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Full Length Article

Relationship between type of unprovoked venous thromboembolism and cancer location: An individual patient data meta-analysis

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ABSTRACT

Background: Unprovoked venous thromboembolism (VTE) may be the first manifestation of an underlying cancer. We aimed to assess the period prevalence of occult cancer detection stratified by VTE location (deep vein thrombosis [DVT], pulmonary embolism [PE] or both) and the anatomical relationship between occult cancer and VTE.

Methods: Post-hoc analysis of a systematic review and individual patient data meta-analysis of adults with unprovoked VTE with at least 12 months of follow-up. Cancer types were grouped according to thoracic, abdomino-pelvic, or other locations.

Results: A total of 2300 patients were eligible including 1218 with DVT only (53%), 719 with PE only (31%), and 363 with both PE and DVT (16%). The pooled 12-month period prevalence of cancer in DVT only, PE only, and DVT + PE was 5.6% (95% CI, 4.4 to 7.2), 4.3% (95% CI, 2.7 to 6.9), and 5.6% (95% CI, 1.7 to 15.5), respectively. Most occult cancers were located in the abdomen (68.4%). The proportion of patients with an abdomino-pelvic cancer was not different in patients with DVT + PE (81%; 95% CI, 54 to 96) than in those with DVT (68%; 95% CI, 57 to 78) or PE alone (65%; 95% CI, 48 to 79).

Conclusion: The 12-month prevalence of occult cancer was similar in patients with DVT only, PE only, or both. Most cancers were located in the abdomen, and there was no relationship between VTE type and cancer location.

Abbreviations: DVT, deep vein thrombosis; I^2, heterogeneity; OR, odds ratio; PE, pulmonary embolism; VTE, venous thromboembolism

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1. Introduction

Unprovoked venous thromboembolism (VTE) may be the first manifestation of an underlying cancer. Occult cancer screening aims to detect cancer at a potentially curable stage to reduce cancer-related mortality by early treatment. One study suggested that an extensive screening strategy may detect more cancers than a limited screening approach, but others could not confirm these findings [1–5]. Therefore, current clinical guidance suggests a limited occult cancer screening for these patients consisting of medical history, physical examination, limited laboratory testing, chest X-ray, and age- and gender-specific screening tests according to national guidelines [6].

VTE encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE). It is unclear whether the risk of occult cancer is similar in patients presenting with DVT, PE, or both. Imaging modalities used for diagnosis of DVT and PE are different, and may potentially influence occult cancer detection. For example, patients with suspected PE usually undergo computed tomographic pulmonary angiography, which could result in a higher rate of occult cancers detected in the thorax or upper abdomen as compared to patients undergoing compression ultrasonography for suspected DVT. Role of different tumors on the thrombotic cascade allow us discriminate in low or high-risk cancers to develop VTE. Furthermore, it remains unknown if there is an anatomical relationship between occult cancer and VTE locations. For example, pelvic cancers could predispose patients to DVT due to vein compression. Intuitively, clinicians may think that patients with PE are more likely to be diagnosed with occult cancer during follow-up. As a result, they may use different screening approaches for patients with PE than for those with DVT. Therefore, we assessed the 12-month period prevalence of occult cancer detection based on the type of VTE (DVT, PE, or both) and assessed the relationship between the locations of unprovoked VTE (DVT, PE, or both) and occult cancers.

2. Methods

2.1. Study design

This was a post-hoc analysis of data previously collected for a systematic review and individual patient data meta-analysis (PROSPERO: CRD42016033371) [7]. Two reviewers (N.v.E. and NK) independently assessed the potential risks of bias for each study using the Newcastle–Ottawa Scale and the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies, revised) tool [8], which was adapted to the present research question (e-Appendix 1 and e-Appendix 2). Disagreements were resolved by consensus.

2.2. Outcome assessment

The primary objective of the present analysis was to estimate the period prevalence of occult cancer at 12 months in patients with unprovoked DVT, PE, or both, defined as the proportion of patients in whom solid or hematological cancer (excluding benign tumors) was objectively confirmed by histology or cytology or unequivocally diagnosed by imaging or tumor markers. All studies that enrolled patients before any screening procedures were included in the primary analyses. We also evaluated the association between the locations of unprovoked VTE (DVT, PE, or both) and occult cancers. Cancer detection refers to detection by screening tests with subsequent confirmation by additional, targeted testing. Cancer diagnosis refers to all cases confirmed either at screening or during follow-up. Limited screening was defined as the combination of medical history, physical examination, basic blood tests (at least complete blood count, creatinine, and liver enzymes), chest radiography, and age- and sex-specific tests, such as mammography or prostate-specific antigen testing. Results of limited screening were considered positive if they led to additional investigations for possible cancer detection. Extensive screening strategies were heterogeneous across the studies but often included imaging with CT-scanning or ultrasonography of the abdomen or a whole-body PET-CT [9]. Cancer had to be histologically confirmed. Cancer types were grouped according to thoracic location (lung, breast, esophageal, or thyroid cancer), abdomino-pelvic location (stomach, pancreatic, colorectal, hepatobiliary, renal, bladder, adrenal, endometrial, prostate, ovarian, or testicular cancer), or other locations (sarcoma, brain cancer, melanoma, head- or neck cancer, cancer of unknown primary, or hematological cancer) depending on primary tumor location. The period prevalence of occult cancer detection was also stratified by gender (male vs. female), age (≤70 vs. > 70 years), and smoking habit (non-smoker vs. former or current smoker).

2.3. Statistical analysis

All patients enrolled with lower extremity DVT and/or PE were included in the analyses. Summary probability estimates were obtained through a one-stage meta-analysis using a generalized linear mixed-effects model, in which a study-specific random effect was included to account for the clustering of observations within studies. Subgroup differences were analyzed with an indicator variable as a fixed effect. When analyzing the effect of screening type, we added a random effect because of the differences in extensive screening strategies across studies. Time to cancer detection during a maximum of 2 years of follow-up was estimated separately for each study with Kaplan–Meier curves, censoring the time to detection in case of death, loss to follow-up, or end of follow-up. We did a two-stage meta-analysis to analyze heterogeneity (I^2) across the studies. Forest plots were generated to visualize potential between-study heterogeneity.

All analyses were undertaken on an intention-to-screen basis and performed in R, version 3.3.2 (R Foundation for Statistical Computing), by using the *lme4* package, version 1.1–12, for the mixed-effects models. Methods have been previously described in detail [7,9].

3. Results

Of the 2316 patients, 16 (0.7%) were excluded from the dataset because they had upper extremity DVT. Of the remaining 2300 patients, 1218 (53%) had DVT only, 719 (31%) had PE only, and 363 (16%) had both PE and DVT. Mean age was 60 years and 61% were men. Clinical characteristics and outcomes stratified by type of VTE are provided in Table 1.

In studies that enrolled patients before screening (n = 1987), the pooled 12-month period prevalence of cancer, in patients with DVT only, was 5.6% (95% CI, 4.4 to 7.2; I^2: 0%), of which 3.7% (95% CI, 2.7 to 5; I^2: 0%) was detected at initial screening (Table 2; Fig. 1 and e-Fig. 1). The risk of a cancer diagnosis in the first 12 months was 6.6% (95% CI, 4.8 to 9; I^2: 0%) in patients with DVT receiving extensive screening compared to 4.4% (95% CI 2.9% to 6.7%; I^2: 0%) in those receiving a more limited screening (odds ratio [OR] 1.4; 95% CI, 0.9 to 2.3; P = 0.15).

In studies that enrolled patients before screening, the pooled 12-month period prevalence of cancer, in patients with PE only, was 4.3% (95% CI, 2.7 to 6.9; I^2: 14.1%), of which 3% (95% CI, 1.6 to 5.9%; I^2: 37%) was detected at initial screening (Table 2; Fig. 1). The risk of a cancer diagnosis in the first 12 months in PE patients receiving extensive screening was 4.3% (95% CI, 2.7 to 6.8; I^2: 0%) as compared to 4.5% (95% CI, 2.2 to 9.0; I^2: 48.5%) in those receiving a more limited screening (OR, 1.0; 95% CI, 0.5 to 1.9; P = 0.93) (e-Figs. 1–5).

In studies that enrolled patients before screening, the pooled 12-month period prevalence of cancer was 5.6% (95% CI, 1.7 to 15.5; I^2: 63%), in patients with both PE and DVT, of which 3.7% (95% CI, 2.1 to 6.5; I^2: 19%) was detected at initial screening (Table 2; Fig. 1). In this group, the risk of a cancer diagnosis in the first 12 months was 6.5% (95% CI, 2.2 to 17.8%; I^2: 46.8%) in patients receiving extensive screening compared to 3.3% (95% CI, 1.4% to 7.7%; I^2: 0%) in those

Table 1
Clinical characteristics and outcomes of unprovoked VTE patients by VTE location.

	DVT (n = 1218)	PE (n = 719)	DVT plus PE (n = 363)	VTE (n = 2300)
Age, mean (SD), y	59.9 (14.7)	58.2 (16)	62.8 (15.1)	59.8 (15.3)
Male, n (%)	781 (64.1%)	409 (56.9%)	215 (59.2%)	1405 (61.1%)
Smoking				
Current of former smoker, n (%)	489 (40.1%)	270 (37.6%)	131 (36.1%)	890 (38.7%)
Never smoked, n (%)	504 (41.4%)	325 (45.2%)	157 (43.3%)	986 (42.9%)
Missing, n (%)	225 (18.5%)	124 (17.2%)	75 (20.7%)	424 (18.4%)
Previous VTE, n (%)	63 (5.2%)	69 (9.6%)	60 (16.5%)	192 (8.3%)
Lost to follow-up, n (%)	24 (2%)	13 (1.8%)	8 (2.2%)	45 (2%)
Death, n (%)	69 (5.8%)	28 (3.9%)	14 (3.9%)	111 (4.9%)

Abbreviations: VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism; SD: standard deviation.

Table 2
Pooled period prevalence of cancer by VTE location.

	Estimate	95% CI	I^2	P-value
Pooled period prevalence of cancer in the first 12 months after VTE				
DVT	5.6%	4.4–7.2%	0%	0.98
PE	4.3%	2.7–6.9%	14.1%	0.32
DVT plus PE	5.6%	1.7–15.5%	63%	0.02
Pooled prevalence of cancer at screening				
DVT	3.7%	2.7–5%	0%	0.63
PE	3.0%	1.6–5.9%	37%	0.15
DVT plus PE	3.7%	2.1–6.5%	19%	0.29
Pooled period prevalence of cancer in the first 12 months after limited screening				
DVT	4.4%	2.9–6.7%	0%	0.93
PE	4.5%	2.2–9.0%	48.5%	0.41
DVT plus PE	3.3%	1.4–7.7%	0%	0.73
Pooled period prevalence of cancer in the first 12 months after extensive screening				
DVT	6.6%	4.8–9%	0%	0.95
PE	4.3%	2.7–6.8%	0%	0.67
DVT plus PE	6.5%	2.2–17.8%	46.8%	0.09

I^2 is a measure of heterogeneity.
Abbreviations: VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism; CI: confidence interval.

receiving a more limited screening (OR, 2.1; 95% CI, 0.7 to 6.2; P = 0.15) (Fig. 1 and e-Figs. 1–5).

During the first 12 months, patients with DVT and those with both DVT and PE who were current or former smokers did not have a significantly higher risk of being diagnosed with cancer than those who never smoked: 3.3% (95% CI, 1.7 to 6.3) vs. 3.9% (95% CI, 1.8 to 8.0), corresponding to a summary adjusted odds ratio of 0.73 (95% CI, 0.30 to 1.75) (e-Fig. 6). The 12-month period prevalence of a cancer diagnosis was significantly higher in patients of 70 years or older compared to those younger than 70 years: 7.8% (95% CI, 4.5 to 13.2) vs. 3.3% (95% CI, 1.8 to 6.0) corresponding to a summary adjusted odds ratio of 0.46 (95% CI, 0.21 to 1.04) (e-Fig. 7).

3.1. Cancer locations

The most frequent cancer location was colon (16%), followed by lung (14%), pancreas (11%), and hematological cancer (11%). Solid cancers were stage 3 and 4 according to the American Joint Committee on Cancer in 11% and 48% of patients, respectively (Table 3). Cancer was located in the abdomen, chest, or other locations in 68.4%, 25.3%, and 6.3% of patients, respectively. The proportion of cancers with an abdomino-pelvic location was non-significantly higher in patients with DVT and PE (13/16; 81.2%; 95% CI, 54.3 to 96) than in those with DVT only (68%; 95% CI, 57 to 78; P = 0.15) or PE only (65%; 95% CI, 48 to 79; P = 0.12) (Table 4). This finding was consistent when the analysis was restricted to cancers detected at screening.

4. Discussion

The present individual patient data meta-analysis of ten prospective studies showed that the 12-month period prevalence of cancer after an unprovoked VTE was similar among patients with DVT only, PE only, or both. Two-thirds of the cancers diagnosed were localized in the abdomen. No relationship between the locations of VTE and occult cancers was observed.

This study confirms that there is no difference in the prevalence of occult cancer according to VTE location (DVT vs. PE). These findings are in line with findings from some studies [10,13], while in disagreement with others [11–13]. For example, an observational study conducted by Ferreyro and colleagues reported a rate of occult cancer detection following DVT and PE of 8.8% and 10.9% (P = 0.27), respectively [11]. Similarly, another retrospective study reported a rate of occult cancer detection following DVT and PE of 10.8% and 19.4% (P = 0.06), respectively [12]. Finally, another study reported 2.8 (95% CI, 2.6 to 2.9) for DVT and 3.3 (95% CI, 3 to 3.5) for PE (P = 0.06), during the first year [13]. In contrast, a prospective study reported a correlation between occult cancer detection and a diagnosis of DVT and of DVT + PE, but not in patients with PE only [10]. A study by Sorensen and colleagues demonstrated that the risk of cancer after 1-year follow-up was similar in patients with DVT (1.1%) and in those with PE (1.2%) [14]. Our observation of a similar risk of cancer in patients with DVT and PE could be clinically relevant because, intuitively, clinicians may think that patients with PE are more likely to be diagnosed with occult cancer during follow-up. As a result, different screening approaches could be used for patients with PE than for those with DVT, while this appears not to be justified based on the absolute risk.

Our results also do not support an association between the locations of the index VTE and occult cancers. For example, patients with PE are not more likely to have occult cancers detected in a thoracic or abdomino-pelvic location. Interestingly, just only one-third of the occult cancers detected in patients with PE were only located in the thorax. This paradox can be potentially explained by the fact that in patients with PE, enrolment in the studies for occult cancer screening was not considered in most of cases if CT-scan showed findings of cancer, because no benefit of screening could be obtained.

A strength of this study is the use of patient-level data from ten studies including 2300 patients of whom > 100 were diagnosed with occult cancers. We used a one-stage meta-analysis, which appears to be more appropriate in the setting of low numbers of events while it also allows for adjusting of confounders. Some period prevalence estimates had moderate heterogeneity. Sensitivity analyses, could not be performed due to the low number of events

A few limitations of our analysis should be acknowledged. First, despite the availability of patient-level data, there were differences across the studies with regard to patient selection, patient characteristics, and screening strategies [8]. These differences could have resulted in cancers being diagnosed sooner or later, but it likely did not influence the proportion of cancer diagnosed in a certain location.

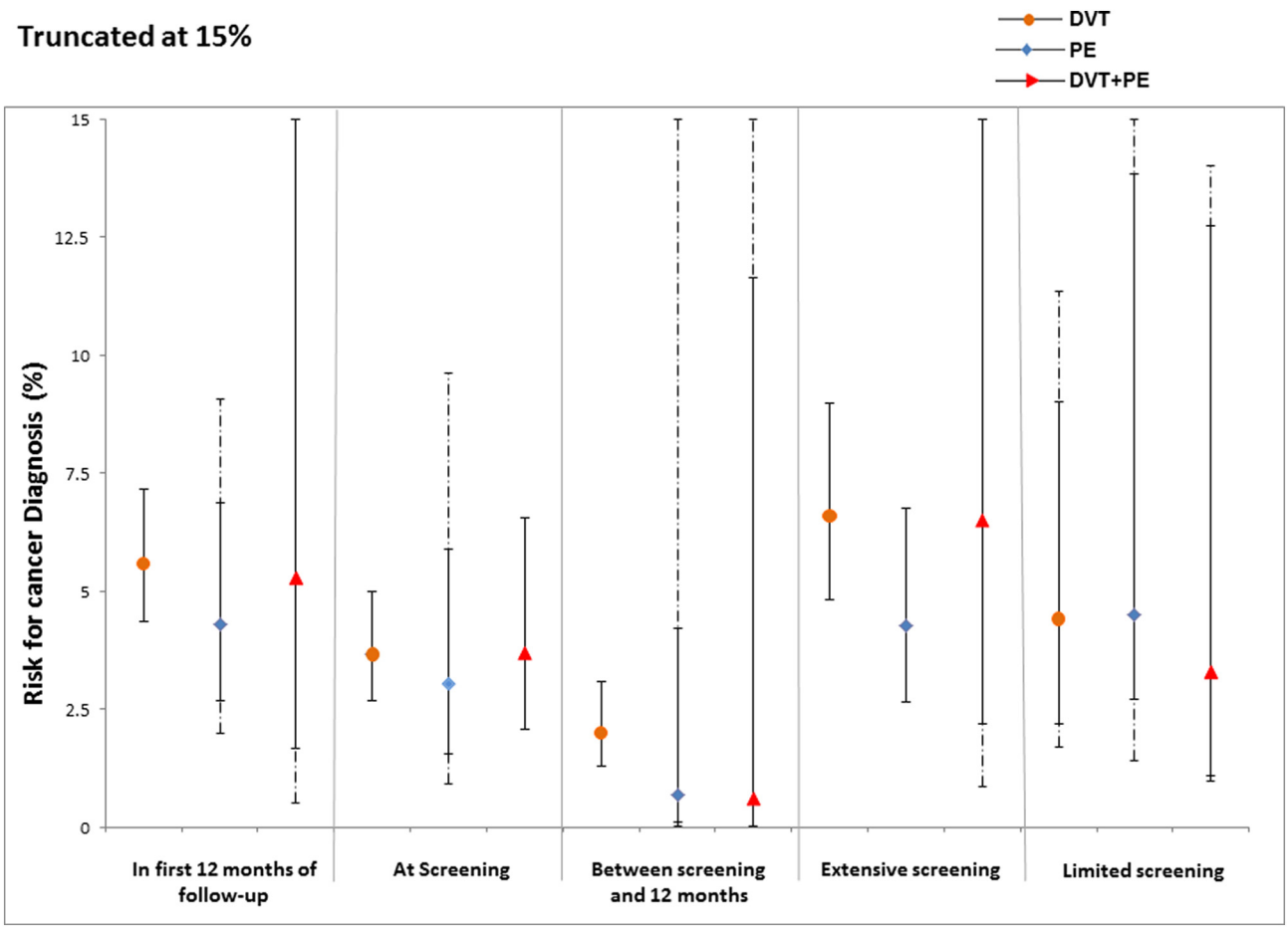

Fig. 1. Period prevalence of cancer, according to time points and VTE locations. Solid error bars represent the 95% confidence intervals and dashed error bars represent the 95% prediction interval. The y-axis is truncated at 15%.

Second, some additional analyses are based on relatively small numbers of event rates resulting in wide confidence intervals that reflect the uncertainty around the estimates. As a result, some of the comparisons may have been underpowered to detect significant differences. Third, we arbitrarily classified the cancer location according to three groups, but this was considered a practical way to include different cancer from a clinical point of view. Fourth, patients with DVT may have received CT-scanning of the chest, which could bias potential differences in location of occult cancer to the null if only compression ultrasonography would have been performed. Fifth, patients with PE confirmed by CT-scanning in whom a concomitant cancer was diagnosed were probably excluded from many of the studies used for this analysis. Sixth, standardized diagnostic imaging was not performed to diagnosed DVT in patients with confirmed PE or vice versa in the included studies. This could have potential lead to misclassification bias. Our study is pragmatic and focused only on symptomatic VTE in order to reflect current clinical practice. Two of the included studies performed computed tomography of the thorax as part of their extensive occult cancer screening and, hence, patients undergoing extensive screening could potentially have more PE diagnosis [2,15]. Interestingly, the proportion of patients diagnosed with PE in combination with DVT were similar in both groups which provide reassurance that misclassification is unlikely [2].

Although the prevalence of occult cancer in patients with unprovoked VTE is substantial, an extensive occult cancer screening strategy does not appear to be beneficial [8]. The PROSPR consortium suggests a five-step approach to evaluate and improve cancer screening, which can be applied to the setting of unprovoked VTE [16–18]. The first step is to identify high-risk patients. Several works have identified risk factors associated with occult cancer detection among patients with VTE, of which age seems to be most important [1,9,11,19–22]. Our results are consistent with the previous literature and demonstrate that age is an important predictor of occult cancer detection irrespective of the location of the index VTE. In addition to identifying a high-risk population, it is also crucial to know where to look for, and our study adds new data on this knowledge gap.

In summary, the 12-month period prevalence of occult cancer is not different among patients with unprovoked DVT, PE, or both. Overall, two-thirds of occult cancer detected will be located in the abdomen, but there is no relationship between locations of VTE and occult cancers.

Acknowledgments

Author contributions

Dr. Jara-Palomares confirms that the study objectives and procedures were honestly disclosed. Moreover, he has reviewed study execution data and confirms that procedures were followed to an extent that convinces all authors that the results are valid and generalizable to a population similar to that included in this study. L. Jara-Palomares had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; Study concept and design: L. Jara-Palomares, N. van Es and M. Carrier; Acquisition, analysis, or interpretation of data: All authors; Drafting of the manuscript: All authors; Critical revision of the manuscript for important intellectual content: All authors; Statistical analysis: J. M. Praena-Fernandez and L. Jara-Palomares; Study supervision: L. Jara-Palomares, N. van Es and M. Carrier.

Table 3
Cancer types and stages.

	Overall n/N = 151/2316[a] No. (%)	In first year n/N = 101/2001[b] No. (%)	Beyond first year n/N = 22/1624[a] No. (%)	Detected by limited screening tests n/N = 54/2001[b] No. (%)	Detected by extensive screening tests n/N = 17/2001[b] No. (%)
Solid cancer	136 (90)	90 (89)	18 (82)	47 (87)	16 (94)
Thorax location					
Lung	21 (15)	15 (14)	1 (5.6)	7 (15)	2 (13)
Breast	7 (5.1)	5 (4.7)	1 (5.6)	4 (8.5)	0 (0)
Esophagus	3 (2.2)	2 (1.9)	0 (0)	1 (2.1)	0 (0)
Thyroid	2 (1.5)	0 (0)	0 (0)	0 (0)	0 (0)
Abdomino-pelvic location					
Stomach	7 (5.1)	3 (2.8)	0 (0)	1 (2.1)	1 (6.2)
Endometrial	6 (4.4)	5 (4.7)	1 (5.6)	4 (8.5)	0 (0)
Bladder	6 (4.4)	2 (1.9)	3 (17)	1 (2.1)	0 (0)
Hepatobiliary	6 (4.4)	5 (4.7)	0 (0)	1 (2.1)	3 (19)
Prostate	13 (9.6)	10 (9.4)	2 (11.1)	7 (15)	0 (0)
Renal	9 (6.6)	4 (3.8)	1 (5.6)	2 (4.3)	1 (6.2)
Pancreas	14 (10)	11 (11)	0 (0)	6 (13)	2 (13)
Colorectal	26 (19)	17 (16)	7 (39)	7 (15)	5 (31)
Ovarian	2 (1.5)	1 (0.9)	0 (0)	1 (2.1)	0 (0)
Testicular	1 (0.7)	1 (0.9)	0 (0)	0 (0)	0 (0)
Adrenal	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)
Other location					
Sarcoma	1 (0.7)	0 (0)	1 (5.6)	0 (0)	0 (0)
Brain	1 (0.7)	0 (0)	1 (5.6)	0 (0)	0 (0)
Unknown primary	3 (2.2)	3 (2.8)	0 (0)	3 (6.4)	0 (0)
Melanoma	2 (1.5)	2 (1.9)	0 (0)	1 (2.1)	0 (0)
Head/neck	2 (1.5)	2 (1.9)	0 (0)	0 (0)	1 (6.2)
Two tumors	3 (2.2)	2 (1.9)	0 (0)	1 (2.1)	0 (0)
Ovarian and uterus	1 (0.7)	1 (0.9)	0 (0)	1 (2.1)	0 (0)
Uterus and breast	1 (0.7)	1 (0.9)	0 (0)	0 (0)	0 (0)
Breast and lung	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)
Hematological cancer	15 (10)	11 (11)	4 (18)	7 (13)	1 (6)
Lymphoma	9 (59.7)	1 (64.1)	2 (50)	5 (71)	1 (100)
Acute leukemia	3 (20)	3 (27)	0 (0)	1 (14)	0 (0)
Polycythemia vera	2 (13)	1 (9.1)	1 (25)	1 (14)	0 (0)
Multiple myeloma	1 (6.7)	0 (0)	1 (25)	0 (0)	0 (0)
Solid cancer staging					
Stage 0	5 (3.7)	4 (4.4)	1 (5.6)	3 (6.4)	0 (0)
Stage 1	31 (23)	22 (24)	5 (28)	10 (21)	4 (25)
Stage 2	20 (15)	10 (11)	5 (28)	3 (6.4)	4 (25)
Stage 3	23 (17)	10 (11)	1 (5.6)	6 (13)	2 (13)
Stage 4	56 (41)	43 (48)	6 (33)	25 (53)	5 (31)
Unknown	1 (0.7)	1 (1.1)	0 (0)	0 (0)	1 (6.2)

[a] Data from all ten studies (N = 2316).
[b] Data from seven studies enrolling patients prior to screening (N = 2001).

Table 4
Comparison between location of unprovoked VTE (DVT, PE, or both) and occult cancer.

Cancer location	DVT (n = 1218)	PE (n = 719)	DVT plus PE (n = 363)	VTE (n = 2300)
Thorax, n (%)	20 (25.3%)	12 (30%)	2 (12.5%)	34 (25.2%)
Abdomino-pelvic, n (%)	54 (68.4%)	26 (65%)	13 (81.2%)	93 (68.9%)
Other, n (%)	5 (6.3%)	2 (5%)	1 (6.2%)	8 (5.9%)

Abbreviations: VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism.

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Disclosures

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Appendix A. Supplementary data

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