Long-term risks after splenectomy among 8,149 cancer-free American veterans: a cohort study with up to 27 years follow-up

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ABSTRACT

Although preservation of the spleen following abdominal trauma and spleen-preserving surgical procedures have become gold standards, about 22,000 splenectomies are still conducted annually in the USA. Infections, mostly by encapsulated organisms, are the most well-known complications following splenectomy. Recently, thrombosis and cancer have become recognized as potential adverse outcomes post-splenectomy. Among more than 4 million hospitalized USA veterans, we assessed incidence and mortality due to infections, thromboembolism, and cancer including 8,149 cancer-free veterans who underwent splenectomy with a follow-up of up to 27 years. Relative risk estimates and 95% confidence intervals were calculated using time-dependent Poisson regression methods for cohort data. Splenectomized patients had an increased risk of being hospitalized for pneumonia, meningitis, and septicemia (rate ratios=1.9-3.4); deep venous thrombosis and pulmonary embolism (rate ratios=2.2); certain solid tumors: buccal, esophagus, liver, colon, pancreas, lung, and prostate (rate ratios =1.3-1.9); and hematologic malignancies: non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, and any leukemia (rate ratios =1.8-6.0). They also had an increased risk of death due to pneumonia and septicemia (rate ratios =1.6-3.0); pulmonary embolism and coronary artery disease (rate ratios =1.4-4.5); any cancer: liver, pancreas, and lung cancer, non-Hodgkin lymphoma, Hodgkin lymphoma, and any leukemia (rate ratios =1.3-4.7). Many of the observed risks were increased more than 10 years after splenectomy. Our results underscore the importance of vaccination, surveillance, and thromboprophylaxis after splenectomy.

Introduction

In the past, the spleen was considered unnecessary for life. Today, we know that the spleen is a reticuloendothelial organ with important hematologic and immunological functions, including clearance of bacteria from the blood and generation of immune responses to certain pathogens.[1]

Although preservation of the spleen following abdominal trauma and spleen-preserving surgical procedures have gained significant attention in recent years,[2] about 22,000 splenectomies are still conducted annually (for all causes) in the USA.[3] In most hospitals, trauma and incidental splenectomy remain the primary indications; however, spleen removal in trauma patients is becoming less common as a result of more conservative non-operative management of splenic injury.[3] The most frequent medical indication is a hematologic disorder, such as autoimmune hemolytic anemia.

Bacterial infections, mostly by encapsulated organisms, are the best known complications of splenectomy[4-14] but other types of infections also occur, including those caused by Gram-negative bacteria.[15-17] Immunological and hematologic abnormalities have been described as well, including depressed phagocytic activity, diminished immunoglobulin M (IgM) production, depressed T-cell function, and leukocytosis and thrombocytosis, all of which may contribute to late complications.[4,18-21] Post-splenectomy infections may be fatal, particularly in younger patients, those with an underlying malignant disease, and during the initial years following splenectomy.[5,6,8,9]

More recently, venous thromboembolism has become appreciated as another potential complication of splenectomy,[9,22,23] although some studies have reported no excess risk.[24] Portal vein thrombosis has been reported most often,[25-27] while the risk of other types of thromboembolism is poorly defined.

It is unclear whether splenectomy increases the risk of developing cancer. In both rat and mouse models splenectomy has been associated with a significant increase of malignant tumor induction,[28,29] along with a decrease in the peripheral blood lymphocyte count after tumor inoculation in a mouse model.[30] In some,[9,31] but not all,[10,32] epidemiological studies, splenectomy has been associated with an excess risk of developing cancer. An important limitation of these studies is their lack of exclusion of patients with a malignancy prior to splenectomy.

To expand our insights regarding long-term risks of splenectomy, we have conducted the largest follow-up study to date of cancer-free subjects who have undergone this procedure. In over four million male military veterans admitted to Veterans Affairs (VA) hospitals we identified 8,149 cancer-free

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veterans who underwent splenectomy with a follow-up of up to 27 years. In this cohort, we assessed patterns of hospitalization for infections, thromboembolism, and malignancies following splenectomy.

Methods

Study population

Based on USA census data, an estimated 30 million veterans were entitled to admission to VA hospitals during the study period.[33] The VA database has been previously described.[34,35]

In the present study, splenectomized patients were identified from the hospital discharge summary records [coded in the 8th and 9th revisions of the USA version of the International Classification of Diseases (ICD): ICD8 45.1, ICD9 41.2, 41.43, 41.5] and were included in the study (n=8,149). To minimize the influence of reverse causality (i.e., undetected cancer requiring the splenectomy), all analyses were restricted to individuals whose first VA discharge with a splenectomy occurred at least 1 year prior to the first hospitalization listing a diagnosis of cancer. Thus, patients were followed from 1 year after their initial hospital discharge until the first discharge diagnosis of infection, thromboembolism, malignancy, death, or end of study, whichever occurred first. The time to develop infection, thromboembolism, or malignancy (i.e., latency) was estimated by subtracting the date of discharge from the first hospitalization listing a splenectomy from the date of the first hospitalization listing a diagnosis of infection, thromboembolism, or malignancy.

Dates of death were ascertained from record linkage to Social Security Administration mortality files. With such linkage, death reporting is believed to be 96% complete.[36] Among the 8,149 splenectomized men who were selected for the study, 6,731 were eligible for matching to the National Death Index (alive as of January 1, 1979). In addition, a random sample (n=6,731) of the eligible VA cohort was selected to match these patients on the basis of race and year of birth (1:1 sample). The National Death Index provided death certificate matching for the men who had undergone splenectomy and for the matched controls (n=13,462).

Statistical analysis

Relative risk (RR) estimates and 95% confidence intervals (CI) were calculated using time-dependent Poisson regression methods for cohort data.[37] Calculations were performed using the AMFIT program (Epicure Version 2.0; HiroSoft International Corporation, Seattle, Washington, USA). All risk estimates were adjusted for attained age (<40, 40-49, 50-59, 60-69, 70-79, 80 or more years) and calendar year (1969-1974, 1975-1979, 1980-1984, 1985-1989, 1990-1996), race (African-American or white), number of hospital visits (1-2, 3-4, 5 or more), and time between study entry and exit (2-3, 4-5, 6-9, 10-14, 15 or more years). Risk estimates for buccal, esophageal, and liver cancers were also adjusted for a hospital discharge diagnosis of alcohol-related disorders because inclusion of this variable in the regression models resulted in a >10% change in the risk estimates. Adjustment for a hospital discharge diagnosis of hypertension was necessary for the kidney cancer analysis. No other diagnoses were found to materially (>10%) change the risk estimates for the other outcomes. All *P* values and confidence intervals were two-sided, and *P* values <0.05 were considered statistically significant. We conducted sensitivity analyses when numbers allowed (>5 exposed cases). Analyses were stratified by race, age at splenectomy/entry (<50, 50+), calendar year at splenectomy/entry (1969-1979, 1980-1996), latency (2-5 years, 5+), and subsets of patients with only trauma or no autoimmune conditions (as in previous splenectomy studies).

An exemption from Institutional Review Board review was obtained from the NIH Office of Human Subjects Research because we analyzed existing data without personal identifiers. Informed consent was waived because there was no contact with study subjects.

Results

Among over 4.5 million military USA veterans admitted to a VA hospital, a total of 8,149 cancer-free men were splenectomized during the study period. The characteristics of the study population are shown in Table 1. The majority were white (84%) and their median age at splenectomy was 53 years.

Risk and mortality due to infection

Risk of hospitalization for infections and associated mortality due to infections is shown in Table 2. Splenectomized patients had a significantly increased risk of pneumococcal pneumonia (RR=2.06; 95% CI 1.85-2.30), pneumonia not otherwise specified (RR=1.94; 95% CI 1.84-2.04), meningitis (RR=2.44; 95% CI 1.77-3.38), and septicemia (RR=3.38; 95% CI 3.12-3.67). Splenectomized patients had a 1.58-fold and 3.02-fold increased risk of death from pneumonia (95% CI 1.20-2.08) and septicemia (95% CI 1.80-5.06), respectively. When analyzing risk and mortality by race, calendar year at splenectomy/entry (1969-1979 *versus* 1980-1996), age at splenectomy/entry (below *versus* above 50 years), in trauma patients only (n=1,831), and in patients with a previous autoimmune disease (n=1,843), the risk estimates were essentially the same in all subgroups (*Online Supplementary Tables S1 and S2*). In analyses based on latency (the time between splenectomy and subsequent infection), the risk of infectious diseases was still significantly elevated more than 10 years after splenectomy (Table 3). Risk of death from infections was also significantly increased more than 10 years after splenectomy (*data not shown*).

Risk and mortality due to thromboembolism

Table 2 shows risks of hospitalization for thromboembolic disease and associated mortality. Splenectomized patients had an increased risk of developing deep vein thrombosis (RR=2.18; 95% CI 1.99-2.40) and pulmonary embolism (RR=2.24; 95% CI 1.97-2.55), but not acute myocardial infarction, coronary artery disease, or ischemic

Table 1. Patients' characteristics.

Variable	Splenectomized patients Incidence (SIR) analysis	Splenectomized patients Mortality (SMR) analysis
Total number of patients, n. (%)	8149 (100)	6731 (100)
Blacks, n. (%)	1284 (16)	1076 (16)
Person-years, n.	102615	95886
Median age at splenectomy, years	53	52
Age <50 at splenectomy, n. (%)	3366 (41)	2914 (43)
Age 50+ at splenectomy, n. (%)	4783 (59)	3817 (57)
Splenectomy before 1980, n. (%)	4844 (59)	3809 (57)
Splenectomy 1980 or later, n. (%)	3305 (41)	2922 (43)

stroke. Splenectomized patients also had an increased risk of death from pulmonary embolism (RR=4.53; 95% CI 1.92-10.73) and coronary artery disease (RR=1.44; 95% CI 1.07-1.92; Table 4). Risk estimates were not significantly different when analyzing risk and mortality by latency (Table 3), race, calendar year and age at splenectomy/entry (*data not shown*), in trauma patients only, and in patients with a previous autoimmune disease (*Online Supplementary Tables S1 and S2*).

Risk and mortality due to malignancy

A total of 1,094 (13%) splenectomized patients were diagnosed with cancer during the follow-up. As shown in Table 4, there was an increased risk of any cancer (RR=1.51; 95% CI 1.42-1.60). In particular, the risk was significantly elevated for buccal (RR=1.26; 95% CI 1.00-1.58), esophageal (RR=1.60; 95% CI 1.12-2.27), liver (RR=1.88; 95% CI 1.22-2.89), colon (RR=1.33; 95% CI 1.01-1.76), pancreatic (RR=1.87; 95% CI 1.27-2.75), lung (RR=1.24; 95% CI 1.09-1.40), and prostate cancer (RR=1.26; 95% CI 1.06-1.48), and also non-Hodgkin lymphoma (RR=3.21; 95% CI 2.47-4.17), Hodgkin lymphoma (RR=3.74; 95% CI 2.01-6.97), multiple myeloma (RR=1.82; 95% CI 1.08-3.07), acute myeloid leukemia (RR=6.04; 95% CI 3.92-9.29), chronic lymphocytic leukemia (RR=2.86; 95% CI 1.80-4.55), chronic myeloid leukemia (RR=5.81; 95% CI 3.54-9.51), and any leukemia (RR=5.20; 95% CI 4.23-6.39).

Furthermore, splenectomized patients had an increased risk of death from any cancer (RR=1.53; 95% CI 1.36-1.73); especially liver (RR=1.8; 95% CI 1.20-3.13), pancreatic (RR=2.18; 95% CI 1.20-3.98), and lung cancer (RR=1.32; 95% CI 1.10-1.59), as well as non-Hodgkin lymphoma (RR=4.69; 95% CI 1.97-11.18) and any leukemia (RR=2.45; 95% CI 1.36-4.42). When analyzing risk estimates and mortality stratified by race, calendar year and age at splenectomy/entry, and in analyses limited to trauma patients, the risk estimates were essentially the same as the overall pattern. In sensitivity analyses limited to patients with previous autoimmune disease, the risks were also similar, except that the risks for hematologic malignancies were higher (*Online Supplementary Tables S3 and S4*). When

Table 2. Risk of being hospitalized (SIR) and risk of dying (SMR) due to selected infectious and thromboembolic conditions following splenectomy.

Condition	SIR				SMR			
	Splenectomized	Not splenectomized	RR*	95% CI	Splenectomized	Not splenectomized	RR*	95% CI
Pneumococcal pneumonia	347	70647	2.06	1.85-2.30	2	5	0.51	0.09-2.74
Septicemia	620	72216	3.38	3.12-3.67	60	20	3.02	1.80-5.06
Meningitis	40	6439	2.44	1.77-3.38	5	0	--	
All pneumonias	1648	361053	1.94	1.84-2.04	133	93	1.58	1.20-2.08
Deep vein thrombosis	451	83460	2.18	1.99-2.40	3	0	--	
Pulmonary embolism	252	45420	2.24	1.97-2.55	24	8	4.53	1.92-10.73
Coronary artery disease	190	71151	0.98	0.85-1.14	102	96	1.44	1.07-1.92
Myocardial infarction	525	218624	0.97	0.89-1.06	286	347	1.10	0.94-1.30
Ischemic stroke	224	99080	1.06	0.93-1.22	20	13	1.89	0.91-3.90

**Adjusted for attained age and calendar time, latency, race (when appropriate) and number of visits. All study subjects were followed from 1 year after their initial hospital discharge until the first discharge diagnosis of infection, thromboembolism, death, or end of study, whichever occurred first. The time to develop infection, thromboembolism, or malignancy (i.e., latency) was estimated by subtracting the date of discharge from the first hospitalization listing a splenectomy from the date of the first hospitalization listing a diagnosis of infection, thromboembolism, or malignancy. To minimize the influence of reverse causality (i.e., undetected cancer necessitating the splenectomy), all analyses were restricted to individuals with their first VA discharge with a splenectomy at least 1 year prior to the first hospitalization listing a diagnosis of cancer. RR: relative risk; CI: confidence intervals.*

Table 3. Risk of being hospitalized (SIR) due to selected infectious and thromboembolic conditions following splenectomy, by latency.

Condition	SIR											
	2-5 years				5-10 years				>10 years			
	Splenectomized	Not splenectomized	RR*	95% CI	Splenectomized	Not splenectomized	RR*	95% CI	Splenectomized	Not splenectomized	RR*	95% CI
Septicemia	244	17237	4.69	3.72-5.92	167	17208	3.85	3.22-4.61	209	37771	3.10	2.80-3.43
Meningitis	17	1349	2.98	1.12-7.97	7	1177	5.01	2.83-8.85	16	3463	1.84	1.20-2.83
All pneumonias	616	94313	2.31	2.00-2.66	394	82159	2.03	1.82-2.27	638	184581	1.86	1.75-1.97
Pneumococcal pneumonia	129	16921	2.19	1.56-3.07	74	16280	2.26	1.79-2.85	144	37446	1.99	1.74-2.27
Deep vein thrombosis	172	17684	3.44	2.65-4.47	104	17983	2.62	2.13-3.23	175	47793	1.94	1.73-2.18
Pulmonary embolism	86	11434	2.93	2.11-4.07	60	9999	1.83	1.33-2.51	106	23987	2.25	1.93-2.62
Coronary artery disease	61	12863	1.14	0.65-2.01	49	16685	0.74	0.49-1.14	80	41603	1.02	0.86-1.20
Myocardial infarction	182	51486	0.75	0.54-1.05	138	53738	1.01	0.83-1.23	205	113400	0.99	0.89-1.10
Ischemic stroke	63	18331	0.75	0.47-1.21	68	24656	1.01	0.74-1.36	93	46093	1.13	0.97-1.33

** Adjusted for attained age and calendar time, latency, race and number of visits. All study subjects were followed from 1 year after their initial hospital discharge until the first discharge diagnosis of infection, thromboembolism, death, or end of study, whichever occurred first. The time to develop infection, thromboembolism, or malignancy (i.e., latency) was estimated by subtracting the date of discharge from the first hospitalization listing a splenectomy from the date of the first hospitalization listing a diagnosis of infection, thromboembolism, or malignancy. To minimize the influence of reverse causality (i.e., undetected cancer necessitating the splenectomy), all analyses were restricted to individuals with their first VA discharge with a splenectomy at least 1 year prior to the first hospitalization listing a diagnosis of cancer. RR: relative risk; CI: confidence intervals.*

excluding patients with a prior autoimmune disease, the risks of malignancies were still significantly elevated (*Online Supplementary Tables S3 and S4*).

In analyses stratified by latency, the risk of most malignancies tended to be highest during the first 2-5 years following splenectomy. However, after more than 10 years, there was still a significantly increased risk of esophageal, liver and lung cancers, as well as non-Hodgkin lymphoma, Hodgkin lymphoma, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, and any leukemia (Table 5).

Discussion

This large study involving over four million USA veterans enabled several important observations. Based on 8,149 cancer-free veterans who underwent splenectomy, compared to all other subjects in the database, we observed an increased risk of infections, thromboembolism, and malignancies. Furthermore, we found the overall risk of death from these disorders to be elevated. Increased risks persisted even more than 10 years after splenectomy.

Splenectomized patients had a 2- to 3-fold increased risk of pneumococcal pneumonia, other pneumonias, meningitis, and septicemia. It is well known that splenectomized patients have an increased risk of infections due to Gram-positive encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitides*, and *Haemophilus influenza* type B.[4-14] We did not have information on the underlying pathogen, but a large proportion of community-acquired pneumonias and meningitis are caused by encapsulated microbes.[38,39] The excess risk of septicemia may be caused by Gram-positive or Gram-negative bacteria, as previously reported.[15-17] The patterns of risk and mortality in our study and in others indicate the importance of pneumococcal vaccination in this population of patients. We previously showed that antibody levels are decreased in immunocompromised individuals and patients who undergo splenectomy because of chronic lymphocytic leukemia or Hodgkin lymphoma.[40] These patients might require re-evaluation of antibody levels to determine if there is a need to re-vaccinate. Furthermore, patients with a poor response to vaccination might benefit from prophylactic penicillin[41] or prompt treatment with antibiotics in the event of fever or other signs of infections.[42]

We found a 2-fold increased risk of deep vein thrombosis and pulmonary embolism following splenectomy, and 4.5-fold and 1.4-fold increased risks of death from pulmonary embolism and coronary artery disease, respectively. These complications appear due to a hypercoagulable state post-splenectomy along with a transient thrombocytosis. Underlying mechanisms may include platelet activation, disturbance and activation of endothelium, and altered lipid profile.[3] In our study, the risk of thrombosis was increased not only in the immediate period following splenectomy, but also more than 10 years following the procedure, suggesting a life-long susceptibility state. In the Swedish mortality study, a significant 3- to 5-fold increase

Table 4. Risk of being hospitalized (SIR) and risk of dying (SMR) due to selected hematologic and solid tumors following splenectomy.

	SIR				SMR			
	Splenectomized	Not splenectomized	RR*	95% CI	Splenectomized	Not splenectomized	RR*	95% CI
All Cancer	1094	370716	1.51	1.42-1.60	643	497	1.53	1.36-1.73
Buccal	76	29170	1.26	1.00-1.58	23	17	1.62	0.84-3.11
Esophagus	32	10311	1.60	1.12-2.27	28	20	1.60	0.89-2.87
Stomach	19	7496	1.50	0.96-2.35	12	11	1.27	0.55-2.94
Liver	21	5139	1.88	1.23-2.89	32	23	1.79	1.02-3.13
Colon	54	12263	1.33	1.01-1.76	18	15	1.53	0.75-3.13
Pancreas	31	7608	1.87	1.27-2.75	32	18	2.18	1.20-3.98
Larynx	30	13767	1.13	0.79-1.62	15	11	1.23	0.55-2.76
Lung	253	102174	1.24	1.09-1.40	251	228	1.32	1.10-1.59
Bladder	42	19258	1.16	0.85-1.57	13	9	2.12	0.86-5.21
Kidney	20	8185	0.99	0.61-1.63	12	13	1.08	0.47-2.44
Prostate	146	653317	1.26	1.06-1.48	34	39	0.89	0.55-1.43
Non-Hodgkin lymphoma	62	9434	3.21	2.47-4.17	26	7	4.69	1.97-11.18
All leukemias	105	9730	5.20	4.23-6.39	39	15	2.45	1.36-4.42
Hodgkin lymphoma	11	1569	3.74	2.01-6.97	0	0	-	-
Multiple myeloma	17	4624	1.82	1.08-3.07	5	4	1.71	0.43-6.71
Acute myeloid leukemia	21	1884	6.04	3.92-9.29	12	5	2.74	0.93-8.09
Chronic lymphocytic leukemia	19	3661	2.86	1.80-4.55	4	4	1.36	0.31-5.90
Chronic myeloid leukemia	22	15500	5.81	3.54-9.51	8	1	1.87	0.46-7.52

** Adjusted for attained age and calendar time, latency, race (when appropriate) and number of visits. Kidney cancer also adjusted for hypertension. Buccal, esophagus and liver cancers also adjusted for alcohol use. All study subjects were followed from 1 year after their initial hospital discharge until the first discharge diagnosis of malignancy, death, or end of study, whichever occurred first. The time to develop infection, thromboembolism, or malignancy (i.e., latency) was estimated by subtracting the date of discharge from the first hospitalization listing a splenectomy from the date of the first hospitalization listing a diagnosis of infection, thromboembolism, or malignancy. To minimize the influence of reverse causality (i.e., undetected cancer necessitating the splenectomy), all analyses were restricted to individuals with their first VA discharge with a splenectomy at least 1 year prior to the first hospitalization listing a diagnosis of cancer. RR: relative risk; CI: confidence intervals.*

Table 5. Risk of being hospitalized (SIR) due to selected hematologic and solid tumors following splenectomy, by latency.

Condition	SIR											
	2-5 years				5-10 years				>10 years			
	Splenect-omized	Not splenect-omized	RR*	95% CI	Splenect-omized	Not splenect-omized	RR*	95% CI	Splenect-omized	Not splenect-omized	RR*	95% CI
All Cancer	543	152316	2.05	1.82-2.32	271	100383	1.44	1.28-1.62	280	118017	1.35	1.24-1.47
Buccal	33	12451	1.29	0.78-2.14	28	8460	1.44	0.99-2.10	15	8259	1.25	0.80-1.58
Esophagus	14	4106	0.87	0.28-2.71	9	3071	1.54	0.80-2.96	9	3134	1.88	1.20-2.96
Stomach	10	3318	2.67	1.27-5.61	4	2061	1.33	0.5-3.22	5	2117	1.11	0.53-2.33
Liver	8	1826	2.42	0.91-6.46	6	1373	1.09	0.35-3.40	7	1940	2.09	1.24-3.54
Colon	26	9610	1.96	1.18-3.26	11	6058	1.14	0.64-2.00	17	6595	1.20	0.80-1.79
Pancreas	22	3266	3.87	2.14-7.01	4	2098	1.78	0.85-3.73	5	2244	1.12	0.56-2.25
Larynx	12	5673	1.36	0.65-2.86	8	3746	1.08	0.54-2.15	10	4348	1.08	0.65-1.79
Lung	105	40874	1.31	0.98-1.74	70	28612	1.25	0.99-1.59	78	32688	1.21	1.01-1.43
Bladder	19	8412	0.98	0.47-2.05	11	4907	1.41	0.82-2.43	12	5939	1.10	0.72-1.69
Kidney	9	3236	0.35	0.05-2.52	4	2147	1.19	0.50-2.87	7	2802	1.11	0.60-2.06
Prostate	59	25057	1.27	0.84-1.93	39	16773	1.32	0.95-1.84	48	23487	1.23	0.99-1.52
Non-Hodgkin lymphoma	45	3832	8.47	5.84-12.30	9	2470	2.50	1.38-4.52	8	3132	1.74	1.08-2.80
All leukemias	78	4059	11.23	8.15-15.47	17	2550	3.63	2.25-5.85	10	3121	3.80	2.73-5.28
Hodgkin lymphoma	6	796	6.81	2.82-16.43	2	385	-	-	3	388	4.26	1.76-10.29
Multiple myeloma	9	1903	3.37	1.40-8.12	3	1200	1.06	0.25-4.07	5	1521	1.64	0.78-3.45
Acute myeloid leukemia	14	808	12.61	6.52-24.37	5	467	4.35	1.62-11.64	2	609	4.33	2.15-8.69
Chronic lymphocytic leukemia	11	1385	3.06	0.99-9.52	5	982	1.93	0.62-5.99	3	1294	3.20	1.81-5.65
Chronic myeloid leukemia	17	640	12.49	5.91-26.37	4	370	2.81	0.70-11.28	1	490	4.71	2.23-9.93

** Adjusted for attained age and calendar time, latency, race and number of visits. Kidney cancer also adjusted for hypertension. Buccal, esophagus and liver cancers also adjusted for alcohol use. All study subjects were followed from 1 year after their initial hospital discharge until the first discharge diagnosis of malignancy, death, or end of study, whichever occurred first. The time to develop infection, thromboembolism, or malignancy (i.e., latency) was estimated by subtracting the date of discharge from the first hospitalization listing a splenectomy from the date of the first hospitalization listing a diagnosis of infection, thromboembolism, or malignancy. To minimize the influence of reverse causality (i.e., undetected cancer necessitating the splenectomy), all analyses were restricted to individuals with their first VA discharge with a splenectomy at least 1 year prior to the first hospitalization listing a diagnosis of cancer. RR: relative risk; CI: confidence intervals.*

in death due to venous thromboembolism was observed in splenectomized patients, but no latency analyses were presented.[9]

An older epidemiological study based on 740 USA veterans who underwent splenectomy after trauma during the Second World War found no increase in the risk of cancer.[10] Similarly, in a Danish study of 1,103 patients (average follow-up of 6.8 years), no increase in cancer was observed in those who underwent splenectomy after traumatic rupture of the spleen; however, an increased risk for some specific cancer sites was found among 5,212 patients who underwent splenectomy for non-traumatic reasons.[31] A Swedish study of 1,295 patients (average follow-up 11.1 years) splenectomized for external trauma showed no significant excess of cancer, while 985 patients (average follow-up 9.0 years) whose splenectomy accompanied surgical treatment of non-malignant conditions of adjacent organs (mostly peptic ulcers) had a non-significant 40% elevated risk of total cancer, with significant increases of lung and ovarian cancers.[32] Based on sparse data, rat and mouse models have suggested that splenectomy is associated with increased tumor induction.[28,29] On the basis of 8,149 cancer-free splenectomized patients (average follow-up 12.6 years), excluding cancer diagnoses <1 year post-splenectomy, we observed a 50% increased risk of solid and hematologic malignancies (n=1,094); the risks were significantly elevated more than 10 years after splenectomy. To minimize the effect of underlying disease, we performed subanalyses restricted to patients with an ICD code of trauma at the time of splenectomy and found essentially the same results. Because autoimmunity is associated with an increased risk of cancer[43] we conducted sensitivity analyses excluding patients with an autoimmune disease prior to splenectomy. In these analyses, the risks of malignancies remained significantly elevated. Furthermore, on the basis of 6,731 cancer-free splenectomized patients, we found a 50% increased risk of death from solid and hematologic malignancies (n=497). Future epidemiological and molecular investigations are needed to confirm and expand our findings.

Physicians and patients need to be aware of the long-term complications associated with splenectomy. Laparoscopic removal of the spleen is increasingly being used and is associated with fewer immediate complications than open surgery.[44,45] The substantial risks of infections, thrombosis and possibly malignancy need to be weighed against the benefits of the splenectomy. Splenectomized patients should be vaccinated and given empirical antibiotics according to international guidelines.[42] The possible increase in the risk of developing malignancy, suggests that asplenic patients should have life-long surveillance for cancer.

The strengths of the current study include its large size in a population of patients with relatively stable and stan-

dardized access to medical care that is provided to USA veterans independently of their socioeconomic status. Medical diagnoses were obtained from medical records and were not, therefore, subject to recall bias. Study subjects were followed for up to 27 years, so the numbers of incident cases and mortality outcomes were high. Furthermore, several sensitivity analyses were performed, including comparability over time, age, race, and for subsets of patients with diagnoses of autoimmune disease or trauma, without changing the overall results. Limitations of the study include the incompleteness of clinical and laboratory data for individual patients (including vaccination status), potential under-ascertainment of cancer due to passive rather than active ascertainment of cases, and lack of independent validation of cancer diagnoses. However, we previously found a very high validity for cancer diagnoses in VA discharge records.[46,47]

In summary, we found that cancer-free splenectomized patients have an increased risk of infections, thromboembolism, and possibly cancer. Risks were increased after a long latency period (>10 years) underscoring the importance of life-long follow-up including vaccination and thromboprophylaxis. Future studies are needed to clarify the risks of cancer, the mechanisms underlying susceptibility to infection and thromboembolism, and clinical strategies aimed at preventing and managing the complications.

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