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ORIGINAL RESEARCH

Lung cancer risk in painters: results from the SYNERGY pooled case–control study consortium

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ABSTRACT

Objectives We evaluated the risk of lung cancer associated with ever working as a painter, duration of employment and type of painter by histological subtype as well as joint effects with smoking, within the SYNERGY project.

Methods Data were pooled from 16 participating case–control studies conducted internationally. Detailed individual occupational and smoking histories were available for 19 369 lung cancer cases (684 ever employed as painters) and 23 674 age-matched and sex-matched controls (532 painters). Multivariable unconditional logistic regression models were adjusted for age, sex, centre, cigarette pack-years, time-since-smoking cessation and lifetime work in other jobs that entailed exposure to lung carcinogens.

Results Ever having worked as a painter was associated with an increased risk of lung cancer in men (OR 1.30; 95% CI 1.13 to 1.50). The association was strongest for construction and repair painters and the risk was elevated for all histological subtypes, although more evident for small cell and squamous cell lung cancer than for adenocarcinoma and large cell carcinoma. There was evidence of interaction on the additive scale between smoking and employment as a painter (relative excess risk due to interaction >0).

Conclusions Our results by type/industry of painter may aid future identification of causative agents or exposure scenarios to develop evidence-based practices for reducing harmful exposures in painters.

Key messages

What is already known about this subject?

- 'Occupational exposure as a painter' has been classified as carcinogenic to humans by the International Agency for Research on Cancer, primarily due to an increased risk of lung cancer in epidemiological studies. Most of the published studies reported on ever employment as a painter; few presented detailed analyses by type of painter, duration of employment, histological subtype of lung cancer or adjustment for exposure to other occupational lung carcinogens.

What are the new findings?

- This pooled analysis of 19 369 cases (684 painters) and 23 674 controls (532 painters) is the largest study to corroborate the increased risk of lung cancer in painters. The highest risks were observed for construction and repair painters and for the small cell, and squamous cell histological subtypes. The analyses accounted for detailed individual smoking habits and employment in other occupations with potential exposure to lung carcinogens.

INTRODUCTION

Lung cancer is the most common cancer diagnosis worldwide and is the major cause of cancer mortality in men; an estimated 1 368 524 men and 725 352 women were diagnosed with incident lung cancer in 2018.[1] Approximately 70% of the lung cancer burden can be attributed to smoking alone[2 3]; however 'occupational exposure as a painter' has also been classified as an independent risk factor[4] by the International Agency for Research on Cancer (IARC). Most of the published studies reported on ever employment as a painter; few studies have presented detailed analyses by type of painter, duration of employment, histological subtype of lung cancer or adjustment for exposure to

Key messages

How might this impact on policy or clinical practice in the foreseeable future?

- As several million people are employed as painters worldwide, even a modest increase in lung cancer risk is notable for prevention efforts to reduce the burden of occupational lung cancer. Our results by type/industry of painter may aid future identification of causative agents or exposure scenarios to develop evidence-based practices for reducing harmful exposures in painters.

other occupational lung carcinogens. Painters are exposed to many known and suspected lung carcinogens, such as silica, asbestos, talc containing asbestos fibres, chromium VI compounds and cadmium compounds[4 5]; however, it is currently unclear to what extent these agents contribute to the increased lung cancer risk in painters and whether there are other factors that may contribute. Reporting data by type of painter may further elucidate the role of different potential causative agents and have important implications for workplace policies and compensation of occupational cancer in painters. Therefore within the SYNERGY study, a large international pooled analysis of 16 case–control studies of lung cancer, we assessed associations with employment as a painter, type of painter and duration of employment with adjustment for detailed smoking history and employment in other occupations with known or suspected lung cancer risk. We also assessed the joint effects of occupation as a painter and tobacco smoking in the risk of lung cancer, by histological subtype when possible.

METHODS

This manuscript is formatted according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement for reporting case–control studies.[6]

Data for the SYNERGY project were pooled from 16 population-based or hospital-based case-control studies of lung cancer from Europe, Canada, China and New Zealand conducted between 1985 and 2010; 15 of these studies collected lifetime tobacco smoking and occupational histories. The IARC multicentre INCO study was composed of seven study centres. The SYNERGY project has been described previously.[7] Seven of the 16 studies previously published results on lung cancer in painters: AUT,[8] HdA,[9 10] INCO,[11] TURIN/VENETO and ROME,[12] MONTREAL[13] and HONG-KONG.[14]

Some noteworthy design features of the included studies: (1) most frequency-matched cases and controls on age and sex, conducted face to face interviews (84%), and asked about lifetime history of jobs held for more than 1 year[15]; (2) the Hong Kong, LUCAS and LUCA studies were restricted to men and the PARIS study included only regular smokers; (3) all studies, except MORGEN, provided data on lifetime smoking habits and complete self-reported occupational history until diagnosis or recruitment. MORGEN is a case–control study nested in the European Prospective Investigation into Cancer and Nutrition study in the Netherlands, where 45% of those invited completed a questionnaire at recruitment; (4) the occupational data were coded or recoded from national classifications into the International Standard Classification of Occupations (ISCO-68).[16] Ethical consent was obtained in accordance with the legislation in each country and also by the IARC Ethics Committee. The SYNERGY project is coordinated by IARC, the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, and the Institute for Risk Assessment Sciences at Utrecht University. More information is available at http://synergy.iarc.fr.

Exposure assessment

Painters were categorised by job and industry codes into painting industry/'type of painter" by two industrial hygienists (HK, RV). The categories of painting industry are comprised of combinations of 5-digit ISCO and 4-digit ISIC codes (ISCO 9–3 X.XX), as described in online supplemental table 1, to categorise by chemical composition of paint and type of application. 'Spray painters' were a subset of manufacture painters believed *a priori* to have a different exposure profile than manufacture painters.

Duration of employment was determined using the total number of years employed as a painter in the persons' working life. 'Ever painter' was defined as minimum 1 year of employment. Seventeen painters (6 cases, 11 controls) that had missing data on start and/or end date of employment were omitted from the analyses of duration (data not shown).

Statistical analysis

To investigate the association between occupational exposure as a painter and lung cancer risk, ORs and 95% CIs were computed using unconditional logistic regression models. Two exposure metrics were considered: ever vs never being employed as a painter, and the duration of employment as painters (years). Duration of employment was categorised into tertiles (1–5, 6–17, >17 years) based on the duration distribution among control subjects that had worked as painters. Subjects who were never employed as painters were considered as the reference category in analysis for both exposure metrics. Models were adjusted for study (individual centres of the IARC study in Central and Eastern Europe and the UK (INCO) were treated as separate studies), age, cigarette pack-years (cPY), time-since-quitting smoking cigarettes (categorised as current smokers; quitting 2–7, 8–15, 16–25, 26–35, 36+ years before diagnosis/interview and never-smokers), ever-employment (yes/no) in an industry or occupation with known (list A) or suspected (list B) association with the risk of lung cancer.[17 18] Painters were excluded from list A for this analysis (online supplemental table 2). Current smokers were defined in most studies as having smoked at least one cigarette per day for 6 months or more, and also included those who had stopped smoking in the last 2 years before diagnosis or interview, as recent smoking cessation could be due to early symptoms of the disease. The cPY was calculated as follows: Σ duration (years) X average cigarette smoked per day/20 (cigarettes per pack) and was included as log(1+cPY) in the logistic regression models in order to approximate log-normal distribution.

Analyses were performed both overall and separately by sex to account for potential sex differences in job tasks and subsequent exposures. Stratified analyses were also performed by type of painter and by lung cancer subtype. Linear trends in ORs across categories of duration of employment as painters, starting from never being a painter, were examined by treating categories as equally spaced ordinal variables in the logistic regression models. In female painters, the analyses by duration of employment, and by histological subtype, were dropped because there were too few exposed cases.

Interactions on a multiplicative scale were assessed using an interaction term between occupation as a painter (never vs ever painter) and smoking status (never vs ever smoker) in logistic regression models.

Interactions on an additive scale were assessed by fitting linear OR models and calculating the relative excess risk due to interaction (RERI), in order to test the departure from additivity of the effects of both risk factors (painter and smoking status).[19] Linear OR models were adjusted for study, age, and list A and B, and performed both overall and by sex. RERI estimates along with 95% CIs based on the delta method are reported.[20 21] Never smokers and never painters were considered as the reference category. RERI-based analyses in women are not presented due to the sparse number of female painters who never smoked in certain sub-categories. The RERI measures the extent to which the effect of both exposures combined exceeds the sum of the effects of each considered separately and is thus given by OR_{11} - OR_{10} - OR_{01} +1, where OR_{ij} is the OR for lung cancer comparing the group with exposures i and j to the reference category. A RERI>0 indicates a positive additive interaction where the effect of both exposures together exceeds the sum of the two exposures considered separately. We also reported the attributable proportion (AP) of cancer risk that is due to the additive interaction between the two exposures (range −100 to 100%), which is defined by the ratio of the RERI to the risk among the doubly exposed group, OR_{11}, (RERI/ OR_{11}).

Random effects meta-analyses, using the adjusted ORs by centre, was conducted using the STATA 'metan' command (online supplemental figure 1) in order to (1) compute summary estimates and 95% CIs comparing 'ever' with 'never' being a painter across studies and (2) to explore heterogeneity between studies, expressed as a percentage (I^2). The I^2 statistic quantifies the amount of inconsistency between studies[22] and estimates the percentage of total variation across studies that is due to heterogeneity rather than chance. I^2 ranges from 0% and 100%; a value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. There will be differences in the summary estimates produced from the pooled and meta-analysis due to differences in weighting.[23]

Various sensitivity analyses were conducted to investigate factors contributing to heterogeneity in the summary estimate (online supplemental table 3). The robustness of the overall risk estimate was also assessed by dropping individual studies one at a time. Analyses were performed using SAS V.9.3, Stata (V.11.0) and R statistical software (V.3.4.1). P values are two sided.

RESULTS

Table 1 describes selected characteristics of participants in the SYNERGY pooled analysis by ever-painter status. Roughly 5% of ever-painters were women, while the corresponding proportion among never-painters was around 20%. Ever-painters were slightly younger than never-painters, more often current smokers and less often never smokers.

Table 2 describes the 16 studies included in the SYNERGY pooled analysis, comprising 19 369 cases (684 painters) and 23 674 controls (532 painters). Case and control participation ranged from 53% to 98% and 41% to 100%, respectively.

The meta-analysis and additional sensitivity analyses show no to low/moderate heterogeneity (I^2 <50%) by various strata (ie, control source, region, sample size and the end year of data collection) (online supplemental table 3 and figure 1). Omitting studies one at a time had no effect on the overall meta-OR (meta-OR, 1.26; 95% CI 1.09 to 1.44; I^2=0); the meta-OR changed slightly but remained elevated when dropping the three studies with the largest weights (AUT, ICARE, EAGLE) (meta-OR, 1.19; 95% CI 0.99, 1.43; I^2=0) but did not change significantly when restricting to studies with control participation >50% (OR, 1.23; 95% CI 1.06 to 1.44; I^2=0%; 19 studies) and >75% (OR, 1.24; 95% CI 0.99 to 1.55; I^2=18.7%; 14 studies).

Painters experienced an increased risk of lung cancer (table 3). Men who were ever employed as a painter (for at least 1 year) had an OR for lung cancer of 1.30 (95% CI 1.13 to 1.50; 649 exposed cases). Painters were also categorised by industry/painter type according to ISCO and ISIC codes (online supplemental table 1). The highest risk was observed for construction painters (OR in men=1.31; 95% CI 1.11 to 1.55) and repair painters (OR in men=1.38; 95% CI 0.87 to 2.20). Similar patterns were observed for women—although on much smaller numbers—and also in the analyses of men and women combined. A trend with duration of employment was observed for construction painters (p≤0.001).

Table 4 shows that the results were comparable across histological subtypes. Generally, the magnitude of lung cancer risk was highest in the highest category of duration of employment; however, the test for trend was significant only among all subjects (p values for trend <0.05) but not when excluding never painters (p values for trend >0.05). Similar patterns were observed in the analyses for men and women combined. When analyses were restricted to women only, numbers were too small for any meaningful analyses by histological subtype.

Joint effects of smoking status and ever/never employment as a painter are presented overall and by lung cancer subtype, separately by sex and also for men and women combined in table 5. Among never smokers who had ever worked as a painter, there was a twofold increased risk of lung cancer for all subtypes (OR 2.04; 95% CI 1.18 to 3.53) and was highest for the adenocarcinoma subtype (OR 2.63; 95% CI 1.33 to 5.18). Results for other histological subtypes were not informative due to the small number of painters who never smoked (n<5). Compared with the reference category of those who had never smoked nor worked as a painter, the highest risk of lung cancer was observed among smokers who had ever worked as a painter (overall OR in men=16.48; 95% CI 14.05 to 19.33). There was evidence of interaction on the additive scale (RERI>0) for lung cancer in men (RERI 3.93; 95% CI 1.55 to 6.30); nearly a fourth of the lung cancers among those who had ever worked as a painter and also ever smoked could be attributed to the interaction (AP 23.85; 95% CI 12.07 to 35.62). While similar patterns were observed in analyses for men and women combined, there was no evidence of additive interaction for women (data not shown).

DISCUSSION

This is the largest study to date to assess the association between occupation as a painter and risk of lung cancer, by type of painting activity as well as histological subtype, while accounting for lifetime smoking habits and other occupations with potential exposure to occupational lung carcinogens. Our results are in line with several publications that reported increased relative risks for lung cancer among painters after adjustment for smoking.[4] Ever having worked as a painter was associated with an increased risk of lung cancer of similar magnitude in this pooled analysis (OR 1.29; 95% CI 1.12 to 1.48) and in a meta-analysis (RR 1.35; 95% CI 1.21 to 1.51)[24] which included 4 of the 16 studies from the present pooled analysis.[8 9 12 25] The SYNERGY pooled analysis had additional advantages over the meta-analysis in that there was harmonised and refined exposure assessment and adjustment for potential confounders using the raw data. The association was strongest for construction and repair painters and the risk was elevated for all histological

Table 1 Selected characteristics of study participants in the SYNERGYy analysis of painters

Study participants' characteristics	Ever painters				Never painters			
	Cases n=684	%	Controls n=532	%	Cases n=18 685	%	Controls n=23 142	%
Sex								
Men	649	94.9	504	94.7	14 959	80.1	18 027	77.9
Women	35	5.1	28	5.3	3 726	19.9	5 115	22.1
Age, years								
<45	45	6.6	29	5.5	758	4.1	1 456	6.3
45–49	52	7.6	38	7.1	1 115	6	1 413	6.1
50–54	99	14.5	68	12.8	1 915	10.3	2 254	9.7
55–59	125	18.3	77	14.5	2 833	15.2	3 388	14.6
60–64	131	19.1	96	18.1	3 485	18.6	4 051	17.5
65–69	103	15.1	108	20.3	3 892	20.8	4 818	20.8
70–74	100	14.6	86	16.2	3 319	17.8	4 371	18.9
75+	29	4.2	30	5.6	1 368	7.3	1 391	6
Histological subtype								
SqC	279	40.8	–	–	6904	36.9	–	–
SCLC	110	16.1	–	–	2913	15.6	–	–
AC	176	25.7	–	–	5462	29.2	–	–
LCC	30	4.4	–	–	836	4.5	–	–
Others*	89	13	–	–	2570	13.8	–	–
Ever employed in a list A/B job†								
No	445	65.1	342	64.3	12 959	69.4	17 819	77
List A	53	7.7	42	7.9	1 040	5.6	810	3.5
List B	156	22.8	133	25	4 134	22.1	4 107	17.7
List A and List B	30	4.4	15	2.8	552	2.9	406	1.8
Smoking status								
Never smokers	25	3.7	99	18.6	1 429	7.6	7 681	33.2
Former smokers	160	23.4	232	43.6	5 840	31.3	9 021	39
Current smokers	497	72.7	199	37.4	11 377	60.9	6 371	27.5
Unknown/missing	2	0.3	2	0.4	39	0.2	69	0.3
Pack-years cigarette smoking, ever smoker: AM (SD)	42.53 (25.6)		28.56 (24.0)		42.42 (27.9)		26.25 (23.8)	
Time since quitting smoking, former smokers: AM (SD)	12.05 (9.2)		18.01 (11.7)		12.99 (10.3)		20.10 (12.1)	
Time since quitting smoking, years								
2–7	58	8.5	39	7.3	1 850	9.9	1 341	5.8
8–15	39	5.7	61	11.5	1 649	8.8	2 002	8.7
16–25	36	5.3	58	10.9	1 207	6.5	2 468	10.7
26–35	13	1.9	42	7.9	466	2.5	1 623	7
>35	2	0.3	16	3	216	1.2	1 062	4.6
Missing	14	2	18	3.4	491	2.6	594	2.6
Never smoker	25	3.7	99	18.6	1 429	7.6	7 681	33.2

*Others include others, unspecified and missing values.
†Occupation with known (list A) or suspected (list B) association with the risk of lung cancer.
AC, adenocarcinoma; AM, arithmetic mean; LCC, large cell carcinoma; SCLC, small cell lung cancer; SqC, squamous cell carcinoma.

subtypes, although more expressed for small cell and squamous cell lung cancer than for adenocarcinoma and large cell carcinoma. We believe our results are generalisable to other populations not studied in this pooling project as the data come from 16 studies conducted in globally diverse populations from China, New Zealand, Canada and across Europe.

There was evidence of interaction on an additive scale between smoking and employment as a painter (RERI >0), suggesting that public health consequences of an intervention on occupational exposure as a painter would have greater benefit among ever smokers than among never smokers. It is noteworthy that an increased risk of lung cancer was also observed in never smokers who had worked as painters, relative to those who were never smokers and never painters.

Complete individual job histories in the form of job titles were available in SYNERGY. Although job titles were self reported, there is no reason to suspect that cases would over report employment as a painter compared with controls. Therefore, any potential exposure misclassification would likely be non-differential and bias the risk estimates towards the null. Furthermore, occupation as a painter is a clear cut job title, which reduces the potential for exposure misclassification.

Not all painters have the same exposures, not even within subcategories, and this is even more an issue when the lung cancer excess may be the result of a mix of various carcinogenic exposures. Several factors will determine exposures in painters. For example, construction painters most often use rollers and brushes, rather than spray-guns, which result in relatively low

Table 2 Characteristics of studies included in the SYNERGY pooled analysis

Study acronym	Country	Data collection (years)	Time period, occupation as painter	Source of controls	Cases (n=19 369)	Case Participation %	Cases Ever painter %	Controls (n=23 674)	Control participation %	Controls-Ever painter %
AUT	Germany	1990–1995	1932–1994	P	3 180	77	3.1	3 249	41	2
CAPUA	Spain	2000–2010	1941–2004	H	875	91	3.4	838	96	3
EAGLE	Italy	2002–2005	1942–2005	P	1 943	87	3.9	2 116	72	2.2
HdA*	Germany	1988–1993	1926–1993	P	1 004	69	4.7	1 004	68	2.8
HONG-KONG*	China	2003–2007	1940–2007	P	1 207	96	2.7	1 069	48	0.8
ICARE	France	2001–2007	1944–2007	P	2 926	63	5	3555	77	2.5
INCO_ Cz. Rep*	Czech Republic	1998–2002	1941–2001	H	304	94	2.3	453	80	0.6
INCO_Hungary*	Hungary	1998–2001	1952–1999	H	402	90	2.7	315	100	2.2
INCO_Poland*	Poland	1999–2002	1946–2000	H+P	800	88	3.3	841	88	2
INCO_Romania*	Romania	1998–2001	1955–2000	H	181	90	3.9	228	99	2.6
INCO_Russia*	Russia	1998–2000	1949–2000	H	600	96	1.8	580	90	3.6
INCO_Slovakia*	Slovakia	1998–2002	1942–2002	H	346	90	2	285	84	1.4
INCO_UK*	UK	1998–2005	1934–2002	P	442	78	5.7	918	84	4
LUCA	France	1989–1992	1938–1991	H	309	98	4.5	302	98	2.3
LUCAS	Sweden	1985–1990	1927–1990	P	1 042	87	2	2 356	85	2.2
MONTREAL*	Canada	1996–2002	1935–1999	P	1 203	85	2.2	1 509	69	1.5
MORGEN	The Netherlands	1993–1997	1953–1993	P	71	N/A	1.4	202	N/A	1.5
OCANZ	New Zealand	2003–2008	1954–2008	P	457	53	2.2	792	48	2
PARIS	France	1988–1992	1942–1991	H	173	95	2.3	234	95	4.3
ROME	Italy	1993–1996	1933–1995	H	347	74	3.5	365	63	3
TURIN/VENETO*	Italy	1990–1994	1928–1993	P	1 132	79	5.9	1 553	80	3
TORONTO	Canada	1996–2003	1949–2000	H+P	425	62	1.2	910	71	0.9

*These studies have previously published their results on painters: AUT (Bruske-Hohlfeld et al 2000),[8] HdA (Jöckel *et al*[10]; Jahn *et al*),[9] INCO (Zeka *et al*),[25] MONTREAL (Ramanakumar *et al*)[13]; TURIN/VENETO (Richiardi *et al*)[12]; HONG-KONG (Tse *et al*). These published studies, except for Ramanakumar *et al*[13] and Tse *et al*,[14] were included in a meta-analysis that assessed lung cancer risk in painters (Guha *et al*[24], published online 2009)
H, hospital based; P, population based.

exposure to solvents and paint. However, the work needed to prepare a surface before painting can involve high exposure to dust from paint and may result in exposures like asbestos, lead and silica.[26]

Repair painters are generally exposed for shorter times. The actual paint spraying takes place for a limited period of time in body shops since repair painters must perform several other tasks before the painting can take place.[27]

Spray painters in SYNERGY had an increased risk of lung cancer, consistent with previously published studies.[14] Spray painters may experience exposure to higher solvent concentrations and are exposed to aerosolised compounds which may be hazardous to the lung.[28] Spray painters in truck and aeroplane manufacturing may have had exposure to hexavalent chromium used as a pigment to prevent rusting. Although spray painters often use personal protective equipment (eg, coveralls and respiratory protection), this may not have been true for earlier time periods of exposure.

There was, however, low precision for some of the analyses by type of painter, which was mostly due to small numbers in some strata. These limitations create challenges to identifying specific causative agents. Nevertheless, our analyses by type of painter and the characterisation of exposures by work environments in online supplemental table 1 can inform future studies to identify the agents responsible for the increased lung cancer risk in different subsets of painters. Future epidemiological studies that specifically assess exposure to these compounds among painters are needed to identify to what extent the known carcinogens contribute to the increased lung cancer risk and whether other causative agents play an additional role.

The higher OR 1.35 (95% CI 1.05 to 1.74) observed for studies conducted before 1995 compared with after 1995 (OR 1.19; 95% CI 1.00 to 1.42) (online supplemental table 3) may illustrate changes to the composition of paints over time[29] that were undertaken in response to directives to reduce emissions of volatile organic compounds from 1999 onwards.[30]

The observed associations were lower in the hospital-based case-control studies; most enrolled only patients with diseases that were not related to smoking and were careful in including several diagnostic groups with a varied referral pattern.[31] The hospital-based studies were also generally smaller in size, so it is possible that they were underpowered to detect a potential risk in painters in the individual studies. Although participation in the studies using population-based controls was generally lower than in studies using hospital-based controls, only a few studies included in the pooled analysis had <50% participation among population controls. Low participation can endanger representativeness and therefore provide opportunity for bias; however, low response does not result in selection bias any more than high response guarantees unbiased estimates.[32] Although there is a potential for non-response bias due to the low level of subject participation, a low response rate in itself is not necessarily an indicator for the presence of non-response bias.[33 34] Furthermore, the overall meta-OR (OR, 1.26; 95% CI 1.09 to 1.44; I^2=0; 22 studies) was neither affected by omitting studies one at a time nor restricting to studies with control participation >50% (OR, 1.23; 95% CI 1.06 to 1.44; I^2=0%; 19 studies) or >75% (OR, 1.24; 95% CI 0.99 to 1.55; I^2=18.7%; 14 studies).

We consider the impact of potential recall bias has been at most moderate in SYNERGY because there was no emphasis placed on any particular occupation. It is generally accepted that for jobs held longer, the validity and reliability of self-reported job history obtained with an interviewer-administered questionnaire is not an important source of recall bias.[18 35 36] More

Table 3 Risk of lung cancer by type of painter and duration of employment, stratified by sex*

		All painters		Spray painters†		Construction painters		Manufacture painters†		Repair painters†		Other painters‡
Work as a painter	**Cases**	**OR (95% CI)***	**Cases**	**OR (95% CI)***	**Cases**	**OR (95% CI)***	**Cases**	**OR (95% CI)***	**Cases**	**OR (95% CI)***	**Cases**	**OR (95% CI)***
Men												
Never	14 959	1	14 959	1	14 959	1	14 959	1	14 959	1	14 959	1
Ever	649	1.30 (1.13 to 1.50)	56	1.27 (0.80 to 2.02)	445	1.31 (1.11 to 1.55)	194	1.21 (0.94 to 1.55)	64	1.38 (0.87 to 2.20)	26	1.16 (0.60 to 2.24)
Duration of employment (years)												
1–5	192	1.19 (0.93 to 1.52)	29	1.80 (0.91 to 3.58)	114	1.18 (0.87 to 1.60)	88	1.47 (1.00 to 2.14)	27	1.29 (0.62 to 2.69)	10	0.73 (0.28 to 1.91)
6–17	171	1.38 (1.05 to 1.81)	14	1.21 (0.51 to 2.88)	126	1.52 (1.10 to 2.09)	53	1.10 (0.70 to 1.71)	14	2.21 (0.80 to 6.08)	7	1.71 (0.51 to 5.81)
>17	280	1.42 (1.14 to 1.77)	12	0.74 (0.29 to 1.88)	203	1.57 (1.22 to 2.02)	50	1.11 (0.69 to 1.77)	22	1.60 (0.74 to 3.47)	7	2.14 (0.45 to 10.08)
Test for trend, p value		<0.001		0.7		<0.001		0.23		0.06		0.32
Women												
Never	3 726	1	3 726	1	3 726	1	3 726	1	3 726	1	3 726	1
Ever	35	1.05 (0.51 to 2.14)	12	0.94 (0.30 to 2.99)	12	2.10 (0.57 to 7.79)	20	0.72 (0.30 to 1.73)	3	1.37 (0.10 to 19.36)	1	–
Men and women												
Never	18 685	1	18 685	1	18 685	1	18 685	1	18 685	1	18 685	1
Ever	684	1.29 (1.12 to 1.48)	68	1.20 (0.78 to 1.85)	457	1.32 (1.12 to 1.56)	214	1.16 (0.91 to 1.47)	67	1.37 (0.86 to 2.16)	27	1.19 (0.62 to 2.28)
Duration of employment (years)												
1–5	213	1.18 (0.93 to 1.50)	37	1.51 (0.81 to 2.83)	122	1.15 (0.85 to 1.57)	100	1.35 (0.94 to 1.95)	28	1.26 (0.61 to 2.58)	11	0.77 (0.30 to 1.98)
6–17	179	1.33 (1.02 to 1.73)	16	1.02 (0.45 to 2.31)	128	1.39 (1.01 to 1.91)	58	1.05 (0.67 to 1.62)	15	2.02 (0.74 to 5.51)	7	1.69 (0.50 to 5.75)
>17	286	1.44 (1.16 to 1.79)	14	0.83 (0.34 to 2.02)	205	1.48 (1.15 to 1.91)	53	1.14 (0.71 to 1.84)	23	1.36 (0.62 to 2.99)	7	2.13 (0.45 to 10.03)
Test for trend, p value		,l0.001		0.85		<0.001		0.29		0.14		0.32

*Adjusted for age, study, pack-years, time since quitting smoking, occupational exposures (list A and B jobs), sex (only for analysis of men and women combined)
†There is some overlap between manufacture, spray and repair painters
‡Painters who were not categorised as a construction, manufacture, spray or repair painter, as indicated by the combination of ISCO and ISIC codes listed in online supplemental table 1
ISCO, International Standard Classification of Occupations; ISIC, **International Standard Industrial Classification** of All Economic Activities.

Table 4 Risk of lung cancer in painters, stratified by histological subtype

Work as painter	SqC Cases n=6414	SqC OR (95% CI)*	SCLC Cases n=2426	SCLC OR (95% CI)*	AC Cases n=4014	AC OR (95% CI)*	LCC Cases n=667	LCC OR (95% CI)*
Men								
Never	6 139	1	2 322	1	3 854	1	637	1
Ever	275	1.38 (1.16 to 1.64)	104	1.4 (1.09 to 1.78)	160	1.23 (1.00 to 1.51)	30	1.22 (0.80 to 1.86)
Duration employment (years)								
1–5	83	1.28 (0.93 to 1.72)	29	1.2 (0.77 to 1.87)	45	1.02 (0.70 to 1.48)	14	1.53 (0.81 to 2.91)
6–17	79	1.52 (1.09 to 2.12)	27	1.52 (0.95 to 2.42)	40	1.29 (0.86 to 1.94)	6	0.99 (0.39 to 2.51)
>17	109	1.46 (1.11 to 1.92)	48	1.61 (1.12 to 2.31)	75	1.48 (1.09 to 2.03)	10	1.17 (0.58 to 2.37)
Test for trend, p value								
Men and Women								
Never	6 904	1	2 913	1	5 462	1	836	1
Ever	279	1.35 (1.14 to 1.61)	110	1.39 (1.09 to 1.76)	176	1.23 (1.01 to 1.51)	30	1.18 (0.77 to 1.80)
Duration employment (years)								
1–5	89	1.24 (0.92 to 1.67)	32	1.21 (0.79 to 1.86)	54	1.05 (0.74 to 1.49)	14	1.48 (0.78 to 2.82)
6–17	80	1.48 (1.07 to 2.04)	28	1.46 (0.92 to 2.31)	44	1.26 (0.85 to 1.87)	6	0.97 (0.38 to 2.45)
>17	109	1.47 (1.12 to 1.93)	50	1.65 (1.15 to 2.37)	78	1.53 (1.12 to 2.08)	10	1.17 (0.58 to 2.37)
Test for trend, p value		*<0.001*		*0.001*		*0.004*		*0.50*

*Adjusted for study, age, pack-years, time since quitting smoking, occupational exposures (list A and B jobs), sex (only for analysis of men and women combined).
AC, adenocarcinoma; LCC, large cell carcinoma; SCLC, small cell lung cancer; SqC, squamous cell carcinoma.

than one-third of the painters in our study were employed long term, minimising the impact of potential information bias (40% employed as a painter for >17 years, the highest employment duration category (range 1–57 years).

Recall bias can affect the measurement of confounders, resulting in reduced ability to control for confounding. Smoking data were collected through self-report and there was potential for misclassification. The ORs in men were higher for squamous cell and small cell carcinomas, the histological subtypes of lung cancer most strongly associated with smoking.[37] Residual confounding by tobacco smoking was possible, although less likely than in many other case-control studies due to the high quality of smoking data, as reflected by the very high ORs for smoking and lung cancer.[37] The adjustment for smoking, modelled by cumulative exposure (log cPY) and time since quitting may have been imperfect. Adjusting for cigarette smoking alone likely had a negligible impact on the results since few study participants smoked other types of tobacco. The number of cases among painters who never smoked were too few in the analyses of squamous cell and small cell carcinomas, precluding further interpretation. However, it is noteworthy that painters who never smoked experienced a statistically significant increased risk of lung cancer, for all histologies combined and for adenocarcinomas.

In summary, we observed an association between employment as painter and risk of lung cancer in our large international pooled study, which is in agreement with the IARC classification of 'occupational exposure as a painter' as being carcinogenic to humans. These results were robust to accounting for smoking behaviour as well as coemployment in industries or occupations with known or suspected lung cancer risk and are further supported by positive exposure-response trends. Our findings by type of painter may aid the identification of agents or exposure scenarios that contribute to the increased risk, which is necessary to develop evidence-based practices for reducing harmful workplace exposures. As several million people are employed as painters worldwide,[38] even a modest increase in lung cancer risk is notable for prevention efforts targeted to reducing harmful exposures.

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Table 5 Effect modification between smoking and employment as painter, stratified by sex and histological subtype

		All lung cancer			AC			SqC			SCLC		
Stratum	Controls	Cases	OR*	95% CI	Cases	OR*	95% CI	Cases	OR*	95% CI	Cases	OR*	95% CI
Men													
Never smoker and never painter	4666	459	1	Ref	240	1	Ref	69	1	Ref	25	1	Ref
Never smoker and ever painter	87	16	2.04	1.18 to 3.53	10	2.63	1.33 to 5.18	3	2.35	0.72 to 7.64	1	2.46	0.33 to 18.45
Ever smoker and never painter	13 360	14 483	11.5	10.40 to 12.73	3 607	6.08	5.29 to 6.98	6 063	28.44	22.37 to 36.17	2 294	31.34	21.08 to 46.58
Ever smoker and ever painter	416	631	16.48	14.05 to 19.33	149	8.02	6.34 to 10.14	271	41.86	31.47 to 55.69	103	47.14	30.01 to 74.05
P value for interaction on multiplicative scale			*0.21*			*0.06*			*0.44*			*0.63*	
Additive interaction: RERI			*3.93*	*1.55 to 6.30*		*0.31*	*−2.04 to 2.65*		*12.06*	*4.45 to 19.68*		*14.33*	*1.61 to 27.05*
AP			*24%*	*12.07 to 35.62*		*4%*	*−24.94 to 32.63*		*29%*	*15.75 to 41.89*		*30%*	*11.64 to 49.19*
Women													
Never smoker and never painter	3015	970	1	ref	580	1	ref	127	1	ref	62	1	ref
Never smoker and ever painter	12	9	1.58	0.64 to 3.88	5	1.54	0.52 to 4.54	1	1.34	0.17 to 10.66	0	–	–
Ever smoker and never painter	2099	2751	4.72	4.28 to 5.21	1 027	2.83	2.50 to 3.20	636	9.49	7.68 to 11.73	528	13.89	10.51 to 18.34
Ever smoker and ever painter	16	26	6.12	3.19 to 11.74	11	4.29	1.92 to 9.62	3	4.82	1.31 to 17.70	6	20.41	6.91 to 60.29
P value of interaction on multiplicative scale			*0.72*			*0.98*			*0.43*			*0.96*	
Men and Women													
Never smoker and never painter	7681	1429	1	ref	820	1	ref	196	1	ref	87	1	ref
Never smoker and ever painter	99	25	1.58	1.01 to 2.48	15	1.91	1.09 to 3.35	4	1.51	0.55 to 4.15	1	1.24	0.17 to 9.03
Ever smoker and never painter	15 459	17 234	7.24	6.78 to 7.73	4 634	3.9	3.58 to 4.25	6 699	15.98	13.78 to 18.52	2 822	18.48	14.85 to 23.02
Ever smoker and ever painter	432	657	10.61	9.23 to 12.20	160	5.34	4.35 to 6.56	274	23.49	18.97 to 29.09	109	28.4	20.89 to 38.62
P value of interaction on multiplicative scale			*0.75*			*0.27*			*0.96*			*0.83*	
Additive interaction: RERI			*2.79*	*1.29 to 4.30*		*0.53*	*−0.93 to 2.00*		*7.01*	*2.92 to 11.09*		*9.68*	*2.74 to 16.62*
AP			*26 %*	*14.96 to 37.70*		*10%*	*−16.24 to 36.20*		*30 %*	*17.00 to 42.65*		*34 %*	*17.19 to 51.00*

*Adjusted for centre, age, occupational exposures (list A and B jobs). Models were also adjusted for sex in analyses of men and women combined.

AC, adenocarcinoma; AP, attributable proportion due to interaction; RERI, relative excess risk due to interaction; SCLC, small cell lung cancer; SqC, squamous cell carcinoma.

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