Incidence of Venous Thromboembolism and Its Effect on Survival Among Patients With Common Cancers

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Background: The incidence of venous thromboembolism after diagnosis of specific cancers and the effect of thromboembolism on survival are not well defined.

Methods: The California Cancer Registry was linked to the California Patient Discharge Data Set to determine the incidence of venous thromboembolism among cancer cases diagnosed between 1993 and 1995. The incidence and timing of thromboembolism within 1 and 2 years of cancer diagnosis and the risk factors associated with thromboembolism and death were determined.

Results: Among 235 149 cancer cases, 3775 (1.6%) were diagnosed with venous thromboembolism within 2 years, 463 (12%) at the time cancer was diagnosed and 3312 (88%) subsequently. In risk-adjusted models, metastatic disease at the time of diagnosis was the strongest predictor of thromboembolism. Expressed as events per 100 patient-years, the highest incidence of thromboembolism occurred during the first year of follow-up among cases with metastatic-stage pancreatic (20.0), stomach (10.7), bladder (7.9), uterine (6.4), renal (6.0), and lung (5.0) cancer. Adjusting for age, race, and stage, diagnosis of thromboembolism was a significant predictor of decreased survival during the first year for all cancer types (hazard ratios, 1.6-4.2; $P<.01$).

Conclusions: The incidence of venous thromboembolism varied with cancer type and was highest among patients initially diagnosed with metastatic-stage disease. The incidence rate of thromboembolism decreased over time. Diagnosis of thromboembolism during the first year of follow-up was a significant predictor of death for most cancer types and stages analyzed. For some types of cancer, the incidence of thromboembolism was sufficiently high to warrant prospective clinical trials of primary thromboprophylaxis.

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ALTHOUGH CANCER IS known to be a major risk factor associated with the development of venous thromboembolism, the exact incidence and time course of symptomatic thromboembolism among patients with different types and stages of cancer is largely unknown. Small cohort studies from single institutions or from clinical trials have reported the incidence of venous thromboembolism (deep-vein thrombosis and pulmonary embolism) among patients with different clinical manifestations of cancer to be up to 4%.[1-3] Larger epidemiologic studies have used hospital administrative data and reported that the highest incidence of symptomatic thromboembolism among patients who required hospitalization was in patients with ovarian, brain, or pancreatic cancer (110-120 cases per 10 000 patients).[4,5] Autopsy studies have reported that patients with cancers involving organs of the abdominal cavity, particularly ovarian, biliary, or stomach cancer, have a high prevalence of pulmonary embolism at the time of death.[6] No population-based study, to our knowledge, has determined the incidence of thromboembolism among patients diagnosed with specific types and stages of cancer.

There is some evidence that patients with cancer who develop thromboembolism have shortened survival.[7] If primary thromboprophylaxis for high-risk patients were shown to improve survival, knowing the incidence of venous thromboembolism for each cancer type and stage would help define the subgroups of patients who might benefit the most.[5] Furthermore, thromboprophylaxis might be useful in high-risk patients who are exposed to additional risk factors for thromboembolism, such as chemotherapy and tamoxifen citrate therapy.

Using the California Cancer Registry linked to the California Patient Discharge Data Set,[8] we assembled a large cohort of cancer cases defined by site, histologic type, and stage and determined the incidence and time course of the development of acute venous thromboembolism.

METHODS

DATA SETS

Since July 1990, the State of California Office of Statewide Health Planning and Development has maintained a linked Patient Discharge Data Set that lists up to 25 discharge diagnoses and 20 procedures for every patient hospitalized in the state, except for those admitted to a federal or military hospital. All codes use the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*). An encrypted version of the Social Security number permits linkage of all serial hospitalizations and linkage with other data sets. This data set is linked to the state death registry, allowing identification of all patients who die or are buried in California. Patients who move out of California are lost to follow-up.

Since 1988, the California Cancer Registry has collected information on all residents with clinical, radiologic, or pathologic evidence of cancer, with the exception of nonmelanoma skin cancer and carcinoma in situ of the cervix. The registry estimates that 99% of cancer cases are captured and that approximately 95% of all cancer cases are diagnosed pathologically, with only 5% diagnosed at autopsy or without tissue diagnosis.[9] Registry data include the date of initial diagnosis, primary site, histologic type, clinical stage, and demographic information, including race. Approximately 5% of registry cases cannot be linked to the Patient Discharge Data Set because of the absence of a Social Security number.

The study was approved by the California Health and Welfare Agency Committee for the Protection of Human Subjects, and the University of California, Davis, Human Subjects Committee.

STUDY DESIGN AND CANCER COHORTS

Cases analyzed included all cancer registry cases that had a diagnosis of a primary cancer of the prostate, breast, lung, colon or rectum, uterus, bladder, pancreas, stomach, ovary, or kidney, or melanoma or non-Hodgkin lymphoma, diagnosed between January 1, 1993, and December 31, 1995. This time frame was selected because, before 1997, nearly all patients with symptomatic venous thromboembolism were routinely hospitalized for treatment. Registry information was merged with the hospital discharge data, which included all admissions between January 1, 1991, and December 31, 1997. Cases diagnosed in military or veterans hospitals were excluded. Cases with rare or unusual histologic findings were also excluded, as were cases with a previous diagnosis of cancer identified in the discharge data set (V10 code or other cancer code). Eighty-one percent of all the remaining cancer cases had at least 1 hospitalization identified in the discharge data set between 1991 and 1997. Pathologic stage was defined according to site by means of the Surveillance, Epidemiology, and End Results program (http://seer.cancer.gov/tools/ssm/).

Lower extremity deep-vein thrombosis and pulmonary embolism were defined according to previously validated *ICD-9-CM* codes: 451.1x; 451.2; 451.81; 453.1; 453.2; 453.8; 453.9; or 415.1x; or 997.2 or 997.3 in the principal position plus a code for thromboembolism in the second position.[10-12] Cases with superficial venous thrombosis or upper extremity thrombosis were not included. *Definite* venous thromboembolism was defined as a principal diagnosis of thromboembolism plus a hospital stay of 3 or more days but included patients with thromboembolism who died in the first 2 days. *Probable* venous thromboembolism was defined as a secondary diagnosis of thromboembolism together with the presence of a procedure code to diagnose thromboembolism. These procedure codes were pulmonary arteriography (88.43, 88.44), venography (88.66), vascular ultrasound (88.77), ventilation-perfusion lung scan (92.15), computed tomography of the chest (87.41), impedance plethysmography (89.59), injection of an anticoagulant (99.19), and insertion of an inferior vena cava filter (38.7). Cases with *possible* venous thromboembolism had only a secondary diagnosis of thromboembolism and a length of stay of 3 or more days. In this analysis, only cases categorized as definite or probable were included.

A venous thromboembolic event was classified as being *concurrent* with the cancer diagnosis if it was diagnosed during the hospitalization when cancer was diagnosed, determined by (1) a registry diagnosis date that overlapped the time of hospitalization, (2) a cancer diagnosis code that matched the cancer type in the registry, or (3) a less specific cancer code indicating the presence of cancer in the same organ as the registry diagnosis. All thromboembolic events diagnosed during a hospitalization that followed the registry diagnosis date were classified as *subsequent*. To identify only incident cases of venous thromboembolism, all cases that had a history of having any thromboembolism code (principal or secondary) back to January 1, 1991, were excluded.

STATISTICAL ANALYSIS

Primary outcomes were the incidence and time of diagnosis of venous thromboembolic events within 1 and 2 years of the cancer diagnosis. Incidence rates were calculated as both cumulative incidence and as person-time (events per 100 patient-years) for both the first year and the second year after diagnosis. Kaplan-Meier incidence curves were generated to illustrate the temporal pattern of onset of venous thromboembolism over time for different types and stages of cancer. To assess the associations of cancer stage, age, race, and sex with the development of venous thromboembolism, Cox proportional hazards models were fit for each type of cancer. Proportionality assumptions of the models were checked and were met by the data. To assess the effect of concurrent or subsequent venous thromboembolism on the risk of death within 1 year of the diagnosis of cancer, multivariate models were created for each cancer type, with venous thromboembolism used as a time-dependent covariate and with adjustment for age, race, and stage. Individual models for each cancer type stratified by stage were also generated. All analyses were performed in SAS stastical software (SAS Institute Inc, Cary, NC), and $P<.05$ was considered statistically significant.

RESULTS

A total of 235 149 eligible cancer cases were identified during the 3-year study period. Demographic characteristics of each cancer cohort and cancer stage at diagnosis are summarized in **Table 1**. Caucasians composed 76.6% of the cohort; African Americans, 6.2%; Hispanics, 9.8%; Asian–Pacific Islanders, 6.0%; and other, 1.3%. The majority of patients with cancers of the prostate, breast, bladder, uterus, or kidney or melanoma had localized disease, whereas most patients diagnosed with cancer of the lung (including small cell and non–small cell), pancreas, or ovary or non-Hodgkin lymphoma (includ-

Table 1. Clinical Characteristics of Cancer Cohorts

Cancer Type	No.	Sex, % F	Median Age, y	Cancer Stage at Time of Diagnosis, No. (%)			
				Localized	Regional	Remote	Unknown
Prostate	50 926	0	70	33 383 (66)	7041 (14)	3515 (7)	6987 (14)
Breast	44 744	99	62	27 014 (60)	13 629 (30)	2029 (5)	2072 (5)
Lung	45 215	45	69	6558 (15)	8775 (19)	22 486 (50)	7396 (16)
Colon/rectum	32 157	50	71	10 623 (33)	12 766 (40)	6409 (20)	2359 (7)
Melanoma	9930	44	55	8065 (81)	431 (4)	466 (5)	968 (10)
Non-Hodgkin lymphoma	9503	43	63	2577 (27)	1706 (18)	4416 (46)	804 (8)
Uterus	8744	100	66	6437 (74)	1302 (15)	598 (7)	407 (5)
Bladder	10 078	26	71	8411 (83)	833 (8)	324 (3)	510 (5)
Pancreas	6712	52	71	467 (7)	1889 (28)	2933 (44)	1423 (21)
Stomach	6221	39	70	1020 (16)	2168 (35)	2050 (33)	983 (16)
Ovary	5904	100	64	899 (15)	500 (8)	3948 (67)	557 (9)
Kidney	5015	38	64	2445 (49)	1021 (20)	1180 (24)	369 (7)
Total	**235 149**			**107 899** (46)	**52 061** (22)	**50 354** (21)	**24 835** (11)

ing low grade, aggressive, and high grade) had metastatic disease.

Thromboembolism was categorized as definite or probable in 3775 cases (1.6%), and an additional 1257 cases (0.5%) were classified as possible. Of all thromboembolism cases, 55% were classified as definite, 20% as probable, and 25% as possible. Tabulating only cases with definite or probable thromboembolism stratified by stage and type of cancer, **Table 2** summarizes the 2-year cumulative incidence of thromboembolism, the incidence of concurrent thromboembolism, the incidence rate of thromboembolism (expressed as events per 100 patient-years) during follow-up years 1 and 2, and the percentage of patients who died during the first year and within 2 years of cancer diagnosis. Results for the cases classified as unknown stage are not shown.

There were 463 patients (0.2%) with concurrently diagnosed definite or probable thromboembolism, and of these, 265 were admitted with a principal diagnosis of thromboembolism or had a test for thromboembolism on the first or second day of hospitalization. Among the concurrent cases, 259 (56%) had metastatic disease, compared with a 21% prevalence of metastatic disease among patients without concurrent thromboembolism ($P<.001$). The highest incidence of concurrent thromboembolism, 1.3%, occurred among patients with metastatic pancreatic cancer. An additional 3312 patients (1.4%) were subsequently diagnosed with thromboembolism during the 2-year follow-up period.

The incidence rate of thromboembolism was higher during the first year of follow-up than the second year for all types and stages of cancer, except for localized pancreatic cancer. Cancers with the highest 1-year incidence rate of thromboembolism were metastatic-stage cancer of the lung, uterus, bladder, pancreas, stomach, and kidney, and for these cancer types, the thromboembolism rate was 4 to 13 times higher among cases with metastatic disease than cases with localized disease.

A Kaplan-Meier plot illustrating the time course of incident venous thromboembolism among cases with metastatic-stage cancer of the breast, prostate, lung, ovary, and pancreas is shown in **Figure 1**. A similar plot for cases with regional-stage disease at the time of diagnosis is shown in **Figure 2**.

The results of multivariate analysis of potential risk factors associated with the development of venous thromboembolism within 1 year of cancer diagnosis are shown in **Table 3**. Cases with metastatic disease at the time of diagnosis had a 1.4- to 21.5-fold higher risk of thromboembolism than cases with localized disease for all the cancer types analyzed. Sex was not a significant predictor of thromboembolism. Asian–Pacific Islanders had significantly lower risk than Caucasians of developing venous thromboembolism among cases with prostate, breast, lung, colorectal, pancreatic, and stomach cancer, as well as non-Hodgkin lymphoma. African Americans with uterine cancer had more than a 2-fold higher risk of developing venous thromboembolism, whereas African Americans with lung cancer or non-Hodgkin lymphoma had significantly lower risk than Caucasians. Increasing age was not associated with any clinically meaningful differences in the incidence of thromboembolism, with only a modest increase in risk associated with advancing age among cases with cancer of the breast or ovary or non-Hodgkin lymphoma.

In the multivariate model to predict death within 1 year, after adjustment for age, race, and stage, the diagnosis of venous thromboembolism was a significant predictor for each cancer type analyzed (range of hazard ratios, 1.6-4.2; $P<.01$). However, the strongest predictor of death in these models was metastatic disease at the time of cancer diagnosis (range of hazard ratios, 1.8-49.0; $P<.001$). As shown in **Table 4**, stratified analyses demonstrated that venous thromboembolism was associated with an increased risk of death for all stages and cancer types, significant for all but regional and metastatic renal cancer, with a median overall relative risk of 3.7 (range of hazard ratios, 1.3-14.4).

COMMENT

This study enumerates the magnitude and time course of incident venous thromboembolism after the diagno-

Table 2. Venous Thromboembolism in Cancer Cohorts Stratified by Known Stage

Cancer and Stage (No.)*	2-y Cumulative Incidence, No. (%)†	Concurrent Diagnosis of VTE and Cancer, No. (%)‡	Rate of VTE/Patient-Years, %		Death, %	
			Year 1	Year 2	Year 1	Year 2
Prostate						
Localized (33 383)	324 (1.0)	14 (<0.1)	0.8	0.2	2.7	5.8
Regional (7041)	93 (1.3)	2 (<0.1)	1.0	0.3	2.6	6.6
Remote (3515)	43 (1.2)	6 (0.2)	0.9	0.8	25.1	45.9
Breast						
Localized (27 014)	216 (0.8)	1 (<0.1)	0.5	0.3	1.8	4.4
Regional (13 629)	182 (1.3)	2 (<0.1)	1.0	0.4	4.4	12.4
Remote (2029)	53 (2.6)	2 (0.1)	2.8	1.4	43.6	62.0
Lung						
Localized (6558)	85 (1.3)	7 (0.1)	1.1	0.5	24.6	41.2
Regional (8775)	193 (2.2)	22 (0.2)	2.3	1.1	46.2	68.7
Remote (22 486)	544 (2.4)	96 (0.4)	5.0	1.7	81.1	92.7
Colon/rectum						
Localized (10 623)	108 (1.0)	4 (<0.1)	0.9	0.2	8.3	13.3
Regional (12 766)	313 (2.4)	26 (0.2)	2.3	0.5	14.5	26.3
Remote (6409)	186 (2.9)	37 (0.6)	4.3	1.1	59.9	80.0
Melanoma						
Localized (8065)	27 (0.3)	0	0.2	0.1	2.2	6.5
Regional (431)	4 (0.9)	0	0.7	0.3	12.3	33.2
Remote (466)	12 (2.6)	1 (0.2)	4.4	0	64.8	77.9
Non-Hodgkin lymphoma						
Localized (2577)	40 (1.5)	4 (0.2)	1.7	0.2	25.3	34.4
Regional (1706)	55 (3.2)	8 (0.5)	3.5	0.6	28.3	39.1
Remote (4416)	95 (2.1)	20 (0.4)	2.5	0.6	40.6	51.2
Uterus						
Localized (6437)	77 (1.2)	6 (0.1)	0.8	0.4	2.8	6.0
Regional (1302)	29 (2.2)	1 (0.1)	1.5	1.1	15.4	27.4
Remote (598)	29 (4.8)	4 (0.7)	6.4	1.9	52.7	69.1
Bladder						
Localized (8411)	74 (0.9)	3 (<0.1)	0.6	0.3	9.5	17.0
Regional (833)	17 (2.0)	3 (0.4)	2.6	0	38.4	57.3
Remote (324)	14 (4.3)	0	7.9	1.9	76.9	87.7
Pancreas						
Localized (467)	15 (3.2)	3 (0.6)	4.2	4.5	71.5	87.8
Regional (1889)	56 (3.0)	7 (0.4)	4.9	2.1	75.0	90.0
Remote (2933)	160 (5.4)	38 (1.3)	20.0	3.3	93.8	97.4
Stomach						
Localized (1020)	24 (2.3)	1 (0.1)	2.5	0.4	26.0	38.5
Regional (2168)	73 (3.4)	6 (0.3)	3.8	1.3	45.2	65.9
Remote (2050)	90 (4.4)	18 (0.9)	10.7	1.5	84.6	94.7
Ovary						
Localized (899)	7 (0.8)	1 (0.1)	0.7	0.1	2.9	5.7
Regional (500)	13 (2.6)	6 (1.2)	2.0	0.9	11.2	18.2
Remote (3948)	131 (3.3)	26 (0.7)	3.6	0.9	31.9	49.7
Kidney						
Localized (2445)	33 (1.3)	9 (0.4)	1.2	0.3	5.9	9.6
Regional (1021)	39 (3.8)	9 (0.9)	3.7	0.9	17.7	29.4
Remote (1180)	41 (3.5)	11 (0.9)	6.0	1.5	68.6	82.5

Abbreviation: VTE, venous thromboembolism.
*Does not include 24 835 patients with unknown or undefined stage of cancer.
†Includes concurrent and subsequent cases.
‡The percentage represents the percentage of cases of that cancer type and stage.

sis of 12 common cancers. Other studies have either reported small case series[2,13,14] or enumerated the incidence only among patients who required hospitalization for specific types of cancer of unknown stage.[4] The most striking finding of the present study was the strong association between metastatic-stage cancer at the time of diagnosis and the incidence of thromboembolism. Metastatic-stage cancer was diagnosed in 56% of the cases in which thromboembolism was concurrently diagnosed even though only 21% of the entire cohort had metastatic-stage disease at the time of diagnosis. In addition, in multivariate models to predict venous thromboembolism, there was a consistent and strong relationship between metastatic disease at the time of diagnosis and development of thromboembolism for most of the cancer types analyzed. Compared with patients with localized disease, the relative risk of developing symptomatic thromboembolism was more than 20-fold higher for meta-

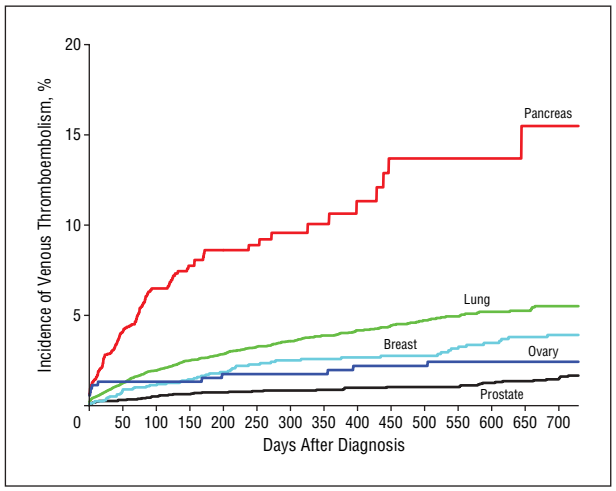

Figure 1. Kaplan-Meier plot of the incidence of venous thromboembolism within 2 years of diagnosis of 5 different types of cancer with metastatic-stage disease at the time of diagnosis.

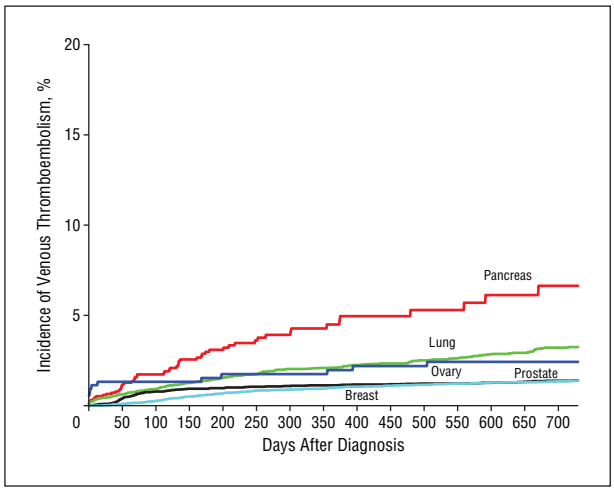

Figure 2. Kaplan-Meier plot of the incidence of venous thromboembolism within 2 years of diagnosis of 5 different types of cancer with regional-stage disease at the time of diagnosis.

static melanoma, 9-fold higher for metastatic bladder cancer, and 5- to 6-fold higher among patients with metastatic breast or uterine cancer. Finally, although the overall 2-year cumulative incidence of thromboembolism was just 1.6%, when measured in person-time, the incidence during the first year after cancer diagnosis was high among cases with certain metastatic stage cancers, particularly cancer of the pancreas (20.0 events per 100 patient-years), stomach (10.7 events per 100 patient-years), kidney (6.0 events per 100 patient-years), bladder (7.9 events per 100 patient-years), uterus (6.4 events per 100 patient-years), and lung (5.0 events per 100 patient-years).

The incidence of thromboembolic events among patients with either metastatic- or regional-stage disease was highest in the first few months after diagnosis, with the incidence decreasing over time for most cancers. Coupled with the very strong association between metastatic-stage disease and development of thromboembolism, this finding suggests that the biological aggressiveness of the cancer may be the principal risk factor associated with development of thromboembolism. However, it is possible that other factors, such as major surgery, chemotherapy, or radiation treatment, contribute to the high incidence of thromboembolism in the months immediately following the diagnosis of cancer. Unfortunately, reliable information regarding chemotherapy or radiation treatment was not available in the registry database.

The 2-year cumulative incidence of thromboembolism was 1.6% in this large, population-based series. This figure is consistent with individual clinical trials that have reported thromboembolism as an adverse event. For example, adjuvant breast cancer trials have reported thromboembolism rates of less than 1% to 5%.[15-17] Furthermore, cases of upper extremity thromboembolism and superficial thrombophlebitis were excluded in the present study, which lowers the incidence in comparison with treatment trials.

After adjustment for age, race, and stage of disease, a diagnosis of thromboembolism at the time of or within 1 year of cancer diagnosis was a significant predictor of death within that year for each of the 12 cancer types analyzed. These results extend the findings of Sorensen et al,[7] who reported that patients diagnosed concurrently with thromboembolism and cancer had decreased survival compared with a control group of patients (unmatched for stage) who were diagnosed with cancer but without thromboembolism. The current findings also demonstrate that the effect of venous thromboembolism on survival was similar for many cancers among patients with localized, regional, or metastatic-stage disease. Further studies are required to determine the reason that venous thromboembolism is so strongly associated with decreased survival. Patients with venous thromboembolism may have more biologically aggressive cancer, have greater underlying comorbidity, or simply die earlier because of complications associated with thromboembolism and/or its treatment. A recent trial[18] failed to demonstrate a survival benefit among patients with advanced cancers without symptomatic thromboembolism, given up to 1 year of prophylactic low-molecular-weight heparin compared with placebo. However, this trial was underpowered to detect a small survival difference and included a heterogeneous patient population with a poor prognosis and median survival of 1 year.

Race or ethnicity significantly influenced the incidence of thromboembolism. For all cancers, Asian–Pacific Islanders had a lower risk than Caucasians, and this was statistically significant among patients with prostate, breast, lung, colorectal, pancreas, and stomach cancer and non-Hodgkin lymphoma. To our knowledge, this finding has not been previously reported in a cancer cohort, but other studies,[19,20] including a recent analysis of the National Hospital Discharge Survey,[21] have reported that Asian–Pacific Islanders have an approximately 5-fold lower incidence of thromboembolism. It is possible that the lower incidence of thromboembolism among Asian–Pacific Islanders reflects the low prevalence of inherited genetic conditions associated with development of thromboembolism, such as factor V Leiden, in this ethnic

Table 3. Effect of Race, Age, Cancer Stage, and Sex on the Development of Venous Thromboembolism Within 1 Year of Cancer Diagnosis

	Hazard Ratio (95% CI)						
	Race*				Stage†		
Cancer	Hispanic	Asian/PI	African American	Age, 10-y Increments	Regional	Metastatic	Sex, M
Prostate	0.8 (0.5-1.1)	0.4 (0.2-0.8)‡	0.8 (0.6-1.2)	0.9 (0.8-1.1)	1.3 (1.0-1.7)§	1.1 (0.7-1.6)	NA
Breast	0.7 (0.5-1.0)	0.2 (0.1-0.4)‖	0.7 (0.4-1.2)	1.05 (1.0-1.1)‖	1.9 (1.5-2.5)‖	5.2 (3.6-7.3)‖	0.5 (0.2-1.2)
Lung	0.8 (0.6-1.0)	0.4 (0.2-0.6)‖	0.6 (0.5-0.9)‖	0.9 (0.8-0.9)‖	1.9 (1.4-2.6)‖	3.5 (2.7-4.5)‖	1.1 (0.9-1.2)
Colon/rectum	0.8 (0.6-1.1)	0.3 (0.2-0.5)‖	0.8 (0.6-1.2)	1.0 (1.0-1.1)	2.7 (2.1-3.4)‖	4.3 (3.3-5.6)‖	1.0 (0.9-1.2)
Melanoma	NA¶	NA¶	NA¶	1.0 (1.0-1.1)	3.7 (1.1-12.8)§	21.5 (10.1-46.0)‖	1.3 (0.7-2.3)
Lymphoma	1.0 (0.6-1.5)	0.3 (0.1-0.8)§	0.1 (0.0-1.0)§	1.1 (1.0-1.2)‡	2.0 (1.3-3.1)‡	1.4 (0.9-2.1)	1.1 (0.8-1.4)
Uterus	1.2 (0.7-2.3)	0.6 (0.2-1.9)	2.8 (1.5-5.1)‖	1.1 (1.0-1.3)	1.7 (1.0-2.9)	6.1 (3.7-9.8)‖	NA
Bladder	1.4 (0.7-3.0)	0.9 (0.3-2.9)	2.2 (1.0-5.1)	1.1 (0.9-1.3)	3.8 (2.2-6.7)‖	9.6 (5.1-17.8)‖	1.5 (1.0-2.3)
Pancreas	0.7 (0.4-1.0)	0.4 (0.2-0.8)§	0.9 (0.5-1.4)	0.9 (0.8-1.0)§	1.1 (0.6-2.1)	3.3 (1.8-6.2)‖	1.0 (0.8-1.3)
Stomach	0.8 (0.5-1.1)	0.2 (0.1-0.3)‖	1.2 (0.7-1.9)	0.9 (0.8-1.0)§	1.3 (0.8-2.2)	2.8 (1.7-4.5)‖	0.9 (0.7-1.3)
Ovary	0.5 (0.2-1.1)	0.4 (0.2-1.2)	1.8 (1.0-3.3)	1.2 (1.0-1.3)§	2.5 (0.9-7.1)	3.8 (1.7-8.8)‡	NA
Kidney	1.0 (0.6-1.6)	0.4 (0.1-1.4)	1.1 (0.5-2.3)	1.0 (0.8-1.1)	3.1 (1.8-5.1)‖	3.8 (2.3-6.2)‖	1.2 (0.8-1.7)

Abbreviations: CI, confidence interval; NA, not applicable; PI, Pacific Islander.
*Caucasian as reference group.
†Localized disease as reference stage.
‡$P<.01$.
§$P<.05$.
‖$P<.001$.
¶Number of cases too small to estimate.

group.[22,23] There was little difference between Caucasians and African Americans in the incidence of thromboembolism except for a modestly higher risk among cases with uterine cancer and a lower hazard ratio among cases with lung cancer or non-Hodgkin lymphoma.

Sex was not a significant predictor of thromboembolism in any of the cancers analyzed in this large database. Although a recent study reported that men had a higher risk of recurrent idiopathic venous thromboembolism than women, that study specifically excluded cancer patients.[24]

There are several limitations to this study. As mentioned previously, the California Cancer Registry collected limited data on treatment during the period analyzed. Specifically, there was no information about chemotherapy, radiotherapy, or the use of tamoxifen or hormone therapy. Second, there was no information regarding which patients may have received primary thromboprophylaxis, although this was not a routine practice among cancer patients during the period studied. Third, the inclusion of the 265 patients who presented with venous thromboembolism and were concurrently diagnosed with cancer could be viewed as inflating the incidence of thromboembolism among cancer cases. It is possible that acute thromboembolism triggered a cancer workup, resulting in an earlier diagnosis of cancer than in patients without thromboembolism. However, these patients who presented with thromboembolism accounted for only 7% of all the patients who developed thromboembolism within 2 years, and including them does not substantially alter the overall conclusions of this study. Finally, not all cancer types were analyzed, but the 12 cancers included represent approximately 80% of cancer patients in the United States.[25]

The diagnosis of venous thromboembolism was based on *ICD-9-CM* coding in the Patient Discharge Data Set.

Table 4. Effect of Venous Thromboembolism on the Risk of Death Within 1 Year of Cancer Diagnosis Stratified by Stage, Adjusted for Age and Race

	Hazard Ratio (95% CI), by Stage		
Cancer	Local	Regional	Remote
Prostate	5.6 (3.8-8.5)*	4.7 (1.9-11.5)*	2.8 (1.5-5.0)†
Breast	6.6 (3.7-11.8)*	2.4 (1.3-4.5)†	1.8 (1.1-2.9)‡
Lung	3.1 (2.1-4.5)*	2.9 (2.3-3.5)*	2.5 (2.3-2.7)*
Colon/rectum	3.2 (1.8-5.5)*	2.2 (1.7-3.0)*	2.0 (1.7-2.4)*
Melanoma	14.4 (4.6-45.2)*	NA§	2.8 (1.5-5.3)†
Non-Hodgkin lymphoma	3.2 (1.9-5.3)*	2.0 (1.3-3.2)†	2.3 (1.7-3.1)*
Uterus	7.0 (3.4-14.2)*	9.1 (4.8-17.2)*	1.7 (1.0-3.0)‡
Bladder	3.2 (1.7-6.2)*	3.3 (1.7-6.4)*	3.3 (1.8-6.2)*
Pancreas	2.3 (1.2-4.6)‡	3.8 (2.8-5.1)*	2.3 (1.9-2.7)*
Stomach	2.4 (1.1-5.1)‡	1.5 (1.0-2.1)‡	1.8 (1.4-2.3)*
Ovary	11.3 (2.5-51.7)†	4.8 (1.1-20.4)‡	2.3 (1.7-3.0)*
Kidney	3.2 (1.2-8.8)‡	1.4 (0.6-3.2)	1.3 (0.9-2.0)

Abbreviations: CI, confidence interval; NA, not applicable.
*$P<.001$.
†$P<.01$.
‡$P<.05$.
§Not enough venous thromboembolism cases to estimate.

On the basis of previous validation studies, we estimate that among the cases classified as having definite or probable thromboembolism, approximately 90% to 95% had objectively documented disease.[10-12,26,27] The cases classified as having possible thromboembolism (n=1257, 25% of the total) were not included in this analysis, and assuming that 80% to 85% of these cases had documented thromboembolism,[28-30] it is likely that the incidence values reported underestimate the true incidence by approximately 20%.

In summary, this study used population-based data to estimate the incidence and time course of incident venous thromboembolism among patients with common types of cancer, stratified by stage. The development of venous thromboembolism was a significant predictor of death within 1 year for all cancer types analyzed, and this was true for patients with localized, regional-, or metastatic-stage disease. These findings identify potential populations that might be considered for primary thromboprophylaxis, particularly patients with metastatic cancer of the pancreas, stomach, kidney, bladder, uterus, or lung. Further randomized clinical trials are necessary to determine whether thromboprophylaxis reduces mortality or thromboembolic complications or improves quality of life in these high-risk populations.

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