

## RESEARCH ARTICLE

# Lung cancer screening in patients with Libby amphibole disease: High yield despite predominantly environmental and household exposure

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**Abstract**

**Background:** Lung cancer screening with low-dose computed tomography (CT) scanning (LDCT) is accepted as a screening tool, but its application to populations exposed to recognized occupational or environmental carcinogens is limited. We apply LDCT to a population with a predominantly nonoccupational exposure to a recognized human lung carcinogen, Libby amphibole asbestos (LA).

**Methods:** Patients in an asbestos disease clinic in Libby, Montana who were aged 50 to 84 years, greater than or equal to 20 pack-year history of tobacco use (irrespective of quit date), and asbestos-related pleuropulmonary disease on high-resolution CT scan were offered free annual lung cancer screening over a 39-month period.

**Results:** Of 2897 clinic patients, 1149 (39.7%) met eligibility criteria, and 567 (49%) were screened with 1014 low-dose CT scans. Most screened patients had principally environmental (333 or 59%) or household exposure (145 or 25%) to LA. Seventeen primary lung cancers were identified, mostly in early stages: 10 at stage 1, two at stage 2, three at stages 3 to 4, and two at limited small-cell cancers. The screening yield was 1.9 at baseline scan and 1.5% on the first annual scan.

**Conclusions:** Consistent with the guidelines of the National Comprehensive Cancer Network and American Association of Thoracic Surgery, LDCT for early lung cancer detection should be offered to people with significant exposure to occupational or environmental human lung carcinogens.

**KEYWORDS**

asbestos, Libby, low-dose CT scan, lung cancer screening

## 1 | INTRODUCTION

On the basis of the United States Preventive Services Task Force (USPSTF) recommendations, age and smoking are the only lung

cancer risk factors currently used to determine eligibility for annual low-dose computed tomography (LDCT) for lung cancer screening that is reimbursed by Medicare or private insurance in the United States.<sup>1</sup> Occupational and environmental exposures to lung

[Correction updated after publication dated 27 September 2019: List of author names in the title page have been corrected as well as the article title.]

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carcinogens are among other lung cancer risk factors that are included in other screening guidelines, including those of the National Comprehensive Cancer Network (NCCN)<sup>2</sup> and the American Association of Thoracic Surgery (AATS),<sup>3</sup> but empirical support for these alternative guidelines is limited.<sup>4-6</sup>

Until 1990, a vermiculite mine outside Libby, Montana, produced ore that contained up to 26% by weight amphibole fibers characterized as winchite, richterite, and tremolite,<sup>7</sup> now known as Libby amphibole (LA). This ore was processed in Libby and transported by open rail cars to additional processing plants throughout North America; trees along the railroad tracks were laden with LA. The vermiculite was distributed in the Libby area for soil and playground treatment as well as building insulation in homes and businesses. Human LA exposure in the Libby area included: environmental (child and adult, playing on town and school sports fields, gardening and insulating with vermiculite, and hunting or other outdoor activities); household (living with either a mine or lumber worker); and occupational (mine and lumber workers).

Libby amphibole causes a variety of chest illnesses, including lung cancer, malignant mesothelioma, asbestosis, pleural plaques, and a distinctive form of lamellar parietal pleural fibrosis that may progress to frank respiratory failure.<sup>8-16</sup> The Center for Asbestos-Related Disease (CARD) in Libby, Montana has diagnosed 2897 persons with asbestos-related pleural diseases in the past two decades and initiated an LDCT lung cancer screening for these patients in 2012.

## 2 | METHODS

In 2012, CARD's ongoing surveillance program for LA-exposed workers and residents identified 1149 patients who met the following eligibility criteria: 50 to 84 years of age; more than 20 pack-years of cigarette smoking; were free of symptoms of lung cancer; and had evidence of asbestos-related disease on high-resolution chest CT scan that was taken a mean of 32 months before invitation to the LDCT lung cancer screening program. Evidence of asbestos-related disease on chest CT scan included bilateral interstitial fibrosis, pleural plaques, or lamellar pleural thickening. Patients who had nodules or suspected lung cancers on the prior high-resolution chest CT scan were referred to their treating physician for appropriate follow-up.

A 16 slice GE Lightspeed CT scanner was used to obtain chest images in accordance with the protocol of the International Early Lung Cancer Action Program (I-ELCAP; www.elcap.org), delivering 1 to 3 mSv of radiation. All LDCT images underwent an initial review by local radiologists, a secondary review by clinic physicians, and a final reading by experienced academic radiologists of I-ELCAP. The clinic physician consulted with I-ELCAP radiologists to reconcile any differences before dissemination of results to patients. Positive findings and diagnoses of lung cancer were reviewed by a regional multidisciplinary tumor board for therapeutic recommendations. Nodule identification and follow-up were based on I-ELCAP protocols (www.elcap.org). Lung cancer was verified on the pathology report (with the exception of two cases, as noted in the Section 3).

Outreach for the program was conducted by newsletter, individual recruitment letters sent to those who met the eligibility criteria, and at routine clinic visits. Those who entered the program were educated about smoking cessation, and lung cancer risk. Participants who had a baseline scan were offered annual scanning.

The screening was performed according to the Health Insurance Portability and Accountability Act (HIPAA)-compliant protocols, and publication of data was approved by the Providence Health Care Institutional Review Board of Spokane, Washington.

## 3 | RESULTS

Five hundred and sixty-seven patients participated in the LDCT program between February 2013 and May 2016. The demographic, LA exposure

**TABLE 1** Lung cancer risk factors in the screened population, Libby

Risk factors	LCS eligible		Lung cancer, %
	Not enrolled, %	Enrolled in LCS, %	
Sex	582	567	17
Male	378 (65)	371 (65)	10 (59)
Female	204 (35)	196 (35)	7 (41)
Duration of exposure, y	495	567	17
0-20	24 (5)	62 (11)	1 (6)
21-40	79 (16)	135 (24)	4 (24)
41-60	219 (44)	254 (45)	9 (53)
61-80	173 (35)	116 (20)	3 (18)
Predominant exposure <sup>a</sup>	536	567	17
Occupational	92 (17)	89 (16)	4 (24)
Household	197 (37)	145 (25)	5 (29)
Environmental	247 (46)	333 (59)	8 (47)
Smoking history	582	567	17
Current	176 (30)	173 (30)	2 (12)
Former	406 (70)	394 (70)	15 (88)
Mean age [SD], y	69 [9]	68 [7]	71 [6]
Mean pack-years [SD]	43 [21]	42 [19]	42 [19]
20-29 pack-years	178 (31)	146 (26)	6 (35)
≥30 pack-years	404 (69)	421 (74)	11 (65)
Mean years quit [SD]	13 [13]	13 [12]	22 [8]
Quit ≤15 years prior	378 (65)	355 (63)	9 (53)
Quit >15 years prior	204 (35)	212 (37)	8 (47)

Note: Limited missing data for some variables means that some sums do not equal the column totals.

Abbreviation: LCS, lung cancer screening.

<sup>a</sup>Occupational exposure refers to mineworkers and lumber mill workers. Household exposure refers to household residents of mineworkers or mill workers. Environmental exposures occurred in childhood and/or adulthood (eg, ball field, schools, track and field vermiculite, gardening vermiculite use, hunting or outdoor activities, etc).

and smoking characteristics of LDCT participants and nonparticipants are shown in Table 1. Most participants were women (65%) and had environmental (59%) or household (25%) exposure to LA. Participants were exposed to LA for shorter duration and were more likely to have had environmental exposure to LA than nonparticipants.

Over half (56%) of the participants had more than the baseline CT depending on when they entered the program. Two hundred and forty-two participants had only one LDCT, 213 had two LDCTs, 102 had three LDCTs, and 10 had four LDCTs. Participants were added or dropped out of the screening at will as it was offered and encouraged as a free preventative health service.

Seventeen lung cancers were identified in the enrolled population of 567 people (Table 2). The screening yield (number of cancers among people screened, expressed as a percentage) was 1.9% (11 of 567) at baseline scan, 1.5% (5 of 325) at first annual scan, 0.99% (1 of 102) at second annual scan, and 0 at the third (0 of 10) annual scan. The stage distribution at diagnosis was: 10 cancers at stage 1; two cancers at stage 2; three cancers at stages 3 to 4; and two cancers were limited small-cell cancers.

Fifteen of the lung cancer cases underwent a confirmatory CT-guided needle biopsy before treatment. The remaining two patients

exhibited nodule growth consistent with stage 1A non-small-cell lung cancer and had fluorodeoxyglucose avidity on positron emission tomography scan. These two presumed cancers did not undergo biopsy and were treated with stereotactic body radiotherapy based on the local hospital multidisciplinary tumor board recommendation.

Cell type (Table 2) for the 15 resected cancers was predominantly adenocarcinoma (n = 9). There were two cases with squamous cell, one case with squamous cell combined with adenocarcinoma, two with small-cell carcinoma, and one large-cell neuroendocrine. In addition to the lung cancers, a thymic carcinoma was diagnosed in one participant, and a diffuse large B-cell lymphoma was diagnosed (stage IVB) in another. All patients received definitive therapy for cancer.

Of the 567 patients screened, 478 (84%) of the exposures were nonoccupational (Table 1), either through household contact with a mine or lumber worker or environmental exposure.

In the 17 lung cancer cases, the pattern of asbestos-related fibrosis seen radiographically included: diffuse (lamellar) pleural thickening (with or without plaques) in 14 patients, discrete pleural plaques alone in one patient, and interstitial fibrosis alone in two patients. Frank emphysema was seen only on one CT scan in the

**TABLE 2** Risk factor and lung cancer characteristics of screen-detected lung cancer cases, Libby

Age at diagnosis, y	Sex	Pack-years	Quit year (former smokers)	Asbestos fibrosis pattern	Airway obstruction (Spirometry)	Exposure type <sup>a</sup>	Stage	Cell type	Screening round at Dx	Met NLST criteria
62	F	30	2012	LPT	Yes	Environmental	1A	Adenocarcinoma	1	Yes
62	F	39	2014	LPT/P	No	Environmental	1A	Squamous cell carcinoma	2	Yes
69	M	54	2014	LPT/P	Yes	Environmental	2B	Adenocarcinoma	1	Yes
63	F	45	Current	LPT/P	No	Household	2A	Small-cell neuroendocrine	1	Yes
75	F	38	2005	LPT	No	Household	1A	Non-small-cell lung cancer	1	No
70	M	53	2014	LPT/P	No	Environmental	1A	Small-cell neuroendocrine	1	Yes
78	F	60	Current	A	No	Environmental	4	Large-cell neuroendocrine	1	No
65	M	22	2012	LPT	Yes	Environmental	1A	Adenocarcinoma	2	No
68	M	29	1990	LPT	No	Occupational	1A	Adenocarcinoma	2	No
65	M	38	2004	LPT/P	No	Household	2A	Adenocarcinoma	1	Yes
72	M	26	1986	LPT/P	No	Household	3A/B	Adenocarcinoma	1	No
68	M	24	1980	LPT/P	No	Occupational	1A	Adenocarcinoma	1	No
76	F	22	1975	P	No	Environmental	1A	Non-small-cell lung cancer	2	No
74	M	32	1990	A	No	Environmental	3A	Squamous cell carcinoma	1	No
75	M	29	1982	LPT	No	Occupational	1A	Adenocarcinoma	1	No
73	F	39	1997	LPT/P	Yes	Household	1A	Adenosquamous	3	No
64	M	32	1995	LPT/P	Yes	Occupational	1A	Adenocarcinoma	2	No

Abbreviations: A, parenchymal asbestosis; FDG, fluorodeoxyglucose; LPT, lamellar pleural thickening; NLST, National Lung Screening Trial; P, pleural plaques; PET, positron emission tomography.

<sup>a</sup>Presumed non-small-cell lung cancer based on growth rate and PET scan FDG avidity.

group with lung cancer. Of the 17 patients with lung cancer, six (18%) had airways obstruction, and three had severe airways obstruction (FEV1, 30%-50% of predicted) on pulmonary function testing completed before the date of cancer diagnosis (Table 2).

Using the USPSTF recommended screening eligibility criteria, only 41% (7 of 17) of patients with lung cancer would have been eligible for lung cancer screening. The other 59% (10 of 17) would not have been eligible, because more than 15 years had elapsed since the cessation of smoking and/or they had less than a 30 pack-year history of smoking. Using the National Lung Screening Trial (NLST) study criteria, only 35% (6 of 17) of patients with lung cancer would have been eligible for lung cancer screening.

## 4 | DISCUSSION

USPSTF guidelines, which determine reimbursability for LDCT scans for lung cancer screening in the United States, address only age and smoking history as lung cancer risk factors, highlighting the need for empirical studies of populations that address additional lung cancer risk factors, including exposure to asbestos and other occupational or environmental carcinogens. The current study adhered to the NCCN group 2 lung cancer-screening guidelines using the presence of asbestos-related fibrosis as the additional lung cancer risk factor. The screening yields and stage distribution were highly favorable and similar to those achieved in the NLST,<sup>17</sup> providing empirical support for the use of the NCCN group 2 lung cancer-screening guidelines. Indeed, application of the USPSTF criteria to our cohort would have left undetected over one-half of the lung cancers that we detected using our protocol.

Our study results are consistent with an increasing body of literature that supports the use of occupational or environmental risk factors as a determinant for lung cancer-screening eligibility. Markowitz et al<sup>4</sup> screened 7189 former nuclear weapons workers with occupational lung cancer risk and found that participants who met the NCCN group 2 eligibility criteria had a 1.36% screening yield on baseline CT scan, which was greater than the 1.0% screening yield on the NLST baseline scan. Welch et al<sup>6</sup> used LDCT screening of 1260 construction workers likely to be exposed to asbestos and other lung carcinogens. On LDCT scan, 26% of the population showed interstitial lung disease, and 20% had the pleural disease. At baseline, 21 lung cancers were detected for a screening yield of 1.6% similar to that of the NLST, despite the lesser smoking burden. Indeed, only 43.5% of their participants met entry criteria for the NLST. The lung cancer stage distribution was favorable: 20 of the 26 (77%) of the non-small-cell lung cancers were stage I or II.<sup>6</sup>

Brimms et al<sup>18</sup> reported lung cancer screening of 906 asbestos-exposed individuals in Wittenoom, Australia, 38% of who were exposed primarily to residential use of crocidolite. Screening participants were required to have radiographic evidence of pleural plaques or more than 3 months of occupational exposure. Over one-third of the study population never smoked, and the median smoking intensity was only 17.1 pack-years. This study is similar to the

present one in the high frequency of residential exposure and in the use of radiographic evidence of ARPD. In this group, seven lung cancers were identified with LDCT. The prevalence of lung cancer was limited (0.77%), consistent with the much smaller smoking burden. None of the seven patients with lung cancer met the USPSTF guidelines, and all were early stage and treated by surgery with curative intent.<sup>18</sup> Recently, Italian investigators demonstrated that LDCT screening reduced the lung cancer mortality in shipyard workers exposed to asbestos when screened workers were compared with both regional and national rates and a nonscreened control group (0.55 vs 2.07).<sup>19</sup>

A distinctive aspect of the current study is the predominance of environmental and household exposure rather than occupational exposure to asbestos. Indeed, the existing literature documenting excess lung cancer risk among populations environmentally or paraoccupationally exposed to asbestos is modest. Yet, our lung cancer-screening yield of 1.9% on baseline scan and 1.5% on the first annual scan is comparable to the occupational studies noted above.<sup>4,6</sup>

Limitations of our study include a relatively small cohort; incomplete annual scan compliance, a 49% participation rate, and lack of tissue confirmation in two cases of lung cancer. Ours was not a population-based sample but enrollees in an LA disease surveillance program, limiting its generalizability. Participants had a prior CT scan on average 2.5 years before the onset of the screening program, so slow-growing lung cancers may have already been detected at a prior scan, lowering the screening yield of our program.

In conclusion, current study results add to growing evidence that environmental or occupational exposure to lung carcinogens can usefully be included in eligibility criteria for lung cancer screening, expanding the population that can benefit from low-dose CT screening for lung cancer.

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## CONFLICTS OF INTEREST

Drs Black and Loewen have provided expert testimony on behalf of plaintiffs in this field. Remaining authors declare that there are no conflicts of interest.

## DISCLOSURE BY AJIM EDITOR OF RECORD

Steven Markowitz declares that he has no conflict of interest in the review and publication decision regarding this article.

## AUTHOR CONTRIBUTIONS

All authors worked together in the creation of this study including conception and design; data acquisition, analysis, and interpretation; drafting and critically revising the work, and providing the final approval of the version to be submitted for publication. All authors also agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

## ETHICS APPROVAL AND INFORMED CONSENT

Providence Health Care Institutional Review Board reviewed and approved the study (IRB 2096—Center for Asbestos-Related Disease's [CARD's] Lung Cancer-Screening Program Publication). No informed consent was obtained because the waiver of consent and HIPAA authorization were approved by the IRB in accordance with 45 CFR 46.116(d) and 21 CFR 56.109(c)(1).

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