ORIGINAL ARTICLE

Stopping Smoking Reduces Mortality in Low-Dose Computed Tomography Screening Participants

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ABSTRACT

Introduction: The National Lung Screening Trial has achieved a 7% reduction in total mortality with low-dose computed tomography (LDCT) screening as compared with in the chest radiography arm. Other randomized trials are under way, comparing LDCT screening with no intervention. None of these studies was designed to investigate the impact of smoking habits on screening outcome. In the present study, we tested the effect of stopping smoking on the overall mortality of participants undergoing repeated LDCT screening for many years.

Methods: Between 2000 and 2010, 3381 smokers aged 50 years or older were enrolled in two LDCT screening programs. On the basis of the last follow-up information, subjects were divided into two groups: current smokers throughout the screening period and former smokers.

Results: With a median follow-up time of 9.7 years and a total of 32,857 person-years (PYs) of follow-up, a total of 151 deaths were observed in the group of 1797 current smokers (17,846 PYs) versus 109 among 1584 former smokers (15,011 PYs), corresponding to mortality rates of 8.46 and 7.26 for every 1000 PYs, respectively. Compared with current smokers, former smokers had an adjusted mortality hazard ratio of 0.61 (95% confidence interval: 0.44–0.83), with a 39% reduction in mortality. A similar reduction in mortality was observed in the subset of 712 late quitters, with a hazard ratio of 0.65 (95% confidence interval: 0.44–0.96).

Conclusions: Stopping smoking significantly reduces the overall mortality of smokers enrolled in LDCT screening programs. The beneficial effect of stopping smoking on total mortality appears to be threefold to fivefold greater than the one achieved by earlier detection in the National Lung Screening Trial.

Keywords: Smoking; Lung cancer; Screening; LDCT; Mortality

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Introduction

Lung cancer kills 1.3 million people every year worldwide,[1] more than breast, colon, and prostate cancer combined.[2] In Western countries, lung cancer mortality has constantly declined in men during the past 40 years, 20 years after a similar reduction in tobacco consumption, whereas it is still rising in women from several European countries, as well as in major developing countries such as China.[3] The figures for lung cancer represent a major determinant of the otherwise moderate reduction in total cancer mortality observed in the United States.[2]

According to the European Cancer Registry Based Study on Survival and Care of Cancer Patients project, 5-year survival after diagnosis of lung cancer has improved in all European countries from 8% to 13% in the past 30 years.[4–6] Despite expectations from therapeutic advances, however, the survival numbers remain dismal.[7]

Genuine hope for better lung cancer survival and major reduction in mortality was generated by the use of low-dose computed tomography (LDCT) for early detection in heavy smokers.[8,9] However, the present evidence from randomized trials shows a reduction in mortality of approximately 1% per year in the LDCT arm of National Lung Screening Trial (NLST),[10] but no benefit in the three smaller European studies with a pure observational control arm.[11–13] None of these studies was designed to investigate the impact of smoking habits on LDCT screening outcome.

Lung cancer accounts for less than one-third of overall mortality in heavy smokers,[14] and earlier detection, even if minimally effective, cannot modify in a significant manner the risk profile of screening participants who continue to smoke.[14] On the contrary, smoking cessation may have a profound and rapid effect in these individuals.[15]

We considered the effect of smoking cessation on the overall mortality of 3381 participants included from 2000 until 2015 in two prospective screening trials of repeated annual or biennial LDCT.[11,16]

Methods

Study Population

The current study is based on two LDCT screening programs launched in Milan since 2000. Details of these screening programs have been reported elsewhere.[11,16] Briefly, the first pilot trial started in 2000, offering yearly LDCT for a minimum of 5 years to 1035 current or former smokers who had a smoking history of at least 20 pack-years, were 50 years of age or older, and did not report a history of cancer in the past 5 years.[16] The second trial, called Multicentric Italian Lung Detection (MILD), started in 2005 and included 4099 smoker participants with the same characteristics as in the previous trial; 1723 were randomized to the control group, 1190 to annual LDCT screening, and 1186 to biennial LDCT screening.[11] Thirty participants from the pilot study were randomized in the MILD trial after 5 years of screening. Both studies included a smoking cessation component for all subjects, with repeated counseling at each screening clinic and specific advice on different pharmacologic supports for those who expressed a motivation for quitting. In the MILD cohort, a group of 187 subjects who were persistent smokers after 4 years of LDCT screening entered a smoking cessation program with varenicline.[17]

Cohort Selection

As shown in Figure 1, we included all 3381 smokers aged 50 years or older who during the period from 2000 until 2010 received LDCT in the context of the two Italian screening programs (i.e., the 1723 participants who were randomized to the control group in the MILD trial were excluded from the current study). The dynamic nature of inclusion in the cohort means that individuals contributed person-years (PYs) of observation from the date of the first screening visit (baseline) until they were censored from further observation, either because of death (from lung cancer or other causes) or because they had reached the end of follow-up.

Data Collection and Follow-Up

At the time of initial registration, as well as at each annual or biennial clinical visit during the entire LDCT

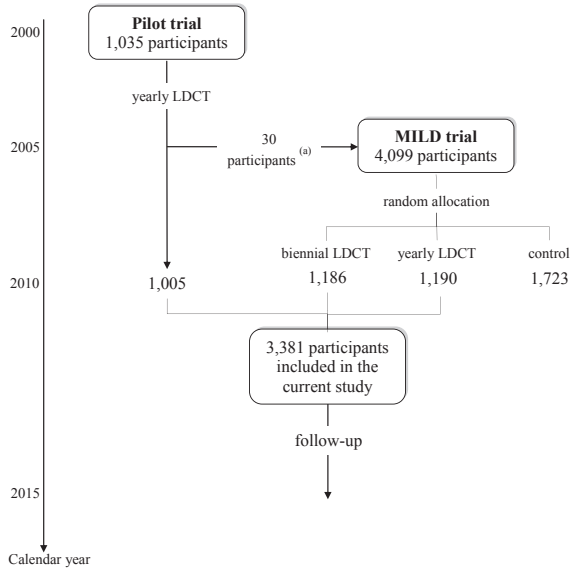

Figure 1. Flow diagram of inclusion criteria in the current study from previous pilot and Multicentric Italian Lung Detection (MILD) trials. Thirty subjects from the pilot study were randomized in the MILD trial after 5 years of screening. LDCT, low-dose computed tomography.

screening period, smoking status was assessed by medical interview and a detailed self-administered questionnaire. For the purpose of the present analysis, an independent telephone interview focusing on late smoking status and final date of quitting was conducted with all subjects with inconsistencies between questionnaires or missing information from the past 2 years.

On the basis of the last available information, all participants were classified into two groups: current smokers (i.e., patients who remained active smokers throughout the LDCT screening period or stopped smoking less than a year before the end of follow-up or death) and former smokers otherwise. Former smokers were further classified according to whether they stopped smoking before baseline (early quitters) or during follow-up (late quitters). Overall, two hierarchic categorizations were used for the purpose of the current study, the first one including current and former smokers and the second one dividing former smokers into early and late quitters.

Life course smoking exposure of each participant was measured at baseline and expressed by the cumulative number of cigarettes smoked and the average number of pack-years. Other baseline features included sex, age, and lung function (percent predicted forced expiratory volume in the first second of expiration [FEV_1]). Finally, we recorded the date of detection of lung cancer during follow-up.

Follow-up was closed on January 30, 2015, through outpatient clinic, active telephone calls, and record linkage with the vital status National Registry Office database. For deceased subjects, we obtained the death certificate from the Italian Institute of Statistics. No patient was lost to follow-up: 3351 participants (99.1%) were either dead or followed up for more than 5 years; the median follow-up of the remaining 30 participants was 55 months, with a minimum of 48 months.

Data Analysis

Descriptive statistics were used for summarizing the baseline characteristics of the entire cohort as well as those of the current and former smokers and early and late quitters. The chi-square test, or its version for the trend where appropriate, was used to test between-group differences or trends.

Mortality rates were calculated from the observed number of deaths and the corresponding PY experienced by the cohort members. The 95% confidence interval (CI) was estimated under the assumption that the number of deaths followed a Poisson distribution. Rates were stratified according to smoking status, and between-group differences were tested according to normal approximation of the natural logarithm of rate ratio. The overall mortality curves of current and former smokers were calculated by the Kaplan-Meier estimator and compared by the log-rank test.

The multivariable Cox proportional hazard regression model was used to estimate the hazard ratio (HR) and 95% CI for predictors of time of death onset. The effect of smoking status (i.e., the main predictor of interest) was obtained by contrasting current and former smokers, as well as current smokers and late and early quitters. Adjustments were made for factors characterizing patients at baseline, i.e., sex, age (quartile categories), FEV_1 ($\geq$100%, 80%–100%, and $<$80%), and number of pack-years (20–39 and 40 or more). In addition, because a diagnosis of lung cancer could affect quitting behaviors,[18] detection of lung cancer during follow-up was considered. Because both smoking status and cancer detection may vary over follow-up, assessment of their value requires proper accounting for their cumulative and varying nature. This was done by including smoking and cancer detection as time-dependent variables in the model.

The SAS statistical software package, version 9.4, (SAS Institute, Cary, NC) was used for the analyses.

For all hypotheses tested, two-tailed p values less than 0.05 or, in an equivalent manner, a 95% CI of the HR that did not contain the value expected under the null hypothesis (i.e., the value 1) were considered to be significant.

The first pilot trial was approved by the institutional review board and ethics committee in 2000,[16] MILD trial in 2005,[11] and varenicline study in 2009 (European Clinical Trials Database 2009-014301-14).[17]

Results

Smoking Features

In total, 3381 smokers enrolled in LDCT screening programs were included in the current study. Fifty-three percent of the cohort members (1797) were smokers according to the last available (current) information. Fifty-five percent of the former smokers had already stopped smoking at baseline (872 early quitters), whereas the remaining 45% stopped smoking during follow-up (712 late quitters). Table 1 gives some selected characteristics of participants according to their smoking status. Sixty-nine percent were men, the median age was 58 years, and the median smoking exposure was 40 pack-years. Women, participants younger than 54 years, and those who had smoked for more than 40 pack-years had a significantly higher likelihood of being current rather than former smokers.

Smoking Cessation and Mortality

Overall, 32,858 PYs were accumulated and 260 deaths occurred during follow-up, with a mortality rate

Table 1. Selected Features of the 3381 Individuals Included in the Study Cohort according to Their Smoking Status

Characteristic	Former Smokers, n (%)[a] (n = 1584)	Current Smokers, n (%)[a] (n = 1797)	Total, n (%) (n = 3381)	*p* Value[b]
Sex				
Male	1200 (75.8)	1144 (63.7)	2344 (69.3)	<0.0001
Female	384 (22.2)	653 (36.3)	1037 (30.7)	
Age, y				
<54	349 (22.0)	492 (27.4)	841 (24.9)	0.2812
54-58	370 (23.4)	466 (25.9)	836 (24.7)	
58-62	385 (24.3)	429 (23.9)	814 (24.1)	
≥62	480 (30.3)	410 (22.8)	890 (26.3)	
Percentage predicted FEV_1				
≥100	684 (43.2)	701 (39.0)	1385 (41.0)	0.2007
80-100	642 (40.5)	822 (45.7)	1464 (43.3)	
<80	258 (16.3)	274 (15.3)	532 (15.7)	
Lung cancer detected during follow-up				
No	1510 (95.3)	1732 (96.4)	3242 (95.9)	0.1233
Yes	74 (4.7)	65 (3.6)	139 (4.1)	
Average no. pack-years				
20-39	803 (50.7)	833 (46.4)	1636 (48.4)	0.0118
≥40	781 (49.3)	964 (53.6)	1745 (51.6)	

[a]Patients who still smoked and those who had stopped smoking during the last screening visit were regarded as current and former smokers, respectively (see the text for further specifications).
[b]The *p* values refer to chi-square testing homogeneity of smoking status between strata (sex, lung cancer detection, and category of average no. pack-years) or its trend over strata (age and FEV_1).
FEV_1, predicted forced expiratory volume in the first second of expiration.

of 7.9 deaths for every 1000 PYs (95% CI: 6.9–8.9). Deaths due to lung cancer, other cancers, and other causes, respectively, accounted for 28%, 34%, and 38% of all deaths; 22%, 36%, and 42% of deaths in early quitters; 29%, 39%, and 32% of deaths in late quitters; and 30%, 32%, and 38% of deaths in current smokers.

Men and participants who had smoked for more than 40 PYs had a significantly higher mortality rate than did women and participants who had smoked less (Table 2). As expected, a trend toward increased mortality rate with increasing age and decreasing FEV_1 was observed. Although current smokers had a higher mortality rate than did former smokers, the difference was not significant.

Figure 2 further shows that current smokers experienced a higher mortality than did former smokers, with corresponding overall mortality rates of 6.4% and 5.1%, respectively. The difference, however, was of borderline significance ($p = 0.0503$).

Figure 3 shows even stronger effects of smoking cessation on mortality reduction by accounting for covariates, including the time-dependent cancer detection rate and smoking habits during follow-up. Of interest, both early and late quitters had significantly reduced mortality with respect to current smokers. Over a median follow-up period of 9 years (minimum of 48 months), compared with current smokers, former smokers had a reduction in mortality of 3% to 5% per year. According to the multivariable Cox model, other than smoking cessation, factors affecting mortality were male sex (HR = 1.56, 95% CI: 1.08–2.26), age older than 62 years (HR = 3.18, 95% CI: 1.92–5.26), FEV_1 lower than 80% (HR = 2.32; 95% CI: 1.55–3.47), and lung cancer diagnosis during follow-up (HR = 13.69; 95% CI: 9.55–19.63).

Discussion

Large cohort studies based on hundreds of thousands of individuals have demonstrated a two to three times higher mortality due to all causes in lifelong smokers compared with in never-smokers, with more than two-thirds of all deaths that occurred in individuals aged 55 to 74 years being associated with smoking.[19] Time trends in the past 50 years showed a dramatic increase in rates of death from chronic obstructive pulmonary disease in male and female smokers and a significant decrease in never-smokers.[19] Marked differences in overall mortality according to smoking status (current, former, or never) have been clearly shown in the British Physician Cohort study.[20] New studies have revealed that a portion of the excess mortality in current smokers is attributable to previously unestablished causes, such as renal failure, hypertension, or infections.[14] These studies prove that even quitting smoking at an older age (≥60 years) dramatically reduces mortality due to all causes.[15,19]

Table 2. Observed Number of Deaths and Mortality Rates for Every 1000 Person-Years according to Selected Characteristics of Participants for their Effect on Mortality Rate

Characteristic	No. Deaths (PYs)	MR (95% CI)	*p* Value[a]
Sex			
Female	50 (10,095)	4.95 (3.58-6.32)	<0.0001
Male	210 (22,763)	9.23 (7.98-10.47)	
Age, y			
<54	31 (8062)	3.85 (2.49-5.20)	<0.0001
54-58	34 (8428)	4.03 (2.68-5.39)	
58-62	59 (7993)	7.38 (5.50-9.27)	
≥62	136 (8376)	16.24 (13.51-18.97)	
Percentage predicted FEV_1			
≥100	57 (12,862)	4.43 (3.28-5.58)	<0.0001
80-100	118 (14,751)	8.00 (6.56-9.44)	
<80	85 (5246)	16.21 (12.76-19.65)	
Average no. pack-years			
<40	75 (15,686)	4.78 (3.70-5.86)	<0.0001
≥40	185 (17,172)	10.77 (9.22-12.33)	
Lung cancer detected during follow-up			
No	204 (31,683)	6.44 (5.56-7.32)	<0.0001
Yes	56 (1175)	47.66 (35.18-60.14)	
Smoking status[b]			
Current smokers	151 (17,846)	8.46 (7.11-9.81)	0.2235
Former smokers	109 (15,012)	7.26 (5.89-8.62)	

[a]The *p* values refer to comparison between strata-specific mortality rates or version for the trend when proper (age and FEV_1).
[b]Patients who still smoked and those who had stopped smoking during the last screening visit were regarded as current and former smokers, respectively. Former smokers who stopped smoking before baseline and during follow-up were regarded as late and early quitters, respectively.
PYs, person-years; MR, mortality rate; CI, confidence interval; FEV_1, predicted forced expiratory volume in the first second of expiration.

Although current U.S. guidelines emphasize the importance of tobacco cessation treatment,[21–23] in the past decade the expectations for lung cancer screening with LDCT have diverted the efforts from primary prevention to early detection, particularly in heavy smokers. The results of NLST showed that the absolute benefit of LDCT in this population is relatively modest (less than 1% reduction in mortality per year), and the costs great. One of the reasons for such a limited benefit is the relative weight of lung cancer in the overall mortality burden.[14,19] In fact, the results of our study confirm that lung cancer accounts for less than 30% of all deaths in each of the smoking subgroups. None of the ongoing trials on LDCT screening was specifically designed to investigate the impact of smoking habits on LDCT screening outcome. The proportion of current smokers in the LDCT arm who quit was 12% at 1 year among participants in the Danish trial[24] and 14% at 2 years in a sample of the Dutch-Belgian Lung Cancer Screening Trial trial.[25]

The data reported here show that 28% of lifelong current smokers who enter an LDCT screening program with a median age of 57 years and smoking history of 40

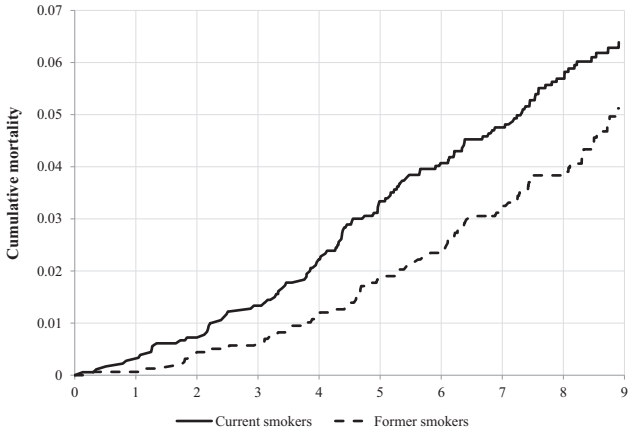

Figure 2. Kaplan-Meier overall mortality experienced by current and former smokers. Patients who still smoked and those who had stopped smoking during the last screening visit were regarded as current and former smokers, respectively.

pack-years can stop smoking during screening intervention as a consequence of counseling. However, the experience derived from a small subset of 187 subjects (7.9%) from the MILD trial who were offered antitobacco therapy with varenicline for 3 months revealed a carbon monoxide–confirmed quit rate of 49% at 3 months and 20% abstention at 12 months.[17] These findings are consistent with those of a recent study that was performed in the context of the NLST trial and showed that pharmacologic support delivered by a primary care provider is effective for smoking cessation.[18] On the basis of our findings, it is reasonable to estimate that systematic treatment of all current smokers with varenicline within the MILD trial, including repeated administration for a first failed attempt, might have significantly improved the proportion of ex-smokers at the end of the LDCT screening program from the observed 53% to a cumulative rate of 70% to 80%.

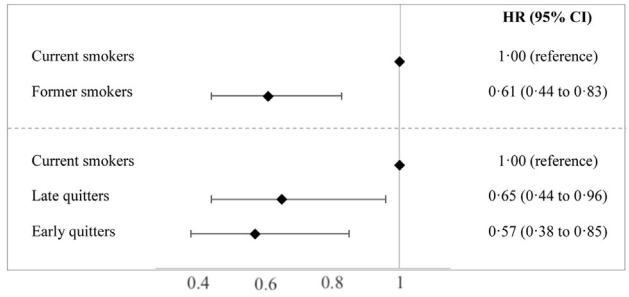

Figure 3. Effect of smoking cessation on overall mortality. Hazard ratios (Cox model) and corresponding 95% confidence intervals estimating the effect of smoking cessation on mortality. Estimates are adjusted for covariates measured at baseline (sex, age, predicted forced expiratory volume in the first second of expiration, and average number of pack-years) and during follow-up (lung cancer detection and smoking status). HR, hazard ratio; CI, confidence interval.

Our study of 3381 smokers enrolled in two screening programs for early detection of lung cancer corroborates and expands evidence from previous investigations in observational cohorts[15] by showing that smoking cessation is beneficial in reducing mortality. Although the difference between current and former smokers in terms of mortality rate during follow-up was of borderline significance according to unadjusted analysis ($p = 0.0503$), significant evidence of the beneficial effect of smoking cessation was observed after having adjusted for lung cancer detection and the time-varying nature of quitting smoking in a Cox proportional hazard model. Of interest, the effect of smoking cessation during the LDCT screening period was statistically significant according to the Cox multivariable model, with a 35% reduction in mortality compared with that when smoking was continued.

A recent study showed that the status of former smoker at the time of enrollment in the NLST trial is a favorable prognostic factor, with corresponding all-cause mortality reduced by approximately 45% versus in current smokers (i.e., the same magnitude of reduction in all-cause mortality among early quitters observed in our study).[26] The NLST-based study, however, assumed that smoking status did not change during follow-up, which may not always be true, as shown in our investigation. Our study clearly shows that there is still a large potential benefit of smoking cessation once individuals enter a screening program.

Notwithstanding the limited pharmacologic antitobacco support in our LDCT trials, the overall reduction in mortality in ex-smoker cohorts was 3% to 5% per year, representing a threefold to fivefold greater benefit than the one achieved by LDCT screening in the NLST trial. These results suggest that smokers who are older than 50 years and undergoing LDCT screening provide the opportunity to test the efficacy of primary prevention strategies with a prospective and randomized design.

In the next 2 years, the mature results of the Dutch-Belgian Lung Cancer Screening Trial trial, as well as pooled analysis of all European randomized LDCT trials, will provide a better understanding of the real benefit of lung cancer screening, the most effective criteria for selection of high-risk individuals, and the optimal diagnostic algorithms. Regardless of the results of LDCT screening, it is reasonable to expect that public policies on early detection will have to be combined with active intervention in smoking-related mortality to improve their cost-benefit ratio. Although the ongoing studies will demonstrate the efficacy of blood-based biomarkers in improving LDCT performance and defining individuals at higher biologic risk,[27] current smokers undergoing LDCT screening could be randomized to pharmacologic antitobacco therapy versus counseling only, with minimal increase in the total costs.

We are facing a revolutionary change in the prospects of molecular medicine, with unprecedented outcome improvements in chronic diseases such as hepatitis C and cancer and a more than proportional growth in drug expenditures. To be able to sustain the costs of potentially curative treatments for unpreventable diseases, we must reduce the costs of palliative management of preventable ones, such as metastatic lung cancer, if we want to make molecular medicine affordable for our aging populations. Smoking cessation can produce significant and meaningful survival benefits in the context of lung cancer screening, and pharmacologic antitobacco intervention therefore becomes a fundamental priority in public health strategies.

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