Lung Cancer 138 (2019) 72–78

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Decreased cardiovascular mortality in the ITALUNG lung cancer screening trial: Analysis of underlying factors

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ARTICLE INFO

Keywords:
Lung cancer screening
Cardiovascular mortality
Coronary arteries calcifications

ABSTRACT

Objectives: In the ITALUNG lung cancer screening trial after 9.3 years of follow-up we observed an unexpected significant decrease of cardiovascular (CV) mortality in subjects invited for low-dose CT (LDCT) screening as

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https://doi.org/10.1016/j.lungcan.2019.10.006
Received 28 June 2019; Received in revised form 2 October 2019; Accepted 7 October 2019

compared to controls undergoing usual care. Herein we extended the mortality follow-up and analyzed the potential factors underlying such a decrease.

Materials and methods: The following factors were assessed in screenes and controls: burden of CV disease at baseline, changes in smoking habits, use of CV drugs and frequency of planned vascular procedures after randomisation. Moreover, in the screenes we evaluated inclusion of presence of coronary artery calcification (CAC) in the LDCT report form that was transmitted to the participant and his/her General Practitioner.

Results: The 2-years extension of follow-up confirmed a significant decrease of CV mortality in the subjects of the active group compared to control subjects (15.6 vs 34.0 per 10,000; p = 0.001) that was not observed in the drops-out of the active group. None of the explaining factors we considered significantly differed between active and control group. However, the subjects of the active group with reported CAC experienced a not significantly lower CV mortality and showed a significantly higher use of CV drugs and frequency of planned vascular procedures than the control group.

Conclusions: LDCT screening for lung cancer offers the opportunity for detection of CAC that is an important CV risk factor. Although the underlying mechanisms are not clear, our results suggest that the inclusion of information about CAC presence in the LDCT report may represent a candidate factor to explain the decreased CV mortality observed in screened subjects of the ITALUNG trial, possibly resulting in intervention for patient care to prevent CV deaths. Further studies investigating whether prospective reporting and rating of CAC have independent impact on such interventions and CV mortality are worthy.

1. Introduction

Chest low dose computed tomography (LDCT) screening reduces mortality from lung cancer (LC) in high-risk smokers and former smokers by revealing early stage pulmonary lesions amenable to surgical resection [1–4; de Koning H, oral communication, IASLC 19th world Conference on lung cancer, Toronto 2018]. The LDCT screening examination is also capable in the same subjects to reveal coronary artery calcification (CAC). CAC is associated with history of smoking and represents a recognized risk factor for potentially life threatening cardiovascular (CV) events [5,6]. In particular, several retrospective studies demonstrated that the presence, grading and number of CAC in subjects undergoing LDCT were associated with an increased incidence and risk of cardiac events and an increased CV mortality [7–11]. At the moment, recommendations to CT as a stand- alone screening test for CAC in asymptomatic subjects with no history of CVD are conflicting [12,13]. However in the context of LC LDCT screening, information about CAC presence and severity can be obtained without any additional radiation exposure or economic cost [14]. Accordingly, some investigators suggest that prospective CAC assessment could reduce CV morbidity and mortality and enhance the cost effectiveness of LDCT screening in heavy smokers [15–19].

In the ITALUNG randomized controlled trial, after 9.3 years of follow-up, smokers and former smokers invited to undergoing 4 annual LDCT showed an unexpected statistically significant lower CV mortality as compared to controls undergoing “usual care” with a 0.51 rate ratio [2]. In the present study we extended the follow-up of the subjects enrolled in the ITALUNG trial to a median of 11.3 years and we attempted to identify which factors might underlie this effect. In particular, we investigated whether the inclusion of CAC presence in the LDCT screening report form may be associated with this collateral beneficial effect of LDCT.

2. Methods

ITALUNG is a randomized LC screening trial carried out in the Tuscany Region (Italy), whose design, LC incidence and mortality were previously reported [2,20–22]. Briefly, subjects who were resident in one of three districts (Florence, Pisa and Pistoia) were recruited from the list of 269 General Practitioners (GPs) and were considered eligible if they were aged 55–69 years and had a smoking history of at least 20 pack-years in the last 10 years. Eligible subjects were randomized into one active and one control group. The active group received an annual invitation to LDCT for 4 years and the controls received usual care without any radiological examination. Both groups received an invitation to a free smoking cessation program. The results of the LDCT test including presence of CAC (see below) were transmitted by mail to both the participant subject and his/her GP who in the Italian Health System is the referring physician for prescription of any diagnostic and therapeutic intervention for his/her patient.

2.1. Update of mortality follow-up

Through the linkage with the regional mortality registry the follow-up for vital status was extended to 31 December 2016. The revision of the cause of deaths was performed using a specified algorithm previously described [2].

2.2. LDCT scanning and information about CAC

CT scanners and protocols for LDCT acquisition and reading were detailed previously [21–23]. In particular 8 scanners were used with 1, 4, 16 or 64 rows of detectors and the scanning parameters ranged between 3 and 0.75 mm section collimation with 120–140 kV, 20–43 mA s and pitch 1–2 [23]. This variability implied a non-homogenous contrast to noise ratio.

The presence of CAC in the LDCT examination was visually evaluated by the radiologist and was included in the ITALUNG LDCT report. Neither specific instructions for rating CAC severity was provided to the 17 certified radiologists who read the LDCT screening test, nor inter-reader reproducibility was assessed. Hence, for the purpose of the present investigation, we could only binarily categorize all screened subjects as subjects with CAC (if the presence of CAC, of any degree was provided in at least one screening report) or without CAC. Notably information about CAC was contained in the screening report that was transmitted to both the subject and his/her GP. This information was not available in subjects randomized to the active group who refused the LDCT screening test (drop- out) and in all subjects of the control group.

2.3. Data sources

All subjects enrolled in the ITALUNG trial were linked with the pharmaceutical prescriptions of the years 2006-2007-2008 in order to identify the users of:

- low-dose aspirin;
- diabetes drugs;
- cardiovascular system drugs (cardiac therapy, antihypertensive drugs, diuretics drugs, beta blocking agents; calcium channel blockers; agents acting on the renin–angiotensin system, lipid modifying agents).

The ATC codes of these drugs and the method for the assessment of therapy adherence was detailed in the Supplementary material (eMethods).

All subjects were linked with Hospital Discharge Database in order to collect all hospital admissions for CV diseases and all planned hospital admissions for vascular procedures for diagnostic aims (arteriography and angiocardiography using contrast material) and therapeutic aims (operations on vessels of heart) performed within 31 December 2016. Detailed information on the ICD-9 codes used was reported in the Supplementary material (eMethods).

2.4. Statistical analyses

For the purpose of investigating the factors that might explain the lower CV mortality observed in the active group, in the present study we analysed the following potential explaining factors.

First, we explored possible differences in the burden of CV disease at baseline between active and control group by comparing hospital admissions for CV diseases in the two years before randomization.

Second, we assessed whether there have been different changes in the smoking habits after randomization. Smoking history and smoking status, collected by a questionnaire at baseline, were well balanced between active and control group due to randomization [2,16]. Changes in smoking habits during the screening period were estimated by a self-administered postal questionnaire at 3-years of follow-up. Subjects who filled the follow-up questionnaire were classified in 1) *persistent smokers*, if they declared to be smokers in both questionnaires 2) *persistent ex- smokers*, if they declared to be former smokers in both questionnaires and 3) *quitters*, if they declared to be smokers at baseline and former smokers at the follow-up. Former smokers at baseline who have restarted smoking 3-years later (n = 64) were not included in this analysis. Subjects who did not fill the follow-up questionnaire were classified as persistent smokers or ex- smokers on the basis of their smoking status at baseline if they were deceased during the screening period (n = 84), whereas they were excluded from this analysis if they were still alive (n = 500). Frequency distribution of smoking habits in the first 3-years of follow-up was compared between active and control group. Moreover, the rate ratio of CV mortality was calculated separately for the three smoking categories (persistent smokers, persistent ex-smokers and quitters).

Third, we assessed the use and adherence of CV drugs and the frequency of planned diagnostic and therapeutic vascular procedures in the whole active group and in the control group for the period between 2006 and 2008, namely after randomization.

Fourth we hypothesized that the inclusion of information about presence of CAC in the LDCT screening report might have alerted both the subject and his/her referring GP and, consequently, might have induced a “take in charge” of the patient. In order to evaluate this hypothesis, we preliminarily analyzed whether the CV mortality reduction occurred only in the screened subjects of the active group. Accordingly, we compared the CV mortality in screened and unscreened (drop-out) subjects of the active group with that observed in controls. Since this analysis is not part of an intention-to-treat approach, these comparisons were adjusted for the main known confounders (age, sex, smoking habits and pack-years) using a Poisson regression models. Then we compared the use and adherence of CV drugs and the frequency of planned diagnostic and therapeutic vascular procedures in the subgroup of active subjects with CAC with the controls.

Comparisons of frequency distribution between categories were performed using Chi- square test. All data analyses were conducted using Stata software, version 12.0. Two-sided statistical tests resulting in p-value less than 0.05 were considered statistically significant.

3. Results

3.1. Extended mortality follow-up

In the two years of extended follow-up, 113 additional deaths were registered, 49 in the active and 64 in the control group. Deaths from LC were 15 and 14 in the active and control group respectively. Overall and cause-specific mortality rates (with a median follow-up of 11.3 years) are reported in Table 1. The extension of the follow-up yielded an overall mortality rate significantly lower in the active as compared to control group (RR = 0.80; 95%CI:0.66–0.96) whereas the reduction of LC mortality remained not statistically significant (RR = 0.76, 95%CI:0.54–1.07). Notably, in the analysis of cause-specific mortality, only mortality rates for CV illness were significantly lower in the active than in the control group (17.6 vs 34.0 per 10,000 person-years; p = .003). The absolute mortality rate difference (per 10,000) between the active and control group was 10.4 for LC and 16.4 for CV illness. Analysis of the CV sub-category suggested that the mortality reduction was similar in all subcategories with exception of that for cerebrovascular diseases. Finally, we observed a 45% reduction (not statically significant, p = 0.18) for respiratory illness mortality.

Table 1
Mortality rates per 10,000 person years (on brackets absolute number of deaths) and rate ratios by group.

	Active Group	Control Group	RR (95% CI)	p-value
Subjects	1613	1593		
Person years at risk[a]	17 587	17 051		
Overall mortality rate	115.4 (n = 203)	144.3 (n = 246)	0.80 (0.66 – 0.96)	.018
Lung cancer mortality rate	33.0 (n = 58)	43.4 (n = 74)	0.76 (0.54 – 1.07)	.12
Cancers mortality rate (except lung cancer)	42.6 (n = 75)	41.6 (n = 71)	1.02 (0.74 – 1.42)	.89
Cardiovascular illness	17.6 (n = 31)	34.0 (n = 58)	0.52 (0.34 – 0.80)	.003
Ischaemic heart diseases	*n = 14*	*n = 29*	*0.47*	*.017*
Other heart diseases	*n = 4*	*n=10*	*0.39*	*.10*
Cerebrovascular diseases	*n = 9*	*n=10*	*0.87*	*.77*
Other diseases	*n = 4*	*n = 9*	*0.43*	*.15*
Respiratory illness	4.5 (n = 8)	8.2 (n = 14)	0.55 (0.23 – 1.32)	.18
Other causes	17.6 (n = 31)	17.0 (n = 29)	1.04 (0.63 – 1.72)	.89

[a] Follow-up at 31 December 2016.

3.2. Baseline burden of CV illness

The number of hospital admissions for CV diseases in the two years before randomization was 129 (8.0%) in the active and 122 (7.7%) in the control group (p = .75). Likewise, the proportion of subjects with at least one hospital admission for CV diseases in the two years before randomization was comparable in the two groups (5.6% and 5.2% in the active and control group respectively, p = .62). Similar results were obtained by restricting analyses to hospital admissions for heart diseases or for ischemic heart diseases (data not shown).

3.3. Changes in smoking habits

Subjects were classified on the basis of smoking habits at baseline and 3-years follow-up questionnaires in persistent smokers (n = 1435), persistent ex-smokers (n = 876) and quitters (n = 331). As showed in Table 2, smoking habits in the first 3-years of follow-up were balanced between active and control group (p = .25). Moreover, after adjustment for age, sex and pack-years, the CV mortality reduction observed in active group was similar across smoking categories, with a rate ratio equal to 0.48, 0.39 and 0.51 among persistent smokers, persistent ex-smokers and quitters, respectively (p = .75).

3.4. Use of cardiovascular drugs and therapy adherence

The use and adherence to CV therapy in the period 2006–2008 was almost the same in the active and control group for all drug categories considered (Table 3**)**. Overall 63% of the subjects both in the active and control group assumed at least one of these drugs in the considered period (p = .96). Among subjects with at least one prescription, 72% and 71% in the active and control group respectively assumed these drugs according the average dose provided by the medical guidelines (p = .55).

3.5. Planned admissions for diagnostic and therapeutic vascular procedures

Fig. 1a and b report the cumulative percentage of planned diagnostic (1a) and therapeutic (1b) vascular procedures by year since randomisation. The proportion of subjects who performed a planned diagnostic procedure in the 12 years after the randomisation was 7.1% in the active and 7.3% in the control group (p = .83; Fig. 1a). As shown in Fig. 1b, the cumulative percentage of therapeutic surgical procedures was exactly the same in the first 5 years. Thereafter the two curves slightly diverged until to reach 2.8% and 3.4% in the active and control group respectively (p = .33).

3.6. CAC

The presence of CAC was reported in 44% of screened subjects (624/1406). Supplementary eTable 1 reports demographic characteristics and smoking habits of the enrolled subjects stratified by presence of CAC and group. Subjects with CAC were older (mean age: 61.9 vs 59.6, p < .001), more frequently male (73% vs 58%, p < .001) and stronger smokers (median pack years: 42 vs 39, p = .001) than subjects without CAC.

Characteristics of not screened subjects of the active and control group– for which information on the presence of CAC was not available – were well balanced.

Table 4 reports CV mortality stratified by screening participation, reported presence of CAC and group. The comparison between screened and unscreened subjects of the active group and the control group was adjusted for age, sex and smoking habits (smoking status at baseline and pack- years) to take into account the different baseline characteristics. Notably the CV mortality reduction occurred only in the actively screened subjects, in whom a significant 55% reduction was observed (p = 0.001), whereas unscreened subjects of the active group (dropout) experienced a CV mortality similar to that of the control group (p = .88). In the screened group, subjects with CAC had a CV mortality rate much higher than subjects without CAC (28.2 vs 5.8 per 10,000 person-years; p = .002) and slightly lower than controls (28.2 vs 34.0 per 10,000 person-years; p = .48).

Subjects with reported CAC more frequently assumed CV drugs in the first years after randomization (73% vs 63%, p < .001) and more frequently assumed these drugs regularly (77% vs 71%, p = .023) - as compared to controls. The proportion of subjects with reported CAC who performed a planned vascular procedure was higher than those of controls both for diagnostic (10.4% vs 7.3%, p = .017) and therapeutic aims (4.6% vs 3.3%, p = .14) (data not shown in the Figure). Subjects with CAC showed a significantly (p = 0.003) higher therapy adherence (77%) than subjects without CAC (68%).

4. Discussion

The 2-years extension of follow-up in the ITALUNG trial confirmed a significant decrease in the overall mortality (RR = 0.80; p = .018) in subjects invited to undergoing 4 annual LDCT compared to controls undergoing “usual care”, whereas the LC mortality remained not significantly lower (RR = 0.76; p = .12). It is noteworthy that the number of LC deaths observed in the two years of

extended follow-up was almost the same in the two groups (15 and 14 in the active and control

group respectively). Analysis by year since randomisation (data not shown) suggested that the benefit in terms of LC mortality observed in the active group disappeared at the 9th year from randomisation, i.e. about 5 years after the last LDCT screening test. This result is compatible with the expected lead time [24] and explains why the extension of follow-up led to a slight increase of the LC mortality rate ratio (from 0.70 to 0.76). Remarkably, the CV was the only cause-specific mortality that showed a significant and persistent decrease in subjects of the active group (from 0.51 to 0.52) as compared to controls.

The intention-to-treat analysis of the factors possibly associated with the decreased CV mortality observed in the ITALUNG participants revealed that it was not accounted for by differences between screenes and controls in the CV burden, as reflected in the number of hospital admissions for CV diseases in the two years before randomization, in smoking habits, as reflected by the comparable CV mortality rate ratios in persistent smokers and ex-smokers and quitters, in the use of and adherence to CV drugs therapy and, finally, in the frequency of planned CV diagnostic and surgical procedures. On the other hand, inclusion of CAC presence in the LDCT report was capable to differentiate CV mortality in the screened group. In fact, as expected subjects with CAC had a CV mortality rate much higher than subjects without CAC.

However it is noteworthy that subjects with reported CAC in our study experienced a CV mortality lower than expected. In fact, assuming that the percentage of subjects with CAC is the same in the active and control groups and that the relative risk of CV mortality for subjects with CAC (all degrees) is about 4 [10], we assumed the CV mortality rate in subjects with CAC to be 58.6 per 10,000 (obtained from (34.0*4)/(0.56 + 0.44*4)) rather than the 28.2 per 10,000 we observed. This lower figure suggests that the benefit might pertain to

Table 2
Number (percentage) of subjects of the active and control group and CV mortality rate ratio stratified by smoking habits at baseline and follow-up.

Smoking habits at baseline and follow-up	Active Group No. (%)	Control Group No. (%)	Adjusted[a] CV mortality RR (95% CI)
Persistent smokers	678 (54%)	757 (55%)	0.48 (0.27 – 0.87)
Persistent ex-smokers	406 (32%)	470 (34%)	0.39 (0.14 – 1.08)
Quitters	171 (14%)	160 (12%)	0.51 (0.11 – 2.40)

[a] Adjusted for age, sex and pack-years.

Table 3
Use of cardiovascular drugs and therapy adherence by group (period 2006–2008).

ATC category:	Subjects with at least one prescription		Therapy adherence[a]	
	Active Group No. (%)	Control Group No. (%)	Active Group No. (%)	Control Group No. (%)
B01AC06: Low-dose aspirin	26% (n = 417)	25% (n = 400)	52% (n = 215)	50% (n = 201)
A10: Diabetes drugs	12% (n = 188)	12% (n = 187)	65% (n = 122)	63% (n = 117)
C01: Cardiac therapy	9% (n = 149)	8% (n = 127)	51% (n = 76)	54% (n = 68)
C02: Antihypertensive drugs	5% (n = 78)	4% (n = 67)	51% (n = 40)	40% (n = 27)
C03: Diuretic drugs	16% (n = 264)	17% (n = 265)	20% (n = 53)	21% (n = 56)
C07: Beta blocking agents	18% (n = 294)	17% (n = 278)	39% (n = 115)	40% (n = 111)
C08: Calcium channel blockers	17% (n = 273)	17% (n = 276)	63% (n = 171)	65% (n = 179)
C09: Agents acting on the renin-angiotensin system	39% (n = 631)	39% (n = 620)	77% (n = 483)	75% (n = 462)
C10: Lipid modifying agents	25% (n = 399)	23% (n = 359)	56% (n = 222)	54% (n = 195)
Total	**63% (n = 1018)**	**63% (n = 1004)**	**72% (n = 738)**	**71% (n = 716)**

[a] Proportion of subjects with a therapy adherence ≥ 0.80 on the total of subjects with at least one prescription.

the subjects in whom presence of CAC was communicated in the LDCT report.

Since information concerning presence of CAC was forwarded to the subject and his/her referring GP, we speculate that this might have constituted, on the one hand, a valuable 'teachable moment' for the subjects increasing awareness of their own risk and, on the other hand, an improved "take in charge" by the GPs, both effects ultimately promoting advice about how to address the individual CV risk. Indeed, although in the intention-to-treat analysis the use of and adherence to CV drugs therapy and the frequency of planned CV surgical procedures did not significantly differ between active and control groups, they were significantly higher in screened subjects with CAC. The possibility that the CV mortality reduction could be explained by a better management of affections that are frequent in subjects at risk of or affected by smoking-related disease is also supported by the non-statistically significant 45% decrease of respiratory illness mortality reduction we observed in the active group.

In NLST [1], after a median follow-up of 6.5 years, no difference in CV mortality was observed between the group of subjects receiving annual LDCT screening and the group receiving annual chest-radiography, for 3 years each. This result *per se* is not inconsistent with our data. In fact two conditions are necessary for LDCT screening to reduce CV mortality. First, that the presence of CAC is routinely reported in the screening results and, second, that this result is communicated to the GP – or to another medical doctor – who takes in charge the patient. As far as we know, in the NLST the presence of CAC was not routinely included in the screening report form (and, consequently, no actions to prevent coronary events could be undertaken). Moreover the control group of NLST was screened by chest radiography and, although less sensitively, this may have led to detect coronary calcifications. Other European RCTs published until now did not report CV mortality [3,4].

Overall, our study is the first to suggest that prospective transmission of information about CAC to heavy smokers and former smokers undergoing LDCT screening for LC and to his/her GP may have a beneficial effect on CV mortality.

We are aware of the following limitations of our study. First, the ITALUNG trial was designed for the evaluation of the effect of LDCT screening on LC mortality and no evaluation of CV risk factors or CV mortality was planned. For this reason, the prospective CAC evaluation at the time of screening was limited to visual assessment of CAC and due to lack of a shared scoring system and of assessment of the agreement among the radiologists reading the LDCT, we were forced here to merely consider the reported presence of CAC (of any degree). So, our estimate of CV mortality in subjects with CAC is not fully comparable with that of other studies in which subjects were retrospectively stratified according to the CAC score. Second, we have no information about CAC in the control group and in the drops out of the active group. Third we hypothesized that awareness of CAC presence might have led the subject to change his/her lifestyle assuming healthier behavior. However the only factor we assessed was the smoking habits at 3 years after randomisation. We have no information about other factors, like diet or physical activity, which are well known to be strongly associated with CV morbidity and mortality. Thus, we cannot exclude that the CV mortality reduction could be explained by changes in the lifestyle of the subjects enrolled in the active group.

In conclusion, our study indicates that in the ITALUNG RCT the inclusion in the LDCT report of the presence of a CV risk factor like CAC was associated with significant decrease of CV mortality. The underlying mechanisms are not clear, but it may be that the inclusion of information about CAC in the LDCT report resulted in intervention for patient care to prevent CV deaths. Further studies investigating whether prospective reporting and rating of CAC have independent impact on such interventions and CV mortality are worthy.

Funding

The study was completely funded by the local government of Tuscany (Decree N. 1014 of 02.25.2004) and by a Research Grant (PRIN 2003) to Professor Mario Mascalchi of the Italian Ministry of Education, University and Research.

Funding sources had no role in the design, conduct, analysis and reporting of the study.

Ethics committee

The study was approved by the Local Ethics Committee of each participating institution (approval number 29-30 of September 30, 2003; number 23 of October 27, 2003; and number 00028543 of May 13, 2004).

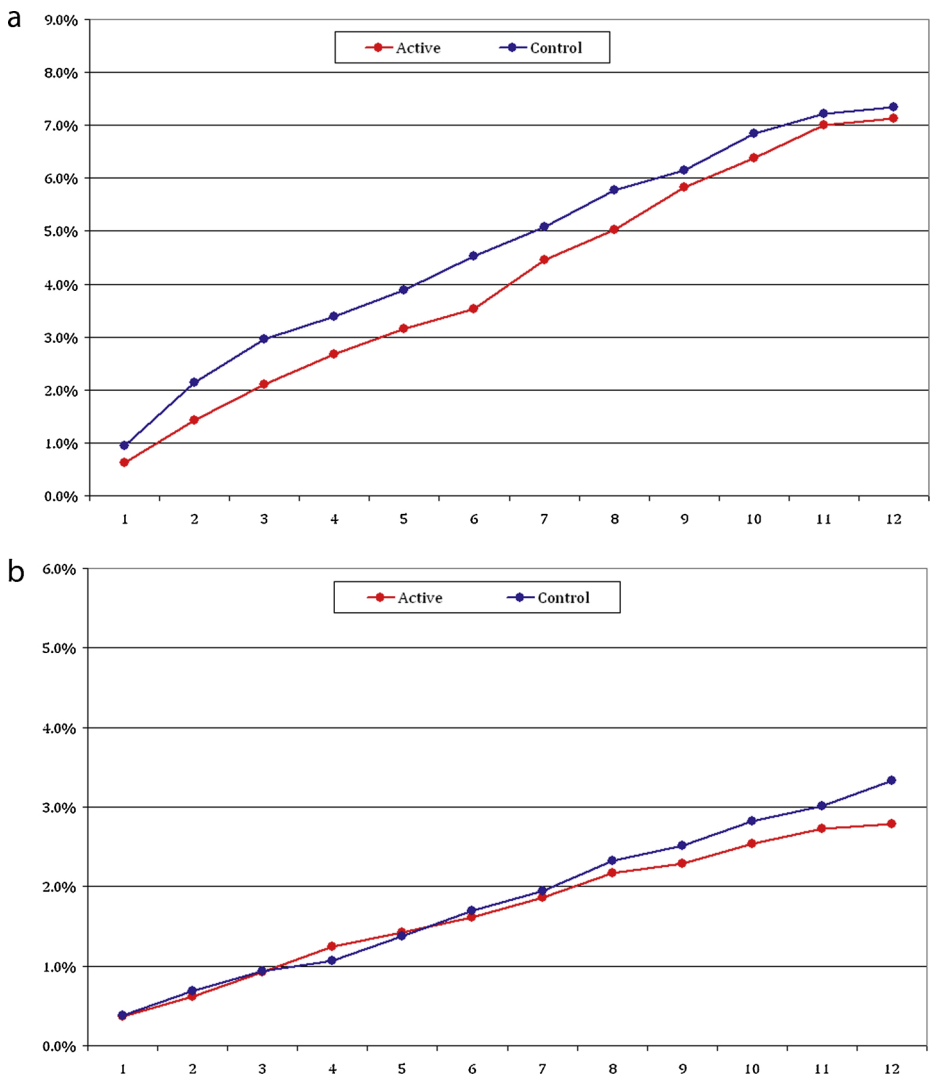

Fig. 1. a) Cumulative percentage of planned admissions with diagnostic vascular procedures (88.4: arteriography using contrast material or 88.5: angiocardiography using contrast material) by year from randomization. b) Cumulative percentage of planned admissions with therapeutic vascular surgical procedures (36.*: operations on vessels of heart) by year from randomisation.

Authors contributions

DP and MZ conceived the study design and interpreted data; MM, FMC, LC, FF, EP, ALP, FA, AB, MB, MG, GP, FP, AR have made significant contributions to interpretation of data; DP performed data collection, quality controls and statistical analysis; DP, MM and MZ wrote the manuscript; FMC, LC, FF, EP, ALP, FA, AB, MB, MG, GP, FP, AR critically reviewed the manuscript; all authors approved the final version.

MZ is responsible for the overall content as guarantor.

Transparency declaration

MZ affirms that the manuscript is an honest, accurate and transparent account of the study and no important aspects have been omitted. As reported both in the Abstract and in the Discussion, the ITALUNG trial was designed for the evaluation of lung cancer mortality and no evaluation on cardiovascular risk factors or cardiovascular mortality was originally planned.

Table 4
CV mortality rate per 10,000 person-years (on brackets absolute number of CV deaths) and adjusted rate ratios stratified by screening participation, presence of coronary artery calcifications and group.

Group and presence of CAC	CV mortality rate	Adjusted[a] CV mortality RR (95%CI)	p-value
Control Group	34.0 (n = 58)	*Ref*	–
Active Group: screened subjects	15.6 (n = 24)	**0.45** (0.28 – 0.72)	.001
Active group: subjects with CAC	*28.2 (n = 19)*		
Active Group: subjects without CAC	*5.8 (n = 5)*		
Active Group: not screened subjects	32.1 (n = 7)	**0.94** (0.43 – 2.06)	.88

[a] Adjusted for age, sex, smoking habits (smoking status at baseline and pack-years).

Data sharing statement

At this time, data could not be shared because a pooled analysis of all European lung cancer screening trials has been planned (as soon as NELSON trial outcomes will be published). After that, we are available to share data of the present paper.

Trial registration

The trial was registered in ClinicalTrials.gov Protocol Registration System with id = NCT02777996.

Declaration of Competing Interest

The authors declare no potential conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.10.006.

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