Association between socioeconomic position and lung cancer incidence in 16 countries: a prospective cohort consortium study



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Summary

Background Studies have reported higher lung cancer incidence among groups with lower socioeconomic position (SEP). However, it is not known how this difference in lung cancer incidence between SEP groups varies across different geographical settings. Furthermore, most prior studies that assessed the association between SEP and lung cancer incidence were conducted without detailed adjustment for smoking. Therefore, we aimed to assess this relationship across world regions.

Methods In this international prospective cohort consortium study, we used data from the Lung Cancer Cohort Consortium (LC3), which includes 20 prospective population cohorts from 16 countries in North America, Europe, Asia, and Australia. Participants were enrolled between 1985 and 2010 and followed for cancer outcomes using registry linkages and/or active follow-up. We estimated hazard ratios (HRs) for the association between educational level (our primary measure of SEP, in 4 categories) and incident lung cancer using Cox proportional hazards models separately for participants with and without a smoking history. The models were adjusted for age, sex, cohort (when multiple cohorts were included), smoking duration, cigarettes per day, and time since cessation.

Findings Among 2,487,511 participants, 53,830 developed lung cancer during a 13.5-year median follow-up (IQR = 6.5–15.0 years). Among participants with a smoking history, higher education was associated with decreased lung cancer incidence in nearly every cohort after detailed smoking adjustment. By world region, this association was observed in North America (HR per one-category increase in education [HR_{trend}] = 0.88, 95% CI = 0.87–0.89), Europe (HR_{trend} = 0.89, 95% CI = 0.88–0.91), and Asia (HR_{trend} = 0.91, 95% CI = 0.86–0.96), but not in the Australian study (HR_{trend} = 1.02, 95% CI = 0.95–1.09). By histological subtype, education associated most strongly with squamous cell carcinoma and more weakly with adenocarcinoma (p-heterogeneity < 0.0001). Among participants who never smoked, there was no association between education and lung cancer incidence in any cohort (all p-trend > 0.05), except the USA Southern Community Cohort Study (HR_{trend} = 0.75, 95% CI = 0.62–0.90).

Interpretation Based on longitudinal data from 2.5 million participants from 16 countries, our findings suggest that higher educational attainment was associated with lower lung cancer risk among participants with a smoking history, but not among participants who never smoked. Limitations of our study include that cohort participants cannot fully represent the general populations of the geographical regions included, and education was the only measure of SEP consistently available across our consortium.

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Keywords: Lung cancer; Incidence; Socioeconomic position; Geographical differences

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide.¹ Smoking is the primary cause of lung cancer, but other risk factors include air pollution, radon, and a family history of lung cancer.² Beyond these risk factors, studies from Europe and the USA have reported lower lung cancer risk among those with higher socioeconomic position (SEP) as measured by education, income, and occupation (Supplementary Table S1).³.⁴ SEP refers to group of factors defined by educational attainment, income, and occupation that reflect a person's social hierarchy.⁵

There are several uncertainties regarding the association between SEP and lung cancer incidence. First, it is unclear whether this association is similar across different world regions, and across countries within regions. Geographical differences could occur due to variations in educational and social structures, and differences in the association between SEP and lung cancer risk factors. Further, people with lower-SEP smoke more frequently and quit less often in most countries, 6.7 but the extent to which smoking behavior mediates the relationship between SEP and lung cancer is unclear. Improved understanding of the relationship between SEP and lung cancer risk is relevant for the elimination

Research in context

Evidence before this study

We searched PubMed using the search terms ("socioeconomic position" OR "socioeconomic status" OR "social class" OR "occupational category" OR "occupational classification" OR "educational level" OR "income") AND ("lung cancer" OR "lung neoplasm" OR "lung cancer incidence" OR (("lung" OR "lung") AND "neoplasm incidence")) to identify studies published between January 1, 1990 and June 1, 2024. We identified 16 studies that reported associations between socioeconomic position (SEP) and lung cancer incidence, with results suggesting reduced lung cancer incidence among individuals with higher SEP. However, studies did not assess whether and how this disparity in lung cancer incidence varies across geographical settings. In addition, many prior studies assessing this relationship were conducted without detailed adjustment for smoking.

Added value of this study

We analyzed data from the Lung Cancer Cohort Consortium, including 2.5 million participants from 16 countries in North America, Europe, Asia, and Australia. Among participants with a smoking history, after detailed adjustment, we observed lower risk of lung cancer among higher education groups.

However, this association was not observed for participants who never smoked. These patterns were largely consistent across countries and world regions. Employment was associated with further reduced lung cancer risk among people with a smoking history in Europe and North America, and with reduced risk among people who never smoked in North America, while there were no strong associations with marital status after detailed adjustment. To our knowledge, this is the largest and most comprehensive study to describe the association between SEP and lung cancer incidence.

Implications of all the available evidence

Taken together, evidence supports that smoking-related lung cancer risk is higher among people with lower education in most geographical settings. One limitation of our study is that education was the only measure of SEP consistently available across our consortium, although we were able to evaluate employment and marital status across multiple cohorts. Our results highlight that increasing the engagement of disadvantaged groups in interventions such as tobacco prevention/cessation is an important strategy to reduce the burden of lung cancer globally.

of inequities in low-dose computed tomography (LDCT) lung cancer screening, which can substantially reduce lung cancer mortality among people with a smoking history.⁸

In this study, we aimed to describe the relationship between SEP and lung cancer risk across different parts of the world. We analysed data from 20 prospective cohorts in the Lung Cancer Cohort Consortium (LC3, https://lc3.iarc.who.int/), which comprise 2.5 million participants in Europe, Asia, North America, and Australia, among whom 54,000 developed lung cancer. Throughout the analysis, we separately analysed participants with and without a smoking history. We used highest attained educational level as the primary measure of SEP because it is consistently available in LC3, but we also assessed other measures of SEP (marital status and occupation) where possible.

Methods

Data source

Our project used data from the LC3, restricting to 20 cohorts with available information on educational level at baseline. The 20 cohorts comprise 2.5 million participants from Europe, North America, Australia, and Asia who were enrolled between 1985 and 2010. A detailed description of the cohorts and data harmonization approach has been published previously. The study was approved by the IARC Ethics Committee (IEC 22–31) and by institutional review boards of the

participating institutes, as required. Each of the participating cohorts obtained written informed consent from all participants. This study adheres to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational studies.

We harmonised highest attained educational level into 4 internationally comparable categories using the International Standard Classification of Education (ISCED, 2011)¹⁰ as follows: lowest (no education to lower secondary education, ISCED 0–2); low (upper secondary education to post-secondary non-tertiary education, ISCED 3–4); middle (short-cycle tertiary education to some college, ISCED 5); and high (Bachelor's to Doctorate or equivalent level, ISCED 6–8). A detailed description of the harmonisation of educational level is provided in Supplementary Table S2. Information on marital status was available in 8 cohorts, and occupation in 4 cohorts.

Statistical analysis

All analyses separately analysed participants with and without a smoking history. Within each group, we initially carried out risk analyses by cohort, and then pooled by world regions (Europe, North America, Asia, and Australia). We imputed missing data using predictive mean matching as described previously.

To estimate hazard ratios (HRs) for incident lung cancer by educational level, we fit a series of Cox proportional hazards models with incident lung cancer as

the endpoint. Participants entered analysis at baseline and exited at the first of lung cancer diagnosis, death, or end of follow-up for lung cancer. First, we estimated HRs for education modeled as a 4-level categorical variable with the lowest-education category set as the reference, stratified by world region. Based on these results, we subsequently modeled education as a 4-level ordinal variable. Using this ordinal variable, for each cohort-specific model and model pooled by world region, we first estimated the unadjusted HR (adjusted for cohort when multiple cohorts were included), followed by the HR adjusted for age, sex, cohort (when multiple cohorts were included), and smoking status (when analyzing currently and formerly smoking participants together). Then, for participants with a smoking history, we estimated a fully adjusted HR after additional adjustment for smoking duration, cigarettes per day, and time since cessation. Age and smoking duration, cigarettes per day, and cessation time were modeled continuously with restricted cubic splines with 3 knots to allow for nonlinear relationships. All models including data from multiple cohorts were adjusted for cohort. To assess whether the association between educational level and lung cancer incidence varied by histological subtype (adenocarcinoma, squamous cell carcinoma, and small cell carcinoma) and by stage at diagnosis (stage I-II and stage III-IV), we fit multivariable joint Cox proportional hazards models which treat tumors outside the outcome subtype of interest as competing risks. 11 In each model, the outcome is time to diagnosis of lung cancer of the histology/stage category of interest, and diagnoses of the other histology/stage categories are censored.12 Heterogeneity across strata was tested using a global Wald test. The proportional hazards assumption for Cox models was assessed using Schoenfeld residuals.

We performed stratified analyses according to age at baseline (<60 and ≥60 years), sex (male and female), smoking status (further stratifying by current and former), and race/ethnicity among the US cohorts. These analyses were motivated by considerations that the importance of education in the socioeconomic environment, and therefore for lung cancer risk, might vary across these groups. To assess whether incident lung cancer was further associated with other measures of SEP, we fit similar smoking-specific Cox proportional hazards models with marital status and employment in addition to education. We also conducted a mediation analysis using the counterfactual framework¹³ to estimate the degree to which the association between education and lung cancer incidence is mediated by smoking. This analysis pooled cohorts by world region and used a smoking score generated by a Cox model with lung cancer as the outcome and smoking duration, cessation time, and cigarettes per day, adjusted for age, sex, and cohort. For various analyses throughout the manuscript, where applicable, we generated results after stratifying by cohort to assess consistency of associations. A two-sided p-value < 0.05 was considered statistically significant. All statistical analyses were conducted using R version 4.1.2.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Four authors (JUO, HZ, XF, KA) had access to the data in the study and all authors had final responsibility for the decision to submit for publication.

Results

Study population

The study population included 1,281,595 participants with a smoking history and 1,205,916 participants without a smoking history from 20 cohorts in the LC3 consortium (Table 1). Most participants with a smoking history were male (54%) while most participants without a smoking history were female (67%). During 33,164,715 person-years of follow-up, 53,830 participants were diagnosed with lung cancer (median within-cohort follow-up ranging from 9.6 years for the Generations Study to 30 years for the NYU Women's Health Study). Among participants with a smoking history, 31% were in the group with high educational attainment, 27% in the middle group, 23% in the low group, and 19% in the lowest group. Corresponding proportions among participants without a smoking history were 35%, 18%, 25%, and 22%, respectively. The percentage of participants in the lowest educational attainment group ranged from 8% in North America to 53% in Asia while the percentage in the high educational attainment group ranged from 9% in Asia to 38% in North America (Supplementary Table S3).

Overall associations between educational attainment and lung cancer risk

Hazard ratio (HR) estimates for incident lung cancer for individual educational categories are shown in Fig. 1 (Kaplan–Meier curves shown in Supplementary Figs. S1 and S2). Cohort-specific trend HR estimates are shown in Fig. 2 for participants with a smoking history and in Fig. 3 for participants without a smoking history.

Amongst participants with a smoking history (excluding participants from the Shanghai Women's Health Study [SWHS], see below), higher educational attainment was associated with reduced lung cancer risk (Fig. 1). This inverse association followed a doseresponse behavior and was apparent in European, North American, and Asian cohorts (all *p*-trend < 0.0001), but not the one Australian cohort (*p*-trend = 0.64). The HR trend-estimate for a one-level increase in education (across 4 levels) for European participants was 0.82 (95% CI = 0.81–0.83) in minimally adjusted models and

0.89 after accounting for detailed smoking exposure (95% CI = 0.88-0.91). The corresponding smoking-adjusted HR-trend estimate in North American participants was 0.88 (95% CI = 0.87 - 0.89), in Asian participants was 0.91(95% CI = 0.86-0.96), and in Australian participants was 1.02 (95% CI = 0.95-1.09). Fig. 2 shows that the inverse association between education and lung cancer risk among participants with a smoking history was observed in most cohorts, with the notable exception of SWHS where we observed strongly discrepant results indicative of a positive association between education and lung cancer risk. This discrepancy motivated the exclusion of SWHS in the pooled analysis for Asia. Additional adjustment for BMI, which has been shown to associate with both educational level and lung cancer risk, had negligible effect (Supplementary Fig. S3).

In contrast to participants with a smoking history, analyses among participants without a smoking history did not suggest an association between education and lung cancer risk (Figs. 1 and 3), with overall *p-trend* ranging between 0.15 in North American and 0.83 in Asia (Fig. 1). A notable exception was people who never smoked in the Southern Community Cohort Study (SCCS-USA) where higher education was associated with a HR of 0.75 per 1-unit increase (95% CI = 0.62–0.90, *p*-trend = 0.0024) (Fig. 3). Additional adjustment for BMI had negligible effect (Supplementary Fig. S4).

Employment and marital status as measures of SEP

We investigated measures of SEP beyond education in cohorts with available information (Table 2). Among participants with a smoking history, analyzing cohorts with information on employment (Europe and North America), we observed lower risk for lung cancer among people with any employment (vs. lack of employment). After detailed adjustment for age, sex, smoking, and education, the HR for employment vs. lack of employment among European participants was 0.79 (95% CI = 0.74–0.84) and among North American participants was 0.84 (95% CI = 0.79-0.90) (cohort-stratified results in Supplementary Table S4). Among participants without a smoking history, after adjustment for age, sex, and education, we observed lower risk of lung cancer among people with employment in North America (HR = 0.68, 95% CI = 0.56-0.82, Table 2), but not in Europe. This association was particularly strong in the SCCS cohort (HR = 0.51, 95% CI = 0.33-0.81, Supplementary Table S4). More detailed categories of employment (employed, retired, homemaker, unemployed, unable to work) are analysed in Supplementary Table S5.

When analyzing 16 cohorts with available information on marital status, among participants with a smoking history and after detailed adjustment for age, sex, smoking, and education, we observed weakly increased risk for lung cancer among married vs. non-married participants only in Asia (HR = 1.19, 95% CI = 1.01–1.40, Table 2). No

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EPIC UK 37,930 (44%) 48,130 (56%) 697 (86%) 116 (14%)
GS UK 36,993 (36%) 67,036 (64%) 139 (71%) 57 (29%)
HUNT Norway 42,137 (55%) 33,869 (45%) 675 (95%) 34 (5%)
UKB UK 225,673 (45%) 273,369 (55%) 4225 (86%) 675 (14%)
North America 630,062 (59%) 437,237 (41%) 30,871 (92%) 2798 (8%)
AARP USA 347,443 (64%) 196,436 (36%) 20,201 (93%) 1452 (7%)
CLUE USA 14,552 (48%) 15,905 (52%) 693 (91%) 69 (9%)
CPSII USA 78,433 (54%) 66,099 (46%) 3297 (88%) 446 (12%)
CSDLH Canada 5731 (52%) 5277 (48%) 293 (82%) 64 (18%)
PLCO USA 40,069 (54%) 34,277 (46%) 1633 (92%) 143 (8%)
NYUWHS USA 6494 (52%) 6074 (48%) 360 (82%) 77 (18%)
SCCS USA 52,599 (64%) 29,752 (36%) 1685 (94%) 109 (6%)
VITAL USA 39,609 (52%) 36,439 (48%) 1232 (92%) 110 (8%)
WHI USA 45,132 (49%) 46,978 (51%) 1477 (82%) 328 (18%)
Asia 79,833 (31%) 175,636 (69%) 2971 (64%) 1684 (36%)
SCHS Singapore 15,909 (31%) 35,053 (69%) 907 (70%) 393 (30%)
SCS China 10,351 (57%) 7718 (43%) 931 (85%) 167 (15%)
SMHS China 42,805 (70%) 18,664 (30%) 991 (85%) 173 (15%)
SWHS China 2113 (2.8%) 72,824 (97%) 77 (8%) 898 (92%)
Golestan Iran 8655 (17%) 41,377 (83%) 65 (55%) 53 (45%)
Australia
MCCS Australia 17,651 (43%) 23,812 (57%) 715 (84%) 139 (16%)

AARP: NIH-AARP Diet and Health Study; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CLUE: Campaign Against Cancer and Heart Disease II; CPS-II: American Cancer Society Cancer Prevention Study-II Nutrition Cohort; CSDLH: Canadian Study of Diet, Lifestyle and Health (weighted case-cohort sample); GCS: Golestan Cohort Study; GS: Generations Study; HUNT: Trøndelag Health Study; MCCS: Melbourne Collaborative Cohort Study; NYUWHS: New York University Women's Health Study; PLCO: Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SCCS: Southern Community Cohort Study; SCHS: Singapore Chinese Health Study; UK Biobank: UK Biobank; VITAL: VITamins And Lifestyle Study; WHI: Women's Health Initiative. EPIC (Denmark, Germany, Italy, Norway, Spain, Sweden, The Netherlands, UK): European Prospective Investigation into Cancer and Nutrition. We excluded participants who received intervention at baseline in the PLCO (77436) and WHI (68094) cohorts.

Table 1: Description of 2.5 million participants in the Lung Cancer Cohort Consortium (LC3) included in analysis of socioeconomic position and lung cancer incidence.

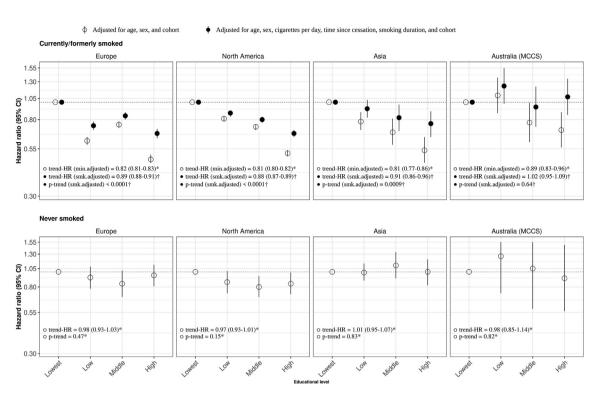


Fig. 1: Association between lung cancer incidence and educational level among Lung Cancer Cohort Consortium participants with and without a history of smoking in Europe, North America, Asia, and Australia. Footnote: Hazard ratios (HRs) are shown with adjustment for: *age, sex, and cohort (with and without history of smoking) and †age, sex, smoking duration, cigarettes per day, time since cessation, and cohort (with history of smoking). Some confidence intervals extend outside of the plot area. Pooled in each region: Europe (ATBC (Finland), EPIC (Denmark), EPIC (Germany), EPIC (Italy), EPIC (Norway), EPIC (Spain), EPIC (Sweden), EPIC (Netherlands), EPIC (UK), GS (UK), UK Biobank (UK), HUNT (Norway)); Australia (MCCS); North America (CPSII (USA), NYUWHS (USA), PLCO (USA), SCCS (USA), VITAL (USA), WHI (USA), AARP (USA), CLUE (USA)), CSDLH (Canada); Asia (SCHS (Singapore), SCS (China), SMHS (China), Golestan (Iran)). The SWHS (China) was excluded because results differed from those in other cohorts (see later figures).

associations were apparent in Europe, North America, or Australia, nor in any world region among people without a smoking history. Results for marital status stratified by cohort are shown in Supplementary Table S6.

Stratified analyses

Supplementary Tables S7–S11 present results of stratified analyses evaluating potential heterogeneity in the association between education and lung cancer incidence by age, sex, smoking status, and (for US cohorts) race/ethnicity. Among participants with a smoking history, the association between education and lung cancer incidence appeared stronger among participants aged < 60 vs. ≥60 years in Asia and North America (both *p-interaction* < 0.05, Supplementary Table S7, further stratification by cohort in Supplementary Table S8). Despite the potential for sex to alter the influence of education on one's social environment, the relationship between education and lung cancer risk did not appear to vary by sex (Supplementary Table S7).

When separately analyzing participants who had a current vs. former smoking history, the reduction in lung cancer risk with increasing education was stronger in participants who had quit smoking in North America, Europe, and Asia (*p-interaction* < 0.0001 for all), but not in Australia (*p-interaction* = 0.60) (Supplementary Table S7). In North America, Europe, and Asia, the HR-trend for a 1-unit increase in educational level ranged from 0.82 to 0.80 among participants who had quit smoking, compared to 0.98–0.93 in participants who reported currently smoking. This interaction was present in most cohorts (Supplementary Table S9). Among participants with a smoking history, the association between education and lung cancer was consistent between Non-Hispanic Black and Non-Hispanic White participants in the USA (*p-interaction* = 0.20) (Supplementary Table S10).

Among participants without a smoking history, among whom no overall association between education and lung cancer risk was consistently observed, stratified analyses by age and sex are shown in Supplementary Tables S7 and S11. In the SCCS cohort, where an overall association was observed, it did not vary by race/ethnicity (*p-interaction* = 0.96, Supplementary Table S10).

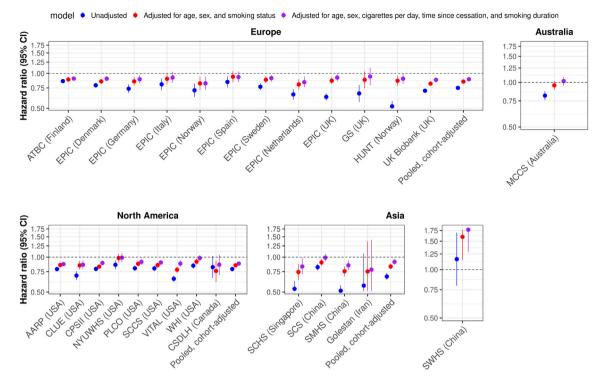


Fig. 2: Association between lung cancer incidence and educational level among Lung Cancer Cohort Consortium participants with a history of smoking. Footnote: Educational level is modeled as an ordinal variable in 4 categories. Hazard ratios (HRs) are shown without adjustment (for single cohort analyses) or with adjustment for cohort only (for pooled analyses) [in blue], with adjustment for age, sex, smoking status, and (for pooled analyses) cohort [in red], and with adjustment for age, sex, smoking duration, cigarettes per day, time since cessation, and (for pooled analyses) cohort [in purple]. Some confidence intervals extend outside of the plot area.

Histological subtype and stage at diagnosis

The association between education and lung cancer risk was heterogeneous between histological subtypes among participants with a smoking history (p-heterogeneity < 0.0001, Fig. 4). For both participants who currently smoked and those who formerly smoked, the reduced risk with higher education was strongest for squamous cell carcinoma and small cell carcinoma, and weaker for adenocarcinoma. No associations with education were observed for any histological subtype among participants who never smoked, consistent with the overall result in this group. No heterogeneity in associations between education and lung cancer risk was observed by stage at diagnosis.

Mediation analysis

We carried out a mediation analysis to estimate the extent to which smoking mediates the observed association between education and lung cancer risk. Among European participants reporting a smoking history, we estimated that smoking mediated 42% of the lower risk observed in participants with higher education. The corresponding mediation estimate was 42% for North American participants and 61% for Asian participants (Supplementary Fig. S5).

Discussion

In this large international study from the Lung Cancer Cohort Consortium (LC3), comprising 20 prospective cohorts from 16 countries in Europe, North America, Asia, and Australia, we assessed the association between socioeconomic position and lung cancer risk. After detailed adjustment, we consistently observed lower risk of lung cancer with higher education among participants with a smoking history, but not among those without a smoking history.

In our study, participants with higher SEP—as measured by educational attainment—generally had lower lung cancer risk than participants with lower SEP. In participants with a history of tobacco exposure, this relationship was consistent across Asia, Europe, and North America. Considering *i*) that tobacco exposure causes at least 80% of lung cancer cases worldwide, ¹⁴ *ii*) that higher SEP is generally associated with lower smoking exposure, ^{6,7} and *iii*) that we did not observe clear evidence for an association between SEP and lung cancer in participants without a smoking history—a natural assumption is that the majority of risk differences by SEP can be explained by differences in smoking exposure. This would be in line with a previous study suggesting that the association between SEP and

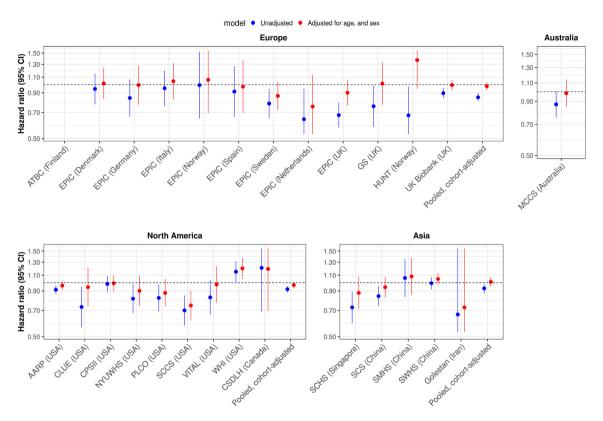


Fig. 3: Association between lung cancer incidence and educational level among Lung Cancer Cohort Consortium participants without a history of smoking. Footnote: Educational level is modeled as an ordinal variable in 4 categories. Hazard ratios (HRs) are shown without adjustment (for single cohort analyses) or with adjustment for cohort only (for pooled analyses) [in blue], and with adjustment for age, sex, and (for pooled analyses) cohort [red]. Some confidence intervals extend outside of the plot area.

lung cancer may be attributable to incomplete adjustment for smoking.¹⁵ However, we found that even after detailed adjustment for smoking history (smoking duration, cigarettes per day, and time since cessation), a strong association between educational level and lung cancer incidence remained. We estimated that 42%–61% of the association between education and lung cancer risk is mediated through smoking exposure, consistent with results from a prior, smaller study.¹⁶ These observations suggest that other factors—in addition to smoking exposure—may be involved in mediating the lung cancer risk differences by SEP, which we further discuss below.

As pointed out by Doll and Peto,¹⁷ questionnaire information of cigarette consumption is "an inaccurate measure of the current (let alone past) extent of exposure of the bronchial epithelial stem cells to the carcinogenic agents in cigarette smoke." Indeed, owing to differential and random measurement error, as well as bronchial physiology, type of cigarette, number and size of puffs, butt length, and inhalation depth,^{17,18} it is safe to assume important between-participant exposure differences that cannot be adequately captured in questionnaires. This implies that confounding or mediation

by smoking will remain partially unaddressed. This inherent inability to fully account for tobacco history may also vary between SEP-groups. The association between SEP and lung cancer risk was stronger in participants who had quit smoking than in participants who currently smoke in adjusted analyses, a potentially important observation that would be in line with poorer accounting for tobacco exposure history amongst this group. A possible solution to this issue would be to apply more objective methods of measuring smoking exposure using biological markers such as cotinine and DNA methylation.^{18,19}

Another explanation for the independent association between education and lung cancer risk is the association of education with risk factors other than tobacco use. Healthier lifestyle patterns may be more common among higher-education groups in many settings.²⁰ Factors like consumption of fruits and vegetables and higher physical activity are associated with lower lung cancer risk among participants with a smoking history.^{21,22} However, these associations may not be causal, nor sufficiently strong to explain our observations. Another possible explanation is that lower-SEP groups experience higher levels of exposure to environmental

Region	Currently/formerly smoked						Never smoked			
	Minimally adjusted		Smoking adjusted		Detailed adjustment		Minimally adjusted		Detailed adjustment	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Lung cancer incidence and any employment (vs. lack of employment) ^a										
Europe	0.68 (0.64-0.73)	<0.0001	0.77 (0.72-0.81)	<0.0001	0.79 (0.74-0.84)	<0.0001	0.89 (0.76-1.05)	0.17	0.89 (0.76-1.05)	0.18
North America	0.75 (0.70-0.80)	<0.0001	0.83 (0.78-0.88)	<0.0001	0.84 (0.79-0.90)	<0.0001	0.68 (0.56-0.82)	<0.0001	0.69 (0.57-0.83)	0.0001
Lung cancer incidence and marital status (married vs. non-married) ^b										
Europe	0.89 (0.84-0.94)	<0.0001	0.97 (0.91-1.03)	0.30	0.98 (0.92-1.04)	0.42	0.81 (0.64-1.04)	0.11	0.81 (0.63-1.04)	0.10
North America	0.77 (0.73-0.80)	<0.0001	0.96 (0.92-1.01)	0.11	0.96 (0.91-1.01)	0.09045	0.98 (0.85-1.12)	0.75	0.98 (0.85-1.12)	0.76
Australia	0.76 (0.64-0.90)	0.01	0.91 (0.77-1.09)	0.30	0.92 (0.77-1.09)	0.34	0.84 (0.57-1.25)	0.40	0.85 (0.57-1.26)	0.42
Asia	1.12 (0.95–1.32)	0.19	1.19 (1.01-1.41)	0.036	1.19 (1.01-1.40)	0.036	1.03 (0.88-1.20)	0.71	1.03 (0.88-1.20)	0.71

^aThe reference group is lack of employment which includes homemakers, unemployed, retired, people who are unable to work, and students. Employment includes working/employed. Minimally adjusted: model adjusted for age and sex. Smoking adjustment: model adjusted for age, sex, smoking duration, cigarettes per day, time since cessation. Detailed smoking adjustment: model adjusted for age, sex, and smoking duration, cigarettes per day, time since cessation, and education in participants with smoking history; age, sex, and education in participants without smoking history. ^bThe reference group is non-married which includes widowed, divorced/separated, and never married. Minimally adjusted: model adjusted for age and sex. Smoking adjusted: model adjusted for age, sex, smoking duration, cigarettes per day, and time since cessation. Detailed adjusted: model adjusted for age, sex, and education.

Table 2: Association between lung cancer incidence and employment and marital status among Lung Cancer Cohort Consortium participants with and without a history of smoking.

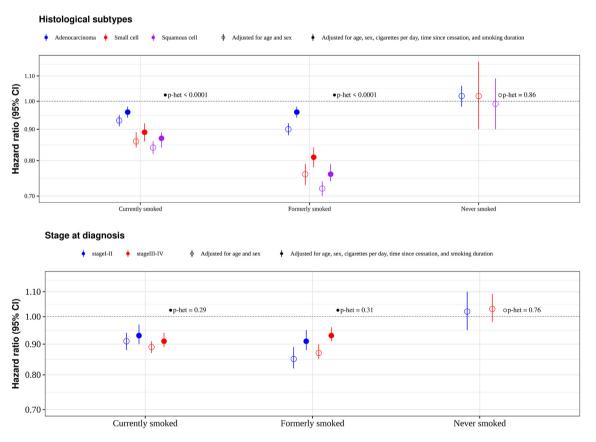


Fig. 4: Association between lung cancer incidence and educational level by stage and histological subtype among Lung Cancer Cohort Consortium participants with and without history of smoking. Footnote: Educational level is modeled as an ordinal variable in 4 categories. Hazard ratios (HRs) are shown for histological subtypes [adenocarcinoma (blue), small cell (red) and squamous cell (purple)] and stage at diagnosis [Stage I-II (blue) and Stage III-IV (red)]. Models are adjusted minimally for age, sex, and cohort; and for age, sex, smoking duration, cigarettes per day, time since cessation, and cohort. p-het: p-heterogeneity for model adjusted for age, sex, smoking duration, cigarettes per day, time since cessation, and cohort. We pooled all cohorts (19% and 24% missing and other histology respectively and 66% missing stage), except Golestan (Iran, 100% missing stage and histology) and CSDLH (Canada, 100% missing stage and 14% missing histology). We used a competing risk analysis which considers each histology/stage category of interest by treating outcomes of the other histology/stage categories as censored observations.

and occupational carcinogens, including indoor and outdoor air pollution, or perhaps radon. A recent global review showed that low-SEP communities experience higher concentrations of air pollutants in North America, New Zealand, Asia, and Africa, though there is conflicting evidence regarding the association in Europe.²³ If exposures such as air pollution are associated with education, and also act as promoters of tumors that are initiated by tobacco smoking (rather than acting as mutagens),²⁴ then this might explain why education associates with lung cancer risk among participants with a smoking history, but not among those who never smoked.

An important exception to the lack of association between SEP and lung cancer risk among participants who never smoked was the SCCS cohort (USA). The SCCS comprises a low-income population, of whom the majority is non-Hispanic Black,25 though we found no evidence for variation by race/ethnicity. Beyond the reduction in lung cancer incidence among highereducation participants who never smoked in SCCS (HR-trend = 0.75), there was a further, large reduction in risk for participants who were employed (HR = 0.51). It is possible that there are influences in SCCS that increase risk for lung cancer among participants who never smoked and are correlated with SEP, such as occupational or environmental exposures, which are less prevalent in the other cohorts which did not explicitly enroll low-income populations. In line with our finding in SCCS, in the US Black Women's Health Study, Erhunmwunsee et al. observed that higher levels of neighborhood concentrated disadvantage associated with increased lung cancer risk in Black women who never smoked.26 Therefore, although our study largely ruled out an increased risk of lung cancer among lowereducation groups in participants without a smoking history, we recommend that research efforts further characterize lung cancer risk among low-income and minority populations.

Another exception to the patterns observed in our study was women with a smoking history in the Shanghai Women's Health Study, among whom more education associated with *higher* lung cancer incidence. A possible explanation for this is opportunistic lung cancer screening, which would increase lung cancer incidence, and would occur more frequently among higher-education participants.

The association between education and lung cancer risk among participants with a smoking history was strongest for squamous cell carcinoma and small cell carcinoma, but weaker for adenocarcinoma which is more weakly associated with smoking.²⁷ Because smoking increases the risk of squamous and small cell carcinoma more than the risk of adenocarcinoma of the lung, this finding is in line with smoking having an important role in mediating the relationship between SEP and lung cancer risk.

To consider other dimensions of SEP beyond education, we assessed associations of lung cancer risk with employment and marital status in cohorts with available information. Among participants with a smoking history in both Europe and North America, employment was associated with reduced lung cancer risk, even after detailed adjustment for smoking and education. This is similar to findings from Poland, where unemployment was related to elevated risk of lung cancer in males.²⁸ As noted above, employment was associated with a further risk reduction beyond education among participants who never smoked in the SCCS cohort. For marital status, we observed increased risk of lung cancer among married compared with non-married participants with a smoking history in Asia, but not in Europe, North America, or Australia. A previous study in China also reported reduced lung cancer risk among unmarried participants.²⁹ These results support that the association between SEP and lung cancer risk among people spans socioeconomic dimensions beyond education.

Our results have implications for LDCT screening programs, which are increasingly being implemented in North America, Europe, Asia, and Australia.30 The success of lung cancer screening depends on the identification of individuals at high risk. Considering that lower-SEP individuals have higher risk of lung cancer in most geographical settings, our findings emphasize the importance of engaging individuals with lower SEP in screening. A method to achieve this is by use of risk prediction models that include measures of SEP, coupled with outreach efforts targeted to lower-SEP communities. Incorporating SEP into lung cancer risk prediction models can enhance the identification of individuals at highest risk of lung cancer, allowing more lung cancers to be detected without screening additional people.

Our study is unique for its large size, deriving from 20 large high-quality longitudinal cohort studies, and its geographic diversity across North America, Europe, Asia, and Australia. While we observed no association between education and lung cancer incidence in Australia, we caution that only a single cohort was available for analysis, and this conclusion should not be assumed to be generally applicable to Australia. Even for other regions where multiple cohorts were available to support our conclusions, the study participants cannot fully represent the general population due to healthy volunteer effects and specific recruitment aspects. Another limitation of our study is that education was the only measure of SEP consistently available across our consortium, although we were able to evaluate employment and marital status across multiple cohorts. The proportional hazards assumption of the Cox model was sometimes statistically violated due to the large sample size, but based on visual inspection, the hazard ratios provided a reasonable summary of the associations over follow-up time.

In conclusion, based on 2.5 million longitudinally followed cohort participants and 53,000 incident lung cancer cases from 16 countries, we observed consistently lower risk of lung cancer with higher educational level among participants with a smoking history. This association was partly explained by self-reported smoking history, and was not observed among participants who never smoked. Future research should aim to pinpoint the factors that mediate this association, including by considering objective methods of measuring smoking exposure using biological markers, and to clarify the importance of other risk factors across SEP groups. Our study highlights the global importance of engaging groups with lower SEP to increase the impact of primary and secondary prevention of lung cancer.

Contributors

HAR and JUO conceived of and designed the study. HAR, JUO, and MJ developed the methodology. HAR, MJ, PB, DA, AAA, JB, QC, CC, NDF, WH, MEJ, RK, WK, AL, LML,RM, RLM, TER, MJS, MS, RS, XS, LFT, KV, YW, RW, SJW, EW, JY, and WZ curated the data. HAR, JUO, MJ and HZ, PF conducted the statistical analysis. HAR, MJ, and PB provided study resources. HAR and MJ acquisition funding. HAR, MJ, and KA did project management and administration HAR and MJ provided supervision. Drafted the manuscript HAR, JUO, and MJ HAR, JUO, MJ, LE, RMW, MCA, ND, MRJ, and JSA did review and editing. All authors approved the final version of the manuscript. JUO, HZ, XF, and KA have access to and verify the underlying study data.

Data sharing statement

Access to data from the Lung Cancer Cohort Consortium (LC3) is governed by the LC3 Access Policy, which is available at the following link: https://www.iarc.who.int/wp-content/uploads/2021/12/LC3_Access_Policy.pdf. Interested investigators are encouraged to contact Dr Johansson or Dr Robbins

Declaration of interests

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Articles

12

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103152.

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