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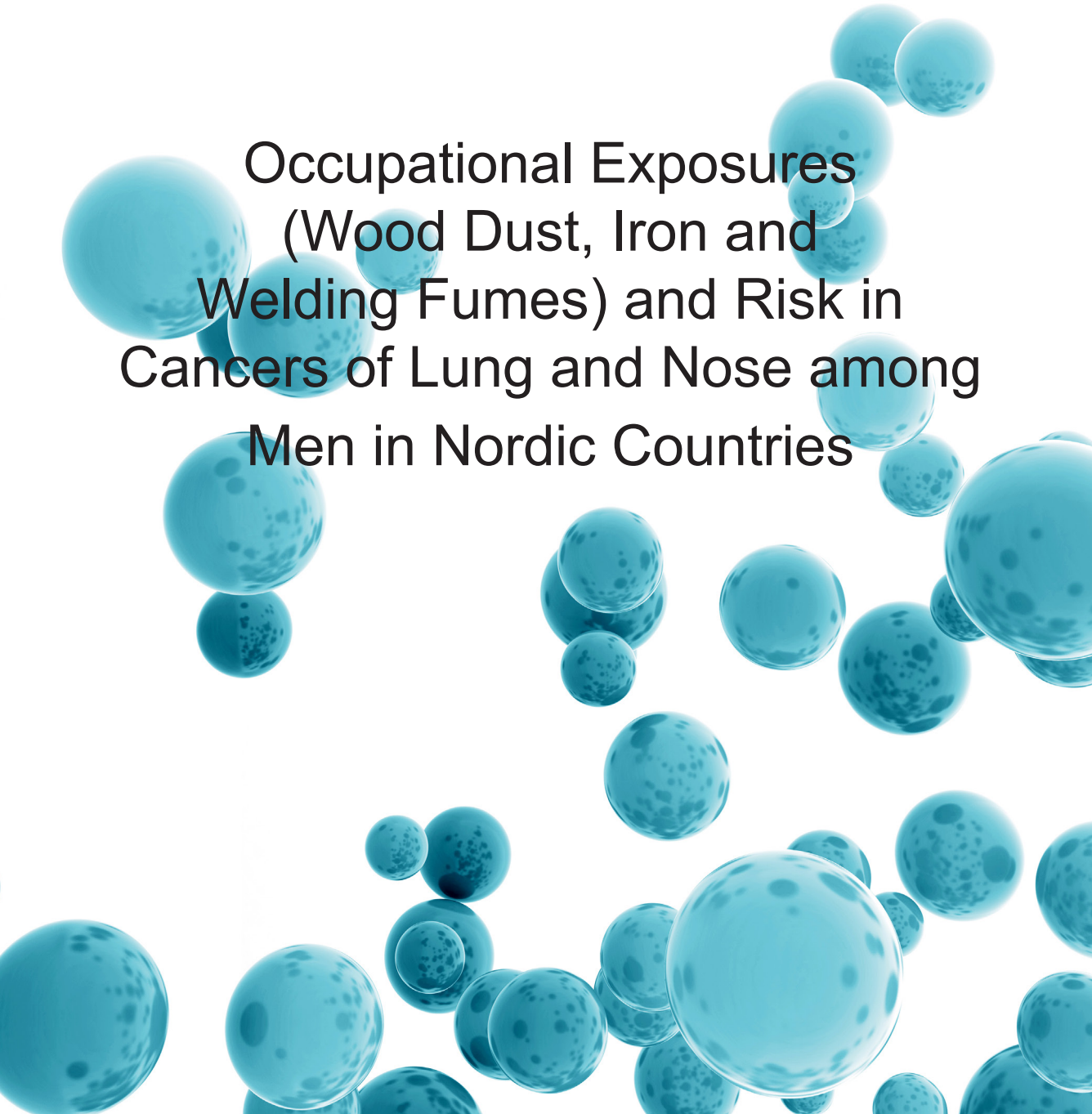
SIE SIE SIEW

Occupational Exposures (Wood Dust, Iron and Welding Fumes) and Risk in Cancers of Lung and Nose among Men in Nordic Countries



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■

ACADEMIC DISSERTATION
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UNIVERSITY OF TAMPERE

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This book (dissertation) is specifically/ independently written and dedicated to the workers for improvement of health in international scale, with resolutions that bring research into best practices in the "real world".

Helsinki, March 27, 2018

Sie Sie Siew

ABSTRACT

National cancer registry and population censuses that accumulate nationwide data are useful tools to facilitate large scale historical occupational studies on epidemiology of cancer. The current registry-based study was conducted with a record linkage between cancer registries and employment history from census record, started through registration systems in Finland, and later extended to three other Nordic countries (Iceland, Norway, and Sweden).

The aim of the study was to explore associations between selected occupational exposures and the targeted cancer sites in the entire national workforce recorded in censuses. Occupational exposures were estimated from occupational titles obtained from the censuses. Quantitative job exposure estimates were estimated according to the Finnish national job exposure matrix (FINJEM) or the Nordic Occupational Cancer Study job exposure matrix (NOCCAJEM). The job exposure matrix translates information on occupational title (employment history) to quantitative estimates of specific work-related exposures. FINJEM or NOCCAJEM cover more than 300 specific job titles, tens of exposure agents, and four exposure periods: 1945–59, 1960–74, 1975–84, to 1985–94.

The Nordic study cohort consists of all male workers who had participated in the censuses 1970–1990 in Finland, 1960–1980 in Norway, 1960–1990 in Sweden, and 1981 in Iceland. Three other papers specifically included the Finnish part of cohort i.e. the cohort in Finland only. The range of population covered was 1.2 million (Paper 1^{Fe} & Paper 2^{Fe}), 1.7 million (Paper 3^{Wood}) in Finland, and 14.9 million in four Nordic countries (Paper $4^{NordWood}$). The census files are maintained by national statistics offices, who also take care of updates of death and emigration information, and hence, it enabled the current study to derive person-years calculation after the first available census data for the entire workforce, according to the occupation held in censuses. The occupations of each individual worker were converted to exposure to iron and welding fumes (Paper 1^{Fe} & Paper 2^{Fe}), wood dust (Paper 3^{Wood} & Paper $4^{NordWood}$), and the relevant co-exposures. This conversion of occupational information in JEM is helpful to further characterize exposure, using a formula that defines **cumulative exposure** (CE) for each occupational group as a product of the proportion of exposed person (P), mean level of the exposure (L among the exposed workers in each occupation) and the estimated duration of the exposure.

Cancer cases in this thesis were diagnosed in 1971–1995 (Paper 1^{Fe} & Paper 3^{Wood}), 1961–2005 (Paper $4^{NordWood}$) and 1971–2005 (Paper 2^{Fe}) after the first available census. Altogether 30,137 incidence cases of primary lung cancer in Paper 1^{Fe} and 44,492 cases in

Paper 2[Fe] were obtained from the Finnish Cancer Registry. The numbers of men diagnosed with primary nasal cancer and nasopharyngeal cancer were 292 and 149 in Finland (Paper 3[Wood]), and 2839 and 1747 when combining with three other Nordic countries (Paper 4[NordWood]).

For each occupation with exposure to 'iron and welding fumes' in Paper 1[Fe], standardized incidence ratios (SIRs) of lung cancer were calculated (i.e. ratio of observed to expected number of cases). SIRs for nasal cancer, nasopharyngeal cancer and lung cancer were calculated in occupations with exposure to wood dust or formaldehyde in Paper 3[Wood]. For both papers, relative risks (RRs) of each cancer were calculated by comparing three categories of cumulative exposures (CEs) with the unexposed category using Poisson regression models and with an adjustment for confounding factors.

Papers 2[Fe] and 4[NordWood] applied a case-control study design setting. Hazard ratios (HRs) were calculated based on individual-level data derived from occupational history recorded in all available census data in conditional logistic regression models. Work-related co-exposures (e.g. asbestos and silica) and confounding factors (socio-economic status, SES, and smoking) were adjusted whenever available.

The results demonstrated that in comparison to the unexposed, workers most heavily exposed to iron/welding fumes had 40% more lung cancer risk, when asbestos and silica were controlled, without adjustment for SES and smoking. When these two non-occupational risk factors were also controlled, the RR decreased but remained >1 in all CE categories. One novel finding was the detection of an association between one histological subtype of lung cancer, squamous-cell lung carcinoma, and exposure to iron fume and dust (2-fold risk) as well as to welding fumes (55% excess).

Independent roles between CE to iron and welding fumes could not be properly distinguished due to high correlation of both exposures in same individuals. Co-exposure to asbestos contributed up to 40% greater lung cancer risk at the heaviest asbestos exposure level (>13.23 fibers/cm^3-years). Risk attributable to co-exposure to silica was small.

In general, Finnish workers exposed to the greatest level of wood dust had 60% more risk to develop nasal cancer as compared to non-exposed workers (Paper 3[Wood]). Elevated risks at all CE levels were above RR 2.0 in the study extended to workers in four Nordic countries (Paper 4[NordWood]). Drastic excess from adenocarcinoma histological subtype appears to dominate the risk. The most heavily exposed workers (CE ≥ 28.82 mg/m^3-years) has a 29-fold risk of nasal adenocarcinoma. Experiencing light wood dust exposure (≤ 6.70 mg/m^3-years) led to a three-fold risk even after formaldehyde exposure was controlled in the model.

The study managed to involve the exposed workers beyond the basic wood-processing industries (e.g. furniture and sawmill) i.e. to a broader industrial landscape relevant to wood-processing sectors, including construction, lumber, forestry, boatbuilding, etc. Likewise, to explore the exposure to iron (dust and fume) and welding fumes, a wider range of occupations beyond the boundary of the traditionally presumed high-risk ironworkers (e.g.

in iron and steel mining, smelting, and foundry) have been taken into consideration. As a result, the study covered the workers in indirect/secondary iron and steel industries ranging from building, construction, transportation, utility, to manufacturing, maintenance, repairing, and assembly.

In this study, the findings with wood dust exposure confirmed the risks in nasal cancer, which is in line with the increased risks detected by the previous studies, but no association with nasopharyngeal cancer. Weak but persistent lung cancer risk was observed in all levels of exposure to iron and welding fumes. Detection of risks were noticeable already at the lowest CE level when regulatory limits were applied, which rises the concern relating to adequacy of existing occupational exposure standards or recommended guidelines.

This study provides reasonable confidence in results due to the strengths and quality in size, reliability of nationwide registered cancer data, and at least partial adjustment for exposures contributed from both work-related and non-work-related confounding factors.

Assigning numerical exposure estimates to workers in the absence of personal monitoring data is challenging. Large-scale record linkage is a considerably efficient solution as it can generate a tremendous volume of nationwide and even multinational data on decade-long work history. This method, with the aid of national JEMs, has repeatedly proven its usefulness to reconstruct quantitative historical workplaces exposure database for nationwide workforce that are needed in large-scale epidemiological studies.

ABBREVIATIONS

CE	Cumulative Exposure
CI	Confidence Interval
FCR	Finnish Cancer Registry
FINJEM	Finnish Job Exposure Matrix
FIOH	Finnish Institute of Occupational Health
HR	Hazard Ratio
IARC	International Agency for Research on Cancer
JEM	Job Exposure Matrix
OEL	Occupational Exposure Limit
PEL	Permissible Exposure Limit
L	Level of Average Exposure among the Exposed Persons
NOCCA	Nordic Occupational Cancer Study
NOCCAJEM	Nordic Occupational Cancer Study Job Exposure Matrix
P	Proportion of Exposed Persons
p	p-value indicating significance level
RR	Relative Risk
SIR	Standardized Incidence Ratio
ICD 10	International Classification of Diseases for Oncology 10

List of IARC Classifications of Carcinogenicity and Number of Agents in Each Group (as of January 26, 2018):

Group 1	Carcinogenic to humans	120 agents
Group 2A	Probably carcinogenic to humans	81
Group 2B	Possibly carcinogenic to humans	299
Group 3	Not classifiable as to its carcinogenicity to humans	502
Group 4	Probably not carcinogenic to humans	1

LIST OF PUBLICATIONS

This dissertation is composed of a summary and the following original publications, reproduced here by permission.

I Siew SS, Kauppinen T, Kyyrönen P, Heikkila P, Pukkala E. *Exposure to iron and welding fumes and the risk of lung cancer*. Scand J Work Environ Health. 2008;34(6):444-450. doi:10.5271/sjweh.1296. [Paper 1^{Fe}]

II Siew SS, Kyyrönen P, Pukkala E. Occupational exposure to iron and welding fumes and risk in lung cancer among Finnish men: a registry-based case-control study. (Submitted to Eur J Cancer). [Paper 2^{Fe}]

III Siew SS, Kauppinen T, Kyyrönen P, Heikkila P, Pukkala E. *Occupational exposure to wood dust and formaldehyde and risk of nasal, nasopharyngeal, and lung cancer among Finnish men*. Cancer Manag Res. 2012; 4: 223–232. doi: 10.2147/CMAR.S30684. [Paper 3^{Wood}]

IV Siew, S. S., Martinsen, J. I., Kjaerheim, K., Sparén, P., Tryggvadottir, L., Weiderpass, E. and Pukkala, E. (2017), *Occupational exposure to wood dust and risk of nasal and nasopharyngeal cancer: A case-control study among men in four nordic countries—With an emphasis on nasal adenocarcinoma*. Int. J. Cancer, 141: 2430–2436. doi:10.1002/ijc.31015. [Paper $4^{NordWood}$]

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1 INTRODUCTION

Occupational diseases are entirely or partly caused by hazardous exposures at work. If a substance or circumstance of exposure is carcinogenic, it may lead to occupational cancer. Occupational cancer epidemiology is therefore needed, it involves strategies and techniques in identification of specific carcinogenic exposure or work situation throughout generations of workforce to address exposure-disease relationship, taking into account the effects from relevant workplace co-exposures and latency period.

Since 1970, the International Agency of Research on Cancer (IARC) has classified at least 500 substances or exposure circumstances as carcinogenic based on sufficient evidence in human and/or experimental animals (Group 1 and 2A) and possibly carcinogenic to humans (Group 2B) within its exhaustive 120 volumes of monograph, where at least 168 of them (Siemiatycki et al., 2004) occur at work (IARC monographs http://monographs.iarc.fr/ENG/Classification/). Workplace exposures that have not demonstrated a definite risk or have not been evaluated do not infer a non-carcinogenic impact, rather often caused by barrier in adequate and justifiable evidence from epidemiological studies, in additional to scanty interpretable data to evaluate upon. Nearly half of all recognized human carcinogens were discovered from workplaces (Siemiatycki et al., 2004), and much of them are IARC-classified carcinogens. These exposures and occupations should be regarded as carcinogenic to humans on any occasion (Cogliano et al., 2011) or in any routine work, through direct or indirect course, at primary or secondary/contractors' workplaces. The final goal is to aid national agencies and industries develop effective regulations and guidelines, implementing improved preventive measures that can effectively safeguard workers' safety and health.

Nationwide data in European population have showed occurrence of carcinogenic exposure circumstances of workforce extensively across broad industrial sectors e.g. approximately 23% of the total employed (about 32 million workers) in Europe (EU 15) had experienced some exposure listed in CAREX 1990–1993 (Kauppinen et al., 2000). This estimate was the ever exposed workers at some point during the time when CAREX study was conducted, which implies that a much larger proportion has had the exposure. These carcinogenic occupational exposures are still widespread today, including wood dust, heavy metals, asbestos, and silica, expectedly at much severe condition in developing countries and thus putting more workforce at more serious work-induced respiratory cancer risk.

Occupational cancers are not always fatal, although occupational lung cancer and nasal cancer are two leading carcinomas attributable to a significant proportion of work-induced respiratory cancer, with the greatest level of terminal cases and often contributing to most

mortality. Work-related cancer generally contributed two times more deaths each year than work-related accidents i.e. three-quarter-millions of occupational deaths (Takala, 2015). In Europe (EU28) the estimated total work-related cancer deaths is over one hundred thousand, about twenty times far exceeding the number of deaths from work-related accidents.

When a substance or agent of exposure is (i) an abundant natural resource [e.g. iron, wood, and asbestos], (ii) commercially important, (iii) pervasive/widespread at workplaces in global landscape, and (iv) associated with frequently diagnosed fatal cancer – high incidence rate, that can contribute to (v) an increased disease rate or death rate, then, the implication of such an exposure becomes cumbersome, adding weight to global burden of occupational cancer, even before the epidemiological evidence can be perfectly confirmed. The de facto is that: a perfect study is likely to be non-existent, or extremely rare if found, ever since anecdotal discovery from Sir Percivall Pott (Pott, 1775); when implementing primary preventive strategies, low exposure to a substance could practically be regarded as unsafe in the presence of another co-carcinogen (Tomatis et al., 2001). Risk can exist before human effects at specific levels of exposure are fully confirmed (Tomatis et al., 2001; Tomatis et al., 1997).

Occupational cancers are mostly caused by man-made circumstances in workplaces and therefore humanly solve-able, preventable, and eliminable. Even if the number of affected workers is small for specific exposures (e.g. in case the woodworkers' nasal adenocarcinoma), the preventive measures should be in fact much easier to handle with such a marginal magnitude from the entire workforce. Control measures are often feasible to be drawn up for implementation after identification of exposure occurrence at work. Estimating the risk of specific exposures in the workforce is a strategic approach to primary prevention of occupational cancer. The departure point of this current research that keeps the author motivated is – "to bring research into practice" and to protect workers' safety and health at a global level, where/when these exposures still exist.

Economic impact of these occupational cancers adds weight to the burden of occupational cancer. In 2007, occupational cancer contributed to 23% of all work-related medical cost for death, the direct cost was about eight billion, one third of it was caused by lung cancer (Leigh et al., 2011). In 2010s, occupational cancer continues to be a greater problem than workplace injury that aggravates disability-adjusted life-years (DALY) and mortality with a radically accelerated rate, the estimates for occupational cancers have gone up radically in ten years (Takala et al., 2017).

Nearly all cost incurred (98%) was shared by individual workers. Hence, the British study reflected occupational cancer from their society as – largely due to 'human' costs – a monetary value on the effects of cancer on quality of life or both fatal and non-fatal cancers (£12.3 billion) of workers; in comparison, the employers bear a marginal negligible portion at £461 million (HSE, 2016). In other words, society had been responsible for about £12.3 billion caused by occupational cancer with more than half of it consumed on lung cancer

(£6.8 billion). In Canada, compensation for occupational cancer in 1996–2013 was $1.2 billion, approximately $68 million each year (Wranik et al., 2017). The currently available economical assessments are underestimated, because data on socioeconomic impact assessment for occupational cancer that adequately includes all real costs incurred does not exist (e.g. healthcare, diagnostic, treatment, productivity, loss of workability, quality of life, administrative, insurance, travel, costs associated with pain and suffering, pharmaceutical supplements or naturopathy intake, intangible personal care, nursing home, and loss of workdays or loss of jobs from the associated individuals and family members, etc.). Thus, the financial burden that occupational cancer contributes to is greater than generally assumed.

Occupational medicine/cancer should not be restricted to preventive medicine only, because the burden of disease is extended to clinical practice in diagnosing and treating affected workers when symptoms or problems (from the past exposure) arise later in life. Applying integrated knowledge of industrial hygiene and occupational cancer epidemiology is essential in the diagnosis of work-related conditions for workers (patients) across in all sectors. This should not be limited to developed countries, but should be a more emphasized standardized practice in developing countries. Lorenzo Tomatis addressed the concern in primary prevention of cancer "Occupational risks are becoming a serious problem in developing countries, largely as a consequence of mitigating hazardous industries from industrialized countries where certain industries are judged to be unacceptable" (Tomatis, 1997). Occupational cancer and its consequences (economical, DALYs, job loss, etc.) has not been alleviated nor solved, just mainly mitigated.

Assuming carcinogenic exposure at work is on the decrease with the progress in developed countries, having regulated workplaces and successfully mitigating all high-risk jobs/industries to developing countries (Hutchings et al., 2012), occupational cancer nevertheless, is a malignant disease that occurs due to the past exposure that can trace back to decade(s) – the impact can persist later with magnitude and geographical variation. Increasingly more occupational carcinogenic exposures were identified during the past 50 years, but not solved – because "we have merely succeeded in moving consumption [of carcinogens and banned exposures] to developing countries" (Pearce, 2007). The rise of occupational cancers is predictable in the area experiencing the exposure that the developed countries had passed several decades ago, if proper control measures are not strategically implemented. Eliminating occupational cancers is a meaningful aim, it means zero carcinogenic exposure (zero attributable fraction) and zero expense on occupational cancers, which lead to better quality of life, improved work, productivity, and sustainable work-life – an entirely different (positive) future prospect as compared to inaction.

1.1 Specific respiratory cancers in nationwide industries

The main purpose of the current research is to identify the associations between occupational inhalable/respirable exposures and cancers: the most common respiratory

cancer (of the lung) and two of the least common (of the nasopharynx and nasal, including nasal adenocarcinoma histology) among nationwide male workers from all industries.

Shortage of epidemiological data was the main motivation to initiate and complete this research: occupational exposure to iron and welding fumes have been studied in the past 50 years, but the carcinogenicity of iron in relation to lung cancer remains unclear and not yet separately evaluated (by IARC). Wood-processing is a globally important industry, but there is a lack of epidemiological data that can help conclude on the role of exposure to softwood-dominated mixed wood dust in the aetiology of nasal cancers.

1.1.1 Lung cancer

For more than half a century, **lung cancer** (International Classification of Diseases for Oncology 10, ICD 10, C33–C34) has consecutively to be the leading cancer site (in 2012 alone, 1.8 million cases), 2–5 times more common in developing countries, and the leading cause of cancer death (>88.3% mortality rate) among seven billion global population (Torre et al., 2012). These 1.8 million lung cancer deaths in the world would mean 357,000 deaths at work, out of the total 747,000 occupational cancer deaths, excluding (in the absence of data on) exposure to iron and welding iron (GBD, 2016). As compared to 2012, the number of new lung cases is estimated to double by 2030 for men aged ≥ 65 and with a 50% increased for men aged younger than 65 (GLOBOCAN, 2012). Occupational air-borne carcinogens are estimated to have co-contributed to 21.1% (95% CI 19.2–24.7) for lung cancer and twice more for nasal cancer 46% (27.3–74.0) (Rushton et al., 2010). When taking into account for a total of 3.3 billion global workforce, the marginal magnitude of high-risk workers is considerably amplified to tens of thousands. Among which, welding deserves a reasonable concern, considering that 1–4% (Kauppinen et al., 1998; IARC, 2014) of the workforce perform this task and experience exposure to welding fumes, primarily centralized in industrialized countries. National Institute of Occupational Safety and Health (NIOSH) and Centers for Disease Control and Prevention (CDC) confirmed that partial roles of smoking or asbestos incurred at work are irrelevant to welders' lung cancer risk (CDC/NIOSH, 1998). Hence, having this proportion of exposed workers would mean having a large number of high-risk workers that could develop occupation-induced lung cancer.

In Finland, 443 lung cancer cases were registered between 1971–2005 for occupation as a welder, which means that welders have a 17% elevated risk to develop lung cancer as compared to the average population (Pukkala et al., 2009). IARC has nominated welding fumes as the candidate with high priority for re-evaluation (IARC, 2014), before re-classifying welding and UV radiation from welding as (Group 1) carcinogens for humans in 2017 (Guha et al., 2017). However, occupational exposure to iron and welding fumes in relation to lung cancer has not been evaluated by IARC. Data on average proportion of iron in welding fumes derived from direct workplace measurement are rare. The data evaluated by IARC was based on iron being mentioned as the main constituent of welding

fumes (the greatest level was 55% in mild steel metal inert gas welding, compared to manual metal arc mild steel welding, with up to 32%) (IARC, 1990). The main source of the fume is from the consumables (i.e. electrode or wire), not the work piece, excluding exceptional conditions such as surface coating. Composition of wire used that creates welding fume is almost entirely iron in mild steel welding, ranging from 92–98% (Jenkins et al., 2005). Stainless steel welding and 'iron and steel' industry increase the risk of lung cancer due to high levels of exposure to nickel and chromium VI (IARC 100F 2012; Weiss et al., 2013). Whether exposure to mild steel or stainless steel could lead to higher lung cancer risk is unclear (Moulin, 1997; Ambroise et al., 2006). What distinguishes mild steel welding from stainless steel welding are its richer iron content, none-to-low levels of nickel and chromium content, and its generation of more respirable particles because of high-emission techniques (Lehnert et al., 2012; NIOSH 1998). In epidemiological studies related to 'iron and steel industries' and welding fumes, iron is constantly neglected, the attention being focused on nickel, chromium, and other known lung carcinogens.

Evaluating exposure to welding fumes is complex, the nature of the fumes (composition and quantity) are largely dependent on the electrodes used, process or technique applied, type of alloy, and ventilation at workplaces. Because the primary composition of welding fumes generated from most welding is iron, the feasible solution is to study substance-specific exposure and risk of substance-induced disease.

National analyses on occupational lung cancer risk in Nordic countries have repeatedly showed excess incidence in ironworkers and welders (Andersen et al., 1999; Pukkala et al., 2009). This cohort consists of half-million employed workers in the entire Nordic workforce distributed in a wide range of ironwork, including smelters, metalware workers, mechanics, plumbers, etc. who had experienced concurrent occupational exposures to iron and welding fumes (Table 1 in Paper 1). To identify whether ironworkers and welders have an elevated risk to occupational induced lung cancer, the current research was conducted to explore the substance-specific exposure-disease relationship (considering other co-exposures ordinarily present) among the entire national workforce in the Nordic countries.

1.1.2 Nasal cancer

Nasal cancer (ICD 10, C30–C31) is extremely rare in general population (<1.5 per 100,000 in men). It is a known occupational cancer among woodworkers (IARC, 1995), about one fifth of nasal cancer (mainly nasal adenocarcinoma) patients were woodworkers (Mohtashamipur et al., 1989). The attributable fraction of occupational nasal cancer is at the high-side with wood dust exposure (43.4%) and number of years of life lost per individual case is 16.4 in a recent British ranking, slightly more than that of lung cancer (13.2%) (Hutchings et al., 2012). Cancers of the nasal cavity appear to be among the most complicated tumours with large histological variation (Barnes et al., 2005). Contrary to the earlier studies, it is not exclusively restricted within carpentry or hardwood

processing industries, softwood dust has also been associated to this site (IARC, 1981). The characteristic of exposure to wood dust in workplaces is diverse, mixed wood with undistinguishable proportion of wood types is used in wood-processing industries.

1.1.3 Nasopharyngeal cancer

Nasopharyngeal cancer (ICD 10, C11) is a very rare cancer type, with an incident rate of 1 per 100,000 in European countries. Exposure to wood dust and formaldehyde were suggested as possible risk factors in occupational scenarios (IARC, 1981). Occupational attributable fraction for this site is 11%, with almost all cases had experienced exposure to wood dust (Rushton et al., 2010); however, the wood worker in five Nordic countries had not experienced an elevated risk in this site (Pukkala et al., 2009). The results reviewed by IARC have not supported a causal link between wood-related occupations and nasopharyngeal cancer (IARC, 1995).

1.2 Registry-based study and job-exposure matrix

Rare cancer type such as nasal and nasopharyngeal cancer can only be studied by large epidemiological studies such as nationwide registry-based epidemiological studies (with extensive coverage of national cancer cases), wherein occupational exposure is estimated by applying a national job-exposure matrix. A job-exposure matrix is a database that contains information on level of exposure to potentially harmful agents for each selected occupational title, and usually includes past-decades working conditions. Scarce data on distribution of occupational exposure limits studies to adequately characterize the risk for occupational groups and individual workers. Without reliable estimates on exposure, occupational cancer risk cannot be characterized as a function of exposure concentration in a period for (any) workforce. Therefore, this approach presents an ideal solution for research in occupational cancer epidemiology.

Epidemiological studies often report only mortality rates due to difficulties in characterization of exposure-disease relationship, while studies that explore relative risks encounter the same difficulties when workers are exposed to several compounds simultaneously, such as iron and welding fumes with asbestos (IARC, 1990; Moulin, 1997; Ambroise et al., 2006). Wood dust-induced nasal cancer is not a novel occupational disease, it is a compensable well-established occupational cancer in the Great Britain under the Department for Work and Pensions Industrial Injuries and Disablement Benefit (IIDB) scheme (IIDB, 2015). However, to what degree the carcinogenic risk corresponds to CE levels and mixed-wood species is largely unknown.

1.3 Background information of the study

The causative occupational exposures and the targeted respiratory cancer sites that this study explored are illustrated in Table 1. The main exposures of concern are wood dust, iron and welding fumes. Others are co-exposures.

The estimated attributable fractions, deaths, and new registration in Great Britain by cancer sites for male workers in 2005 (deaths) and 2004 (new registrations) are shown in Table 2. This is a snapshot of respiratory cancers of the lung, nose, and nasopharynx attributable to occupational risk factors. The exposures responsible for these occupation-induced respiratory cancers among welders are wood dust, asbestos, silica, etc. (Table 3) (Hutchings et al., 2012).

Table 1. Occupational exposures and co-exposures considered in this study

Inhalable and respirable	IARCs classification of human carcinogenicity and target site with sufficient evidence in humans		Based on IARC Monograph volume (year)
	Class	Site(s)	
Formaldehyde	1	Nasopharynx	88, 100F (2012)
Polycyclic aromatic hydrocarbon			
Benzo(a)pyrene	1	Lung	92, 100F (2012)
Organic dust			
Wood dust	1	Nose and nasal cavity	62, 100C (2012)
Inorganic mineral dust			
Asbestos	1	Lung	14, Sup 7, 100C (2012)
Quartz dust (crystalline silica)	1	Lung	68, 100C (2012)
Metals fumes & dusts (inorganic)			
Iron	–	–	(not evaluated)
Chromium	1	Lung	49, 100C (2012)
Nickel	1	Lung	49, 100C (2012)
Lead	2A	Lung	23, 87 (2006)
Welding fumes	1	Lung	49, 118 (2012)

Table 2. Estimated attributable fractions of cancer attributable to occupation (for the respiratory cancer sites studied), calculated for Britain (source: Hutchings et al., 2012)

Cancer site	Code (ICD 10)	Attributable Fraction (AF)	
		AF (%)	95% CI
Lung	C33–C34	21.1	19.2–24.7
Nose	C30–C31	43.4	27.3–74.0
Nasopharynx	C11	10.8	2.3–47.9

Table 3. Registrations of incident respiratory cancer cases attributable to occupation (by selected work exposures) in the total attributable registrations in Great Britain in 2004 (source: Hutchings et al., 2012)

Workplace carcinogen or circumstances	Cancer site		
	Lung	Nasal	Nasopharynx
Main exposure			
Welders	175		
Wood dust	14	39	
Co-exposure			
Asbestos	2223		
Silica	907		
formaldehyde			1
PAHs (indicated by BaP)	1		
Chromium VI	67	22	
Nickel	9		
Steel foundry workers	29		

Finnish men had the highest lung cancer incidence and mortality rate in 1971–2005 as compared to men in the other Nordic countries (Table 4). Middle-age and older men had the greatest lung cancer risk (Figure 1), although the overall nationwide time trend is on the decline since the 1980s (Figure 2). Lung cancer has been the most popular respiratory cancer site in new diagnosis, it is the leading, single, most fatal cancer with the highest mortality rate as compared to cancers of any sites from 1971 to 2005 (Figure 3).

On the contrary, nasal cancer is a rare cancer type with an increased rarity during the later decade in most regions (Figures 4–5); the incidence is varied by geographical distribution in the Nordic countries.

Nasal adenocarcinoma has been linked to woodworkers since the 1960s (Acheson et al., 1968), and recent information on exposure-specific diagnosis showed that woodworkers' nasal adenocarcinoma appears to originate at the olfactory clef, according to CT and MRI imaging (Figures 8–9). This finding can further enhance the contribution of occupational cancer epidemiology from prevention to clinical medicine (diagnosis and treatment), improving the efficacy of early- and precise-diagnosis of occupational cancer among the affected workers.

Table 4. Mortality and incidence of lung cancer for men aged 30 to 85+ in four Nordic countries 1971–2005 (source: http://www-dep.iarc.fr/NORDCAN/english/frame.asp)

	Incidence					Mortality				
Country	Number	Crude rate	ASR(W)	ASR(E)	ASR(N)	Number	Crude rate	ASR(W)	ASR(E)	ASR(N)
Nordic countries	238618	103.6	85.0	96.6	111.9	225587	97.9	78.2	90.4	108.3
Finland	**63481**	**134.3**	**127.0**	**145.6**	**171.3**	**56076**	**118.7**	**111.1**	**129.1**	**156.3**
Iceland	1688	78.7	72.5	82.0	94.3	1440	67.2	60.2	69.3	82.3
Norway	37900	92.3	74.7	84.7	97.8	33417	81.4	64.2	73.8	87.4
Sweden	61578	69.9	53.0	60.4	70.5	64268	72.9	53.2	61.9	75.5

Remarks:
Crude rate and age-standardized rate (ASR) per 100,000.
ASR (W): World population.
ASR (E): European population.
ASR (N): Population in Nordic countries.

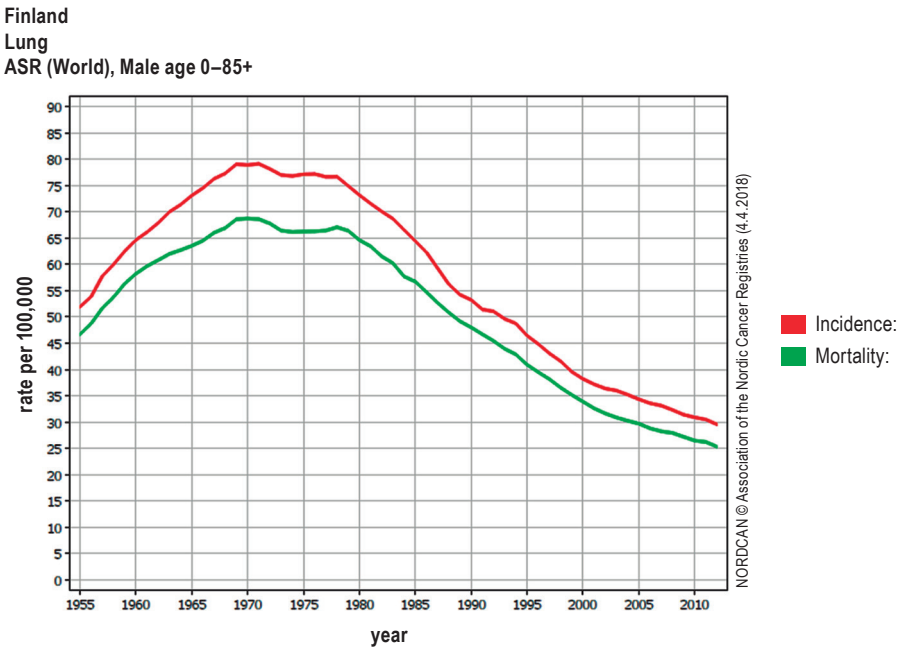


Figure 1. Incidence and mortality rates of lung cancer among Finnish male population (source: http://www-dep.iarc.fr/NORDCAN/english/frame.asp)

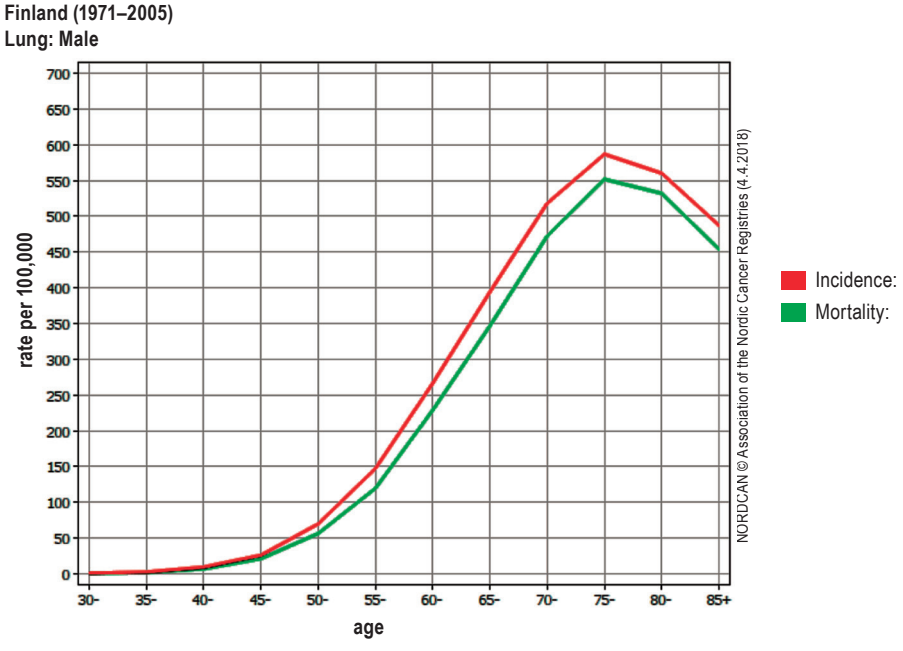


Figure 2. Time trend of age-standardized incidence and mortality rates of lung cancer between 1955 and 2012 (source: http://www-dep.iarc.fr/NORDCAN/english/frame.asp)

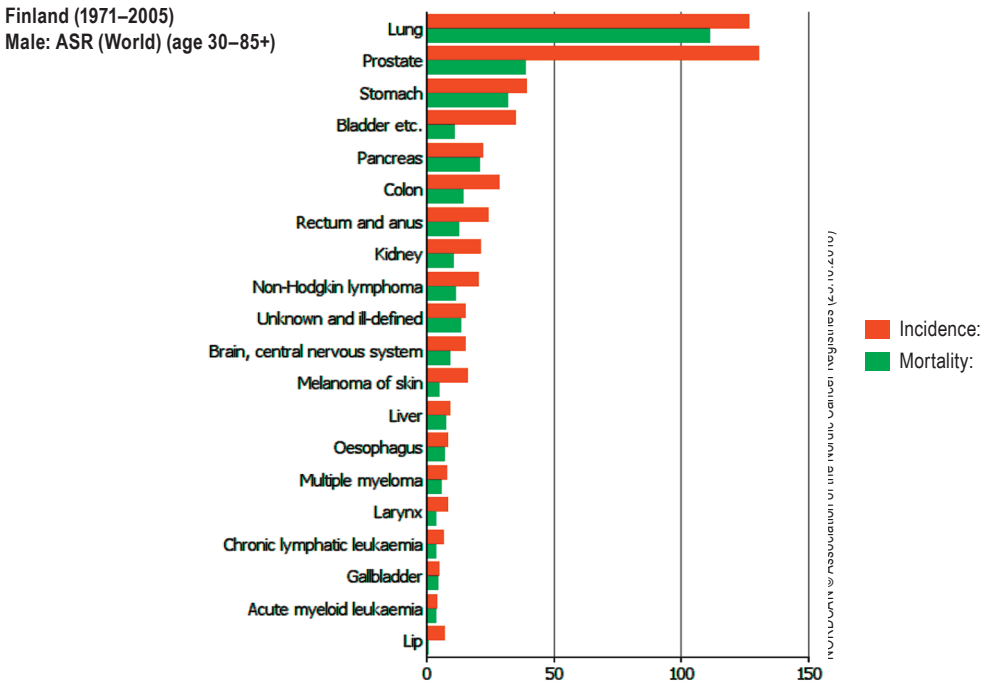


Figure 3. Numbers of new cases and mortality from the most popular cancer sites of Finnish male workers between 1971 and 2005, ages 30+ (source: http://www-dep.iarc.fr/NORDCAN/english/frame.asp)

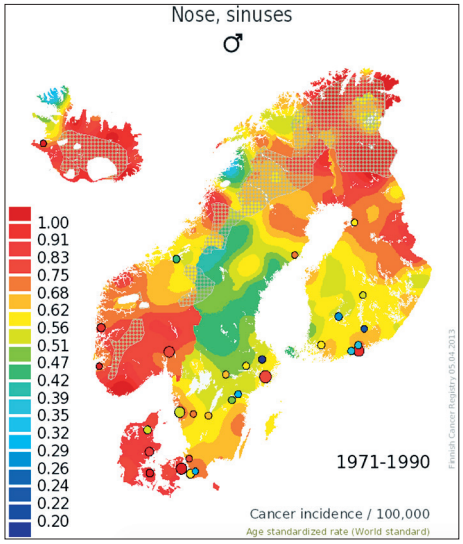


Figure 4. Regional distribution of nasal cancer among male population in Nordic countries between 1971 and 1990 (source: http://www-dep.iarc.fr/NORDCAN/english/frame.asp)

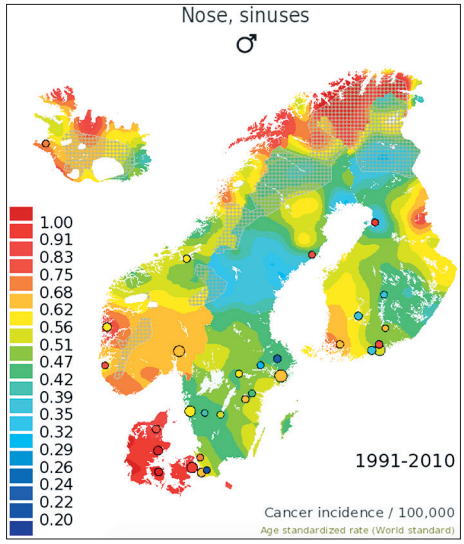


Figure 5. Regional distribution of nasal cancer among male population in Nordic countries among male population between 1991 and 2010 (source: http://www-dep.iarc.fr/NORDCAN/english/frame.asp)

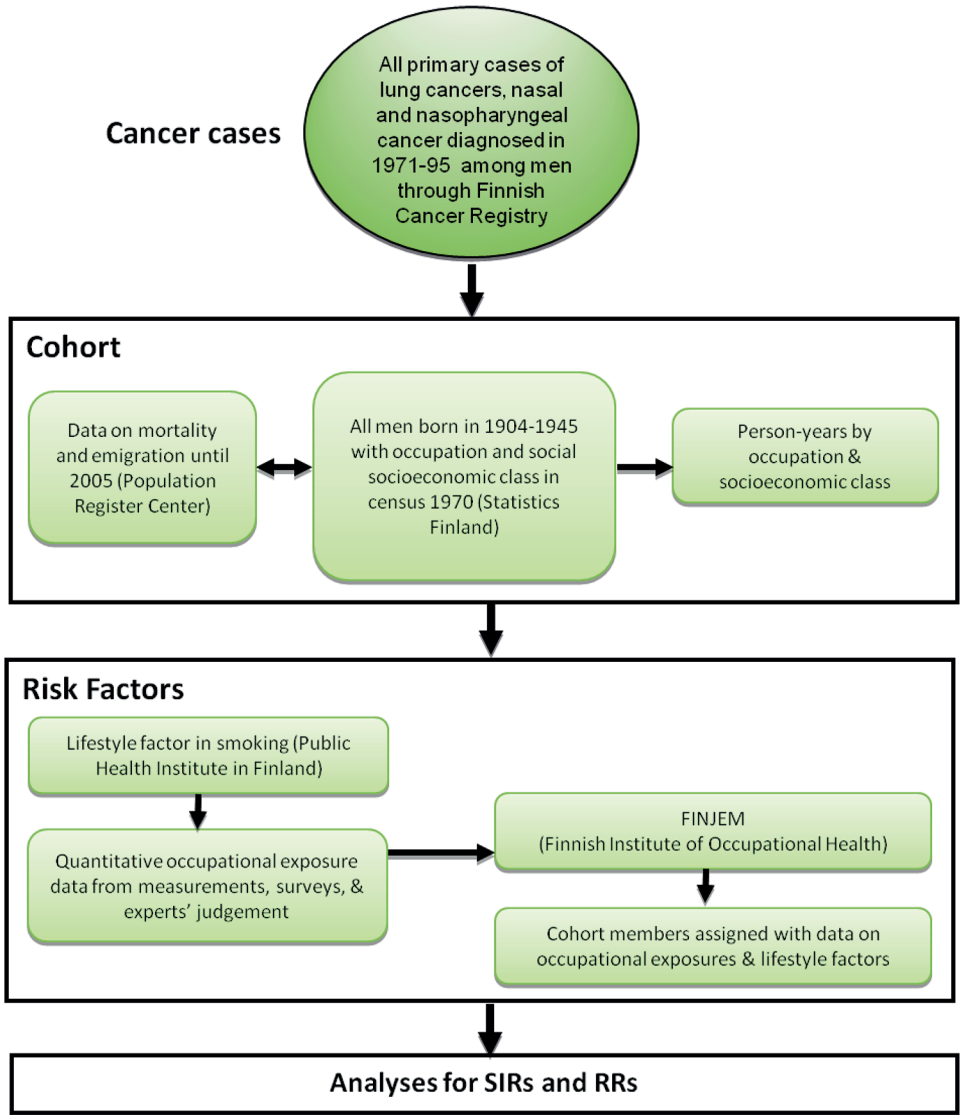


Figure 6. Operational framework (I) of the study – Study design 1 (Paper 1[Fe] & Paper 3[Wood]) – registry-based cohort studies

Remarks:
SIRs = Standardised Incidence Ratios. RRs = Relative Risks. FINJEM = Finnish job exposure matrix. NOCCAJEM = Nordic job exposure matrix.

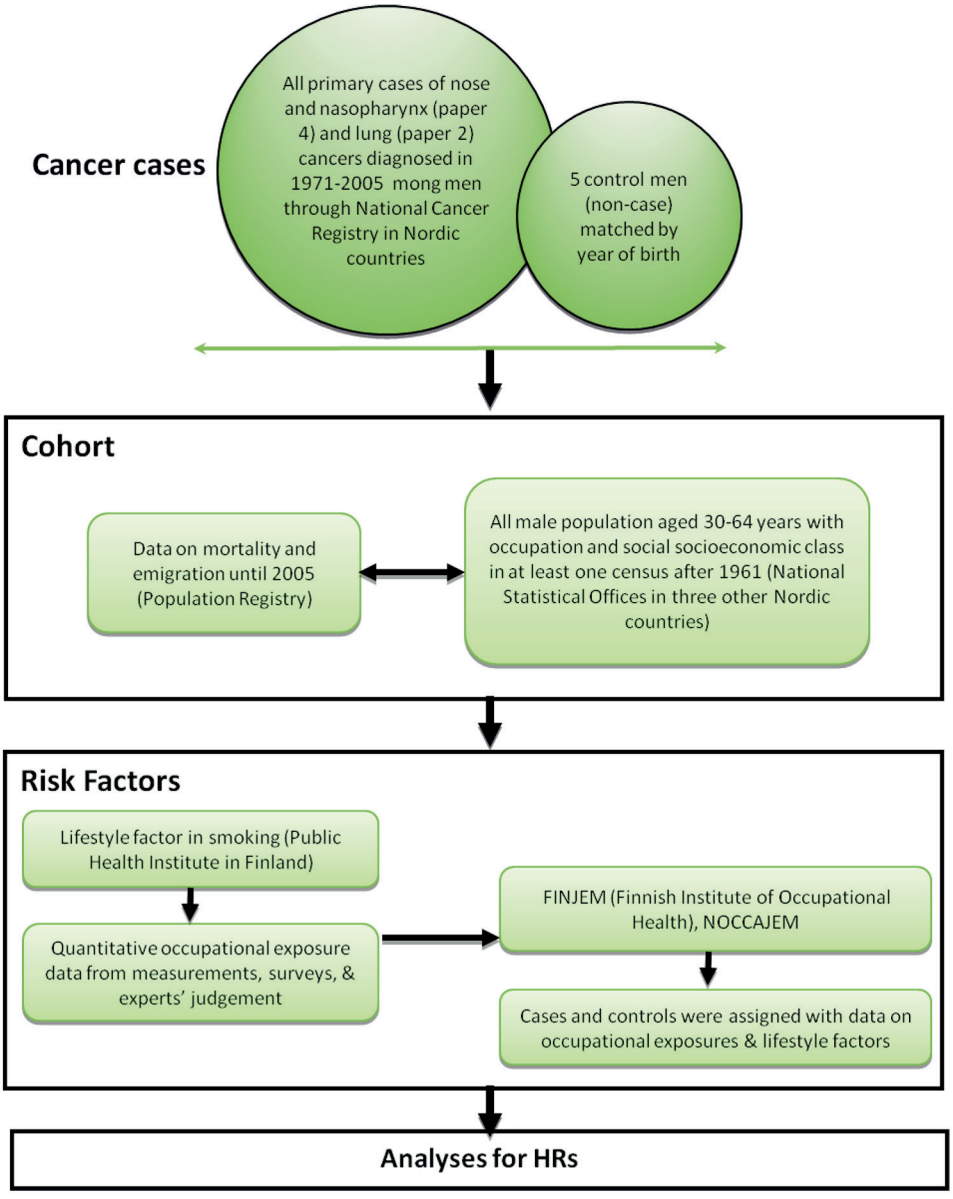


Figure 7. Operational framework (II) of the study – Study design 2 (Paper 2^{Fe} & Paper $4^{NordWood}$) – registry-based case-control studies

Remarks:
HRs = Hazard Ratios. NOCCAJEM = Nordic job exposure matrix.

1.4 Occupational exposures

1.4.1 "Iron and welding fumes" and wood dust (Papers 1 to 4)

About half-million ironworkers, including smelters, metal-ware workers, mechanics, plumbers, etc. in Nordic countries had an elevated lung cancer risk as compared to other occupational groups (Andersen et al., 1999; Pukkala et al., 2009). These ironworkers had common exposure to iron and/or welding fumes.

Both iron ore mining (with high-grade radon) and iron and steel foundry have been classified as Group 1 human carcinogenic industrial work exposures for three decades (IARC, 1987; IARC 100F, 2012). In 2012, IARC further confirmed that occupational exposure during iron and steel work can increase risk of lung cancer, with an associated cumulative exposure-response (years of employment) pattern, adjusted for smoking (IARC 100F, 2012). However, whether iron itself could be a human carcinogen is difficult to determine because several lung carcinogens co-exist in iron industry: mortality studies frequently reported an excess for workers that had exposure to iron in smelting and mining industries, where co-exposures to known carcinogens are common, including radon and other IARC-Classified-Group-1 carcinogenic metals (IARC, 1987); iron and steel foundry encounters the same impacts from co-exposure to lung carcinogens (silica, asbestos, polycyclic aromatic hydrocarbon [PAH], nickel, etc.); and the list continues – nickel in mining, smelting, refinery; chromium IV in welding, and other possible human carcinogen such as lead in smelting and manufacturing (IARC, 1987).

Iron fumes and dust in other circumstances have not been reviewed formally by IARC. The exposure occurs mainly in mining, smelting, foundry and refining industries. Little is known for lung cancer risk in broader sectors, where the exposure frequently occurs, i.e. in secondary industries (building, construction, transportation, utility and production – manufacturing, processing, and assembly) that this study has managed to include (Table 5).

Welding is defined as "a metal-joining process wherein coalescence is produced by heating to suitable temperature with or without the use of filler metal", by The American Welding Society. Advancement in various welding techniques and tools create different workplace condition (exposure) for a diverse group of welders across broad industrial sectors. A conservative estimate on the number of exposed workers to welding fumes is over three million worldwide (IARC, 1990), which presents an imminent concern for global burden of occupational cancer as well as for public health. Still much larger unknown number of workers weld on routine or periodical basis for different work processes, installations, fabrication, applications, repair and maintenance from upstream exploration and production, manufacturing, to midstream and downstream assembly line and miscellaneous tasks. Based on the direct national data, about 4% of the workforce had been exposed to welding fumes, amongst which, manufacturing and construction were two major industries that included the largest workforce in European countries (Kauppinen et

al., 1998). The most recent estimate showed that up to 1% of the workforce at global scale (of 3.3 billion) is exposed to welding fumes occupationally (IARC, 2014). If the risk of lung cancer among this large occupationally exposed population is confirmed, it will lead to an important occupational health hazard.

Welding fumes was classified as "possibly carcinogenic to humans" (Group 2B) based on limited evidence in humans and inadequate evidence in animals (IARC, 1990), thus, welders' lung cancer risk had not been sufficiently evidenced. The recent IARC's re-classification confirmed welding fumes as a Group 1 human lung carcinogen (Guha et al., 2017). The challenge in each evaluation is that studies suggesting a positive association with lung cancer risk were often accompanied by risk estimates that could not be explained by the exposure alone due to unadjusted confounding factors arising from both occupational and non-occupational aspects (Ambroise et al., 2006; Simonato et al., 1991).

The respirable iron fumes, which are the major constituent of welding fumes, have never been separately/specifically evaluated by IARC. The possible carcinogenic effects related to levels of exposure and time course (cumulative exposure or decade-length exposure) associated with lung cancer remain undefined.

Excess risk in nasal adenocarcinoma has often been more distinguishable among woodworkers than other national workforce in four Nordic countries for two decades (Andersen et al., 1999; Pukkala et al., 2009). Since the 1960s, the initial anecdotal report of wood dust-induced occupational cancer came from the discovery of excessive nasal adenocarcinoma deaths among the British furniture workers, suggesting wood dust as an occupational carcinogen (Acheson et al., 1968). Routine wood dust exposure has occurred for at least 3.6 million European workers, where 1.5 million were exposed to low levels (<0.5 mg/m^3) and 0.2 million were exposed to high levels (>5 mg/m^3), particularly in the furniture industry (Kauppinen et al., 2006).

Wood dust is a substance evaluated separately by IARC as a Group 1 human carcinogen based on high levels of exposure to mixed wood and/or hardwood dust, use of deciduous (hardwood) tree species, or both (IARC, 2012; Straif, 2009). The overall carcinogenicity evidence appears to be the strongest for dust generated from hardwood species and risk of nasal adenocarcinoma, but rather weak or non-existent in softwood exposure scenario. To date, there is no clear agreement on carcinogenicity of softwood, softwood-dominated mixed wood dust, and exposure circumstances in broader wood-processing industries (that this study attempted to include in Table 6).

Softwood (or softwood-dominated mixed wood) dust alone has not reflected an excess at any cancer sites. Literature on carcinogenicity of wood dust and existing regulatory levels have left two confusing key issues opened, which motivated the current study to explore: (i) the magnitude of carcinogenic risk due to exposure to mixed wood dust and (ii) whether decade-long cumulative exposure at the levels experienced in Nordic countries could elevate the risk in nasal and nasopharyngeal cancers.

1.4.1.1 Global trade, employment, and widespread occupational exposure to iron and welding fumes

Iron is the most infinite natural resource, the third largest world's reserve of minerals after coal and oil and gas (British Geological Survey, 2011). For several decades, iron and steel industry set the price and benchmark trade deal for the rest of the industry to follow in financial market. Production of steel is considered as a prosperity index of a country, being the essential core material for heavy industrial sectors (construction, machinery, infrastructure, transportation, industrial equipment and tools, etc.). Iron and steel industry accelerate modernization in industrial era, countries are supplied with energy, infrastructure, transportation, urban building, safe food supply, and much more advantages beyond economical profits due to iron and steel. Likewise, the industry employs a substantial number workers, directly supporting one million jobs in the USA alone (American Iron and Steel Institute, 2017). This has not included employment from the equally large iron and steel scrap recycling industry and the associated production and supplier pipelines. The common exposures in this large group of ironworkers (mainly in iron and steel industry) are iron fume/dust and welding fumes. These exposures are routinely experienced by workers in 15 nationwide occupations (according to classification of occupation in Finland and other Nordic regions, quite similar with International Standard Classification of Occupations, ISCO 1958), including metal smelting furnacemen, foundry workers, all occupations in smelting, metallurgical and foundry work, welders and flame cutters, etc. (Table 5). Iron and welding fumes are the top two to three most common industrial exposure circumstances, with the highest number of workers employed, although most of them experience low to moderate exposure level (Kauppinen et al., 2014).

Table 5. List of occupations across broad industries in Finland (based on NOCCAJEM) that experienced exposure to iron fume and dust, welding fumes, asbestos and silica – information on P (proportion) and L (level) of each occupation during the period 1945–1960 (Paper 1[Fe] & Paper 2[Fe]).

Occupation	Iron		Welding		Asbestos		Silica	
	P	L	P	L	P	L	P	L
Miners, shot firers					40	3.00	95	0.20
Well drilling and quarrying							95	0.30
Concentration plant workers					3	15.00	40	0.03
Miners and quarrymen					20	0.20	50	0.60
Railway engine drivers, steam engine firemen					80	0.30		
Metal smelting furnacemen	70	1.50	10	0.90	5	0.05	80	0.40
Heat treaters, hardeners, temperers	90	0.50	10	0.90				
Cold- and hot-rolling metal workers	90	0.50	10	0.90				
Smiths	90	0.50	15	0.90				
Foundry workers	90	2.00	5	0.90			95	0.60
Wire and pipe drawers	60	0.50	10	0.90				
Occupations in smelting, metallurgical and foundry work	70	0.50	5	0.50			40	0.40
Turners, toolmakers and machine-tool setters	90	0.50	5	0.90				
Fitter-assemblers	50	0.20	40	0.90	20	0.15		
Machine and engine mechanics	50	0.20	40	0.30	51	0.20		
Sheet metal workers	90	2.20	75	7.00	30	2.00		
Plumbers	50	0.05	80	0.50	56	0.50		
Welders and flame cutters	90	3.00	90	9.00	40	2.00		
Metal plating and coating work	50	0.03	5	0.20				
Assemblers and other machine and metalware occupations	25	0.50	10	0.90				
Electricians					40	0.03		
Electronics and telecommunications workmen					10	0.0		
Construction carpenters					40	0.50	40	0.15
Painters, lacquerers and floor layers					10	0.05		
Bricklayers, plasterers and tile setters					40	0.30		
Bricklayers, plasterers and tile setters							95	0.30
Reinforced concrete layers, stonemasons							95	0.30
Concrete shutterers and finishers							90	0.30
Insulation workers					90	2.00		
Assisting building workers					40	1.00	70	0.10

Occupation	Iron		Welding		Asbestos		Silica	
	P	L	P	L	P	L	P	L
Assisting construction workers					6	0.70	60	0.30
Building occupations					10	1.00	70	0.08
Glass moulders					20	0.20	50	0.20
Potters							90	0.30
Glass and ceramics kilnmen							90	0.40
Glass and ceramics decorators, ceramics dippers							50	0.20
Glass and clay mixers							90	0.40
Occupations related to glass, ceramic and fine earthenware							50	0.20
Paper and cardboard mill workers					20	0.01		
Refinery workers, other occupations in the chemical industry					5	0.08	5	0.30
Stone cutters							95	0.92
Concrete-mixer operators and cast concrete product workers							95	0.15
Occupations in manufacturing					4	4.00		
Crane operators					25	0.10		
Machine setter operators (not in textile industry) and riggers					41	0.08		
Warehousemen					0	0.00		
Chimney sweeps					80	0.10		

1.4.1.2 Global trade, employment, and widespread occupational exposure to wood dust

Wood is another crucial natural resource in global commerce. Wood industry, or lumber/timber industry concerns with forestry, logging, primary wood processing industries (furniture, carpenter), and the secondary industry in building (bridge, housing, transportation e.g. boatbuilding) and construction. Softwood is the most commercially important wood species worldwide, covering two-thirds of woods used in wood-processing industry (IARC, 1990). In the Nordic countries, deciduous forest only covered a small part (4%). Exposure to mixed wood dust is routinely experienced by workers distributed around 10 nationwide occupations in Nordic countries, including: sawyers, carpentry, furniture, and non-traditional wood industries (not primary timber industry) such as construction, boat-building, wooden surface-finishing builders, etc. (Table 6).

Table 6. List of occupations across broad industries in Finland (based on NOCCAJEM) that experienced exposure to wood dust and formaldehyde – information on P (proportion) and L (level) of each occupation during the period 1945–1960 (Paper 3[Wood] & Paper 4[NordWood])

Occupation	Wood Dust		Formaldehyde	
	P	L	P	L
Technical nursing assistants			12	0.35
Livestock breeders			10*	0.15*
Forestry workers and lumberjacks			16*	0.05*
Textile finishers, dyers			5	0.19
Textile inspectors			5	0.10
Patternmakers and cutters (also leather garments and gloves)			5	0.02
Industrial sewers etc. (also leather garments and gloves)			6	0.10
Foundry workers			0	0.00
Welders and flame cutters			5	0.04
Metal plating and coating work			10	0.01
Electronics and telecommunications workmen			0	0.00
Timbermen	60	0.70		
Upholsterers	70	0.10		
Sawyers	95	0.80		
Plywood and fibreboard workers	70	1.00	60	2.00
Construction carpenters	95	0.20		
Wooden boatbuilders, coach-body builders	90	0.20	10	0.10
Bench carpenters	95	1.20	10	0.10
Cabinetmakers and joiners etc.	95	1.40	20*	0.16*
Woodworking machine operators	95	2.50	10	0.20
Wooden surface finishers	80	0.20	5	2.00
Woodworking occupations (not elsewhere categorized)	95	0.20	5	0.10
Painters, lacquerers and floor layers			30**	0.86**
Cookers and furnacemen (chemical processes)			10	0.50
Paper and cardboard mill workers			7*	0.50*
Refinery workers, other occupations in the chemical industry			9	0.34
Plastic product workers			56	0.08
Paper products workers			9	0.20

Remarks:
*Exposures 1960–1974; no exposure before 1960.
** Exposures 1960–1974; formaldehyde was not used in paints and glues in the 1950s.

1.4.1.3 Exposure profile – Finland, Nordic, and beyond (EU)

Exposure to iron and welding fumes is complicated, so far, the characterization of exposure profile is not available from any national surveillance system. Average exposure has been documented in national JEMs and in the NOCCAJEM. The exposure is dependent on the type of processing work for ferrous metal and welding, base metal and filler metals used, composition of welding rod, work environment (open air, enclosed, or confined space), industrial hygiene practices at workplaces, ventilation or air movement, protective equipment, etc.

Studies on measurement and estimates of wood dust in Europe that aimed for workplace surveillance (Kauppinen et al., 2006) has identified the exposure levels, industries and the total numbers of workers employed for European (EU-25) population (Table 7 and Table 8).

Table 7. Exposure to inhalable wood dust in Finland, Sweden, United Kingdom, and Europe (EU 25) in terms of number of workers, 2000–2003 (source: Kauppinen et al., 2006)

Country	Finland	Sweden	UK	EU 25
Employed (thousand)	2372	3975	22843	179400
Exposed (thousand)	65	58	384	3600
Exposed (% of employed)	2.7	1.5	1.7	2.0
< 0.5 mg/m^3	24	17	53	747
0.5–1 mg/m^3	12	11	58	597
1–2 mg/m^3	12	12	84	763
2–5 mg/m^3	11	12	108	897
>5 mg/m^3	6	6	81	563

Table 8. A snapshot in 2000–2003 for European (EU 25) wood-processing industries and the total numbers of employed workers, where a proportion of them had experienced exposure to inhalable wood dust (source: Kauppinen et al., 2006)

Industries	Number employed persons
Construction	13 million
Manufacture of furniture	1.2 million
Manufacture of joinery	472000
Forestry	445000
Building of ships and boats	294000
Sawmilling	259000
Manufacture of other wood products	147000
Manufacture of wood boards	124000
Manufacture of wooden containers	80000
All other employment	163 million
Total	**179 million**

2 REVIEW OF LITERATURE

Selection of literature was specifically focused on all available review studies, meta-analyses, and good-quality studies that have been included in these reviews. Search was conducted through the keywords or the context of the literature: "occupational exposure, iron, welding fumes, lung cancer, job-exposure matrix, mild steel, and stainless steel" and "occupational exposure, wood dust, mixed wood dust, nasal cancer, nasal adenocarcinoma, lung cancer, and job-exposure matrix".

2.1 Exposure to iron and welding fumes and risk in lung cancer

A few examples of studies on mortality and morbidity, industrial-based cohort, and population-based settings illustrated an increased risk in all types of welding (Table 9). The general problems in previous studies include too short follow-up, in addition to inadequate control of occupational co-exposures and other confounders. For instance, shipyard welders and car mechanics could have had exposure to asbestos, smelters and foundry workers to silica and benzo(a)pyrene (in FINJEM, benzo(a)pyrene is an indicator for PAH), plumbers and some subgroups of welders to asbestos, silica and BAP, and sheet metal workers to nickel and chromium. Effect of confounding to asbestos, silica, and smoking were the main difficulties of these studies that complicated the interpretation of their results.

The largest meta-analysis (Ambroise et al., 2006) based on 60 studies with 13 population surveys, 20 case-control studies, and 27 industry-based cohorts assessed a combined smoking-adjusted excess of 26% (RR 1.26, 95% CI 1.20–1.32) in lung cancer among welders. Confounding due to asbestos exposure is possible. In the second largest study, smoking appears to be a synergistic co-carcinogen that explained 20% elevated risk in welders' lung cancer (Kendzia et al., 2013). Positive smoking-adjusted risks were consistently detected in their study for both regular welders (44%) and occasional welders (19%).

Exposure to asbestos has long been suggested as an unexplainable or non-adjustable cofactor to have more likely occurred in shipyard than in other manufacturing plants (Moulin, 1997; Simonato et al., 1991; McMillan et al., 1980; Sheers et al., 1980; Danielsen et al., 1993). Shipyard welders has not reflected to have greater lung cancer risk than welders in other workplaces (Ambroise et al., 2006; Simonato et al., 1991).

The review studies addressed several common limitations with regard to the lack of adjustments in workplace co-exposures and smoking. Other non-occupational risk factor e.g. SES was entirely overlooked. Paper 1^{Fe} & Paper 2^{Fe} attempted to fill the research gaps

Table 9. Exposure to iron and welding fumes and risk in lung cancer

Author, year/ Country, follow-up	Industry	Main findings
Mortality studies		
Menck, et al., 1976/ United States, 1970–1973	All types of welding	Reviewed deaths from lung cancer in Los Angeles County Surveillance Program for occupations and industries based on records from hospital and death certificates. 48 cases. SMR 1.37, 95% CI 1.01–1.82
Population census, 1978/ United Kingdom 1970–1972	All types of welding	Study that utilized registration data and census data to study occupational mortality, conducted by Office of Population Censuses and Surveys that initiated by William Farr. 246 cases. SMR 1.51, 1.33–1.71
Gottllieb et al., 1980/ United States, 1960–1975	All types of welding	Survey based on death certificates for mortality from lung cancer and non-cancer for occupations in oil mining and refinery. Greater risks were observed for welders and beyond (boiler-man, operators, field workers, etc.) 8 cases. MOR 3.50, 0.74–16.70
Gallagher, 1983/ Canada, 1950–1978	Metal workers	Study on metal workers for 10,036 employed in British Columbia. Occupational history of each workers was derived from registry data (death) to estimate for age-standardized proportional mortality ratios (PMRs). 74 Cases. PMR 1.45, 1.15–1.83
Burnett et al., 1997/ United States, 1984–1988	All types of welders and cutters	Joint project with NIOSH, 24 State health departments, and Health Statistics. Cohort consists of 1.7 million persons. 1097 Cases. PMR 1.24, 1.18–1.30
Incidence Studies		
Andersen et al., 1999/ Nordic countries, 1971–1991	All welders	Registered-based cohort study. The cohort included men aged 30-64, who were in the same occupation derived from censuses. Work exposures were evaluated at occupational level by JEM. 650 Cases. SIR 1.23, 1.14–1.33
Pukkala et al., 2009/ Nordic countries, 1971–2005	All welders	Registered-based cohort study. The cohort included men aged 30–64, who were in the same occupation derived from censuses. Work exposures were evaluated at occupational level by JEM. 1798 cases. SIR 1.33, 1.27–1.40

Industry based cohort study		
Simonato et al., 1991/ Nine European countries	All types of welding	European study for welders (11 092 male) distributed in 135 companies. Asbestos was likely to have confounded the results. 116 cases. RR 1.34, 1.10–1.60
Danielsen et al., 1993/ Norway	Shipyard	Authors noted that exposure to smoking and asbestos were confounding variables. 9 cases. SMR 2.50, 1.14–4.75
Moulin et al., 1993 (Meta-analysis)		Meta-analysis on studies published between 1954 and 1994. Up to 40% welders' lung cancer risk cannot be accounted for exposure to chromium (or chromium VI) and nickel exposure from stainless steel. Asbestos is thought to be responsible partly for the risk.
	All industries Shipyard Non-shipyard Mild steel Stainless steel	1028 cases. RR 1.38, 1.29-1.48 305 cases. RR 1.30, 1.14–1.48 173 cases. RR 1.35, 1.15–1.58 137 cases. RR 1.50, 1.18–1.91 114 cases. RR 1.50, 1.10–2.05
Ambroise et al., 2006 (Meta-analysis)		Meta-analysis assessing lung cancer risk among welders over 1954–2004. Altogether 60 studies were reviewed. No heterogeneity was observed. Effect from asbestos was not assessed or controlled. Smoking has not confounded the risk. Risk in lung cancer was detected for all types of welders (RR 1.26, 1.20–1.32).
Population-based cohort or case-control study		
Jill et al., 2016/ Canada, 1992–2010		Population-based Canadian Census Health, unadjusted for occupational factors, comparisons were made between blue-collar workers and industries. Increased risk was detected for lung cancer (HR 1.16, 1.03–1.31) in additional for mesothelioma (HR 1.78, 1.01–3.18).

Table 10. Exposure to wood dust and risk in lung and nasal cancer

Author, year	Study & Outcomes	Main findings
Binazzi et al., 2015	Systematic review and meta-analysis, Nasal cancer	Out of 63 reviewed articles published after 1986, 28 were analysed for nasal cancer attributable to a wide range of exposures at work from wood, formaldehyde, metal, construction, etc. Exposure to wood dust had the strongest association with risk in nasal adenocarcinoma (RR 29.43, 95% CI 16.46–52.61), and a lesser extent in overall nasal cancer (5.91, 4.31–8.11) for case-control studies, whereas (1.61, 1.10–2.37) for cohort studies. Subset analysis suggested an exposure-disease trend for wood dust (p=0.001). The study suggested future studies to explore specific occupational groups to confirm causative agents. A slightly elevated risk of nasal cancer for exposures to formaldehyde was found (1.68, 1.37–2.06) for case control and (1.09, 0.66–1.79) cohort studies.
Alonso-Sardón et al., 2015	Systematic review and meta-analysis, Nasal cancer	From a total of 114 studies published between 1957–2013, 70 were selected for review for association between occupational exposure to wood dust and different types of cancer. Of these, 42 studies focused on the relationship between wood dust and respiratory cancers. nasal cancer (n = 22), lung cancer (n =11), and other types of cancer (n = 9). The strongest association was observed in nasal adenocarcinoma for exposure to wood dust. A weak link for lung cancer. Workers exposed to wood dust had higher rates of nasal adenocarcinoma as compared to all other workers (OR 10.28, 95% CI 5.92–17.85). Only 11 studies had confounders controlled, that were mostly published in the recent decade. Degree of heterogeneity was observed to be large.
Demers et al., 1995	Pooled analysis, Nasal cancer	A pooled reanalysis of 12 case-control studies in male workers that consists of 680 cases, 2349 controls in seven countries. The RR associated with wood-related jobs and with exposure to wood dust, by applying JEM using job titles. Risk of adenocarcinoma has proven to be associated with wood-related occupations (OR 13.5, 95% CI 9.0–20.0). This is particularly true with men experiencing exposure to wood dust to the greatest extent (45.5, 28.3–72.9), although the level of the excess risk varied between studies. Strong evidence for wood dust induced nasal adenocarcinoma is established.
Zhang et al., 2014	Meta-analysis, Cancer of the nose and nasopharynx	The meta-analysis included 20 case-control studies for nasal and nasopharyngeal cancer in ten countries that have been published from 1980 to 2010. The ORs for nasal adenocarcinoma were 8.67 (CI 95% 6.64–11.32) in men. The overall OR for nasal cancer was 2.32 (2.10–2.67) and for nasopharyngeal 1.87 (1.57–2.38). OR for nasal cancer were slightly higher in Caucasians (2.19, 1.91–2.51) than in Asian (2.03, 1.69–2.44). The detected risk was lower in nasopharyngeal cancer among Caucasians 1.45 (1.00–2.11) and 2.05 (1.64–2.55) Asian.

Jansing et al., 2003	Case series study, Nasal cancer	Study performed analysis on a group of 28 patients, selected from archives, with wood dust-induced nasal cancer registered over a 7-year period in North Rhine-Westphalia, Germany. No significant differences between all subgroups that consist of: hardwood or mixed wood types, type of work (occupations), smoking or non-smoking, and histological subtypes. Visual analysis of several types of wood dust did not reveal any differences in morphology and size (>10 µm). Cases of nasal adenocarcinoma is apparently slightly more common histology. The authors recommend amending the German, Austrian and Luxembourg regulations and to recognise nasal cancer as official work-induced disease, regardless of the type of wood dust exposure, and regardless of the tumour histology as also recommended by IARC.
Pukkala et al., 2009	Census cancer incidence linkage study	Study included woodworkers in all five Nordic countries. SIR for nasal adenocarcinoma (N=122) was 5.5 (4.6–6.6), for overall nasal cancer (N=355) 11.8 (1.7–2.04), and for lung cancer (N=10,941) was 0.96 (0.94–0.97).

by exploring these confounding factors that might have affected the inconclusiveness of results in the previous literature. Furthermore, this study has managed to include the exposed occupations in broader iron-related industries (Table 5). The findings add relevant new information in the body of literature.

2.2 Exposure to wood dust and risk in cancers of the lung and nose – with an emphasis on nasal adenocarcinoma

The overall carcinogenicity evidence appears to be the strongest for exposure to hardwood dust and risk of nasal adenocarcinoma, but quite weak or non-existent for softwood dust (Table 10). Although about 5-fold excesses were reported among workers primarily exposed to softwood dust in Northern Europe (Hernberg et al., 1983; Jappinen et al., 1989) and in the United States (Vaughan et al., 2000), at least three studies found no association, specifically between softwood dust nasal adenocarcinoma (Hernberg et al., 1983; Jappinen et al., 1989; Robinson et al., 1990). These studies lacked sufficient power essential to identify rare cancer type such as nasal cancers (even in a joint-Nordic study) and the exposure observed was generally very low e.g. in sawmill and plywood industries (Binazzi et al., 2015; Alonso-Sardón, 2015). To date, there is still no clear agreement on the carcinogenicity of softwood dust.

Formaldehyde affects exclusively the tissue in-contact surrounding the respiratory tract. It was suggested as a causative agent in excess of several respiratory cancers, mainly for nasopharyngeal cancer, inconclusively for nasal cancer, and no evidence for lung cancer (Blair et al., 1990; IARC, 2012). Most data on nasal cancer implies difficulties in confounding control of effect from wood dust. Carcinogenicity of formaldehyde in human is scarce, when exist, the inconclusiveness of the reported results makes it more difficult to be interpreted when the control of confounding by exposure to wood dust is incomplete.

Epidemiological studies have demonstrated a clear association between exposure to wood dust and nasal cancer, primarily nasal adenocarcinoma. Paper 3^{Wood} and Paper 4^{NordWood} aimed to refine the assessment by identifying the risk and its intensity (through CE) among a population that consists of soft-wood dominated woodworkers. Exposed occupations beyond the classic wood-processing sectors outside furniture and sawmill (Table 6) were included. The findings aid in understanding of cancer aetiology, providing significant new pieces of information in the body of literature.

3 AIM OF THE STUDY

1. To identify associations between occupational exposures to iron and welding fumes and risks of lung cancer among nationwide population in Finland by applying a national JEM.
2. To identify associations between occupational exposures to wood dust and risk of nasal cancer, nasopharyngeal cancer, and lung cancer – with an emphasis on nasal adenocarcinoma – among nationwide population in the entire Nordic region (except Denmark) by applying national JEMs.

4 MATERIAL AND METHODS

4.1 Study design

Since 1961, Finnish cancer registration was compiled from clinical and pathological departments on compulsory. The compulsory reporting of new cancer cases has similarly implemented at the cancer registries in three other Nordic countries. In Finland, registration of new cases of cancer is based on reports from clinical and pathological departments, private clinics, general practitioners, and information from the causes of death registry (Pukkala et al., 2018). The completeness was good (about 99%) for most diagnoses of primary malignant cancers.

The first three studies were conducted in Finland (Papers 1–3 or Paper 1^{Fe}, Paper 2^{Fe} & Paper 3^{Wood}), including all Finnish men, nationwide, enrolled in national censuses in 1970, 1980, and 1990. The last study (Paper $4^{NordWood}$) was based on population in four Nordic countries, where the cohort consisted of all men, who participated in population censuses. Occupational information was obtained from census records from: 1960, 1970 and 1980 in Norway; 1960, 1970, 1980 and 1990 in Sweden; 1970, 1980, 1990 in Finland; and from 1981 in Iceland.

This study applied record-linkage for information on cancer, death, and emigration accessed through personal identity codes, which were linked to national cancer registries (Pukkala et al., 2018) and national population registries.

The operational framework (I) of the study is illustrated in Figure 6. Exposure was estimated according to the job held of each individual workers during the census by using a job-exposure matrix (JEM). FINJEM was applied in Paper 1^{Fe} and three other papers adopted NOCCAJEM. In census-based cohort study (Paper 1^{Fe} & Paper 2^{Fe}), exposure-based approached was applied by assigning quantitative value from FINJEM to each occupational group. In registry-based nested case-control studies (Paper 3^{Wood} and Paper $4^{NordWood}$), it was cancer-based approached that linked each individual case to numerous exposures and co-exposures (operational framework II, Figure 7).

The research started with the traditional approach by following up a census (in 1970) of economically active persons in the Finnish (male) workforce who were born in 1906–1945 through record linkage in Finnish Cancer Registry for lung cancer incidence diagnosed between 1971 and 1995 (Paper 1^{Fe}). Occupations from census were converted to quantitative exposures to iron and welding fumes and the relevant co-exposures to: other metal fumes

(nickel, chromium, lead), PAH compound i.e. benzo(a)pyrene, air-borne silica dust, and asbestos fibre. Likewise, exposure to mixed wood dust and co-exposure to formaldehyde were assigned to relevant occupations (Paper 3^{Wood}). CE was calculated by multiplying P, L, and estimated duration of exposure (in years).

SIRs of lung cancer were calculated for occupations that experienced exposure to iron and welding fumes (Paper 1^{Fe}). Similarly, SIRs were calculated of nasal, nasopharyngeal, and lung cancer in occupations with exposure to wood dust or formaldehyde (Paper 3^{Wood}). General population was the reference group. The exposure–response patterns were studied with the Poisson regression analysis of the stratum-specific observed numbers of cases and person-years at risk. The unexposed persons formed the reference category. RR estimates of each cancer were calculated by comparing three categories of CE with the unexposed category.

In nested case-control studies (Paper 2^{Fe} & Paper $4^{NordWood}$), all cases were identified from the existing national workforce i.e. the entire population in Finland (Paper 2^{Fe}) and in four Nordic countries (Paper $4^{NordWood}$). Based on occupational code of each person, a corresponding CE value that comprises of P and L from JEM was assigned at individual level based on the main exposures wood dust and co-exposure to formaldehyde (Paper $4^{NordWood}$), while for Paper 2, iron and welding fumes with co-exposure to asbestos and silica. HRs were calculated for nasopharyngeal and nasal cancer with an emphasis on nasal adenocarcinoma (Paper $4^{NordWood}$) as well as for lung cancer (Paper 2^{Fe}) with conditional logistic regression and Cox regression.

4.2 Cohort (Study base)

The cohort of 'study base' consists of the entire population extracted from all economically active Finnish men born between 1906–1945, who participated the first national population census in 1970, altogether about one million men (Paper 1^{Fe} & Paper 2^{Fe}). The Finnish census data maintained by Statistics Finland were updated for vital status to allow exact person-year calculation. Data on the occupations held for the longest time in 1970 were obtained from the population census 1970 records.

The subsequent study (Paper 3^{Wood}) is a registry-based incidence case-control study nested in the Finnish part of all 1,670,815 men aged 30–64 years in the end of census years 1970, 1980 or 1990 extracted of the cohort of 15 million persons in the Nordic Occupational Cancer Study (NOCCA).

Occupational information of the study population was obtained from census records. The occupation classification applied was based on adaptation of International Standard Classification of Occupation in 1958. Socio-economic status (SES) for each person was determined based on his occupation, education, and industrial status in census 1970, and classified into five categories: farmers, upper white-collar, lower white-collar, skilled blue-collar, and unskilled blue-collar workers.

The cohort has been extended to three other Nordic countries (Paper 4[NordWood]), with the region-wide population in Iceland, Norway, and Sweden, aged 30–64 who had participated at least one census after 1960. This case-control study was nested in the cohort of 14.9 million individuals who participated in population censuses. Occupational information was obtained from census records since 1960, 1970 and 1980 in Norway, 1960, 1970, 1980 and 1990 Sweden, 1970, 1980, 1990 in Finland and from 1981 in Iceland. Each person was followed from the first available census until the date of emigration, death or December 31 of the following years: 2003 in Norway, 2004 in Iceland, 2005 in Finland and Sweden. A detailed description of the NOCCA cohort was given in an earlier publication by Pukkala et al. (2009). Individual records from Denmark was inaccessible, hence Danish data were not included. Individual's information on cancer, death and emigration were accessed through personal identity codes, which were linked to cancer registries and national population registries.

4.3 Cancers

All lung cancer cases (N=30137) in Finnish men, who were born between 1906 and 1946, and who participated in the population census in 1970, were followed through the Finnish Cancer Registry in 1971–1995 (Paper 1[Fe]). The follow-up period was prolonged to 2005 in the newer paper (Paper 2[Fe]). Only Paper 1Fe included histological subtypes: squamous cell carcinoma, small cell carcinoma, and adenocarcinoma. Cancers of the nose (N=2446) and nasopharynx (N=1747) in the same population were followed-up similarly (Paper 3[Wood]).

The prolonged follow-up for cancer of nasal regions until 2005 was extended to three other Nordic countries (Paper 4[NordWood]). The cases were all men diagnosed with nasal adenocarcinoma (N=393), other nasal cancer (N=2,446) and nasopharyngeal cancer (N=1,747) in Finland, Iceland, Norway, and Sweden, after the first available census and before the end of follow-up.

To ensure the homogeneity of the study base and to eliminate the gender disparity, the study is only conducted among male population. Table 11 is a piece of tabulation (in the Chapter of Summary of Results) indicating the distribution of exposure-specific cancer cases in four papers, it illustrates all cancer cases occurred in relation to occupationally-exposed workers that this study has included.

Table 11. Number of cancer cases in relation to occupational exposure

Cancer site	ICD 10[4]	Paper 1		Paper 2		Paper 3		Paper 4	
		Fe[1]	W[1]	Fe[2]	W[2]	WD[2]	FM[2]	WD[3]	FM[3]
Lung	C34	2908	2945	4913	2828	5500	1831		
Squamous cell carcinoma		992	1009						
Adenocarcinoma		540	532						
Small cell carcinoma		382	395						
Nasal	C30–31					64	17	206	242
Adenocarcinoma						–	–	138	111
Squamous cell carcinoma						42	9		
Nasopharyngeal	C11					7	5	135	161

Remarks:
Fe=iron, W=welding, WD=wood dust, FM=formaldehyde
[1]Follow-up in 1971–1995 in Finnish population, 20-year latency period
[2]Follow-up in 1971–2005 in Finnish population, 10-year latency period
[3]Follow-up in 1971–2005 in Nordic population, 10-year latency period
[4]ICD 10 = International Classification of Diseases for Oncology 10 and its classification of topography codes for cancer.

4.4 Occupational exposure based on job-exposure matrix

Half of the study (Paper 1^{Fe} & Paper 2^{Fe}) utilized quantitative exposure estimates from FINJEM according to the Census 1970 occupational records of each individual (Kauppinen et al., 1998), another half of the study was based on the occupational record in at least one of the Census in Finland (Paper 3^{Wood}) and three other Nordic countries (Paper $4^{NordWood}$), utilizing the Nordic national job exposure matrices for each country.

All JEMs used in the study covered changes of exposure during the time periods from 1945 to 1994 as a result of progress and development in industries, safety and health policies, and new collection of workplace exposure monitoring reports.

All employment periods before 1945 were assigned with the same average exposure proportion and level in 1945–59 from JEM; and from 1960 onwards, three periods (1960–74, 1975–84, and 1985–94) were assigned according to the calendar period of individual's job history.

The length of exposure was accumulated as the total number of years the men spent in an exposed occupation (person-years) during his employment history. Persons included in our study had data on work history according to one or more censuses. In case when a worker held more than a job, we assumed the change occurred in the mid-year of censuses that he participated in. In this case, the exposure history of the men consisted of more than one PxLxT values.

The accumulated exposure time (T) for each person (person-years) was dependent on the years of employment period. Cumulative exposure was the total sum of the PxLxT

values of all these individuals. Our analyses were based on a latency (lung cancer developed over a time period after exposure) interval assumption of ten years, which excluded exposures within the most recent ten years before the index date when calculating CE of all individuals. In each calendar year, the annual average exposure was the product of the proportion of exposed persons (P) and the mean level of exposure in that occupation (L).

The model procedure to calculate cumulative exposure was as the followings: For each occupational code, a corresponding value of P and L from JEM was assigned. This value was multiplied by employment period (T) in years during which the individual was in the occupation. As a result, we had the CE as the value of PxL*x*T. The CEs for all exposures and co-exposures were calculated based on the same procedure.

Occupational-specific exposure circumstance was used to calculate CE for every 5-year birth cohort (from 1906–1910 to 1941–1945) and 5-year calendar periods of observation from (1971–1975 to 1991–1995) (see the Lexis diagram in Figure 8). Each birth cohort was assumed to have started experiencing the exposure at the average age of 20 years and ended in the middle year of the observation period minus 20 years (latency) or at 65 years of age, whichever came first.

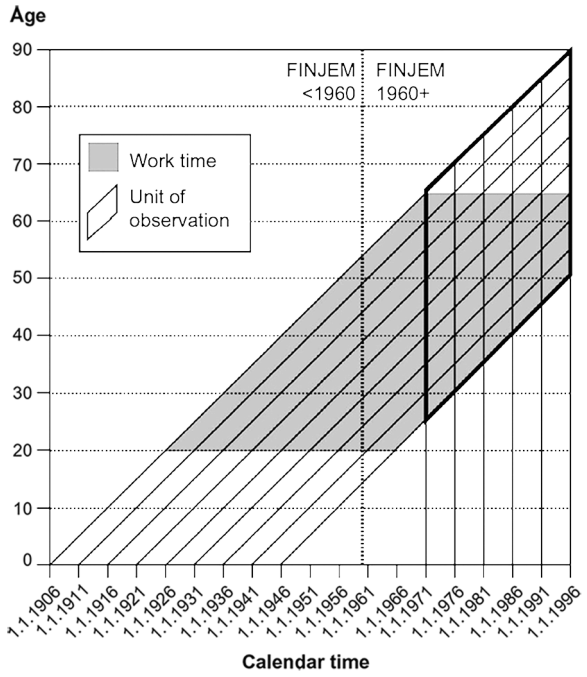


Figure 8. Units of observation, defined by birth year of the persons in the cohort (1906–1910, …, 1941–1945) and calendar period of follow-up (1971–1975, …, 1991–1995), theoretical work (exposure) time, and FINJEM (Finnish national job-exposure matrix) periods used for exposure estimation

The accumulated exposure time (T) for each person (person-years) was dependent on the years of employment period. Cumulative exposure was the total sum of the PxLxT values of all these individuals. Our analyses were based on a latency (lung cancer developed over a time period after exposure) interval assumption of ten years, which excluded exposures within the most recent ten years before the index date when calculating CE of all individuals.

The exposure was assumed to start as the employment started (when the worker was 20) and censored in either one of the two conditions: at aged 65 or 10 years (latency period) before the index date.

Figure 9 illustrates FINJEM and NOCCAJEM exposure system. This procedure is based on the construction of international matrices on occupational exposure to carcinogens (CAREX) (Kauppinen et al., 2000) and wood dust (WOODEX) (Kauppinen et al., 2006).

The national exposure circumstances to iron and welding fumes in the period from 1960s to 1980s was estimated with exceptional consideration towards routine and occasional welding tasks for all types of welders, thanks to the inflow of massive volume of monitoring reports (Kauppinen et al., 2014).

The national exposure circumstances to wood dust and formaldehyde were estimated based on the same procedures from CAREX and WOODEX. Some exposures at work are frequently monitored, providing more than a thousand pieces of data: asbestos (3161

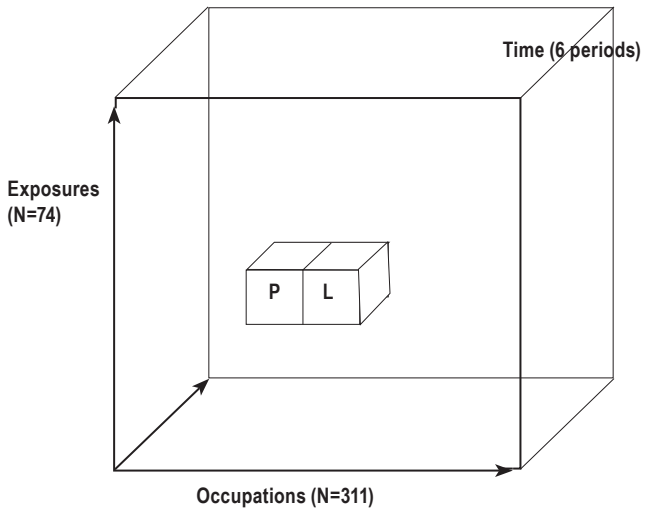


Figure 9. Finnish job-exposure matrix (FINJEM), exposure information system (Kauppinen et al., 1998). This figure is modified. FINJEM = Finnish national job-exposure matrix. Periods: 1945–59, 1960–84, 1985–94, 1995–97, 1998–00, 2001–03. P: prevalence of exposure (%). L: level of exposure (ppm, mg/m^3)

pieces), wood dust (5277), formaldehyde (9001), nickel and nickel in urine (3060), and quartz dust (3852) (Kauppinen et al., 2014).

4.5 Statistical Analyses

Confounding occurs when a causal risk factor is associated with both exposure and disease (Rothman, 1986) and when that risk factor is distributed unequally in the compared groups. One should note that in occupational cancer epidemiological study, there may be confounding factors of non-occupational origin in addition to known work-related co-exposures. Social class or socioeconomic status (SES) and age are regarded as two inherited potential confounding factors, even though both risk factors might not lead to a direct causal-effect. The Finnish part of JEM contains estimated data on proportion of daily smokers for each occupation. It has been applied to adjustment of smoking habit in analyses on lung cancer (Paper 1^{Fe} & Paper 2^{Fe}).

All analyses were adjusted for SES, age or/and known potential occupational confounding factor(s). In Paper 1^{Fe} and Paper 2^{Fe}, adjustments were made on exposure to relevant potential carcinogens: metal fumes, (nickel, chromium, lead), BaP, silica and asbestos. In Paper 3^{Wood} and Paper $4^{NordWood}$, formaldehyde was separately modelled and further used as an adjustment in modelling for wood dust.

In generating SIR, the expected numbers of male cases for every occupation were calculated for each 5-year birth cohort and 5-year calendar period (see Lexis diagram in Figure 8) by multiplying person-years lived by each individual in that occupation with the cancer incidence rate of the total economically active male Finnish population in the respective stratum. SIR, which is used for external comparison, was defined as the ratio of the observed number of cases to the expected number of cases. The 95% CIs were defined assuming that the observed number of cases followed a Poisson distribution.

The RR and 95% CI comparing the exposed and unexposed workers to each work-related exposure in multi-modelling was estimated by Poisson Regression and Cox Regression. Age, socio-economic status, latency period, smoking, plausible occupational co-exposures were stratified and/or adjusted in multivariate relative risk estimates.

In Paper 1^{Fe} and Paper 2^{Fe}, the exposure–response patterns were studied with the Poisson regression analysis of the stratum-specific observed numbers of cases and person-years at risk, which is used for internal comparison. RR was estimated as the output. The unexposed persons formed the reference category. The 95% CI was calculated for RR, adjusting for confounding factors.

In Paper 3^{Wood} and Paper $4^{NordWood}$, HR and 95% CI for each exposure by conditional logistic regression and Cox proportional hazard mode. The exposure hazard ratio (HR) was then averaged over all these comparisons of odds, and over several risk-sets within the dynamic population. The output generated HRs that equals to, and directly estimate to RR.

One advantage of applying Cox Regression modelling method in two newer case-control studies (Paper 2[Fe] & Paper 4[NordWood]), using design and individual-level data, is to take into consideration the changes in the "dynamic population", where a control could later be a case during the periods of follow-up. This approach is not novel, but very suitable, it enables the model to more precisely calculate the risk that includes the changing status of the controls (to cases). Hence, the results it generates are more representative. In addition, Cox Regression modelling permits straightforward calculation of effect estimate of each risk factor in the model, which is useful in exploring the magnitude of individual risk factor in epidemiological studies (Vandenbroucke & Pearce, 2012).

5 SUMMARY OF THE RESULTS

The distribution of exposure-specific cancer cases in papers 1–4 is illustrated in Table 11.

5.1 Lung cancers in iron workers and welders (Paper 1^{Fe} and Paper 2^{Fe})

The results from Paper 1^{Fe} suggested an association between an increased risk of lung cancer and exposure to iron or welding fumes at any cumulative exposure (CE) level.

SIRs in almost all exposed occupation consistently exceeded 1.0; RRs in all CE levels of iron or welding fumes exceeded 1.0 after adjusting for asbestos, silica, SES and smoking. When CE level was 50 mg/m^3-years and above, risk in squamous-cell lung carcinoma was elevated by 2-fold, RR 1.94 (95% CI 1.35–2.78) for iron; and to a lesser extent (a 55% increase) for welding fume RR 1.55 (1.08–2.24).

Positive results persist in prolonged follow-up of lung cancer (Paper 2^{Fe}). Iron-related occupations were slightly associated with an increased lung cancer risk when CE level was at as low as 5.06 mg/m^3-years [HR 1.05 (1.00–1.10)]. As for welding fumes, an excess risk was shown already with CE level at as low as 13.19 mg/m^3-years [HR 1.09 (1.02–1.16)].

The overall excess ranged from 9% to 15% for welding fumes and 11% to 35% for iron dust and fume in cohort study. Positive risks continued to be observed in stratified analyses when medium-to-high concurrent exposures [i.e. nickel, chromium, lead, and benzo(a) pyrene] were excluded. In case-control study, increased risks associated to both exposures were detectable even after confounding factors were adjusted (i.e. asbestos, silica, smoking and SES).

Exposure to asbestos to the greatest extent (exceeded 13.23 f/cm^3-years) accounted for a consistent 40–55% increase lung cancer risk among ironworkers. Positive results persist after adjustment for SES and smoking.

5.2 Cancers in woodworkers (Paper 3^{Wood} and Paper $4^{NordWood}$)

Working as a woodworker was associate with a significant elevated risk in nasal cancer RR 1.59 (1.06–2.38) and nasal squamous cell carcinoma (1.98, 1.19–3.31) (Paper 3^{Wood}).

The risk in nasal adenocarcinoma rises with the increase of CE to wood dust, accounting for a 29-fold excess when the CE level exceeded 28.82 mg/m^3-years (Paper $4^{NordWood}$). After adjustment for formaldehyde, the risk remained, HR 16.5 (5.05–54.1). For exposure to

wood dust, an excess risk is shown already with CE-level at as low as 6.70 mg/m^3-years, HR 3.11 (2.04–4.75). After adjustment with formaldehyde, the risks for nasal adenocarcinoma remained significant and increased consistently from threefold in the low-CE to eightfold in the moderate-CE and 17-fold in the high-CE category (Table 3, Paper 4[NordWood]).

A ten-fold excess risk in nasal adenocarcinoma was associated with moderate CE to formaldehyde but the excess decreased to 2.06 (95% CI 1.16–3.60) when the exposure to wood dust was added to the model. Neither non-adenocarcinoma of the nose nor nasopharyngeal cancer could be linked to wood dust exposure.

Neither nasal cancer other than adenocarcinoma nor nasopharyngeal cancers could be associated to CE to formaldehyde.

Both wood dust and formaldehyde exposure were not associated with lung cancer.

6. DISCUSSION

6.1 Findings

6.1.1 Iron and welding fumes

Exposure to iron and welding fumes is not overlapped but inter-related. Iron is known as the main compositions of welding fumes. Workers who are exposed to iron fume experience concurrent exposure to the rest of the fumes from welding process, according to NOCCA-JEM. This concurrent exposure is similarly characterized in INTEROCC-JEM [INTEROCC has the database on life-length job histories for workers across seven countries in collaboration with Australia, Canada, France, Germany, Israel, New Zealand and the UK] (Parent et al., 2017). Iron and welding fumes can be described as a joint-occurrence in varying ironwork. In this population, there has not been a single occupation that was exposed to iron but not to welding fumes or vice versa. The roles of these two exposure factors are inseparable.

Exposure to iron fume and dust is generally low (below 5 mg/m3) in this study. The legal airborne permissible exposure limits (PEL) of iron oxide or iron fume, measured as iron, is 10 mg/m^3 averaged over an 8-hour work-shift (i.e. time weighted average, TWA-8), according to OSHA. This PEL is two times more than NIOSH's recommended exposure limit (5 mg/m^3, averaged over an 10-hour work-shift, TWA-10). ACGIH recommended 5 mg/m^3 as the TWA-8 for respirable fraction. However, these standards were decided primarily based on pulmonary siderosis and benign pneumoconiosis, both are non-cancerous outcomes.

The overall risk of lung cancer in relation to exposure to iron and welding fumes was studied and extended (from Paper 1^{Fe} to Paper 2^{Fe}) by a prolonged period of cancer follow-up to 10 more years, with refined study setting (case-control study design with individual-level data) and modelling method (Cox regression that handles the changing status when each control became case at each point in time). This new approach aimed to define the initial findings "why RR of lung cancer was stronger for iron than for welding fumes, if the constituents of welding fumes are apparently more carcinogenic to humans?", simultaneously, to explore the extent to which the co-exposures and confounding factors have contributed to the elevated risk of lung cancer when more recent exposure periods are included.

The carcinogenicity of iron has been on a rising concern and there is an unexplained risk, which cannot be accounted for co-exposures in previous studies (IARC 1990; Moulin, 1997) i.e. lung cancer has not been shown as an occupational cancer with regard to exposure to iron. When considering the context of exposure scenario for iron workers and welders, simultaneous exposure to plausible and established lung carcinogen(s) can present in almost all work conditions, including varied metal fumes, benzo(a)pyrene, and radon gas (Stokinger, 1984; Tossavainen, 1990). On the other hand, metal fumes from nickel and chromium VI, asbestos, and smoking could not explain the excess of RR in lung cancer among ironworkers (Guha et al., 2017; IARC 1990; Ambroise et al 2006). This is particularly true in industries other than iron and steel mining, smelting, and foundry. A series of animal study supports the possibility that iron can act as a co-carcinogen (Mohr et al., 2006). Consequently, these all make it extremely difficult for studies to determine whether iron could be a sole cause of lung cancer in ironworkers, or whether iron acts as a co-carcinogen, accounting for the synergistic carcinogenic effect with other lung carcinogen(s) present in the workplaces.

Most lung cancer are diagnosed after retiring age (Figure 1). Diseases relevant to welders' lung are likely to be accumulated with iron (siderosis and siderofibrosis), which are non-malignant, although a possible cancer link was suggested (Lasfargues et al., 1991; Samet et al., 2006). Other welders' lung diseases include: bronchopneumonia (mainly diagnosed) among older people after retiring age (after 65) that leads to few deaths; lobar pneumonia among younger patients below age 65 (Palmer et al., 2003) has not shown a link to carcinogenic end-point; none of these diseases implied a competing risk for lung cancer in the literature (IARC, 1990).

6.1.1.1 Iron, asbestos, and silica

The slightly elevated risks of lung cancer in most of the studies among welders in stainless steel, mild steel, and unspecified welding were suggested without a chronological order (Ambroise et al., 2006; Moulin, 1997; Sjögren et al., 2004). In the current study, a higher SIR was found for mild steel welders in comparison with stainless steel welders (Table 1, Paper 1^{Fe}). The result was quite in line with the findings that indicated a larger lung cancer mortality risk for mild steel welders as compared stainless steel workers (Moulin et al., 1993). Several studies did not support the conclusion that nickel and chromium VI (in stainless steel welding) could be the prime causative agents in increased lung cancer mortality among welders (Sjögren et al., 2004).

SIR in shipyard welders was not particularly greater than that of other welders (Paper 1^{Fe}), as implied in other large studies (Ambroise et al., 2006; Simonato et al., 1991). Exposure to asbestos and silica has long been suggested as an unexplainable or non-adjustable cofactor to have more likely occurred in shipyard than in other manufacturing plants (Moulin, 1997; Simonato et al., 1991; Danielsen et al., 1993). Because ironworkers

and welders generally smoked more than other workers in occupational groups (Paper 1^{Fe} Table 1; Simonato et al., 1999), in this study, separate adjustments on exposure to asbestos and smoking were essentially applied in the Cox Regression model (Paper 2^{Fe}), considering the potential multiplicative effect (IARC 100C, 2012). A certain magnitude of risk attributable to exposure to asbestos (and/or smoking) exists, although NIOSH concluded that there is an elevated risk of lung cancer among welders that cannot be completely accounted for by smoking or asbestos exposure (NIOSH, 1998).

Asbestos appears to be the leading risk factors (Paper 2^{Fe}) that makes silica's role relatively negligible. This population of Finnish welders are the same individuals nested from NOCCA study (Pukkala et al., 2009). Most likely these workers had encountered co-exposure to asbestos because they had a 2-fold increased risk in mesothelioma (SIR 1.98). Mesothelioma death is an indication of exposure to asbestos, it has been used by IARC as a proxy for exposure to asbestos (McCormack et al., 2012). Hence, the SIRs from NOCCA study on mesothelioma (in the pleural) can also reflect a greater extent of exposure to asbestos among the workers in repairing, insulation, and refurnishing than in welding.

In addition to the secondary iron industry (construction, shipyards, transport, and heavy-industry related manufacturing, apart from mechanical repair), asbestos has also been used as an added constituent in welding electrode in the form of powder (dust), in the flux mixture, or as the coating of electrodes (IARC, 1990). The impact of asbestos in the lung of welders with mesothelioma was presumed to be less severe as in the case from asbestos manufacturing and insulation sector (Neumann et al., 2001; Kendzia et al., 2013). However, one should note that all types of asbestos fibres kill at least twice as many people through lung cancer than through mesothelioma, except for crocidolite (McCormack et al., 2012). Asbestos has its integral part in lung cancer risk although the risk of mesothelioma is probably the only respiratory cancer that it could explain entirely (e.g. about 97%, McCormack et al., 2012). Lung cancer appears to be a more common and severe problem among welders, the British data illustrated that the number of lung cancer registered by welders was twice more than the total mesothelioma cases registered by asbestos-exposed workers in 2004–2005 (Brown et al., 2012).

Asbestos use is gradually reduced or ceased in work environment around the globe between 1990s and 2000s (IARC 100C, 2012). But its latent effect on mesothelioma and asbestos-related lung cancer continues to be an occupational burden in Europe, Japan and Australia today and in the next decades, and it will get worsen in Asian countries, since it is expected to peak in regions with the greatest current consumptions, including China, Russia, India, and Thailand (McCormack et al., 2012).

One worth mentioning innovation is that, cessation of asbestos usage has introduced refractory ceramic fibres into iron and steel founding industry as a technically ideal replacement. Whether the pleural plaque that caused by this new replacement (Pairon et al., 2014) could also be an independent risk factor for lung cancer risk as asbestos had for mesothelioma risk is not known, what is known is the exposure (to the replacement)

can be considerably high (up to 23 fibre/mL) during installation and removal of furnace insulation (IARC 100F, 2012).

6.1.1.2 Smoking and SES

Most workers that had exposure to iron and welding fumes in this study held occupations that have higher proportion of daily smokers, with varied degree of prevalence across occupations. The 70 human carcinogens contained in each cigarette (IARC, 2004) cause it extremely significant to (and impossibly not to) include smoking in the model as a risk factor for lung cancer. Varying associations between occupation and smoking often affect the quality and conclusiveness of epidemiological studies that explored lung cancer, industry-wide smoking prevalence was thus constructed used to aid interpretation of analytical studies that lack smoking data (Stellman, 1997; Stellman & Stellman, 1980; Sterling & Weinkam, 1976). Table 1 in Paper I^{Fe} suggested one percent-unit increase in the prevalence of smokers corresponds to 15% increased risk in lung cancer. Therefore, adjustment for smoking strongly decreased the observed HRs.

However, since the 1970s, studies have showed only a limited degree of RR for lung cancer that smoking is likely to account for (Axelson, 1978; Siemiatycki et al., 1988), suggesting the non-occupational aspect of risk to be the factors other than smoking e.g. SES. For a period of time in the earlier century, smoking has been a popular lifestyle habit in the upper social class and among the wealthy people. Smoking habits simply cannot be taken as equivalent with difference between social classes (Stellman et al., 1997). This is evidenced in studies among welders that smoked Vallières et al., 2012). The study that explored within-group risk through a stratified analysis restricted to only blue-collar workers among welders indicates that some of the excess lung cancer risk is likely attributable to residual confounding from smoking; furthermore, residual confounding by smoking even exists among non-smokers and light-smokers (Vallières et al., 2012).

SES has an independent role in risk of lung cancer in Finnish population (Pukkala, 1995; Pukkala et al., 2009) and beyond (Hovance et al., 2018). Adjusting both non-occupational confounders (SES and smoking) enabled the findings to reflect different social dimensions or circumstances that are mostly related to unequal distribution between classes e.g. education and income, which are also associated with diet, housing, health knowledge, and access to health care. SES itself has been studied as an independent risk factor in several cancers, "cancer occurrence can be seen within industrialized countries between the more and less favoured socioeconomic groups", Lorenzo Tomatis's famous quote (Tomatis, 2001).

Social inequality that affects tobacco smoking, cancer, and social class was addressed in a "IARC-cooperated study" – while the medical and epidemiological literature tends to focus narrowly on specific lifestyle and environmental agents, such as tobacco use and occupation, the social processes that trigger exposure to these agents are frequently neglected (Hurowitz, 1993; Stellman & Resnicow, 1997). The recent "IARC-cooperated

study" found SES to be a persistent risk factor for workers' lung cancer, even after adjusting for smoking and education (Hovanec et al., 2018).

Skilled blue-collar workers is an example that addresses the complexity of social inequality, reflecting the heterogeneous in income and education – they could have greater income, better education, but much worse smoking habit (e.g. high-prevalence of smoking habit is common among welders), as compared to workers in several other social classes.

The conclusions from the previous literature were generally made without taking into account smoking, SES and quantitative estimates of occupational exposure and co-exposures. Only a few studies have explored long-term CE and looked at exposure-disease relation of lung cancer risk as what has been done in the present study. Adjustment of SES can control the residual confounding factors that smoking could not cover, and thus more adequately taking into account the socioeconomic and lifestyle habit of the study population.

An indirect approach to adjustment for SES in the model means control for other lifestyle confounding factors. SES is strongly associated with occupational cancers in Finnish population (Pukkala, 1995). The SES assigned for each occupation in the current research was not the direct mechanical conversion from a single piece of information according to job title, instead, it was designed as the results from social studies, primarily, based on occupation, education, and industrial status (Pukkala et al., 2009).

This study recapitulated an increased risk of lung cancer that is considerably in line with IARC's most recent review (Guha et al., 2017), after smoking and SES were adjusted. In our population, the risk was reduced by half in average, however, it existed, and half-remained, due to exposure to iron and welding fumes.

6.1.2 Wood dust and risk in nasal cancers

In this study, exposure to wood dust was generally low and occurred within the regulatory limit (i.e., below 5 mg/m^3), according to NOCCAJEM. The findings supported the link between CE to low exposure to "softwood-predominant mixed wood dust" and nasal cancer, an association that has not been fully confirmed earlier on (IARC, 2012; Demers et al., 2005). Formaldehyde exposure was uncommon for workers that experienced moderate or high exposure to wood dust, as in agreement with other studies (IARC, 2012). Even when formaldehyde was controlled, RR for lung cancer was not attenuated, on the contrary, it showed a 20-fold excess in the most heavily exposed CE level.

The use of wood species in wood industries generally differ widely by geographical location and product range. Wood processing/manufacturing industries and none-wood based industry in building and construction utilize several wood types from domestic source and imported, that generated an indefinite of mixed wood dust to the ambient air surrounding the workers that perform the tasks. The exposure profile of general workers on mixed wood dust reflects wood consumption or application in their industries, although

some minor wood species or unspecified wood type are used irregularly. The most common woodworking activities in the Nordic countries use trees grown locally, which is softwood (mainly pine and spruce).

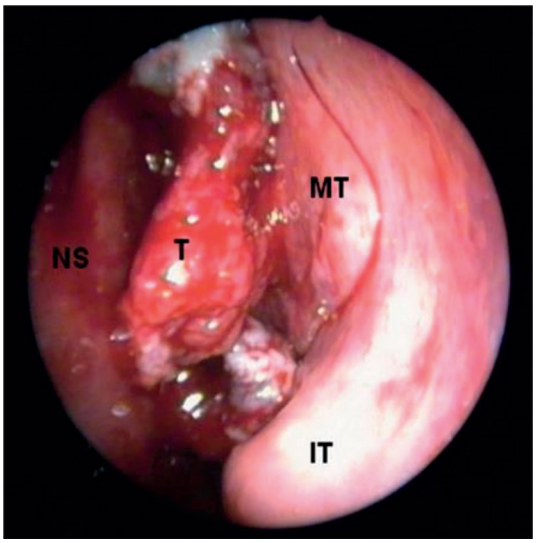
The accurate etiological factors and mechanisms that initiated nasal adenocarcinoma in woodworkers are not known (IARC, 1996; IARC, 2012).

The particle size for both hardwood and softwood in the same work activities is identical (>10 μm), there is no difference in particle size or morphology (IARC, 2012; Jansing et al., 2003). Fibre size of the wood dust between work activities is distinguishable, however, unlike asbestos fibres that persist for almost a lifetime on human tissues, wood dust can get degraded, decreased, and removed through muco-ciliary clearance. Therefore, it has been argued that fibre size and morphology were not relevant to carcinogenicity of wood dust (IARC, 2012; Jansing et al., 2003). It is probably impossible to provide satisfactory explanations on the questions: what is the plausibility of the mechanical-related consequence of mucosal injuries caused by wood dust before the clearance on epithelial tissues surrounding the nasal regions, in the respiratory epithelial and around the olfactory epithelial tissues (as illustrated in Figures 10–12)? What damage could have happened with the deposit of wood dust at the epithelial tissues even temporarily? What is the plausible mechanical related to mucosal injuries that could be caused by passing through of the dust, even if muco-cillary clearance occurred?

Almost half of nasal cancer are localized at the nasal cavity (43%), most others originated in the maxillary (35.9%), or ethmoid (9.5%) (Turner et al., 2012). These lesions were generally tumours of epithelial origin, including adenocarcinoma (12.6%). For woodworkers' nasal adenocarcinoma, the site of origin has been traditionally believed to be in the nasal cavities of ethmoid. Particle deposition in human airway has not been studied since the 1980s (IARC, 1995). Instead, the debate was focus on questions surrounding inter-individual variation on flow rates, and type of breathing and the implication on muco-ciliary transport, until the recent study on surgical oncology navigated the growth of adenocarcinoma i.e. being originated from the olfactory cleft, and advancing into the nasal cavity (Georgel et al., 2009). Because the morphological aspect on wood dust retains at >10 μm, and by inhalation, larger particles (>10 μm aerodynamic dimeter) are almost completely captured and/or deposited in the nose, it is reasonable to expect larger wood dust particles to hit the olfactory cleft at the surrounding area before clearance, if any, regardless the breathing style or flow rate. Unlike the respiratory epithelial tissues that experience frequent clearance, olfactory epithelial tissues could be at the lack of such functional capability, this could prolong the retention of the deposit wood dust in its structure and the thus accommodate the sequential carcinogenicity phases.

The French study (Georgel et al., 2009) will further their study to learn possible reasons that can explain their findings (Figures 10–12).

This input will possibly lead to an area to arise: exposure-specific site-of-origin in occupational cancer epidemiology, which will drastically increase the usefulness,



Remarks:
IT = inferior turbinate
MT = middle turbinate
NS = nasal septum
T = tumour into the olfactory cleft

Figure 10. Nasal adenocarcinoma was found to be originate from olfactory cleft, according to French study (Endoscopic surgical image courtesy of Georgel et al., 2009. Reproduced with permission from American Journal of Neuroradiology)

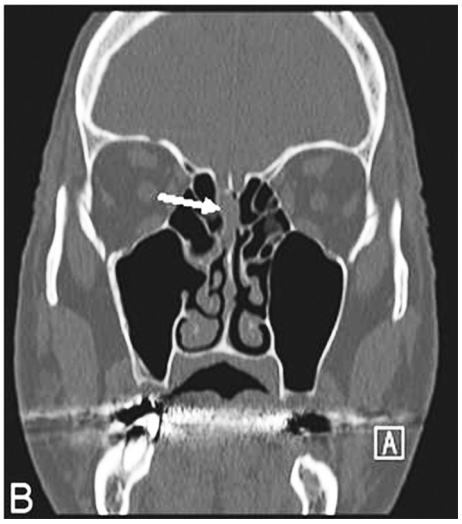


Figure 11. Computed Tomography (CT) scan has succeed in early-detection strategy in diagnosis of woodworkers' nasal adenocarcinoma. CT image shown a tiny pea size adenocarcinoma located at the right side of olfactory cleft (pointing arrow) (Image courtesy of Georgel et al., 2009. Reproduced with permission from American Journal of Neuroradiology)

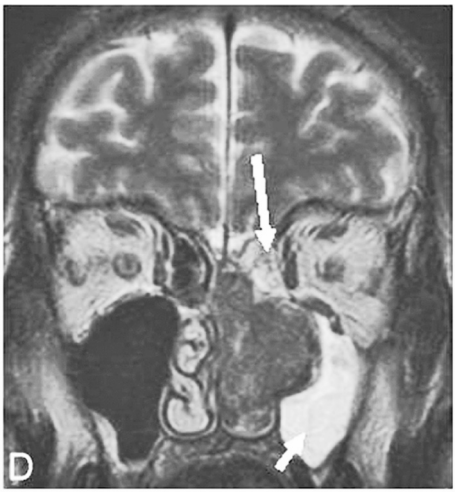


Figure 12. Image from Magnetic Resonance Imaging (MRI) scan in the French study verified the finding on the origin of woodworkers' nasal adenocarcinoma in olfactory cleft with retention in the squeezed ethmoidal labyrinth (pointing arrow) (Image courtesy of Georgel et al., 2009. Reproduced with permission from American Journal of Neuroradiology)

practicality, and effectiveness of research data, specifically in early-diagnosis and precise-diagnosis. To the least extent, this effort provides a revolutionary improvement to better understand aetiology of occupational nasal adenocarcinoma among woodworkers.

Although to specify histological subtypes of the responsible carcinogens is absolutely of importance, one should also note that the plausible metaplasia is histopathological change additionally to responses on cellular and tissue i.e. that normal respiratory or olfactory epithelium could undergo cell differentiation pathway towards tissue types that do not normally exist in the nasal cavities. For this reason, while the link between wood dust and all other histological subtypes other than adenocarcinoma is either weak or non-existent, the German State Institute for Occupational Health and Safety of North Rhine-Westphalia. Düsseldorf (Jansing et al., 2003) proposed regulatory institutions to recognize nasal cancer as an occupational disease irrespective the histological subtypes (besides another proposals on lowering the current regulatory and non-binding occupational exposure limits).

In animal study, evidence on deposited wood dust has been shown to induce secondary adverse health effect both mechanically (at the local mucosal site) and biochemically (due to plausible toxic elements from the natural/bare wood). Mice treated with mutagenic wood dust extract from semi-dry beech wood (hardwood) developed precancerous skin lesion (epithelial hyperplasia and hyperkeratosis) and both benign and malignant tumour of the skin and mammary glands directly beneath the treated skin area (IARC, 1995). On the contrary, the survival of other mice treated with other plausible carcinogens i.e. acetone and benzo(a)pyrene did not show a significant difference from that of untreated mice (IARC, 1995). IARC Working Group further emphasized a significant trend on observed skin tumours in particular for mammary gland adenocarcinoma. This hypothesis might as well rise a concern on whether the lesion could occur around the inner nasal skin i.e. the respiratory epithelial and olfactory epithelial tissues.

Acheson and colleagues suggested an increased (nasal adenocarcinoma) risk almost entirely limited to very dusty bare-wood-processing work, where machining, sanding, etc. are done, instead of cleaner departments e.g. polishing, vanishing, and upholstering area, because the presence of (a certain amount of) wood dust in the ambient air could spoil the finishing products (Acheson et al., 1968; Acheson et al., 1972). This finding also implied a greater risk among the workers suffered from greater wood dust exposure on routine basis. Since 1995, IARC has concluded this independent effect of wood dust on human carcinogenicity that "the excess appears to be attributable to wood dust rather than to other exposures in the workplace, since the excess was observed in various countries during different periods and among different occupational groups, and because direct exposures to other chemicals do not produce relative risks of the magnitude associated with exposure to wood dust" (IARC, 1995). The evaluation has included studies of hardwood dust where softwood dust could not be ruled out (IARC, 1995). Although the exposure levels were often lower than the EU Occupational Exposure Limit (OEL) i.e. 5 mg/m^3 in

the European Union, elevated risks in cancers of the nasal regions are still detectable (Straif et al., 2009; IARC 1995; IARC, 2012).

The current binding and non-binding regulatory level for mixed (unspecified) wood dust in the USA vary between organizations. Before 1985, Occupational Safety and Health Administration (OSHA) controlled wood dust with standard that regulate nuisance dust (below 15 mg/m^3). Since 1985 the level has been adjusted to 5 mg/m^3, which is still the most lenient limit as compared to the common standard i.e. 1 mg/m^3 recommended by the non-binding limits from National Institute of Occupational Safety and Health (NIOSH) and American Conference of Governmental Industrial Hygienists (ACGIH). Since 2004, ACGIH set 0.5 mg/m^3 as a recommended standard on Western Red Cedar (softwood) and 1 mg/m^3 for all other species, solely due to the allergenic health concern. Decisions that set occupational exposure standards seldom regard carcinogenic contemplation as influential function of health outcomes.

The OEL of wood dust has evolved throughout the decades in the EU countries as the concerns rise towards the carcinogenicity and other (non-cancer) health end-points designation. A proposal on lowering OEL to 0.2 mg/m^3 was submitted by The Dutch Expert Committee on Occupational Safety of the Health Council (DECOS) (DECOS, 1992) to European Commission Scientific Committee on Occupational Exposure Limits (SCOEL) two decades ago. In 2008, German Federal Ministry of Labour and Social Affairs (BMAS) and Federal Institute for Occupational Safety and Health (BAuA) lowered the German legal-binding OEL to 2 mg/m^3 through the national legislation adopted from the Technical Rules for Hazardous Substances (TRGS 553; Die Technischen Regeln für Gefahrstoffe, 2008), and 1 mg/m^3 has been suggested to strive for, since 2003. The changes suggested by the Dutch and German regulatory agencies are a good initiative of improvement. Enactment of a new standard would be the practical concern – whether the authority would reduce the exposure level if a harmonized European "permissible" limit is not implementable, and whether the new standard is implemented at global scale.

New Zealand Department of Labour proposed the following Workplace Exposure Standard (WES) specifically for softwood dust: a TWA-8 of 1 mg/m^3 and a general excursion limit (GEL) of 3 mg/m^3. GEL includes short-term exposure limit that often on the ground of insufficient toxicology data.

The general misinterpretation is whether the regulatory limits should be applied (or taken into consideration) to the ambient air or the air trapped inside the respiratory protective equipment. Carcinogenic effects on decade-long (or nearly career-length) cumulative exposure under the regulatory permissible limit is largely unknown. The availability of such exposure data specifically to mixed wood types is sparse or almost non-existent. Based on conventional high-dose findings, regulators have set maximum acceptable levels, assuming all doses below that level are safe.

With millions of workers in the world affected by the results of CE to wood dust, it is crucial and inevitable to find a way so that the life-changing realities of such exposure can

be ceased and be prevented in the next generation of workers in the places, where exposure still occurs.

6.1.2.1 Wood dust and risk in Lung cancers

In consistent with the previous studies (IARC, 1995; Straif et al., 2009; Demers et al., 1995; Partanen et al., 1993), lung cancer was not a causative risk factor for exposure to wood dust in this population.

The slight excess risk for formaldehyde is considered to be caused by the residual confounding effect of smoking and of co-exposure to formaldehyde and asbestos or crystalline silica. The epidemiological evidence did not support a causal role for formaldehyde in lung cancer (Straif et al., 2009; IARC, 2006; Bosetti et al., 2006). The carcinogenicity may not reach the lower airway and lungs because of the highly reactive and rapid metabolite properties, suggesting that organs without direct contact with formaldehyde do not develop neoplasia (Bosetti et al., 2006; Nielsen & Wolkoff, 2010). Only 10% of inhaled formaldehyde, at the greatest extent, reaches the lower airway at resting condition in humans (Nielsen & Wolkoff, 2010; Garcia et al., 2009).

6.2 Strengths and limitations

The conclusions drawn from the previous literature were generally decided in the absence of data on smoking, SES and quantitative estimates of occupational exposure and co-exposures. Only few studies have explored CEs and looked at exposure-response relation of lung cancer risk as was done in the present study. This study has an attempt to take into consideration for both the of the quantitative occupational risk factors and lifestyle habits to better understand possible associations among workers that were distributed across broad industrial sectors.

Identification of national-level cancer risk attributable from occupational exposure, either for common or rare cancer type, requires a powerful study design and quantitative exposure data with a good level of representativeness of the population. This can be facilitated by geographically well-defined population of a disease or cancer registry that has high-coverage and a regularly updated national surveillance database on occupational exposure.

This study has been the only scientific research ever existed that reflected data on nationwide and decade-length quantitative exposures involving broad industrial workers distributed in iron and wood sectors. It is free from common weaknesses that challenge most studies: recall bias, insufficient latency time, inadequate size of the population and incidence cases for rare cancer, although could inherit potential limitations: misclassification of exposure, as a result from heterogeneity of exposure levels within-group due to the generic

JEM. A large-scale nation-wide and region-wide study, other than the current study, that uses individual level information to identify all these fundamental risk factors (plus the magnitude of cancer risk in mixed wood dust and iron/welding fumes), is however non-existent. Applying JEM to census data in registered-based study can be of advantage in terms of cost, time and completeness of coverage (of cancer cases), it also enables utilization of nationwide data on decade-length exposure across all relevant national industries to reflect the risk in a population. Quantitative wood dust exposure data or long-period CE data are rarely available for studies on occupational cancer risk. The elevated risk of nasal cancer suggested in previous studies was generally based on association with heavy exposure to mixed wood and hardwood dust, use of deciduous (hardwood) tree species or both.

The snapshot of job held by nationwide workers, recorded through one, two, or three censuses, might not perfectly represent an absolute the entire career-length employment history. Nevertheless, NOCCA study has repeatedly emphasized the risk diluting effect of misclassification small, as compared with results derived from industry-based study (Pukkala et al., 2009) and both types of studies had managed to adjust for the confounding factors in age, smoking, etc.

General JEMs with group level analysis has been initially thought to have lower accuracy level in exposure assessment of individual worker as compared to direct individual level data, it has however demonstrated its strength in detection of both common and rare cancer risks in consistence with the high-quality studies in the literature. This method – to apply national estimates of occupational exposure using general JEM in population-based and registry-based study (Pukkala, 1995) has shown its ability to produce the similar results (on risk estimates) as compared to a well-done questionnaire study (Partanen et al., 1994). Without JEM, to facilitate individual level measurement for the entire national workforce could a near impossibility, if not cumbersome and tremendously time-consuming. Another difficulty is that the measurements are thought to be collected from heavily exposed workers (Kauppinen et al., 2014), while such data is still scarce in small-to-medium industries generally due to limited (economical and human capital) resources and knowledge (expertise on industrial hygiene and occupational health).

The past exposures are more meaningful than the recent in cancer-epidemiological study, and JEM appears to be the only source to allocate these retrospective exposures in the circumstance when each individual's measurement data is not feasible to be traced.

All papers included in the current study contain incidence cases and exact person-years that minimize survival bias to zero. A substantial number of previous studies, mostly in the earlier decades, are largely dependent on results derived from mortality studies instead of incidence. This could have induced bias due to varying factors: causes of death (e.g. non-occupational), advancement of medical diagnosis and treatment, affordability of individuals, and the better survival in upper social classes.

National occupational cancer mortality surveillance system rarely exists even in developed countries. This epidemiological study, based on national surveillance, promulgates

the importance of identifying the distribution of specific work-induced cancers and the trends in incidence through collection of large-scale data. It has shown the feasibility to produce nationwide or region-wide epidemiological study and the subsequent systematic evaluation in (occupational cancer) epidemiological study for workplace carcinogens, and thus generate the findings that are utilizable in strategic control measure and allocation of resources (solutions).

7 CONCLUSIONS AND RECOMMENDATIONS

7.1 Study Setting

Application of JEM in registry-based studies among the national population is feasible for hypothesis testing and generation. Studies in the future are encouraged to apply a similar study setting and procedures for preliminary assessment of association between occupational exposure and primary cancer. To some extent, it could be of advantage to assign priory that directs future research, probably in combination with other types of study.

7.2 Iron and welding fumes

Weak association was identified between lung cancer and CE to iron and/or welding fumes. As the challenges that the previous studies have encountered, complex exposure profile at varying magnitude can complicate the interpretation of the independent role of iron fume and dust. Future studies are encouraged to solve the challenges in possible synergistic or antagonistic effects of the mixed exposures, to better understand the independent roles of exposure to iron, welding fumes, and the possible confounding factors e.g. exposure to other metals and co-carcinogens through large-scale studies, using exact individual-level information on all these factors.

Prevention of lung cancer and cessation of smoking habit should be recommended for workers that experience exposure to iron and welding fumes. As mentioned in Chapter 1, when a carcinogen or even a probable/possible carcinogen present at workplace has an important role in commerce and for the society, abundant in resources, without a safe substitute, this can be a burden for occupational/public health, occupational medicine, as well as for the industries. One strategy is to endorse and apply the up-to-date findings directly, rapidly, and effectively, in compliance to improved occupational exposure standards through international bodies and multi-partite co-operation. I would recommend enterprises to implement Kaizen strategy – the continual improvement practiced by ancient Chinese and Japanese since several centuries ago. Implementation of excellent practice that integrates the combined knowledge of occupational hygiene and occupational cancer is of advantage in places where exposures are mitigated to. In case each

workplace has the aspiration to improve work condition and eliminate specific exposures, the result will be a definite success – the goal of zero occupational cancers (attributable from the specific exposures) is not a dream, it is achievable. Workers' compensation scheme is recommended to provide compensations adequately to workplace victims who had experienced carcinogenic exposures independent of their smoking status e.g. the asbestos-exposed ironworkers and welders, or idealistically, to incorporate the scheme with tobacco companies, as the success achieved in Montréal, contributed by Jack Siemiatycki (Udemnouvelles, 2015).

7.3 Wood dust

A strong exposure-disease association was detected between nasal adenocarcinoma and CE to wood dust even at low level. Given the totality of the exposure picture and exposure-respond trend, with abundance of positive results addressed from the studies over half of a century, it is recommendable to implement the best practice(s) of industrial hygiene for exposure and risk reduction (by elimination, minimization and other engineering control alongside with effective personal protective equipment) at the workplaces, where this exposure is still occurring i.e. wood dust of any species. It is recommended to re-evaluate all wood dust related guidelines and binding regulatory standards and implementation strategy.

7.4 Recommendations

A sense of responsibility for workers can often motivate action-taking in reduction or elimination of workplace-induced cancers. Promulgating and implementation for improvement of best practice is crucial. The role of occupational cancer epidemiology integrated industrial hygiene and health, safety, environment (HSE) practices should not be barren. Sufficient control measure should be in place, while science continues to advance and the future research continues to explore new risk in old/mitigated exposures or potential risk in new exposures (replacements of old carcinogens). Workplace medical surveillance should apply effective early-diagnostic tools as an excellent clinical precautious measure, taking consideration to cover the cost of CT scan for relevant ironworkers and woodworkers. The future challenge is to extend improvement of industrial hygiene conditions and preventive strategies to smaller enterprises and developing countries, where significant problems of exposure present, while maintaining best practices in larger enterprises.

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ORIGINAL PUBLICATIONS

Paper I

Siew SS, Kauppinen T, Kyyrönen P, Heikkilä P, Pukkala E. (2008). Exposure to iron and welding fumes and the risk of lung cancer. Scand J Work Environ Health; 34(6), 444–450. doi:10.5271/sjweh.1296.

Paper II

Siew SS, Kyyrönen P, Pukkala E. Occupational exposure to iron and welding fumes and risk in lung cancer among Finnish men: a registry-based case-control study. (Submitted to Eur J Cancer)

Paper III

Siew SS, Kauppinen T, Kyyrönen P, Heikkilä P, Pukkala E. (2012). Occupational exposure to wood dust and formaldehyde and risk of nasal, nasopharyngeal, and lung cancer among Finnish men. Cancer Manag Res., 4, 223–32. doi: 10.2147/CMAR.S30684.

Paper IV

Siew, S. S., Martinsen, J. I., Kjaerheim, K., Sparén, P., Tryggvadottir, L., Weiderpass, E. and Pukkala, E. (2017). Occupational exposure to wood dust and risk of nasal and nasopharyngeal cancer: A case-control study among men in four nordic countries—With an emphasis on nasal adenocarcinoma. Int. J. Cancer, 141, 2430–2436. doi:10.1002/ijc.31015.

Original article

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Exposure to iron and welding fumes and the risk of lung cancer

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Siew SS, Kauppinen T, Kyyrönen P, Heikkilä P, Pukkala E. Exposure to iron and welding fumes and the risk of lung cancer. *Scand J Work Environ Health* 2008:34(6):444–450.

Objectives Exposure to iron fumes and dust and welding fumes is widespread and may increase the risk of lung cancer. The aim of this study was to identify associations between exposure to iron and welding fumes and the incidence of lung cancer among Finnish men.

Methods The cohort of all economically active Finnish men, born in 1906–1945, who participated in the national census in 1970 was followed through the Finnish Cancer Registry for lung cancer cases (N=30 137) during 1971–1995. Their census occupations in 1970 were converted to estimates of cumulative exposure to iron and welding fumes with the Finnish job-exposure matrix on the basis of likelihood, average level, and estimated duration of exposure. Relative risk estimates for categorized cumulative exposure were defined by a Poisson regression, adjusted for smoking, socioeconomic status, and exposure to asbestos and silica dust.

Results The relative risks for lung cancer increased as the cumulative exposure to iron and welding fumes increased. The relative risks in the highest exposure category was 1.35 [95% confidence interval (95% CI) 1.05–1.73] for iron and 1.15 (95% CI 0.90–1.46) for welding fumes. The respective relative risks estimated for squamous-cell carcinoma of the lungs were 1.94 (95% CI 1.35–2.78) and 1.55 (95% CI 1.08–2.24). There was no excess risk of small-cell carcinoma in any exposure category.

Conclusions Occupational exposure to iron and welding fumes was associated with an increase in lung cancer risk, mainly that of squamous-cell carcinoma. The simultaneous exposure to both of these agents and other potential work-related carcinogens complicates the interpretation of the independent roles of the risk factors.

Key terms job-exposure matrix; register-based study; occupational epidemiology.

There is extensive exposure to iron fumes or dust and welding fumes in the work environment across various industries worldwide. In Finland, the estimated number of workers exposed to iron fumes or dust or welding fumes in 1960–1984 was about 100 000 (ie, 4% of the 2.3 million economically active population) (1). Two-thirds of them were exposed to welding fumes, which contain iron fumes as one component. If it is assumed that 1% of the 2.9 billion global workforce perform welding as part of their work duties, the number of exposed workers would be about 30 million. In Finland, the most common occupations with exposure to welding fumes are welder (N=15 000), machine and engine mechanic (N=12 000), sheet metal worker (N=15 000), and plumber (N=12 000). There are also occupations with no exposure to welding fumes but which have exposure to iron fumes or dust, such as foundry and steel work. Due to the widespread exposure, the number of cancer cases attributable to exposure to iron fumes or dust or welding fumes would be very high if iron fumes or dust or welding fumes turn out to be carcinogenic.

In 1990, the International Agency for Research on Cancer (IARC) categorized welding fumes as possibly carcinogenic to humans (group 2B) on the basis on 23 epidemiologic studies. The National Institute of Occupational Safety and Health (NIOSH) concluded that there is an elevated risk of lung cancer among welders that cannot be completely accounted for by smoking or asbestos exposure (2). More recent papers also support the view that welding fumes could increase the risk of lung cancer (3–10).

On the other hand, iron dust and fumes were not classified as carcinogenic by the American Conference of Governmental Industrial Hygienists (10), and they have

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not been evaluated by IARC. Although numerous studies suggest that there is an association between exposure to iron fumes or dust at work and lung cancer risk (11–14), the possible effect from other agents in simultaneous exposure could not be ruled out completely. Exposure to iron fumes or dust and welding fumes is associated because the main constituent of welding fumes is iron and its compounds. In most cancer studies in relation to welding fumes, iron is generally neglected because the focus falls upon nickel, chromium or chromium VI, and other possible carcinogens. In addition, there has been a debate about whether exposure to mild steel or stainless steel could lead to an increased risk of lung cancer among welders.

The aim of our present study was to identify the exposure–response relationship of occupational exposure with iron fumes or dust and welding fumes and the risk of lung cancer in a follow-up of the entire Finnish workforce.

Study population and methods

The study cohort consisted of all of the 1.2 million economically active Finnish men who were born in 1906–1945 and who participated in the national population census on 31 December 1970. The Finnish census data maintained by Statistics Finland were updated for vital status to allow exact person-year calculation. Data on the occupations held for the longest time in 1970 were obtained from the population census 1970 records (15). The occupational classification was based on a modification of the International Standard Classification of Occupations in 1958. Some of the 311 basic occupational codes were further divided according to industry. The cohort was also categorized into the following five socioeconomic strata: higher white-collar, clerical, skilled blue-collar, and unskilled workers, and also farmers. The socioeconomic status of each person was determined on the basis of occupation and education in 1970 (16).

The cancer data were obtained from the Finnish Cancer Registry, which has maintained a nationwide database on all cancer cases in Finland since 1953. It is the responsibility of all physicians, hospitals, institutions, and laboratories to notify the Registry of all diagnosed cancer cases. In addition, Statistics Finland sends the Registry the death certificates on which cancer is mentioned. The data in the Registry are accurate and virtually complete (17). An 11-digit personal identification code has been given to every resident in Finland since 1967, and it is used in health care and all registers throughout the country. The codes allow reliable computerized record linkage. In our present study, the incident cases of lung cancer diagnosed between 1971 and 1995 among men born between 1906 and 1945 (30 137 cases) were extracted from the Finnish Cancer Register and sent to Statistics Finland for linkage with the data in the population census in 1970. Cancer cases of persons who had no record in the 1970 census (2.2%) were excluded.

The occupational exposure estimates used in this study were based on the Finnish job-exposure matrix (FINJEM) (1). Each occupational category is characterized by the proportion of exposed persons (P) and the mean level of exposure among the exposed (L). The exposure estimates were based on the judgment of about 20 experts at the Finnish Institute of Occupational Health. In our study, iron fumes or dust exposure is defined as the occupational inhalation exposure to iron dust or fumes from welding, smelting, grinding, or other processing of steel and other materials containing iron. It includes metallic iron and all iron compounds. Welding fume exposure is defined as occupational inhalation exposure to fumes from welding. The level of exposure to iron fumes or dust and welding fumes is expressed in milligrams of agent in cubic meters of workroom air. Occupations that had more than 5% of the persons exposed to the individual agent at any time between 1945 and 1984 are considered as potentially exposed occupations in the FINJEM. For welding fumes, the P-values were collected mainly from the work and health surveys carried out by the Finnish Institute of Occupational Health in 1997–2003, whereas the mean levels of exposure were estimated on the basis of exposure measurements made by the the same institute. The FINJEM also includes exposure estimates for asbestos, silica, nickel, chromium, lead, benzo(a)pyrene, and smoking, which are potential confounders in our current study. Smoking is expressed as the proportion of those in the occupation who smoked daily, according to data from annual surveys on the health behavior of the Finnish adult population in 1978–1991 (18).

We estimated the agent-specific and occupation-specific cumulative exposure (cumulative exposure) for every 5-year birth cohort (from 1906–1910 to 1941–1945) and 5-year calendar periods of observation from 1971–1975 to 1991–1995 (figure 1). For each birth cohort, it was assumed that the exposure started when the average age of the birth cohort was 20 years and ended in the middle year of the observation period minus 20 years (latency) or at 65 years of age, whichever came first. In each calendar year, the annual average exposure was the product of the proportion of exposed persons and the mean level of exposure in that occupation. When the exposure occurred before 1960, we used the FINJEM estimates for the period 1945–1959; otherwise the estimates for the period 1960–1984 were used.

The limits of the cumulative exposure categories for all of the chemical agents were set a priori on the basis

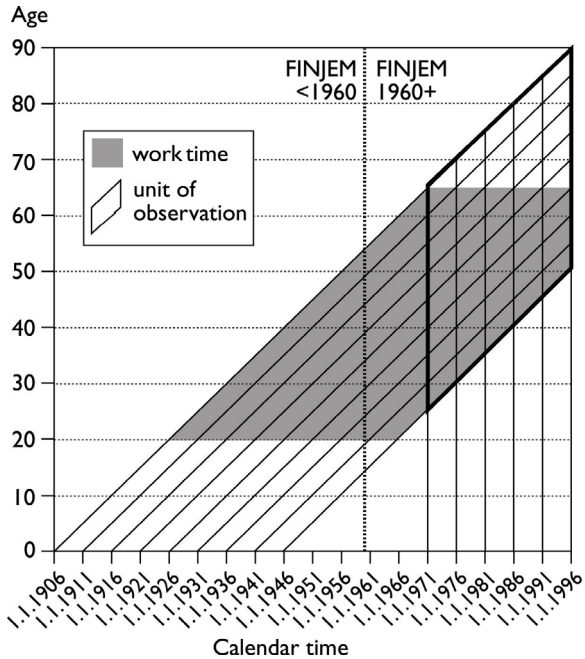

Figure 1. Units of observation, defined by birth year of the persons in the cohort (1906–1910 through 1941–1945) and calendar period of follow-up (1971–1975 through 1991–1995), theoretical exposure (work) time, and the periods of the Finnish job-exposure matrix (FINJEM) used for estimating the exposure.

of the distribution of the exposures in such a way that the highest category included only the cluster of workers with evidently the highest exposure (ie, not automatically to include, for example, one-fourth of the population). The rest of the potentially exposed workers were divided into medium and low categories. The categorized cumulative exposures to iron fumes or dust were 0.1–9.9 mg/m^3-years (low), 10–49.9 mg/m^3-years (medium), and ≥50 mg/m^3-years. The respective thresholds for welding fumes were 100 and 200 mg/m^3-years.

The expected numbers of cases for every occupation were calculated for each 5-year birth cohort and 5-year calendar period (figure 1) by multiplying person-years lived by persons in that occupation with the cancer incidence rate of the entire Finnish population in the respective stratum. The standardized incidence ratio was defined as the ratio of the observed number of cases to the expected number of cases.

The exposure–response patterns were studied with the Poisson regression analysis of the stratum-specific observed numbers of cases and person-years at risk. The unexposed persons formed the reference category.

Statistical analyses were conducted separately for exposure to iron fumes or dust and welding fumes because they were strongly correlated with each other. Smoking and occupational exposure to asbestos and silica could be controlled in the Poisson regression models because their mutual correlations and the correlations with iron fumes or dust and welding fumes were rather weak. Occupational exposure to nickel, chromium, lead, and benzo(a)pyrene were so strongly correlated with iron fumes or dust and welding fumes that they could not be included in the statistical model. The Pearson correlations of the cumulative exposure between iron fumes or dust and nickel, chromium, lead, and benzo(a)pyrene were 0.79, 0.66, 0.62, and 0.63, respectively, and those for welding fumes were 0.80, 0.68, 0.64, and 0.53, respectively. Their potential confounding effect was limited by excluding the workers who had high or moderate cumulative exposure to these agents from the cohort.

Results

Table 1 shows the occupations exposed to iron fumes or dust and welding fumes and the standardized incidence ratios (SIR) of lung cancer in these occupations. The exposure decreased slightly from 1945–1959 to 1960–1984. The highest standardized incidence ratio [SIR 1.81, 95% confidence interval (95% CI) 1.42–2.27] was found for sheet metal workers in the building industry.

The relative risk for lung cancer increased as the cumulative exposure increased for iron fumes or dust and welding fumes (tables 2–3). The relative risk in the highest exposure category was 1.35 (95% CI 1.05–1.73) for iron fumes or dust (table 2) and 1.15 (95% CI 0.90–1.46) (table 3) for welding fumes. The parameter correlation for exposure to iron fumes or dust and welding fumes is so high (correlation 0.86) that it was not possible to put both factors in the same model.

The exclusion of the high-exposure categories of nickel, chromium, lead, and benzo(a)pyrene did not change the relative risk estimate for the highest cumulative exposure to iron fumes or dust but increased the relative risk for medium exposure (table 2). Further exclusion of the high-exposure categories of welding fumes increased the relative risk (RR) for the highest cumulative iron fumes or dust exposure (RR 1.57, 1.17–2.09).

The exclusion of the high-exposure categories for nickel, chromium, lead, benzo(a)pyrene, and iron fumes or dust did not markedly change the relative risk estimate for welding fume exposure (table 3).

Of the histological subtypes of lung cancer, squamous-cell carcinoma showed the strongest dose–response relationship (tables 4 and 5). The relative risk of the highest category of iron fumes or dust was 1.94 (95% CI 1.35–2.78) and that of the highest category of welding fumes was 1.55 (95% CI 1.08–2.24). The pattern for adenocarcinoma was less consistent, and there was virtually no excess risk in any exposure category for small-cell carcinoma.

Table 1. Exposure to iron fumes or dust and welding fumes, according to the Finnish job-exposure matrix, and the incidence of lung cancer by occupation among the Finnish men who were born in 1906–1946 and who participated in the population census in 1970. [P = proportion of exposed persons, L = level (mean) of exposure, SIR = standardized incidence ratio, 95% CI = 95% confidence interval, NEC = not elsewhere classified]

Occupation [a]	Iron fumes or dust				Welding fumes				Daily smoking (1978–1991)	Risk of lung cancer (1971–1995)		
	1945–1959		1960–1984		1945–1959		1960–1984					
	P (%)	L (mg/m³)	P (%)	L (mg/m³)	P (%)	L (mg/m³)	P (%)	L (mg/m³)	P (%)	Observed cases (N)	SIR [b]	95%CI
Smelter worker, iron or steel (6301)	100	1.5	100	0.9	10	0.9	10	0.9	54	28	1.04	0.69–1.50
Smelter worker, NEC (6309)	85	0.80	85	0.50	10	0.9	10	0.9	54	14	0.85	0.46–1.43
Hardener, temperer, etc (6310)	90	0.50	90	0.25	10	0.9	10	0.9	47	10	1.33	0.64–2.45
Hot-roller (6320)	90	0.50	90	0.25	10	0.9	10	0.9	47	19	1.40	0.85–2.19
Cold-roller (6330)	90	0.20	90	0.10	10	0.9	10	0.9	47	5	0.91	0.30–2.13
Blacksmith (6340)	90	0.50	90	0.25	15	0.9	15	0.9	47	117	1.43	1.18–1.71
Foundry worker, iron or steel (6351)	90	2.00	90	1.70	5	0.9	5	0.9	46	43	1.27	0.92–1.70
Foundry worker, NEC (6359)	90	1.00	90	0.80	5	0.9	5	0.9	46	73	0.25	0.98–1.57
Wire and tube drawer (6360)	60	0.50	60	0.25	10	0.9	10	0.9	47	14	1.29	0.71–2.17
Metal mill worker, iron or steel (6391)	70	0.50	70	0.25	5	0.5	5	0.5	44	24	1.33	0.85–1.97
Metal mill worker, NEC (6399)	70	0.20	70	0.10	5	0.5	5	0.5	44	42	1.15	0.83–1.56
Turner, machinist (6500)	90	0.50	90	0.30	5	0.9	5	0.9	36	522	0.98	0.89–1.06
Fitter–assembler, etc (6510)	50	0.20	50	0.20	40	0.9	40	0.9	37	212	0.91	0.79–1.04
Car mechanic (6521)	50	0.20	50	0.17	40	0.3	40	0.3	39	266	1.14	1.01–1.29
Machine repairer, except cars (6529)	50	0.20	50	0.17	40	0.3	40	0.3	39	305	1.00	0.89–1.12
Sheetmetal worker, building (6531)	90	1.50	90	1.00	75	4.0	90	3.5	40	75	1.81	1.42–2.27
Sheetmetal worker, except building (6539)	90	2.70	90	2.00	75	8.0	90	7.0	40	203	1.18	1.02–1.35
Plumber, building (6541)	50	0.05	50	0.05	50	0.5	50	0.5	35	243	1.30	1.14–1.47
Plumber, except building (6549)	50	0.05	50	0.05	50	0.5	50	0.5	35	134	1.17	0.98–1.39
Welder and flame cutter, stainless steel >10% (6551)	100	2.00	100	1.50	100	6.0	100	4.5	44	110	0.95	0.78–1.15
Welder, shipyard (6552)	100	3.30	100	2.60	100	10.0	100	8.0	44	26	1.05	0.69–1.55
Welder, building (6553)	80	2.00	80	1.50	80	6.0	80	4.5	44	24	1.31	0.84–1.95
Welder, NEC (6559)	80	3.00	70	2.10	80	9.0	70	6.5	44	102	1.39	1.14–1.69
Plate or constructional steel worker (6560)	80	0.80	80	0.80	60	2.0	60	2.0	40	69	0.97	0.75–1.23
Metal plater and coater (6570)	50	0.03	50	0.03	5	0.2	5	0.2	40	23	1.63	1.03–2.45
Machine shop worker, NEC (6590)	25	0.50	25	0.50	10	0.9	10	0.9	40	260	1.16	1.02–1.31

[a] The occupational code of the Finnish job-exposure matrix is given in parentheses after the occupation.
[b] Reference population: all Finnish men.

Discussion

The excess risk of lung cancer among the Finnish male workers having the highest exposure to welding fumes was 15%, which is in accordance with the excess risk suggested by a meta-analysis of 60 studies related to welding fumes in 1954–2004 (4). The excess related to the highest exposure to iron fumes or dust was 35%. Due to the high correlation of exposure to iron fumes or dust and welding fumes in several occupational categories, the observed excess risk may not have been allocated accurately between these two exposures. Simultaneous exposure to iron fumes or dust, welding fumes and other potential lung carcinogens at the workplace complicated the interpretation of the independent roles of the risk factors.

A restriction of the analysis to categories without major exposure to the potential confounding agents tended to give slightly higher risk estimates and to illustrate the exposure–response characteristics. The risk related to iron fumes or dust exposure was the strongest for squamous-cell carcinoma, weaker for adenocarcinoma, and nonexisting for small-cell carcinoma of the lung.

An excess risk of lung cancer in relation to iron fumes or dust exposure has been suggested only in a few studies (10, 14, 19–21). Our findings are in line with these studies. Exposure to iron fumes or dust may give rise to siderosis, an accumulation of iron in the lungs (14, 22, 23), interstitial pulmonary fibrosis, or siderofibrosis (24), which have been suspected to be associated with an increased risk of lung cancer (25, 26). IARC has defined welding fumes as possibly carcinogenic to humans (27). The IARC evaluation of carcinogenicity did not differentiate between exposure to stainless steel welding and mild steel welding, although some previous studies explain the carcinogenic effects as being predominantly related to stainless steel welding. A slight excess risk of lung cancer was suggested in most of the studies among welders, including stainless steel, mild steel, and unspecified welding

Table 2. Observed number of cases and the relative risk (RR) and 95% confidence interval (95% CI) for lung cancer, with a 20-year latency period for cumulative exposure to iron fumes or dust among the Finnish men who were born in 1906–1946 and who participated in the population census in 1970. The workers who had simultaneous high or medium exposure to welding fumes, nickel, chromium, lead, or benzo(a)pyrene were excluded.

Exclusion due to concurrent work-related co-exposure	Cumulative exposure to iron fumes or dust								
	Low (0.1–9.9 mg/m³-years)			Medium (10–49.9 mg/m³-years)			High (≥50 mg/m³-years)		
	Observed cases (N)	RR [a]	95% CI	Observed cases (N)	RR [a]	95% CI	Observed cases (N)	RR [a]	95% CI
No exclusion	2536	1.11	1.06–1.16	311	1.10	0.97–1.23	61	1.35	1.05–1.73
Categories with ≥100 mg/m³-years of exposure to welding fumes	2341	1.10	1.05–1.15	282	1.08	0.96–1.22	4	1.33	0.50–3.55
Categories with ≥200 mg/m³-years of exposure to welding fumes	2494	1.11	1.06–1.15	306	1.10	0.97–1.24	50	1.54	1.17–2.04
Categories with medium and high exposure to nickel or chromium or lead or benzo(a)pyrene	1156	1.09	1.03–1.75	45	1.26	0.94–1.69	57	1.35	1.04–1.75
Categories with high exposure to nickel or chromium or lead or benzo(a)pyrene	2460	1.11	1.07–1.16	137	1.27	1.08–1.51	57	1.35	1.04–1.75
Categories with medium and high exposure to welding fumes or nickel or chromium or lead or benzo(a)pyrene	975	1.07	1.00–1.14	21	1.23	0.80–1.88	0	–	–
Categories with high exposure to welding fumes or nickel or chromium or lead or benzo(a)pyrene	2418	1.11	1.06–1.16	132	1.28	1.08–1.52	46	1.57	1.17–2.09

[a] Adjusted for smoking, exposure to asbestos and silica, socioeconomic status, age, and periods of follow-up, the reference category being workers unexposed to iron.

Table 3. Observed number of cases and the relative risk (RR) and 95% confidence interval (95% CI) for lung cancer, with a 20-year latency period for cumulative exposure to welding fumes, among the Finnish men who were born in 1906–1946 and who participated in the population census in 1970. Workers who had simultaneous high or medium exposure to iron, nickel, chromium, lead, and benzo(a)pyrene were excluded.

Exclusion due to concurrent work-related co-exposure	Cumulative exposure to welding fumes								
	Low (0.1–99.9 mg/m³-years)			Medium (100–199.9 mg/m³-years)			High (≥200 mg/m³-years)		
	Observed cases (N)	RR [a]	95% CI	Observed cases (N)	RR [a]	95% CI	Observed cases (N)	RR [a]	95% CI
No exclusion	2591	1.09	1.05–1.14	287	1.16	1.03–1.31	67	1.15	0.90–1.46
Categories with ≥10 mg/m³-years of exposure to iron	2305	1.10	1.05–1.15	217	1.09	0.95–1.65	51	1.25	0.95–1.65
Categories with ≥50 mg/m³-years of exposure to iron	2587	1.09	1.05–1.14	241	1.11	0.98–1.26	56	1.23	0.95–1.61
Categories with medium and high exposure to nickel or chromium or lead or benzo(a)pyrene	926	1.07	1.00.1.15	213	1.31	1.14–1.50	49	1.13	0.85–1.50
Categories with high exposure to nickel or chromium or lead or benzo(a)pyrene	2332	1.10	1.06–1.16	275	1.18	1.04–1.33	58	1.11	0.86–1.44
Categories with medium and high exposure to iron or nickel or chromium or lead or benzo(a)pyrene	905	1.07	1.00–1.15	143	1.25	1.06–1.47	38	1.24	0.90–1.71
Categories with high exposure to iron or nickel or chromium or lead or benzo(a)pyrene	2332	1.10	1.06–1.16	229	1.12	0.98–1.28	47	1.19	0.90–1.59

[a] Adjusted for smoking, exposure to asbestos and silica, socioeconomic status, age, and periods of follow-up, the reference category being workers unexposed to welding fumes.

(4, 5, 28). In our study, we found a higher standardized incidence ratio for mild steel welders in comparison with stainless steel welders (table 1).

The mechanism of carcinogenicity for welding fumes is unresolved. Exposure to any kind of granular biodurable particles may lead to lung cancer, as reported in a series of animal studies (29). Iron particles have also been suggested to contribute to the generation of reactive oxygen or nitrogen species, which may lead to cancer (30).

The general problems in previous studies include too short a follow-up and inadequate control of occupational co-exposures and other confounders. For instance, shipyard welders and car mechanics could have had exposure to asbestos, smelters and foundry workers to silica and

Table 4. Observed number of cases and the relative risk (RR) and 95% confidence interval (95% CI) for lung cancer according to its three main types and all types with a 20-year latency period, for cumulative exposure to iron fumes or dust among the Finnish men who were born in 1906–1946 and who participated in the population census in 1970.

Cancer type	Cumulative exposure to iron fumes or dust											
	None			Low (0.1–10 mg/m³ -years)			Medium (10.1–49.9 mg/m³ -years)			High (≥50 mg/m³ -years)		
	Observed cases (N)	RR [a]	95% CI	Observed cases (N)	RR [a]	95% CI	Observed cases (N)	RR [a]	95% CI	Observed cases (N)	RR [a]	95% CI
All lung cancers	27229	1.00	..	2536	1.11	1.06–1.16	311	1.10	0.97–1.23	61	1.35	1.05–1.73
Squamous-cell carcinoma	9292	1.00	..	853	1.08	1.00–1.16	109	1.16	0.95–1.41	30	1.94	1.35–2.78
Small-cell carcinoma	4652	1.00	..	475	1.21	1.09–1.33	58	1.16	0.88–1.52	7	0.98	0.47–2.01
Adenocarcinoma	3392	1.00	..	336	1.07	0.95–1.21	38	1.15	0.83–1.61	8	1.49	0.74–2.98

[a] Adjusted for smoking, exposure to asbestos and silica, socioeconomic status, age, and periods of follow-up, the reference category being unexposed workers.

Table 5. Observed number of cases and the relative risk (RR) and 95% confidence interval (95% CI) for lung cancer according to its three main types and all types with a 20-year latency period, for cumulative exposure to welding fumes among the Finnish men who were born in 1906–1946 and who participated in the population census in 1970.

Cancer type	Cumulative exposure to welding fumes											
	None			Low (0.1–10 mg/m³ -years)			Medium (10.1–49.9 mg/m³ -years)			High (≥50 mg/m³ -years)		
	Observed cases (N)	RR [a]	95% CI	Observed cases (N)	RR [a]	95% CI	Observed cases (N)	RR [a]	95% CI	Observed cases (N)	RR [a]	95% CI
All lung cancers	27192	1.00	..	2591	1.09	1.05–1.14	287	1.16	1.03–1.31	67	1.15	0.90–1.46
Squamous-cell carcinoma	9275	1.00	..	870	1.07	0.99–1.15	110	1.26	1.04–1.53	29	1.55	1.08–2.24
Small-cell carcinoma	4570	1.00	..	479	1.15	1.04–1.27	46	1.10	0.82–1.48	7	0.83	0.40–1.75
Adenocarcinoma	3379	1.00	..	342	1.08	0.95–1.21	46	1.42	1.06–1.91	7	1.14	0.54–2.40

[a] Adjusted for smoking, exposure to asbestos and silica, socioeconomic status, age, and periods of follow-up, the reference category being unexposed workers.

benzo(a)pyrene (in the FINJEM, benzo(a)pyrene is an indicator for polyclic aromatic hydrocarbons), plumbers and some subgroups of welders to asbestos, silica and benzo(a)pyrene, and sheet metal workers to nickel and chromium. We minimized the effect of confounding by adding exposure to asbestos, silica, and smoking to the models and excluding worker groups with high exposure to confounders from the study population.

The strengths of our study were the large population-based cohort, a sufficient latency period, the high-coverage data on incident cancer cases from the Finnish Cancer Register, and the availability of exposure estimates for major confounders. The identification of the cohort and the follow-up for incident cancer cases, emigration, and vital status are virtually complete (17). Stability is relatively high in most occupations (31), and therefore the cross-sectional information on occupation corresponds rather well to life-long occupational history. This correspondence is especially true for the older populations in Finland, whose turnover rate between occupations is low.

Social class was a satisfactory approximation for a whole range of lifestyle-related factors in the present study. The adjustment for social class often gives the same results as the use of carefully collected data on specific lifestyle factors (32). Therefore we adjusted the relative risks for socioeconomic status.

Although, nowadays in Finland, smoking coincides with poor socioeconomic status, in our modeling, smoking had an effect on lung cancer that was partially independent of social class and was therefore included in the final model. Our smoking data (1978–1991) are partially too recent in terms of the causation of the cancers diagnosed in 1971–1995. An adjustment based on these smoking data might have biased the relative risk estimates if the recent occupation-specific smoking habits did not correlate with those in earlier decades. Fortunately the time trends for smoking among Finnish men have shown a rather parallel decrease in most population subgroups, and therefore it is justified to use the smoking estimates from 1978–1991 to represent the long-time relative differences in smoking prevalence (16). Still, as in any study related to the etiology of lung cancer, residual confounding may have had an effect on the relative risk estimates.

The current FINJEM-based method has been adopted for the analysis of registered-based data sets in studies in

European countries, and this study method replicates a risk ratio similar to that found in previous studies (16). The ecological fallacy that theoretically might dilute or artificially create associations in a study based on aggregated data like the current one has been a problem in earlier studies in which it has been possible to compare relative risks derived from individual-level data and group-level data (32).

In conclusion, our study suggests that iron fumes or dust and welding fumes may have caused an elevated risk of lung cancer among Finnish male workers. Simultaneous exposure to other potential lung carcinogens in the workplace may have affected these results. The clustering of the excess risk especially with regard to squamous-cell cancer is a new finding and requires further investigation. The possible synergic and antagonistic effects of the mixed exposures are a challenge for future studies on exposure to iron fumes or dust and welding fumes.

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ORIGINAL RESEARCH

Occupational exposure to wood dust and formaldehyde and risk of nasal, nasopharyngeal, and lung cancer among Finnish men

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Abstract: Controversy exists over whether or not occupational inhalation exposure to wood dust and/or formaldehyde increases risk for respiratory cancers. The objective of this study was to examine the risk of nasal, nasopharyngeal, and lung cancer in relation to occupational exposure to wood dust and formaldehyde among Finnish men. The cohort of all Finnish men born between the years 1906 and 1945 and in employment during 1970 was followed up through the Finnish Cancer Registry for cases of cancers of the nose (n = 292), nasopharynx (n = 149), and lung (n = 30,137) during the period 1971–1995. The subjects' occupations, as recorded in the population census in 1970, were converted to estimates of exposure to wood dust, formaldehyde, asbestos, and silica dust through the Finnish job-exposure matrix. Cumulative exposure (CE) was calculated based on the prevalence, average level, and estimated duration of exposure. The relative risk (RR) estimates for the CE categories of wood dust and formaldehyde were defined by Poisson regression, with adjustments made for smoking, socioeconomic status, and exposure to asbestos and/or silica dust. Men exposed to wood dust had a significant excess risk of nasal cancer overall (RR, 1.59; 95% confidence interval [CI], 1.06–2.38), and specifically nasal squamous cell carcinoma (RR, 1.98; 95% CI, 1.19–3.31). Workers exposed to formaldehyde had an RR of 1.18 (95% CI, 1.12–1.25) for lung cancer. There was no indication that CE to wood dust or formaldehyde would increase the risk of nasopharyngeal cancer. Occupational exposure to wood dust appeared to increase the risk of nasal cancer but not of nasopharyngeal or lung cancer. The slight excess risk of lung cancer observed for exposure to formaldehyde may be the result of residual confounding from smoking. In summary, this study provides further evidence that exposure to wood dust in a variety of occupations may increase the risk of nasal cancer.

Keywords: job-exposure matrix, inhalation exposure, cumulative exposure, cancer risk

Introduction

There is ongoing debate on whether occupational exposure to wood dust and formaldehyde increases the risk of specific respiratory cancers.[1–3] Such exposures have been repeatedly linked to cancers of the nose, nasopharynx, and lung, but the carcinogenicity is not firmly established.[4]

In 1995 the International Agency for Research on Cancer (IARC) classified wood dust as carcinogenic to humans (ie, in the IARC category of Group 1), based on evidence of exposure to hardwood dust and the risk of adenocarcinoma of the nasal cavities and paranasal sinuses among exposed woodworkers.[3] In 2009 the IARC concluded that wood dust causes cancer of the nasal cavities, paranasal sinuses, and nasopharynx.[5] In Demers et al's[6] pooled reanalysis there was a notation with respect

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to the wood type and histological subtype of the disease: the excess risk of nasal squamous cell carcinoma indicated for softwood dust was consistent across the cohorts but it was less than that for hardwood dust.[5] Limited studies that investigated the details of tumor histology have noted substantial risks for nasal adenocarcinoma.[5]

The epidemiological studies published by the IARC after 1995 have shown contradictory evidence on carcinogenicity and occupational exposure to wood dust.[4,7–11] Several paradoxical findings have offered opportunities for new studies to recapitulate the plausible carcinogenicity with stronger evidence, such as a much greater risk by exposure to softwood dust suggested in northern Europe than in North America,[12] the conflicting dose-response pattern (strong link between nasopharyngeal cancer with low intensity and a short-duration exposure),[6,9] and the uncommon evidence in lung cancer.[4,13] Natural chemical substances exist in wood, wood preservatives, varnishes, plausible combined effects led by complex exposure to formaldehyde and other confounders within those revealed links. There has been a major weakness in lack of data in terms of quantitative exposure assessment and cancer cases; these data are necessary to enable adequate detection of the excess risks, and thus it is a logical presumption that previous findings could be somewhat underestimated.

Categorized by the IARC as Group 2A (probably carcinogenic to humans) in 1995,[3] the carcinogenicity classification of formaldehyde was shifted to Group 1 in 2006.[14] This reevaluation was based on evidence from North American studies in nasopharyngeal cancer risk. Several subsequent epidemiological studies also indicated a link between formaldehyde exposure and nasopharyngeal cancer.[11,15–17] Some studies have suggested the effect from possible exposures to other substances at work[18] and prolonged contact with formaldehyde.[19] The IARC Monograph Working Group recently reaffirmed that exposure to formaldehyde is likely to be responsible for increased risk in nasopharyngeal cancer.[5]

Although the suggestion of lung cancer risk is reported,[3] neither wood dust nor formaldehyde has been consistently associated with an elevated risk, particularly among the population who experience the highest exposures.

Nasal cancer is a rare disease. The age-adjusted incidence among northern European men varies from 0.4 per 100,000 in Sweden and Finland to 0.8 per 100,000 in Denmark.[20,21] According to the Finnish Cancer Registry (FCR), the incidence rates of nasopharyngeal cancer, nasal squamous cell carcinoma, and nasal adenocarcinoma among Finnish men over the past 3 decades were 0.3, >0.3, and 0.1 per 100,000, respectively; as for lung cancer, it has been the most common cancer of all time, with the incidence rate of 67 per 100,000.

Two percent (62 million workers) of the global workforce is occupationally exposed to wood dust[22] and 1% is exposed to formaldehyde, estimated across a wide range of occupations, with a large fraction of wood-related occupations.[23] At least 2 million workers are routinely exposed to wood dust in the work milieu worldwide.[3] In epidemiological research this widespread occupational exposure has increased the burden of stronger evidence as to whether this working population is a high-risk group. There is also an emerging urgency for in-depth study to further investigate the link between cancer by histological site and occupational exposures among the workers and industries involved.

The objective of this study was to identify the risk of nasal, nasopharyngeal, and lung cancer in relation to occupational exposure to wood dust and formaldehyde among Finnish men.

Methods

The study cohort consisted of all 1.2 million economically active Finnish men born between 1906 and 1945 who participated in the national population census on December 31, 1970. Data on the occupations held for the longest time during 1970 were obtained from the census records.[24] The socioeconomic status of each person was determined based on the person's own occupation and education as of 1970.[25] In the authors' analysis, the cohort was categorized into five socioeconomic strata: (1) higher white-collar workers; (2) clerical workers; (3) skilled, blue-collar workers; (4) unskilled workers; and (5) farmers.

The census data, maintained by Statistics Finland, were updated for vital status to allow exact person-year calculation. The cancer data were obtained from the FCR, which has a nationwide database on all cancer cases in Finland since 1953. All physicians, hospitals, and institutions that handle cancer patients and all pathological, cytological, and hematological laboratories in Finland are obligated to notify the FCR of all cancer cases diagnosed. In addition, Statistics Finland annually provides the FCR with a computerized file on death certificates in which cancer is mentioned. The data coverage in the FCR is virtually complete, and the data accuracy is high.[26] Since 1967, every inhabitant residing in Finland has been assigned a unique 11-digit personal identity code, which facilitates reliable computerized record linkages in registers throughout the country. In the present study, the incident cases of respiratory cancers diagnosed between 1971

and 1995 among Finnish men born between 1906 and 1945 were identified from the FCR for linkage with the population census data from 1970. Cancer patients who had no record in the census (2.2% or 676 cases) were excluded.

The Finnish job-exposure matrix (FINJEM) was used to calculate occupational exposure estimates for the study cohort.[27] The FINJEM covers major occupational exposures in Finland since 1945, and it addresses exposure by occupation and calendar time. Overall, the FINJEM provides exposure estimates for tens of chemical agents and for all occupational categories used in the census.[27] Some occupations were further divided according to industry, to allow for more precise exposure estimations. The proportion of exposed persons and the mean level of exposure in each occupation were used to characterize exposure. The exposure estimates are based on exposure measurements, hazard surveys, and assessments by industrial hygienists of the Finnish Institute of Occupational Health. The smoking data (percentage of workers who were daily smokers) by occupation are also included in the FINJEM. These data were obtained from annual surveys on the health behavior of the Finnish adult population during 1978–1991.[28]

In the present study, exposure to wood dust is restricted to only "inhalable" airborne dusts of any tree species. Wood dust refers to dust from solid wood, including bark; fresh and dried wood dust; dust from wooden boards; dust from chemically treated wood; and unspecified wood dust. Cellulose pulp and paper dust were not included in this definition. Exposure to formaldehyde is defined as occupational inhalation exposure to formaldehyde as gas, mist, or dust or to formaldehyde on a dust carrier. Occupations with more than 5% of persons exposed to the individual agent at any time between 1945 and 1984 are considered as exposed occupations in the FINJEM. The level of exposure to wood dust is quantified in milligrams of wood dust per cubic meter of workroom air (mg/m^3), and exposure to formaldehyde is quantified in parts per million (ppm) in the workroom air.

The authors calculated the occupation-specific cumulative exposure (CE) of the individual agents (ie, wood dust, formaldehyde, asbestos, and silica) for every 5-year birth cohort (from 1906–1910 until 1941–1945) and every 5-year calendar period of observation (from 1971–1975 until 1991–1995) (Figure 1). The exposure of each birth cohort was assumed to start in the year when the average age of

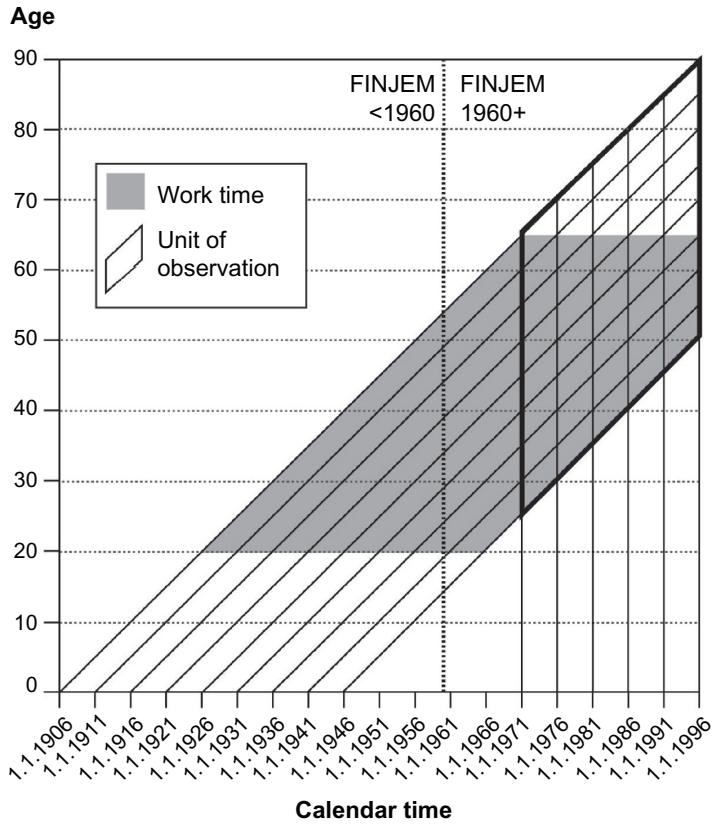

Figure 1 Units of observation, defined by birth year of the persons in the cohort (5-year birth cohorts, from 1906–1910 until 1941–1945) and calendar period of follow-up (5-year calendar periods of observation, from 1971–1975 until 1991–1995), estimated exposure period (work time), and periods in the Finnish job-exposure matrix (FINJEM) used for exposure estimation.

the birth cohort was 20; the exposure of each birth cohort was assumed to end in the year of the midpoint during the observation period, minus 20 years (latency). For instance, to calculate the cancer risk for the observation period 1981–1985 (midpoint, 1983), only the exposures until 1963 were taken into account.

The occupational stability of Finnish workers is high. Most Finnish workers (80%) remain in the same job for 5 or more years.[25] Therefore, in the calculation of exposure duration, the authors assumed that the workers remained in the same job as recorded in the census in 1970 between the ages of 20 and 65 years. In each calendar year, two aspects were used to measure the annual average exposure: the proportion of exposed persons and the mean level of exposure for each occupation. When exposure occurred before 1960, the authors used the FINJEM estimates for the period 1945–1959; otherwise, the FINJEM estimates for the period 1960–1984 were used (Table 1).

Table 1 Exposure to wood dust and formaldehyde based on the Finnish job-exposure matrix and smoking prevalence by occupation among Finnish men who were born between 1906 and 1946 and who participated in the population census in 1970

Code[a]	Occupation	Wood dust				Formaldehyde				Daily smoking, 1978–1991 (%)
		1945–1959		1960–1984		1945–1959		1960–1984		
		P (%)	L (mg/m³)	P (%)	L (mg/m³)	P (%)	L (ppm)	P (%)	L (ppm)	
0370	Technical nursing assistants	–	–	–	–	12	0.35	12	0.20	25
3040	Livestock breeders	–	–	–	–	–	–	10	0.15	23
3120	Livestock workers	–	–	–	–	–	–	10	0.15	29
3400	Forestry and logging workers	–	–	–	–	–	–	16	0.05	38
6050	Textile finishers/dyers	–	–	–	–	–	–	5	0.20	28
6060	Textile quality controllers	–	–	–	–	–	–	9	0.10	28
6140	Upholsterers	70	0.10	65	0.05	–	–	–	–	49
6160	Garment sewers	–	–	–	–	–	–	5	0.10	49
6351	Foundry workers, iron/steel	–	–	–	–	–	–	45	0.80	46
6352	Foundry workers, nonferrous metal	–	–	–	–	–	–	18	0.90	46
6359	Other foundry workers	–	–	–	–	–	–	12	0.70	46
6700	Timber workers	60	0.70	56	0.70	–	–	–	–	33
6710	Sawmill workers	95	0.80	95	0.75	–	–	–	–	43
6720	Plywood, wooden board makers	70	1.00	66	1.00	–	–	40	0.80	33
6731	Floor layers	95	0.20	95	0.50	–	–	20	1.00	37
6739	Construction carpenters	95	0.20	95	0.50	–	–	–	–	37
6740	Boat builders etc	90	0.20	90	0.20	–	–	30	0.20	37
6750	Bench carpenters	95	1.20	95	1.10	–	–	10	0.20	25
6760	Cabinetmakers, joiners	95	1.40	95	1.00	–	–	20	0.20	32
6770	Woodworking machine operators	95	2.50	95	2.50	–	–	20	0.30	44
6780	Wooden surface finishers	80	0.20	80	0.10	–	–	20	0.20	37
6790	Woodworkers, nec	95	0.20	95	0.10	–	–	12	0.20	37
6809	Painters, nec					–	–	18	0.80	43
6811	Varnishers, lacquerers, wood industry	–	–	–	–	–	–	90	1.00	43
7310	Cookers, furnace men (chemical process)	–	–	–	–	10	0.50	18	0.60	34
7350	Paper/paperboard mill workers	–	–	–	–	–	–	7	0.50	37
7392	Paint/pharmaceuticals makers	–	–	–	–	–	–	9	0.60	34
7399	Chemical workers, nec	–	–	–	–	20	0.20	27	0.20	34
7522	Plastic product workers	–	–	–	–	5	0.10	56	0.10	41
7529	Plastic product workers, nec	–	–	–	–	5	0.10	56	0.10	41
7570	Paper product workers	–	–	–	–	10	0.20	10	0.15	55
8312	Char workers, wood industry	80	4.00	79	4.00	–	–	–	–	33

Note: [a]Occupational code of Finnish job-exposure matrix.
Abbreviations: P, proportion of exposed persons (%); L, level (mean) of exposure; nec, not elsewhere classified.

The estimated levels of CE were divided into three categories for analysis: (1) unexposed (reference group), (2) low, and (3) high. The wood dust results in these categories were as follows: unexposed, 0.1–9.9 mg/m^3-years (low), and ≥10 mg/m^3-years (high). The formaldehyde results in these categories were as follows: unexposed, 0.1–0.9 ppm-years (low), and ≥1.0 ppm-years (high). The CEs for occupational exposure to asbestos and silica dust in models for lung cancer were categorized as follows: asbestos – unexposed, 0.1–1.9 fibers/cm^3-years (low), and ≥2 fibers/cm^3-years (high); silica dust – unexposed, 0.1–0.9 mg/m^3-years (low), and ≥1.0 mg/m^3-years (high).

Statistical analysis

The expected numbers of cases for every occupation were calculated for each 5-year birth cohort and 5-year calendar period (Figure 1) by multiplying the number of person-years in each stratum by the corresponding cancer incidence rate of the entire study cohort. The standardized incidence ratio (SIR) was defined as the ratio of the observed to the expected number of cases. The 95% confidence intervals (CIs) for each SIR were estimated assuming that the observed number of cases followed the Poisson distribution.

The exposure-response patterns were studied with the Poisson regression analysis of the stratum-specific observed numbers of cases and person-years at risk. Relative risk (RR) estimates were calculated by comparing the categories of CE with the unexposed category. Smoking was included in all models, and occupational co-exposures to asbestos and silica dust were included in the model for lung cancer. Wood dust and formaldehyde were mutually adjusted in all models. A 20-year latency assumption was used in all models.

Results

Finnish workers were exposed at relatively low formaldehyde levels; out of 27 occupations, only two were detected with average exposure at 1 ppm: (1) floor layers and (2) varnishers, lacquerers in the wood industry. Among the 13 occupational groups that involved wood dust, four occupations at the highest exposure proportions (70%–95%) and levels (1–4 mg/m^3) were in the wood-based industries (Table 1).

Construction carpenter was the only occupation with a significantly increased SIR for lung cancer among the 32 occupations with exposure to wood dust or formaldehyde (Table 2). Construction carpenters had an SIR of 1.19 (95% CI, 1.14–1.25). There were no significantly elevated SIRs for nasal or nasopharyngeal cancer in any occupation (Table 2).

A significantly elevated RR for nasal cancer was observed for wood dust exposure (RR, 1.59; 95% CI, 1.06–2.38); the RR did not vary by CE level (Table 3). Smoking was a significant cofactor in this model (RR, 1.23 per 10% increase in prevalence of smokers in the job category; 95% CI, 1.02–1.47). Nasal squamous cell carcinoma showed excess risk associated with exposure to wood dust (RR, 1.98; 95% CI, 1.19–3.31), and the result was similar in the category of formaldehyde exposure (Table 3).

No associations were found between exposure to formaldehyde and any histological type of nasal cancer (Table 3). Of 22 rare nasal adenocarcinoma cases in the study population, three cases (14%) were exposed to wood dust: a woodworker, a woodworking machine operator, and a construction carpenter. The two former occupations also had co-exposure to formaldehyde. No excess of nasopharyngeal cancer was seen among the workers who were exposed to wood dust or to formaldehyde.

The risk of lung cancer was not detected in relation to exposure to wood dust (Table 3). Workers who experienced any level of CE to formaldehyde were associated with a slightly elevated excess of lung cancer (RR, 1.18; 95% CE, 1.12–1.25).

In the statistical model of lung cancer, smoking was a significant cofactor (RR, 1.22 per 10% increase in prevalence of smokers in the job category; 95% CI, 1. 20–1.24). The category of highest exposure to silica dust showed an RR of 1.39 (95% CI, 1.16–1.65), and that of asbestos showed an RR of 1.29 (95% CI, 1.19–1.38).

Discussion

Wood has been the preeminent renewable energy in the world throughout the centuries. Of the total wood harvested globally, 1700 million cubic meters contribute to industrial use each year.[22] In Finland, the forest sector accounts for 4% of gross domestic product, and 10% in regional terms (southeast and eastern Finland); the number of workers employed by the forest sector has stabilized at 3% of the total workforce. Formaldehyde is a ubiquitous volatile organic compound that has been widely used in various sectors for nearly a century. The largest formaldehyde-consuming industries include furniture and foundry (cast iron, steel, and nonferrous metal). The wood industry is regarded as a high user of formaldehyde-based resin and dyes, used in the production of pressed-wood products such as particleboard, plywood paneling, medium-density fiberboard, and other wooden products for flooring, furniture, and interior and exterior construction material. According to IARC, the heaviest expo-

Table 2 Standardized incidence ratios (SIRs)[a] of nasal, nasopharyngeal, and lung cancer in 1971–1995 among Finnish men in occupations with exposure to wood dust or formaldehyde who were born between 1906 and 1946 and who participated in the population census 1970

Code[b]	Occupations with exposure to wood dust or formaldehyde	Nasal cancer			Nasopharyngeal cancer			Lung cancer		
		Obs (n)	SIR	95% CI	Obs (n)	SIR	95% CI	Obs (n)	SIR	95% CI
0370	Technical nursing assistants	–	–	0.00–256	–	–	0.00–559	1	0.70	0.02–3.88
3040	Livestock breeders	–	–	0.00–26.6	–	–	0.00–60.3	14	0.78	0.42–1.30
3120	Livestock workers	–	–	0.00–7.16	–	–	0.00–17.8	43	0.78	0.56–1.05
3400	Forestry and logging workers	9	0.70	0.32–1.32	5	1.26	0.41–2.93	1453	1.00	0.95–1.05
6050	Textile finishers/dyers	1	3.15	0.08–17.5	–	–	0.00–26.0	37	1.03	0.73–1.42
6060	Textile quality controllers	–	–	0.00–220	–	–	0.00–497	1	0.50	0.01–2.81
6140	Upholsterers	–	–	0.00–11.9	–	–	0.00–21.8	38	1.14	0.81–1.57
6160	Garment sewers	–	–	0.00–31.5	–	–	0.00–64.5	12	0.90	0.46–1.57
6351	Foundry workers, iron/steel	–	–	0.00–12.4	–	–	0.00–27.4	43	1.27	0.92–1.70
6352	Foundry workers, nonferrous metal	–	–	0.00–69.2	–	–	0.00–152	5	0.89	0.29–2.09
6359	Other foundry workers	–	–	0.00–7.18	–	–	0.00–15.7	73	1.25	0.98–1.57
6700	Timber workers	1	2.03	0.05–11.3	–	–	0.00–16.6	69	1.21	0.94–1.53
6710	Sawmill workers	6	2.23	0.82–4.85	1	0.80	0.02–4.48	279	0.89	0.79–1.00
6720	Plywood, wooden board makers	2	2.55	0.31–9.20	–	–	0.00–10.3	82	0.96	0.76–1.19
6731	Floor layers	–	–	0.00–152	–	–	0.00–287	1	0.42	0.01–2.34
6739	Construction carpenters	16	1.28	0.73–2.07	5	0.91	0.30–2.13	1885	1.19	1.14–1.25
6740	Boat builders etc	2	4.25	0.52–15.4	–	–	0.00–15.5	53	0.94	0.71–1.23
6750	Bench carpenters	1	0.85	0.02–4.75	1	1.65	0.04–9.17	110	0.80	0.66–0.96
6760	Cabinetmakers, joiners	1	1.25	0.03–6.98	–	–	0.00–9.33	76	0.84	0.66–1.05
6770	Woodworking machine operators	1	0.80	0.02–4.47	1	1.69	0.04–9.43	122	0.86	0.71–1.02
6780	Wooden surface finishers	–	–	0.00–27.3	–	–	0.00–62.4	21	1.33	0.83–2.04
6790	Woodworkers, nec	2	7.34	0.89–26.5	–	–	0.00–29.1	30	0.96	0.65–1.37
6809	Painters, nec	1	0.99	0.03–5.54	–	–	0.00–8.17	107	0.93	0.76–1.13
6811	Varnishers, lacquerers, wood industry	–	–	0.00–396	–	–	0.00–740	–	–	0.00–5.22
7310	Cookers, furnace men (chemical process)	–	–	0.00–16.0	–	–	0.00–35.8	35	1.31	0.91–1.83
7350	Paper/paperboard mill workers	1	0.65	0.02–3.64	2	2.83	0.34–10.2	143	0.91	0.77–1.07
7392	Paint/pharmaceuticals makers	–	–	0.00–22.4	–	–	0.00–49.5	14	0.75	0.41–1.26
7399	Chemical workers, nec	–	–	0.00–14.0	–	–	0.00–30.6	31	1.10	0.75–1.56
7522	Plastic product workers	–	–	0.00–10.9	–	–	0.00–21.4	31	0.94	0.64–1.34
7529	Plastic product workers, nec	–	–	0.00–26.1	–	–	0.00–49.7	15	1.16	0.65–1.92
7570	Paper product workers	1	7.39	0.10–21.1	–	–	0.00–29.4	21	0.80	0.50–1.23
8312	Char workers, wood industry	–	–	0.00–825	–	–	0.00–2838	–	–	0.00–5.21

Notes: [a]Reference population: all Finnish men; [b]occupational code of Finnish job-exposure matrix.
Abbreviations: Obs, observed cases; CI, confidence interval; nec, not elsewhere classified.

sures to wood dust have been reported in the cabinetmaking and wooden furniture manufacturing industry, followed by the wooden board industry, with wood dust levels frequently above 5 and 1 mg/m^3, respectively.[3] The highest continuous exposures to formaldehyde (frequently above 1 mg/m^3) have been measured in particleboard mills and during the varnishing of furniture and wooden floors.[3] Lower exposures are widely encountered (eg, in construction carpentry). In many occupations (eg, floor layers, plywood makers, cabinetmakers and joiners) there was combined exposure to both wood dust and formaldehyde.

The American Conference of Governmental Industrial Hygienists recognizes wood dust as a confirmed human carcinogen and recommends a permissible exposure limit (PEL) of 1 mg/m^3 for hardwoods and 5 mg/m^3 for softwoods, and a short-term exposure limit of 10 mg/m^3 for softwoods. The US National Institute for Occupational Safety and Health has established a recommended exposure limit for wood dust of 1 mg/m^3 – this covers all soft- and hardwoods except western red cedar. The US Occupational Safety and Health Act of 1970 regulates wood dust as a nuisance dust (western red cedar: PEL, 15 mg/m^3); however, it strongly encourages employers to keep exposures to a minimum and to adopt the levels set by the American Conference of Governmental Industrial Hygienists. The PEL for formaldehyde in the workplace covered by the Occupational Safety and Health Act is 0.75 ppm, the standard includes a short-term exposure limit of 2 ppm.

Table 3 Cancer of the nose, nasopharynx, and lung among Finnish men who were born between 1906 and 1946 and who participated in the population census in 1970, by cumulative exposure to wood dust and formaldehyde: number of observed cases (Obs), relative risk (RR), and 95% confidence interval (CI)

Cancer site	Cumulative exposure to wood dust (mg/m^3-years)				Cumulative exposure to formaldehyde (ppm-years)	
	None	Any	0.1–9.9	≥10	None	Any
Nose						
Obs (n)	260	32	21	11	275	17
RR	1	1.59	1.63	1.57	1	1.11
95% CI	Ref	1.06–2.38	0.85–3.11	0.98–2.52	Ref	0.66–1.87
Nasal squamous cell carcinoma						
Obs (n)	146	21	14	7	158	9
RR	1	1.98	1.94	2.06	1	0.97
95% CI	Ref	1.19–3.31	1.08–3.51	0.91–4.68	Ref	0.47–2.00
Nasopharynx						
Obs (n)	142	7	–	–	144	5
RR	1	0.66	–	–	1	0.87
95% CI	Ref	0.30–1.45	–	–	Ref	0.34–2.20
Lung						
Obs (n)	27387	2750	1898	852	28306	1831
RR	1	0.93	0.95	0.91	1	1.18
95% CI	Ref	0.87–0.98	0.87–1.03	0.84–0.98	Ref	1.12–1.25

Notes: A 20-year latency period was assumed; all RRs were adjusted for socioeconomic status, age, period of follow-up, and smoking; RRs for wood dust were adjusted for formaldehyde exposure and vice versa; RRs for lung cancer were further adjusted for exposure to asbestos and silica dust.
Abbreviation: Ref, reference category.

Nasal cancer

Risk for nasal cancer among Finnish workers exposed to wood dust was considerably lower than the excess risks reported in Scandinavian studies,[27,28] the pooled European case-control study,[6] and the meta-analysis of twelve case-control studies on sinonasal cancer,[29] in which the RRs were generally between 2.0 and 2.5. The average odds ratio of nasal cancer for all wood-related occupations was 2.0 (95% CI, 1.6–2.5) according to the IARC in 1995[3] and 2.6 (95% CI, 2.1–3.3) in a later meta-analysis for male woodworkers.[29] However, the risk detected in the present study was higher than in most of the cohort studies reviewed by the IARC in 1995.[3,14] In Finland, conifer trees (pine and spruce) are the main components of the softwood forest (90%–95% nationwide coverage) although there are also some minor fractions of hardwood species like birch and other deciduous trees. The predominant wood dust exposure to softwood processing may explain why the risk is smaller than in other studies. The small excess was also likely driven by a large cluster in the cohort – the group of construction carpenters at a relatively low exposure level to wood dust.

Cancer in workers in wood-related industries has been highlighted in a recent joint epidemiological study by five Nordic countries (N = 2.8 million cases).[30] The study reported that of the 3523 male workers with an observed case of nasal cancer, 10% were woodworkers (SIR, 1.84; 95% CI, 1.66–2.04); the next-highest percentage was 4% (137 cases), for building hands in construction work (SIR, 1.24; 95% CI, 1.05–1.47). These results reflect the potential cancer risk associated with woodworkers in the similar Nordic population. However, the study was occupation specific and so did not provide RR estimates for the various substances of exposure such as wood dust.

Only a few studies have included details of tumor histology and have shown a substantial risk of nasal adenocarcinoma related to high levels of exposure to hardwood dust, but quantitative exposure data on wood dust has, in general, rarely been reported. The authors' result is consistent with the epidemiological evidence from studies in Nordic countries that reported a modest risk of nasal squamous cell carcinoma among woodworkers who were exposed exclusively to softwood dust,[12] although the probability could be partially due to chance, as specific wood types were not distinguished in the present study. Nasal squamous cell carcinoma has been the most common (70%) type of nasal cavity and paranasal sinus cancers.

Exposure to wood dust varies by species of wood, industrial process, chemical treatment of wood, and distance from the source. Wood itself covers an extensive range of chemical, physical, and mechanical properties (relevant to inhalable particle size); the disparity is mainly between species but could also be within a species. On the other hand, mixed exposure to more than one species of wood was very common in this study, which complicates the exposure assessment and cancer risk profile of different species of wood.

Limited epidemiological evidence has suggested that formaldehyde causes sinonasal cancer in humans.[14] The unconvincing result from the majority of studies on formaldehyde has likely been affected by potential confounders such as wood dust in co-exposure to formaldehyde and wood dust at work, for example.[14] The point estimate of the RR in the present study does not significantly indicate an excess risk in nasal cancer.

Several European studies that assessed the pathogenesis aspect and were reviewed by Blot et al[8] have demonstrated a plausible but inconsistent pattern as to whether exposure to wood dust elevates the risk of a benign precursor lesion, and whether a benign lesion could be a precursor to carcinoma. These studies shared some common weaknesses, such as inability to adjust for co-exposures at work, have affected the findings.

Nasopharyngeal cancer

The absence of increased risk for nasopharyngeal cancer associated with exposure to wood dust or formaldehyde was noted in the present study. Because there are only rare cases and fairly low exposure to formaldehyde in Finland compared with other industrialized countries, the detection of excess risk of nasopharyngeal cancer could be more difficult. This result was not in accordance with the recent reevaluation from the IARC in 2009[5] and two previous meta-analyses,[2,31] all of which suggest that formaldehyde has a causal role for cancer of the nasopharynx among workers exposed to substantial levels of formaldehyde.

There is a lack of information available to distinguish the usage of formaldehyde according to wood types in the industry. Although workers in the Finnish cohort experienced exposure to less formaldehyde in general, the circumstances of processing mixed wood have been unavoidable. Presumably, pressed-wood products containing phenol-formaldehyde resin, which is commonly used in softwood plywood, involve formaldehyde at considerably lower rates than those containing urea-formaldehyde resins, used in hardwood. The metabolite rate of the latter has been believed to be lower, which could pose a greater health risk. The resin-to-wood ratio contained in medium-density fiberboard (80%–100% hardwood – maple, oak, and cherry, for example) is higher than any other urea-formaldehyde- and phenol-formaldehyde-based pressed-wood product.

Lung cancer

Lung cancer was not a suggested risk among workers exposed to wood dust in this study, and most previous studies also lack a consistent association.[3,5,6,31] The increased risk of lung cancer among workers with exposure to formaldehyde is considered to be led by the residual confounding effect of smoking and of co-exposure to formaldehyde and asbestos or crystalline silica, for example. In the stratified analysis, excess risk was absent in the higher CE group (≥1.0 ppm). The epidemiological evidence did not support a causal role for formaldehyde in lung cancer.[5,14,15] The carcinogenicity may not reach the lower airway and lungs because of the highly reactive and rapid metabolite properties, suggesting that organs without direct contact with formaldehyde do not develop neoplasia.[15,32] Only 10% of inhaled formaldehyde, at the greatest extent, reaches the lower airway at resting condition in humans.[32,33]

Discussions of the overall study

The present study has been able to tackle the major weaknesses in previous studies, allowing follow-up of lifetime cumulative exposure from the presumed first exposure at the age of 20 to the cancer observation period in 1971–1995 (at 25 years of cancer follow-up), and to facilitate the analysis for a 20-year latency period with sufficient cancer data. The authors were able to apply mutual adjustment for wood dust and formaldehyde exposures, while controlling for occupational co-exposures and other confounders at the aggregate level. National registries are a useful, effective, practical, and cost-effective, source of data to facilitate large-scale epidemiological study. There is high accuracy and coverage of incident cancer cases, as the FCR covers more than 99% of all malignant solid tumors diagnosed in Finland.[26]

The current FINJEM-based method has been proven to replicate known cancer risks.[25] Job stability is relatively high in most occupations in Finland,[26] and therefore the cross-sectional information on occupation represents the lifelong occupational history rather comprehensively. This is especially true for older populations in which the turnover rate between occupations is low.

The smoking data (1978–1991) were to some extent too recent – in terms of the causation of the cancers diagnosed between 1971 and 1995. Fortunately, the time trends for smoking among Finnish men have been rather similar in most occupations, and it was therefore considered reasonable to use the estimates from the period 1978–1991 to represent relative differences in smoking prevalence by occupation.[26] As in any study utilizing aggregate estimates instead of individual data, residual confounding may still tend to influence the RR estimates.

The ecological fallacy that theoretically might dilute or artificially create associations in a study based on aggregated data has not been a real problem in earlier studies in which it has been possible to compare RR derived from individual-level data and group-level data.[30]

Conclusion

In summary, the current study provides further evidence that exposure to wood dust in a variety of occupations may increase the risk of nasal cancer. The results for formaldehyde are inconclusive. The modest but statistically significant association between lung cancer risk and low cumulative exposure to formaldehyde may result from residual confounding of smoking or exposures to other occupational hazards that have not yet been satisfactorily investigated. The authors conclude that occupational exposure to wood dust appears to elevate the risk of nasal cancer but not of nasopharyngeal or lung cancer. Formaldehyde does not appear to increase risk in any way whatsoever. The present preliminary study also raises the issues of future quantitative individual risk assessment and histology-specific occupational cancer epidemiological study. Assessing the physical and chemical properties, the plausible domino and synergistic effects toward the cluster of complex exposures at work, the associated effect modifiers, and the histopathology of specific cell types are future challenges to further understanding of carcinogenesis as a result of exposure to wood dust and formaldehyde.

Disclosure

The authors report no conflicts of interest in this work.

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Occupational exposure to wood dust and risk of nasal and nasopharyngeal cancer: A case-control study among men in four nordic countries—With an emphasis on nasal adenocarcinoma

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The current study aims to provide stronger evidence to aid in our understanding of the role of cumulative occupational exposure to (softwood-dominated) mixed wood dust in aetiology of nasal cancer. We included broad exposure occurred in a range of wood-processing occupation across varied industries in four Nordic countries. A population-based case-control study was conducted on all male cases with nasal adenocarcinoma (393 cases), other types of nasal cancer (2,446) and nasopharyngeal cancer (1,747) diagnosed in Finland, Sweden, Norway and Iceland between 1961 and 2005. For each case, five male controls, who were alive at the time of diagnosis of the case (index date), were randomly selected, matched by birth-year and country. Cumulative exposures (CE)s to wood dust and formaldehyde before the index date were quantified based on a job-exposure matrix linked to occupational titles derived from population censuses. Hazard ratios (HRs) for the CE of wood dust were estimated by conditional logistic regression, adjusted for CE to formaldehyde and 95% confidence intervals (CIs) were calculated. There was an increasing risk of nasal adenocarcinoma related to wood dust exposure. The HR in the highest CE category of wood dust ($\geq$ 28.82 mg/m^3-years) was 16.5 (95% CI 5.05–54.1). Neither nonadenocarcinoma of the nose nor nasopharyngeal cancer could be linked to wood dust exposure. CE to softwood-dominated mixed wood dusts is strongly linked with elevated risk in nasal adenocarcinoma but not with other types of nasal or nasopharyngeal cancer.

The discovery of excessive deaths due to nasal adenocarcinoma among the British furniture workers has shed light on wood dust as an occupational carcinogen in 1960 sec.[1] Nasal adenocarcinoma is rare among the general population but quite common among the workers, who are heavily exposed to hard wood dust, accounting for up to 500-fold excess risk.[1,2] In the EU, at least 3.6 million workers in the are exposed to wood dust. Among these, 1.5 million were exposed to low levels ($<$0.5 mg/m^3) and 0.2 million were exposed to high levels ($>$5 mg/m^3), particularly in furniture industry.[3]

In the 1980 sec, The International Agency for Research on Cancer (IARC) initially classified carcinogenicity of wood dust in a large variety of wood processing industries and occupations, that is, cabinet and furniture manufacturing (Group 1: Carcinogenic to humans), carpentry or joinery (Group 2B: Possibly carcinogenic to humans), lumber and sawmill industries (Group 3: Not classifiable as to its carcinogenicity to humans) and pulp and paper industry (Group 3).[4,5] Wood dust as a singular substance was evaluated separately when IARC classified it as a Group 1 human carcinogen based on exposure to hardwood dust a decade later.[2] Wood dust was re-evaluated again in 2009,[2,6,7] attaining its status as Group 1 human carcinogen specifically for two primary sites, that is, nose and nasopharynx. The classifications

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What's new?

Nasal adenocarcinoma is rare among the general population but quite common among furniture workers, who are heavily exposed to wood dust. Here, the authors conducted a population-based case-control study on all males with nasal adenomacarcinoma in the Nordic countries. They found that low-level of cumulative exposure to softwood-dominated mixed wood dusts is strongly linked with elevated risk in nasal adenocarcinoma, but not with other types of nasal or nasopharyngeal cancer, raising important questions on the selective carcinogenic potential of different wood dusts.

were based on high levels of exposure to mixed wood and/or hardwood dust, use of deciduous (hardwood) tree species or both.[6,7] The overall carcinogenicity evidence appears to be the strongest for exposure to hardwood dust and risk of nasal adenocarcinoma, but being weak or nonexistent in terms of exposure to softwood dust. Although about fivefold excesses were reported among workers primarily exposed to softwood dust in the Nordic countries[8,9] and the United States,[10] at least three studies have attempted to establish an argument that denies the carcinogenicity link, specifically between softwood dust nasal adenocarcinoma.[8,9,11] These studies faced challenges in getting sufficient power to detect an excess due to rarity of nasal cancer (even in a joint-Nordic study[8]) and very low exposure levels in sawmill[10] and plywood[11] industries. So far, there is no clear agreement on carcinogenicity of softwood dust.

Mixed exposure to more than one species of wood is common in wood processing industries.[3,12] Softwood is the most commercially important wood species worldwide, covering two-thirds of woods used in wood-processing industry.[2] Similarly, in the Nordic countries, deciduous forest only covered a small part (4%).[13]

The evidence of increased cancer risk associated with prolonged or cumulative exposure (CE) to either softwood alone or softwood dominated mixed wood dust has not been reported. Over a half-century of studies on carcinogenicity of wood dust and the progression of regulatory permissive level of exposure to wood dust have left two key issues unanswered, which motivated the current study to explore: (*i*) the magnitude of carcinogenic risk due to exposure to mixed wood dust and (*ii*) whether a prolonged exposure of the levels experienced in Nordic countries elevates the risk in nasal and nasopharyngeal cancers.

Material and Methods

This case-control study was nested in the cohort of 14.9 million individuals who participated in population censuses. Occupational information was obtained from census records since 1960, 1970 and 1980 in Norway, 1960, 1970, 1980 and 1990 Sweden, 1970, 1980, 1990 in Finland and from 1981 in Iceland.[14] Each person was followed from the first available census until the date of emigration, death or December 31 of the following years: 2003 in Norway, 2004 in Iceland, 2005 in Finland and Sweden. A detailed description of the NOCCA cohort was given in an earlier publication by Pukkala *et al.*[14] As we had no access to the individual records from Denmark, Danish data were not included. The individuals' information on cancer, death and emigration were accessed through personal identity codes, which were linked to cancer registries and national population registries.

The cases in this study are all men diagnosed with nasal adenocarcinoma (393 cases), other nasal cancer (2,446) and nasopharyngeal cancer (1,747) in Finland, Sweden, Norway and Iceland after the first available census and before the end of follow-up. We applied the International Classification of Diseases for Oncology (ICD-O) classification of topography codes for cancer of the nose and sinuses (C30–31) and nasopharynx (C11). The cases of adenocarcinoma were identified with histology codes used in the cancer registries in four Nordic countries. All cases had to have a minimum age of 20 years at diagnosis and at least one census record prior to the diagnosis.

Five male controls per case were randomly selected among persons who were alive and free from the cancers studied on the date of diagnosis of the case (hereafter the "index date" of the case–control set). Cases and controls were matched for the year of birth, and country.

The quantitative occupational exposures to wood dust and formaldehyde were estimated for each case and control based on conversions of occupational codes to measurable exposure scenarios utilizing NOCCA job exposure matrix (JEM). The JEM covers over 300 specific job titles, 29 exposure agents and four exposure periods 1945–59, 1960–74, 1975–84 and 1985–94.[15] In the JEM, all exposure agents are characterized by the proportion of exposed (*P*) and the mean level of exposure among the exposed persons (*L*) in each specific occupation and time period.

Wood dust is defined as occupational inhalable exposure to wood dust, both freshly cut and dried wood dust, originating from solid wood including bark from pine, spruce, birch, other softwoods and hardwoods. Occupations with a probability (*P*) of at least 5% of the occupation being exposed to an annual mean level (*L*) of 0.1 mg of wood dust in cubic meter of workroom air at any time in 1945–95 were classified as exposed. The *P*L* estimates were highest among timber men, sawyers, plywood and fibreboard workers, construction carpenters, wooden boat builders, bench carpenters, cabinetmakers and joiners, woodworking machine operators and wooden surface finishers (Table 1).

Formaldehyde is defined by occupational inhalable exposure to formaldehyde as gas, mist, dust or as attached to dust. It was measured in parts per million (ppm) of agent in the workroom air. Occupations with possibly at least 5% of persons in the occupation exposed at work to an annual

Table 1. Occupational exposure to wood dust in varied occupations based on the NOCCA-JEM—a snap shot among the Finnish population in 1945–95 (nonzero exposures only)

Occupations	*P* (1945–59)	*L* (1945–59)	*P* (1960–74)	*L* (1960–74)	*P* (1975–84)	*L* (1975–84)	*P* (1985–94)	*L* (1985–94)
Upholsterers	70	0.10	65	0.05	65	0.05	65	0.05
Timbermen	60	0.70	56	0.68	56	0.68	56	0.30
Sawyers	95	0.80	95	0.75	95	0.75	95	0.60
Plywood and fibreboard workers	70	1.00	66	1.02	66	1.02	66	0.50
Construction carpenters	95	0.20	95	0.47	95	0.47	95	0.50
Wooden boatbuilders, coach-body builders etc.	90	0.20	90	0.20	90	0.20	90	0.20
Bench carpenters	95	1.20	95	1.14	95	1.14	95	1.00
Cabinetmakers and joiners etc.	95	1.40	95	1.00	95	1.00	95	1.00
Woodworking machine operators etc.	95	2.50	95	2.50	95	2.50	95	2.00
Wooden surface finishers	80	0.20	80	0.10	80	0.10	80	0.10
Woodworking occupations, nec	95	0.20	95	0.10	95	0.10	95	0.10
Remarks (For more information, refer to Material and Methods):								
P: Proportion (%)								
L: Level (mg/m3)								

mean level of at least 0.1 ppm at some time in 1945–95 were classified as exposed. Nonoccupational exposure was not included, as its annual mean exposure from indoor emissions (*e.g.*, particleboard, parquet, furniture, textiles) and ambient air (*e.g.*, engine exhaust) does not often exceed 0.1 ppm, based on the NOCCA-JEM.

CE of wood dust and formaldehyde exposure for each case and control was calculated by multiplying the *P* and *L* by employment period (T) in the exposed occupation. The employment period for each individual was presumed to start at the age of 20 and end at the 65. If there were different occupational codes in census records for a given person, the individual was assumed to have changed occupation in the middle of the period between census years. For each occupational code, a corresponding value on proportion and level of exposure ($P \times L$) was assigned from the NOCCA JEM file. This value was then multiplied by employment period (T) in years during which the subject was in that occupation. A 10-year latency period was adopted, that is, exposures occurred 10 years before the index date were exempted. Hazard ratios (HRs) were estimated by conditional logistic regression in both univariate and multivariate models and 95% confidence intervals (CIs) were calculated assuming a Poisson distribution of the cases. In the multivariate models, CEs for wood dust and formaldehyde were mutually adjusted. The CEs are categorized into low, moderate and high corresponding to the 50% and 90% percentiles of CEs distribution among all exposed cases and controls. The nonexposed category was used as the reference.

In models with 10-year latency assumption, exposures that occurred 10 years prior to the index date were not counted. We also made some sensitivity analyses with 20-year latency assumption.

Results

In univariate analysis, a strongly increasing risk with increasing CE to wood dust was observed for nasal adenocarcinoma, with a 29-fold increased risk in the highest CE category (Table 2). After adjustment with formaldehyde, the risks for nasal adenocarcinoma remained significant and increased consistently from threefold in the low to eightfold in the moderate and 17-fold in the high CE category (Table 3). A tenfold excess risk was observed for moderate CE to formaldehyde and risk of nasal adenocarcinoma in a univariate analysis (Table 2) but the excess decreased to 2.06 (95% CI 1.16–3.60) when the exposure to wood dust was added to the model (Table 3).

We did not detect an association between wood dust exposure and nonadenocarcinoma nasal cancer.

Neither nasal cancer other than adenocarcinoma nor nasopharyngeal cancers could be linked to CE to formaldehyde (Table 2).

Discussion

In our study, a strong, dose-response association was observed between CE to wood dust and adenocarcinoma of the nose, but not with other types of nasal cancer or

Table 2. Univariate hazard ratios for nasal and nasopharyngeal cancer in relation to cumulative exposure to wood dust and formaldehyde respectively, with 10-year latency period

Cumulative exposure		Cases	Controls	Hazard ratio	95% CI
		Nasal adenocarcinoma			
Wood dust (mg/m^3-years)					
High	$\geq$ 28.82	22	8	28.86	9.81–84.91
Moderate	6.71–28.81	78	51	11.69	7.71–17.73
Low	$\leq$ 6.70	38	87	3.16	2.08–4.81
None	0	255	1,819	1.00	Ref.
Formaldehyde (ppm-years)					
High	$\geq$ 0.85	21	113	1.26	0.55–2.89
Moderate	0.14–0.84	83	52	10.05	6.83–14.80
Low	$\leq$ 0.13	7	35	1.25	0.79–2.02
None	0	282	1,765	1.00	Ref.
		Nasal cancer other than adenocarcinoma			
Wood dust (mg/m^3 -years)					
High	$\geq$ 28.82	16	81	1.00	0.58–1.72
Moderate	6.71–28.81	68	275	1.26	0.96–1.65
Low	$\leq$ 6.70	122	546	1.13	0.92–1.38
None	0	2,240	11,330	1.00	Ref.
Formaldehyde (ppm-years)					
High	$\geq$ 0.85	30	145	1.04	0.70–1.56
Moderate	0.14–0.84	68	324	1.06	0.81–1.38
Low	$\leq$ 0.13	144	659	1.10	0.91–1.33
None	0	2,204	11,104	1.00	Ref.
		All nasal cancers			
Wood dust (mg/m^3 -years)					
High	$\geq$ 28.82	38	89	2.27	1.54–3.35
Moderate	6.71–28.81	146	326	2.42	1.97–2.97
Low	$\leq$ 6.70	160	633	1.34	1.12–1.60
None	0	2,495	13,149	1.00	Ref.
Formaldehyde (ppm-years)					
High	$\geq$ 0.85	37	180	1.07	0.75–11.53
Moderate	0.14–0.84	151	376	2.08	1.72–2.53
Low	$\leq$ 0.13	165	772	1.11	0.93–1.32
None	0	2,486	12,869	1.00	Ref.
		Nasopharyngeal cancer			
Wood dust (mg/m^3 -years)					
High	$\geq$ 28.82	9	42	1.08	0.52–2.24
Moderate	6.71–28.81	46	205	1.13	0.82–1.57
Low	$\leq$ 6.70	80	374	1.01	0.84–1.38
None	0	1,612	8,114	1.00	Ref.
Formaldehyde (ppm-years)					
High	$\geq$ 0.85	14	82	0.86	0.48–1.51
Moderate	0.14–0.84	55	242	1.14	0.84–1.54
Low	$\leq$ 0.13	92	481	0.96	0.76–1.21
None	0	1,586	7,930	1.00	Ref.

Remarks:
P-trend in univariate models for nasal adenocarcinoma:
Wood dust, $p < 0.0001$.
Formaldehyde, $p < 0.0001$.

Table 3. Hazard ratios for nasal adenocarcinoma in relation to cumulative exposures to wood dust and formaldehyde in multivariate models

Cumulative exposures		Multivariate			
		Cases	Controls	Hazard ratio	95% CI
Wood dust (mg/m^3-years)					
High	$\geq$ 28.82	22	8	16.53	5.05–54.08
Moderate	6.71–28.81	78	51	7.59	4.38–13.13
Low	$\leq$ 6.70	38	87	3.11	2.04–4.75
Formaldehyde (ppm-years)					
High	$\geq$ 0.85	21	113	1.20	0.51–2.82
Moderate	0.14–0.84	83	52	2.06	1.16–3.60
Low	$\leq$ 0.13	7	35	0.81	0.48–1.38

Remarks:
P-trend in multivariate models for nasal adenocarcinoma:
Wood dust, $p < 0.0001$.
Formaldehyde, $p < 0.0872$.

nasopharyngeal cancer. Our study adds to the body of literature, originating from case control and cohort studies, which consistently evidenced an association between wood dust and causes nasal cancer.[6] However, most of the previously published studies could not distinguish histological subtypes of cancer among woodworkers, as we did.

In our study, the exposure to wood dust is generally low and within the regulatory limit (*i.e.*, below 5 mg/m^3). The findings of our study supported the link between cumulative exposure to low exposure to "softwood-predominant mixed wood dust" and nasal cancer, an association that has been disputed earlier on.[6,16]

The high risk of nasal adenocarcinoma associated with high-CE to wood dust in our study is in line with the high excess risks reported in previous studies.[2,6,16–20] Still, the relative risk estimate is lower than the 500-fold increased risk detected in a smaller study among British hardwood workers.[1] Many studies have regarded the causal effect between nasal adenocarcinoma and high exposure to hard wood dust primarily in the furniture-making and cabinetmaking industry.[6,20] Others have suggested the high risk (46-fold excess) from mixed wood dust which was undistinguishable on its proportion of wood species.[16]

In our study, the moderate exposure to wood dust occurred primarily in the absence of (or at lower) exposure to formaldehyde, as in accordance to other studies reviewed by IARC. Exposure to formaldehyde often reaches the greatest level for workers with low or negligible exposure to wood dust. Such exposure was uncommon for workers who experienced high exposure to wood dust.[6]

Our study included both freshly cut and dried wood dust, dust from wooden boards and chemically treated wood which may also contain other chemicals such as glue or wood preservatives. Even when formaldehyde was controlled, the consistent increasing risk remain strong at almost 20-fold in the greatest prolonged CE-category.

The current study supports the link for cumulative low exposure (Table 1) of "softwood-dominated mixed wood dust". In addition, it answered the plausible effect of quantitative wood dust exposure in lower extent, which has often provoked in much discussion on its controversial excesses.

In general, the use of wood species in wood industries differ widely by geographical location and product range. Both hardwoods and softwoods (either domestically grown or imported) of several species are used in the wood-processing and wood related manufacturing industries that generated an indefinite of mixed wood dust exposure at work. Workers in our study were exposed to dust mixture containing different species of wood in the same proportions as used in the industry (excluding minor wood use occasions).[3] The most common woodworking activities in the Nordic countries generally use trees grown locally, that is, softwood (pine and spruce).

A review of studies on wood dust and nasal cancer risk in North America[21] showed that the cohort studies of wood-dust-exposed groups do not reveal excesses of nasal cancer, and that the case-control studies tended to give weak and inconsistent results. The authors conjectured that wood-dust-related nasal adenocarcinoma essentially can be eliminated in Europe and in the United States if wood-dust exposures do not exceed 5 mg/m^3 in average, as they presumed that this permissible level was safe without accounting for the CE.

None of the European studies reviewed by IARC[6] demonstrated positive results for nasopharyngeal cancer, which is in line with our study. Whether wood dust may cause cancer of the nasopharynx is still a controversy.[6] All nine population-based case-control studies on nasopharyngeal cancer published so far outside Europe have showed a 1.5- to 2.5-fold elevated risks between wood dust and nasopharyngeal cancer but were based on very small number of cases and none of them had control for confounding factors.[2]

Although the EU Carcinogen Directive (Council Directive 1999/38/EC and 90/394) has classified wood dust as carcinogenic, the current legal-binding regulatory European Occupational Exposure Limit (OEL) is based on technical feasibility (*i.e.*, 5 mg/m^3) but not on scientific evidence for implication on workers' health in malignant cancer end-point. The directive is

restricted to only hardwood and the mixed wood dust that contains a range of hardwood dusts listed in IARD monograph 1995.[2] Softwood dust is not regulated by EU regulation. There is no separated OEL for exposure softwood alone in the EU.

Epidemiologic studies so far have dealt mostly with high doses of exposure to wood dust taking account on solely cross-sectional exposure, but the effects on CE under the regulatory permissible limit is largely unknown. The availability of such exposure data, especially to mixed wood types, is sparse. Based on conventional high-dose findings, regulators have set maximum acceptable levels, assuming all doses below that level are safe.

With millions of workers in the world affected by the consequences of cumulative exposure to wood dust, it is essential decrease exposure can to prevented nasal adenocarcinoma risk in the next generation of workers.

Our study represents the first attempt to investigate nasal cancer attributable to CE to wood dust in a whole-population setting. We have manged to generate and apply quantitative exposure data. We also extended the exposure estimate to nonwood industry such as forestry, construction and building and repairing of ships and boats.

We adjusted our results for exposure to the main potential confounding, formaldehyde exposure. Inclusion of both formaldehyde and wood dust exposure would be complicated if these exposures would be highly correlated. That was not the case. This is in accordance to other studies reviewed by IARC: exposure to formaldehyde often reaches the greatest level for workers with low or negligible exposure to wood dust. Such exposure was uncommon for workers who experienced high exposure to wood dust.[6]

However, our registered based study has also limitations, including exposure misclassification rising from the heterogeneity of exposure levels within-group due to the generic JEM,[22,23] and from work histories solely based on the cross-sectional records of occupation at time the census, which may not correspond to accumulated occupational history of a person. However, comparison with results of special occupational cancer studies indicate that the risk diluting effect of misclassification is small. Utilizing the similar context from Pukkala *et al*. many studies[14,24,25] were able to find well-known, confirmed occupational risks, such as a high lip cancer incidence in farmers and fishermen. Even the numerical relative risk estimates derived from register-based analyses, like the present one, have repeatedly entailed similar results to those obtained in studies investigating more specific hypotheses. Because our study was based on incident cancer cases and exact person-years, there was no survivor bias, which could have been caused by occupational variation in cancer survival and mortality from competing causes of death; these may be a serious problem in analyses based on cancer mortality and cross-sectional proportionate analyses.[14]

Conclusion

Woodworkers had elevated risk in nasal adenocarcinoma but not in other types of nasal or nasopharyngeal cancer. Since the woodworkers in our population are primarily exposed to softwood dust, the results imply that softwood could also be carcinogenic. European OEL for softwood and mixed wood dust that content soft wood could, therefore, be considered as potential carcinogenic even at low exposure levels. Future research on whether softwood dust alone increase risk of nasal adenocarcinoma, or if a certain proportion of hardwood is needed for the mixed wood dust to be carcinogenic, is warranted.

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