**Lung Cancer Risk in Painters: Results from the SYNERGY pooled case-control study consortium**

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1. 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, in part due to an increased risk of lung cancer in epidemiologic studies. Most of the published studies reported on ever employment as a painter; few presented detailed analyses by type of painter, duration of employment, histologic subtype of lung cancer or adjustment for exposure to other occupational lung carcinogens.

1. What are the new findings?

This pooled analysis of 19369 cases and 23674 controls is the largest study to confirm the increased risk of lung cancer in painters. The highest risks were observed for painters working in construction and repair and the small cell, and squamous cell histologic subtypes. The analyses accounted for detailed individual smoking and occupational histories, a proxy for exposure to lung carcinogens.

1. 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. 

**ABSTRACT (216 words)**

**Objectives** We evaluated the risk of lung cancer associated with ever working as a painter, duration of employment, and type of painter by histologic 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 19369 lung cancer cases (684 ever employed as painters) and 23674 age- and sex-matched controls (532 painters). Multivariable unconditional logistic regression models were adjusted for age, centre, tobacco pack-years, time-since-smoking cessation, lifetime work in jobs that entailed exposure to lung carcinogens and sex.

**Results** Ever having worked as a painter was associated with an increased risk of lung cancer in men (OR =1.30; 95% CI, 1.13-1.50). The association was strongest for construction and repair painters and the risk was elevated for all histological subtypes, although more expressed for small cell and squamous cell lung cancer than for adenocarcinoma and large cell carcinoma. There was evidence of interaction between smoking and employment as a painter on the additive scale (Relative Excess Risk due to Interaction (RERI) > 0) but not on the multiplicative scale.

**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.

**Keywords:** Lung Neoplasms, Paint, Occupational exposures, Cigarette Smoking, Epidemiologic Effect Modifiers

**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 20181. Approximately 70% of the lung cancer burden can be attributed to smoking alone2 3; however ‘occupational exposure as a painter’ has also been classified as an independent risk factor4 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, histologic subtype of lung cancer or adjustment for exposure to other occupational lung carcinogens. Painters are exposed to many known and suspected lung carcinogens, such as silica, asbestos, talc containing asbestos fibers, chromium VI compounds, and cadmium compounds4 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 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**

**Studies**

This manuscript is formatted according to the STROBE statement for reporting case-control studies6.

Data for the SYNERGY project were pooled from 16 population- or hospital-based case–control studies of lung cancer from Europe, Canada, China, and New Zealand conducted between 1985-2010; 15 of these studies collected lifetime tobacco smoking and occupational histories. The IARC multicentre INCO study was comprised of seven study centres. The SYNERGY project has been described previously7. Six of the 16 studies previously published results on lung cancer in painters: AUT8, HdA9 10, INCO11, TURIN/VENETO and ROME12, MONTREAL13.

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 year14; 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 occupational history until diagnosis or recruitment. MORGEN is a case–control study nested in the European Prospective Investigation into Cancer and Nutrition (EPIC) 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)15. 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 DGUV (IPA), and the Institute for Risk Assessment Sciences (IRAS) at Utrecht University. More information is available at <http://synergy.iarc.fr>.

**Exposure Assessment**

Painters were categorized into 'type of painter' by two industrial hygienists (HK, RV), based on their 5-digit ISCO and 4-digit ISIC codes (ISCO 9-3X.XX), as described in Supplemental Table 1. 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 as a painter. 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, odds ratios (ORs) and 95% confidence intervals (CIs) were computed using unconditional logistic regression models. Two exposure metrics were considered: ever vs never being a painter, and the duration of employment as painters (years). Subjects who were never employed as painters were considered as the reference category in analysis. Duration of employment was categorized into tertiles based on the duration distribution among control subjects that had worked as painters. Models were adjusted for study (individual centers of the IARC study in Central and Eastern Europe and the United Kingdom (INCO) were treated as separate studies), age, cigarette pack-years (cPY), time-since-quitting smoking cigarettes (categorized 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 cancer16. Painters were excluded from List A for this analysis. Current smokers were defined as having smoked at least one cigarette per day for 1 or more years, and also included those who had stopped smoking in the last 2 years before diagnosis or interview. Cigarette pack-year was calculated as follows: Σ duration (years) X average cigarette smoking intensity per day/20 (cigarettes per pack) and was included as log(1 + cPY) in order to approximate log-normal distribution in the logistic regression models.

Analyses were performed both overall and separately by sex to account for potential sex differences in job tasks and subsequent exposures. 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, overall and among painters only. In female painters the analysis by duration of employment, and by histological subtype, was dropped because there were too few exposed cases.

Interactions on the multiplicative scale between the occupational exposure as a painter (never painter, ever painter) and smoking status (never smoker, ever smoker) were tested in unconditional logistic regression models. Additive interactions were also assessed by fitting linear odds ratio models and calculating the relative excess risk due to interaction (RERI), in order to test the departure from additivity of the effects of both exposures (painter and smoking status)17. Linear odds ratio 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 reported18 19 . Never smokers and never painters were considered as the reference category. RERI-based analyses in females were not performed where too few double exposed cases were observed. A RERI greater than 0 in this analysis indicated that public health consequences of an intervention on occupational exposure as a painter would be larger among ever smokers than among never smokers. We also reported the attributable proportion (AP), based on the RERI, which measures the proportion of the cancer risk due to the additive interaction in the group of ever smokers and ever painters. The AP can range from negative to positive values.

Prior to pooling the data, random effects meta-analyses were conducted using the STATA “metan” command (Supplemental Figure 1) in order to 1) compute summary estimates with their respective 95% CIs comparing ‘ever’ with ‘never’ being a painter across studies and 2) to explore heterogeneity between studies, expressed as a percentage (I2). The I2 statistic quantifies the amount of inconsistency between studies20 and estimates the percentage of total variation across studies that is due to heterogeneity rather than chance. I2 ranges from 0% and 100% and 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 weighting21.

Various sensitivity analyses were conducted to investigate which factors contribute to heterogeneity in the summary estimate (sample size of the study, age, design and geographical region) (Supplemental Table 2). Sensitivity analyses were also conducted to assess the robustness of the overall risk estimate by dropping individual studies one at a time.

 Analyses were performed using SAS version 9.3 (Cary, NC), STATA (version 11.0) and R statistical software (version 3.4.1). P-values are two-sided and the significance level was set to 0.05.

**RESULTS**

Table 1 describes selected characteristics of participants in the SYNERGY pooled analysis. Roughly 80% of cases and controls were men and about two thirds were aged > 60 years. As expected, a higher proportion of controls were never smokers (33% controls vs. 8% cases) whereas a higher proportion of cases were current smokers (28% controls vs. 61% cases).

[CITE TABLE 1 HERE]

Table 2 describes the 16 studies included in the SYNERGY pooled analysis and the study-specific association between ever worked as painter and lung cancer. A total of 19 369 cases (684 employed as painter) and 23 674 controls (532 painters) were included in the analysis. Case and control participation ranged from 53-98% and 41-100%, respectively.

[CITE TABLE 2 HERE]

The meta-analysis and additional sensitivity analyses that were conducted prior to pooling the data show no to low/moderate heterogeneity (*I*2 <50%) by various strata (e.g, control source, region, sample size, and the ending date of data collection) (Supplemental Table 2, Supplemental Figure 1). Omitting studies one at a time had no effect on the overall meta-OR (meta-OR, 1.26; 95% CI, 1.09-1.44; *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).

Painters were categorized by industry according to ISCO and ISIC codes before conducting analyses (Supplemental Table 1). 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, 1.13-1.50; 649 exposed cases). When stratified by type of painter, the highest risk was observed for construction (OR in men = 1.31; 95% CI, 1.11-1.55) and repair painters (OR in men = 1.38; 95% CI, 0.87-2.20). Similar patterns were observed for women – albeit on much smaller numbers - and also in the analyses of men and women combined. An exposure-response trend with years of employment was observed among all subjects (p-value =<0.0002) but not among those who worked as painters (p-value > 0.05).

[CITE TABLE 3 HERE]

Table 4 shows that the results were comparable across histological subtypes: squamous cell carcinoma (OR in men = 1.38; 95% CI, 1.16-1.64), small cell lung cancer (OR in men = 1.40; 95% CI, 1.09-1.78), adenocarcinoma (OR in men = 1.23; 95% CI, 1.00-1.51), and large cell carcinoma (OR in men = 1.22; 95% CI, 0.80-1.86). 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-value for trend < 0.05) but not when excluding never painters (p-value for trend > 0.05) for small cell lung cancer, squamous cell carcinoma, and adenocarcinoma. 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.

[CITE TABLE 4 HERE]

Joint effects of smoking status and ever/never employment as a painter on lung cancer risk are presented overall and by lung cancer subtype for men and also for men and women combined in Table 5. Among never smokers who had ever worked as a painter, the highest risk of lung cancer was found for adenocarcinoma. Results for other histological subtypes were not informative due to the small number of painters who never smoked (n < 5). Compared to 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, 14.05-19.33). There was evidence of interaction on the additive scale (RERI >0) but not on the multiplicative scale (all p-values > 0.05) for overall lung cancer in men. The RERI for additive interaction for lung cancer risks for men was 3.93 (95%CI, 1.55-6.30); 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, 12.07-35.62). While similar patterns were observed in analyses for men and women combined, there was no evidence of additive interactions for women.

[CITE TABLE 5 HERE]

**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 lifelong employment histories (a proxy for exposure to occupational lung carcinogens). Our results are in line with several other publications that have previously reported increased relative risks for lung cancer among painters after adjustment for smoking4. 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, 1.12-1.48) and in a meta-analysis (RR, 1.35; 95% CI, 1.21-1.51)22 which included four of the sixteen studies from the present pooled analysis8 9 12 23. The association was strongest for construction and repair painters and the risk was elevated for all histological subtypes, although more expressed for small cell and squamous cell lung cancer than for adenocarcinoma and large cell carcinoma. 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. We believe our results are generalizable to other populations not studied in this pooling project because our data come from 16 studies conducted internationally in China, New Zealand, Canada, and across Europe.

We carefully interpreted these results in the context of exposure misclassification, information bias, selection bias, and potential for confounding. The use of job titles in SYNERGY allowed us to classify workers according to job history. While occupation as a painter is a clear cut job title (reducing the potential for exposure misclassification), not all painters have the same exposures, not even within sub-categories, and this is even more an issue when the lung cancer excess may be the result of a mix of various carcinogenic exposures. Construction and spray painters may be exposed to several established lung carcinogens, including asbestos, cadmium, chromium, respirable crystalline silica and polycyclic aromatic hydrocarbons (PAH) which could explain their higher risks of lung cancer compared to other types of painters. There was, however, low precision for some of the analyses by specific painter type, which was mostly due to small numbers in some strata. These limitations create challenges to identifying specific causative agents. Future epidemiologic 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.

There is the potential for selection bias, in that the selection of controls may not be representative of the underlying source population from which the cases arose. Although several of the studies used hospital-based controls, most of these studies enrolled only patients with diseases that were not related to smoking and were careful in including several diagnostic groups with a varied referral pattern, as noted previously24. There was relatively low participation among population-based controls; however this was true for only a few studies included in the pooled analysis. 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 bias25 26. Notably, the observed associations were lower in the hospital-based case-control studies.

Information bias, particularly recall bias, can be a concern in case-control studies. We consider the impact of recall bias has been at most moderate in SYNERGY because there was no emphasis placed on any particular occupation and the general population is not necessarily aware that painters are at an increased risk for lung cancer. Furthermore, 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 generally good and usually not an important source of recall bias27-29. More than a third of the painters in our study were employed long-term, minimizing the impact of information bias (40% employed as a painter for >17 years, the highest employment duration category. Range, 1-57 years). We acknowledge that 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. Residual confounding by tobacco smoking was also possible. The ORs in men were higher for squamous cell and small cell carcinomas, the histologic subtypes of lung cancer most strongly associated with smoking30.The adjustment for smoking, modelled by cumulative exposure (cigarette pack-years) 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. The positive monotonic trend in the risks by length of employment (for all painters and construction painters) and the increased risk of lung cancer in painters who never smoked, lends support to the hypothesis that the lung cancer excess in painters is in fact due to workplace exposure to carcinogenic substances.

 In summary, we observed an association between employment as painter and risk of lung cancer in our large international pooled study. These results were robust to accounting for smoking behaviour as well as lifetime employment in industries or occupations with known or suspected lung cancer risk. Exposure-response relationships were also observed, lending further support to the observation that the lung cancer excess in painters is due to their workplace exposures to carcinogenic substances. Our findings, which are in agreement with the IARC classification of ‘occupational exposure as a painter’ as a human carcinogen, may aid the identification of the agents that contribute to this increased risk. Identification of the contribution by different causative agents or exposure scenarios is necessary to develop evidence-based practices for reducing harmful exposures in painters. As several million people are employed as painters worldwide31, even a modest increase in lung cancer risk is notable for prevention efforts targeted to reducing harmful exposures in painters.



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