–3.0)	2.6 (1.3–5.1)
Salivary gland	9/2.6	3.5 (1.6–6.6)	4.6 (1.5–14.8)
Pharyngeal cavity and tonsils	11/5.1	2.2 (1.1–3.8)	3.3 (1.4–7.9)
Oesophagus	34/20.4	1.7 (1.2–2.3)	1.8 (1.2–2.9)
Stomach	41/36.6	1.1 (0.8–1.5)	1.0 (0.7–1.5)
Colon	178/181.0	1.0 (0.8–1.1)	1.0 (0.8–1.2)
Rectum	74/81.0	0.9 (0.7–1.2)	0.9 (0.7–1.2)
Anal canal	6/4.7	1.3 (0.5–2.8)	1.7 (0.6–4.7)
Liver	34/16.5	2.1 (1.4–2.9)	1.7 (1.1–2.7)
Gallbladder and biliary tract	17/14.7	1.2 (0.7–1.9)	1.2 (0.6–2.1)
Pancreas	55/53.6	1.0 (0.8–1.3)	1.0 (0.7–1.3)
Larynx	9/10.9	0.8 (0.4–1.6)	0.4 (0.2–0.9)
Lung, bronchus, and trachea	309/215.5	1.4 (1.3–1.6)	1.4 (1.2–1.6)
Pleura	6/4.6	1.3 (0.5–2.9)	2.6 (0.9–7.6)
Malignant melanoma	39/44.0	0.9 (0.6–1.2)	0.9 (0.6–1.3)
Breast	179/230.1	0.8 (0.7–0.9)	0.7 (0.6–0.9)
External female genitalia	12/6.9	1.7 (0.9–3.0)	1.4 (0.6–2.8)
Cervix of uterus	19/18.2	1.0 (0.6–1.6)	0.9 (0.5–1.6)
Uterus	40/48.6	0.8 (0.6–1.1)	0.8 (0.5–1.1)
Ovary	29/36.6	0.8 (0.5–1.1)	0.7 (0.5–1.1)
Prostate	138/153.4	0.9 (0.8–1.1)	1.0 (0.8–1.2)
Kidney	41/29.4	1.4 (1.0–1.9)	1.4 (0.9–2.0)
Renal pelvis	8/6.3	1.3 (0.6–2.5)	1.6 (0.7–3.7)
Ureter	5/2.4	2.1 (0.7–4.9)	1.5 (0.5–4.4)
Urinary bladder	112/102.1	1.1 (0.9–1.3)	1.2 (0.9–1.5)
Meninges	12/12.8	0.9 (0.5–1.6)	1.0 (0.5–1.9)
Brain	31/31.3	1.0 (0.7–1.4)	0.9 (0.6–1.4)
Thyroid gland	7/5.6	1.2 (0.5–2.6)	0.9 (0.4–2.4)
Hodgkin's disease	9/3.0	3.0 (1.4–5.7)	2.0 (0.8–4.9)
Non-Hodgkin lymphoma	86/46.0	1.9 (1.5–2.3)	2.1 (1.5–2.7)
Malignant immunoproliferative disease	20/1.9	10.6 (6.5–16.3)	83.0 (9.4–733.2)
Lymphoid leukemia	29/25.5	1.1 (0.8–1.6)	1.0 (0.6–1.6)
Myeloid leukemia	35/16.3	2.2 (1.5–3.0)	2.8 (1.7–4.4)
Multiple myeloma	56/19.9	2.8 (2.1–3.7)	3.5 (2.3–5.1)
Squamous cell carcinoma of skin	122/91.1	1.3 (1.1–1.6)	1.2 (1.0–1.5)
Basal cell carcinoma of the skin	393/390.4	1.0 (0.9–1.1)	1.0 (0.8–1.1)
Metastases and nonspecified cancer in lymph nodes	50/51.8	1.0 (0.7–1.3)	1.0 (0.7–1.5)
Other cancer with poorly specified site and nonspecified cancer	29/26.0	1.1 (0.8–1.6)	1.0 (0.7–1.6)

[a]Sites with five or more recorded cancers.
[b]Adjusted for overall level of comorbidity, recent infection, and autoimmune disease.

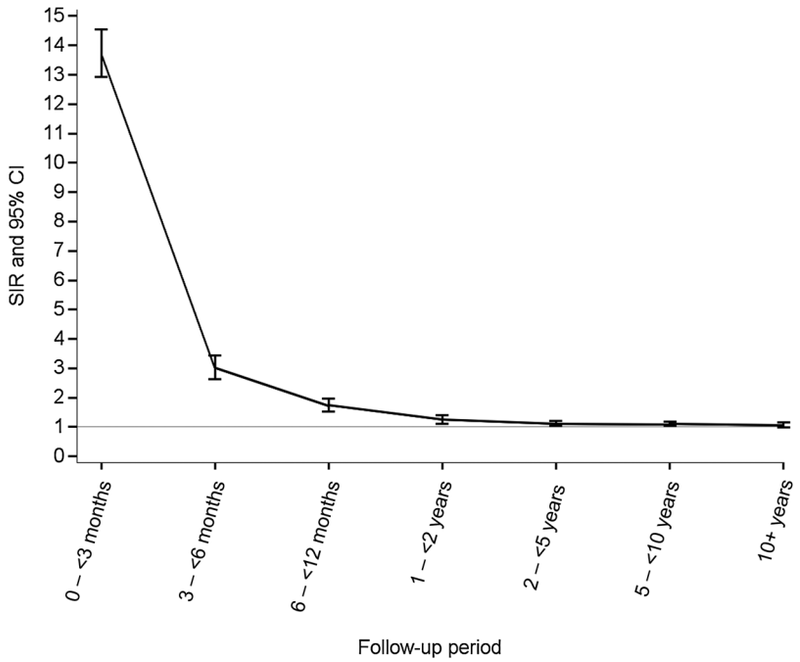

Figure 1.
SIRs for any cancer. The relative risk of cancer versus the general population in different follow-up periods among 18,540 patients with a first-time hospital contact for elevated ESR. The "I" bars represent 95% CIs.

in Tables 1–3. The SIRs for any cancer by follow-up period are shown in Fig. 1.

Survival after cancer diagnosis

Mortality after cancer diagnosis among patients with elevated ESR diagnosed within 12 months prior to cancer diagnosis was 50.8% versus 45.1% among the cancer comparison cohort after 1 year and 76.2% versus 70.5% after 5 years. The corresponding mortality estimates among patients with elevated ESR diagnosed more than 12 months prior to cancer diagnosis were 40.5% versus 35.5% after 1 year and 67.8% versus 60.3% after 5 years. Patients with elevated ESR diagnosed within 12 months prior to cancer diagnosis had poorer survival than members of the cancer comparison cohort independent of comorbidity [unadjusted and adjusted mortality rate ratio (MRR) 1.2 (95% CI, 1.2–1.3) and 1.2 (95% CI, 1.1–1.3). Unadjusted and adjusted MRR for patients with elevated ESR diagnosed more than 12 months prior to cancer diagnosis were 1.3 (95% CI, 1.2–1.4) and 1.1 (95% CI, 1.1–1.2) compared with members of the cancer comparison cohort (Figs. 2 and 3).

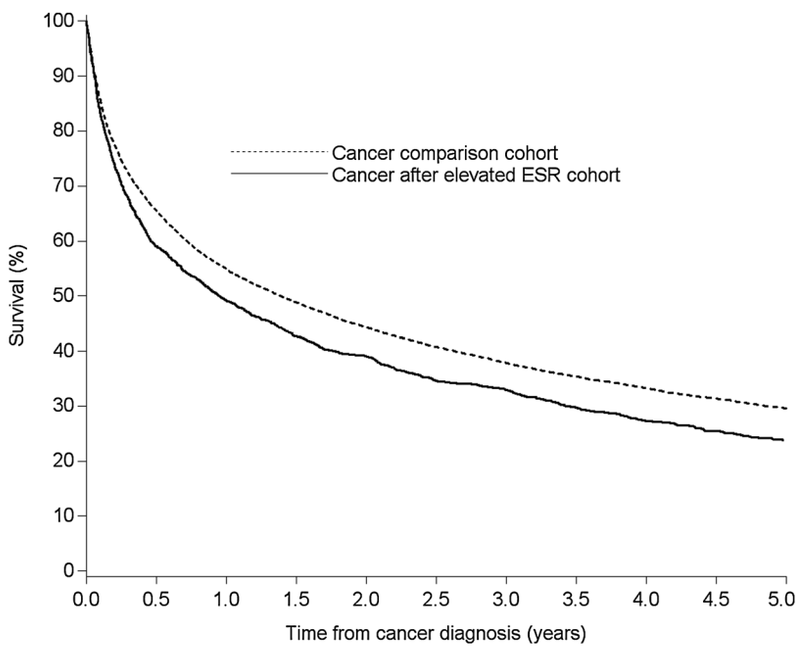

Figure 2.
Survival after cancer diagnosis. The survival of patients diagnosed with cancer within 1 year after first hospital contact for elevated ESR and the survival of cancer comparison cohort members.

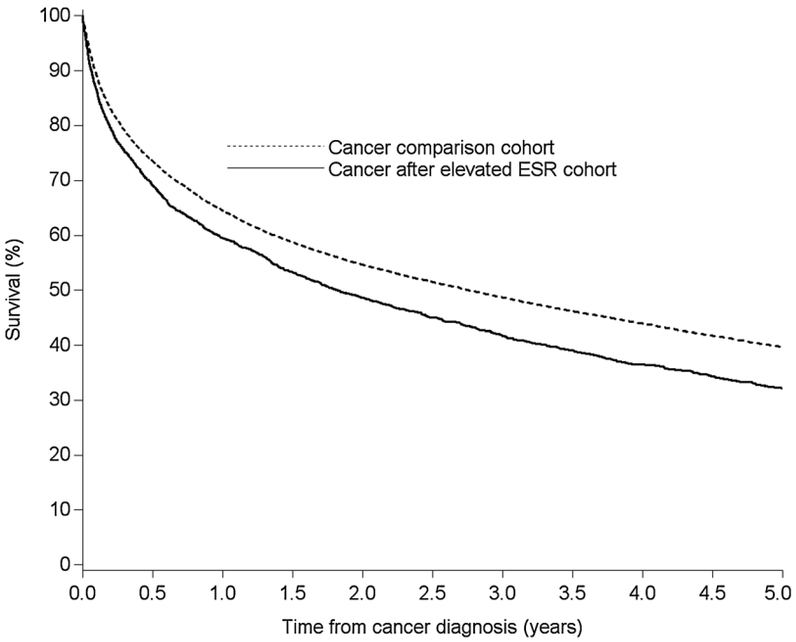

Figure 3.
Survival after cancer diagnosis. The survival of patients diagnosed with cancer more than 1 year after first hospital contact for elevated ESR and the survival of cancer comparison cohort members.

Discussion

We observed an increased risk of cancer after a hospital contact with elevated ESR. In the first year of follow-up, the cancer risk was 8.5% and the increase in cancer risk was greater than 5-fold, compared with general population rates. The risk was elevated in all age groups, but a particularly high relative risk associated with elevated ESR was found among persons younger than age 30. The overall risk was more than 3-fold elevated for most hematologic cancers, as well as cancers of the peritoneum and connective tissue in the abdominal wall, kidney, and adrenal glands. After the first year of follow-up, the risk of cancer at any site was only slightly increased compared with the risk in the general population. However, a hospital contact for elevated ESR remained a clear marker of long-term risk of cancer, especially of hematologic cancers. Also, patients with cancer with a previous hospital-based diagnosis of elevated ESR had poorer survival compared with similar cancer patients without this history.

Our findings extend those of the few previous studies on this topic. In Liljestrand and colleagues' 1955 Swedish case series, 790 outpatients with an elevated ESR (>35 mm/hour in women and >30 mm/hour in men) were examined (6). The elevated ESR remained unexplained in 41 patients after an initial examination. After 10 years of subsequent follow-up, 2 patients (4.9%) were diagnosed with cancer. In their 1979 study, Rafnsson and colleagues screened 1,462 Swedish middle-aged women, among whom 42 women had an unexplained elevated ESR. At reexamination 6 years later, none had developed cancer (8). Similar results were found in a more recent study. Mönig and colleagues followed 38 patients discharged from a university hospital with the diagnosis "elevated ESR of unknown origin." Two patients (5.3%) developed cancer during the subsequent 5 years (7). These earlier studies had limitations. They lacked controls and did not have adequate power to estimate accurately overall and site-specific cancer incidence in patients with unexplained ESR elevation.

Comparison of our study with previous studies also is complicated by use of different study populations [outpatients attending the medical department of Karolinska Sjukhuset with unexplained elevated ESR (6), or asymptomatic women with unexplained elevated ESR (8)]. In contrast, our study was based on patients with either a hospital inpatient or outpatient ESR diagnosis, who may have more severe or persistent disease than patients diagnosed in other settings.

Our study was based on data from nationwide population-based health registries, which made complete long-term follow-up feasible. The large sample size provided relatively high statistical precision, and enabled us to identify the cancer sites most commonly associated with a diagnosis of elevated ESR. Furthermore, use of routinely recorded health care data, collected independently of the study, reduced the risk of information bias. Some coding errors may have occurred, but in subanalyses the positive predictive value of a hospital diagnosis of elevated ERS was more than 90%. Another limitation was the lack of complete laboratory data on the extent of ESR elevation, which may have influenced the association between a diagnosis of elevated ESR and cancer. As well, we lacked data on possible signs and symptoms characterizing patients with a hospital contact for elevated ESR, as well as information on diagnostic investigations performed during the contact. These limitations prevent us from suggesting guidelines for the clinical care of patients with unexplained elevated ESR.

In conclusion, we found evidence that a first-time hospital diagnosis of elevated ESR is a clear marker of finding undiagnosed cancer, in particular within the first 12 months after elevated ESR. Although the excess cancer risk decreases much after 12 months, patients remain at slightly increased long-term cancer risk, especially for hematologic cancers. Furthermore, cancer following elevated ESR is associated with worse prognosis, compared with cancer without ESR elevation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The study sponsors had no influence on the study design, collection, analysis, and interpretation of the data or in the writing of the report.

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Study supervision: H.T. Sørensen

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