**Venous Thromboembolism After Major Cancer Surgery: Temporal Trends and Patterns of Care**

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**IMPORTANCE**
There is limited data on the prevalence and mortality of venous thromboembolism (VTE) following oncologic surgery.

**OBJECTIVE**
To evaluate the trends, factors, and mortality of VTE following major cancer surgery.

**DESIGN, SETTING, AND PARTICIPANTS**
Patients undergoing colectomy, cystectomy, esophagectomy, gastrectomy, hysterectomy, lung resection, pancreatectomy, or prostatectomy were identified retrospectively using the Nationwide Inpatient Sample between January 1, 1999, and December 30, 2009, resulting in a weighted estimate of 2,508,916 patients.

**MAIN OUTCOMES AND MEASURES**
Venous thromboembolism following major cancer surgery was assessed according to date, patient, and hospital characteristics. The determinants of in-hospital VTE were evaluated using logistic regression analysis.

**RESULTS**
Venous thromboembolism showed an estimated annual percentage increase of 4.0% (95% CI, 2.9% to 5.1%), which contrasts with a 2.4% (95% CI, -4.3% to -0.5%) annual decrease in mortality in VTE after major cancer surgery. In multivariate logistic regression analysis, older age (odds ratio [OR], 1.03; P < .001), female sex (OR, 1.25; P < .001), black race (vs white; OR, 1.56; P < .001), Charlson comorbidity index score of 3 or more (OR, 1.85; P < .001), and Medicaid (vs private insurance; OR, 2.04; P < .001), Medicare (OR, 1.39; P < .001), and uninsured (OR, 1.49; P < .001) status were associated with an increased risk of VTE. Conversely, other (nonwhite and nonblack) race (OR, 0.75; P < .001) was associated with a lower risk of VTE. Among hospital characteristics, urban location (OR, 1.32; P < .001) and teaching status (OR, 1.08; P = .01) were associated with greater odds of VTE. Patients with vs without VTE experienced 5.3-fold greater odds of mortality.

**CONCLUSIONS AND RELEVANCE**
During our study period, VTE events following major cancer surgery increased in frequency; however, associated VTE mortality decreased. Changing VTE detection guidelines and better management of this condition may explain our findings.

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Venous thromboembolism (VTE), which comprises deep vein thrombosis (DVT) and pulmonary embolism (PE), ranks among the leading causes of preventable mortality and morbidity, with 5% to 10% of hospital deaths attributed to PE. 1-2 The annual economic burden of VTE in the United States is estimated at $1.5 billion.3 Major risk factors for VTE include cancer, surgery, advanced age, and trauma.4 Patients with cancer undergoing surgery represent a special population at increased risk of VTE, the incidence of which is estimated at 1.5% to 2.1%.5-8 Moreover, previous investigators have shown that patients undergoing oncologic procedures are at a 2- to 3-fold higher risk of fatal PE relative to their counterparts without cancer.9-12 Past reports have described the prevalence and mortality of VTE following oncologic surgery.13,14 As well as mortality rates following VTE.9 However, these studies were limited by small sample size and homogeneous populations from single-institution series. To address these limitations, we performed a population-level assessment of the likelihood of VTE following major cancer surgery (MCS) for 8 solid cancers. Specifically, we performed time-dependent analyses to establish the temporal trends of VTE in these patients. Moreover, we sought to identify specific patient or hospital characteristics associated with VTE following MCS. Finally, since VTE is known to predispose to in-hospital mortality, we also tested the association between those 2 events.

Methods

Data Source
Relying on the Nationwide Inpatient Sample (NIS), we abstracted hospital discharges in the United States between January 1, 1999, and December 30, 2009. The NIS is a set of longitudinal hospital inpatient databases included in the Healthcare Cost and Utilization Project family, created by the Agency for Healthcare Research and Quality through a federal-state partnership.15 The database includes discharge abstracts from 8 million hospital stays and incorporates patient and hospital information, including patients covered by Medicare, Medicaid, private insurance, and other insurance types.

Each discharge includes up to 15 inpatient diagnoses and procedures per hospitalization. All procedures and diagnoses are coded using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Included patient and sociodemographic characteristics are patient sex, race, age, expected source of payment, outcome (in-hospital mortality), and hospital information (unique hospital identifier, hospital location, and hospital volume). Patients’ socioeconomic status was evaluated using a proxy income, defined by county-specific zip code according to the US Census. In accordance with institutional policy with regard to publicly available data, this study was exempt from institutional review board approval.

Study Population
Eight major surgical oncologic procedures were selected for evaluation of the VTE event: colectomy, cystectomy, esophagectomy, gastrectomy, hysterectomy, lung resection, pancreatectomy, and prostatectomy. Analyses were restricted to cancer diagnoses only. Relying on specific ICD-9-CM procedure codes, each surgical procedure was assessed independently.

Primary Outcome
Venous thromboembolism was defined as the occurrence of DVT and/or PE, according to previously defined criteria.16 Respective disease codes were ICD-9-CM 451.0, 451.1x, 451.2, 451.81, 451.9, 453.4x, 453.8, and 453.9 for DVT and ICD-9-CM 415.x for PE.

Patient and Hospital Characteristics
Available independent variables for analyses included patient age at hospitalization, race, sex, insurance status, baseline comorbidities, median household income by zip code, and hospital location. Information on race was categorized as white, black, Hispanic, other (Asian or Pacific Islander or Native American), or unknown. Insurance status was classified based on the expected primary payer and included Medicare, Medicaid, private insurance, and other insurance types, including those who were uninsured. Patient age was considered a continuous variable. Baseline comorbidities were determined using a Charlson comorbidity index–derived score,17 adapted by Deyo and colleagues.18 Income at the patient level was not available within the NIS. In consequence, we relied on the median household income of the patient’s zip code of residence, derived from the US Census. Four categories were available within the database: (1) less than $25 000, (2) $25 000 to $34 999, (3) $35 000 to $44 999, and (4) $45 000 or more.

Hospital characteristics, including US Census Bureau region (Northeast, Midwest, South, and West), population density (rural vs urban), and teaching status, were obtained from the American Hospital Association Annual Survey of Hospitals. A hospital was considered a teaching institution if it had an American Medical Association–approved residency program, was a member of the Council of Teaching Hospitals, or had a ratio of 0.25 or higher full-time–equivalent interns and residents to non–nursing home beds.19 Annual hospital volume, representing the number of procedures done by each participating institution during every study calendar year, was calculated independently for each of the 8 procedures. Patients were divided according to 4 equal hospital volume quartiles, categorized as very low, low, high, and very high.

Statistical Analysis
Data distribution was adjusted according to the provided NIS population weights to render estimates more accurate nationally. All analyses were performed on the weighted population.

First, descriptive statistics were generated on frequencies and proportions for categorical variables (sex, race, insurance status, median zip code household income, Charlson comorbidity index, annual hospital volume, hospital location, hospital region, and hospital teaching status), stratified according to VTE occurrence. Means, medians, and interquartile ranges were reported for continuously coded variables (age). Independent t tests, χ² tests, and Kruskal-Wallis tests
were used to compare the statistical significance of differences within categorical and continuous variables.

Second, temporal trends in rates were analyzed by the estimated annual percentage change, which uses the least squares linear regression method as suggested by Anderson et al.20

Third, multivariable logistic regression analyses were fitted to predict VTE following MCS. Year of surgery, age, race, baseline Charlson comorbidity index, median zip code household income, hospital location, hospital region, and hospital teaching status were considered covariates. Fourth, separate models were fitted with mortality as the outcome and VTE as an independent variable. Finally, to adjust for clustering within hospitals, we fitted multivariable logistic regression models with generalized estimating equations.21

All statistical analyses were performed using the R statistical package (R Foundation for Statistical Computing), with a 2-sided significance level set at \( P < .05 \).

### Results

#### Baseline Descriptives

A weighted estimate of 2,508,916 patients underwent 1 of the 8 examined procedures. Baseline sociodemographic characteristics in the entire cohort are described in Table 1.

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Table 1. Weighted Descriptive Characteristics of 2,508,916 Patients Older Than 18 Years Undergoing Major Cancer Surgery, Nationwide Inpatient Sample, January 1, 1999, Through December 30, 2009^a

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (%)</th>
<th>Without VTE (%)</th>
<th>With VTE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weighted No. (%) of patients</td>
<td>2,508,916 (100.0)</td>
<td>2,475,507 (98.7)</td>
<td>33,409 (1.3)</td>
</tr>
<tr>
<td>Age, y^b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>65.9 (11.7)</td>
<td>65.9 (11.7)</td>
<td>70.3 (11.9)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>66.0 (58-74)</td>
<td>66.0 (58-74)</td>
<td>72.0 (62-79)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>60.3</td>
<td>60.5</td>
<td>51.3</td>
</tr>
<tr>
<td>Female</td>
<td>39.7</td>
<td>39.5</td>
<td>48.7</td>
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<tr>
<td>Race</td>
<td></td>
<td></td>
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<tr>
<td>White</td>
<td>60.8</td>
<td>60.8</td>
<td>59.3</td>
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<tr>
<td>Black</td>
<td>7.1</td>
<td>7.1</td>
<td>10.0</td>
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<tr>
<td>Hispanic</td>
<td>3.9</td>
<td>3.9</td>
<td>3.7</td>
</tr>
<tr>
<td>Other</td>
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<td>3.7</td>
<td>2.7</td>
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<td>Unknown</td>
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<td>24.5</td>
<td>24.3</td>
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<td>62.6</td>
<td>54.2</td>
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<td>1</td>
<td>24.9</td>
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<td>25.7</td>
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<td>5.1</td>
<td>5.1</td>
<td>4.9</td>
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<td>≥3</td>
<td>7.6</td>
<td>7.5</td>
<td>15.1</td>
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<td>Insurance status</td>
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<tr>
<td>Private</td>
<td>42.2</td>
<td>42.4</td>
<td>25.9</td>
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<tr>
<td>Medicaid</td>
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<td>3.2</td>
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<td>Other</td>
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<td>4.2</td>
<td>3.9</td>
</tr>
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<td>Annual hospital volume</td>
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<tr>
<td>Very low</td>
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<td>23.6</td>
<td>21.8</td>
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<tr>
<td>Low</td>
<td>25.5</td>
<td>25.5</td>
<td>25.5</td>
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<tr>
<td>High</td>
<td>25.4</td>
<td>25.4</td>
<td>25.7</td>
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<tr>
<td>Very high</td>
<td>25.5</td>
<td>25.5</td>
<td>26.8</td>
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<tr>
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<td>10.7</td>
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<td>8.8</td>
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<tr>
<td>Urban</td>
<td>89.3</td>
<td>89.3</td>
<td>91.2</td>
</tr>
<tr>
<td>Hospital region</td>
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</tr>
<tr>
<td>Northeast</td>
<td>21.0</td>
<td>21.0</td>
<td>23.3</td>
</tr>
<tr>
<td>Midwest</td>
<td>24.3</td>
<td>24.3</td>
<td>24.3</td>
</tr>
<tr>
<td>South</td>
<td>35.2</td>
<td>35.2</td>
<td>34.4</td>
</tr>
<tr>
<td>West</td>
<td>19.6</td>
<td>19.6</td>
<td>18.0</td>
</tr>
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<td>45.3</td>
<td>43.7</td>
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<tr>
<td>Teaching</td>
<td>54.7</td>
<td>54.7</td>
<td>56.3</td>
</tr>
</tbody>
</table>

Abbreviations: CCI, Charlson comorbidity index; IQR, interquartile range; VTE, venous thromboembolism.

^a Values are given as percentages unless otherwise indicated. \( P < .001 \) for all.

^b Mann-Whitney test.
VTE After MCS Rates and Trends

During the entire study span, the in-hospital VTE rate was 1.3%. Temporal trends are described in the Figure. Venous thromboembolism events showed a rising annual prevalence of 4.0% (95% CI, 2.9% to 5.1%), while mortality rates in patients with VTE demonstrated a declining annual rate of 2.4% (95% CI, –4.3 to –0.5). Conversely, overall mortality rates in all patients undergoing MCS also showed an equivalent annual decrease in prevalence of 2.4% (95% CI, –2.9% to –2.0%).

Patient Characteristics and VTE After MCS

Multivariable logistic regression analyses predicting the occurrence of VTE after MCS are reported in Table 2. Increased odds of VTE was associated with older age (odds ratio [OR], 1.03; P < .001), female sex (OR, 1.25; P < .001), black race (vs white; OR, 1.56; P < .001), Charlson comorbidity index score of 3 or more (OR, 1.85; P < .001), and non-private insurance status, including Medicaid (OR, 2.04; P < .001), Medicare (OR, 1.39; P < .001), and uninsured (OR, 1.49; P < .001).

Hospital Characteristics and VTE After MCS

In multivariable logistic regression models, urban location (OR, 1.32; P < .001) and teaching hospitals (OR, 1.08; P = .01) were associated with increased odds of VTE. Non-Northeast regions were associated with lower rates of VTE (Midwest: OR, 0.90; P = .01; South: OR, 0.89; P = .001; and West: OR, 0.88; P = .001). Annual hospital volume did not affect the outcome.

Mortality and VTE After MCS

Mortality varied according to cancer type, as shown in Table 3. Overall, patients with VTE after MCS showed a 5.3-fold increase in the risk of mortality relative to patients who did not experience VTE (P < .001 for all procedures). Prostatectomy (3.9%) and hysterectomy (5.2%) were associated with the lowest mortality after VTE, but the effect of VTE on mortality was most pronounced in the following procedures: prostatectomy (OR, 5.42; P < .001) and hysterectomy (OR, 10.93; P < .001). The effect of VTE on mortality was smallest following esophagectomy (OR, 2.01; P = .02) and gastrectomy (OR, 2.81; P < .001). Lung resection (19.8%) and gastrectomy (14.7%) were associated with the highest mortality after VTE.
Venous thromboembolism is a common complication in oncologic care and represents a major cause of preventable death associated with MCS. Among VTE survivors, subsequent complications, such as recurrent VTE and postthrombotic syndrome, have a profound effect on the patient’s quality of life and the costs of health care. In the past decade, the detection and prevention of VTE has been a major health policy concern, and numerous guidelines have been advanced. On the basis of these considerations, we sought to examine population-level trends in VTE prevalence and mortality following MCS. We hypothesized that improvement in the processes of care advanced by new guidelines has led to a decrease in mortality associated with VTE. We also sought to examine hospital and patient factors associated with VTE and disparities in care to establish the areas in greatest need of further improvement.

Several of our findings are noteworthy. First, we report an overall prevalence of in-hospital VTE after MCS of 1.3%, which is comparable to previous reports of 1.5% to 2.1%. Rate differences can be explained by differences in procedures examined, study period, and follow-up. Indeed, a large proportion of VTE cases occurs after discharge; estimates vary between 30% and 56%. Similarly, recurrent VTE events that necessitated a second admission were not accounted for in our study.

Interestingly, temporal trend analyses indicate a rise in the prevalence of VTE after MCS during the study period, whereas the rate of mortality after VTE decreased at the same rate as overall MCS mortality. Our findings are in agreement with 2 previous population-based reports, the first of which reported a 33.1% increase in the prevalence of VTE between 2002 and 2006, and the second recorded a 3.1-fold increase in DVT rates between 1989 and 2006 and a 2.5-fold increase in PE between 1992 and 2006. However, we observed that these increases did not affect mortality. These findings may be explained by the increasing adoption of tests, such as D-dimer assays and spiral computed tomography scanning, which have detected a new subset of nonfatal VTEs. We can further corroborate this with 2 long-term studies that established a plateau in VTE incidence from 1980 through 1995, with a subsequent increase in incidence around 2000. Of note, a sudden spike in mortality was noted in 2007. Since the number of events is relatively low, the reported incidences are more liable to small variations in hospital sampling that occurred during the study years. Indeed, hospitals participating in a given year may not be the same for the following year and so on.

Second, we identify several patient characteristics associated with VTE after MCS at the population level. As expected, regression models showed a significant increase in the odds of VTE for older and sicker patients. Rates of VTE also varied according to race, which has been consistently reported as a predisposing factor for VTE. The difference in recorded VTE rates between black and white patients has been attributed to both genetic variability and socioeconomic factors. Nonetheless, median zip code income, used here as a surrogate for socioeconomic status, was not an independent predictor of VTE in our analyses. On the other hand, the patient’s insurance status was independently associated with the risk of VTE. In adjusted analyses, relative to private insurance, Medicaid fared the worst, followed by uninsured status and Medicare. Similar to the recorded racial disparities, previous studies suggest that insurance-related disparities may be explained by reduced access to health care, specifically high-quality care; these patients may be diagnosed at a more advanced stage and grade, thus being at a higher risk of VTE. In addition, a previous report has shown that non–privately insured and/or black patients have decreased access to high-volume hospitals with specialized and subspecialized procedures. Yet, other reports suggest that certain processes of care are better implemented at high-volume institutions, and these may include the use of thromboprophylaxis and prompt diagnosis and management of VTE. Unfortunately, the NIS did not allow adjustment for tumor stage and grade or for the use of prophylaxis. Although such biases apply to previous population-based contributions, they undermine our ability to identify the root causes of the recorded differences. Specifically, the increased rates of VTE in patients with non–private insurance could be due to reduced access to health care, leading to diagnosis at an advanced cancer stage and/or diminished access to hospitals that use better prophylactic guidelines. If the
results had been adjusted for either prophylaxis or cancer stage, we would have been able to pinpoint the exact cause.

Third, several hospital characteristics affected VTE sequence after MCS. Multivariable logistic regression models detected significant effects with regard to demographic characteristics. Urban hospitals were associated with a 33% increased risk of VTE relative to rural hospitals. Teaching hospitals were also associated with an increased risk of VTE relative to their nonteaching counterparts. One can hypothesize that the ongoing regionalization of cancer care has also led to selective referrals of more complex cases to urban and teaching centers. Indeed, higher rates of VTE would be expected in patients with a higher stage and grade.

Interestingly, regional trends were also recorded, with the Midwest, South, and West reporting lower VTE rates than the Northeast. It is possible that these differences could be ascertained by differences in VTE detection guidelines and thromboprophylaxis that were adopted in different hospital regions. Moreover, it is also possible that subtle differences in cancer stage and grade may explain these findings.

Fourth, we corroborate the relationship between VTE and mortality after MCS. Overall, there is a 5.3-fold increased risk of mortality when VTE is present after MCS (OR, 5.30; P < .001). Mortality associated with VTE was highest for lung resection (19.8%) and gastrectomy (14.7%) and least for prostatectomy (3.9%) and hysterectomy (5.2%). When mortality rates were examined, prostatectomy and hysterectomy showed the strongest effects, with a 56-fold and 10-fold increased probability, respectively. This may be due to the lower stage and grade of prostate and endometrial cancers relative to lung and gastric tumors, which are generally diagnosed at later stages and associated with lower overall survival.

The strength of our analyses relies on the size of the population and the temporal trend analyses during an 11-year time span. Nonetheless, several limitations apply to our study. More important, the NIS data set does not code for tumor stage and grade, nor is it possible to examine the temporality of diagnostic codes. It is possible that some patients might have had VTE at surgery, although such an occurrence would likely be rare. Similarly, a PE diagnosed right before death may have different implications than one diagnosed earlier in the inpatient episode. The location of DVT is another piece of information missing with important clinical ramifications. Specifically, VTEs below the knee may have a lesser clinical significance. Moreover, we were unable to control for several risk factors for VTE such as body mass index, the presence of central venous lines, and estrogen use. For example, occurrence below the knee shows less potential for embolization than proximal events. Finally, it is important to consider that ICD-9-CM codes were used to determine VTE. Claims-based data can underestimate or overestimate the prevalence of VTEs.

Despite these limitations, we were able to corroborate previous studies while adding new insight. We observe that consistently increasing VTE rates recorded during the past decade are likely due to improved detection methods and evolving guidelines. These added cases do not seem to affect mortality rates, at least in the context of MCS. Moreover, we describe several patient and hospital attributes associated with the occurrence of VTEs after MCS. Disparities in VTE prevalence and mortality based on race and insurance coverage highlight the need for improved access to quality health care to avoid a potentially devastating outcome due to preventable VTE.

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**Administrative, technical, and material support:** Sammon, Sun, Shariat, Tian, Kim, Kowalczyk.

**Study supervision:** Karakiewicz, Sun, Sukumar, Hu, Menon, Q.-D. Trinh.

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**REFERENCES**

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