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Risk of Site-Specific Cancer in Incident Venous Thromboembolism: A Population-Based Study

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Abstract

Background—The risk of venous thromboembolism (**VTE**) by cancer site is uncertain.

Objective—To estimate VTE risk by tumor site.

Methods—We enumerated observed active cancers by cancer site for Olmsted County, MN residents with incident VTE over the 13-year period, 1988–2000 (n=345 of 1417). We used 1988–2000 Iowa State Surveillance, Epidemiology, and End Results (**SEER**) data to estimate the expected age-specific prevalence of cancer by cancer site for all VTE cases; standardized Morbidity Ratios (**SMR**) for each cancer site were estimated by dividing the observed number of cancers in the VTE incident cohort by the expected number. Relative risk regression was used to model the observed number of cancers of each site, adjusting for the expected value based on SEER prevalence data, using generalized linear regression with a Poisson error and the natural log of the age- and sex-group expected count as an offset.

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Addendum: J.A. Heit conceived the study idea, and developed it in collaboration with other coauthors. All authors contributed to the study design. R.S. Marks and A.A. Ashrani verified the ICD-O cancer classification of incident VTE cases. T.M. Petterson and K.R. Bailey directed the analysis. All authors participated in the interpretation of data. T.M. Petterson wrote the initial draft. All authors participated in critical revision of the manuscript for intellectual content and approved the final version of the manuscript for publication. Research was supported by grants to J.A. Heit from the National Heart, Lung and Blood Institute, the National Institutes of Health.

Results—For men and women with VTE, all cancer sites had an increased SMR, ranging from 4.1 for head neck cancer to 47.3 for brain cancer. Among women, the SMR for breast, ovarian and other gynecologic cancers were 8.4, 13.0 and 8.4, respectively; for men, prostate cancer SMR was 7.9. Adjusting for age and sex, the relative risk (**RR**) of cancer in VTE cases was associated with cancer site in a multivariable model ($p<0.001$). Adjusting for age and sex, pancreatic, brain, other digestive cancers, and lymphoma had significantly higher RRs than the grouped comparison cancers.

Conclusions—Incident VTE risk can be stratified by cancer site.

Keywords

Venous Thrombosis; Pulmonary Embolism; Thrombophlebitis; Neoplasms; epidemiology; Risk

Introduction

The association between cancer and VTE was first noted in 1823 by Bouillaud, and later by Armand Trousseau.[1, 2] Active cancer is an independent risk factor for VTE, with an overall 4- to 7-fold increased risk,[3–10] and accounts for 20–30% of all new VTE events.[11–15] Venous thromboembolism is one of the most common complications seen in cancer patients.[16–18]

Cancer is also an independent predictor of reduced seven-day survival after VTE.[19] Cancer patients with VTE have worse survival than cancer patients without VTE.[14, 15, 18, 20–26] Unfortunately, available data do not allow one to predict which cancer patient will develop VTE.[27] While the risk of VTE appears to vary by cancer site, the magnitude of risk for each site remains uncertain.[27–31] To address this important gap in knowledge, we performed a population-based study to estimate the relative risk of incident VTE by cancer site.

Methods

Study Setting and Design

Using the resources of the Rochester Epidemiology Project,[32, 33] we identified the inception cohort of all Olmsted County, MN residents with incident DVT and PE over the 35-year period, 1966–2000, as previously described.[34, 35] Olmsted County provides a unique opportunity for investigating the natural history of VTE.[11, 34, 36] Rochester, the county seat, is approximately 80 miles from the nearest major metropolitan area. Mayo Clinic, together with Olmsted Medical Center (**OMC**), a second group practice and their affiliated hospitals, provide over 95% of all medical care delivered to local residents.[37] Since 1907, every Mayo patient has been assigned a unique identifier; all information from every provider contact is contained within a unit record for each patient. Diagnoses assigned at each visit are coded and entered into continuously updated files. Under auspices of the REP, the unique identifiers, diagnostic index, and medical records linkage were expanded to include the few other providers of medical care to local residents, including OMC and the few private practitioners in the area in 1965, thereby linking the medical records for community residents at the individual level.[32, 33] Using REP resources, we performed a

cohort study. For this study, we restricted our analyses to residents with incident DVT or PE over the 13 year period, 1988–2000. The study was approved by the Mayo Clinic Institutional Review Board.

Definition of Deep Vein Thrombosis and Pulmonary Embolism

A DVT was categorized as objectively-diagnosed when symptoms or signs of acute DVT were present and the diagnosis was confirmed by venography, compression venous duplex ultrasonography, impedance plethysmography, computed tomographic venography, magnetic resonance imaging or pathology examination of thrombus removed at surgery or autopsy. A PE was categorized as objectively-diagnosed when symptoms and/or signs of acute PE were present and the diagnosed was confirmed by pulmonary angiography, a ventilation/perfusion lung scan interpreted as high probability for PE, computed tomographic pulmonary angiography, magnetic resonance imaging or pathology examination of thrombus removed at surgery or autopsy. Mayo Clinic pathologists performed all autopsy examinations and completed the death certificates of persons dying within Olmsted County during the study period.

Classification of Cancer Site

The Mayo Clinic Cancer Registry began in 1972 and collects diagnostic information at the time of initial diagnosis or management for all patients with *in situ* or invasive cancer treated at the Mayo Clinic. The Registry is accredited by the American College of Surgeons and is fully compliant with the reporting requirements of the Minnesota Cancer Surveillance System and the Iowa Surveillance, Epidemiology, and End Results (**SEER**) registry.[38] The registry incorporates an application that classifies cancers according to the International Classification of Disease (**ICD**)-O 2nd Edition (see Appendix, Section 1). Mayo Clinic oncologists (RSM, AAA) verified the ICD-O classification of all Olmsted County incident VTE cases with active cancer over the 35-year period, 1966–2000.

Analyses

The expected age- and sex-specific prevalence of cancer by cancer site in Olmsted County was estimated using 1988–2000 Iowa SEER data. SEER is a population registry which collects and publishes the incidence of cancer, along with site and stage at diagnosis and subsequent survival.[39] We used the limited-use data from the November 2006 submission.[38] We used prevalence of cancer rather than incidence because for our cohort of interest, VTE, we have not followed cancer cases forward in time to see whether or not they develop VTE, but rather have recorded cancer at the time of first VTE, .i.e., cancer's prevalence in this specific population.

To obtain the expected number of prevalent cancers for each cancer site we used the period prevalence: the probability that a person (VTE case) would be a (cancer) case at any time during the interval of interest.[40] All persons with cancer at the start of the interval of interest and all incident cases of cancer during the interval of interest are counted as prevalent cases.[40] We used period prevalence in our analysis because the duration at risk of cancer was not available for the Olmsted County population at large (in its entirety), and not always available for our incident VTE cases.[40] We determined the expected count of

all persons with each cancer type on 1/1/1988 using the SEER limited duration prevalence algorithm and the 13 years prior to 1988 (prevalent on 1/1/1988). All death certificate and autopsy only cases were excluded. Age was age on 1/1/1988. We determined the expected incidence count of each cancer type during the 13-year interval, 1988–2000, inclusive, using the SEER rate algorithm for each specific cancer site, 1988–2000. Age was age at diagnosis. We added the prevalence count and the incident count to determine the sex and age-group specific expected number of cancers of each type (numerator). We used the sex and age-group population from Iowa 1988–2000 as provided by SEER for the denominator to determine the period prevalence for each age and sex group. We then multiplied the sex and age-group specific period prevalence by the total number of incident VTE cases (with or without cancer) in Olmsted County 1988–2000 in the corresponding sex and age-group to get the expected number of each cancer type for each age and sex group in our VTE incident cohort. Age groups were 0–14 years, 5 year intervals through 84 years, and 85+. Expected values were computed for each sex separately and for both sexes combined. The expected number of people for each cancer site was the sum across age and gender groups. Cancer site was collapsed in our study to one of 26 possible locations (**see** Appendix, Section 1). These can be characterized by ICD-O codes which can be directly matched to the same ICD-O codes in SEER. In order to get the SEER software to match those locations, we used the SEER*Stat 6.3.6 specific Site and Morphology codes (Appendix, Section 2). For the myeloproliferative and myelodysplastic cancers which were not available in SEER prior to 2000, we used SEER data from 2000–2004 and 2000–003, respectively and modified our estimates (**See** Appendix 2.24 and 2.25). Observed cancers among the total 1988–2000 VTE incidence cohort were tallied for each cancer site. Persons with multiple active cancers at the time of the incident VTE were counted once for each cancer site.

The null hypothesis for our study was that the observed number of cancers in a “random” group of Olmsted County residents in 1988–2000 (who happened to have an incident VTE) would be no different than expected as determined by the Iowa SEER registry during that same time interval. These cancer prevalence rates were chosen because Iowa state demographics most closely resemble those of Olmsted County (http://quickfacts.census.gov/qfd/states/19000.html). Alternatively, if incident VTE was associated with cancer then the observed number of cancers among our VTE cases would exceed the calculated expected number, and we would reject this null hypothesis. The standardized morbidity ratio (**SMR**) for each cancer type was calculated by dividing the total number of observed cancers found in the VTE cohort by the expected number as given by our SEER period prevalence calculation. Sex-specific cancers were determined using the sex-specific period prevalence from the Iowa SEER registry. The observed number of cancers was assumed to follow a Poisson distribution; exact 95% confidence intervals were calculated based on the relationship between the Poisson and the χ^2 distribution.[41] Although they are random variables, for the purposes of estimation the sex- and age-specific expected values are assumed to be constant, measured without error. This is an approximation, but is reasonable based on the fact that the coefficient of variation in the denominator (expected number of cases) is far smaller than that of the numerator (observed number of cases), since the underlying population (state of Iowa) is far larger than that of Olmsted County.

Relative risk regression was used to model the observed cancer count, adjusting for the expected value based on SEER prevalence data, using generalized linear regression with a Poisson error and the natural log of the age- and sex-group expected count as an offset.[42–44] To do this modeling, the data had to be subsetted to each cancer site. Age values were integers from 0 to 101 and for each sex the number of the cancers in the VTE cohort of that integer age at that specific cancer site was recorded. As might be expected, most cells were zero (no cancers at the location for that integer age). All locations were then set together so that the cancer site might be compared to a standard site (or to a "reference" combined set of cancer sites). The rarer cancers were categorized into a comparison group for purposes of analysis. Expected values for the combined cancers in the comparison group were done in the same way as for site-specific cancer types, i.e., by determining period prevalence using SEER 6.3.6 Site and Morphology codes which summed all of the grouped cancers. Sex-specific cancers (ovarian, uterine, and prostate) and cancers that in this small dataset were effectively sex-specific (breast) were treated as a sex by site interaction and only modeled for the sex of interest (no data values were included for the other sex). The generalized linear model tested whether or not the risk in any one particular cancer site was significantly different from the risk in the comparison group after adjusting for age and gender. We further tested whether or not there were any interactions between these adjusting variables and cancer site. The adequacy of the Poisson assumption was tested by comparing the distribution of observed cell counts to that of expected under the Poisson distribution.

Results

Over the 13-year period, 1988–2000, 1417 Olmsted County residents developed an incident DVT, PE or both. Of these VTE cases, 345 had active cancer at the time of incident VTE; of these 17 had multiple active cancers. Of the 1417 total incident VTE, 1340 (94.6%) were objectively diagnosed. The distribution of incident VTE by age and sex is shown in Table 1.

The overall distribution of observed and expected cancers by cancer site is shown in Table 2. For single cancer sites, the expected number of patients with a cancer of a specific type was <1 except for colon/rectal, prostate, breast, lung, and bladder cancer. Thus, the SMR exceeded 5.0 for almost all cancer sites (range 3.5 to 47.5, all p-values<0.05 except for soft tissue cancer, stomach [women only] and multiple myeloma [women only]); Tables 1–3). However, compared to published overall univariate VTE odds ratios of 7–10 for active cancer compared to no cancer,[3] the SMR for some cancer sites were particularly increased. Four cancer sites – brain cancer, pancreatic cancer, other digestive cancer (esophagus, small intestine, gallbladder, other biliary), and lymphoma - had unusually high risk, with SMRs exceeding 25. Eye and liver cancers had SMRs of approximately 25, and leukemia and stomach cancer had SMRs of nearly 20. Of note, the SMR for many common cancers (breast, colorectal, prostate) were essentially the same as the reported odds ratio for overall cancer [3] (their risk ratio ranged between 7.3 and 8.6); lung cancer was slightly higher (SMR=13). The SMR for VTE by cancer site among women (Table 3) and among men (Table 4) were similar for all non sex-specific cancers. All breast cancers occurred among women.

In this population-based cohort of incident VTE cases the relative risk of cancer was associated with cancer site in a multivariable model adjusted for age and sex ($p<0.001$; Table 5). Among this cohort of incident VTE cases, the relative risk of pancreatic cancer was over 8-fold higher ($p<0.0001$) than the grouped comparison cancers (head and neck, other thorax, bone, soft tissue, melanoma, other genitourinary, eye, miscellaneous cancer), after adjusting for age and sex. The relative risk of other digestive cancer and brain cancer were each 5.6-fold higher than the comparison cancers ($p<0.0001$) in the VTE incident cohort, adjusting for age and sex. The relative risk for leukemia, lymphoma, stomach and liver cancer ranged from 3.5-fold higher to 4.7-fold higher than the grouped comparison cancers (all p-values<0.004). Risk ratios for colorectal cancer and the sex-specific cancers of breast, other gynecologic, and ovarian cancer were not significantly different from the comparison group. Prostate cancer, with a 1.7 fold higher risk than the reference group, was just marginally significant (p-value=0.048). In this generalized linear model including cancer site, the relative risk of cancer in the VTE incident cohort decreased with age (RR=0.95; 95%CI: 0.95, 0.96 per year of age, $p<0.0001$) and was marginally higher for women (RR=1.35, 95%CI: 1.06, 1.73, $p=0.015$). The highly significant interaction of age and cancer site ($p=0.008$) suggests that the effect of age on RR varied across cancer site. We confirmed the fit of the Poisson distribution: the observed overall cell frequency (0, 1, 2, 3, 4,…) compared well to the predicted frequency.

Discussion

We estimated the SMR by cancer site among a cohort of incident VTE cases from a well-defined geographic area that included the full spectrum of VTE disease in all clinical settings (the community, nursing home, and hospital) where VTE may occur.[32, 33] In addition to our access to both outpatient and inpatient medical records, we used information from autopsy findings and death certificates to insure essentially complete ascertainment of clinically recognized VTE. We avoided the potential misdiagnosis and/or misclassification of VTE associated with administrative codes [45] by directly reviewing the complete medical records in the community for each potential case and confirming the DVT and/or PE diagnosis by review of all available imaging studies.

We found that brain cancer, pancreatic cancer, other digestive cancer (esophagus, small intestine, gallbladder, other biliary cancer) and lymphoma had the highest SMRs, similar to the high rates of VTE observed in these neoplasms in the Dutch Cancer Registry.[10] Patients with leukemia, liver cancer and stomach cancer were at intermediate risk. While the SMRs associated with multiple myeloma and cancer of the bladder, breast, colon/rectum, ovary, lung, prostate and remaining cancers were significantly increased (above 1.0), these risks did not exceed the risk of VTE associated with overall active cancer.[3–9]

While study heterogeneity makes it difficult to compare the risk by tumor site among VTE cases between studies; the rank order of SMR among our incident VTE cases -- brain cancer, pancreatic cancer and lymphoma -- are similar to those from a recent systematic review and meta-analysis[31] and a cohort study using linked United Kingdom databases,[9] although our estimated SMRs were about two- to three-fold higher than the relative risks in those populations. Similarly, the estimated SMRs among Olmsted County VTE patients for

lung, colorectal, breast and prostate cancer also were significantly higher than the respective risks reported in the meta-analysis.[31] The estimated SMR in our population were higher for stomach, kidney, ovarian and bladder cancer, and leukemia, compared to a study of the general population and cancer patients hospitalized for VTE in Denmark, 1997–2006,[8] although the corresponding confidence intervals were quite broad and overlapped. We believe our higher SMR estimates is due to more complete VTE case ascertainment (e.g., rapidly fatal cases, non-hospitalized cases, cases occurring among nursing home residents, etc.) in our study.

Our study has several important limitations. We had to use period prevalence rather than following a population cohort of all cancers in Olmsted County. For a cancer such as pancreatic cancer which is usually at an advanced stage when discovered, the true period prevalence may be lower than we estimated. This would mean that we may have underestimated the SMR for some cancers since our denominator may be high. As there were very few VTE cases noted in rarer cancers (e.g., eye, liver, other genitourinary cancers and myelodysplastic syndrome), the estimated SMR may be imprecise, as reflected by the wide 95% confidence intervals. We could not estimate the independent risk of VTE by tumor site after controlling for surgery, hospitalization, chemotherapy or extremity paresis, [3, 46] nor could we test for the effect of tumor stage, tumor progression, and site of local invasion or metastases on VTE risk.[27] For example, 90% of our incident VTE cases with pancreatic cancer had advanced (e.g., stage III/IV) disease. Thus, the risk imparted by pancreatic cancer may be due to advanced disease rather than pancreatic cancer per se.

Leukemia and lymphoma patients with chronic central venous catheters placed for chemotherapy are at increased risk factor for upper extremity deep vein thrombosis.[3, 47–50] However, of the 33 incident cases with active lymphoma and 18 incident cases with active leukemia, only 14 of 50 (28%) had a central venous catheter within the three months prior to the VTE event (1 case had both active lymphoma and active leukemia at the time of the incident VTE), and only 12 of 50 (24%) events were arm DVT. All 18 incident cases with active leukemia had resided in Olmsted County for at least one year prior to the venous thromboembolism event. Most of the incident cases with active leukemia had chronic lymphocytic leukemia (n=11 of 18 [61%]), which is not typically treated with L-aspariginase, a known risk factor for VTE.[51, 52]

Similarly, the incident VTE events among multiple myeloma patients occurred prior to current therapy with immunomodulator therapy (e.g., thalidomide, lenolidamide, etc.), also a known risk factor for VTE;[53–55] the VTE rate with multiple myeloma patients receiving these therapies is substantially higher than our estimates.[9] Finally, we cannot separate the VTE risk associated with breast cancer from the risk imparted by tamoxifen therapy,[56, 57] or from the risk imparted by angiogenesis inhibitor therapy.[58] Additional studies are needed to address these issues.

Our study has several strengths. We were able to take advantage of our close proximity and similarity to the Iowa SEER registry population to derive a period prevalence for each cancer of interest which accurately reflected a population similar to ours and so provided a reasonable estimate of expected cancer. We were able to match the SEER registry to the

Mayo Cancer Registry collected data using the same ICD-O codes which also increased the reliability of our estimates. We were able to do this over a long enough period of time (13 years) to ensure stability in our estimates. Further, we were able to use this information to comment on the relative risk of these cancers within this population, with pancreatic cancer having the highest relative risk (8-fold higher) and other digestive and brain cancer having over 5-fold higher relative risk over the baseline comparison cancer group. Conversely, we were able to show that other more common cancers, often posited as related to VTE (such as colon cancer), may in fact not have any higher baseline risk of VTE than any other cancer. Further, these estimates take into account age which is an important contribution given that both VTE and cancer risk increase with age.[34, 59] In our model, we showed that the relative risk of these cancers in a cohort of incident VTE diminished as age increased. Finally, our SMR values (Tables 2) are potentially useful for deriving a continuous prognostic variable ("score") which includes cancer site and stage. Cancer site and stage are often confounded (e.g., pancreatic cancer is usually discovered at stage IV), resulting in multi-dimensional variables which are complicated, non-intuitive, and prone to over fitting. [26] Overall SMRs in Table 2 estimate the variable risk of VTE across different cancer sites and as such might be used as a parsimonious way to account for cancer site in modeling VTE risk in future studies.

In summary, cancer of pancreas, brain, other digestive (esophagus, small intestine, gallbladder, other biliary), liver, lymphoma and leukemia have the highest risk for incident VTE. Prior estimates of VTE risk by tumor site may have been biased by studies of prevalent cancers among hospitalized patients or patients referred for care in tertiary care centers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- The risk of incident VTE is increased for all cancer sites but varies by site
- Pancreas, brain, other digestive cancers, and lymphoma are the highest risk cancers
- VTE risks for breast and ovarian cancer were increased 8.4- and 13.0-fold
- VTE risk for prostate cancer was increased 7.9-fold

Table 1

Distribution of Olmsted County, MN Residents with Incident Venous Thromboembolism, 1988–2000, by Age Group and Sex (total n=1417)

Age Group (years)	Number of Incident VTE Events	
	Male	Female
0–14	4	2
15–19	3	5
20–24	9	14
25–29	11	25
30–34	19	35
35–39	20	25
40–44	39	30
45–49	45	41
50–54	42	41
55–59	46	44
60–64	54	64
65–69	78	49
70–74	86	74
75–79	76	87
80–84	52	92
85+	46	159

Table 2

Cancer Site Standard Morbidity Ratio (SMR) among Olmsted County, MN Residents with Incident Venous Thromboembolism, 1988–2000.

Cancer Site	Observed	Expected	SMR	95% CI	p-value
	----------n----------				
Brain	11	0.23	47.25	23.59, 84.54	<0.001
Pancreatic	27	0.64	41.95	27.64, 61.04	<0.001
Other digestive	14	0.45	30.88	16.88, 51.81	<0.001
Lymphoma	33	1.14	28.82	19.84, 40.48	<0.001
Leukemia	18	0.91	19.84	11.76, 31.36	<0.001
Stomach	7	0.38	18.17	7.31, 37.45	<0.001
Multiple myeloma	5	0.36	13.98	4.54, 32.62	<0.001
Kidney	8	0.57	13.92	6.01, 27.44	<0.001
Lung	45	3.45	13.03	9.50, 17.43	<0.001
Ovary[‡]	6	0.46	13.02	4.78, 28.33	<0.001
Myeloproliferative neoplasm	9	0.71	12.59	5.76, 23.90	<0.001
Bladder	18	1.64	10.99	6.52, 17.38	<0.001
Melanoma	8	0.82	9.72	4.20, 19.16	<0.001
Breast[‡]	38	4.40	8.64	6.12, 11.86	<0.001
Other gynecologic[‡]	14	1.67	8.36	4.57, 14.03	<0.001
Prostate[§]	39	4.96	7.86	5.59, 10.75	<0.001
Colon/rectal	39	5.34	7.31	5.20, 9.99	<0.001
Head and Neck	5	1.22	4.09	1.33, 9.54	0.008
Eye	2	0.07	26.84	3.25, 96.95	0.003
Liver	4	0.15	25.85	7.05, 66.22	<0.001
Other genitournary	3	0.28	10.58	2.18, 30.92	0.003
Myelodysplastic syndrome	3	0.42	7.05	1.45, 20.60	0.009
Soft Tissue	1	0.20	4.97	0.12, 27.68	0.18
Other Thorax	0	0.04	0	0, 87.78	------
Bone	0	0.03	0	0, 135.58	------

Cancer Site	Observed	Expected	SMR	95% CI	p-value
	----------n----------				
Miscellaneous	6	0.66	9.08	3.33, 19.76	<0.001
Cancers combined 1†	38	4.30	8.84	6.26, 12.14	<0.001
Cancers combined 2*	31	3.93	7.90	5.36, 11.21	<0.001
Cancers combined 3**	24	3.34	7.17	4.60, 10.67	<0.001

‡Women only;

§Men only.

†Remaining cancers combined (kidney, head and neck, gastric, other thorax, bone, soft tissue, melanoma, other genitourinary, eye, misc. cancer [other]).

*Remaining cancers combined (head and neck, liver, other thorax, bone, soft tissue, myelodysplastic syndromer, melanoma, other genitourinary, eye, misc. cancer [other]).

**Remaining cancers combined: head and neck, other thorax, bone, soft tissue, melanoma, other genitourinary, eye, misc. cancer [other]).

Table 3

Cancer Site Standard Morbidity Ratio (SMR) among Olmsted County, MN Women with Incident Venous Thromboembolism, 1988–2000.

Cancer Site	Observed	Expected	SMR	95% CI	p-value
	----------n----------				
Brain	5	0.11	46.31	15.04, 108.07	<0.001
Pancreatic	14	0.35	39.99	21.86, 67.10	<0.001
Other digestive	7	0.21	33.01	13.27, 68.01	<0.001
Lymphoma	17	0.59	28.95	16.86, 46.35	<0.001
Leukemia	9	0.41	21.99	10.06, 41.74	<0.001
Stomach	1	0.16	6.37	0.16, 35.51	0.14
Multiple myeloma	1	0.18	5.71	0.14, 31.81	0.16
Kidney	5	0.23	21.57	7.00, 50.34	<0.001
Lung	21	1.15	18.20	11.27, 27.82	<0.001
Ovary	6	0.46	13.02	4.78, 28.33	<0.001
Myeloproliferative neoplasm	6	0.33	18.11	6.64, 39.41	<0.001
Bladder	7	0.44	16.07	6.46, 33.12	<0.001
Melanoma	3	0.38	7.98	1.64, 23.31	0.007
Breast	38	4.40	8.64	6.12, 11.86	<0.001
Other gynecologic	14	1.67	8.37	4.57, 14.03	<0.001
Colon/rectal	19	2.91	6.54	3.93, 10.21	<0.001
Head and Neck	2	0.41	4.83	0.58. 17.44	0.06
Eye	1	0.03	31.90	0.81, 177.72	0.03
Liver	2	0.06	31.10	3.76, 112.33	0.002
Other genitournary	1	0.07	13.84	0.35, 77.09	0.07
Soft Tissue	0	0.11	0	0, 34.20	------
Myelodysplastic syndrome	1	0.20	4.87	0.12, 27.12	0.18
Other Thorax	0	0.01	0	0, 361.38	------
Bone	0	0.01	0	0, 255.10	------
Miscellaneous	3	0.37	8.04	1.66, 23.50	0.006

Cancer Site	Observed	Expected	SMR	95% CI	p-value
	----------n----------				
Cancers combined 1†	15	1.79	8.38	4.69, 13.83	<0.001
Cancers combined 2*	13	1.67	7.77	4.14, 13.29	<0.001
Cancers combined 3**	10	1.40	7.13	3.42, 13.11	<0.001

† Remaining cancers combined (kidney, head and neck, gastric, other thorax, bone, soft tissue, melanoma, other genitourinary, eye, misc. cancer [other]).

* Remaining cancers combined (head and neck, liver, other thorax, bone, soft tissue, myelodysplastic syndrome, melanoma, other genitourinary, eye, misc. cancer [other]).

** Remaining cancers combined: head and neck, other thorax, bone, soft tissue, melanoma, other genitourinary, eye, misc. cancer [other]).

Table 4

Cancer Site Standard Morbidity Ratio (SMR) among Olmsted County, MN Men with Incident Venous Thromboembolism, 1988–2000.

Cancer Site	Observed	Expected	SMR	95% CI	p-value
	----------n----------				
Brain	6	0.13	47.46	17.42, 103.30	<0.001
Pancreatic	13	0.30	43.42	23.12, 74.25	<0.001
Other digestive	7	0.25	27.81	11.18, 57.29	<0.001
Lymphoma	16	0.56	28.33	16.19, 46.00	<0.001
Leukemia	9	0.52	17.45	7.98, 33.13	<0.001
Stomach	6	0.24	25.12	9.21, 54.68	<0.001
Multiple myeloma	4	0.19	21.46	5.85, 54.94	<0.001
Kidney	3	0.36	8.41	1.73, 24.58	0.006
Lung	24	2.43	9.87	6.32, 14.68	<0.001
Myeloproliferative neoplasm	3	0.40	7.58	1.56, 22.15	<0.001
Bladder	11	1.27	8.63	4.31, 15.45	<0.001
Melanoma	5	0.46	10.76	3.49, 25.11	<0.001
Prostate	39	4.96	7.86	5.59, 10.75	<0.001
Colon/rectal	20	2.49	8.04	4.91, 12.42	<0.001
Head and Neck	3	0.86	3.47	0.71, 10.13	0.06
Eye	1	0.04	22.10	0.56, 123.15	0.04
Liver	2	0.10	20.86	2.53, 75.35	0.004
Other genitournary	2	0.22	9.10	1.10, 32.86	0.02
Soft Tissue	1	0.09	10.74	0.27, 59.84	0.09
Myelodysplastic syndrome	2	0.23	8.83	1.07, 31.91	0.02
Other Thorax	0	0.03	0	0, 108.02	------
Bone	0	0.01	0	0, 279.01	------
Miscellaneous	3	0.29	10.25	2.11, 29.95	0.003
Cancers combined 1[†]	23	2.62	8.76	5.55, 13.14	<0.001
Cancers combined 2[*]	18	2.36	7.63	4.52, 12.07	<0.001

Cancer Site	Observed	Expected	SMR	95% CI	p-value
	----------n----------				
Cancers combined 3**	14	2.04	6.88	3.76, 11.54	<0.001

† Remaining cancers combined (kidney, head and neck, gastric, other thorax, bone, soft tissue, melanoma, other genitourinary, eye, misc. cancer [other]).

* Remaining cancers combined (head and neck, liver, other thorax, bone, soft tissue, myelodysplastic syndrome, melanoma, other genitourinary, eye, misc. cancer [other]).

** Remaining cancers combined: head and neck, other thorax, bone, soft tissue, melanoma, other genitourinary, eye, misc. cancer [other]).

Table 5

Age- and Sex-adjusted Risk Ratio (RR) of Cancer* in a Population-Based Cohort of Incident Venous Thromboembolism

Cancer Site	Ratio of RR†	95% CI‡	Wald Chi-squared	p-value
Pancreas	8.25	4.73, 14,48	55.5	<0.0001
Other digestive	5.61	2.82, 10.73	26.0	<0.0001
Brain	5.55	2.61, 11.07	22.1	<0.0001
Liver	4.69	1.38, 12,18	8.2	0.0043
Lymphoma	4.27	2.54, 7.31	29.3	<0.0001
Leukemia	3.66	1.95, 6.72	17.2	<0.0001
Stomach	3.53	1.40, 7.80	8.5	0.0035
Multiple myeloma	2.62	0.88, 6.34	3.8	0.0510
Lung	2.18	1.34, 3.65	9.4	0.0022
Kidney	2.16	0.91, 4.62	3.6	0.0593
Bladder	2.14	1.14, 3.96	5.9	0.0155
Myeloproliferative neoplasm	2.02	0.89, 4.20	3.2	0.0722
Prostate**	1.70	1.01, 2.92	3.9	0.0484
Ovary**	1.58	0.58, 3.67	1.0	0.3193
Myelodysplastic syndrome	1.48	0.35, 4.26	0.4	0.5223
Colon/rectal	1.44	0.87, 2.44	1.9	0.1645
Other gynecologic**	0.64	0.32, 1.24	1.7	0.1962
Breast**	1.16	0.69, 2.00	0.3	0.5714

*P-value for cancer type <0.001 in generalized linear model.

†Compared to cancer subgroup of ‘remaining cancers’ (head and neck, other thorax, bone, soft tissue, melanoma, other genitourinary, eye, misc. cancer).

‡Profile likelihood confidence intervals.

**Only males (prostate) or females (ovary, other gynecologic, breast) are included