ORIGINAL ARTICLE

Screening for Occult Cancer in Unprovoked Venous Thromboembolism

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ABSTRACT

BACKGROUND

Venous thromboembolism may be the earliest sign of cancer. Currently, there is a great diversity in practices regarding screening for occult cancer in a person who has an unprovoked venous thromboembolism. We sought to assess the efficacy of a screening strategy for occult cancer that included comprehensive computed tomography (CT) of the abdomen and pelvis in patients who had a first unprovoked venous thromboembolism.

METHODS

We conducted a multicenter, open-label, randomized, controlled trial in Canada. Patients were randomly assigned to undergo limited occult-cancer screening (basic blood testing, chest radiography, and screening for breast, cervical, and prostate cancer) or limited occult-cancer screening in combination with CT. The primary outcome measure was confirmed cancer that was missed by the screening strategy and detected by the end of the 1-year follow-up period.

RESULTS

Of the 854 patients who underwent randomization, 33 (3.9%) had a new diagnosis of occult cancer between randomization and the 1-year follow-up: 14 of the 431 patients (3.2%) in the limited-screening group and 19 of the 423 patients (4.5%) in the limited-screening-plus-CT group (P=0.28). In the primary outcome analysis, 4 occult cancers (29%) were missed by the limited screening strategy, whereas 5 (26%) were missed by the strategy of limited screening plus CT (P=1.0). There was no significant difference between the two study groups in the mean time to a cancer diagnosis (4.2 months in the limited-screening group and 4.0 months in the limited-screening-plus-CT group, P=0.88) or in cancer-related mortality (1.4% and 0.9%, P=0.75).

CONCLUSIONS

The prevalence of occult cancer was low among patients with a first unprovoked venous thromboembolism. Routine screening with CT of the abdomen and pelvis did not provide a clinically significant benefit. (Funded by the Heart and Stroke Foundation of Canada; SOME ClinicalTrials.gov number, NCT00773448.)

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Venous thromboembolism, which comprises deep-vein thrombosis and pulmonary embolism, is the third most common cardiovascular disorder.[1-3] It is classified as provoked when it is associated with a transient risk factor (e.g., trauma, surgery, prolonged immobility, or pregnancy or the puerperium) and as unprovoked when it is associated with neither a strong transient risk factor nor overt cancer.

Unprovoked venous thromboembolism may be the earliest sign of cancer[4,5]; up to 10% of patients with unprovoked venous thromboembolism receive a diagnosis of cancer in the year after their diagnosis of venous thromboembolism.[6] More than 60% of occult cancers are diagnosed shortly after the diagnosis of unprovoked venous thromboembolism.[6] Thereafter, the incidence rate of cancer diagnosis gradually declines and returns to the rate in the general population after 1 year.[5-7]

Faced with these troubling statistics, clinicians, patients, and policymakers struggle with how aggressive to be in screening for occult cancers in patients who present with unprovoked venous thromboembolism. The rationale for screening is to allow early detection and intervention and ultimately reduce cancer-related mortality. However, owing to the paucity of data in this context, there is great variation in practice. Whereas some studies have suggested that a limited screening strategy for occult cancer — including history taking, physical examination, routine blood testing, and chest radiography — is adequate to detect most occult cancers, other studies have suggested that a more extensive screening strategy (e.g., incorporating ultrasonography or computed tomography [CT] of the abdomen and pelvis, measurement of tumor markers, or a combination of these) can substantially increase the rate of detection of occult cancer.[8-11] We conducted a randomized clinical trial to assess the efficacy and safety of adding CT of the abdomen and pelvis to a limited screening strategy for occult cancer.

Methods

Study Design and Oversight

The Screening for Occult Malignancy in Patients with Idiopathic Venous Thromboembolism (SOME) trial was a multicenter, open-label, randomized clinical trial comparing comprehensive CT of the abdomen and pelvis in addition to limited occult-cancer screening with limited occult-cancer screening alone in patients with unprovoked venous thromboembolism. The members of the steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) had final responsibility for the study design, clinical protocol, study oversight, and analyses of the data. The institutional review board at each participating center approved the protocol, which is available at NEJM.org, and written informed consent was obtained from all participants. Data were collected at the sites and were entered into a database managed by the Methods Center of the Ottawa Hospital Research Institute. A central adjudication committee whose members were unaware of the study-group assignments reviewed all suspected outcome events. An independent data and safety monitoring board regularly evaluated the conduct and safety of the trial.

The manuscript was written by the authors, who vouch for the accuracy and completeness of the data and adherence to the protocol. No one who is not an author contributed to writing the manuscript.

Study Population

Patients with a new diagnosis of first unprovoked symptomatic venous thromboembolism (proximal lower-limb deep-vein thrombosis, pulmonary embolism, or both) who were referred to a thrombosis clinic in one of nine participating Canadian centers were potentially eligible to participate in the study. Unprovoked venous thromboembolism was defined as venous thromboembolism in the absence of known overt active cancer, current pregnancy, thrombophilia (hereditary or acquired), previous unprovoked venous thromboembolism, or a temporary predisposing factor in the previous 3 months, including paralysis, paresis, or plaster immobilization of the legs; confinement to bed for 3 or more days; or major surgery. Standard strategies and objective criteria were used to diagnose proximal deep-vein thrombosis and pulmonary embolism. Patients were excluded if they met any of the following criteria: an age of less than 18 years, refusal or inability to provide informed consent, allergy to contrast media, a creatinine clearance of less than 60 ml per minute, claustrophobia or agoraphobia, a weight of more than 130 kg, ulcerative colitis, or glaucoma.

STUDY PROCEDURES

The trial statistician generated the randomization list using random-number tables. Randomization was performed in permuted blocks of two or four with stratification according to center and age category (<50 or ≥50 years of age), because older patients are at higher risk for an occult-cancer diagnosis. Patients were randomly assigned to a screening strategy within 21 days after receiving a diagnosis of venous thromboembolism, with the use of a central Web-based randomization system that ensured assignment concealment.

Patients assigned to the limited screening strategy underwent a complete history taking and physical examination, measurement of complete blood counts and serum electrolyte and creatinine levels, liver-function testing, and chest radiography. On the basis of recommendations by the Canadian Task Force on Preventive Health Care[12] and the U.S. Preventive Services Task Force,[13] sex-specific screening was conducted if it had not been performed in the previous year. A breast examination, mammography, or both were performed in women older than 50 years of age, and Papanicolaou (Pap) testing and a pelvic examination were performed in women 18 to 70 years of age who had ever been sexually active. A prostate examination, prostate-specific antigen test, or both were performed in men older than 40 years of age.

Patients assigned to limited screening plus CT also underwent comprehensive CT of the abdomen and pelvis. Before CT, patients underwent a bowel preparation with the use of Pico-Salax (Waymar Pharmaceuticals). CT included a virtual colonoscopy and gastroscopy, biphasic enhanced CT of the liver, parenchymal pancreatography, and uniphasic enhanced CT of the distended bladder. CT imaging was standardized. With the patient in the prone position, scout views were obtained with the use of a low-radiation protocol, automatic mA modulation, and a noise index of 32 (base on 5 mm; mA range, 80 to 200). With the patient right side up and then supine, scout views were obtained with the use of an intravenous contrast agent (Omnipaque 300; total dose, 100 to 110 ml at a rate of 3 ml per second) at 35 seconds, automatic mA modulation, and a noise index of 12.5 (base on 5 mm; mA range dependent on equipment). Insufflation with ambient air or carbon dioxide was used to ensure proper colonic distension.

SURVEILLANCE AND FOLLOW-UP

Any abnormal findings detected with the use of either strategy were further investigated as directed by the local treating physician, to confirm or rule out suspected cancer. Patients were followed for 1 year and assessed at fixed intervals with the use of a checklist to elicit information about a new cancer diagnosis, recurrent venous thromboembolism, or other adverse events. Patients were instructed to contact the study coordinator immediately if any of those events occurred. In case of suspected occult cancer or recurrent venous thromboembolism, the study protocol required biopsy confirmation or objective testing for venous thromboembolism, respectively.

OUTCOME ASSESSMENT

The primary outcome was newly diagnosed cancer during the follow-up period in patients who had had a negative screening result for occult cancer. Data on patients with confirmed cancer that was detected by the occult-cancer screening were censored from the primary analysis. Secondary outcome measures included the total number of occult cancers diagnosed and the total number of early cancers ($T_{1\text{-}2}$, N_0, M_0 according to the World Health Organization tumor–node–metastasis [TNM] classification system) diagnosed by means of occult-cancer screening and during the subsequent 1-year follow-up, 1-year cancer-related mortality, 1-year overall mortality, and the time to cancer diagnosis. The incidence of recurrent venous thromboembolism was also a secondary outcome.

STATISTICAL ANALYSIS

A systematic review of studies of occult-cancer screening had previously shown that 6.1% (95% confidence interval [CI], 5.0 to 7.1) of patients with unprovoked venous thromboembolism had an occult cancer at the time of their diagnosis of venous thromboembolism.[6] At 12 months, the prevalence increased to 10.0% (95% CI, 8.6 to 11.3)[6] — that is, the proportion of patients who received a diagnosis of cancer increased by nearly 4 percentage points during follow-up. The current study was designed to have 80% power to detect a relative risk reduction of 75% (i.e., absolute reduction of 3 percentage points) in the primary-outcome event rate if CT were added to limited screening. The null hypothesis was that limited occult-cancer screening plus CT would

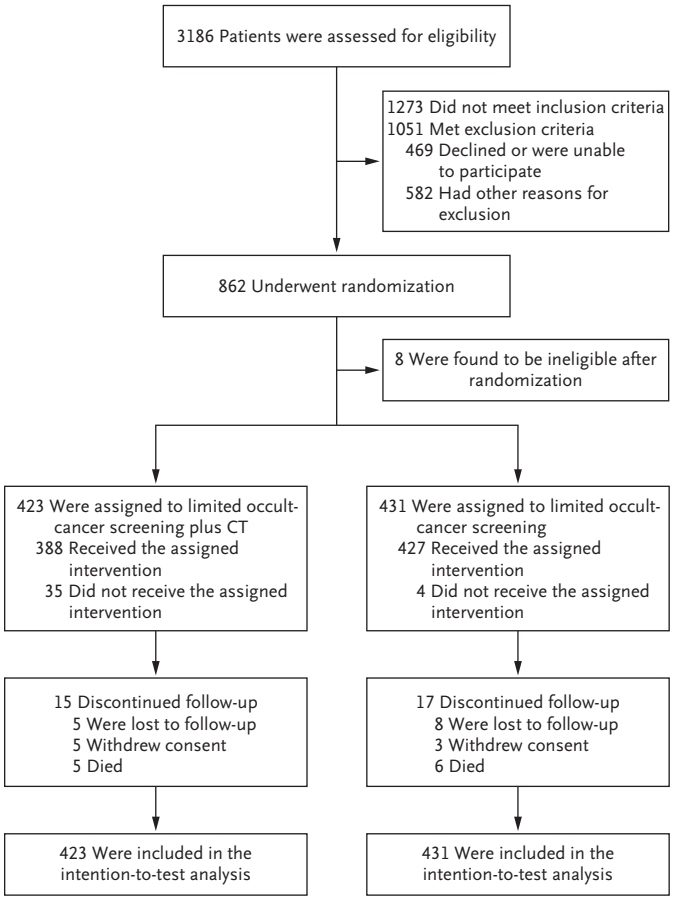

Figure 1. Screening, Randomization, Follow-up, and Analysis of the Study Patients.

Reasons for ineligibility are shown in Table S1 in the Supplementary Appendix. Patients who were assigned to the strategy of limited occult-cancer screening plus computed tomography (CT) underwent comprehensive CT of the abdomen and pelvis.

miss as many cancers as limited occult-cancer screening. Because it is implausible that the limited screening strategy would detect more occult cancers than a strategy of limited screening plus CT, a one-sided statistical test of significance was used (one-tailed alpha level of 0.05) for the sample-size calculation. To achieve these standards, we calculated that a sample size of 798 patients would be required. After adjustment for 8% nonadherence to the protocol and loss to follow-up, the final sample-size estimate was 862.

Descriptive statistics were used to examine the baseline characteristics of the enrolled participants. Standard deviations were reported for all characteristics expressed as continuous variables. Means and standard deviations were presented for discrete data.

Analyses were performed on an intention-to-test basis and were supplemented by a sensitivity analysis that excluded patients who did not complete their assigned screening strategy. The proportion of biopsy-confirmed occult cancers that were missed by screening was compared between the groups by means of a two-sided, unadjusted Fisher's exact test of proportions. The 95% binomial confidence intervals were calculated for these proportions with the use of the Wilson method. The proportions of patients with secondary outcomes were also compared by means of a two-sided, unadjusted Fisher's exact test.

A Kaplan–Meier analysis was performed to examine the time to detection of a missed occult cancer over the 1-year follow-up period for each group. Log-rank tests were performed to assess equality of the survival functions across groups.

RESULTS

PATIENTS

During the period from October 2008 through April 2014, a total of 3186 patients were assessed for eligibility, of whom 862 underwent randomization. Eight patients were deemed ineligible after randomization, did not undergo trial interventions, and were not subsequently followed. Therefore, 854 patients were included in the intention-to-test analysis (Fig. 1). The two study groups were well balanced with respect to baseline demographic and disease characteristics (Table 1). The majority of patients were men, and the mean age was 54 years. Among the patients included in the analysis, 67.4% had deep-vein thrombosis, 32.6% had a pulmonary embolism, and 12.3% had both deep-vein thrombosis and a pulmonary embolism. A total of 6.7% of the patients 50 years of age or older in the limited-screening group and 10.2% of the patients 50 years of age or older in the limited-screening-plus-CT group had colon-cancer screening investigations (i.e., fecal occult-blood testing, sigmoidoscopy, or colonoscopy) ($P=0.16$). After completion of the initial screening strategy, 14.4% of the patients in the limited-screening group and 14.9% of the patients in the limited-screening-plus-CT group underwent additional testing for investigation of a potential cancer diagnosis ($P=0.85$).

CLINICAL OUTCOMES

Of the 854 patients in the intention-to-test population, 33 (3.9%; 95% CI, 2.8 to 5.4) received a new diagnosis of cancer in the interval between randomization and the 1-year follow-up. A total of 14 patients (3.2%; 95% CI, 1.9 to 5.4) in the limited-screening group and 19 patients (4.5%; 95% CI, 2.9 to 6.9) in the limited-screening-plus-CT group received a diagnosis of occult cancer (P=0.28). Table 2 shows the tumor types of occult cancer that were diagnosed.

In the primary outcome analysis, 4 of 14 occult cancers (29%; 95% CI, 8 to 58) were missed by the limited screening strategy (i.e., cancer was diagnosed after the screening strategy had deemed the patient as being free from cancer and before the end of the 1-year follow-up period), whereas 5 of 19 occult cancers (26%; 95% CI, 9 to 51) were missed by the strategy of limited screening plus CT (P=1.0). Therefore, after the completion of the initial screening, the absolute rates of occult-cancer detection were 0.93% (95% CI, 0.36 to 2.36) with the limited screening strategy and 1.18% (95% CI, 0.51 to 2.74) with the strategy of limited screening plus CT (absolute difference, 0.25 percentage points; 95% CI, –1.12 to 1.63). Acute leukemia (2 cases), gynecologic tumors (2), and colorectal tumors (2) were the most frequent cancers missed by the screening strategies, with no significant differences between the two strategies (Table 2). A Kaplan–Meier analysis examining the time to detection of a missed occult cancer over the 1-year follow-up period indicated no significant between-group difference (log-rank chi-square test with 1 degree of freedom, 0.03; P=0.87) (Fig. 2). The sensitivity per-protocol analysis did not significantly alter the results. In the primary per-protocol analysis, 31% (95% CI, 14 to 56) of occult cancers were missed by the limited screening strategy, whereas 24% (95% CI, 10 to 47) were missed by the strategy of limited screening plus CT (P=0.71).

In the secondary outcome analyses, there was no significant between-group difference in the mean time to cancer diagnosis (4.2 months in the limited-screening group and 4.0 months in the limited-screening-plus-CT group, P=0.88), the rate of recurrent venous thromboembolism (3.3% and 3.4%, P=1.0), overall mortality (1.4% and 1.2%, P=1.0), or cancer-related mortality (1.4% and 0.9%, P=0.75). The rate of detection of early cancers was 0.23% among those in the limited-screening group and 0.71% in the limited-screening-plus-CT group (P=0.37). Sensitivity per-protocol secondary analyses did not significantly alter the results. Neither screening strategy was associated with reported serious adverse events.

Table 1. Baseline Characteristics of the Intention-to-Test Population.*

Characteristic	Limited Occult-Cancer Screening (N=431)	Limited Occult-Cancer Screening plus CT (N=423)
Age — yr	53.7±13.8	53.4±14.2
Male sex — no. (%)	277 (64.3)	299 (70.7)
White race — no. (%)†	395 (91.6)	397 (93.9)
Weight — kg	89.8±18.3	90.4±17.7
Medical history — no. (%)		
Hypertension	86 (20.0)	101 (23.9)
Myocardial infarction	13 (3.0)	9 (2.1)
Stroke	5 (1.2)	6 (1.4)
Congestive heart failure	2 (0.5)	0
Diabetes	17 (3.9)	22 (5.2)
Previous cancer	20 (4.6)	30 (7.1)
Prior provoked venous thromboembolism	29 (6.7)	18 (4.3)
Current smoker	69 (16.0)	63 (14.9)
Past smoker	140 (32.5)	144 (34.0)
Venous thromboembolism — no. (%)		
Deep-vein thrombosis	289 (67.1)	287 (67.8)
Pulmonary embolism	142 (32.9)	136 (32.2)
Deep-vein thrombosis and pulmonary embolism	52 (12.1)	53 (12.5)
Medications — no. (%)		
Oral contraceptive	29 (6.7)	19 (4.5)
Exogenous estrogen	8 (1.9)	11 (2.6)
Antiplatelet agent	21 (4.9)	19 (4.5)

* Plus–minus values are means ±SD. There were no significant between-group differences, except for the difference in sex (P=0.045). Patients who were assigned to the strategy of limited occult-cancer screening plus computed tomography (CT) underwent comprehensive CT of the abdomen and pelvis.
† Race was self-reported.

DISCUSSION

In our trial, a screening strategy for occult cancer that included comprehensive CT of the abdomen and pelvis did not lead to fewer missed cancers than the number missed with a limited screening strategy. Furthermore, the screening

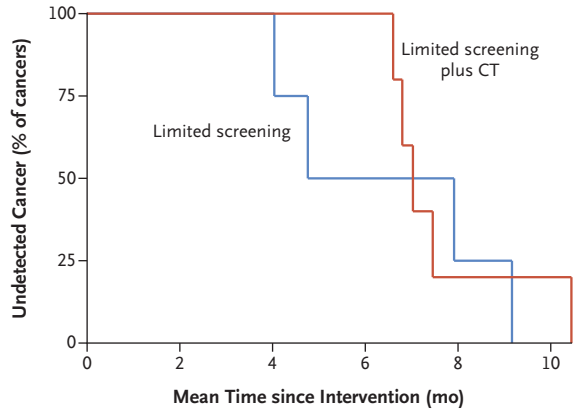

Figure 2. Kaplan–Meier Curves for Time to Detection of Missed Occult Cancer.

Table 2. Occult Cancer Tumor Types.

Tumor Type	Limited Occult-Cancer Screening (N=14)	Limited Occult-Cancer Screening plus CT (N=19)
	no. of tumors/total no. (%)	
During screening period		
Acute leukemia	0/10	0/14
Gynecologic	3/10 (30)	0/14
Skin: melanoma	1/10 (10)	0/14
Colorectal	0/10	3/14 (21)
Prostate	2/10 (20)	0/14
Pancreatic	2/10 (20)	0/14
Cholangiocarcinoma	1/10 (10)	2/14 (14)
Lymphoma	1/10 (10)	3/14 (21)
Breast	0/10	2/14 (14)
Urologic	0/10	3/14 (21)
Unknown primary	0/10	1/14 (7)
During follow-up period		
Acute leukemia	1/4 (25)	1/5 (20)
Gynecologic	1/4 (25)	1/5 (20)
Skin: melanoma	0/4	1/5 (20)
Colorectal	1/4 (25)	1/5 (20)
Prostate	0/4	1/5 (20)
Pancreatic	1/4 (25)	0/5

strategy that included CT did not appear to detect significantly more occult cancers (including early cancers), shorten the time to cancer diagnosis, or reduce cancer-related mortality.

Patients with unprovoked venous thromboembolism and a negative screening result for occult cancer with the limited screening strategy had an incidence of cancer diagnosis of 0.93% (95% CI, 0.36 to 2.36) over the following year, which is similar to the incidence reported in patients without venous thromboembolism.[7] Our results suggest that a limited screening strategy for occult cancer (history taking, physical examination, basic blood testing, chest radiography, and age-specific and sex-specific cancer screening) may be adequate for patients who have a first unprovoked venous thromboembolism.

The 95% confidence interval around the absolute difference in missed occult cancers between the two screening strategies (0.25 percentage points; 95% CI, −1.12 to 1.63) excludes our hypothesized absolute risk reduction of 3 percentage points. That is, our trial excludes a clinically relevant difference in missed occult cancers with CT. In a best-case scenario (i.e., lower boundary of the confidence interval), limited screening plus CT would miss fewer occult cancers than limited screening alone by a margin of 1.12 percentage points. This best-case scenario translates into a number needed to screen of 91 to detect one missed occult cancer. Furthermore, radiation exposure is a consideration with CT. Multiphasic CT of the abdomen and pelvis is associated with a median effective dose of radiation exposure of 31 millisieverts (interquartile range, 21 to 43), which is equivalent to 442 chest radiographs.[14] The estimated number of patients undergoing multiphasic CT of the abdomen and pelvis required for the development of one radiation-induced cancer is 460 (interquartile range, 330 to 680) for women 40 years of age and 498 (interquartile range, 360 to 730) for men 40 years of age.[14] Hence, it is exceedingly unlikely that CT permits early detection of clinically relevant numbers of cancers and even less likely that early detection of these cancers would provide an overall net clinical benefit.

The rate of detection of occult cancer in our study was lower than expected. A systematic review and meta-analysis of the literature that pooled data from older clinical studies showed a

rate of occult-cancer detection of up to 10% at 12 months after a diagnosis of unprovoked venous thromboembolism.[6] However, more recently published studies suggest a much lower risk, perhaps owing to the effect of better cancer screening in developed countries.[7,15] A study comparing the risk of cancer diagnosis among patients with unprovoked venous thromboembolism with that among matched controls over a 30-month follow-up period showed a cumulative incidence of 3.2% (95% CI, 2.3 to 4.4) among patients with venous thromboembolism and 2.9% (95% CI, 2.0 to 4.0) among patients without venous thromboembolism.[7] Similarly, a prospective cohort study showed rates of occult-cancer diagnosis of 3.7 to 5.0% over a median of 2.5 years of follow-up after the completion of cancer screening.[15]

Two previous studies have directly compared limited and extensive screening strategies for occult cancer.[10,15] Our results are consistent with those of a prospective, nonrandomized, concurrent-controlled cohort study comparing a limited screening strategy for occult cancer (288 patients) with a strategy that also included mammography in women and CT of the chest, abdomen, and pelvis in all patients (342 patients). The study did not show any significant difference in the number of occult cancers subsequently diagnosed (5.0% in the limited-screening group and 3.7% in the extensive-screening group) or in overall mortality (8.3% and 7.6%, respectively) over a 2.5-year follow-up period.[15] In the other study, a randomized, controlled trial involving patients who had a negative screening result for occult cancer with a limited screening strategy, patients were randomly assigned to no further testing or additional testing with ultrasonography and CT of the abdomen and pelvis, measurement of tumor markers, and endoscopy.[10] The trial was stopped early (after 200 participants had been enrolled) owing to difficulties in recruitment. The extensive screening strategy had a sensitivity of 93% and increased detection of early-stage (T_{1-2}, N_0) cancer (64% of cancers detected vs. 20% with the limited screening strategy, $P=0.047$). A nonsignificant absolute 1.9-percentage-point lower risk of cancer-related death with the extensive-screening group over the 2-year follow-up period was also reported. Although the lack of a significant between-group difference in cancer-related mortality might be due to a lack of power, methodologic limitations (e.g., Zelen randomization procedure) and possible lead-time bias undermined the findings of the study.

A limitation of our trial is the open-label design, which theoretically could be associated with a risk of bias with regard to the frequency of the outcome, as compared with the frequency that might have been observed in a placebo-controlled trial. However, the primary end point (biopsy-proven cancer) in our trial is a hard outcome, making bias less likely. We also minimized this type of bias by instructing all trial participants about the signs and symptoms of primary and secondary outcomes and safety events, with explicit instruction to contact study staff should any of these occur. It is also possible that a more extensive screening strategy would have missed fewer occult cancers. CT of the chest was not included in the strategy of limited screening plus CT because CT pulmonary angiography had been performed in many patients to establish the diagnosis of pulmonary embolism. Approximately a third of patients had a diagnosis of pulmonary embolism (Table 1), and in a majority of these patients (78%), the diagnosis was made by CT pulmonary angiography. Reexposing these patients to additional radiation for study purposes did not seem reasonable. Furthermore, no occult lung cancers were diagnosed (during the screening or follow-up period) in our trial (Table 2). Therefore, it is unlikely that CT of the chest would have changed the conclusions. Finally, we started the study by screening more than 3000 patients, of whom 862 underwent randomization. It is possible that our study population had demographic characteristics that put them at a lower risk for cancer than the population as a whole. However, it is unlikely that the screening methods would have produced significantly different results even if the incidence of cancer had been higher.

In conclusion, we found that the prevalence of occult cancer was low among patients who had a first unprovoked venous thromboembolism. Routine screening with CT of the abdomen and pelvis did not provide a clinically significant benefit.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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