SUPPLEMENTARY APPENDIX

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

Sigurdur Y. Kristinsson,[1] Gloria Gridley,[2] Robert N Hoover,[2] David Check,[2] and Ola Landgren[2,3]

[1]Faculty of Medicine, University of Iceland and Department of Hematology, Landspitali National University Hospital, Reykjavik, Iceland; [2]Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, MD, USA; and [3]Center for Cancer Research, National Cancer Institute, NIH, Bethesda, MD, USA

 doi:10.3324/haematol.2013.092460
Manuscript received on May 30, 2013. Manuscript accepted on September 16, 2013.
Correspondence: sigyngvi@hi.is

SUPPLEMENTARY METHODS

Study population

Based on U.S. census data, an estimated 30 million veterans were entitled for admission to VA hospitals during the study period.[33] The VA database has been previously described.[34,35] In brief, the study cohort was identified from the VA database of inpatient records from 142 VA hospitals, including admissions between July 1, 1969, and September 30, 1996. All African American and white male veterans hospitalized at age 18-100 with no prior malignancy were initially eligible for the study. Due to small numbers, other ethnic/racial groups and females were not included in this study. Also non-veterans, patients with prevalent cancers (on their first admission or within one year after first admission), and patients who died on their first admission or within one year after first admission were excluded, yielding a final analytic cohort of 4.5 million U.S. male veterans.

In the present study, splenectomized patients were identified from the hospital discharge summary records (coded in the 8th and 9th revisions of the U.S. 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 one year prior to the first hospitalization listing a diagnosis of cancer. Thus, patients were followed from one 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 a linkage, death reporting is believed to be 96% complete.[36] Among the 8,149 splenectomized men who were selected for study, 6,731 were eligible for matching to the National Death Index (NDI) (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 race and year of birth (1:1 sample). NDI 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). 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, esophagus, 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).

Supplemental Table 1. Risk of medical disorders (SIR) following splenectomy, by underlying condition.

	Trauma only			AIs only			AIs removed		
	sp+/sp-	RR*	95% CI	sp+/sp-	RR*	95% CI	Sp+	RR*	95% CI
pneumococcal pneumonia	98/10967	2.09	1.71-2.54	80/7692	1.80	1.45-2.25	246	2.03	1.79-2.30
Septicemia	119/9106	2.86	2.38-3.42	144/10533	2.15	1.82-2.53	431	3.57	3.25-3.93
Cirrhosis	246/32012	1.68	1.48-1.90	183/18787	1.61	1.40-1.87	733	2.07	1.93-2.23
Hypertension	838/145964	1.31	1.23-1.41	469/63096	1.23	1.13-1.35	2341	1.33	1.28-1.39
pulmonary hypertension	5/905	1.11	0.46-2.68	16/3172	0.79	0.48-1.29	18	0.82	0.51-1.30
DVT	99/11708	1.86	1.53-2.27	113/9009	2.03	1.68-2.44	314	2.12	1.89-2.36
PE	66/6628	2.31	1.82-2.95	62/5419	1.95	1.52-2.50	175	2.19	1.89-2.54
chronic rheumatic heart disease	32/5841	1.30	0.92-1.84	182/59404	0.62	0.53-0.71	20	1.82	1.17-2.82
cardio arteriosclerosis	28/6376	0.90	0.62-1.31	54/8631	0.98	0.75-1.28	122	0.93	0.78-1.11
Dysrhythmia	221/38025	1.35	1.18-1.54	327/58505	0.98	0.88-1.09	766	1.09	1.01-1.17
heart failure	155/31996	1.14	0.97-1.33	302/53739	1.02	0.91-1.14	609	1.03	0.95-1.11
acute mi	92/17297	1.14	0.93-1.40	127/20306	1.01	0.85-1.21	359	0.93	0.84-1.04
occlusion of cerebral arteries	46/9104	1.20	0.89-1.60	60/8931	1.18	0.92-1.52	152	0.99	0.84-1.16
intracerebral hemorrhage	10/2056	1.13	0.60-2.09	10/1164	1.43	0.77-2.66	23	0.95	0.63-1.43
Meningitis	6/1114	1.17	0.53-2.62	14/668	3.33	1.96-5.66	23	1.96	1.30-2.96
Total Pneumonia	388/50236	1.80	1.63-1.99	419/38700	1.83	1.66-2.02	1128	1.86	1.76-1.97

RR* models adjusted for attained age and calendar time, latency, race and number of visits.

All study subjects were followed from one 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 requiring 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.

Abbreviations: RR=relative risk; CI=confidence intervals

Supplemental Table 2. Risk of death (SIR) following splenectomy, by underlying condition.

	Trauma only			AIs only			AIs removed		
	sp+/sp-	RR*	95% CI	sp+/sp-	RR*	95% CI	sp+	RR*	95% CI
pneumococcal pneumonia	0/2	0.00		0/1	0.00		2	0.72	0.12-4.25
Septicemia	15/4	2.78	0.92-8.42	15/2	3.00	0.68-13.26	45	2.94	1.68-5.15
Cirrhosis	28/8	2.53	1.15-5.59	35/6	3.35	1.40-8.01	80	1.77	1.26-2.49
Hypertension	7/3	1.96	0.47-8.12	2/2	0.68	0.10-4.89	39	1.75	1.07-2.84
pulmonary hypertension	0/0	--		2/0	--		1	0.29	0.03-2.70
DVT	2/0			0/0	0.00		3	--	
PE	7/1	5.74	0.70-46.67	5/0	--		19	4.09	1.68-9.94
chronic rheumatic heart disease	1/0	--		2/2	0.68	0.10-4.80	1	0.68	0.06-8.40
cardio arteriosclerosis	29/10	2.38	1.15-4.93	18/6	1.79	0.68-4.72	83	1.43	1.05-1.96
Dysrhythmia	26/12	1.57	0.79-3.15	22/10	1.15	0.53-2.48	60	1.52	1.04-2.21
heart failure	5/7	0.63	0.20-2.05	7/7	0.42	0.14-1.30	27	1.06	0.62-1.79
acute mi	66/45	1.20	0.82-1.76	69/23	1.61	0.99-2.61	217	1.03	0.86-1.24
occlusion of cerebral arteries	3/0	--		3/1	1.49	0.15-15.03	17	1.97	0.91-4.24
intracerebral hemorrhage	3/6	0.36	0.09-1.46	3/3	0.57	0.11-3.06	20	1.78	0.89-3.55
Meningitis	1/0	--		0/0	0.00		5	--	
total pneumonia	35/16	1.63	0.90-2.97	29/14	0.95	0.50-1.82	103	1.66	1.23-2.25

RR* models adjusted for attained age and calendar time, latency, race and number of visits.

All study subjects were followed from one 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 requiring 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.

Abbreviations: RR=relative risk; CI=confidence intervals

Supplemental Table 3. Risk of cancer (SIR) following splenectomy, by underlying condition.

	Patients with trauma only				Patients with AIs only					AIs removed		
	sp-	sp+	RR*	95% CI	sp-	sp+	RR*	95% CI		sp+	RR*	95% CI
All Cancer	44114	211	1.20	1.05-1.38	24135	192	1.48	1.28-1.70	All cancer	837	1.51	1.41-1.61
Buccal	4782	20	1.01	0.65-1.57	1642	9	0.97	0.50-1.87	Buccal	66	1.31	1.03-1.67
Esophagus	1627	5	0.82	0.34-1.96	613	4	1.22	0.46-3.27	Esophagus	27	1.66	1.14-2.42
Stomach	820	4	1.33	0.50-3.55	504	2	0.80	0.20-3.22	Stomach	17	1.64	1.02-2.65
Liver	607	4	1.52	0.57-4.07	471	5	1.75	0.73-4.23	Liver	16	1.82	1.12-2.98
Colon	2262	9	1.07	0.55-2.06	1512	11	1.41	0.78-2.55	Colon	40	1.30	0.95-1.77
Pancreas	900	4	1.14	0.43-3.05	496	3	1.13	0.36-3.51	Pancreas	23	2.03	1.35-3.06
Larynx	2022	8	0.95	0.47-1.90	747	4	0.96	0.36-2.56	Larynx	26	1.19	0.81-1.74
Lung	13246	61	1.12	0.87-1.44	6231	34	0.99	0.71-1.39	Lung	211	1.30	1.14-1.49
Bladder	1936	9	1.13	0.59-2.18	1301	6	0.84	0.38-1.88	Bladder	35	1.23	0.88-1.72
Kidney	879	4	1.06	0.40-2.84	574	7	2.10	0.99-4.42	Kidney	9	0.70	0.36-1.35
Prostate	6156	31	1.34	0.94-1.90	4364	24	1.08	0.72-1.61	Prostate	116	1.30	1.08-1.56
Hematop	2560	12	1.21	0.68-2.13	2029	51	4.58	3.47-6.05	Hematop	120	3.37	2.81-4.03
NHL	894	3	0.84	0.27-2.60	788	26	5.76	3.89-8.52	NHL	30	2.21	1.55-3.17
HL	170	1	1.48	0.21-10.56	117	1	1.43	0.20-10.22	HL	9	4.28	2.22-8.25
MM	481	2	1.11	0.28-4.47	330	2	1.17	0.29-4.71	MM	12	1.95	1.10-3.43
Leukemia	1015	6	1.54	0.69-3.44	794	22	5.22	3.41-7.99	Leukemia	69	4.99	3.94-6.33
AML	178	1	1.53	0.21-10.93	164	5	5.48	2.25-13.36	AML	16	5.90	3.60-9.66
CLL	370	1	0.71	0.10-5.08	243	6	4.79	2.13-10.80	CLL	12	2.37	1.35-4.18
CML	155	2	3.37	0.83-13.61	122	4	6.04	2.22-16.40	CML	12	5.50	3.11-9.72

RR* models 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.

All study subjects were followed from one 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 requiring 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.

Abbreviations: RR=relative risk; CI=confidence intervals

Supplemental Table 4. Risk of cancer death (SMR) following splenectomy, by underlying condition.

	Trauma only			AIs only			AIs removed		
	sp+/sp-	RR*	95% CI	sp+/sp-	RR*	95% CI	sp+	RR*	95%CI
All cancer	153/63	1.80	1.34-2.42	117/40	1.42	0.98-2.05	525	1.55	1.37-1.77
Buccal	7/0	--		0/2	0.00		23	2.07	1.05-4.10
Esophagus	6/1	4.18	0.50-35.23	1/1	0.07	0.00-1.24	27	1.68	0.92-3.07
Stomach	3/3	1.02	0.20-5.34	2/0	--		11	1.24	0.52-2.95
Colon	8/4	1.40	0.42-4.70	5/4	0.47	0.12-1.87	27	2.13	1.15-3.93
Liver	2/3	0.41	0.06-2.68	5/0	--		13	1.15	0.53-2.49
Pancreas	8/3	2.04	0.54-7.73	6/2	1.44	0.29-7.23	26	2.31	1.21-4.42
Larynx	5/0	--		2/1	1.25	0.09-17.32	12	1.22	0.52-2.86
Lung	65/25	1.92	1.21-3.06	35/19	0.94	0.53-1.67	216	1.42	1.17-1.73
Bladder	3/0	--		5/0	--		8	1.57	0.58-4.29
Kidney	3/4	0.59	0.13-2.72	6/1	2.40	0.27-21.31	6	0.71	0.26-1.95
Prostate	11/8	0.97	0.39-2.44	10/4	1.25	0.39-4.06	24	0.83	0.48-1.41
Hematop	8/4	1.46	0.43-4.93	21/2	5.49	1.26-23.90	49	2.49	1.53-4.05
NHL	5/1	3.41	0.40-29.34	5/0	--		21	4.21	1.73-10.23
MM	2/1	1.86	0.16-21.87	0/0	--		5	1.77	0.45-6.98
Leukemia	1/2	0.34	0.03-3.73	16/2	3.99	0.90-17.76	21	1.87	0.94-3.69
AML	1/1	0.71	0.04-11.32	5/1	1.88	0.21-16.91	7	2.42	0.67-8.79
CLL	0/0	--		3/0	--		1	0.34	0.04-3.18
CML	0/1	0.00		3/1	1.53	0.16-14.85	3	1.88	0.31-11.31

RR* models 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.

All study subjects were followed from one 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 requiring 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.

Abbreviations: RR=relative risk; CI=confidence intervals