Why Women Appear to Have Better Outcomes When Undergoing Screening for Lung Cancer

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Abstract

Rationale: Randomized controlled trials (RCTs) of lung cancer (LC) screening (LCS) using computed tomography (CT) documented LC mortality reductions between 7.2% and 29.2%, compared with a chest radiograph (CXR). Women appear to have a greater reduction than men.

Objectives: We sought to determine why women appear to have better outcomes from LCS compared with men.

Methods: We used a secondary analysis of the National Lung Screening Trial, an RCT comparing CXR with CT among screen-eligible individuals ages 55–74 years. Descriptive statistics and a competing risk proportional hazards model that included an interaction between sex and screening arm were used to examine differences in screening outcomes by sex.

Results: Of 31,530 men and 21,922 women, 648 (2.1%) and 373 (1.7%) died of LC during the study, respectively. Overall mortality was higher in men: 2,771 (8.8%) versus 1,198 (5.5%). In an adjusted competing cause of death analysis, the LC mortality subdistribution hazard ratio (sHR) favoring CT was significant in women (sHR = 0.74; 95% confidence interval [CI] = 0.6–0.9; $P = 0.003$) but not men (sHR = 0.91; 95% CI = 0.78–1.06; $P = 0.24$). The interaction between screening arm and sex was not significant ($P = 0.1$). Chronic obstructive pulmonary disease and heart disease, which are more prevalent in men, were independently associated with LC death. LC deaths were consistently greater in the CT arm (vs. the CXR arm), for preexisting COPD and diabetes mellitus in men, but not women. Of those with LC, women in the CT arm had 53.7% prevalence of adenocarcinoma (AD) histology, whereas women in the CXR arm and men in both arms had approximately 36–41% AD prevalence. However, there was no overall difference between sexes in the screening difference for AD lethality.

Conclusion: Women in the National Lung Screening Trial had a greater reduction in LC mortality that, although not statistically significant, could be the result of more prevalent comorbid disease in men, which contributed to greater all-cause and LC mortality.

Keywords: lung cancer; lung cancer screening; outcome differences by sex

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This article has a related editorial.

This article has a data supplement, which is accessible at the Supplements tab.

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After the findings of four randomized controlled trials (1–4), annual computed tomography (CT) lung cancer (LC) screening has been widely recommended in the United States and Europe (5–6). These studies reported relative risk reductions in LC mortality between 7% and 29% for follow-up between 6.5 and 10 years (1–4, 7, 8). In these studies, women appeared to have a greater LC mortality reduction than that of their male counterparts (*see* Table E1 in the data supplement) (3, 7–9); however, the reasons for this are poorly understood, and most studies were not adequately powered to examine this question. Possible explanations include differences in the prevalence of some comorbid conditions and their association with mortality, as well as differences in the prevalence or behaviors of histological subtypes of identified malignancies. In several large studies, women were shown to have a higher incidence of adenocarcinoma, to present with LCs of less advanced stage, and to have better survival than men after

adjustment for confounders such as smoking exposure (10–13). Although the basis of these differences remains unexplained, it is possible that LC biology and outcomes may be related to sex (13–14) and, possibly, comorbid disease (15).

Although our primary focus involves developing a better understanding of sex differences in screening efficacy for LC death, it is important to consider differences in all-cause mortality, because the LCS benefit may be attenuated by other competing causes of death. This concept is particularly important for LC because, relative to those eligible for breast and colorectal screening, LCS involves older subjects with heavy smoking histories and with high background morbidity and mortality during screening (16–17). We undertook this study in an attempt to better understand why women appear to have better outcomes than men.

Methods

Participants

The 53,452 participants in the National Lung Screening Trial (NLST) have been described in detail elsewhere (1, 8). Briefly, subjects from 33 U.S. sites were randomized to low-dose CT or CXR in a 1:1 ratio between 2002 and 2004. Inclusion criteria included ages between 55 and 74 years, either currently smoking or having quit within 15 years, and having a 30+ pack-year history of cigarette smoking. Subjects were screened at baseline and then annually for 2 additional years and were followed for up to 7 years. We used results that were based on an event cutoff date of December 31, 2009, as discussed by Pinksy and colleagues, who reported that this cutoff was later than that used in the original NLST report (January 15, 2009) to take advantage of a more complete endpoint verification of LC deaths (8).We included the full NLST cohort; when examining spirometry, we used only patient data from the American College of Radiology Imaging Network (ACRIN) subcohort (18) ($n = 18,840$) because, as opposed to the full NLST cohort, they also underwent baseline prebronchodilator spirometry, from which 18,463 had usable spirometry at baseline.

Clinical and Demographic Variables

Demographic variables included age, sex, race, ethnicity, and education level. Sex, race, and ethnicity were self-reported. Ethnicity was reported as Hispanic or Latino. Race was reported as White, Black or African-American, Asian, American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, and more than one race. Those with missing race were grouped as other or missing. Randomization was stratified by screening center, sex, and age. Clinical variables included body mass index and self-reported comorbidities (COPD, chronic bronchitis, emphysema, [or "composite COPD" for one or more], adult asthma, pneumonia, heart disease, hypertension, stroke, diabetes mellitus [DM], and any cancer). LC variables included histology subtype and LC stage. Smoking variables included pack-years, cigarettes per day, years since quitting, total smoking duration, and family history of LC.

Pulmonary Function Testing

In the NLST-ACRIN cohort, prebronchodilator spirometry was measured at baseline screening (Time 0). The severity of airflow limitation was defined according to the Global Initiative on Chronic Obstructive Lung Disease criteria Grades 1–4.

LC Cases

Those who were diagnosed during the trial ($n = 2,058$) or postmortem ($n = 44$) were included. Stage, surgery, and histology data were available for cases identified during the trial. All histologic subclasses were recorded by screening group as follows: small cell carcinoma, squamous cell carcinoma, adenocarcinoma, bronchioloalveolar carcinoma, large cell carcinoma, adenosquamous carcinoma, pleomorphic/sarcomatoid, carcinoid tumor, unclassified carcinoma or missing. The proportion of adenocarcinoma (AD) inclusive of bronchioloalveolar carcinoma was also reported.

We calculated the relative reduction in the rate of LC deaths (CT vs. CXR), absolute LC deaths averted per 100,000 person-years (screening efficacy), LC deaths as a percentage of all LCs diagnosed (lethality), and the rate ratio of LC deaths (CT vs. CXR).

Statistical Analysis

Summary statistics were calculated for clinical and demographic variables and study outcomes for each sex. Effect sizes were reported for each comparison; odds ratios and 95% confidence intervals (CIs) were reported for two-level categorical variables and by Cramer's V for categorical variables with more than two levels (race and ethnicity, education level). Cohen's *d* was reported for continuous variables. For Cohen's *d*, values of 0.2, 0.5, and 0.8 are usually interpreted as small, medium, and large effects, respectively. Cramer's V has a roughly similar interpretation. Next, a competing risk subdistribution hazard model (also known as a Fine–Gray model) was used to estimate the risk of LC death, with non-LC death acting as the competing risk (19). Here, the primary exposure was screening group (CT vs. CXR), with adjustment for COPD severity, age, sex, race or ethnicity, body mass index, years since quit smoking, pack-years, current smoking status, and all comorbidities. We included an interaction between screening arm and sex so that we would be able to compare the screening effect between sexes. The proportional hazards assumption was verified by examination of plots of Schoenfeld residuals. Next, in an exploratory analysis, we made comparisons using descriptive subgroup analyses to assess changes in screening efficacy and relative reduction in the rate of LC deaths when groups with DM, chronic bronchitis, self-reported COPD, emphysema, or severe airflow limitation (Global Initiative on Chronic Obstructive Lung Disease Grades 3–4) were excluded; these were all chronic respiratory conditions or other diseases with a weak association with LC death in the competing risk model ($P < 0.10$). We next compared women and men for odds of survival versus LC death and odds of non-LC death versus LC death by risk quintiles from the Prostate Lung Colorectal Ovarian Model 2012 (or, $PLCO_{M2012}$) for 6-year LC in multinomial models stratified by risk quintiles. *P* values for each comparison (e.g., men with DM vs. men without DM) were determined by testing the interaction between the comorbidity of interest and screening group for significance using the Wald chi-square test in a Poisson regression model for LC death (log link). *P* values were adjusted within each sex to control the false discovery rate as described by Benjamini and Hochberg (20). All analyses were performed using SAS, Version 9.4 (SAS Institute Inc.).

Results

Baseline Smoking History and Clinical Comparison

Of the 53,452 NLST subjects, 31,530 (59%) were men and 21,922 (41%) were women (Table 1). Relative to men, women were more likely to be currently smoking (50.1% versus 46.8%). Women also had a lower pack-year history (45 vs. 52 pack-years) and less airflow limitation (30.2% vs. 36.0%). Women were more likely to self-report a diagnosis for one or more of

Table 1. Baseline demographic and clinical variables of the entire National Lung Screening Trial cohort according to sex

Variable	Total Cohort (*N* = 53,452)	Men (*n* = 31,530; 59.0%)	Women (*n* = 21,922; 41.0%)	Effect Size*
Demographics†				
Race/ethnicity, *n* (%)				
Non-Hispanic White	47,902 (89.6)	28,146 (89.3)	19,756 (90.1)	0.04 (0.03, 0.05)
Non-Hispanic Black	2,361 (4.4)	1,294 (4.1)	1,067 (4.9)	
Hispanic	935 (1.7)	589 (1.9)	346 (1.6)	
Other or missing	2,254 (4.2)	1,501 (4.8)	753 (3.4)	
Age, median (IQR)	60 (57–65)	61 (57–65)	60 (57–64)	0.08 (0.06–0.10)
Current smoking status, *n* (%)	25,760 (48.2)	14,771 (46.8)	10,989 (50.1)	1.14 (1.10–1.18)
Pack-years, median (IQR)	48 (39–66)	52 (40.5–72)	45 (38–60)	0.32 (0.31–0.34)
Cigarettes/d, median (IQR)	25 (20–35)	30 (20–40)	20 (20–30)	0.27 (0.25–0.29)
Years quit, median (IQR)	0 (0–7)	0 (0–8)	0 (0–7)	0.08 (0.06–0.10)
Smoking duration, years, median (IQR)	40 (35–45)	40 (35–45)	40 (35–44)	0.14 (0.12–0.16)
Family history of lung cancer, *n* (%)	11,621 (21.7)	6,408 (20.3)	5,213 (23.8)	1.22 (1.17–1.27)
BMI, median (IQR)	27.3 (24.4–30.5)	27.6 (25.1–30.6)	26.6 (23.5–30.5)	0.14 (0.12–0.15)
Education level, *n* (%)				
High school or less	15,961 (29.9)	8,664 (27.5)	7,297 (33.3)	0.12 (0.11–0.13)
Post–high school training	7,434 (13.9)	4,229 (13.4)	3,205 (14.6)	
Some college	12,277 (23.0)	6,855 (21.7)	5,422 (24.7)	
College graduate	8,946 (16.7)	6,154 (19.5)	2,792 (12.7)	
Postgraduate–professional	7,600 (14.2)	5,017 (15.9)	2,583 (11.8)	
Other or unknown	1,234 (2.3)	611 (1.9)	623 (2.8)	
Clinical variables				
Premorbid disease (self-reported), *n* (%)				
COPD, emphysema, or chronic bronchitis	9,326 (17.4)	4,707 (14.9)	4,619 (21.1)	1.52 (1.45–1.59)
Adult asthma	3,319 (6.2)	1,220 (3.9)	2,099 (9.6)	2.63 (2.44–2.82)
Chronic bronchitis	5,137 (9.6)	2,103 (6.7)	3,034 (13.8)	2.25 (2.12–2.38)
COPD	2,690 (5.0)	1,283 (4.1)	1,407 (6.4)	1.62 (1.50–1.75)
Emphysema	4,093 (7.7)	2,522 (8.0)	1,571 (7.2)	0.89 (0.83–0.95)
Pneumonia	11,809 (22.1)	5,983 (19.0)	5,826 (26.6)	1.55 (1.48–1.61)
Heart disease	6,797 (12.7)	5,161 (16.4)	1,636 (7.5)	0.41 (0.39–0.44)
Hypertension	18,930 (35.4)	11,503 (36.5)	7,427 (33.9)	0.89 (0.86–0.94)
Stroke	1,512 (2.8)	927 (2.9)	585 (2.7)	0.91 (0.81–1.01)
Diabetes mellitus	5,174 (9.7)	3,530 (11.2)	1,644 (7.5)	0.64 (0.60–0.68)
Personal history of cancer	2,289 (4.3)	597 (1.9)	1,692 (7.7)	4.33 (3.94–4.77)
Childhood asthma	1,909 (3.6)	1,258 (4.0)	651 (3.0)	0.74 (0.67–0.81)
Lung function/airflow limitation‡	*N* = 18,463	*n* = 10,207 (55.3%)	*n* = 8,256 (44.7%)	—
FEV_1, % predicted, mean (SD)	81.3 (20.5)	81.4 (21.1)	81.2 (19.6)	0.009 (−0.02, 0.04)
FEV_1/FVC, mean (SD)	71.6 (11.0)	70.8 (11.2)	72.5 (10.6)	0.16 (0.13–0.18)
COPD, all severities, baseline spirometry, *n* (%)	6,160 (33.4)	3,670 (36.0)	2,490 (30.2)	0.77 (0.72–0.82)
COPD GOLD 1, *n* (%)	1,499 (8.1)	965 (9.5)	534 (6.5)	0.66 (0.59–0.74)
COPD GOLD 2, *n* (%)	3,412 (18.5)	1,983 (19.4)	1,429 (17.3)	0.87 (0.81–0.94)
COPD GOLD 3–4, *n* (%)	1,249 (6.8)	722 (7.1)	527 (6.4)	0.89 (0.80–1.01)

Definition of abbreviations: ACRIN = American College of Radiology Imaging Network; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; IQR = interquartile range; SD = standard deviation.

*Effect sizes are reported as odds ratios (and 95% confidence intervals), women referenced to men, for binary (two-level) categorical variables; as Cohen's *d* for continuous variables; and as Cramer's V for categorical variables with more than two levels (race–ethnicity, education level).

†Missing data: All variables were fully observed with the exception of race: 220 (0.4%) were missing. For ethnicity and education level, 268 (0.4%) were missing. Those with missing values were included in the "Other or missing" category so that they were included in all analyses.

‡ACRIN cohort with spirometry data only.

the following: COPD, chronic bronchitis, or emphysema (composite COPD; 21.5% vs. 15.3%). Women were less likely to report heart disease or DM but were more likely to report adult asthma and pneumonia.

LC Characteristics and Mortality Comparison

The mean and maximum follow-up times were 6.4 and 8.2 years, respectively, during which there were 2,058 LC diagnoses, including 44 diagnosed at postmortem, and 3,969 deaths overall (Table 2). The incidence of premortem LC diagnoses was comparable between men and women (3.9% vs. 3.8%, respectively) (Table 2). However, women had fewer squamous cancers (16.2% vs. 26.8%) and more AD subtypes (47.4% vs. 39%). Stage at diagnosis was similar between sexes except at Stage 4, where fewer women than men were diagnosed: 218 (26.3%) versus 378 (30.8%).

All-cause mortality was 38% lower (relative difference) in women (5.5% vs. 8.8%), LC mortality was 19% lower (1.7% versus 2.1%), and non-LC mortality was 45% lower (3.7% vs. 6.7%) (Table 2). LC lethality was lower (i.e., LC deaths among LC cases) in women versus men (42.9% vs. 50.5%). LC accounted for a larger proportion of all deaths in women compared with men (31.1% vs. 23.4%). Lower non-LC mortality among women was attributed to a lower rate of deaths

Table 2. Characteristics of lung cancer cases diagnosed before death and cause-specific mortality according to sex

Characteristic	Total Cohort	Men	Women	Effect Size*
LC cases, diagnosed premortem, *n* (%)	2,058 (3.9)	1,229 (3.9)	829 (3.8)	0.97 (0.89–1.06)
LC outcomes, *n* (%)				
LC mortality among screened[†]	1,021 (1.9)	648 (2.1)	373 (1.7)	0.82 (0.73–0.94)
LC mortality among cases	977 (47.5)	621 (50.5)	356 (42.9)	0.74 (0.62–0.88)
LC treatment for all stages	1,901 (92.4)	1126 (91.6)	775 (93.5)	1.26 (0.93–1.71)
LC treatment for Stage 1–2 LCs	946 (96.8)	549 (96.5)	397 (97.3)	1.31 (0.62–2.78)
LC histology, *n* (%)				
Small cell	306 (14.9)	181 (14.7)	125 (15.1)	1.03 (0.80–1.32)
Squamous cell	463 (22.5)	329 (26.8)	134 (16.2)	0.53 (0.42–0.66)
Adenocarcinoma[‡]	872 (42.3)	479 (39.0)	393 (47.4)	1.42 (1.19–1.69)
Non–small cell or NOS	300 (14.6)	170 (13.8)	130 (15.7)	1.15 (0.90–1.47)
Large cell/other	93 (4.5)	58 (4.7)	35 (4.2)	0.89 (0.58–1.37)
LC stage at dx, *n* (%)				
I–II	977 (47.5)	569 (46.3)	408 (49.2)	1.12 (0.94–1.34)
III	459 (22.3)	269 (21.9)	190 (23.0)	1.06 (0.86–1.31)
IV	596 (29.0)	378 (30.8)	218 (26.3)	0.80 (0.66–0.98)
Occult carcinoma/unknown	26 (1.3)	13 (1.1)	13 (1.6)	1.49 (0.69–3.23)
Screen detection				
Cancer yr, *n* (%)				
T0 (first yr screening)	490 (23.8%)	291 (23.7%)	199 (24.0%)	1.02 (0.83–1.25)
T0–T2 (screening interval)	1,191 (57.9)	710 (57.8%)	481 (58.0%)	1.01 (0.85–1.21)
T3–T7 (follow-up interval)	867 (42.1)	519 (42.2%)	248 (42.0)	0.99 (0.83–1.18)
Cancer screen, *n* (%)				
Screen detected	928 (45.1)	549 (44.7)	379 (45.7)	1.04 (0.87–1.25)
Missed/interval	263 (12.8)	161 (13.1)	102 (12.3)	0.93 (0.71–1.21)
Follow up	867 (42.1)	519 (42.2)	348 (42.0)	0.99 (0.83–1.18)
Medical complications of work-up[§]	431 (0.8)	262 (0.8)	169 (0.8)	0.93 (0.76–1.26)
Mortality[‖]				
Total deaths, *n* (%)	3,969 (7.4)	2,771 (8.8)	1,198 (5.5)	0.60 (0.56–0.64)
LC deaths, *n* (%)	1,021 (1.9)	648 (2.1)	373 (1.7)	0.82 (0.73–0.94)
Proportion of all deaths, %	25.7	23.4	31.1	1.48 (1.27–1.72)
Non-LC deaths, *n* (%)	2,948 (5.5)	2,123 (6.7)	825 (3.8)	0.54 (0.50–0.59)
Proportion of all deaths, %	74.3	76.6	68.9	0.68 (0.58–0.78)
Cardiovascular disease–related deaths, *n* (%)	944 (1.8)	715 (2.3)	229 (1.0)	0.46 (0.39–0.53)
Proportion of all deaths, %	23.8	25.8	19.1	0.68 (0.57–0.80)
Respiratory deaths, *n* (%)	395 (0.7)	261 (0.8)	134 (0.6)	0.74 (0.60–0.91)
Proportion of all deaths, %	10.0	9.4	11.2	1.21 (0.97–1.51)
Other cancer deaths, *n* (%)	814 (1.5)	566 (1.8)	248 (1.1)	0.63 (0.54–0.73)
Proportion of all deaths, %	20.5	20.4	20.7	1.02 (0.86–1.20)
Other deaths, *n* (%)	795 (1.5)	581 (1.8)	214 (1.0)	0.52 (0.45–0.61)
Proportion of all deaths, %	20.0	21.0	17.9	0.82 (0.69–0.98)

Definition of abbreviations: BAC = bronchioalveolar cancer; dx = diagnosis; LC = lung cancer; NOS = not otherwise specified; T = time.
*Effect sizes are reported as odds ratios (and 95% confidence intervals) for women referenced to men.
[†]Includes 44 cases diagnosed postmortem.
[‡]BACs are now considered a subgroup of adenocarcinomas.
[§]Medical complications after a positive scan or lung cancer diagnosis.
[‖]For specific causes of death, two percentages are given: first, the mortality rate within the full cohort, and second, the proportion of all deaths.

from cardiovascular disease (57% lower) and other cancer-related deaths (39% lower) (*see* Figure E1). There were no important sex differences for receipt of LC treatment or in medical complications of work-up.

Screening Outcomes

In the competing risk model for LC death, LC mortality subdistribution hazard ratios (sHRs) for CT versus CXR were protective (below 1.0) for both sexes but were only significant for women, for whom the protective effect in the adjusted model was largest: sHR = 0.74 (95% CI = 0.6–0.9; $P = 0.003$) versus sHR = 0.91 (95% CI = 0.78–1.06; $P = 0.24$) for men (Table 3). The interaction between screening arm and sex was not significant ($P = 0.10$), meaning that there was no overall difference in screening effect between sexes. Full results from the adjusted model are given elsewhere (*see* Table E2), where other covariates associated with LC death were smoking status (52% greater risk for those currently smoking), smoking history (approximately 1% greater risk per additional pack-year), and years since quit smoking (approximately 5% lower risk for each year since quitting). Several comorbidities were associated with substantial risk: composite COPD (sHR = 1.4; 95% CI = 1.21–1.62; $P < 0.0001$) and heart disease (sHR = 1.28; 95% CI = 1.08–1.52; $P = 0.005$). Of note, DM approached significance (sHR = 1.19; 95% CI = 0.97–1.47; $P = 0.10$).

We compared the prevalence and lethality of LC cases by histology and sex (*see* Table E3). Among those with LC, women in the CT arm had a 53.7% prevalence of AD (largely attributable to an increased prevalence of the bronchioloalveolar carcinoma subgroup among women but not men), whereas women in the CXR

Table 3. Competing risk subdistribution hazard models predicting lung cancer death

Comparison: CT vs CXR	Unadjusted Results		Adjusted Results		CT		CXR	
	sHR (95% CI)	*P* Value	sHR (95% CI)	*P* Value	Randomized, *n*	LC Deaths, *n* (%)	Randomized, *n*	LC Deaths, *n* (%)
Male	0.92 (0.79–1.07)	0.27	0.91 (0.78–1.06)	0.24	15,769	311 (1.97)	15,761	337 (2.14)
Female	0.73 (0.59–0.90)	0.003	0.74 (0.60–0.90)	0.003	10,953	158 (1.44)	10,969	215 (1.96)

Definition of abbreviations: CI = confidence interval; CT = computed tomography; CXR = chest radiograph; sHR = subdistribution hazard ratio.
Competing risk sHR models for LC deaths, where the competing risk was non-LC death. Results for screening arm versus sex are shown. The *P* value for the Screening Arm × Sex interaction estimate was 0.10, indicating no overall screening difference by sex. The CT versus CXR screening effect was estimated to be protective (sHR < 1.0) for both men and women, but the effect was larger for women, for whom the 95% confidence intervals for adjusted and unadjusted models both fell completely below 1.0.

arm and men in both arms had 36.9–40.8% prevalence of AD ($P = 0.049$ for the interaction between prevalence and screening arm). However, despite this increase in AD in women, the difference in LC lethality by screening arm and sex was not significant ($P = 0.52$).

Although the study was not powered to explore the effects of specific comorbidities on LC screening outcomes, we undertook an exploratory analysis where we compared the LC deaths according to screening arm, by each comorbidity, in men and women separately. LC deaths were greater in those randomized to CXR (relative to CT), for men and women separately, but we hypothesized that this may not be the case by comorbid status. For men, there are excess LC deaths in the CT arm relative to CXR in subjects reporting COPD (+18), chronic bronchitis (+9), emphysema (+14), and DM (+5)

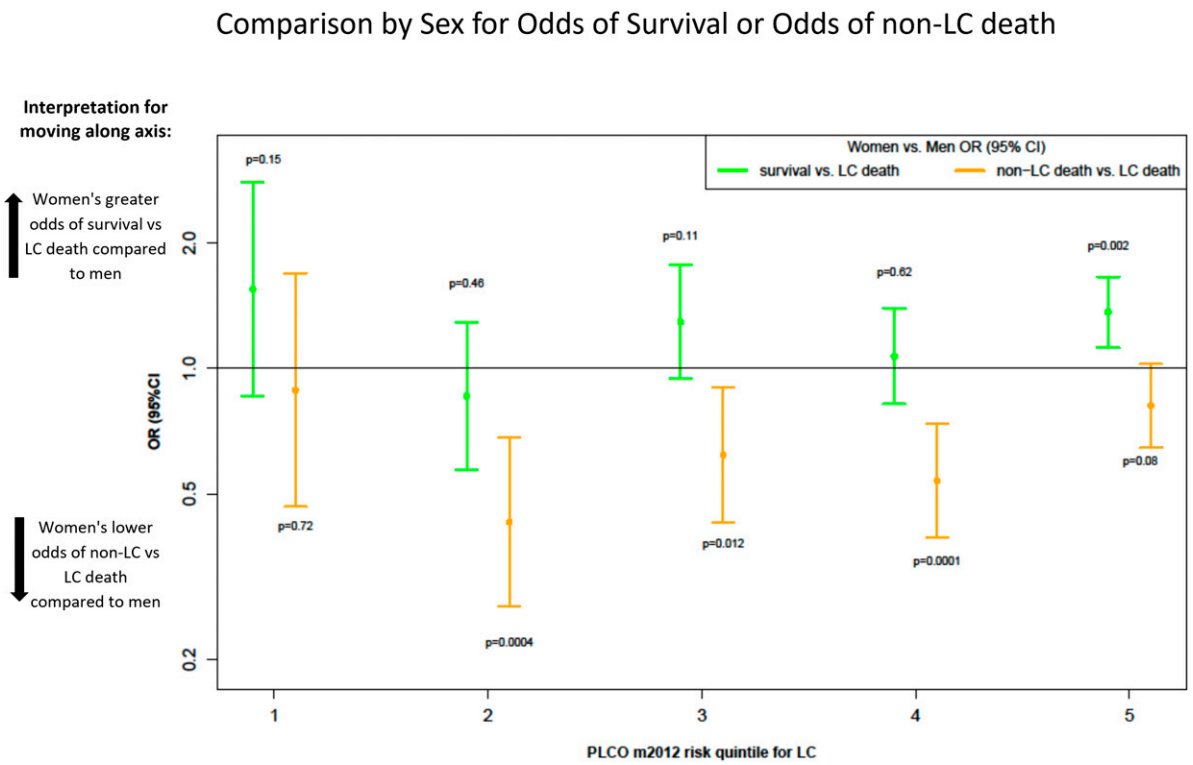

Figure 1. Comparison by sex for odds of survival or odds of non–lung cancer (non-LC) death, relative to dying from LC, stratified by LC risk (using the Prostate, Lung, Colorectal, and Ovarian Model 2012; $PLCO_{M2012}$) quintile (referenced against men) in a multinomial model. Comparison between women and men for odds of survival versus LC death (green) and odds of non-LC death versus LC death (orange) by risk quintiles from the $PLCO_{M2012}$) for 6-year LC. Results are from multinomial models stratified by risk quintile, with a three-level outcome: survival, LC death, or non-LC death. For non-LC death (indicated in orange), differences between women and men are most visible in the intermediate risk quintiles (2–4), in which odds ratios (ORs) are significantly lower than 1.0, meaning that non-LC death plays a smaller role than LC death for women when compared with men in the same risk groups. This, in turn, suggests that comorbidities that contribute to non-LC death may play a larger role for men in these intermediate risk groups than for women. For survival versus LC death (indicated in green), the OR is significant only in the highest risk group (fifth quintile), where the odds of women surviving versus dying of LC are significantly greater than the odds for men. CI = confidence interval.

(*see* Tables E4 and E5). For women, an excess of deaths was observed for chronic bronchitis (+5) and heart disease (+5) only.

We next compared women and men for odds of survival versus LC death and odds of non-LC death versus LC death by risk quintiles from the $PLCO_{M2012}$ model for 6-year LC in multinomial models stratified by risk quintiles (Figure 1) (28). Differences between women and men for non-LC death were most apparent in the intermediate risk quintiles (2–4), meaning that non-LC death played a smaller role than LC death for women when compared with men in the same risk groups. This, in turn, suggests that comorbidities that contribute to non-LC death may play a larger role for men in these intermediate risk groups compared with women. When comparing survival versus LC death, the most important differences were seen in the highest risk group (fifth quintile), where the odds of women surviving versus dying of LC were significantly greater than for men.

Discussion

This analysis of the NLST examined the combined effects of sex and screening on LC mortality and reports three findings that may help explain why women appear to benefit more from LCS. First, comorbid disease (e.g., DM, heart disease) was more prevalent in men who experienced 60% greater all-cause mortality than women. This was largely attributable to deaths from cardiovascular disease or other cancers. After adjustment for age and smoking status, self-reported heart disease and composite COPD (one or more COPD, chronic bronchitis, or emphysema) were independently associated with LC death in a competing-cause proportional hazard model. Second, in an exploratory analysis, we consistently found that there were excess LC deaths in the CT arm, relative to the CXR arm, for men reporting COPD-related comorbidities and DM, with a lesser effect observed in women. Although women had a larger reduction in LC mortality by screening arm relative to men, that reduction was somewhat offset by an increase in deaths from cardiovascular disease. This suggests comorbidities play an important role in screening outcomes but in ways that may differ by sex. Finally, sex differences in histology did not appear to contribute to an important screening advantage for women. Despite the substantially higher prevalence for AD among women in the CT arm only, the relatively low lethality for this group suggests possible overdiagnosis for some cases. Therefore, we concur with Pinksy and colleagues (8), while accepting the limitations of underpowering in the NLST dataset, that sex differences in histology with CT screening might better explain some degree of overdiagnosis but is unlikely to account for the screening advantage observed in women over men (8, 21, 22).

In every major randomized trial of LCS screening that reported results by sex, women in the CT screening arm had a greater risk reduction in LC mortality compared with men, although this never reached statistical significance in any individual trial (3, 4, 7, 8). For example, Pinksy and colleagues (8) stratified NLST results by sex and reported LC mortality risk reductions of 27% and 8% for women and men, respectively, with an insignificant interaction between screening arm and sex ($P = 0.08$). In a meta-analysis, comparing screening outcomes by sex, Hoffman and colleagues reported results from three randomized trials and found a 31% reduction in women and 14% in men ($P = 0.11$ for interaction) (9). In our competing risk model, we report 26% and 9% reductions for women and men, respectively ($P = 0.1$ for interaction). However, we extend this work by comparing the differing effects of comorbid disease on LC mortality reduction by sex.

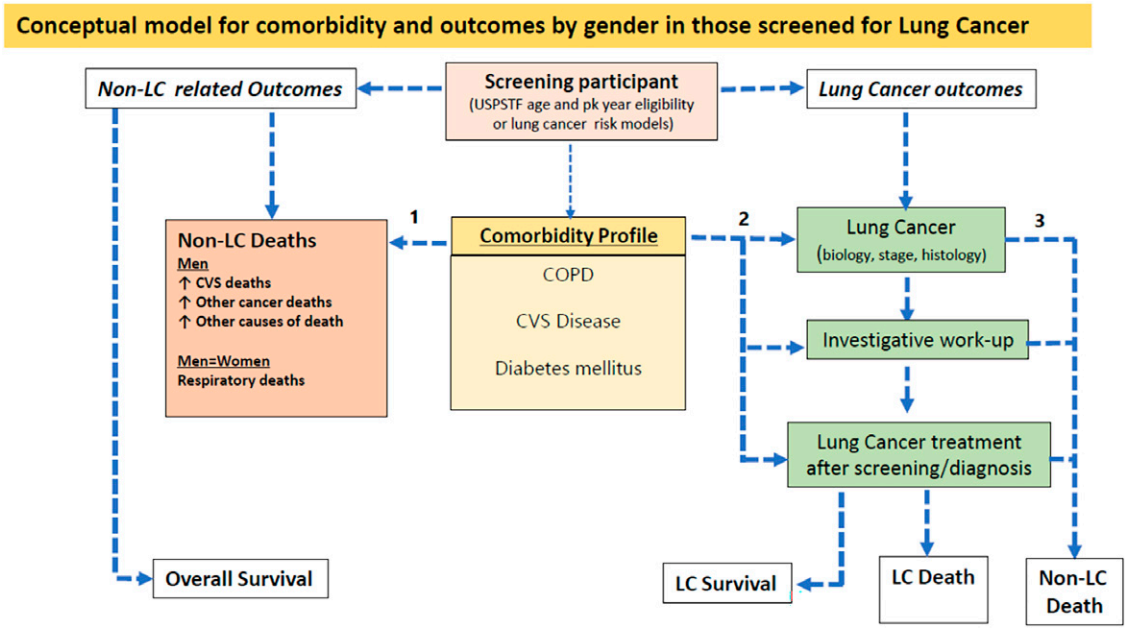

Figure 2. Conceptual model for comorbidity and outcomes by sex in those screened for lung cancer. The numbers 1–3 refer to the potential effect of comorbidity on non–lung cancer (non-LC) deaths in the screening continuum where 1 = dying of a non-LC death before LC diagnosis, 2 = direct effects of comorbidity on LC biology and treatment response, and 3 = non-LC deaths among patients with LC. COPD = chronic obstructive pulmonary disease; CVS = cardiovascular; pk year = pack-year; USPSTF = U.S. Preventive Services Task Force.

How might comorbidities differentially affect men and women? We hypothesize that there are three possible scenarios in the screening continuum in which the influence of comorbid disease may affect LC and non-LC outcomes (Figure 2). First, patients with greater numbers of comorbidities such as COPD, DM, or cardiovascular disease may die of a non-LC cause before the diagnosis of LC and the downstream benefits of LCS (i.e., a competing cause of death). Second, some comorbid conditions may directly confer greater LC mortality through effects on LC biology/behavior, compromise investigative work-up, and/or reduce treatment efficacy (e.g., a postoperative death due to COPD) (23). Third, reductions in LC death after successful screening and treatment of LC, may be partially offset by a subsequent non-LC death.

Competing causes of death appear to affect men more than women (17). In our study, LC deaths in women accounted for over 30% of all deaths compared with 23% in men, where rates of preexisting heart disease and cardiovascular disease deaths are twofold greater. Further, in the competing risk proportional hazards model, cardiovascular disease, more prevalent in men, was strongly associated with LC death after adjustment for age, sex, smoking history, and screening arm. DM, also more prevalent in men, approached significance ($P = 0.10$) in the same model. These observations likely contribute to the greater apparent LCS benefit in women by suggesting that more prevalent heart disease and DM, together with a nearly twofold greater rate of non-LC deaths, play a more significant role in men. If the results reported here correctly link these comorbidities to adverse outcomes from screening, then this represents a paradigm shift in our understanding of the relevance of competing risk. In this analysis, these comorbid diseases also contributed to significantly greater non-LC mortality in men (approximately twofold greater cardiovascular disease, other cancers, and other-cause mortality) compared that with women. This can be attributed to greater baseline comorbid cardiovascular disease, including DM and more severe airflow obstruction (15, 16). These findings are supported by results from the Milan LCS trial (the Multicentric Italian Lung Detection, or MILD), which showed that men experienced a twofold increase in LC, cardiovascular disease, and all-cause mortality compared with women (24). Although it is notable that, in this and other studies, women report more symptoms of respiratory disease (14, 25), they experienced a similar proportion of respiratory deaths compared with men.

Two observations suggest that these comorbid conditions may also confer greater LC mortality and that this effect appears more likely to occur in men. First, men had significantly greater LC mortality (and lethality) than women, despite comparable risk (incidence). Second, after randomization to CT, we unexpectedly found, for men reporting COPD-related comorbidities and DM, greater LC deaths compared with those randomized to CXR. The former observation was not seen in women. This was not the case for other respiratory or cardiovascular disease comorbidities; notably, adult asthma, pneumonia, heart disease, or hypertension. These findings should be confirmed in larger population-based studies, as we acknowledge the limitations of subgroup analyses that this study was not powered to detect (20). However, a recently published LCS microsimulation model confirmed our findings by showing not only that does comorbid disease reduce the life years–gained from screening but also that the effect of one or more combinations of COPD, heart disease, and DM attenuates LCS efficacy (26).

How do we place these findings into clinical context? First, although researchers and those who implement LCS have largely focused on risk stratification to better target those at greatest risk and optimize screening efficacy (27, 28), this does not account for other important outcomes. Screening programs in both Canada and the United Kingdom have limited LCS to only those with a risk of developing LC of more than 1.5–2% over a 6-year period (29, 30). However, risk-based approaches are more likely to select older subjects who smoke and who have more comorbid disease, including cardiovascular and respiratory disease (16, 17, 31). This may inadvertently reduce screening efficacy for those with combinations of these diseases. Rivera and colleagues suggest that incorporating coexisting chronic illness into decisions about patient selection for LCS is an increasingly important concept (17). Investigators are beginning to explore the intersection between the risk of developing LC and how comorbid disease affects life expectancy in the screening setting (32, 33). Cheung and colleagues developed a life-gained–based model and compared that with a risk-based selection model of subjects who were smokers being considered for LCS (32). In their model, comorbidities, similar to those found here, significantly reduced life expectancy and attenuated the screening effect. Second, the findings here should not be interpreted as suggesting that persons with comorbid disease should be excluded from screening but that assessment of comorbidities might be incorporated into the LCS paradigm in two domains. Individualized shared decision-making in those with comorbid disease should reflect the possibility that comorbid disease may attenuate the benefits of screening (34). In addition, several comorbidities, more prevalent in men but important drivers of outcome in both sexes, should be evaluated at the time of first screen, when LC is diagnosed and before curative intent treatment is delivered. For example, a patient who is screen negative, over time, is still at risk for comorbid competing causes of death. Patients diagnosed with LC may benefit from management of their comorbidities such that they can be offered and survive curative intent treatment. Those who are cured of their LC need continued management of their comorbidities, as they remain at risk from subsequent competing causes of death. We propose that the excess cardiovascular disease–related deaths in women randomized to CT reflects a "substitution effect" resulting from fewer LC deaths. This is an important finding, as cardiovascular disease in women remains understudied, underrecognized, underdiagnosed, and undertreated (35). Understanding how and where comorbidities affect screening outcomes may lead to interventions that improve life expectancy for both men and women. Further research is needed to better understand how treatment of comorbidities affects the screening continuum.

Limitations

There are several important limitations. First, some conclusions relied on subgroup analyses for which the original NLST was not powered. By comparing results from descriptive and modeling analyses, it was clear that conclusions from these approaches were suggestive but not conclusive. Next, the population enrolled in this study, unfortunately, was overwhelmingly White such that an investigation of racial and ethnic differences by sex and outcome could not be undertaken, although the importance of such studies in the future cannot be

overstated. Next, patients enrolled in the NLST had a lower comorbidity burden than the eligible U.S. population currently being screened, such that results may not be fully generalizable, and the findings here may underestimate the true impact of comorbid disease (15). Next, information on comorbidities generally depended on self-reported conditions that did not include severity (airflow limitation related to COPD in the ACRIN subgroup is an exception); further, baseline comorbidity data were not sufficient to calculate commonly used indices such as the Charlson Comorbidity Index. Next, the associations between some comorbidities and the risk of LC death may be mediated by non-LC death risk; that is, non-LC death risk may be a necessary factor in the causal pathway between the disease and LC death. Our preliminary indications are that this is frequently the case and that these effects can differ by sex. We leave further exploration of this complex question involving a time-to-event competing risk outcome for future work but note that the existence of mediation does not alter the basic questions posed here for addressing differences in screening efficacy by sex and by comorbidity burden. Finally, the ability to diagnose and treat LC (as well as other comorbid conditions) has changed dramatically since the end of the study period, and those advances may affect LCS outcomes in patients undergoing screening today.

In conclusion, the threefold greater relative reduction in LC mortality in women being screened for LC (26% vs. 8% in men), appears to be influenced by a more favorable comorbidity profile. Although these results require confirmation in large prospective studies, they should give pause by demonstrating that, for some, the benefit of LCS may be attenuated and that a purely risk-based approach to maximizing screening efficacy does not account for this. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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