Current Status of Lung Cancer Screening

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KEYWORDS

• Lung cancer screening • Early detection • Low-dose computed tomography • Overdiagnosis • Biomarkers

KEY POINTS

- Lung cancer risk: Risk is related to age and extent of tobacco smoking. It is less than 1% per year in typical screening populations of heavy smokers above the age of 50.
- Low-dose CT: Multi-slice spiral CT has dramatically improved the detection rate of small pulmonary lesions, in a few seconds, with lower radiation exposure and no intravenous contrast.
- Screening efficacy: This can be assessed by mortality reduction in the whole population under screening but not by the improvement of survival in CT-detected lung cancers.
- Overdiagnosis: Detection and treatment of indolent or slow-growing lung cancer, which would not affect patient's life expectancy without screening, can include resection of benign nodules.
- Biomarkers: There are promising developments of new blood biomarkers that combine safety and better accuracy for individual risk assessment, lung cancer detection, and prediction of outcome.

INTRODUCTION OR BACKGROUND

Lung cancer kills 1.3 million people every year[1] (more than breast, colon, and prostate cancer together)[2] and mortality is constantly rising in countries such as China.[3] In developed countries, smoking regulation has achieved a significant reduction in the prevalence of active smokers and lung cancer mortality in men but not in women.[4] As a consequence of smoking cessation, millions of former smokers remain at high risk of cancer for many years.

Improvements in clinical management of lung cancer have been modest over the last 20 years, with an overall 5-year survival rate just above 10% in Europe and 16% in the United States.[5,6] Presence of metastatic disease at diagnosis, occurring in 70% of all patients, is the main reason for treatment failure,[6] whereas the 5-year survival of patients resected in stage IA is higher than 70%.[7]

HISTORICAL NOTES: EARLY SCREENING TRIALS

Early detection trials with chest radiography (CR) and sputum cytology, funded by the US National Cancer Institute in 1970s, did not reduce lung cancer mortality, despite the higher proportion of early stage cancer identified through screening.[8–12] Active screening with 4-monthly CR doubled the number of early stage lung cancer in the interventional arm compared with annual CR arm, and survival rate of lung cancer patients diagnosed at an early stage in the screening arm was significantly higher (69% vs 54% at 5 years, median 16 years vs 5 years, respectively). Nonetheless, the 25 year follow-up of the Mayo trial showed that overall mortality was higher in the 4-monthly CR arm compared with the annual CR arm, even though the difference did not reach statistical significance ($P = .09$).[13] The reasons for such a detrimental

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effect of screening have never been explored. Altogether, long-term results of the Mayo trial proved the inefficacy and potential danger of CR screening, as well as the occurrence of overdiagnosis in the intervention arm.

OBSERVATIONAL STUDIES WITH LDCT

The introduction of spiral chest LDCT in clinical practice opened a new perspective for early detection, and initial studies conducted in Japan in the 1990s demonstrated the potential value of LDCT for lung cancer screening.[14] The continuous technological development of multi-slice machines improved both sensitivity and reliability of spiral CT, providing a new chance for detecting pulmonary lesions of 3 to 4 mm in size in a few seconds, without the use of intravenous contrast.

In 1999, Cornell University of New York published the first results of Early Lung Cancer Action Project (ELCAP), showing that spiral CT scans had accuracy and sensitivity rates sixfold higher than CR, in identifying very small lung tumors (56% <1 cm) with a 96% resectability rate and an 85% frequency of stage I tumors. This study generated new guidelines for the management of CT-detected pulmonary lesions and needle aspiration biopsy of small nodules.[15]

Table 1 summarizes the results of LDCT screening in observational studies that include more than 70,000 subjects. Median age was 59 (range 53–67), with minimum age ranging from 40 to 60. Five studies included nonsmokers, representing 14% to 54% of participants in each trial, and an overall proportion of 18%. In the remaining 11 studies, the median pack-years (p-y) was 41 (range 30–47).

At baseline, the overall frequency of participants with noncalcified solid lesions was 21% (range 7–53), lung cancer detection rate 1% (range 0.2–2.7), and proportion of stage I lung cancer 78% (range 50%–100%). The two larger Japanese studies,[16,17] including a significant proportion of nonsmokers (38%–54%), also showed the lowest

Table 1
Lung cancer screening: Results of LDCT in observational studies

						Lung Cancers		
	Subjects	Age[a]	Nsm[b]	P-Y[c]	CT Lesions[d]	Baseline[e]	Stage I[f]	First Repeat[g]
Henschke et al,[15] 1999	1,000	67	0	45	233 (23)	27 (2.7)	85	—
Sone et al,[16] 2001	5,483	64	54	—	588 (11)	23 (.4)	100	27 (.5)
Nawa et al,[17] 2002	7,956	56	38	—	541 (7)	36 (.5)	78	4 (.1)
Sobue et al,[18] 2002	1,611	59	14	—	186 (12)	14 (.9)	71	22 (1.4)
Swensen et al,[19] 2003	1,520	59	0	45	780 (51)	27 (1.7)	74	13 (.9)
Pastorino et al,[20] 2003	1,035	58	0	40	199 (19)	11 (1.1)	55	11 (1.1)
Diederich et al,[21] 2004	817	53	0	45	350 (43)	12 (1.5)	64	—
Bastarrika et al,[22] 2005	911	55	0	30	291 (32)	12 (1.3)	83	2 (.2)
Chong et al,[23] 2005	6,406	55	23	—	2,255 (35)	23 (.4)	56	—
Novello et al,[24] 2005	519	59	0	—	241 (47)	5 (1.0)	67	3 (.6)
MacRedmond et al,[25] 2006	449	55	0	45	111 (25)	2 (.4)	50	4 (.9)
I-ELCAP,[26] 2006	31,567	61	17	30	4,186 (13)	410 (1.3)	85	74 (.2)
Callol et al,[27] 2007	466	61	0	36	98 (21)	1 (.2)	100	4 (.9)
Veronesi et al,[28] 2008	5,201	58	0	44	2,754 (53)	55 (1.1)	66	37 (.7)
Wilson et al,[29] 2008	3642	59	0	47	1,477 (41)	53 (1.5)	58	24 (.7)
Menezes et al,[30] 2010	3352	60	0	30	600 (18)	44 (1.3)	65	10 (.3)
Overall	71,935	59	18	41	14,890 (21)	755 (1.0)	78	235 (.4)

[a] Median age of participants.
[b] Proportion of nonsmokers.
[c] Median pack-years.
[d] Subjects with noncalcified solid lesions (percent of participants).
[e] Lung cancers detected at baseline (percent of participants).
[f] Percent of lung cancers detected in stage I at baseline.
[g] Lung cancers detected at first annual CT repeat.