Characteristics and Outcomes of Lung Cancer Screening Among Individuals With or Without Cancer History

Bradley Maller,[1] Vani N. Simmons,[2] Margaret M. Byrne,[3] Tawee Tanvetyanon[4]

Abstract

Epidemiologic studies indicate that smokers with cancer history have a higher risk of developing lung cancer than smokers without cancer history. We analyzed prospectively collected data from our institutional lung cancer screening program. Comparing between the 2 groups, those with cancer history actually had a significantly lower rate of abnormal screening results than their counterparts.

Background: Lung cancer screening with low-dose computed tomography (LDCT) can reduce mortality from lung cancer. Individuals with previous malignancy are at an increased risk of lung cancer but are often underrepresented in clinical trials. This study compares the outcomes of LDCT screening among individuals with and without cancer history. **Materials and Methods:** The study cohort included consecutive participants undergoing LDCT screening at a tertiary care cancer institution. Abnormal screening result was defined as having Lung-RADS 3 or 4 at baseline (T0). Participant information was prospectively collected and predicted risk of lung cancer was calculated per the PLCOm2012 model. **Results:** A total of 454 participants underwent LDCT screening. Abnormal screening result occurred in 57 (13.2%) participants at T0, and lung cancer was diagnosed in 11 (2.4%) participants. Among 153 individuals with cancer history, abnormal result occurred in 9.8%, compared with 15.4% among those without cancer history ($P = .11$). Lung cancer was diagnosed in 1.3%, compared with 3.5% ($P = .22$). The predicted risk of lung cancer at 6 years was higher among individuals with cancer history than those without: 4.8% versus 2.2% ($P < .001$). In a multivariable analysis, cancer history significantly reduced the likelihood of abnormal screening (odds ratio, 0.49; 95% confidence interval, 0.26-0.94; $P = .03$). We observed a higher proportion of participants who had a previous CT scan available for comparison at T0 among individuals with cancer history than those without: 43.1% versus 9.1% ($P < .001$). **Conclusions:** In this single-institutional study, individuals with cancer history were significantly less likely to have abnormal screening results than those without cancer history.

Clinical Lung Cancer, Vol. 22, No. 4, e629-36
Keywords: Cancer survivor, Preventive health service, Secondary malignancy, Survivorship, Tobacco use

Background

Since 2013, lung cancer screening with low-dose computed tomography (LDCT) has been recommended by the United States Preventive Services Task Force (USPTF) for individuals at high risk of lung cancer.[1] According to the USPTF, high-risk criteria encompass adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. This recommendation is based on results from the National Lung Screening Trial (NLST), a randomized clinical trial of LDCT screening versus chest x-ray enrolling over 50,000 participants.[2] The NLST demonstrated that LDCT screening reduced lung cancer death by 20%. Moreover, results published in 2020 from the NELSON trial, a randomized controlled trial in Europe, which included over 13,000 participants, showed that LDCT screening reduced mortality from lung cancer as compared with no screening by 24%.[3]

Although smoking is a key risk factor for lung cancer, previous malignancy also increases the risk of lung cancer. Smokers with cancer history face an even higher risk of lung cancer than those

[1]Department of Internal Medicine, Morsani College of Medicine, University of South Florida, Tampa, FL
[2]Tobacco Research and Intervention Program
[3]Department of Health Outcomes and Behavior
[4]Department of Thoracic Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Submitted: Jul 2, 2020; Revised: Nov 29, 2020; Accepted: Dec 10, 2020; Epub: Dec 19, 2020

Address for correspondence: Tawee Tanvetyanon, MD, MPH, Thoracic Oncology Department, H. Lee Moffitt Cancer Center and Research Institute, 12902 USF Magnolia Drive, FONB1-Thor, Tampa, FL, 33612
E-mail contact: tanvett@moffitt.org

1525-7304/$ - see frontmatter
https://doi.org/10.1016/j.clc.2020.12.006

without cancer history owing to their past cancer treatment, shared risk factors, or genetic predisposition. According to the Surveillance, Epidemiology, and End Results data, nearly 1 in 12 individuals with cancer history will develop a secondary malignancy in their lifetime, the most common of which is lung cancer.[4] The number of cancer survivors is increasing rapidly in the United States, from 14 million in 2012 to nearly 20 million by 2024.[5] Because of this, lung cancer screening for cancer survivors is a large and growing public health concern. However, the NLST excluded many cancer survivors from participation. Specifically, all persons who had treatment for or evidence of invasive cancer other than non-melanoma skin cancer or carcinoma in situ (except transitional cell carcinoma in situ) within 5 years were excluded, along with anyone who ever had lung cancer.[6] As a result, only 4.2% of NLST participants were cancer survivors.[7] As such, there remains a relatively limited pool of data regarding the role of LDCT screening among individuals with cancer history.

Despite the absence of specific evidence from prospective trial for this population, major national organizations, including the National Comprehensive Cancer Network (NCCN), have recommended the use of LDCT screening among cancer survivors.[8] Nevertheless, there are epidemiologic studies to support this. For example, according to data from the Surveillance, Epidemiology, and End Results program, survivors of smoking-related cancers including lung, head and neck, and bladder cancers experienced about 2 to 5 times higher incidence of non−small-cell lung cancer (NSCLC) than their matched general population.[9] Even among survivors of non-tobacco−related cancers such as breast or hematologic cancer, their lung cancer risk may be elevated owing to the carcinogenic effect of past cancer treatment. A meta-analysis of randomized trials investigating radiotherapy for breast cancer demonstrated that women who received radiotherapy experienced about 2 times higher risk of lung cancer than those who did not.[10] Currently, the NCCN criteria for LDCT screening are in line with the USPTF criteria. In addition, the NCCN criteria also allow individuals who are as young as 50 years of age and have as light of a smoking history as 20 pack-years, if there are additional risk factors increasing their predicted risk of lung cancer at 6 years to $\geq$ 1.3%.[8] Beyond the NCCN criteria for LDCT screening, the NCCN also issues a separate guideline recommending the use of LDCT for lung cancer survivors, specifically for those with resected stage I or II NSCLC who are disease-free for 2 years after surgery and, for all others, if disease-free for 5 years after curative treatment.[11]

In a previous study on LDCT screening among 139 individuals with cancer history, abnormal screening results at baseline occurred in 16%, and lung cancer was diagnosed in 5% of participants.[12] However, the study did not provide results among participants without cancer history for comparison, and the predicted risk of lung cancer was not reported. Given the elevated risk of secondary lung cancer among cancer survivors, LDCT screening appears to have a great potential to mitigate the excess risk of lung cancer morbidity and mortality in this population. At our institution, LDCT screenings have been offered regardless of cancer history, thus providing for a unique opportunity to compare the characteristics and outcomes of LDCT screening among those with and without cancer history. In this retrospective observational study, we investigate the differences in characteristics between these 2 populations and present the findings from real-world practice of LDCT screening among individuals with and without cancer history.

Materials and Methods

Designs, Participant Eligibility, and Screening Procedure

After approval by the Scientific Review Committee and Institutional Review Board, a retrospective cohort study based on electronic medical records was conducted, including consecutive participants who underwent LDCT screening at Moffitt Cancer Center from 2011 to 2019. Although the eligibility criteria varied over time, LDCT screening was offered to individuals who met the NCCN eligibility criteria, either category 1 or category 2.[8] Category 1 was based on the NLST eligibility criteria and included those 55 to 74 years of age; 30 or more pack-year history of smoking tobacco; and, if former smoker, had quit within 15 years. Category 2 encompassed other high-risk persons not represented in the original NLST criteria. The persons in category 2 could be younger and have a lower smoking history ($\geq$ 50 years of age, and $\geq$ 20 pack-year smoking history) if they had an additional risk factors increasing their predicted risk of lung cancer at 6 years to $\geq$ 1.3%.

The screening procedure began with potential participants directly contacting the screening center or being referred by a physician. A screening coordinator would then interview prospective participants by phone. Those who did not meet high-risk criteria, had chest CT within the past 12 months, or had symptoms warranting full-dose chest CT scan were advised against LDCT screening. Prior to Medicare coverage in 2015,[13] LDCT screening was offered for an out-of-pocket fee. A shared decision-making visit with a physician or nurse practitioner was required for Medicare beneficiaries since 2015. Self-administered questionnaires on demography, medical, and social history were completed by all participants and retained in their electronic medical records. LDCT was performed with volumetric CT dose index of $\leq$ 3.0 mGy, and lung nodules were reported using mean diameter according to the Lung-RADS system.[14] Participants were notified of screening results by phone. Those with negative LDCT screening received a reminder letter for the next annual screening, whereas those with abnormal screening results were offered more frequent screening or other procedures according to Lung-RADS category or multidisciplinary tumor board discussion.

Definitions and Outcomes of Interest

We reclassified all nodules according to Lung-RADS version 1.1 using size and characteristics of nodules described in the LDCT screening reports.[15] Specifically, solid nodules measuring 6 to $<$ 8 mm at baseline screening (T0) or newly detected solid nodules measuring 4 to $<$ 6 mm during subsequent screenings were classified as Lung-RADS category 3, whereas Lung-RADS category 4 nodules included solid nodules measuring $\geq$ 8 mm at baseline and growing or new nodules 6 mm to $<$ 8 mm. Abnormal LDCT screening was defined as Lung-RADS category 3 or 4. At our institution, all radiology reports were mandated to include the availability and the date of previous film used for comparison.

The primary outcomes of interest in this study were: (1) abnormal screening results defined as Lung-RADS category 3 or 4 and (2) lung cancer diagnosis. Secondary outcomes were diagnosis

of any malignancy owing to incidental findings on LDCT and thoracotomy for benign lesions. Cancer history was defined as having any prior cancer diagnosis, excluding non-melanoma skin cancer. Family history of lung cancer included participants' blood relatives of any degree. Comorbidity score was calculated based on Charlson's index, including chronic obstructive pulmonary disease (COPD) but excluding a previous cancer diagnosis.[16] Predicted risk of lung cancer was calculated using the PLCOm2012 model incorporating factors such as smoking, education, and body habitus.[17] We determined whether participants met the USPTF and NCCN criteria for LDCT screening and finally, distance to screening facility, which may reflect ease of access to cancer screening[18] was calculated from zip code of primary residence.[19]

Statistical Analyses

Descriptive statistics were calculated, including median and range for continuous variables as well as frequency and proportion for categorical variables. To compare groups with and without cancer history, the χ^2 or Fisher exact test was used for categorical variables, whereas non-parametric tests were used for continuous variables. Logistic regression analyses were performed to identify factors associated with abnormal LDCT screening. Variable selection in all multivariable models was conducted using a backward stepwise methodology, where variables were retained if they met a *P*-value threshold of .10. All *P*-values were 2-tailed, and the significance level was set at $P < .05$. Analyses were performed using IBM SPSS Statistics, Version 25.0 (Armonk, NY).

Results

Participant Characteristics and Outcomes of Interest

A total of 454 participants underwent LDCT screening (Table 1). Their median age was 65 years (range, 39-91 years). Notable risk factors for lung cancer, such as COPD and active smoking, were present in 113 (28%) and 136 (30%) participants, respectively. Besides COPD, other common comorbidities included diabetes in 26 (5.7%), connective tissue diseases in 16 (3.5%), and myocardial infarction in 14 (3.1%). The median predicted risk of lung cancer at 6 years was 2.7%. When determining if the USPTF eligibility criteria were met, 41 participants did not have sufficient information for determination, leaving 413 participants available. Of these, 242 (58.6%) participants met the criteria. Reasons for 171 participants not meeting the criteria included age not between 55 to 80 years in 38, smoking < 30 pack-years in 85, and quitting smoking over 15 years ago in 48 participants. When applying NCCN eligibility criteria, 46 participants did not have adequate information, leaving 408 participants available. Of these, only 335 (82.1%) participants met the criteria. Reasons for 73 participants not meeting the criteria included age < 50 years in 10, smoking < 20 pack-years in 36, and predicted risk of lung cancer at 6 years < 1.3% in 27 participants.

Abnormal screening results at T0 occurred in 57 (12.5%) participants, consisting of Lung-RADS 3 in 7.9% and Lung-RADS 4, in 4.6%. At T1, abnormal screening results occurred in 15 (6.5%) of 213 subjects who completed T1 scan at time of analysis. Among participants with Lung-RADS 2 at T0, the median interval between T0 and T1 at T0 was 12.5 months among those without cancer history and 12.4 months among those with cancer history, indicating similar adherence to screening in both groups. Lung cancer was subsequently diagnosed in 11 (2.4%) participants (Table 2). Nine of 11 lung cancer cases had abnormal screening at T0. Most lung cancers were diagnosed at an early stage: stage I in 7, stage II in 2, and stage III in 2 participants. Cancers other than lung cancer were diagnosed in 5 (1.1%) participants. Of these, 3 participants underwent a curative treatment. These were for localized recurrent renal cell carcinoma, new primary localized urothelial carcinoma, or localized lymphoma. Lastly, thoracotomy for benign diagnosis occurred in 3 participants.

Comparison Between Individuals With and Without Cancer History

Of 454 participants, 45 lacked information on cancer history owing to incomplete questionnaires, leaving 407 individuals available for analysis: 254 (63.4%) without and 153 (37.6%) with previous cancer (Table 1). Baseline characteristics in gender, race, smoking status, comorbidity score, history of COPD, family history of lung cancer, and home distance were comparable between individuals with and without cancer history. However, those with cancer history were older (median age, 67.7 years vs. 63.5 years; $P < .001$). In addition, those with cancer history had a higher median predicted risk of lung cancer and were more likely to meet NCCN eligibility criteria ($P < .001$).

No statistically significant differences in the outcomes of interest were found among individuals with versus without cancer history. Abnormal screening at T0 occurred in 15 (9.8%) of 153 individuals with cancer history, compared with 39 (15.4%) of 254 individuals without ($P = .11$). To date, 272 and 693 LDCTs were performed in each group, respectively. Lung cancer was diagnosed in 2 (1.3%) of 153 participants, compared with 9 (3.5%) of 254 participants ($P = .22$). We found that 19.8% of participants had a previous chest CT scan available for comparison at T0 screening with a mean interval since that scan to T0 of 42.6 months. There was a significantly higher proportion of available previous scans among participants with previous malignancy than those without: 66 (43.1%) of 153 participants versus 23 (9.1%) of 254 participants ($P < .001$).

Predictors of Abnormal LDCT Screening at T0

We identified factors potentially associated with abnormal screening results by examining various demographic, medical, and screening-related factors (Table 3). In a univariable analysis, history of COPD and comorbidity score were identified as significant predictors of abnormal screening. In addition, previous cancer and ineligibility per the NCCN criteria were associated with a lower likelihood of abnormal screening. In a multivariable analysis, only 3 factors were identified as independent predictors of abnormal screening result: comorbidity, cancer history, and meeting the NCCN eligibility criteria. Having comorbidity score ≥ 1 predicted the occurrence of abnormal screening results. Meeting the NCCN eligibility criteria also predicted abnormal screening results. However, cancer history predicted a lower likelihood of abnormal screening results.

Individuals With Previous Chest CT Scan at T0

Individuals with previous chest CT scan for comparison at T0 (N = 89) had the previous scan at a median interval of 25 months

Table 1 Characteristics of Participants and Outcomes

Characteristics	Overall Participants (N = 454)	Individuals Without Cancer History (N = 254)	Individuals With Cancer History (N = 153)	*P* Value
Demographics				
Median age, y (range)	65.0 (39-91)	63.5 (42-85)	67.7 (39-91)	<***.001***
Age between 55 and 80 years				.30
Yes	461 (91.6)	230 (90.6)	143 (93.5)	
No	38 (8.4)	24 (9.4)	10 (6.5)	
Gender				.18
Male	224 (49.3)	132 (52.0)	69 (45.1)	
Female	230 (50.7)	122 (48.0)	84 (54.9)	
Race				.22
White	419 (92.3)	239 (94.1)	139 (90.8)	
Other	35 (7.7)	15 (5.9)	14 (9.2)	
Marital status				.35
Currently married	296 (65.2)	161 (63.4)	104 (68.0)	
Other	141 (34.8)	93 (38.6)	49 (32.0)	
Distance from facility, miles				.68
0-15	127 (28.0)	69 (27.3)	42 (27.6)	
15-30	186 (41.2)	105 (41.5)	57 (37.5)	
>30	139 (30.8)	79 (31.2)	53 (34.9)	
Education				.06
High school or under	99 (25.3)	55 (22.4)	44 (30.1)	
Training post high school	133 (33.9)	80 (32.5)	53 (36.3)	
College or above	160 (40.8)	111 (45.1)	49 (33.6)	
Medical history				
Median body mass index (range)	27.6 (14-63)	27.8 (14-63)	27.4 (18-46)	.69
Family history of lung cancer				.55
Yes	133 (29.3)	89 (34.3)	47 (31.3)	
No	268 (59.0)	165 (65.7)	103 (68.7)	
COPD diagnosis				.87
Yes	113 (27.6)	70 (27.6)	41 (26.8)	
No	296 (72.4)	184 (72.4)	112 (73.2)	
Comorbidity score				.24
0	241 (58.8)	156 (61.4)	85 (55.6)	
≥1	169 (41.2)	98 (38.6)	68 (44.4)	
Have previous scan for comparison				<***.001***
Yes	90 (19.8)	23 (9.1)	66 (43.1)	
No	364 (80.2)	231 (90.9)	87 (56.9)	
Social history				
Smoking status				.11
Current	134 (29.5)	75 (29.5)	57 (37.3)	
Former	279 (61.5)	179 (70.5)	96 (62.7)	
Median age at quit, y (range)	54.0 (20-77)	53.0 (22-75)	55.0 (20-77)	.06
Median years smoked (range)	36 (0-64)	35 (0-64)	38 (0-63)	***.03***
Median cigarettes per day (range)	20 (0-70)	20 (0-70)	20 (0-60)	.66
Median years since quitting smoking (range)	10.5 (0-55)	10.1 (0-45)	11.3 (0-55)	
Median predicted lung cancer risk at 6 y (range)	2.7 (0.1-49.0)	2.2 (0.1-49.0)	4.8 (0.1-47.0)	<***.001***
Quit over 15 years ago				.33
Yes	80 (29.2)	69 (36.1)	24 (30.0)	
No	194 (70.8)	122 (63.9)	56 (70.0)	

Table 1 Continued

Characteristics	Overall Participants (N = 454)	Individuals Without Cancer History (N = 254)	Individuals With Cancer History (N = 153)	*P* Value
Smoking < 30 pack-years				.18
Yes	93 (22.8)	63 (24.9)	29 (19.1)	
No	315 (77.2)	190 (75.1)	123 (80.9)	
Meet USPTF eligibility criteria				.06
Yes	242 (58.6)	141 (55.5)	99 (66.1)	
No	171 (41.4)	113 (44.5)	53 (34.9)	
Meet NCCN eligibility criteria				***<.001***
Yes	333 (82.2)	195 (77.1)	138 (90.8)	
No	72 (19.9)	58 (22.9)	14 (9.2)	
Outcomes of screening				
Lung-RADS category at baseline				.26
1-2	394 (86.8)	215 (84.6)	138 (90.2)	
3	36 (7.9)	24 (9.4)	10 (6.5)	
4	21 (4.6)	15 (5.9)	5 (3.3)	
Lung-RADS category 3 or 4				.11
Yes	57 (12.6)	39 (15.4)	15 (9.8)	
No	397 (87.4)	215 (84.6)	138 (90.2)	
Lung cancer diagnosed				.22
Yes	11 (2.4)	9 (3.5)	2 (1.3)	
No	444 (97.8)	245 (96.5)	151 (98.7)	
Other cancer diagnosed				.37
Yes	5 (1.1)	2 (0.8)	3 (2.0)	
No	449 (98.9)	252 (99.2)	150 (98.0)	
Benign thoracotomy				1.00
Yes	4 (0.9)	3 (1.2)	1 (0.7)	
No	451 (99.1)	251 (98.8)	152 (99.3)	

Bold italics indicate a statistically significant *P* value.
Abbreviations: COPD = chronic obstructive pulmonary disease; NCCN = National Comprehensive Cancer Network; USPTF = United States Preventive Services Task Force.

prior to T0. No significant difference in the interval was found between those with and without cancer history. Among those without cancer history (N = 23), the median interval was 20 months, compared with 26 months among those with cancer history (N = 66; $P = .87$). In the subgroup of individuals with cancer history (N = 66), those who had cancer treated within the past 5 years (N = 24) had the previous scan more recently than those who had cancer treated over 5 years ago (N = 42); however, this was not statistically significant. The median interval was 21 months versus 38 months, respectively ($P = .66$).

Subgroup Analyses of Individuals With Cancer History

Among 153 individuals with cancer history, their cancer sites included breast in 52 (34%), prostate in 26 (17%), bladder in 20 (13%), lung in 14 (9%), head and neck in 13 (9%), gastrointestinal tract in 10 (7%), melanoma in 8 (5%), cervix or uterus in 6 (4%), and other sites in 4 (3%). Of note, there were 18 individuals who had 2 cancer sites. The proportion of individuals with abnormal LDCT screening appeared comparable across cancer sites. The median time from cancer treatment completion to LDCT screening was 6 years (range, 0-55 years). This time interval was not significantly associated with abnormal screening results with an odds ratio of 1.007 (95% confidence interval, 0.95-1.07) per year increment. With regard to the availability of a previous chest CT scan for comparison at T0, lung cancer survivors had the highest scan availability at 93% (13 of 14), followed by 80% (8 of 10) gastrointestinal tract cancer survivors, 46% (6 of 13) head and neck cancer survivors, 46% (24 of 52) breast cancer survivors, and 25% (13 of 53) genitourinary or gynecological cancer survivors.

Discussion

We reported on real world experiences of LDCT screening at one of the National Cancer Institute-designated Comprehensive Cancer Centers with the aim to compare between participants with and without cancer history. Among 454 participants, about one-third had a previous cancer. We did not find a positive association between cancer history and either abnormal screening results or lung cancer diagnoses. In fact, after adjusting for comorbidity and risk profile per the NCCN eligibility criteria, cancer history significantly lowered the likelihood of abnormal screening results. Given that an

Table 2 Cases With Malignant Diagnosis or Thoracotomy Prompted by LDCT Screening

Case	Pathologic Diagnosis	Previous Cancer	Lung-RADS at T0	Time From T0 to Diagnosis, mos	Treatment
Lung cancer					
1	T2aN0 lung adenocarcinoma	Bladder cancer	2	45	Lobectomy
2	T3N0 squamous cell carcinoma of lung	Laryngeal cancer	4	4	Lobectomy and adjuvant chemotherapy
3	T3N1 squamous cell carcinoma of lung	None	1	71	Bi-lobectomy, adjuvant chemotherapy
4	T1aN0 squamous cell carcinoma of lung	None	4	6	Wedge resection
5	T1aN2 lung adenocarcinoma	None	4	1	Chemoradiotherapy
6	T3N0 lung adenocarcinoma	None	4	5	Lobectomy and adjuvant chemotherapy
7	T2aN0 lung adenocarcinoma	None	4	1	Lobectomy and adjuvant chemotherapy
8	T1miN0 lung adenocarcinoma	None	3	57	Wedge resection
9	TisN0 lung adenocarcinoma	None	3	30	Wedge resection
10	Pulmonary carcinoid tumor	None	4	5	Stereotactic body radiation
11	Limited stage small-cell lung cancer	None	4	1	Chemoradiotherapy
Other cancer					
12	Recurrent localized renal cell carcinoma	Renal cell carcinoma	2	3	Percutaneous microwave ablation
13	Recurrent metastatic breast cancer	Breast cancer	3	2	Hormonal therapy and chemotherapy
14	Urothelial carcinoma of renal pelvis	Breast cancer	2	6	Nephroureterectomy
15	Localized low-grade lymphoma	None	4	2	Wedge resection
16	Follicular lymphoma grade II-III	None	2	7	Chemotherapy
Benign condition					
17	Hamartoma	Cervical cancer	4	3	Segmentectomy
18	Bronchogenic cyst	None	1	3	Excision
19	Necrotizing granuloma	None	4	2	Wedge resection
20	Atypical mesothelial proliferation	None	2	23	Video-assisted thoracoscopic biopsy

Abbreviation: LDCT = low-dose computed tomography.

abnormal result can serve as the first step to lung cancer detection and the fact that predicted lung cancer risk is higher among cancer survivors, our finding is somewhat unexpected.

To our knowledge, this study is among the first to compare the characteristics and outcomes of LDCT screening between cancer survivors and individuals without history of cancer. We observed that only 1.3% of individuals with cancer history were diagnosed with lung cancer, compared with 3.5% among those without cancer history. In the NLST, throughout the course of 3 annual LDCT screenings, 3.9% of participants were diagnosed with lung cancer.[2] Therefore, the number of lung cancers being diagnosed among cancer survivors seems lower than expected, especially when considering the elevated predicted risk of lung cancer in this population. Although our sample size is modest, it seems unlikely that the true rates of abnormal screening result or lung cancer diagnosis will, in fact, be higher among individuals with cancer history than those without cancer history.

There may be several plausible explanations for the lower rates of abnormal screening results among individuals with previous malignancy. First, for many cancer survivors who are at high risk for pulmonary metastasis or recurrence, full-dose chest CT scan is often indicated. As such, this group of cancer survivors will not be referred to have LDCT screening, thus lowering the chance of abnormal screening results owing to pulmonary metastasis. Second, many cancer survivors may already have undergone chest CT scan or positron emission tomography as part of their cancer care. These tests could have served to detect any incidental lung cancer, leaving only those without lung cancer to be referred to LDCT screening. In fact, our study showed that a much higher proportion of participants with cancer history had a previous chest CT scan for comparison at T0. This could also explain the relatively low number of abnormal results among participants with cancer history because suspicious nodules will not be suspicious if their stability can be confirmed over time. Furthermore, as the number of chest CT being performed increases, abnormal findings will decrease. For example, in the NLST, the incidence of abnormal results dropped from 27.3% at T0 to 16.8% at T2.[2]

It is important to note that the lower rates of abnormal findings or lung cancer diagnosis among individuals with cancer history does not necessarily mean that the benefit from mortality reduction will also be lower. In our study, cases number 8, 9, and 10 (Table 2) were diagnosed with carcinoma in-situ, carcinoid tumor, or minimally invasive adenocarcinoma. These cases may represent an over-diagnosis, a situation in which screening detects slowly progressing tumors that will not cause symptoms during the patient's lifetime.[20] Over-diagnosis cannot be considered as a benefit of cancer screening because it will not result in any improvement in the mortality from the cancer. Interestingly, in our study, all these potentially over-diagnosed cases were found exclusively among individuals without previous cancer. On the opposite extreme, a diagnosis of advanced

Table 3 Factors Predicting Abnormal Screening Result

Factors	Univariable Odds Ratio (95% CI); *P* Value	Multivariable Odds Ratio (95% CI); *P* Value
Age ≥ 65 y	1.23 (0.69-2.19); .48	NS
Female gender	0.82 (0.46-1.46); .49	NS
Caucasian race	2.15 (0.49-9.33); .31	NS
Body mass index ≥ 30	1.09 (0.59-2.00); .78	NS
History of COPD	2.23 (1.24-4.03); ***.01***	NS
History of cancer	0.59 (0.32-1.13); .11	0.49 (0.26-0.94); ***.03***
Comorbid score ≥ 1	2.18 (1.22-3.89); ***.01***	1.99 (1.10-3.59); ***.03***
Current smoker	1.52 (0.84-2.73); .16	NS
Meeting the USPTF criteria	1.75 (0.94-3.22); .07	NS
Meeting the NCCN criteria	6.52 (1.55-27.42); ***.01***	6.57 (1.54-27.98); ***.01***
Having previous scan for comparison	0.90 (0.44-1.83); .78	NS
Predicted lung cancer risk ≥ 2.7% at 6 years	1.59 (0.89-2.87); .12	NS

Bold italics indicate a statistically significant *P* value.
Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; NCCN = National Comprehensive Cancer Network; NS = variables not selected into the final model; USPTF = United States Preventive Services Task Force.

cancer for which there is no effective treatment can also be considered as futile. In our study, case numbers 12 through 15 were diagnosed with cancers other than lung cancer. Nevertheless, in all of them, effective or even curative treatment could be instituted. The findings from our study suggest that LDCT screening is feasible among cancer survivors, and future studies in this population are warranted.

The strength of our study includes the availability of a prospectively collected dataset, enabling the calculation of predicted lung cancer risk among all participants as well as specific details regarding cancer and treatment among those with cancer history. However, the study has some important limitations. First, as with most retrospective and observational studies, there are potential issues with missing documentation and incomplete outcome data. In our study, for example, it is possible that some participants may have been diagnosed with lung cancer at a different facility. However, this issue may be ameliorated in our institution as standard operative protocols mandate documentation of a follow-up phone call for unresponsiveness to recall letters. Second, in retrospect, some participants did not meet the NCCN or USPTF eligibility criteria. These criteria are in flux, and the new USPTF criteria will allow participants age 50 to 80 years with at least 20 pack-years smoking history.[21] Although the screening program at our institution strives to adhere to the NCCN screening eligibility criteria, exceptions are made at times. For example, some pulmonologists use LDCT screening for long-term follow-up of patients with known pulmonary nodules regardless of age or smoking history to reduce exposure to radiation. Furthermore, the NCCN guideline itself recommends LDCT for some lung cancer survivors regardless of other risk factors.[11] Screening low-risk individuals may lower the yield of LDCT screening overall. Nevertheless, because our analysis adjusted for eligibility based on the NCCN criteria, the finding that cancer history is associated with lower likelihood of abnormal screening results should still hold.

In summary, although we observed a higher predicted risk of lung cancer among cancer survivors than individuals without cancer history, we found no evidence that LDCT screening would yield a greater number of abnormal results or lung cancer cases being diagnosed.

Clinical Practice Points

- LDCT is recommended for high-risk individuals to reduce mortality from lung cancer.
- Among high-risk individuals with cancer history, the risk of developing a new primary lung cancer is generally higher than those without cancer history.
- We analyzed data from 454 individuals who participated in LDCT screening at our institution and found that the predicted risk of lung cancer was higher among those with cancer history.
- However, we found that individuals with cancer history were, in fact, significantly less likely to have abnormal screening results.
- An analysis on the proportion of individuals with previous chest CT scan available for comparison at baseline showed that those with cancer history were much more likely to have had a previous CT scan available.
- For high-risk individuals with cancer history, especially those who had chest CT scan in the past, the yield of LDCT screening may not necessarily be higher than those without cancer history, even when the predicted risk of lung cancer is higher.

Acknowledgment

The study was supported by a grant from James Esther King Biomedical Research.

Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Moyer VA, U.S. Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2014; 160:330-8.
2. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011; 365:395-409.

3. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med* 2020; 382:503-13.
4. Donin N, Filson C, Drakaki A, et al. Risk of second primary malignancies among cancer survivors in the United States, 1992 through 2008. *Cancer* 2016; 122:3075-86.
5. de Moor JS, Mariotto AB, Parry C, et al. Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. *Cancer Epidemiol Biomarkers Prev* 2013; 22:561-70.
6. National Lung Screening Trial, Available at: https://clinicaltrials.gov/ct2/show/NCT00047385. Accessed: March 28, 2020.
7. Aberle DR, Adams AM, Berg CD, et al, National Lung Screening Trial Research Team. Baseline characteristics of participants in the randomized National Lung Screening Trial. *J Natl Cancer Inst* 2010; 102:1771-9.
8. Wood DE, Eapen GA, Ettinger DS, et al. Lung cancer screening. *J Natl Compr Canc Netw* 2012; 10:240-65.
9. Wu GX, Nelson RA, Kim JY, Raz DJ. Non-small cell lung cancer as a second primary among patients with previous malignancy: who is at risk? *Clin Lung Cancer* 2017; 18:543-50.
10. Taylor C, Correa C, Duane FK, et al, Early Breast Cancer Trialists' Collaborative Group. Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. *J Clin Oncol* 2017; 35:1641-9.
11. Ettinger DS, Wood DE, Aggarwal C, et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 1.2020. *J Natl Compr Canc Netw* 2019; 17:1464-72.
12. Halpenny DF, Cunningham JD, Long NM, Sosa RE, Ginsberg MS. Patients with a previous history of malignancy undergoing lung cancer screening: clinical characteristics and radiologic findings. *J Thorac Oncol* 2016; 11:1447-52.
13. Centers for Medicare and Medicaid Services. Lung cancer screening, Available at: https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=274. Accessed: May 10, 2020.
14. McKee BJ, Regis SM, McKee AB, Flacke S, Wald C. Performance of ACR Lung-RADS in a clinical CT lung screening program. *J Am Coll Radiol* 2015; 12:273-6.
15. American College of Radiology. Lung CT screening reporting and data system (Lung-RADS). 2014, Available at: http://www.acr.org/Quality-Safety/Resources/LungRADS. Accessed: January 2, 2020.
16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40:373-83.
17. Tammemägi MC, Katki HA, Hocking WG, et al. Selection criteria for lung cancer screening. *N Engl J Med* 2013; 368:728-36.
18. Kim S, Chukwudozie B, Calhoun E. Sociodemographic characteristics, distance to the clinic, and breast cancer screening results. *J Health Dispar Res Pract* 2013; 6:70.
19. The National Bureau of Economic Research. Zip Code Database, Available at: https://data.nber.org/data/zip-code-distance-database.html. Accessed: May 10, 2020.
20. Patz EF Jr, Pinsky P, Gatsonis C, et al, NLST Overdiagnosis Manuscript Writing Team. Overdiagnosis in low-dose computed tomography screening for lung cancer. *JAMA Intern Med* 2014; 174:269-74.
21. United States Preventive Services Task Force. USPSTF Bulletin. US Preventive Services Task Force issues draft recommendation statement on screening for lung cancer, Available at: https://www.uspreventiveservicestaskforce.org/uspstf/sites/default/files/file/supporting_documents/lung-cancer-screening-draft-rec-bulletin.pdf. Accessed: November 29, 2020.