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

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ABSTRACT

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

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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to as "cohort", that was invited to an annual CXR screening programme and prospectively followed up. We previously reported the cohort's demographic characteristics, screening protocol, participants adherence, and LC detection results [11,12]. After completion of the CXR screening programme, here we evaluate its effectiveness in the cohort by estimating the standardized mortality ratio (SMR), an indicator recently used by other investigators to document 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 geographical 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 population 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 registered 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 noneligible 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 for 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 undertook 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 Insubria.

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 suspicious 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 linkage 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 treatment 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 mortality 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 chosen based on the suggestion to add about 4 years after the end of active screening (median in 2002 in our study) to evaluate the effectiveness 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