Assessment of lung cancer mortality reduction after chest X-ray screening in smokers: A population-based cohort study in Varese, Italy

Lorenzo Dominioni\textsuperscript{a,}*, Albino Poli\textsuperscript{b}, William Mantovani\textsuperscript{b}, Salvatore Pisani\textsuperscript{c}, Nicola Rotolo\textsuperscript{a}, Massimo Paolucci\textsuperscript{d}, Fausto Sessa\textsuperscript{e}, Valentina Conti\textsuperscript{a}, Vincenzo D'Ambrosio\textsuperscript{f}, Antonio Paddeu\textsuperscript{g}, Andrea Imperatori\textsuperscript{a}

\textsuperscript{a} Center for Thoracic Surgery, University of Insubria, Ospedale di Circolo, Varese, Italy  
\textsuperscript{b} Department of Public Health and Community Medicine, University of Verona, Verona, Italy  
\textsuperscript{c} Epidemiology Observatory, Azienda Sanitaria Locale, Varese, Italy  
\textsuperscript{d} Department of Radiology, Ospedale S. Antonio Abate, Gallarate, Italy  
\textsuperscript{e} Department of Surgical and Morphological Sciences, University of Insubria, Varese, Italy  
\textsuperscript{f} Thoracic Medicine Unit, Ospedale S. Antonio Abate, Gallarate, Italy  
\textsuperscript{g} Respiratory Care Unit, Ospedale S. Anna, San Fermo della Battaglia, Como, Italy

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\textbf{Abstract}

\textbf{Background:} The effectiveness of screening for lung cancer (LC) in smokers on a population level, as distinct from the special circumstances that may apply in a randomized trial of selected volunteers, has not been thoroughly investigated. Here we evaluate by the standardized mortality ratio (SMR) indicator the impact of a chest X-ray (CXR) screening programme carried out at community level on LC mortality in smokers.

\textbf{Methods:} All smokers of >10 pack-years, of both genders, ages 45–75 years, resident in 50 communities of the Province of Varese, Italy, screening-eligible, in 1997 were invited by their National Health Service (NHS) general practitioner physicians to a nonrandomized programme of five annual CXR screenings. The entire invitation-to-screen cohort (n=5815 subjects) received NHS usual care, with the addition of CXR exams in volunteer participants (21% of invitees), and was observed through December 2006. To overcome participants’ selection bias of LC mortality assessment, for the entire invitation-to-screen cohort we estimated the LC-specific SMR, based on the local reference population receiving the NHS usual care.

\textbf{Results:} Over the 8-year period 1999–2006, a total of 172 cumulative LC deaths were observed in the invitation-to-screen cohort; 210 were expected based on the reference population. Each year in the invited cohort the observed LC deaths were fewer than expected. The cumulative LC SMR was 0.82 (95%CI, 0.67–0.99; p = 0.048), suggesting that LC mortality was reduced by 18% with CXR screening.

\textbf{Conclusion:} Implementation of a CXR screening programme at community level was associated with a significant reduction of LC mortality in smokers.

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1. Introduction

Lung cancer (LC) is a relevant public health problem worldwide. Beyond prevention and cessation of cigarette smoking, other strategies are needed, because most who will succumb to this disease are current or former smokers [1]. No public policy organization recommends chest X-ray (CXR) screening, as randomized studies showed no LC mortality benefit [2–6]. However, the published randomized CXR screening trials present relevant methodological weaknesses [1,4,7,8]; moreover, these studies were performed in highly selected volunteers [2,3,5], and the external value of their results remains uncertain. Notably, the U.S. Preventive Service Task Force concluded that the evidence is insufficient to recommend for or against screening with CXR [9]. The effectiveness of screening for LC in the community, as distinct from the special circumstances that may apply in a randomized trial of volunteers, has not been thoroughly investigated and remains controversial [10]. With the aim to assess whether radiographic screening of smokers in the community setting in Italy decreases LC mortality, in 1997 we started a nonrandomized observational study of CXR screening in the PREDICA cohort [11]. The latter is a clearly defined population-based cohort of smokers of the Varese Province, hereafter referred

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\* Corresponding author at: Center for Thoracic Surgery, University of Insubria, Ospedale di Circolo, Via Guicciardini, 21100 Varese, Italy. Tel: +39 0332 278868; fax: +39 0332 260260.

E-mail address: lorenzo.dominioni@uninsubria.it (L. Dominioni).

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to as “cohort”, that was invited to an annual CXR screening pro-
gramme and prospectively followed up. We previously reported the
cohort’s demographic characteristics, screening protocol, partici-
pants adherence, and LC detection results [11,12]. After completion
of the CXR screening programme, here we evaluate its effective-
ness in the cohort by estimating the standardized mortality ratio
(SMR), an indicator recently used by other investigators to docu-
ment the significant LC mortality reduction achieved by computed
tomography (CT) screening of smokers [13].

2. Materials and methods

2.1. Study design

This is a prospective nonrandomized population-based cohort
study of CXR screening for LC, with a comparison group consisting
of the reference population of the screening catchment geo-
igraphical district. The cohort, made of the totality of residents in 50
communities of the Varese Province who were screening-eligible
cigarette smokers, was invited to annual CXR screening for 5 years
and was observed for 9.5 years. In this geographical area no other LC
screening projects were ongoing. At the end of study, we evaluated
the impact of screening on LC mortality in the cohort. To this effect,
as our endpoint we estimated the cumulative LC SMR, expressed as
the ratio of total LC deaths observed in the entire screening-invited
cohort to total LC deaths expected based on the local reference pop-
ulation receiving usual care. This intention-to-treat approach for
analysis of the screening programme effectiveness overcomes the
participants’ selection bias [14,15].

2.2. The cohort

We aimed to recruit a population-based cohort of approximately
5000 smokers, a sample size similar to that of the intervention arm
in the Kaiser Permanente trial [16] and in the Mayo Lung Project
[2]. Recruitment of the cohort was effected by a pool of 50 general
practitioner (GP) physicians of the Italian National Health Service
(NHS), as previously described [11]. Notably, the medical practices
of these GPs were located in 50 communities scattered over rural
and urban areas, a large sample of the total 230 communities of
the 44-town screening catchment area in the Varese Province [11].
Briefly, based on practice records, in early 1997 the GPs invited to a
CXR screening programme the totality of smokers resident and reg-
istered in their community practice who possessed all the following
inclusion criteria: both genders, birth cohort 1923–1953, current
or ex-smoker of >10 pack-years. Exclusion criteria were: subject
unfit for surgery or with diagnosed/suspected LC. After exclusion of
110 noneigible candidates, 5815 subjects featuring a median
smoking history of 32.8 pack-years [interquartile range (IQR),
22.8–46.0], constituted the population-based cohort of this study.
The screening programme was offered free of charge and consisted
of a baseline two-view CXR exam and an annual repeat screen
4 years. The 1244 individuals (21% of the cohort) who accepted
the invitation undertook the baseline CXR examination during a
4.5-year recruitment period (from July 1997 through December
2001, median in February 1998) and were defined as participants in
screening. All participants signed an informed consent form; for
nonparticipants (79% of the cohort), informed consent was waived.
In addition, during 1997–2001 a total of 1221 uninvited screening-
eligible individuals (resident in the 44-town catchment area, but
outside the 50 communities of cohort recruitment) requested to
participate after learning about the screening programme. Also
these additional candidates signed informed consent, and under-
took the screening protocol, but they constituted a distinct group of
“uninvited participants” that will be evaluated in a separate study.

All names were encrypted, as approved by the Varese Hospital and
Health District Ethics Committee. The data collected in this study
were stored in a secure database at the Center for Thoracic Surgery,
University of Insurbia.

2.3. Standard of care, screening and follow-up of the cohort

The NHS usual care was provided to the entire cohort. In addition,
participants underwent screening by chest radiographs, according to
the previously described protocol [12]. The study lasted from July 1, 1997
until December 31, 2006 and during this interval the entire cohort was observed. After baseline screening, the 1244 participants underwent a total of 4337 annual repeat screens. The standard of care in Varese was used to investigate sus-
picious screen-detected or nonscreen-detected CXR abnormalities,
without special algorithm. Management of LCs was centralized in
the Varese University Hospital, and cases were treated by usual
international criteria [17] regardless of mode of LC detection. At
study cut off, the vital status of 98.5% of cohort individuals were
ascertained by linkage with the Lombardy Health Registry of all
residents in the Lombardy Region. At study cut off 85 subjects (1.5% of
cohort) were untraceable. In deceased cohort subjects, death
 certificates were used to identify LC as the cause of death, by link-
age with the Varese Province Mortality Registry, after review by
the mortality review committee of this study (LD, AI, NR, FS, APo,
WM), as previously described [11]. Deaths attributed to LC treat-
ment complications were filed as deaths from LC. The LC deaths that
occurred in the cohort were recorded by gender and age strata.

2.4. Lung cancer standardized mortality ratio

We excluded from LC mortality analysis the initial period of
study, from July 1997 through December 1998, as we presumed that
screening was unlikely to decrease LC mortality immediately.
Moreover, exclusion of this initial 18-month period minimizes the
healthy-cohort recruitment bias, i.e. an artificially low LC mortal-
ity in the cohort due to enrolment of asymptomatic subjects [18].
Furthermore, a preliminary joinpoint analysis [19] identified in
1999 as the year during which a statistically significant mortality
trend inflexion occurred in the cohort. Accordingly, we confined the
analysis of LC SMR in the cohort to the 8-year interval between
January 1, 1999 and December 31, 2006. This timeframe was cho-
sen based on the suggestion to add about 4 years after the end of
active screening (median in 2002 in our study) to evaluate the effec-
tiveness of screening using LC mortality [5]. Our analysis was not
extended over a longer period, because any benefit from short-term
screening is likely transient [8]. To calculate the cumulative LC SMR
of the cohort during 1999–2006, the ratio’s numerator (number of
observed LC deaths) was available from the cohort follow-up, while
the denominator (number of expected LC deaths) was calculated as
follows:

(a) First, we identified the source population of the cohort alive as
of January 1, 1999, constituted by all individuals of birth cohort
1923–1953 who were alive by that date and resident in all
230 communities of the 44-town catchment area [11] (Fig. 1).
This source population was searched by linkage with the Varese
Province general population registry, and consisted of 122,074
persons, shown by strata in Table 1.

(b) The reference population, constituted by all persons of the above
source population possessing the smoking criteria for screening,
was constructed multiplying the number of individuals in the
source population strata by the corresponding prevalence
rates of smokers (current or former smokers of >10 pack-
years), available from the year 2000 Varese Province population

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Source population \((n = 122,074)\)

**Inclusion criteria**

Reference population \((n = 26,656)\)

**Inclusion criteria**
All source population persons who were current or ex-smokers of >10 pack-years

Fig. 1. Composition of the source population and of the reference population as of January 1, 1999. The reference population was constructed multiplying the number of individuals in the source population strata by the prevalence rates of smokers (current or ex-smokers of > 10 pack-years) in the strata.

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Men, (n (%))</th>
<th>Women, (n (%))</th>
<th>Total, (n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>45–49</td>
<td>10,971 (19.2)</td>
<td>11,318 (17.5)</td>
<td>22,289 (18.3)</td>
</tr>
<tr>
<td>50–54</td>
<td>10,994 (19.2)</td>
<td>11,594 (17.9)</td>
<td>22,588 (18.5)</td>
</tr>
<tr>
<td>55–59</td>
<td>10,437 (18.2)</td>
<td>10,967 (16.9)</td>
<td>21,404 (17.5)</td>
</tr>
<tr>
<td>60–64</td>
<td>9,387 (16.4)</td>
<td>10,727 (16.5)</td>
<td>20,114 (16.5)</td>
</tr>
<tr>
<td>65–69</td>
<td>7,939 (13.9)</td>
<td>9,570 (14.8)</td>
<td>17,509 (14.3)</td>
</tr>
<tr>
<td>70–74</td>
<td>6,387 (11.2)</td>
<td>8,867 (13.7)</td>
<td>15,254 (12.5)</td>
</tr>
<tr>
<td>75–79</td>
<td>1,177 (2.0)</td>
<td>1,799 (2.9)</td>
<td>2,976 (2.4)</td>
</tr>
</tbody>
</table>

* Mean age was 58.7 (8.6 SD) in men, 59.6 (8.8) in women, 59.0 (8.7) in total. SD, standard deviation.

The vital status as of December 31, 2006 of 98.2% of the 122,074 source population individuals were ascertained by deterministic record linkage with the Varese Province population registry and with the Lombardy Health Registry of all residents in the Lombardy Region [21]. At study cut off, 1.8% of subjects of the source population were untraceable. All LC deaths which occurred during 1999–2006 in the source population were searched using the Varese Cancer Registry criteria [22] based on death certificates (not verified by the mortality review committee of this study), by linkage with the Varese Province Mortality Registry [23]. The latter was accessed in 2008, completed with certificates of deaths occurring up to December 31, 2006. The LC deaths occurred in the source population were recorded by strata.

(d) Then, to estimate the number of LC deaths in the reference population strata, we multiplied the number of LC deaths in each gender and age stratum of the source population (c) by the proportion of smoking-attributable LC deaths (0.86). The latter is the most conservative value (range, 0.86–0.90) of the smoking-attributable proportion of LC deaths recorded during the interval 1999–2006 by the Varese Epidemiology Observatory in the population of birth cohort 1923–1953.

(e) Finally, to calculate the LC deaths expected in the cohort we multiplied the estimated number of LC deaths in each reference population stratum (d) by the ratio of cohort subjects alive as of January 1, 1999 to the number of reference population subjects in the stratum. The total number of LC deaths expected in the cohort was the sum of expected LC deaths in each stratum.

For the above calculations we assumed that no substantial changes occurred during 1999–2006 in the proportion of smoking-attributable LC deaths and in the ratio of cohort subjects to reference population subjects.

### 2.5. Statistical analysis

Data are presented as frequency, percentage, mean or median, as appropriate; 95% confidence interval (CI) and IQR are shown. Differences were tested by Student’s \(t\) test, chi square test, Fisher’s exact test, or Mann–Whitney \(U\) test as required by type and distribution of variables.

Joinpoint regression analysis was used to identify the point where a statistically significant change in linear slope of the mortality trend over the study period occurred [19]. The joinpoint analysis was performed with software from the surveillance research programme of the U.S. NCI [24].

The LC SMR was computed using STATA program version 11.2 (Stata Corporation, College Station, TX). Two-tailed \(p\) values of <0.05 were considered significant. Analysis was performed at the Department of Public Health and Community Medicine, University of Verona. Approval of this study and permission to access and analyze the anonymized linked data reported in this paper was granted by the Varese Hospital and Health District Ethics Committee. This study is registered, ISRCTN90639073.

### 3. Results

Over the 8-year period 1999–2006, cumulatively 172 LC deaths were observed in the cohort, while 1405 LC deaths altogether were recorded in the source population (Table 3).

The LC deaths estimated in the reference population strata, and those expected in the cohort are shown in Table 3. In total 210 LC deaths were expected in the cohort. Each year during 1999–2006 the number of LC deaths observed in the cohort was lower than that expected based on the reference population (Fig. 2). During 1999–2006, the cumulative LC SMR was 172/210 = 0.82 (95%CI, 0.67–0.99; \(p = 0.048\)). This result indicates that the risk of LC death for the smokers invited to the screening programme at community level was reduced by 18% compared to that of the reference population smokers receiving usual care. The numbers of observed and expected LC deaths by age in the cohort are given in Table 4.

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Table 3

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Men, n</th>
<th>Women, n</th>
<th>Total, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>45–49</td>
<td>43</td>
<td>37</td>
<td>80</td>
</tr>
<tr>
<td>50–54</td>
<td>85</td>
<td>73</td>
<td>158</td>
</tr>
<tr>
<td>55–59</td>
<td>127</td>
<td>109</td>
<td>236</td>
</tr>
<tr>
<td>60–64</td>
<td>185</td>
<td>159</td>
<td>344</td>
</tr>
<tr>
<td>65–69</td>
<td>275</td>
<td>237</td>
<td>512</td>
</tr>
<tr>
<td>70–74</td>
<td>252</td>
<td>217</td>
<td>469</td>
</tr>
<tr>
<td>75–79</td>
<td>48</td>
<td>41</td>
<td>89</td>
</tr>
<tr>
<td>Total</td>
<td>1015</td>
<td>873</td>
<td>1888</td>
</tr>
</tbody>
</table>

Note. Lung cancer deaths: (A) observed in the source population; (B) estimated in the reference population; (C) expected in the cohort. (A) was estimated multiplying (A) by 0.86 (proportion of smoking-attributable LC deaths); (C) was estimated multiplying (B) by the ratio of cohort subjects to reference population subjects in the stratum. LC, lung cancer.

Table 4
Observed and expected lung cancer (LC) deaths by age in the cohort.

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Rank population, n</th>
<th>LC deaths in the cohort during 1999–2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>45–49</td>
<td>1210</td>
<td>Observed, n</td>
</tr>
<tr>
<td>50–54</td>
<td>1187</td>
<td>16</td>
</tr>
<tr>
<td>55–59</td>
<td>1079</td>
<td>22</td>
</tr>
<tr>
<td>60–64</td>
<td>932</td>
<td>37</td>
</tr>
<tr>
<td>65–69</td>
<td>718</td>
<td>42</td>
</tr>
<tr>
<td>70–74</td>
<td>543</td>
<td>35</td>
</tr>
<tr>
<td>75–79</td>
<td>76</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>5745*</td>
<td>172</td>
</tr>
</tbody>
</table>

Note. Cumulative LC standardized mortality ratio was 0.82 (95% CI 0.67–0.99); \(p = 0.048\).

* Cohort individuals alive as of January 1, 1999. LC, lung cancer; CI, confidence interval.

4. Discussion

In this study we assessed the LC SMR in a well defined population-based cohort of smokers invited to a CXR screening programme at community level. After screening implementation we found that LC mortality over an 8-year period was significantly reduced in the entire invitation-to-screen cohort of smokers. In contrast, no substantial LC mortality benefit from screening with chest radiographs was shown in the PLCO cancer randomized trial after 13 years of follow-up [5]. These opposite results do not surprise, as the subjects targeted for screening in our study were quite different from those of the PLCO. While we investigated the totality of screening-eligible ever-smokers resident in 50 communities of the Varese Province, characterized by high LC incidence (5.15/1000 person-years) [11], the PLCO trial was not specifically designed to investigate smokers [25] and recruited highly selected volunteers, as reflected by the fact that enrolment averaged approximately 1% of the invited population [26]. Moreover, in the PLCO about 80% of the total of intervention group LCs were nonscreen-detected and could be diluting any screening effect [5]. While in theory a population-based randomized trial is the ideal method to assess the efficacy of an LC screening intervention [27], in practice the historical randomized CXR screening trials have subsequently been associated with important methodological weaknesses [1,4,7,8]. In addition, the recently reported findings of the PLCO randomized radiographic screening are difficult to generalize to smokers, as about half of participants were never smokers [5]. Observational studies of CXR screening in all eligible smokers of the population, with appropriate comparator groups, may contribute important information with regard to the effectiveness of screening in the community setting. In our observational study, 21% of the invited population-based cohort chose to participate in screening. This attendance rate is similar to the 20–33% participation recorded in Japanese mass screenings with CXR [28,29], and indicates a generally limited response to LC screening invitation. Because the assessment of screening efficacy may be biased by selection of participants [11], in our study we evaluated the overall impact of screening on LC mortality in all the invitees. The assessment of SMR according to invitation-to-screen has been previously used for the evaluation of population-based cancer screening, in order to eliminate self-selection bias of participants [14,15]. Other investigators, using the SMR to compare the LC mortality experience in a CT screened cohort of smokers in New York State and in two large unscreened cohorts, reported significant reductions in deaths from LC, documented by SMR respectively of 0.64 and 0.36 [13]. In our study the cumulative LC SMR of the CXR screening invited cohort was 0.82, a result that must be interpreted cautiously. Because the design of our study was observational, we assumed that the cohort and the reference population were identical in all important variables except the intervention, or that we could correct for the relevant differences. The LC SMR may reflect the effectiveness of our screening programme only if the LC mortality risk profile in the cohort and in the reference population were identical at baseline, and if the two groups received the same standard of care except for screening in the cohort. As to comparability, it is noteworthy that the cohort and the reference population were contemporary and were extracted by the same smoking history criteria (Table 2) from the Varese Province general population of both genders, of birth cohort 1923–1953, resident in the 44-town catchment area [11]. Under these circumstances, it is highly unlikely that our observational study was vulnerable to confounding by important differences between the cohort and the reference population, except for confounding caused by the absence of subjects unfit for surgery or with LC symptoms in the cohort at baseline. To correct for this healthier-cohort bias that is in favour of screening effectiveness, we excluded from LC mortality analysis the initial 18 months of study, as suggested by other authors [18]. Because the time from LC symptoms to death is rarely longer than a few months, the healthier-cohort bias of the cumulative LC SMR assessed during the subsequent period 1999–2006 was likely negligible. As to the completeness of follow-up and of LC deaths data collection, it must be noted that the vital status ascertainment rates at study cut off were very high, and nearly identical in the cohort and in the source population (98.5% and 98.2%, respectively). Notably, contamination by CXR screening that was performed in approximately 9% of the reference population (1244 participants of the cohort and 1221...
uninvited participants referred to in the methods) possibly biased the LC SMR modestly against screening effectiveness. Strengths of this study are >98% complete follow-up of the cohort, and intent-to-screen analysis of LC mortality. An additional strength is the conservative assessment of LC SMR. To this effect, in order to calculate the expected number of LC deaths in a worst-case scenario, we used the lowest value (0.86) in the range of smoking-attributable proportion of LCs.

While fully acknowledging the limitation of this nonrandomized population-based cohort study with a comparison group, our findings suggest causality between implementation of the CXR screening programme and significant reduction of LC mortality in the invitation-to-screen cohort. It is noteworthy that the LC SMR of 0.82 estimated after CXR screening is consistent with the relative stage shift of LC and with the significantly enhanced long-term (10-year) LC-specific survival in the invitation-to-screen cohort, that we recently reported [12]. It is speculative whether the GPs collaborating in this study had an increased LC awareness and provided better than usual care to the whole cohort they invited to the screening programme, possibly contributing to lower the LC mortality. We also hypothesize that an increased LC awareness among screening participants [11] contributed to decrease LC mortality by improving cancer treatment, as suggested in the setting of breast cancer screening [30]. It is noteworthy that our screening programme was managed for nearly a decade without severe complications. We previously reported few false-positive screening tests (3.4%), and few futile invasive diagnostic procedures (1.6/1000 tests), none of which caused serious adverse events. There were no deaths related to treatment of screen-detected LCs [12].

A complete costs–benefit analysis of our CXR screening programme of smokers at community level remains to be performed, to examine the possibility of whether the 18% LC mortality reduction that we estimated may be relevant for public health policy.

Conflict of interest statement

The authors declare no conflicts of interest.

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