

Sex Differences in Patients With Occult Cancer After Venous Thromboembolism

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Luis Jara-Palomares, MD, PhD¹, Remedios Otero, MD, PhD¹,
David Jiménez, MD, PhD², Juan Manuel Praena-Fernández, PhD³,
Agustina Rivas, MD⁴, Carme Font, MD, PhD⁵, Philip S. Wells, MD⁶,
Raquel López-Reyes, MD⁷, José González-Martínez, MD⁸,
and Manuel Monreal, MD, PhD⁹

Abstract

In patients with venous thromboembolism (VTE), male sex has been associated with an increased risk of occult cancer. The influence of sex on clinical characteristics, treatment, cancer sites, and outcome has not been thoroughly investigated yet. We used the Registro Informatizado Enfermedad TromboEmbólica registry to compare the clinical characteristics, treatment strategies, cancer sites, and clinical outcomes in patients with VTE having occult cancer, according to sex. As of June 2014, 5864 patients were recruited, of whom 444 (7.6%; 95% confidence interval: 6.8-8.2) had occult cancer. Of these, 246 (55%) were men. Median time elapsed from VTE to occult cancer was 4 months (interquartile range: 2-8.4), with no sex differences. Women were older, weighed less, and were less likely to have chronic lung disease than men. The most common cancer sites were the lung ($n = 63$), prostate ($n = 42$), and colorectal ($n = 29$) in men and colorectal ($n = 38$), breast ($n = 23$), uterine ($n = 18$), hematologic ($n = 17$), or pancreas ($n = 15$) in women. Men were more likely to have lung cancer than women (2.18% vs 0.30%; $P < .01$) and less likely to have pancreatic cancer (0.17% vs 0.5%; $P = .03$). Interestingly, breast cancer was more likely found in women aged ≥ 50 years than in those aged < 50 years (0.97% vs 0.14%; $P = .03$). This study highlights the existence of sex differences in patients with VTE having occult cancer. One in every 2 men had lung, prostate, or colorectal cancer. In women, there is a heterogeneity of cancer sites, increasing risk of breast cancer in those aged > 50 years.

Keywords

neoplasm, venous thromboembolism, pulmonary embolism, deep vein thrombosis, sex

Introduction

In a recent study by our group, we built a prognostic model to identify which patients with venous thromboembolism (VTE) were at an increased risk of occult cancer.¹ On multivariable analysis, male sex, age > 70 years, chronic lung disease, anemia, and raised platelet count at baseline were significantly associated with an increased risk of occult cancer, while prior VTE and recent surgery were associated with a lower risk. Then, we built a prognostic score assigning points to each variable according to β coefficient. Among patients scoring ≤ 2 points, the prevalence of occult cancer was 5.8% (241 of 4150 patients). Among those scoring ≥ 3 points, the prevalence was 12% (203 of 1713 patients). However, the influence of sex on clinical characteristics, treatment strategies, cancer site, and clinical outcomes was not reported.

The Registro Informatizado de Enfermedad TromboEmbólica (RIETE) registry is an ongoing, multicenter, international observational registry of consecutive patients with objectively confirmed acute VTE. Data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of

¹ Medical Surgical Unit of Respiratory Diseases, CIBERES, Hospital Virgen del Rocío, Seville, Spain

² Respiratory Department, Ramón y Cajal Hospital and Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain

³ Statistics, Methodology and Research Evaluation Unit, Andalusian Public Foundation for Health Research Management, Hospital Virgen del Rocío, Seville, Spain

⁴ Department of Pneumology, Hospital Universitario Araba, Álava, Spain

⁵ Department of Medical Oncology, IDIBAPS/Translational Genomics and Targeted Therapeutics in Solid Tumors, Hospital Clinic, Barcelona, Spain

⁶ Department of Medicine, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ontario, Canada

⁷ Department of Pneumology, Hospital Universitari i Politècnic La Fe, Valencia, Spain

⁸ Department of Internal Medicine, ALTHAIA, Xarxa Assistencial de Manresa, Barcelona, Spain

⁹ Department of Internal Medicine, Hospital Universitario Germans Trias i Pujol de Badalona, Universidad Católica de Murcia, Barcelona, Spain

Corresponding Author:

Luis Jara-Palomares, Medical Surgical Unit of Respiratory Diseases, Hospital Virgen del Rocío, CIBERES, Av Manuel Siurot s/n, Seville, CP 41013, Spain.
Email: luisoneumo@hotmail.com

recurrent VTE, bleeding and mortality, and risk factors for such outcomes.²⁻⁵ The aim of the current study was to compare the clinical characteristics, treatment strategies, cancer sites, and clinical outcomes in patients with VTE having occult cancer, according to sex.

Material and Methods

Inclusion Criteria

Consecutive patients with symptomatic, acute deep vein thrombosis (DVT) or pulmonary embolism (PE), confirmed by objective tests, were enrolled in RIETE. Patients were excluded if they were currently participating in a therapeutic clinical trial with a blinded therapy. All patients (or their relatives) provided written or oral consent for participation in the registry, in accordance with local ethics committee.

Data were recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. The coordinating center assigned patients with a unique identification number to maintain patient confidentiality and was responsible for all data management. Data quality was regularly monitored electronically, including checks to detect inconsistencies or errors, which were resolved by contacting the local coordinators. Data quality was also monitored by periodic visits to participating hospitals by contract research organizations that compared medical records with the submitted data.

Study Design

We performed a post hoc analysis from a case-control study within a cohort of patients with VTE included in the RIETE registry.¹ Patients with no cancer at the moment of the VTE event were followed up for at least 2 years or until cancer was diagnosed. We defined occult cancer as a cancer diagnosed beyond the first 30 days after VTE. For diagnosing cancer, tissue biopsy was always required. We analyzed and compared the clinical characteristics, treatment strategies, cancer sites, and clinical outcomes in patients with VTE having occult cancer, according to sex.

Baseline Variables

Patients enrolled in the RIETE registry had data collected from around the time of VTE diagnosis that included but were not limited to age; sex; weight; presence of coexisting conditions such as chronic heart or lung disease; recent (<30 days before VTE) major bleeding; presence of risk factors for VTE, including recent immobility (defined as nonsurgical patients assigned to bed rest with bathroom privileges for >4 days in the 2 months before VTE diagnosis); surgery (defined as those who had undergone major surgery in the 2 months before VTE); extent of the venous thrombosis (distal thrombosis was thrombosis confined to the infrapopliteal veins); clinical signs and symptoms on admission; and laboratory results at baseline that included hemoglobin levels, platelet count, and serum

creatinine at baseline. Anemia was defined as hemoglobin levels <13 g/dL for men and <12 g/dL for women.

Treatment and Follow-Up

Patients were managed according to the current clinical practice of each participating hospital (ie, there was no standardization of treatment). The type, dose, and duration of anticoagulant therapy were recorded. During each visit, any signs or symptoms suggesting cancer, symptomatic VTE, or major bleeding were noted. In patients with suspected malignancy, the attending doctors decided what diagnostic tests to be performed.

Statistical Analysis

Quantitative variables are expressed as mean (standard deviation), and the qualitative variables are expressed as percentages. For confidence intervals of 95% (95% CI), we used the Clopper-Pearson exact method. We used the Student *t* test (or Mann-Whitney *U* test when appropriate) and the χ^2 test (or Fisher exact test when appropriate) to compare continuous or categorical variables. We analyzed the time to occult cancer diagnosis using the Kaplan-Meier method (Mantel-Cox log-rank test). Receiver-operator characteristic curve analyses (C-statistic) were generated. We also estimated the clinical usefulness and net benefit of the new predictive models using decision curve analysis, as described by Vickers et al.⁶ For the statistical analysis, we used the IBM SPSS Statistics program (version 19; SPSS Inc, Chicago, Illinois), and a 2-sided *P* < .05 was considered to be statistically significant.

Results

As of June 2014, 5864 patients were followed up for at least 2 years or until they were diagnosed with occult cancer. Of these, 444 (7.6%; 95% CI: 6.90-8.28) were diagnosed with cancer beyond the first 30 days of VTE (occult cancer): 246 (55%) were men and 198 women. Median time elapsed from VTE to occult cancer was 4 months (interquartile range [IQR]: 2-8.4 months), with no differences between men and women (4.2, IQR: 2-8.4 months vs 3.9, IQR: 2-7.7 months, respectively; *P* = .76). However, some differences were observed in time to cancer diagnosis using log-rank test (*P* < .001; Figure 1). At the moment of occult cancer diagnosis, 41% were metastatic, with nonsignificant differences according to sex (males 40% vs females 43%; *P* = .6). Clinical characteristics, attending sex, are in Table 1. In Figure 2, we show a decision tree according to sex and score. There were no sex differences in risk factors for VTE (Table 2), and 2 in every 3 patients were on therapy with vitamin K antagonists when the cancer was diagnosed, with no sex differences either.

Data comparing accuracy of the score according to sex are shown in Table 3, where we can observe better results in male, with better sensitivity, odds ratio, positive predictive value, a C-statistic 0.64 (95% CI: 0.6-0.68), and a number needed to

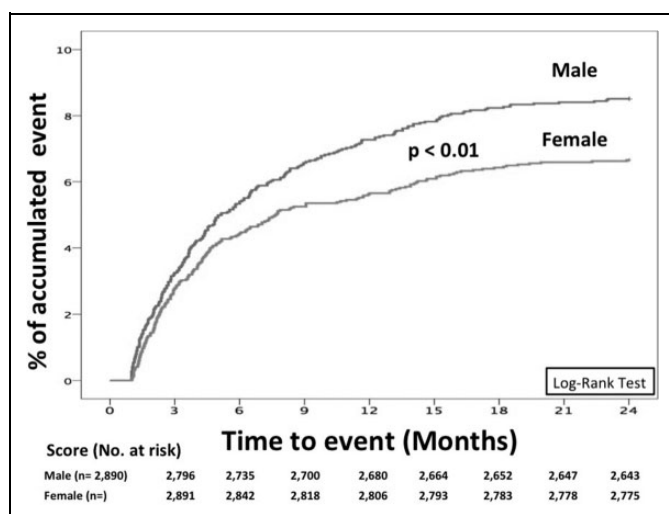


Figure 1. Cumulative rates of occult cancer according to sex. Time-to-event data.

Table 1. Clinical Characteristics, Laboratory Findings, and Outcomes of Patients With Occult Cancer, Attending Sex.

Variable	Men	Women	P
Patients, n	246	198	
Clinical characteristics			
Age, years, mean (SD)	68.9 (12.0)	73.0 (13.7)	<.001
Weight, kg, mean (SD)	77.1 (13.3)	70.0 (13.1)	<.001
Height, cm, mean (SD)	169 (7)	157 (7)	<.001
Comorbid diseases			
Chronic heart failure, n (%)	13 (5.3)	17 (8.6)	.168
Chronic lung disease, n (%)	55 (22.4)	19 (9.6)	<.001
Recent major bleeding, n (%)	4 (1.6)	5 (2.5)	.504
Signs and symptoms			
Cough, n (%)	31 (12.9)	20 (10.3)	.411
Hemoptysis, n (%)	15 (6.2)	2 (1)	.005
Dyspnea, n (%)	90 (37.3)	101 (51.5)	.003
Syncope, n (%)	15 (6.2)	13 (6.7)	.84
Chest pain, n (%)	59 (24.5)	51 (26.3)	.666
Lower limb pain, n (%)	147 (60)	98 (49.7)	.031
Swelling, n (%)	155 (63.5)	106 (53.8)	.039
Side DVT			
Right, n (%)	91 (47.9)	55 (42)	
Left, n (%)	88 (46.3)	67 (51.1)	
Bilateral, n (%)	11 (5.8)	9 (6.9)	
Proximal DVT, n (%)	149 (82.3)	108 (87.8)	.194
Laboratory findings, n (%)			
Hemoglobin levels (g/dL)	13.5 (2.0)	12.3 (1.9)	<.001
Leukocyte count (×1000/mm ³), mean (SD)	9.6 (3.1)	9.5 (3.7)	.26
Platelet count (×1000/mm ³), mean (SD)	242 (103)	261 (94)	.004
Creatinine levels, mg/dL, mean (SD)	1.32 (0.73)	1.16 (0.59)	.013
Outcomes, n (%)			
Recurrences	35 (14.2%)	28 (14.1%)	.98
Major bleeding	16 (6.5%)	17 (8.6%)	.39
Death	64 (26%)	68 (34.3%)	.056

Abbreviations: DVT, deep vein thrombosis; SD, standard deviation.

screen of 14 (95% CI: 11-20). In women, C-statistic was 0.61 (95% CI: 0.57-0.65) and the number needed to screen was 28 (95% CI: 16-94). Net benefit in males and females was 1.9% and 0.6%, respectively. There were no differences in Cox proportional models. A decision curve model was built to show the net benefit of screening based on the prediction model (Supplemental Figure).

The most common cancer sites in men were the lung (n = 63), prostate (n = 42), and colorectal (n = 29), accounting for 54% of all cancers in men. Among women, the most common sites were colorectal (n = 38), breast (n = 23), uterine (n = 18), hematologic (n = 17), and pancreas (n = 15), accounting for 56% of all cancers. When comparing cancer sites according to sex, men were more likely to have lung cancer than women (2.18%, 95% CI: 1.68-2.78 vs 0.30%, 95% CI: 0.14-0.57; $P < .01$) and less likely to have pancreatic cancer (0.17%, 95% CI: 0.06-0.4 vs 0.5%, 95% CI: 0.28-0.83; $P = .03$), as shown in Figure 3. Interestingly, breast cancer was more likely found in women aged ≥ 50 years than in those aged < 50 (0.97% vs 0.14%, respectively, $P = .03$), as shown in Figure 4.

In 2890 men, during the study period, there were 500 VTE recurrences (17.3%), with nonsignificant differences between patients with occult cancer versus no occult cancer (14.2% vs 17.6%, $P = .18$), and 220 bleed (7.6%). Major bleeding was significantly more common in patients with occult cancer than in those without occult cancer (14.6% vs 7%, $P < .001$). In 2974 women, there were 398 VTE recurrences (13.4%), with nonsignificant differences between occult cancer versus no occult cancer (14.1% vs 13.3%, $P = .75$), and 253 bleed (8.5%). Again, major bleeding was more common in women with occult cancer than in those without occult cancer (17.7% vs 7.9%, $P < .001$).

In patients with occult cancer, during follow-up, 132 patients (30%, 95% CI: 25-34) died. The leading causes of death were disseminated cancer (67%), bleeding (3.7%), and objectively confirmed PE (2.7%). In all, 64 men (26%) and 68 women (34%) died during follow-up ($P = .056$). There were 63 recurrences of VTE and 33 major bleeding, with no sex differences (Table 1).

Discussion

Our study is the largest published cohort of patients with acute VTE and occult cancer and provides interesting data on the clinical profile of at-risk patients. Men had an increased risk of occult cancer, particularly in the lung, prostate, or colorectal. Hence, men scoring ≥ 3 points should probably undergo a chest computed tomography (CT) scan (the most frequently used test to confirm PE diagnosis), a rectal examination, and prostate specific antigen (PSA) test. Among women, the risk of cancer was slightly lower, and the most common sites included the colon, breast, uterus, pancreas, and hematologic. Thus, the diagnostic workup for cancer in women scoring ≥ 3 points is more complicated. We found an increased risk of breast cancer in females older than 50 years. Several factors increased the risk of breast cancer, including early menarche, late

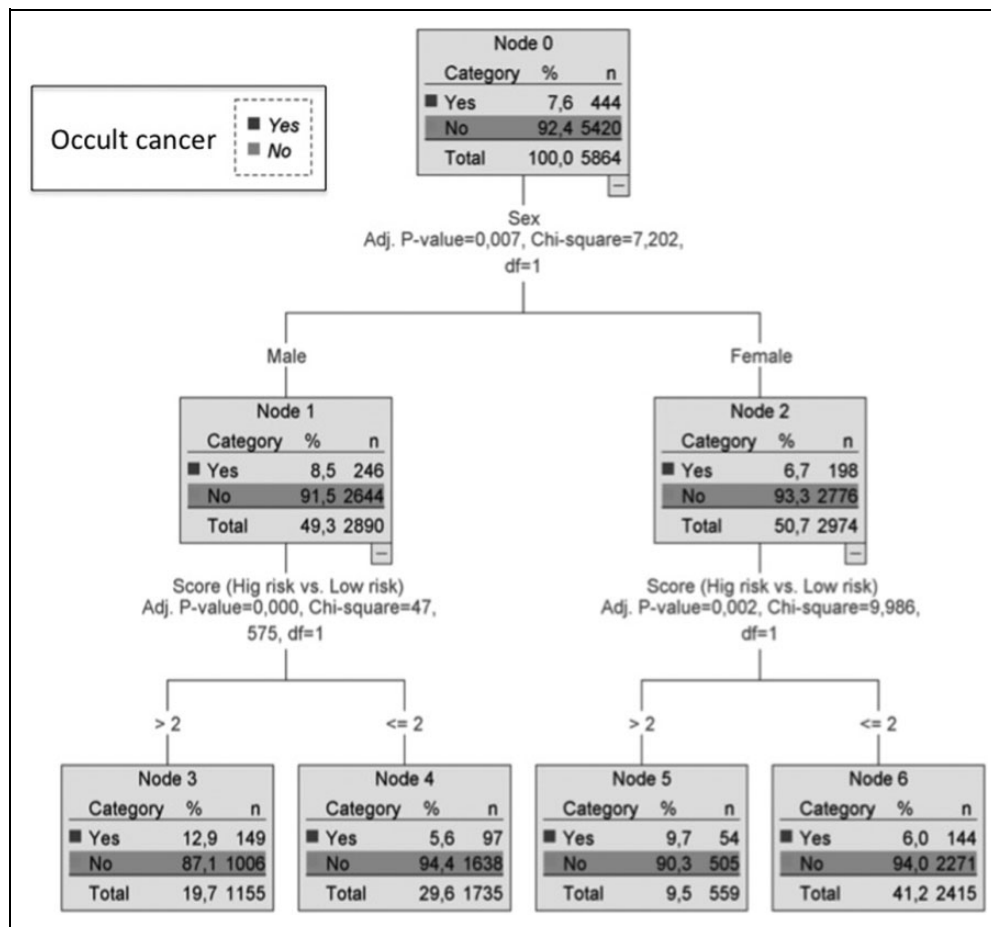


Figure 2. Decision tree. Score as predictor of occult cancer, according to sex. Patient is classified according to sex and as low or high risk according to score (≥ 3 : high risk and ≤ 2 : low risk).

Table 2. Occult Cancer in Patients, Attending to Sex and Risk Factors for VTE.

Variable	Total	Male	Female	P
Patients, n	5864	2890	2974	
Risk factors for VTE, n (%)				
Recent surgery (n = 592)	28 (4.7)	12 (4.9)	16 (4.6)	.87
Recent immobility ≥ 4 days (n = 1184)	90 (7.6)	46 (8.3)	44 (7)	.37
Hormonal therapy (n = 332)	8 (2.4)	1 (20)	7 (2.1)	.27
Recent travel (n = 150)	8 (5.3)	6 (6)	2 (4)	.89
Pregnancy/puerperium (n = 112)	0	-	0	
None of the above (unprovoked; n = 3666)	312 (8.5)	181 (9)	131 (7.9)	.26
Previous VTE (n = 1098)	62 (5.6)	34 (5.8)	28 (5.4)	.78

Abbreviation: VTE, venous thromboembolism.

childbearing, fewer pregnancies, or use of menopausal hormone therapy. The incidence of breast cancer has a distinctive age-specific curve, with a rapid rate of increase before the

Table 3. Accuracy for High- Versus Low-Risk Categories to Predict Occult Cancer, According to Sex.

Variable	Male		Female	
	(246/2644)		(198/2974)	
Occult Cancer/Patients	95% CI		95% CI	
C-statistic	0.64	0.60-0.68	0.61	0.57-0.65
Sensitivity	60.6%	54.3%-66.5%	27.3%	21.5%-33.9%
Specificity	62.0%	60.1%-63.8%	81.8%	80.3%-83.2%
Positive predictive value	12.9%	11.1%-15.0%	9.7%	7.5%-12.4%
Negative predictive value	94.4%	93.2%-95.4%	94.0%	93.0%-94.9%
Odds ratio diagnosis	2.50	1.91-3.27	1.69	1.22-2.34
Positive likelihood ratio	1.59	1.42-1.78	1.50	1.18-1.91
Negative likelihood ratio	0.64	0.54-0.75	0.89	0.81-0.98
Pretest probability (prevalence)	8.5%	7.5%-9.6%	6.7%	5.8%-7.6%
Posttest probability high risk (Bayes)	12.9%	11.1%-14.9%	9.7%	7.5%-12.5%
Number needed to screen	14	11-20	28	16-94

Abbreviation: CI, confidence interval.

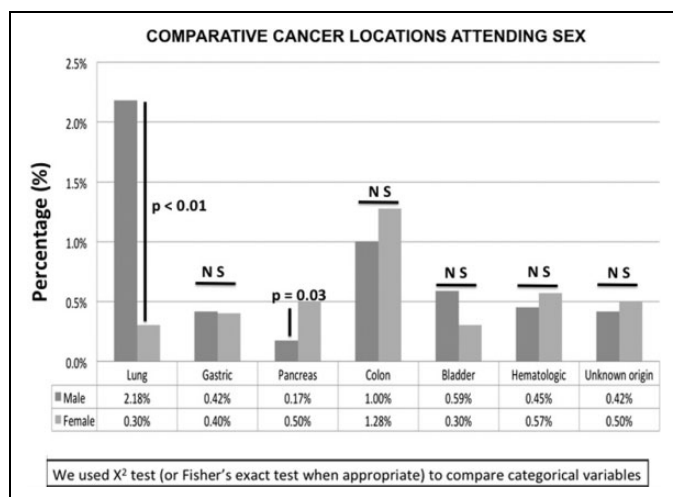


Figure 3. Comparative cancer sites according to sex.

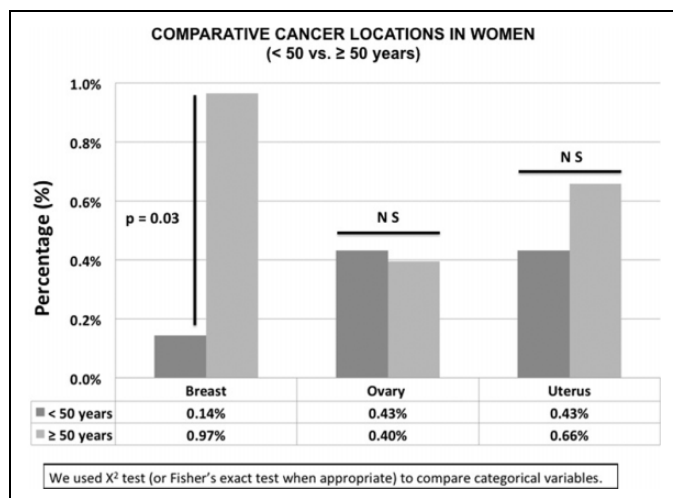


Figure 4. Comparative cancer sites in women by age (<50 vs ≥50 years).

menopause (ages 40-50) and slows down after that, probably owing to diminishing levels of circulating estrogens.^{7,8} In many ways, the incidence of occult breast cancer in females with VTE was higher than expected, particularly in women aged >50 years.

The risk of lung cancer was much higher in men than in women. This difference might be attributed to the higher prevalence of chronic lung disease in men and the likely influence of tobacco smoking on both diseases. Unfortunately, smoking habit was not routinely gathered in the RIETE registry. We also found a nonsignificantly higher mortality rate in women (34% vs 26%; $P = .056$) and there were no differences in the rate of major bleeding or VTE recurrences.

The results in trials emphasize that performing an extensive occult cancer screening strategy does not seem to be beneficial. The Screening for Occult Malignant disease in Idiopathic venous Thromboembolism (SOMIT) trial randomized patients with a first episode of unprovoked VTE and negative limited

occult cancer screening to either no further testing or additional investigations.⁹ Approximately 10% of patients in the control group were diagnosed with cancer over the 2-year follow-up period. The Trousseau's study was a prospective cohort study assessing the added value of performing mammography in women and thoracic and abdominal CT in all patients presenting with unprovoked VTE.¹⁰ Screening for Occult Malignancy in Patients with Idiopathic Venous Thromboembolism (SOME) Occult cancer was diagnosed at enrollment in 2.4% and 3.5% of 630 patients receiving limited screening alone or in combination with CT, respectively. The Screening for Occult Malignancy in Patients with Idiopathic Venous Thromboembolism (SOME) trial failed to demonstrate, in patients with a first unprovoked VTE, any additional benefit of extensive occult cancer screening.¹¹ In this multicenter study, 854 patients were randomized to either a limited screening strategy alone or in combination with comprehensive CT. At 1 year, 33 patients (3.9%, 95% CI: 2.8-5.4) were diagnosed with cancer in the interval between randomization and follow-up, with no significant differences between the 2 groups ($P = .28$). A French randomized controlled trial randomized 494 patients to a limited occult cancer screening alone or in combination with fludeoxyglucose positron emission tomography (FDG-PET)/CT.¹² There was no significant difference in the primary outcome measure, with 2% and 5.6% of patients being diagnosed with occult cancer in the limited screening and limited screening + FDG-PET groups, respectively. Moreover, there were no differences in overall or cancer-related mortality. In a registry-based cohort study based on the entire Danish population of 5.4 million people, the risk of cancer after a diagnosis of superficial venous thrombosis in the legs, DVT, and PE was determined.¹³ They found that patients with a diagnosis of superficial venous thrombosis had a clearly higher occurrence of cancer than expected, particularly during the first year after diagnosis, with a standardized incidence ratio of 2.46 (95% CI: 2.10-2.86). For all these findings, it's important to identify a high-risk population in which screening could obtain benefit.

One limitation of this study is that we do not have information about complete cancer staging (tumor/node/metastasis [TNM] classification) or diagnostic tools used to diagnose occult cancer, although our findings let us identify high-risk population, first step in the screening process.¹⁴ Our study has several strengths. All patients selected from RIETE were followed up for at least 2 years or until occult cancer was diagnosed, thus avoiding selection bias, and the number of involved patients was high ($N = 5864$). The proportion of patients with occult cancer in our series (7.6%) was consistent with that found in similar studies.^{11,15,16} Considering high-risk population, we obtained a number needed to screen of 14 for males and 28 for females, which should be considered relevant because other diseases like breast cancer screening showed number needed to screen of 133 to 588.¹⁷ Also, the increased rate of breast cancer in women aged >50 years should be noted (0.97%, 95% CI: 0.6-1.46 vs 0.14%, 95% CI: 0.003-0.8; $P = .03$).

According to our data, we may conclude that we should have a high suspicion of lung cancer in men scoring ≥ 3 points

(particularly if they also have chronic lung disease), as well as prostate cancer and colorectal cancer. By contrast, women have more variety of cancer sites, though clinicians should be alert for breast and colorectal cancer in those aged ≥ 50 years. Anyway, these results should be externally validated and the prognostic score should be carefully managed.

Conclusions

This study emphasizes the existence of sex differences in patients with VTE who develop occult cancer. In men, there are more lung cancers and fewer pancreatic cancers than in women. In men, 2 cancer sites accounted for more than half the cancers. In women, there is a heterogeneity of cancer sites, with an increased risk of breast cancer in those aged >50 years. Women with occult cancer had a nonsignificantly higher mortality ($P = .056$).

Appendix A

Coordinator of the RIETE registry: Manuel Monreal. RIETE Steering Committee Members: Hervé Decousus, Paolo Prandoni and Benjamin Brenner. RIETE National Coordinators: Raquel Barba (Spain), Pierpaolo Di Micco (Italy), Laurent Bertoletti (France), Inna Tzoran (Israel), Abilio Reis (Portugal), Marijan Bosevski (R. Macedonia), Henri Bounameaux (Switzerland), Radovan Malý (Czech Republic), Philip Wells (Canada), and Peter Verhamme (Belgium). RIETE Registry Coordinating Center: S & H Medical Science Service. Members of the RIETE Group SPAIN: Adarraga MD, Aibar MA, Alfonso M, Arcelus JI, Ballaz A, Barba R, Barrón M, Barrón-Andrés B, Bascuñana J, Blanco-Molina A, Cañas I, Chic N, del Pozo R, del Toro J, Díaz-Pedroche MC, Díaz-Peromingo JA, Falgá C, Fernández-Aracil C, Fernández-Capitán C, Fidalgo MA, Font C, Font L, Gallego P, García I, García MA, García-Bragado F, García-Ródenas M, Gavín O, Gómez C, Gómez V, González J, Grau E, Grimón A, Guijarro R, Guirado L, Gutiérrez J, Hernández-Comes G, Hernández-Blasco L, Jara-Palomares L, Jaras MJ, Jiménez D, Jiménez J, Joya MD, Llamas P, Lobo JL, López P, López-Jiménez L, López-Reyes R, López-Sáez JB, Lorente MA, Lorenzo A, Lumbierres M, Marchena PJ, Martín-Martos F, Mellado M, Monreal M, Nieto JA, Nieto S, Núñez A, Núñez MJ, Otalora S, Otero R, Ovejero A, Pedrajas JM, Pérez G, Pérez-Ductor C, Peris ML, Pons I, Porras JA, Reig O, Riera-Mestre A, Riesco D, Rivas A, Rodríguez M, Rodríguez-Dávila MA, Rosa V, Ruiz-Artacho P, Ruiz-Giménez N, Sahuquillo JC, Sala-Sainz MC, Sampériz A, Sánchez-Martínez R, Sanz O, Soler S, Sopeña B, Suriñach JM, Tolosa C, Torres MI, Trujillo-Santos J, Uresandi F, Usandizaga E, Valero B, Valle R, Vela J, Velez-Mendizábal E, Vidal G, Vila M, Villalobos A, Xifre B; Belgium: Vanassche T, Verhamme P; Brazil: Yoo HHB; Canada: Wells P; Czech Republic: Hirmerova J, Malý R; Ecuador: Salgado E; France: Bertoletti L, Bura-Riviere A, Falvo N, Farge-Bancel D, Hij A, Mahé I, Moustafa F; Israel: Braester A, Brenner B, Tzoran I; Italy: Antonucci G, Barillari G, Bilora F, Bortoluzzi C, Brandolin B, Bucherini E, Candeloro G, Cattabiani C,

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Authors' Note

LJP had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. LJP, MM, ROC, and DJ contributed to study concept and design. All authors contributed to acquisition, analysis, or interpretation of data, drafted the manuscript, and critically revised the manuscript for important intellectual content. JMPF and LJP performed statistical analysis. LJP, ROC, DJ, CF, JMPF RLR, PW, JGM, and MM supervised the study.

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Declaration of Conflicting Interests

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Supplemental Material

Supplementary material is available for this article online.

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