REVIEW

Annals of Internal Medicine

Screening for Occult Cancer in Patients With Unprovoked Venous Thromboembolism

A Systematic Review and Meta-analysis of Individual Patient Data

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Background: Screening for cancer in patients with unprovoked venous thromboembolism (VTE) often is considered, but clinicians need precise data on cancer prevalence, risk factors, and the effect of different types of screening strategies.

Purpose: To estimate the prevalence of occult cancer in patients with unprovoked VTE, including in subgroups of different ages or those that have had different types of screening.

Data Sources: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials up to 19 January 2016.

Study Selection: Prospective studies evaluating cancer screening strategies in adults with unprovoked VTE that began enrolling patients after 1 January 2000 and had at least 12 months of follow-up.

Data Extraction: 2 investigators independently reviewed abstracts and full-text articles and independently assessed risk of bias.

Data Synthesis: 10 eligible studies were identified. Individual data were obtained for all 2316 patients. Mean age was 60 years; 58% of patients received extensive screening. The 12-month period prevalence of cancer after VTE diagnosis was 5.2% (95% CI, 4.1% to 6.5%). The point prevalence of cancer was higher in patients who had extensive screening than in those who had more limited screening initially (odds ratio [OR], 2.0 [CI, 1.2 to 3.4]) but not at 12 months (OR, 1.4 [CI, 0.89 to 2.1]). Cancer prevalence increased linearly with age and was 7-fold higher in patients aged 50 years or older than in younger patients (OR, 7.1 [CI, 3.1 to 16]).

Limitation: Variation in patient characteristics and extensive screening strategies; unavailability of long-term mortality data.

Conclusion: Occult cancer is detected in 1 in 20 patients within a year of receiving a diagnosis of unprovoked VTE. Older age is associated with a higher cancer prevalence. Although an extensive screening strategy initially may detect more cancer cases than limited screening, whether this translates into improved patient outcomes remains unclear.

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For author affiliations, see end of text.
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Unprovoked venous thromboembolism (VTE) may be the first sign of occult cancer. Screening often is considered in these patients, with the aim of detecting underlying cancer at an early, curable stage and reducing cancer-related morbidity and mortality. The extent to which patients with unprovoked VTE should be screened for occult cancer is controversial. Although an early study suggested that an extensive screening strategy may detect more cancer than a more limited one (1), recent studies evaluating extensive screening strategies using computed tomography (CT) of the abdomen (2–4) or whole-body positron emission tomography (PET) (5) could not confirm this finding.

Extensive screening tests may yield false-positive findings, requiring additional, sometimes invasive testing, which increases health care costs, exposes patients to potential procedure-related complications, and may lead to patient anxiety. Given the lack of a clear benefit and the potential harms of extensive screening, a more limited occult cancer screening strategy comprising medical history taking, physical examination, basic blood work, chest radiography, and age- and sex-specific testing currently is suggested for patients with unprovoked VTE (6).

To guide decisions regarding occult cancer screening and to counsel patients, clinicians need precise estimates of the period prevalence of occult cancer at the time of VTE diagnosis and during follow-up. Clinicians also must be informed about the types and stages of cancer that may potentially be detected by screening and about the tests that are useful for detecting occult cancer. To help clinicians tailor screening decisions, we performed a systematic review and a meta-analysis of individual patient data, combining patient-level data from 10 recently published, prospective studies of occult cancer screening in patients with unprovoked VTE.

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Web-Only

Supplement

Methods

Methods were prespecified in a previously published protocol (7). The guidance of the PRISMA-IPD (Preferred Reporting Items for Systematic reviews and

Meta-Analyses of Individual Participant Data) Statement was followed (**Supplement Appendix 1**, available at Annals.org) (8). The systematic review was registered with the International Prospective Registry of Systematic Reviews (PROSPERO: CRD42016033371).

Data Sources and Searches

Our previously published systematic review (9) was updated by searching the MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials databases from 1 November 2007 to 19 January 2016, combining terms for VTE, cancer, and screening (**Supplement Table 1**, available at Annals.org). No language restrictions were applied. In addition, conference proceedings of the International Society on Thrombosis and Haemostasis and the American Society of Hematology were searched from 2007 to 2015. Reference lists of eligible articles were hand-searched. Two authors (N.v.E. and M.C.) independently screened the titles and abstracts of articles and assessed the full texts for eligibility. Any differences of opinion regarding study eligibility were resolved by discussion.

Study Selection

To be eligible, studies must have prospectively included consecutive adult patients with unprovoked, objectively confirmed deep venous thrombosis or pulmonary embolism and followed them for a minimum of 12 months for potential cancer. We accepted the individual study definitions of unprovoked VTE. Studies were required to follow a defined strategy for occult cancer screening, including, at minimum, medical history taking, physical examination, basic blood tests, and chest radiography. Studies that started enrolling patients before 1 January 2000 were excluded, because cancer screening practices (such as age- and sex-specific testing) and diagnostic testing procedures changed substantially since then; therefore, more recent studies were considered more relevant and informative. All studies that enrolled patients before any screening procedures were included in the primary analyses. Studies enrolling patients only after negative results on initial screening were used for additional analyses.

Data Extraction and Quality Assessment

Corresponding authors of eligible studies were invited to participate in this collaborative project. All contacted authors agreed and provided individual patient data. Study-level information was sought regarding each study's aims, definition of unprovoked VTE, screening strategy, follow-up duration, and assessment of outcomes. Patient-level data about baseline characteristics; risk factors; index VTE; cancer screening tests; and outcomes, including cancer, recurrent VTE, death, and loss to follow-up, were obtained. Patients who enrolled more than 90 days after their VTE diagnosis, as well as those in whom the index VTE was not objectively confirmed, were excluded from the data set.

To ensure data consistency, baseline tables and primary analyses reported in the original articles were reconstructed. Discrepancies with the published tables were resolved by contacting the principal investigators. All studies had been approved by the institutional review boards of participating centers.

Two reviewers (N.v.E. and Dr. Noémie Kraaijpoel [Academic Medical Center, Amsterdam, the Netherlands]) independently assessed the potential risks of bias for each study by using the Newcastle–Ottawa Scale (10) and the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies, revised) tool, which was adapted to the present research question (**Supplement Appendix 2**, available at Annals.org) (11). Disagreements were resolved by consensus.

Data Synthesis and Analysis

The primary outcome measure was the point prevalence of previously undiagnosed cancer at 12 months in patients with unprovoked VTE, defined as the proportion of patients in whom solid or hematologic cancer (excluding nonmelanoma skin cancer) was objectively confirmed by histology or cytology or unequivocally diagnosed by imaging or tumor markers. *Cancer detection* refers to detection by screening tests that subsequently was confirmed by additional testing. *Cancer diagnosis* is all cases confirmed either at screening or during follow-up. The period prevalence of cancer also was analyzed at different time points, including at initial screening, between screening and 12 months, and between 12 and 24 months of follow-up. Subgroup analyses assessed the effects of screening type (limited vs. extensive) and patient age (by cohorts of 10 years) on the probability of cancer diagnosis. Finally, the probability of a cancer diagnosis was estimated in men, women, current or former smokers, women receiving estrogen-containing oral contraceptive or hormone replacement therapy, patients presenting with pulmonary embolism, and those with previous VTE. Secondary outcomes were early-stage solid cancer (stage 0, I, or II according to the American Joint Committee on Cancer staging system), stage III and IV solid cancer, and hematologic cancer.

The proportion of positive findings at limited screening that required additional testing and the proportion of patients who subsequently received a cancer diagnosis were evaluated. *Limited screening* was defined as the combination of medical history taking; physical examination; basic blood tests (complete blood count and creatinine and liver function tests); 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 and ultrasonography of the abdomen or whole-body PET-CT (**Supplement Table 2**, available at Annals.org).

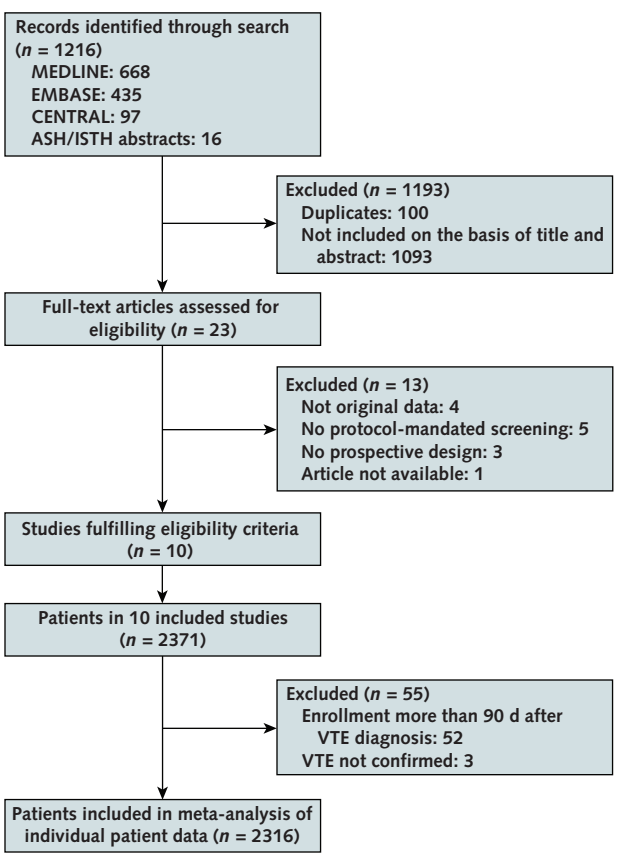
Patient-level information was obtained from source documentation for each cancer case diagnosed at initial screening. Using detailed narratives based on source documents, 3 authors (N.v.E., G.L.G., and M.C.) independently adjudicated which of the screening tests

initially had raised the suspicion of cancer and eventually led to cancer detection.

Summary probability estimates were obtained through 1-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 and adjusted the analysis for age, sex, smoking, and index VTE because 1 of the comparative studies was nonrandomized.

Marginal probability estimates were calculated by integrating the inverse logit of the fixed effect of the intercept over the random-effects distribution by using Gauss–Hermite quadrature approximation, with 10 quadrature points, to arrive at the final point estimates and 95% CIs. The 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.

Figure 1. PRISMA flow chart of systematic reviews.



ASH = American Society of Hematology; Central = Cochrane Central Register of Controlled Trials; ISTH = International Society on Thrombosis and Haemostasis; PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses; VTE = venous thromboembolism.

To illustrate heterogeneity across the studies, 95% prediction intervals were calculated around the point estimates on the basis of the SE of the fixed effect and the variance of the random effect. Forest plots also were generated to visualize potential heterogeneity. In addition, we performed a predefined sensitivity analysis restricted to patients enrolled within 30 days after the index VTE.

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.

Role of the Funding Source

This study received no funding.

RESULTS

Included Studies

A total of 1216 articles were identified, from which 23 full texts were assessed for eligibility (**Figure 1**). Ten prospective studies met the inclusion criteria, and individual patient data for all 2371 participants were obtained (2–5, 12–17). Seven of these studies (n = 2052) had enrolled patients before any occult cancer screening procedures (5, 14–18). Study characteristics are depicted in **Supplement Table 3** (available at Annals.org). The definition of unprovoked VTE was consistent across studies and mostly encompassed symptomatic, objectively confirmed acute pulmonary embolism or deep venous thrombosis in the absence of known cancer, recent surgery, trauma of the leg, immobilization, previous unprovoked VTE, known thrombophilia, pregnancy, or puerperium (**Supplement Table 3**). Study group size ranged from 25 to 854 participants. Patients were enrolled between October 2002 and April 2014 in Europe (2, 5, 12–14, 16, 19) and North America (3, 15, 17). Median follow-up ranged from 1 to 2.5 years (overall median, 500 days). In 8 studies, patients were contacted at fixed time intervals to elicit information about a new cancer diagnosis (2, 4, 5, 13–15, 17, 18). Testing for cancer during follow-up was left to the physician's discretion in all studies.

Of the 7 studies that enrolled patients before any screening procedures, 3 (n = 1878) compared a limited with an extensive screening strategy (2, 3, 5), whereas 4 studies (n = 174) evaluated only an extensive screening strategy (**Supplement Table 3**) (14–17). The other 3 studies (n = 319) enrolled patients after negative results on limited screening; 2 evaluated PET-CT–based screening (12, 13), and 1 compared usual clinical practice with an extensive screening strategy (4).

The results of the risk-of-bias assessment using the QUADAS-2 tool and Newcastle–Ottawa Scale are provided in **Supplement Appendix 2** (available at Annals.org). No potential sources of bias or applicability concerns were identified for our review question for the 7 studies that enrolled patients before screening procedures. The other 3 studies were judged to be at high risk of selection bias, given that they enrolled patients after screening (4, 12, 13). One study was considered

to be at high risk of attrition bias because a considerable proportion of its participants were lost to follow-up (13). One study was at risk of bias because of inadequate outcome assessment (16). One study that compared limited with extensive screening was a nonrandomized trial (2).

Patient-Level Results

Baseline Information

Of the 2371 patients, 55 (2.3%) had to be excluded from the data set because they enrolled more than 90 days after their VTE diagnosis (n = 52) or because the index VTE was not confirmed (n = 3). Baseline characteristics of the 2001 patients included in the 7 studies that enrolled patients before screening, as well as those of all 2316 patients, are shown in Table 1. Mean age was 60 years, 61% of the patients were men, and 47% had pulmonary embolism with or without deep venous thrombosis. Baseline characteristics for the individual studies are provided in Supplement Table 4 (available at Annals.org).

Table 1. Patient Characteristics*

Characteristic	Patients Included in Studies With Prescreening Enrollment (n = 2001)†	Patients in All Studies (n = 2316)‡
Mean age (SD), *y*	58 (15)	60 (15)
Age categories, *n (%)*		
≤49 y	592 (30)	628 (27)
50–74 y	1101 (55)	1263 (55)
≥75 y	308 (15)	425 (18)
Male, *n (%)*	1243 (62)	1416 (61)
Mean weight (SD), *kg*	87 (18)	87 (18)
Missing, *n (%)*	640 (32)	955 (41)
Index VTE, *n (%)*		
PE with or without DVT	950 (47)	1082 (47)
Proximal leg DVT	987 (49)	1132 (49)
Distal leg DVT	42 (2.1)	50 (2.2)
DVT of the leg of unknown location	8 (0.4)	36 (1.6)
Upper-extremity DVT	14 (0.7)	16 (0.7)
Evaluation of PE by CTPA, *n (%)*	750 (38)	750 (32)
Unknown	1 (0)	121 (5.2)
Median time from index VTE to enrollment (IQR), *d*	7 (1–11)	7 (1–13)
Enrollment within 30 d of VTE, *n (%)*	1852 (93)	2119 (92)
Smoking history, *n (%)*		
Current or former smoker	901 (45)	901 (39)
Never smoked	989 (49)	989 (43)
Missing	111 (5.5)	426 (18)
Previous cancer, *n (%)*	75 (3.7)	77 (3.3)
Missing	585 (29)	802 (35)
Previous VTE, *n (%)*	187 (9.3)	192 (8.3)
Unprovoked	49 (2.4)	49 (2.1)
Provoked	91 (4.5)	91 (3.9)
Missing	47 (2.3)	52 (2.2)
Estrogen use, *n (%)*	151 (7.5)	151 (6.5)
Missing	13 (0.6)	35 (1.5)
Screening strategy, *n (%)*		
Limited	885 (44)	982 (42)
Extensive	1116 (56)	1334 (58)

CTPA = computed tomographic pulmonary angiography; DVT = deep venous thrombosis; IQR = interquartile range; PE = pulmonary embolism; VTE = venous thromboembolism.
* Percentages may not sum to 100 due to rounding.
† References 2, 3, 5, and 14–17.
‡ References 2–5 and 12–17.

Period Prevalence of Occult Cancer

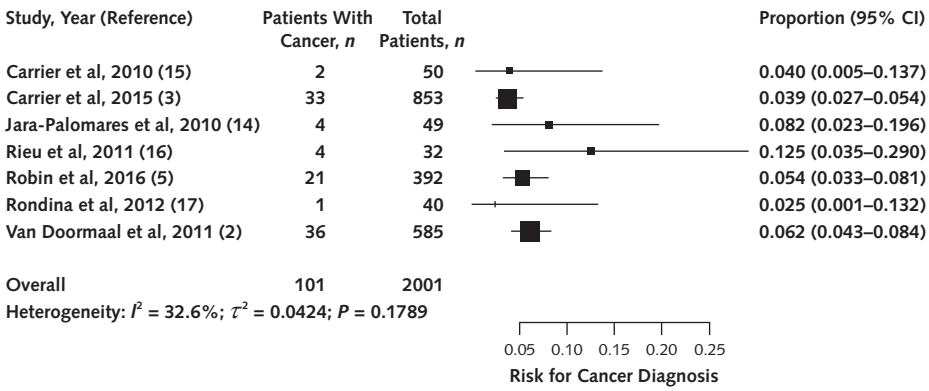
In the 7 studies that enrolled patients before screening (5, 14–18), cancer was diagnosed in 101 of 2001 patients in the first 12 months, corresponding to a pooled period prevalence of 5.2% (95% CI, 4.1% to 6.5%) (Figure 2). When the analysis was restricted to the 1877 patients alive and not lost to follow-up during the first year, the prevalence was 5.7% (CI, 4.3% to 7.4%) (Supplement Figure 1A, available at Annals.org). The different cancer types are summarized in Supplement Table 5 (available at Annals.org). Cancer of the colon was diagnosed most frequently (17%), followed by the lung (15%) and pancreas (11%).

For the studies that enrolled patients before initial screening (5, 14–18), Figure 3 shows the point prevalence of cancer at different time points. Cancer was detected in 71 of 2001 patients at initial screening (3.5% [CI, 2.8% to 4.5%]; 7 studies) (Supplement Figure 1B, available at Annals.org) and diagnosed in 30 of 1930 patients between the initial screening and 12-month follow-up (1.6% [CI, 1.0% to 2.6%]; 7 studies) (Supplement Figure 1C, available at Annals.org). The period prevalence of cancer between 12 and 24 months after the index VTE diagnosis was 1.0% (CI, 0.56% to 1.9% [5 studies]) (Supplement Figure 1D, available at Annals.org). Likewise, in the studies that enrolled patients after initial screening, the period prevalence in the first 12 months of follow-up in those with negative results on initial limited screening was 3.5% (CI, 1.7% to 6.9% [10 studies]) (Supplement Figure 1E, available at Annals.org); the period prevalence between 12 and 24 months was 1.1% (CI, 0.62% to 1.8% [8 studies]) (Supplement Figure 1F, available at Annals.org). The sensitivity analysis, restricted to the 2119 patients who enrolled within 30 days of their VTE diagnosis, yielded similar results (Supplement Figure 2, available at Annals.org). The cumulative incidence of a cancer diagnosis in each study is illustrated in Supplement Figure 3 (available at Annals.org).

Effect of Type of Screening

Three studies directly compared a limited with an extensive imaging-based screening strategy (2,3,5). In these studies, the 12-month period prevalence of cancer was 4.2% (CI, 3.0% to 5.7%) and 5.6% (CI, 4.3% to 7.3%) among the 885 and 945 patients who had limited or extensive screening, respectively (adjusted odds ra-

Figure 2. Period prevalence of cancer in first 12 months of follow-up.



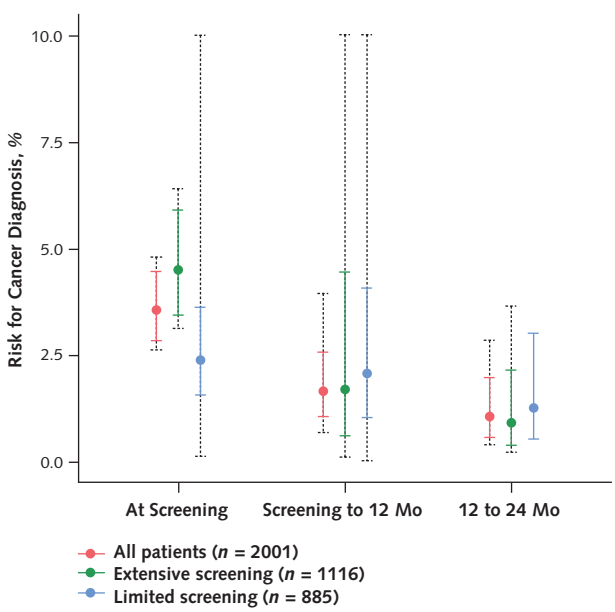
Summary period prevalence is 5.2% (95% CI, 4.1% to 6.5; 95% prediction interval, 3.3% to 8.1%).

tio [OR], 1.4 [CI, 0.89 to 2.1]; $P = 0.146$) (Supplement Figure 1G, available at Annals.org).

Cancer Prevalence in Subgroups

In the 7 studies that enrolled patients before initial screening (5, 14–18), the 12-month period prevalence of cancer was higher in elderly patients, ranging from 0.5% (CI, 0.03% to 8.2%) in patients younger than 40 years to 9.1% (CI, 5.6% to 15%) in those older than 80 years (Figure 4). The 12-month period prevalence in predefined subgroups is shown in Table 2. The 12-month period prevalence was 6.8% (CI, 5.6% to 8.3%) in patients aged 50 years and older, compared with 1.0% (CI, 0.5% to 2.3%) in those younger than 50 years (OR, 7.1 [CI, 3.1% to 16%]; $P < 0.001$) (Supplement Figure 1H, available at Annals.org). The 12-month period prevalence of cancer was 1.3% (CI, 0.3% to 5.1% [4 studies]) among women receiving estrogen and 5.8% (CI, 3.8% to 8.8% [7 studies]) among those not receiving it (Supplement Figure 1I, available at Annals.org).

Figure 3. Period prevalence of cancer, according to time points.



Data are based on studies enrolling patients before screening procedures. Solid error bars represent 95% CIs, and dashed error bars represent 95% prediction intervals. The *y*-axis is truncated at 10%. These analyses used studies that enrolled patients before screening procedures (5, 14-15-16-17-18).

Cancer Detected at Screening

Occult cancer was detected at screening in 21 of 885 patients (2.4% [CI, 1.6% to 3.6%]; 3 studies) who underwent a limited screening strategy, compared with 50 of 1116 (4.5% [CI, 3.4% to 5.9%]; 7 studies) who had extensive screening (Supplement Figure 1J, available at Annals.org). The types of cancer detected are shown in Supplement Table 5 (available at Annals.org). In the studies that directly compared a limited with an extensive screening strategy (2, 3, 5), extensive screening was associated with a 2-fold higher probability of occult cancer detection (adjusted OR, 2.0 [CI, 1.2 to 3.4]; $P = 0.012$; 3 studies) at initial screening (Supplement Figure 1K, available at Annals.org). However, additional investigations to pursue cancer diagnosis were done in 17% of patients undergoing a limited screening strategy, compared with 26% of those receiving extensive screening (OR, 1.7 [CI, 0.89 to 3.1]; $P = 0.112$). Among patients with positive results on limited screening, the probability of cancer detection was 14% (CI, 9.1% to 20% [3 studies]) (Supplement Figure 1L, available at Annals.org).

The screening tests performed in the individual studies are reported in Supplement Table 6 (available at Annals.org). Of the 50 cancer cases detected in patients undergoing an extensive screening strategy, 33 (66%) were found through limited screening investigations (such as medical history taking). Index screening investigations that led to cancer suspicion and subsequent diagnosis are listed in Supplement Table 7 (available at Annals.org). Medical history taking and physical examination detected 32 of the 71 cancer cases (45%) diagnosed at initial screening.

Cancer Stage

Of the 54 cancer cases detected by a limited screening strategy, 16 (30%) were stage 0, I, or II solid cancer; 31 (57%) were stage III or IV solid cancer; and 7 (13%) were hematologic cancer (Supplement Table 5). Of the 17 cases detected by an extensive screening strategy, 8 (47%) were stage 0, I, or II solid cancer; 7 (41%) were stage III or IV solid cancer; and 1 (5.9%) was hematologic cancer; cancer stage could not be determined in 1 patient (5.9%). The difference between the proportion of early-stage solid cancer detected by limited screening (16 of 46 cases) and that detected by extensive screening (8 of 17 cases) was not statistically significant ($P = 0.30$).

DISCUSSION

In this meta-analysis of individual patient data from 2316 persons with unprovoked VTE, cancer was diagnosed in 1 in 20 patients within a year after VTE diagnosis. About two thirds of these cases were detected by screening tests, whereas the remaining third became clinically overt during follow-up. The probability of a cancer diagnosis was strongly associated with age; the 12-month period prevalence in patients younger than 40 years was negligible, whereas it was almost 10% in those older than 80 years. An extensive screening strategy seems to detect approximately twice as many occult cancer cases as a more limited strategy, although no statistically significant difference was observed in the proportion of early-stage cancer cases detected.

A few limitations to our analysis should be acknowledged. Despite the availability of patient-level data, differences were observed among the studies with regard to patient selection, patient characteristics, and screening strategies. This observation especially applies to the variation among extensive screening strategies, which complicates the interpretation of the findings and prevents strong recommendations for clinical practice. Variation also was seen across studies in the time between the index VTE and study enrollment, which may have contributed to the between-study variability. Most studies had a follow-up of 1 to 2 years; hence, long-term data on mortality were not available. Yet, this outcome is most important when assessing the potential benefit of screening strategies. Subgroup analysis based on previous history of cancer diagnosis could not be performed because of a high proportion (approximately 30%) of missing data. We are aware that some of the additional analyses are based on small numbers, resulting in wide prediction intervals that reflect the uncertainty around the estimates. However, the main conclusions are based on data collected from more than 2000 patients with VTE.

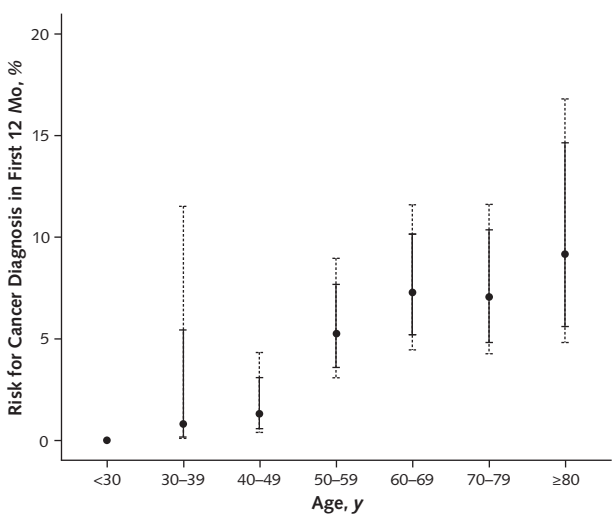
We estimated the 12-month period prevalence of occult cancer detection to be 5.2%. This estimate is approximately 50% lower than the previously reported 12-month period cumulative incidence from another systematic review, which included older studies (9). Besides differences in patient populations, other potential explanations exist for this substantial difference. We excluded studies with a retrospective design, because they may be prone to selection of higher-risk patients. A large proportion of the patients in the present analysis were enrolled in large multicenter trials, which are less prone to overestimation due to single-center bias.

Table 2. 12-Month Prevalence of Cancer in Subgroups*

Subgroup	Patients With Cancer, %	Patients, *n*	Estimated 12-Mo Prevalence (95% CI), %
Age			
≥50 y	6	592	6.7 (5.5–8.2)
<50 y	95	1409	1.0 (0.46–2.2)
Sex			
Female	38	758	5.0 (3.4–7.5)
Male	63	1243	5.7 (3.8–8.5)
Estrogen use			
Yes	2	151	1.3 (0.33–5.1)
No	35	602	5.8 (3.8–8.8)
Smoking history			
Current or former smoker	51	901	5.7 (4.3–7.4)
Never smoked	38	989	3.9 (2.5–6.0)
Index VTE			
PE with or without DVT	42	950	5.2 (3.2–8.2)
DVT only	59	1051	5.6 (4.4–7.2)
Previous VTE			
Yes	12	187	6.4 (3.7–11)
No	89	1814	5.2 (3.8–7.1)

DVT = deep venous thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.
* Analyses are based on studies enrolling patients before screening procedures. Percentages may not sum to 100 due to rounding.

Figure 4. Point prevalence of cancer at 12 months, stratified by age cohorts.



Data are based on studies enrolling patients before screening procedures. Solid error bars represent 95% CIs, and dashed error bars represent 95% prediction intervals. The *y*-axis is truncated at 20%. These analyses used studies that enrolled patients before screening procedures (5, 14–18).

Variation in VTE practice, with more secondary or tertiary care centers in the included sites, also may have resulted in inclusion of a group of patients with lower cancer prevalence. Nonetheless, the rate observed in this analysis more likely represents current VTE practice. Hence, the contemporary probability estimate provided in our meta-analysis of individual patient data allows clinicians to better inform their patients and assess the risk–benefit ratio of screening procedures.

Two other systematic reviews and study-level meta-analyses were identified by searching MEDLINE from inception to May 2017 (20, 21). In contrast to the present patient-level meta-analysis, these studies focused solely on the potential benefit of extensive versus limited screening and did not address the period prevalence of cancer overall and in subgroups.

The period prevalence of cancer in the second year after the index VTE was estimated at approximately 1% in the present study, which is similar to the annual cancer incidence observed in the general population, within the same age group (22). This finding is consistent with previously published population-based and cohort studies, in which the cancer probability in patients with VTE after 6 to 12 months of follow-up mirrored that of the general population (23–25). Hence, continued routine surveillance and increased awareness for cancer beyond the first year may not be indicated.

Age seems to be an important predictor of the presence of occult cancer in patients with unprovoked VTE. Patients aged 50 years and older are 7 times more likely to receive a cancer diagnosis than those younger than 50 years. Although physicians often worry about potential cancer in young patients with unprovoked VTE, the probability actually is much greater in older patients. Similarly, the probability of occult cancer seems to be low in women receiving estrogen. These considerations raise the question of whether screening for occult cancer should be offered to low-risk patients. In the studies included in our analysis, additional diagnostic investigations frequently were done to pursue a cancer diagnosis in patients with abnormalities detected on screening. Given the costs and potential complications associated with these additional investigations, clinicians may consider forgoing screening tests in these low-risk patients.

This meta-analysis highlights that the prevalence of occult cancer in patients with unprovoked VTE is substantial. Clinicians should have a low threshold for suspecting cancer in this patient population. A thorough medical history and physical examination are probably the most important screening components, because they led to the diagnosis of more than one third of the cancer cases at initial screening in the studies included in our analysis. Although a complete blood count and liver function tests also seemed effective, the value of other blood tests (such as lactate dehydrogenase and calcium tests) or Papanicolaou smears seems questionable, given that none led to the detection of occult cancer.

An extensive screening strategy was associated with a 2-fold higher probability of cancer detection at initial screening, at the obvious expense of an increase in the number of targeted tests for cancer. Despite the substantial increase in cancer detection with extensive screening, not enough evidence exists yet to support the routine use of these tests in patients with unprovoked VTE. Individual extensive screening tests, such as CT of the abdomen and whole-body PET-CT, were not associated with a clear increase in detected (early-stage) cancers. The absolute increase of approximately 2% corresponds to a substantial number needed to test—approximately 50. Given the relatively short follow-up of the included studies, it remains unclear whether the increase in cancer detection by extensive screening tests will translate into benefits with regard to important patient outcomes, such as lower morbidity and mortality.

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Reproducible Research Statement: *Study protocol:* Available at BMJ Open (http://bmjopen.bmj.com/content/7/6/e015562.long). *Statistical code:* Available from Dr. van Es (e-mail, n.vanes@amc.nl). *Data set:* The authors are open to sharing data. Requests may be sent to Dr. Carrier (e-mail, m.carrier@toh.ca) and will be discussed with all authors.

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