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Lung cancer risk in welders and foundry workers with a history of heavy smoking in the USA: The National Lung Screening Trial

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Abstract

Objectives—Foundry work is a risk factor for lung cancer; however, the association with welding is unclear, as smoking is common among metalworkers and may mask the relationship. We evaluated whether history of welding and foundry work, independently and jointly, and employment duration were associated with lung cancer risk in heavy smokers.

Methods—We analysed data from the National Lung Screening Trial, a prospective randomised trial of 53 454 heavy smokers (>30 pack-years) in the USA. Cox regression models were used to estimate the HRs and 95% CIs of medically/histologically confirmed incident lung cancer during the follow-up period (2002–2009) in relation to history and duration of welding and foundry work assessed via questionnaires, adjusted for screening arm, component study, sex, age, race/ethnicity, education, smoking status and pack-years, body mass index and personal/family medical history.

Results—There were 2034 incident lung cancer cases throughout the follow-up. Increasing years of employment in welding (p-trend =0.039) and foundry work (p-trend =0.005) were related to increased lung cancer risk among heavy smokers. Having ever been employed (≥1 yr) as either a welder or foundry worker alone was associated with non-significant increased risks of lung cancer (HR=1.12 (95% CI 0.91 to 1.37) and HR=1.09 (95% CI 0.85 to 1.39), respectively). Further, there was a joint-effect in that those who were ever employed in both occupations had significantly increased risks (HR=1.48 (95% CI 1.08 to 2.04)).

Conclusions—Our findings provide further evidence that exposure to welding/metal fumes may be associated with elevated lung cancer risk.

Trial registration number

NCT00047385.

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Patient consent Obtained.

Ethics approval Each of the 33 screening centres from this list obtained their own respective IRB approval: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3009383/table/t04/>

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INTRODUCTION

Welders and foundry workers are employed in occupational environments containing toxic levels of metal-rich fine particulate matter (PM_{2.5}), poly-cyclic aromatic hydrocarbons (PAH) and gases that are emitted from molten metals.¹² Fumes containing heavy and transition metals are a substantial health concern because they can induce local inflammation in lung tissue, lipid peroxidation of cell membranes and oxidative damage to the genome.^{3–5} An International Agency for Research on Cancer (IARC) Monograph Working Group concluded that occupational exposure to iron and steel founding causes lung cancer based on sufficient evidence in human population-based studies (Group 1).⁶ Indeed, numerous studies across Europe, East Asia and the USA reported that foundry workers had elevated risks of lung cancer, with and without accounting for smoking.^{7–17} As opposed to foundry work, an IARC Monograph Working Group stated that there was limited epidemiologic evidence (Group 2B) for an association of welding fumes and gases to risk of lung cancer in 1990; however, a considerable number of studies have found positive relationships with welding since then.^{18–23} For instance, a study in Canada found that exposure to welding fumes was related to an excess risk of lung cancer in light smokers, but not heavy smokers.²⁴ Additionally, a study in Eastern and Central Europe found a significantly increased risk in those with more than years of welding fume exposure adjusted for smoking.²⁵ The equivocal findings for welding may be attributed to differences in adjustment for smoking across studies. Smoking is a strong confounder because it is heavier and more common among metalworkers than the general population, and is an established risk factor for lung cancer. A previous study posited that the strong effect of smoking could mask the relatively smaller effect of welding fumes on lung cancer, especially among heavy-smoking populations.²⁴ Smoking may subsume the effect of welding/metal fumes because of its high prevalence and intensity among metalworkers, and its plethora of components including toxic metals may have similar detrimental biological effects on lung tissue.^{26,27}

We evaluated the associations of history of welding and foundry work, independently and jointly, and employment duration, to risk of incident lung cancer and its subtypes among heavy smokers from the National Lung Screening Trial (NLST). This study of 53 454 heavy smokers is the largest randomised trial in the USA that compared the effectiveness of low-dose CT scan with chest radiographic screening, in relation to lung cancer mortality. The NLST was a unique platform in which to assess the association between occupational metalwork and lung cancer risk in a high-risk population that was annually screened for lung cancer using sensitive methods. Furthermore, lung cancer cases and its subtypes were rigorously medically/histologically confirmed in the NLST, which contributes to the understanding of the aetio-logic mechanism of welding/metal fumes.

METHODS

Study population and design

Characteristics of the NLST are described elsewhere.^{28,29} In brief, participants were enrolled from August 2002 to April 2004 at 33 screening centres across the USA in three component studies (Lung Screening Study group (LSS), the American College of Radiology Imaging Network (ACRIN) without biomarkers and ACRIN with biomarkers). Each centre obtained

institutional review board approval prior to recruitment. The study enrolled 53 454 participants; however, two participants were excluded from the analyses due to double randomisation. Eligible participants were aged 55–74 years at randomisation, current and/or former cigarette smokers with >30 pack-years of active smoking and had quit within the previous 15 years if they formerly smoked. Persons who had previously been diagnosed with lung cancer, had undergone chest CT within 18 months before enrolment, had haemoptysis or had an unexplained weight loss of more than 6.8 kg in the year prior to randomisation were excluded from the parent study. Eligible participants who provided written informed consent were randomised 1:1 into one of two trial arms, low-dose CT or chest radiography. Blocked randomisation was used, with stratification according to age, sex and screening centre. After randomisation, participants completed a questionnaire covering demographic characteristics, smoking behaviour (current/former, pack-years, age at onset and cessation, duration and cigarettes per day), ever exposed to secondhand smoke (works/worked and lives/lived with smokers), medical history and occupational history. Screening was performed in each randomisation arm at baseline and the first two annual follow-up examinations. Analysts were blinded to the screening centres, calendar dates and personal identifiers.

The follow-up period was from August 2002 to 31 December 2009. The primary end point of the parent trial was lung cancer mortality, while the secondary endpoints were lung cancer incidence, overall mortality and screening and treatment-related morbidity. Only those who provided occupational history information were included in the current analyses. The analytic sample size after applying these criteria was 53 224 participants (99.6%). Of the participants included in the analyses, 2.65% were lost to follow-up. Furthermore, the screening trial had an adherence rate over 90%.²⁸

Exposure: occupational history

Information on history and duration of welding, foundry work and other occupations occurring prior to randomisation was collected via questionnaires. Participants were asked, “Do you or did you work in this industry or occupation for 12 months or more? (Yes/No)”, “The total number of years worked in this industry or occupation” and “Do you or did you usually wear a facemask or other equipment to protect your lungs while working? (Yes/No)”. Having ever worked as a welder and/or foundry worker was defined as having ≥ 1 year of employment; otherwise, they were considered to have never worked in these occupations. Four occupational exposure groups were created using combination variables that reflect joint-effects between welding and foundry work: (1) never welder or foundry worker (reference group), (2) ever welder but never foundry worker, (3) ever foundry worker but never welder and (4) ever welder and foundry worker. Further, the number of years in each occupation was obtained and operationalised as quartiles in the analyses. Past employment in other potentially high-risk occupations such as being a butcher, baker, hard rock and coal miner, asbestos worker, chemicals/plastics worker, cotton/jute worker, farmer, fire fighter, grain miller and painter was also ascertained in the questionnaire.

Outcome: incident lung cancer diagnosis

The main outcome was time to incident lung cancer diagnosis. Lung cancer subtypes including adenocarcinoma (AC), squamous cell carcinoma (SCC) and others were also of interest. Ascertainment, classification and clinical/histological confirmation of lung cancer cases have been described in detail elsewhere.²⁸³⁰ Medical records documenting diagnostic procedures and complications were obtained for participants who screened positive for lung cancer and those with diagnosed lung cancer. Pathology and tumour-staging reports, in addition to operative procedures and initial treatment records, were also obtained. Histologic characteristics of the lung cancers were coded according to the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3). Disease stage was determined according to the Cancer Staging Manual of the American Joint Committee on Cancer (Sixth Edition).

Participants completed an annual or semiannual questionnaire for vital status. Participants who were lost to follow-up had their names and social security numbers submitted to the National Death Index to assess probable vital status. Death certificates were obtained for participants who were known to have died. The cause of death was determined by an endpoint verification team, who were blinded to the participants' randomisation status.

Analyses

Between occupational exposure groups, analysis of variance (ANOVA) was used to assess differences in normally distributed variables, Kruskal-Wallis tests were used for non-normally distributed variables and χ^2 tests were used for categorical variables.

Cox proportional hazards (PH) regression models were used to estimate cause-specific HRs and 95% CIs of incident lung cancer, in relation to occupational exposure group. Covariates were chosen based on previous literature and their ability to alter associations by >10%. The models were adjusted for: screening trial arm, NLST component study (LSS, ACRIN without biomarkers, ACRIN with biomarkers), sex (male, female), age at randomisation centred around the mean, self-reported race/ethnicity (non-Hispanic white, others), education (less than high school, graduated high school, some postsecondary and above), pack-years of smoking at randomisation centred around the mean, smoking status at randomisation (current, former), body mass index (BMI, kg/m²) at randomisation centred around the mean, first degree relative with lung cancer (yes, no) and history of diagnosed chronic bronchitis and emphysema prior to randomisation (yes, no). Respirator use, ever asbestos work, secondhand smoke exposure and an indicator variable for <10 years of work in potentially high-risk occupations (asbestos worker, butcher, chemical/plastics worker, coal miner and farmer) were considered, but not adjusted for because they were not statistically significantly associated with the outcome and their inclusion in the models did not change the estimates by >10%. Additionally, there was little variability in secondhand smoke exposure, as over 96% of this study population of heavy smokers lived and/or worked with other active smokers. The Cox PH models accounted for censoring from competing risks from loss to follow-up and death. Effect modification by pack-years of smoking, daily smoking intensity (cigarettes/day) and asbestos work were assessed by including interaction terms with the exposures of interest. The timescale of the Cox PH models was follow-up time (days). Proportional hazards assumptions were assessed using supremum tests and

interaction terms between explanatory variables and time. Separate analyses were conducted for lung AC, SCC and other subtypes as outcomes. Sensitivity analyses to assess the robustness of the findings were performed by: (1) stratifying by smoking status at randomisation (former, current) and further stratifying by daily average smoking intensity (≥ 25 and <25 cigarettes/day), (2) excluding those in certain potentially high-risk occupations aside from welding and foundry work (butcher, baker, hard rock miner and coal miner and asbestos worker) and (3) restricting to men.

We also assessed the risk of incident lung cancer in relation to quartiles (Q) of employment duration (Q1: 1- <3 , Q2: 3- <10 , Q3: 10- <25 and Q4: ≥ 25 years for welders, and Q1: 1- <2 , Q2: 2- <5 , Q3: 5- <21 and Q4: ≥ 21 years for foundry workers). The reference group was those who never worked as a welder or foundry worker. Trend tests were also performed by analysing these categories as ordinal. The models were adjusted for the same aforementioned covariates. Separate analyses were also conducted for lung AC, SCC and other sub-types as outcomes.

Only a small fraction of participants was missing data for explanatory variables pertaining to welding and foundry work (0.4%), BMI (0.6%) and history of chronic bronchitis and emphysema (0.6%); therefore, complete case analysis with participants having all available data was used. p Values <0.05 were considered statistically significant, while p-interactions <0.15 were considered noteworthy. All analyses were performed using SAS v9.3 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Characteristics of welders and foundry workers in the National Lung Screening Trial at randomisation

The study population was predominantly non-Hispanic white (table 1). The proportion of men among welders and foundry workers was 93.9% and 92.2%, respectively, compared with 55.8% in never welders/foundry workers. Welders and foundry workers had higher average BMIs (28.6 kg/m^2 (4.9 SD) and 28.4 kg/m^2 (4.8 SD), respectively) compared with never welders/foundry workers (27.8 kg/m^2 (5.1 SD)). Additionally, foundry workers had a higher proportion of current smokers at randomisation (51.5%) compared with never welders/foundry workers (48.0%). Those who worked as welders and foundry workers had the highest median pack-years of smoking (58 person-years (py) (IQR: 43–79)). Welders had a high proportion of those who did not finish high school (14.1%) and low proportion of postsecondary education (54.0%) compared with never welders/foundry workers (6.0% and 71.0%, respectively).

Clinical characteristics of medically confirmed lung cancer in welders and foundry workers

Among the 2034 cases of incident lung cancer, the lesion sizes and proportions of stage 1, 2, 3 and 4 cancers did not significantly differ at the time of diagnosis among the occupational exposure groups (table 1). Further, the proportions of AC and other subtypes did not

significantly differ. However, those who were welders and foundry worker had a significantly higher proportion of SCC (41%) at time of diagnosis than the other groups.

Lung cancer incidence rates in welders and foundry workers

There were 2034 cases of incident lung cancer in 327 834 py of follow-up censored at first report of lung cancer, death, lost to follow-up or end of study. The lung cancer incidence rates over the 7-year follow-up (2002–2009) in the four occupational exposure groups were: (1) 6.1 (95% CI 5.8 to 6.4) cases/1000 py in those with no welding or foundry experience, (2) 7.2 (95% CI 5.9 to 8.7) cases/1000 py in ever welders but never foundry workers, (3) 7.2 (95% CI 5.7 to 9.1) cases/1000 py in ever foundry workers but never welders and (4) 10.1 (95% CI 7.4 to 13.8) cases/1000 py in ever welders and foundry workers.

The association between welding and foundry work, and risk of incident lung cancer

The unadjusted associations between work history, demographic/anthropometric characteristics, medical history and risk of incident lung cancer are presented in online supplementary table S1, while the adjusted associations with work history are presented in table 2. We found that having ever worked as either a welder or foundry worker for 1 year independent of each other was associated with non-significant increased risks of lung cancer ((HR=1.12 (95% CI 0.91 to 1.37)) and (HR=1.09 (95% CI 0.85 to 1.39)), respectively). Further, a statistically significant joint-effect was found between working as a welder and foundry work on risk of lung cancer, compared with those with no history of metalwork (HR=1.48 (95% CI 1.08 to 2.04)) (table 2). The interaction terms between the welding/foundry work and asbestos work, pack-years of smoking, daily cigarette intensity and current smoking status at baseline were not statistically noteworthy and thus not included in the final model.

When evaluating risk of specific lung cancer subtypes, no significant associations were found between AC, other subtypes and welding or foundry work (table 2). There was suggestive evidence that being ever employed as a foundry worker (HR=1.41 (95% CI 0.92 to 2.15)) and a welder and foundry worker (HR=1.61 (95% CI 0.96 to 2.69)) were related to increased risk of SCC; however, the associations were not statistically significant.

Sensitivity analyses were performed to assess the robustness of the observed trends by smoking status and intensity, excluding other potentially high-risk occupations, and restricted to men. Similar patterns of associations were observed in current and former smokers at randomisation and the tests for interactions were not significant (table 3). However, the increased risk for those who were welders and foundry workers was only significant in current smokers (HR=1.58 (95% CI 1.05 to 2.38)). Further, in current and former smokers, the patterns of association were more apparent in those who smoked 25 cigarettes/ day on average (data not shown). Similar trends and magnitudes of association were observed when excluding past employment in potentially high-risk occupations for lung cancer (see supplementary table S2), and adjusting for an indicator variable for 10 years in other potentially high-risk occupations (data not shown). Finally, similar patterns of association were also observed when restricting the analyses to men (data not shown).

The association between employment duration and risk of lung cancer for welders and foundry workers

In welders, longer employment duration was associated with increased risk of incident lung cancer (p-trend =0.039), independent of foundry work (table 4). Adjusting for potential confounders, the increased risk associated with 3-<10 years of welding compared with no history of metalwork was statistically significant (HR=1.43 (95% CI 1.04 to 1.96)). The associations were predominantly from increased risk of SCC (p-trend =0.003). Welders with 25 years or more of experience had nearly twice the risk of SCC compared with those without a history of metalwork (HR=1.91 (95% CI 1.13 to 3.22)). The interaction terms between employment duration and pack-years of smoking, and employment duration and daily cigarette intensity were not statistically noteworthy and thus not included in the model.

In foundry workers, longer employment duration was associated with increased risk of incident lung cancer (p-trend = 0.005), independent of welding (table 4). Participants with 21 years of foundry work had 1.55 (95% CI 1.11 to 2.14) times the risk of lung cancer compared with those with no metalwork experience. The associations were predominantly from increased risk of SCC (p-trend <0.0001). Foundry workers with over 5 years of experience had nearly twice the risk of SCC compared with those without a history of metalwork (HR=1.96 (95% CI 1.12 to 3.43)). The interaction terms between employment duration and pack-years of smoking, and employment duration and daily cigarette intensity were not statistically noteworthy and thus not included in the model.

DISCUSSION

In this study of heavy smokers, we found that increased employment duration as a welder and foundry worker was associated with increased risks of incident lung cancer, independent of each other. Additionally, we found a joint-effect between welding and foundry work; those who ever worked in both occupations had substantially elevated risks compared with those who never worked in either. Unlike many occupational epidemiology studies of lung cancer, we were able to assess medically/histologically confirmed subtypes of lung cancer. The predominant subtype of lung cancer that was diagnosed in welders and foundry workers during the follow-up was SCC, whereas AC was more common in those without a history of metalwork. Further, increased employment duration in welding and foundry work was associated with increased risk of SCC, but not AC.

Since several factors may explain our findings, we conducted sensitivity analyses to assess their potential influence. First, smoking may be an effect modifier and also a confounder because it is heavier and more common among metalworkers than the general population; ³¹³² therefore, we assessed its influence by stratifying by former and current smoking at randomisation. Similar trends were observed in former and current smokers compared with the overall findings and tests of interactions were not significant. However, the effect for ever being a welder and foundry worker was only significant for current smokers, which may be due to decreased statistical power from limited cases among former smokers. Further, among former and current smokers, the patterns of association were more apparent in those who smoked 25 cigarettes/day. Second, the observed associations for welding and foundry work may have been caused by exposures from other occupations. We found similar

trends and magnitudes of association after excluding several potentially high-risk occupations for lung cancer from the analyses, and accounting for 10 years of employment in other high-risk occupations; suggesting that the observed findings were not due to employment history in these industries.

Even though our study was conducted in heavy smokers, we found that increased employment duration in welding and foundry work, mutually exclusive of each other, was associated with increased risk of lung cancer; particularly with SCC. Since publication of the IARC monograph for welding in 1990, accumulating evidence has supported the role of occupational welding in cancer development.^{18–23} A prominent pooled study of 15 483 male lung cancer cases and 18 388 male controls from 16 studies in Europe, Canada, China and New Zealand conducted between 1985 and 2010 (SYNERGY Project) found significantly increased risks of lung cancer in relation to welding, which were attenuated but still significant in the heaviest smokers (>35 pack-years).¹⁸ Furthermore, similar to our findings, the SYNERGY Project found that the associations were primarily with SCC, as opposed to AC and other subtypes.¹⁸ The associations between welding and SCC were also found in a previous study of Finnish men.²¹ Our findings were also comparable to other occupational studies of welders and foundry workers,^{7,17,22} including two moderately sized case-control studies in Canada that found exposure to welding fumes was related to an excess risk of lung cancer, particularly with SCC, in light smokers but not heavy smokers.²⁴ Additionally, similar findings were reported for welding in a case-control study in Central/Eastern Europe and the UK that controlled for smoking,²⁵ and a population-based case-control study in France.³³ However, a case-case study conducted in French university hospitals from 1997 to 2006 found positive associations predominantly with AC.²⁰ SCC is the predominant lung cancer subtype diagnosed among smokers and the observed associations with SCC across studies may be because the carcinogenic effect of metal fumes operates through similar mechanisms as cigarette smoke; therefore, the patterns of association with histological subtypes may reflect these shared mechanisms.²⁴ The positive work duration-response relationship found in our study for foundry work was in concordance with studies outlined in the IARC monograph for iron and steel founding.⁶ Taken together, our findings suggest that even though smoking may partially mask the detrimental effect of metalwork,²⁴ sufficient exposure duration to welding/metal emissions imparts a detectable elevated risk of lung cancer in heavy smokers.

This study had notable strengths in addressing the questions of interest. First, the sample size was moderate and there was an ample number of lung cancer cases, which increased statistical power. Second, this study focused on heavy smokers, which allowed for the assessment of the relationship between metal-work and lung cancer in a high-risk population. Third, mis-classification of the outcome was unlikely due to vigorous clinical and histological confirmation of lung cancer. Fourth, the NLST had detailed information on lung cancer subtypes, which provided further support for the aetiologic mechanism of welding and metal fume exposure on SCC development. Fifth, unlike many occupational epidemiologic studies with surrogate-reported data, NLST was a prospective cohort with quality participant-reported data collected prior to disease diagnosis.

Despite its strengths, this study had limitations. First, the questionnaire did not collect detailed information on occupational activities and only included information on the number of years employed in various occupations. Second, the follow-up time of the trial was relatively short, which may have limited the number of lung cancer cases captured during the study period. Third, there may be heterogeneity in the composition of welding/metal fumes depending on the factory and primary occupational tasks,³⁴³⁵ in addition to the composition of type of fluxes and base metals that were predominantly used.⁴ Fourth, we did not have sufficient information to disentangle the contributions of asbestos and mixed silica coexposures from metal/welding fumes to lung cancer risk. Prolonged occupational exposure to asbestos and mixed silica that are common to metalworkers may lead to chronic inflammation and scarring of lung tissue, and may further interact with metal fumes to promote cancer development.^{2436–38} We cannot discount residual and unmeasured confounding, and effect modification by asbestos and silica exposure. However, we adjusted for respirator use and history of asbestos work, which did not affect the findings. Finally, although there were 2034 lung cancer cases, only 210 were in welders, foundry workers and those who were both. Given the limited number of cases in metalworkers, we cannot discount the possibility of chance results. Therefore, caution is recommended when interpreting the findings.

In summary, we found that longer employment duration as a welder and foundry worker was related to increased risk of developing lung cancer among heavy smokers in the USA. Additionally, we found a joint-effect of welding and foundry work on lung cancer risk. The positive associations were predominantly from the development of squamous cell carcinoma, as opposed to other subtypes. Future prospective studies that endeavour to investigate further would benefit from longer follow-up times, extended screening regimens and detailed metalwork exposure assessment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What this paper adds

- ▶ Foundry work is an established risk factor for lung cancer; however, the relationship with welding is unclear throughout the body of literature. The equivocal findings for welding may be attributed to differences in adjustment for smoking across studies.
- ▶ Smoking is a strong confounder because it is heavier and more common among metalworkers than the general population, and is an established risk factor for lung cancer. Further, its strong effect could potentially mask or subsume the relatively smaller effect of welding fumes on lung cancer risk in occupational studies, especially among heavy smokers.
- ▶ In the National Lung Screening Trial, a prospective randomised trial of 53 454 heavy smokers (>30 pack-years) in the USA, we found that increased duration of welding and foundry work was associated with increased risk of incident lung cancer, particularly with squamous cell carcinoma. Further, we found a joint-effect in that those who were ever employed in both professions had significant increased risks compared with those who were never metalworkers.
- ▶ Our findings provide further evidence that exposure to welding/metal fumes may be associated with elevated risk of lung cancer, even among heavy smokers.

Characteristics of welders and foundry workers of the National Lung Screening Trial (n=53 224)

Table 1

Characteristic	Never welders or foundry workers n=48 672	Ever welders, never foundry worker n=2311	Ever foundry workers, never welder n=1594	Ever welder and foundry worker n=647	p Value
Screening arm, n, %					
Low dose CT	24 288 (49.9)	1169 (50.6)	831 (52.2)	325 (50.2)	0.33
Chest X-ray	24 384 (50.1)	1142 (49.4)	763 (47.9)	322 (49.8)	
Age, yrs, median, IQR	60 (57–65)	60 (57–64)	61 (57–65)	61 (57–65)	0.51
Sex, n, %					
Male	27 135 (55.8)	2170 (93.9)	1469 (92.2)	633 (97.8)	<0.0001*
Female	21 537 (44.2)	141 (6.1)	125 (7.8)	14 (2.2)	
Body Mass Index, kg/m ² , mean, std	27.8 (5.1)	28.6 (4.9)	28.4 (4.8)	28.6 (4.7)	<0.0001*
Race/ethnicity, n, %					
Non-Hispanic white	43 582 (89.5)	2030 (87.8)	1384 (86.9)	562 (86.9)	<0.0001*
African-American	2044 (4.2)	96 (4.2)	129 (8.1)	49 (7.6)	
Hispanic, white and black	587 (1.2)	31 (1.3)	25 (1.6)	12 (1.9)	
Asian	1032 (2.1)	44 (1.9)	8 (0.5)	2 (0.3)	
Other	904 (1.9)	78 (3.4)	32 (2.0)	20 (3.1)	
Current smoker, n, %	23 385 (48.0)	1143 (49.5)	820 (51.5)	311 (48.1)	0.03*
Pack-years of smoking, median, IQR	48 (39–66)	54 (42–76)	53 (40–74)	58 (43–79)	<0.0001*
Education, n, %					
Less than high school and Unknown	2916 (6.0)	325 (14.1)	157 (9.9)	94 (14.5)	<0.0001*
Graduated high school	11 221 (23.1)	739 (32.0)	505 (31.7)	196 (30.3)	
Some postsecondary or Higher	34 535 (71.0)	1247 (54.0)	932 (58.5)	357 (55.2)	
Marital status, n, %					
Never	2330 (4.8)	47 (2.0)	57 (3.6)	10 (1.5)	<0.0001*
Married	32 095 (65.9)	1722 (74.5)	1162 (72.9)	488 (75.4)	
Widowed	3721 (7.6)	115 (5.0)	75 (4.7)	32 (4.9)	
Separated or divorced	10 205 (21.0)	422 (18.3)	293 (18.4)	115 (17.8)	
Unknown	321 (0.7)	5 (0.2)	7 (0.4)	2 (0.3)	

Characteristic	Never welders or foundry workers n=48 672	Ever welders, never foundry worker n=2311	Ever foundry workers, never welder n=1594	Ever welder and foundry worker n=647	p Value
Family history of lung cancer, n, %	10 482 (21.5)	516 (22.3)	344 (21.6)	146 (22.6)	0.76
Years of employment as a welder and/or foundry worker, median, IQR	-	10 (3–25)	5 (2–21)	21 (8–40)	<0.0001*
Secondhand smoke exposure (ever lived/worked with smokers), n, %	46 789 (96.1)	2242 (97.0)	1550 (97.2)	639 (98.7)	<0.01*
% Employment history, n, %					
Butcher	908 (1.9)	125 (5.4)	75 (4.7)	48 (7.4)	<0.0001*
Baker	955 (2.0)	93 (4.0)	70 (4.4)	30 (4.6)	<0.0001*
Hard rock miner	253 (0.5)	96 (4.2)	30 (1.9)	36 (5.6)	<0.0001*
Coal miner	192 (0.4)	72 (3.1)	32 (2.0)	35 (5.4)	<0.0001*
Asbestos worker	1277 (2.6)	716 (31.0)	224 (14.1)	291 (45.0)	<0.0001*
<i>Clinical characteristics of medically confirmed incident lung cancer in the prospective follow-up (n=2034)</i>					
Number of Cases	1824	101	70	39	
Stage, n, %					
1	735 (40.3)	45 (44.6)	24 (34.3)	15 (38.5)	0.60
2	124 (6.8)	7 (6.9)	9 (12.9)	5 (12.8)	0.13
3	401 (22.0)	29 (28.7)	15 (21.4)	9 (23.1)	0.47
4	539 (29.6)	20 (19.8)	21 (30.0)	10 (25.6)	0.20
Common types, n, %					
Adenocarcinoma	593 (32.5)	28 (27.7)	20 (28.6)	10 (25.6)	0.54
Squamous cell carcinoma	357 (19.6)	29 (28.7)	24 (34.3)	16 (41.0)	<0.0001*
Other non-small cell	184 (10.1)	6 (5.9)	8 (11.4)	3 (7.7)	0.52
Small cell	239 (13.1)	14 (13.9)	7 (10.0)	5 (12.8)	0.89
Other	451 (24.7)	24 (23.8)	11 (15.7)	5 (12.8)	0.12
Lesion size (mm), median, IQR	25 (15–40)	25 (16–44)	30 (17–49)	30 (15–50)	0.16

* p Values <0.05 were considered statistically significant and were calculated using ANOVA for normally distributed variables, Kruskal-Wallis tests for non-normally distributed variables and χ^2 tests for categorical variables.

Welders and foundry workers were defined as working one or more years in the occupations. Discrepancy in counts was due to missing data.

The association between welding and foundry work, and risk of incident lung cancer in heavy smokers of the National Lung Screening Trial.

Table 2

	I) All lung cancer subtypes					II) Lung adenocarcinoma					III) Lung squamous cell carcinoma					IV) Other subtypes				
	Total cases	py	HR	95% CI Lower	95% CI Upper	AC Cases	HR	95% CI Lower	95% CI Upper	SCC Cases	HR	95% CI Lower	95% CI Upper	Other Cases	HR	95% CI Lower	95% CI Upper			
Never welder or foundry worker	1824	300192.4	Ref			593	Ref			357	Ref			874	Ref					
Ever welder, never foundry worker	101	14056.5	1.12	0.91	1.37	28	0.84	0.56	1.25	29	0.99	0.66	1.47	44	1.07	0.78	1.46			
Ever foundry worker, never welder	70	9715.2	1.09	0.85	1.39	20	0.98	0.62	1.54	24	1.41	0.92	2.15	26	0.86	0.58	1.27			
Ever welder and foundry worker [†]	39	3870.6	1.48	1.08	2.04 [*]	10	0.82	0.43	1.54	16	1.61	0.96	2.69	13	1.08	0.62	1.89			

Multivariable Cox PH models were adjusted for: screening trial arm (low-dose CT, chest radiography), NLSST component study, sex, centred age at randomisation, race/ethnicity (white vs others), education (less than high school, graduated high school, some postsecondary and above), centred pack-years of smoking at randomisation, smoking status at randomisation (current, former), centred body mass index at baseline, first degree relative with lung cancer and history of diagnosed chronic bronchitis and emphysema prior to randomisation.

* p Values <0.05 were considered statistically significant.

[†] p Value for heterogeneity among four models was 0.30.

AC, adenocarcinoma; py, person-years; Ref, reference; SCC, squamous cell carcinoma.

Table 3
Welding and foundry work in relation to risk of incident lung cancer in heavy smokers stratified by smoking status

	D Current smokers at randomization				II Former smokers at randomization			
	Total cases	HR	95% CI Lower	95% CI Upper	Total cases	HR	95% CI Lower	95% CI Upper
Never welder or foundry worker	1096	Ref			728	Ref		
Ever welder, never foundry worker	61	1.12	0.86	1.46	40	1.10	0.79	1.52
Ever foundry worker, never welder	49	1.22	0.91	1.63	21	0.87	0.56	1.35
Ever welder and foundry worker	24	1.58	1.05	2.38*	15	1.33	0.80	2.24

Ref, reference.

* p Values <0.05 were considered statistically significant.

The p-values for the interaction terms between smoking status and ever welder/never foundry worker, ever foundry worker/never welder and ever welder/foundry worker were non-significant at 0.97, 0.25 and 0.68, respectively, and not included in the final models.

Multivariable Cox PH models were adjusted for: screening trial arm (low-dose CT, chest radiography), NLS component study, sex, centred age at randomization, race/ethnicity (white vs others), education (less than high school, graduated high school, some postsecondary and above), centred pack-years of smoking at randomisation, centred body mass index at baseline, first degree relative with lung cancer and history of diagnosed chronic bronchitis and emphysema prior to randomisation.

Table 4

The association between employment duration and risk of incident lung cancer for welders and foundry workers in the National Lung Screening Trial

	I) Total lung cancer				II) Lung adenocarcinoma				III) Lung squamous cell carcinoma				IV) Other subtypes			
	Total cases	HR	95% CI Lower	95% CI Upper	Total cases	HR	95% CI Lower	95% CI Upper	Total cases	HR	95% CI Lower	95% CI Upper	Total cases	HR	95% CI Lower	95% CI Upper
Years as a welder																
None	1824	Ref			593	Ref			357	Ref			874	Ref		
Q1, 1<3	12	0.80	0.50	1.25	5	0.97	0.46	2.05	3	1.40	0.69	2.84	4	0.55	0.18	1.72
Q2, 3<10	29	1.43	1.04	1.96*	5	1.07	0.55	2.08	11	1.74	0.97	3.11	13	0.78	0.32	1.88
Q3, 10<25	27	1.24	0.89	1.73	8	0.93	0.46	1.87	4	1.41	0.75	2.66	15	2.12	1.24	3.64*
Q4, 25	30	1.20	0.87	1.67	10	1.39	0.80	2.43	11	1.91	1.13	3.22*	9	0.69	0.28	1.68
p-trend (ordinal)		0.039*				0.418				0.003*				0.587		
Years as a foundry worker																
None	1823	Ref			593	Ref			356	Ref			874	Ref		
Q1, 1<2	6	0.73	0.38	1.41	0	-	-	-	2	1.36	0.50	3.65	4	0.36	0.05	2.53
Q2, 2<5	16	0.93	0.61	1.40	9	1.31	0.70	2.46	4	1.52	0.79	2.95	3	-	-	-
Q3, 5<21	18	1.42	1.03	1.96*	5	1.35	0.74	2.46	5	1.96	1.12	3.43*	8	1.09	0.51	2.30
Q4, 21	30	1.55	1.11	2.14*	6	1.17	0.58	2.37	13	2.38	1.38	4.09*	11	1.30	0.61	2.76
p-trend (ordinal)		0.005*				0.301				<0.0001*				0.744		

Separate Cox PH models were fitted for welders and foundry workers, mutually exclusive of each other. Analyses of years as a welder excluded foundry workers. Analyses of years as a foundry worker excluded welders. Cox PH models were adjusted for: screening trial arm (low-dose CT, chest radiography), NLSST component study, sex, centred age at randomisation, race/ethnicity (white vs others), education (less than high school, graduated high school, some postsecondary and above), centred pack-years of smoking at randomisation, smoking status at randomisation (current, former), centred body mass index at baseline, first degree relative with lung cancer and history of diagnosed chronic bronchitis and emphysema prior to randomisation.

* p Values <0.05 were considered statistically significant.

AC, adenocarcinoma; Q, quartiles, Ref, reference; SCC, squamous cell carcinoma.