Inflammatory status and lung function predict mortality in lung cancer screening participants

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Low-dose computed tomography (LDCT) screening trials have based their risk selection algorithm on age and tobacco exposure, but never on pulmonary risk-related biomarkers. In the present study, the baseline inflammatory status, measured by C-reactive protein (CRP) level, and lung function, measured by forced expiratory volume in 1 s (FEV_1), were tested as independent predictors of all-cause mortality in LDCT-screening participants. Between 2000 and 2010, 4413 volunteers were enrolled in two LDCT-screening trials, with evaluable baseline CRP and FEV_1 values: 2037 were included in the discovery set and 2376 were included in the validation set. The effect of low FEV_1 or high CRP alone or combined was evaluated by Kaplan–Meier mortality curves and hazard ratio (HR) with 95% confidence interval (CI) by fitting Cox proportional hazards models. The overall mortality risk was significantly higher in participants with FEV_1 of up to 90% (HR: 2.13, CI: 1.43–3.17) or CRP more than 2 mg/l (HR: 3.38, CI: 1.60–3.54) and was still significant in the fully adjusted model. The cumulative 10-year probability of death was 0.03 for participants with FEV_1 of more than 90% and CRP up to 2 mg/l, 0.05 with only FEV_1 of up to 90% or CRP above 2 mg/l, and 0.12 with FEV_1 of up to 90% and CRP above 2 mg/l. This predictive performance was confirmed in the two external validation cohorts with 10-year mortality rates of 0.06, 0.12, and 0.14, and 0.03, 0.07, and 0.14, respectively. Baseline inflammatory status and lung function reduction are independent predictors of all-cause long-term mortality in LDCT-screening participants. CRP and FEV_1 could be used to select higher-risk individuals for future LDCT screening and preventive programs. ***European Journal of Cancer Prevention*** **27:289–295 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

Large-scale cohort studies have proven that two-thirds of all deaths in individuals aged 55–74 years are associated with smoking and that quitting smoking after 60 years of age can lead to a marked reduction in mortality of all causes (Harris *et al.*, 2004; Thun *et al.*, 2013; Muezzinler *et al.*, 2015). The accurate definition of individual risk level is a fundamental need to target preventive strategies and improve their efficacy in current and former smokers (Tammemagi, 2015). In the last 15 years, low-dose computed tomography (LDCT) screening trials have based their selection algorithm on age and tobacco exposure (intensity and duration), but the benefit achieved by LDCT in the National Lung Screening Trial (NLST) (National Lung Screening Trial Research Team *et al.*, 2011) and pooled analysis of two European trials (Infante *et al.*, 2016) was a total mortality reduction of only 1% per year. Aiming at a higher-risk population, the United Kingdom Lung Cancer Screening Trial added other factors to the NLST algorithm, such as asbestos exposure, family history, previous pneumonia, or malignant tumor, with a limited increase in the lung cancer detection rate at 12 months (Field *et al.*, 2016) compared with previous trials (Bach *et al.*, 2012).

A new approach to individual risk assessment, on the basis of the objective measurement of cumulative damage because of tobacco smoking, in addition to the standard assessment of carcinogenic exposure, has the potential advantage of improving the cost/benefit balance of LDCT screening and providing new prospects for the prevention of tobacco-related diseases.

We have previously shown that a minimal reduction of lung function at baseline, defined by forced expiratory

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volume in 1 s (FEV_1) of up to 90% of the predicted value, is associated with a higher risk of lung cancer in LDCT-screening participants (Calabro *et al.*, 2010). Beyond the screening context, large cohort studies have shown that baseline inflammatory status, measured by blood level of C-reactive protein (CRP), represents a major risk factor for all-cause (Ridker, 2008; Zacho *et al.*, 2010; Cozlea *et al.*, 2013) and cancer mortality (Shrotriya *et al.*, 2015), and predicts the outcome of resected early-stage lung cancer (Leuzzi *et al.*, 2016). In the present study, we tested the independent ability of baseline CRP and FEV_1 to predict all-cause long-term mortality in LDCT-screening participants.

Participants and methods

Study population

Data of two LDCT-screening programs launched in Milan since 2000 have been used to answer these questions. Details of these programs have been reported elsewhere (Pastorino *et al.*, 2003, 2012) and summarized in the Supplementary data (Supplemental digital content 1, *http://links.lww.com/EJCP/A147*). Briefly, the first pilot study, which was approved by the institutional review board and ethics committee in 2000, offered yearly LDCT for a minimum of 5 years to 1035 current or former smokers with a smoking history of at least 20 pack-years (PY), 50 years of age or older, who did not report a history of cancer in the last 5 years (Pastorino *et al.*, 2003). The second trial, called the Multicentric Italian Lung Detection (MILD), was launched in 2005 (registered in ClinicalTrials.gov NCT02837809) and included 4099 smoker participants with the same characteristics as in the previous trial, 1723 of whom were randomized to the control group and 2376 to LDCT screening (Pastorino *et al.*, 2012). Thirty four participants from the pilot study who were randomized in the MILD trial after 5 years of screening have been assigned to the MILD trial for the current study (e.g. we included 1001 participants in the pilot study).

The current study is based on three separate cohorts obtained from these LDCT-screening programs. In particular, the LDCT arm of the MILD trial (i.e. the proportion of the study population that we called the discovery cohort) was used to construct the prognostic model, whereas the pilot LDCT trial and the control arm of the MILD trial were used as validation cohorts.

Each member of the study cohorts accumulated person-years of follow-up from baseline (i.e. at the date of the first screening visit) until the date of death or 26 June 2016 for survivors. All the eligible patients signed a consent form.

Data collection

Available data at baseline included age, sex, percent of predicted FEV_1, plasma level of CRP, and smoking PY. The CRP was quantified by immunoturbidimetry using a Cobas C6000 automated clinical chemistry analyser (Roche Diagnostics, GmbH, Penzberg, Germany) from the same laboratory throughout the entire study period, with values reporting two decimal places. Data were missing for some patients. In particular, 687 participants of the MILD trial did not have data on both FEV_1 and CRP; thus, the MILD discovery and MILD control cohorts included 2037 and 1375 participants, respectively.

Statistical analyses

Descriptive analyses were used to summarize the baseline characteristics of the study participants according to cohort (MILD LDCT, pilot LDCT, and MILD control cohort). Frequencies and percentages were generated for categorical variables (Table 1). The χ^2-test was used to assess the differences among the three sets.

The ability of the investigated covariates to predict 10-year all-cause mortality was probed by fitting Cox proportional hazards models to the data from the 2037 participants from the MILD LDCT arms (discovery cohort). Covariates were included in the models in a dichotomous form. In the main analysis, cut-offs for FEV_1 and CRP were chosen according to previous experience (Calabro *et al.*, 2010; Leuzzi *et al.*, 2016). However, because of the high degree of arbitrariness in the choice, the best trade-off between sensitivity and specificity in predicting 10-year mortality was identified for both FEV_1 and CRP from the corresponding receiver operating characteristic (ROC) curves, and a sensitivity

Table 1 Baseline characteristics of the study participants according to cohort

	MILD discovery cohort [*n* (%)]	Pilot LDCT cohort [*n* (%)]	MILD control cohort [*n* (%)]
Total	2037	1001	1375
Sex			
Female	635 (31.2)	286 (28.6)	517 (37.6)
Male	1402 (68.8)	715 (71.4)	85.8 (62.4)
Age [mean (SD)] (years)	58 (5.9)	58 (5.7)	57 (6.0)
< 55	663 (32.6)	285 (28.5)	533 (38.8)
≥ 55	1374 (67.4)	716 (71.5)	842 (61.2)
Pack-years [mean (SD)] years	43 (21.3)	40 (22.9)	37 (20.5)
< 30	436 (22.7)	114 (11.4)	408 (29.7)
≥ 30	1574 (77.3)	887 (88.6)	967 (70.3)
FEV_1%[a]			
> 90	1415 (70.1)	470 (56.3)	996 (73.4)
≤ 90	602 (29.9)	365 (43.7)	361 (26.6)
CRP (mg/l)[a]			
≤ 2	1221 (59.9)	597 (60.4)	765 (63.3)
> 2	816 (40.1)	391 (39.6)	443 (36.7)
FEV_1 and CRP[a]			
> 90% and ≤ 2 mg/l	1211 (60.0)	508 (61.6)	754 (63.4)
≤ 90% or > 2 mg/l	510 (25.3)	152 (18.4)	290 (24.4)
≤ 90% and > 2 mg/l	296 (14.7)	165 (20.0)	146 (12.3)
Lung cancer[a]			
No	1954 (95.9)	951 (95.1)	1350 (98.2)
Yes	83 (4.1)	49 (4.9)	25 (1.8)

CRP, C-reactive protein; FEV_1, forced expiratory volume in 1 s; LDCT, low-dose computed tomography; MILD, Multicentric Italian Lung Detection.
[a]Missing data are handled in the analysis.

analysis was carried out to verify the robustness of the results obtained from the main analysis. The cut-off for PY was set to 30 to comply with NLST trial eligibility criteria (National Lung Screening Trial Research Team *et al.*, 2011).

Three Cox proportional hazards regressions were fitted by including each covariate one by one in separate models (model 1), the main term of all covariates together in a unique model (model 2), and adding to model 2 the interaction term between FEV_1 and CRP (model 3). Eventual departure of the joint action from the multiplicative structure (model 2) was tested using the likelihood ratio test. Results, expressed as hazard ratio (HR) and the corresponding 95% confidence interval (95% CI), allowed the construction of the more parsimonious model predictive of 10-year mortality. Internal and external validity of the predictive model was investigated as described in the Supplementary data (Supplemental digital content 1, *http://links.lww.com/EJCP/A147*). After assessing the value of predictors for all-cause mortality, we developed a Cumulative Incidence Competing Risk model to describe the probability of lung cancer cause-specific mortality in the presence of a competing risk (other-cause mortality) among the predictors' levels for the MILD discovery cohort and the pilot LDCT cohort combined (Kim, 2007).

As FEV1 or CRP values were sometimes missing (the latter for 204 and 177 values of FEV1 or CRP, respectively, corresponding to 4.6 and 4.0% of the cohort members included) and because restricting analyses to the subset of patients with all the data observed would result in a significant loss of information and possibly biased estimations, with the aim of generating appropriate values of missing data for those patients with missing covariates belonging to the discovery cohort, a Markov Chain Monte Carlo process (Ake and Carpenter, 2015), involving the following three distinct phases was implemented. First, the Markov Chain Monte Carlo method was implemented to generate 10 complete data sets. Second, the Cox proportional hazards model was separately fitted to the 10 complete data sets. Finally, the MIANALYZE procedure was used to combine the coefficient estimates (and estimations of their variances) to obtain valid statistical inferences of the model coefficients that take within and between variances into account.

The cumulative 10-year probabilities of death were calculated using the Kaplan–Meier estimator and were compared among groups using the log-rank test (Kaplan and Meier, 1958). For all hypotheses tested, two-tailed P values less than 0.05 or, in an equivalent manner, 95% CI of HR that did not contain the value expected under the null hypothesis (i.e. the value 1) were considered to be significant. All analyses were carried out using Statistical Analysis System Software (version 9.4; SAS Institute, Cary, North Carolina, USA).

Results

Study population

In total, 4413 participants were included in the current study (Supplementary Fig. E1, Supplemental digital content 2, *http://links.lww.com/EJCP/A140*): 2037 from the MILD LDCT arm (discovery set), 1001 from the pilot LDCT study (first validation set), and 1375 from the MILD control arm (second validation set).

Baseline characteristics of the study population are shown in Table 1. The mean (SD) age of the participants was 58.0 (5.9) years for the MILD discovery cohort, 58.5 (5.7) years for the pilot LDCT cohort, and 57.3 (6.0) years for the MILD control cohort; the mean (SD) PY was 43.3 (21.3), 47.8 (22.9), and 41.1 (20.5) years for the three cohorts, respectively. There were significantly more male participants, participants with at least 55 years of age, and participants with FEV_1 up to 90% among the pilot LDCT cohort than in both MILD cohorts. Interestingly, there was no relationship between FEV_1 and CRP levels in the MILD discovery cohort (Supplementary Fig. E2, Supplemental digital content 3, *http://links.lww.com/EJCP/A141*).

Overall, 18 940 person-years were accumulated by the MILD discovery cohort members and 102 deaths occurred during follow-up, with a mortality rate for all causes of 5.4/1000 person-years. The corresponding values were 14 317 person-years and 189 deaths, with a mortality rate for all causes of 13.2/1000 person-years for the pilot LDCT cohort, and 11 779 person-years and 63 deaths, with a mortality rate for all causes of 5.3/1000 person-years, for the MILD control cohort.

Table 2 Relationship between selected covariates and time to death

	Model 1[a] HR[b] (95% CI)		Model 2[a] HR[b] (95% CI)	
Sex				
Female	1	Reference	1	Reference
Male	1.57	0.99 – 2.49	1.38	0.86 – 2.00
Age (years)				
< 55	1	Reference	1	Reference
≥ 55	2.85	1.65 – 4.93	2.50	1.44 – 4.35
Smoking pack-years				
< 30	1	Reference	1	Reference
≥ 30	1.30	0.77–2.08	0.95	0.57–1.58
FEV_1%				
> 90	1	Reference	1	Reference
≤ 90	2.13	1.43–3.17	1.85	1.23–2.77
CRP (mg/l)				
≤ 2	1	Reference	1	Reference
> 2	3.38	1.60–3.54	2.06	1.38–3.09

CI, confidence interval; CRP, C-reactive protein; FEV_1, forced expiratory volume in 1 s; HR, hazard ratio.

[a] Models fitted by including each covariate one by one (model 1) and all covariates together (model 2).

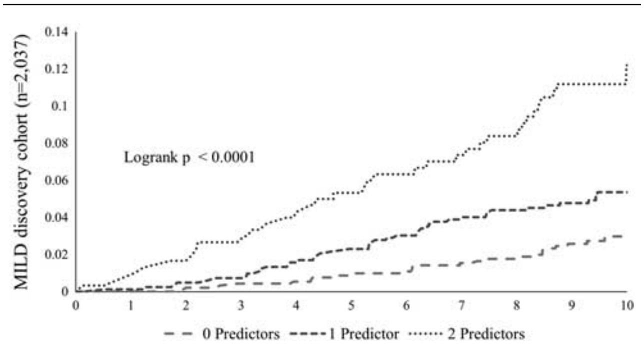
[b]Hazard ratio and 95% confidence interval estimated by means of fitting parametric Cox proportional hazards models.

Forced expiratory volume in 1 s and C-reactive protein predict overall survival

According to multivariate analysis (Table 2), there was an increased risk of overall mortality among patients who were older (HR: 2.85, CI: 1.65–4.93), and had low values of FEV_1 (HR: 2.13, CI: 1.43–3.17) and high values of CRP (HR: 3.38, CI: 1.60–3.54). Older age (HR: 2.50, CI: 1.44–4.35), low FEV_1 (HR: 1.85, CI: 1.23–2.77), and high CRP (HR: 2.06, CI: 1.38–3.09) were still significant in the full model, suggesting their independent effects in predicting 10-year mortality (model 2). No noteworthy departure from the multiplicative structure of interaction between FEV_1 and CRP was observed (model 3, data not shown).

The mortality curves plotted in Fig. 1 show that the cumulative probabilities of death of the MILD LDCT discovery cohort participants were significantly affected by the number of predictors. Indeed, the 10-year probabilities of death were 0.03, 0.05, and 0.12 for participants who had no predictors ($FEV_1 > 90\%$ and $CRP \leq 2$ mg/l), one predictor ($FEV_1 \leq 90\%$ or $CRP > 2$ mg/l), and two predictors ($FEV_1 \leq 90\%$ and $CRP > 2$ mg/l), respectively (Fig. 1). The corresponding values were 0.05, 0.06, and 0.14 for participants who at baseline were 55 years or older and had previously smoked at least 30 PY (NLST eligibility criteria) (Supplementary Fig. E3a, Supplemental digital content 4, *http://links.lww.com/EJCP/A142*) and 0.03, 0.08, and 0.14 by modifying the cut-offs of FEV_1 up to 84% and CRP up to 2.8 according to the ROC curve analysis (Supplementary Fig. E3b, Supplemental digital content 4, *http://links.lww.com/EJCP/A142*). The corresponding values for participants of the pilot LDCT validation cohort were 0.06, 0.12, and 0.14 (Fig. 2a) and those for the participants of the MILD control validation cohort were 0.03, 0.07, and 0.14 (Fig. 2b).

Fig. 1



Cumulative 10-year probabilities of death for participants who had no [forced expiratory volume in 1 s (FEV_1) > 90% and C-reactive protein (CRP) ≤ 2 mg/l], one ($FEV_1 \leq 90\%$ or $CRP > 2$ mg/l), or two ($FEV_1 \leq 90\%$ and $CRP > 2$ mg/l) predictors. All the 2037 participants of the low-dose computed tomography arms of the Multicentric Italian Lung Detection (MILD) trial are included in the discovery set.

Forced expiratory volume in 1 s and C-reactive protein predict lung cancer-specific mortality

Figure 3 shows the cumulative probability of lung cancer-specific mortality, by the Kaplan–Meier estimator, according to the predictors' levels for the two LDCT cohorts combined (3038 participants, 33 258 PY). At any given time, a patient with two predictors was more likely to die of lung cancer than a patient with one predictor, and a patient with one predictor was more likely to die of lung cancer than patients with no predictors: 0.007 for no predictors, 0.018 for one predictor, and 0.035 for two predictors ($P < 0.0001$). The relationship between predictors' level and time to lung cancer-specific death is shown in Table 3: the HR for lung cancer-specific mortality was 2.22 (CI: 0.83–5.91) for one predictor and 5.69 (CI: 2.11–15.39) for two predictors. In summary, 81% of all lung cancer deaths occurred in 57% of participants with one or two predictors.

Discussion

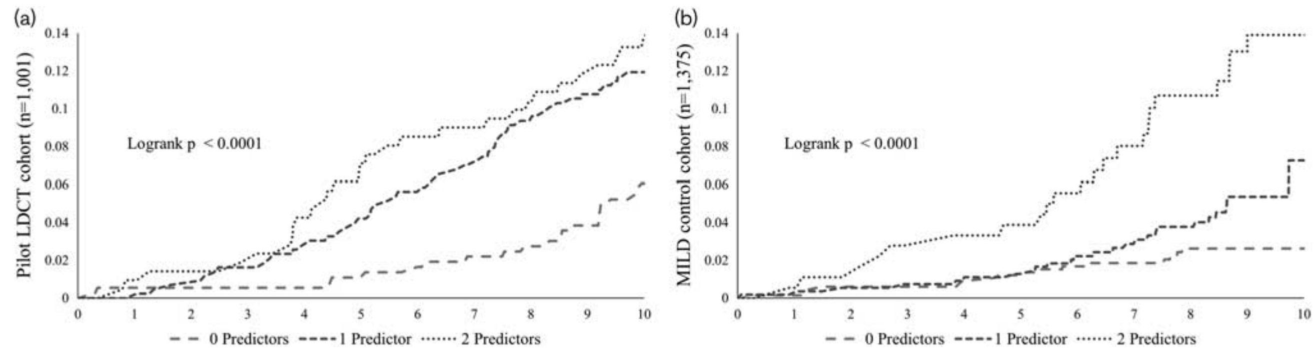
The results presented here show that baseline inflammatory status and pulmonary function, respectively, measured by CRP and FEV_1 levels at baseline, are independent predictors of long-term mortality in LDCT-screening participants. Their predictive value was assessed in the LDCT arm of the MILD trial on the basis of a median follow-up period of 9.5 years and was also evident in the subset of individuals with the highest exposure-related risk according to the NLST criteria, that is, age 55 years and older and smoking at least 30 PY. The predictive value of FEV_1 and CRP was then confirmed using two distinct validation sets: the first pilot LDCT trial, whose median follow-up period was 15.3 years, and the observational arm of the MILD trial.

This observation is of potential clinical value for two reasons. First, it provides the possibility of testing new preventive strategies with an anti-inflammatory intervention in prospective randomized trials. In fact, a baseline CRP level of more than 2 mg/l still represents a modest inflammatory status, well below the normal threshold of 5 mg/l, and might be corrected by preventive actions, such as pharmacologic antitobacco therapy, use of anti-inflammatory drugs, and/or dietary changes. Second, targeting individuals at a higher risk of lung cancer might increase the cost/benefit ratio of LDCT-screening programs.

In the last 50 years, we have observed a marked increase in death rates from chronic obstructive pulmonary disease (COPD) in male and female smokers, and a parallel reduction in never smokers (Thun *et al.*, 2013). Surprisingly, a considerable proportion of this excess of mortality was attributable to previously unsuspected causes, such as renal failure, hypertension, or infectious diseases (Carter *et al.*, 2015).

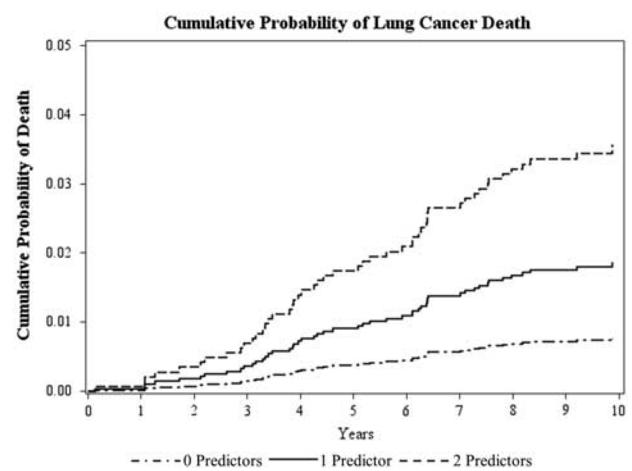
Pharmacologic therapy with antitobacco drugs, such as varenicline, and anti-inflammatory agents, such as cardioASA,

Fig. 2



Cumulative 10-year probabilities of death of the 1001 participants in the pilot low-dose computed tomography cohort (a) and of the 1375 participants in the Multicentre Italian Lung Detection (MILD) control cohort (b) who had no [forced expiratory volume in 1 s (FEV_1) > 90% and C-reactive protein (CRP) ≤ 2 mg/l], one (FEV_1 ≤ 90% or CRP > 2 mg/l), or two (FEV_1 ≤ 90% and CRP > 2 mg/l) predictors. LDCT, low-dose computed tomography.

Fig. 3



Cumulative 10-year probabilities of lung cancer death for patients who had 0 [forced expiratory volume in 1 s (FEV_1) > 90% and C-reactive protein (CRP) ≤ 2 mg/l], one (FEV_1 ≤ 90% or CRP > 2 mg/l), or two (FEV_1 ≤ 90% and CRP > 2 mg/l) predictors.

Table 3 Relationship between predictors' level and time to lung cancer-specific death

Number of predictors	HR	95% CI
0	1.00	Reference
1	2.22	0.83–5.91
2	5.69	2.11–15.39

CI, confidence interval; HR, hazard ratio.

has the potential capacity to slow down the progression of limited pulmonary damage because of severe COPD, but this hypothesis has never been tested by a randomized study.

The primary endpoint of the ongoing LDCT-screening trials is the reduction of lung cancer-specific mortality, even though lung cancer is responsible for less than 30% of all deaths in these populations, and ~10% in former smokers (Thun *et al.*, 2013; Carter *et al.*, 2015).

In fact, antitobacco therapy administered in the context of LDCT programs can increase the cessation rate of lifelong smokers (Park *et al.*, 2015; Pozzi *et al.*, 2015), and quitting smoking during the screening period can lead to a greater reduction of all-cause mortality than early detection itself (Pastorino *et al.*, 2016; Tanner *et al.*, 2016).

The CRP level has been proven to be a simple test to predict the risk of heart attack and stroke (Ridker, 2003), mortality from all causes (Marsik *et al.*, 2008; Zacho *et al.*, 2010), and cardiovascular disease (Ridker, 2008; Cozlea *et al.*, 2013). In a systematic review on adult solid tumors, elevated CRP levels were associated with higher mortality and recurrence rates (Shrotriya *et al.*, 2015).

In COPD patients, high CRP is a strong and independent predictor of future morbidity and mortality (Dahl *et al.*, 2007; Lahousse *et al.*, 2013; Ford *et al.*, 2015), and concurrent increase of CRP and reduction of FEV_1 exerts an even stronger effect on patients' outcome (Zhang *et al.*, 2014). These observations have been confirmed by two recent meta-analyses on early-stage lung cancer (Leuzzi *et al.*, 2016) and COPD (Leuzzi *et al.*, 2017).

An important issue is the optimal CRP cut-off value to predict the life expectancy of heavy smokers. The largest studies in COPD (Dahl *et al.*, 2007; Ford *et al.*, 2015), cardiovascular disease (Zacho *et al.*, 2010), or cancer (Shrotriya *et al.*, 2015) suggest that CRP level above 3 mg/l represents the best cut-off to predict long-term mortality in patients. In high-risk individuals, such as our discovery cohort, the best-performing cut-off from the area under the curve-ROC curve with two decimal values was a CRP of more than 2.8 mg/l. However, in clinical practice, integer values are the rule and the choice would be between 2 and 3. We adopted the lower value (CRP > 2) to reduce the number of individuals classified as low risk and increase the number of participants potentially eligible for future targeted intervention. Nonetheless, in our population, changing cut-off values to FEV_1 up to 84% and CRP up to 2.8 mg/l did not affect the predictive power of our risk algorithm.

The practical utility of targeting LDCT screening on pulmonary impairment is under debate. The evidence from post-hoc analysis of ongoing LDCT trials shows, on the one hand, that focusing on COPD-based risk could halve the number of patients needed to detect one lung cancer (Young *et al.*, 2013; Wille *et al.*, 2016); on the other hand, LDCT screening might be less effective in COPD patients because of competing risks of death (Young *et al.*, 2016). However, there is evidence that CRP levels can be lowered by metformin (Esfahanian *et al.*, 2013) or statins (Ridker *et al.*, 2005; Lee *et al.*, 2008; Young *et al.*, 2009; Lahousse *et al.*, 2013), and our results provide new prospects for chemoprevention in current or former smokers with higher CRP levels enrolled in LDCT-screening trials.

The biological significance of the relationship between CRP and mortality remains largely unknown. Whether CRP represents only a surrogate marker of other relevant pathways or is a specific indicator of microenvironment sickness is yet to be clarified (Kawashima *et al.*, 2015). In current or former smokers, high CRP levels and low FEV_1 can represent independent markers of cumulative pulmonary impairment. However, the interaction of CRP and FEV_1 might express a different degree of microenvironment imbalance and characterize a hyperresponsive innate immune response or a chronic immunodeficiency status.

The ability of circulating biomarkers, such as plasma microRNAs, to identify a protumorigenic microenvironment is currently under evaluation, with a similar purpose of improving the diagnostic performance and clinical outcome of LDCT (Sozzi *et al.*, 2014). Some cancer-related miRNAs are controlled by inflammatory signals, and consequently link the inflammatory responses to tumorigenesis by regulating their cancer-related genes. In fact, recent data indicate that aspirin and celecoxib prevent interleukin-1β-mediated downregulation of the tumor-suppressive miR-101 and let-7 miRNAs in nonsmall-cell lung cancer cells (Wang *et al.*, 2014), raising the possibility that regulation of miRNAs might constitute a novel mechanism for the chemopreventive effects of nonsteroidal anti-inflammatory drugs.

Conclusion

Baseline CRP and FEV_1 provide new tools to assess the severity of tobacco-related damage and target prevention and early detection programs on the individual level of biologic risk. The FEV_1 and CRP levels could be used to design future randomized trials testing the efficacy of antitobacco and anti-inflammatory agents in this high-risk population, monitor the effect of intervention with easily measurable intermediate biomarkers, and select better candidates for LDCT screening.

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U.P., D.M., A.M., P.S., F.T., M.B., G.S., and G.C. conceived and designed the study. D.M., S.S., P.S., and F.T. took part in data collection. U.P., S.S., A.C., and G.C. analyzed the data. U.P., A.M., M.B., G.S., A.C., and G.C. performed data interpretation. U.P., D.M., A.M., S.S., M.B., G.S., A.C., and G.C. contributed to the writing of the manuscript.

Conflicts of interest

There are no conflicts of interest.

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