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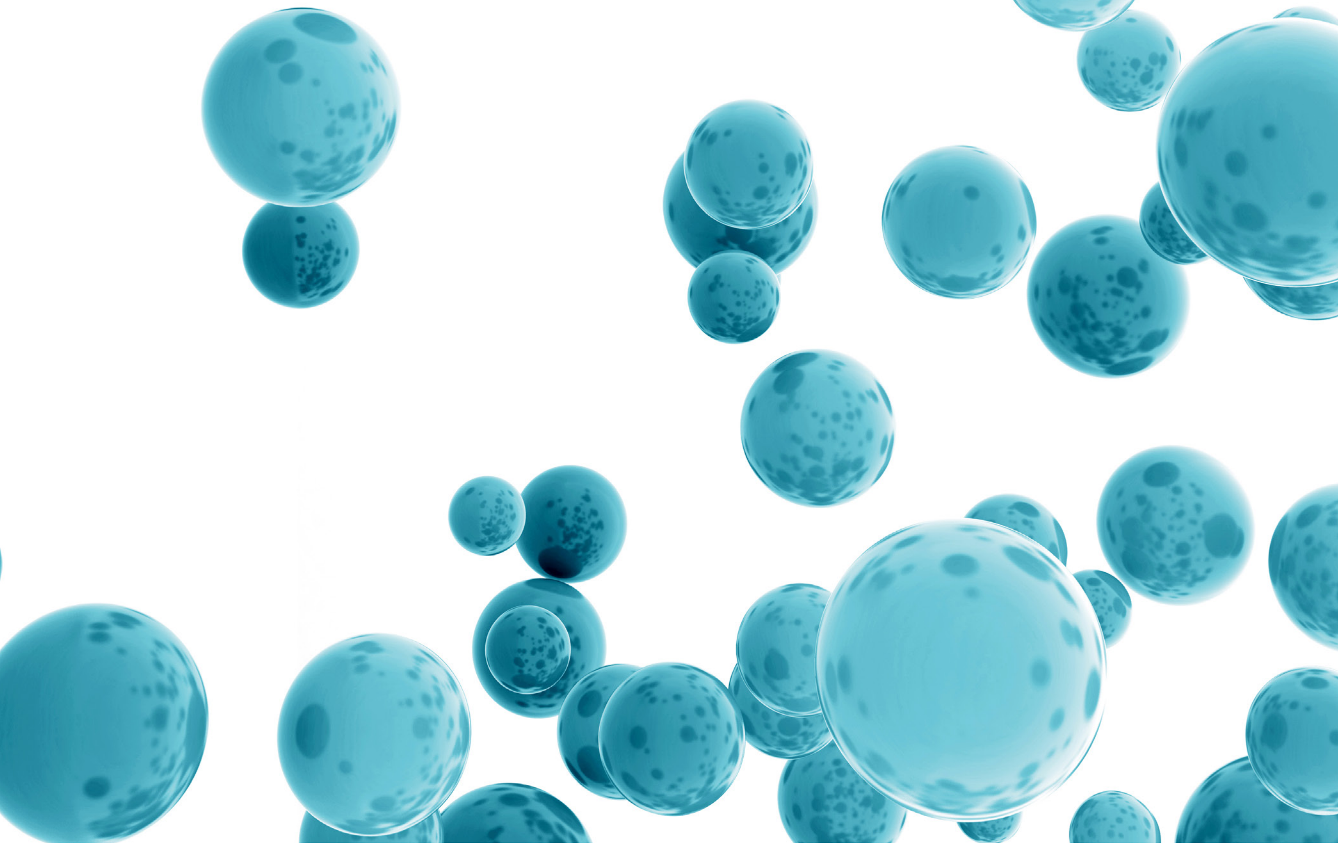
KISHOR HADKHALE

Occupational Exposure and Risk of Bladder Cancer

Population based studies in the Nordic countries and Canada



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Population based studies in the Nordic countries and Canada

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ACADEMIC DISSERTATION
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UNIVERSITY OF TAMPERE

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Dedicated to my father Hari Bhakta Hadkhale

ABSTRACT

Bladder is the part of urinary system that collects and stores urine from kidneys. It has several layers, and bladder cancer usually starts in the innermost layer. The most common type is transitional cell carcinoma. Bladder cancer is more common in men than women, and its rate usually arises after the age of 60 years. It is the ninth most common incident cancer worldwide. Occupation-related factors have been identified as its most important risk factor after smoking. It has been estimated that occupational exposure could account for as much as 20% of all bladder cancer cases in industrialised countries, but studies have shown inconsistent findings. The aim of this study was to assess the association of "work related factors" and risk of bladder cancer.

This study was based on the Nordic Occupational Cancer (NOCCA) Study and the Canadian Census Health and Environment Cohort (CanCHEC). NOCCA comprises the working age populations from Denmark, Finland, Iceland, Sweden and Norway who participated in one or more population censuses in 1960, 1970, 1980/1981 and/or 1990, altogether about 15 million individuals. Follow-up started from the earliest census and continued up to 2005. Census records provided information on demographic variables such as employment history, and these records were linked to national cancer registries in each Nordic country through unique personal identity codes. Likewise, CanCHEC was derived from respondents of the 1991 Canadian census who were included in the Canadian Census Mortality and Follow-up study. This study utilised data from the linkage of the 1991 Canadian census with the Canadian mortality database (1991-2011), Canadian Cancer Registry (1992-2010) and historical tax summary files (1984-2001). The nationally representative cohort included about 2.7 million individuals aged 25 to 74 years on the census day (4 June 1991). The CanCHEC comprises information on demographic, socioeconomic, place of residence, cancer and mortality of Canadian population over a period of 20 years.

For study I, occupational titles of entire populations and their 148,669 cases of bladder cancer diagnosed from 1961 to 2005 in the Nordic countries were classified into 53 categories, and a group of economically inactive persons. Standardised

incidence ratios (SIR) were estimated for these categories. The study identified significantly increased SIRs among tobacco workers SIR 1.57 (95% confidence interval [CI] 1.24-1.96), chimney sweeps SIR 1.48 (95% CI 1.21-1.80), waiters SIR 1.43 (95% CI 1.33-1.53), hairdressers SIR 1.28 (95% CI 1.18-1.40), seamen SIR 1.22 (95% CI 1.16-1.30), printers SIR 1.21 (95% CI 1.14-1.30), and plumbers SIR 1.20 (95% CI 1.13-1.30). Lower but still significantly increased high-risk group included sales workers, beverage workers, drivers, launderers, painters, and smelting workers. Low risks were observed among farmers SIR 0.70 (95% CI 0.68-0.71), forestry workers SIR 0.74 (95% CI 0.70-0.78), and gardeners SIR 0.78 (95% CI 0.75-0.80).

Study II compared the similarity of high and low risk occupational categories in the Nordic countries and Canada. For consistency between the studies, NOCCA results were restricted to the period from 1991 to 2005. In CanCHEC, hazard ratios (HR) for bladder cancer were calculated for 42 occupational categories. During the follow up period, altogether 73,653 cases were observed from NOCCA and 8,170 cases from CanCHEC. A consistently increased risk in both data sets was shown only among sales workers. Teachers and agricultural workers had reduced risk of bladder cancer in both cohorts.

Study III utilised NOCCA information on both lung and bladder cancer cases in males for 53 occupational categories as mentioned above. This study utilised data on 111,458 cases of bladder and 208,297 lung cancer cases. The SIR of lung cancer was used as a proxy for smoking prevalence. After proxy smoking adjustment, the SIRs in all occupations were closer to unity. However, there were some occupations with high risk even after adjustment, suggesting that there are some other risk factors in addition to smoking. Such occupations include chimney sweeps SIR 1.29 (95% CI 1.05-1.56), waiters SIR 1.22 (95% CI 1.07-1.38), hairdressers SIR 1.14 (95% CI 1.02-1.26), cooks and stewards SIR 1.12 (95% CI 1.01-1.25), and printers SIR 1.11 (95% CI 1.04-1.18).

Study IV assessed the association between exposure to solvents and risk of bladder cancer in four Nordic countries (Denmark excluded). This study included 113,343 cases of bladder cancer and 566,715 population controls matched according to the country, sex and birth year. "Census based occupational titles" of the cases and controls were linked with the Job Exposure Matrix created for the NOCCA study (NOCCA-JEM) to estimate quantitative cumulative exposures. Hazard ratios for each solvent - as compared to no exposure level - were estimated using conditional logistic regression. The study observed increased risk for high exposure level of trichloroethylene HR 1.23 (95% CI 1.12-1.40), toluene HR 1.20 (95% CI 1.00-1.38), benzene HR 1.16 (95% CI 1.04-1.31) and aliphatic and alicyclic hydrocarbon solvents HR 1.08 (95% CI 1.00-1.23), and medium level of perchloroethylene HR 1.12 (95% CI 1.02-1.23).

Based on these findings, this study supports the view that occupation is evidently associated with the risk of bladder cancer and smoking is an important risk factor that needs to be taken into account. Workplace carcinogenic exposures such as solvents appeared to play a significant role. NOCCA is the largest occupational cancer incidence study globally and CanCHEC is the largest Canadian cohort to explore the occupational cancer risk. A large number of bladder cancer cases together with accurate registry data information on "decade long occupational history" and use of job exposure matrix to measure "occupation specific quantitative exposure" estimates are important quality cornerstones of this study.

TIIVISTELMÄ

Virtsarakko on virtsateiden osa, joka kerää ja säilöö virtsaa munuaisista. Siinä on useita kerroksia. Virtsarakon syöpä alkaa useimmiten sisimmästä kerroksesta. Yleisin virtsarakon syöpätyyppi on uroteelin karsinooma. Virtsarakon syöpä on yleisempää miehillä kuin naisilla ja se ilmenee yleisimmin yli 60-vuotiaana. Se on yhdeksänneksi yleisin syöpätyyppi maailmanlaajuisesti. Ammattiin liittyvät tekijät on tunnistettu sen merkittävimmäksi riskitekijäksi tupakoinnin jälkeen. On arvioitu, että työperäinen altistus saattaa olla syynä jopa viidennekseen kaikista virtsarakon syöpätapauksista teollistuneissa maissa, mutta tutkimusten tulokset ovat olleet epäjohdonmukaisia. Tämän tutkimuksen tarkoitus oli arvioida työhön liittyvien tekijöiden ja virtsarakon syövän riskin yhteyttä.

Tämä tutkimus perustuu Nordic Occupational Cancer (NOCCA) -aineistoon ja Canadian Census Health and Environment Cohort (CanCHEC) -aineistoon. NOCCA käsittää Tanskan, Suomen, Islannin, Ruotsin ja Norjan koko työikäiset väestöt, jotka osallistuivat yhteen tai useampaan väestönlaskentaan vuonna 1960, 1970, 1980/1981 ja/tai 1990, yhteensä 15 miljoonaa henkilöä. Seurantatutkimus aloitettiin varhaisimmasta väestökyselystä ja se jatkui vuoteen 2005 saakka. Väestönlaskentarekistereistä saatiin demografiset taustamuuttujatiedot, kuten työhistoria, ja nämä rekisterit yhdistettiin kansallisiin syöpätietokantoihin kussakin Pohjoismaassa hyödyntäen henkilöturvatunnuksia. Vastaavasti CanCHEC-aineisto saatiin vuoden 1991 Kanadan väestölaskennan ja kuolleisuusrekisterin (1991-2011) yhdistetyistä aineistoista sekä veroyhteenvetotiedostoista (1984-2001). Kansallisesti edustavaan kohorttiin kuului 2.7 miljoonaa henkilöä, joiden ikä oli 25-74 vuotta väestölaskentapäivänä 4. kesäkuuta 1991. CanCHEC sisältää tietoa demografisista ja sosioekonomisista tekijöistä, asuinpaikasta, syövistä sekä kuolleisuudesta Kanadan väestössä yli 20 vuoden ajalta.

Osatutkimusta I varten pohjoismaisten väestöjen ja niissä tavattujen 148,669 virtsarakon syöpädiagnoosiin saaneen työnimikkeet jaoteltiin 53 kategoriaan. Vakioidut ilmaantuvuussuhteet (*standardised incidence* ratio, SIR) arvioitiin näille kategorioille. Virtsarakkosyövän riski oli huomattavasti väestön keskiarvoa suurempi tupakkateollisuuden työntekijöillä SIR 1.57 (95 prosentinluottamusväli [*confidence*

interval], CI 1.24-1.96), nuohoojilla SIR 1.48 (95% CI 1.16-1.30), tarjoilijoilla SIR 1.43 (95% CI 1.33-1.53), kampaajilla SIR 1.28 (95% CI 1.18-1.40), merimiehillä SIR 1.22 (95% CI 1.16-1.30), painotyöntekijöillä SIR 1.21 (95% CI 1.14-1.30) ja LVI-asentajilla SIR 1.20 (95% CI 1.13-1.30). Vähemmän mutta edelleen tilastollisesti merkitsevästi kohonneen riskin työntekijöihin kuuluivat myyntityöntekijät, juomateollisuustyöntekijät, kuljettajat, pesulatyöntekijät, maalarit sekä valimotyöntekijät. Väestökeskiarvoa selvästi pienempiä riskejä havaittiin maanviljelijöillä SIR 0.70 (95% CI 0.68-0.71), metsätyöntekijöillä SIR 0.74 (95% CI 0.70-0.78) ja puutarhureilla SIR 0.78 (95% CI 0.75-0.80).

Osatutkimus II vertasi korkean ja matalan riskin ammattikategorioiden samankaltaisuutta Pohjoismaissa ja Kanadassa. Vertailukelpoisuuden vuoksi NOCCA-tulokset rajattiin samaan ajanjaksoon Kanadan tutkimuksen kanssa. CanCHEC-tutkimuksen osalta virtsarakon syövän riskitiheyssuhteet (*hazard ratio*, HR) laskettiin 42 ammattikategorialle. Seurantajakson ajalta NOCCA-aineistossa havaittiin yhteensä 73,653 syöpätapausta ja CanCHEC-aineistossa 8,170 syöpätapausta. Molemmissa aineistossa samalla tavalla kohonnut riski havaittiin vain myyntityöntekijöillä. Opettajilla ja maataloustyöntekijöillä oli molemmissa kohorteissa alentunut virtsarakon syövän riski.

Osatutkimus III hyödynsi NOCCA-aineiston miehillä esiintyneiden keuhko- ja virtsarakon syöpätapausten tietoja yllämainituissa 53 ammattikategoriassa. Tämä tutkimus hyödynsi 111,485 virtsarakon syöpä- ja 208,297 keuhkosyöpätapauksen tietoja. Keuhkosyöpätapausten SIR-lukua käytettiin sijaismuuttujana tupakoinnin yleisyydelle kussakin ammatissa. Kun virtsarakkosyövän SIR-luvut vakioitiin tupakoinnin sijaismuuttujalla, SIR-luvut kaikissa ammateissa olivat lähempänä ykköstä kuin tupakointivakioimattomat SIR-luvut. Vakioinnin jälkeen jäljelle jäi kuitenkin muutamia korkean riskin ammatteja, mikä viittaa siihen, että kyseisessä ammatissa työskentelevillä on muitakin rakkosyövän riskiä nostavia tekijöitä kuin tupakointi. Näihin ammatteihin kuuluvat nuohoojat (tupakointivakioitu SIR 1.29 (95% CI 1.05-1.56), tarjoilijat SIR 1.22 (95% CI 1.07-1.38), kampaajat SIR 1.14 (95% CI 1.02-1.26), kokit SIR 1.12 (95% CI 1.01-1.25) sekä kirjapainotyöntekijät SIR 1.11 (95% CI 1.04-1.18).

Osatutkimus IV arvioi liuotinaltistusten ja virtsarakon syövän riskin yhteyttä neljässä Pohjoismaassa (poisluettuna Tanska). Tämä tutkimus sisälsi 113,343 virtsarakon syöpätapausta ja 566,715 verrokkia, jotka oli kaltaistettu asuinmaan, sukupuolen ja syntymävuoden mukaan. Syöpätapausten ja verrokkien väestökyselyyn perustuvat työnimikkeet linkitettiin työaltistusmatriisiin (*Job Exposure Matrix,* JEM), joka oli luotu NOCCA-tutkimuksen yhteydessä kumulatiivisten altistusmäärien arvioimiseksi (NOCCA-JEM). Riskitiheyssuhteet kullekin liuotinaineelle eritasoisesti altistuneille verrattuna altistumattomiin arvioitiin käyttäen logistista regressioanalyysia. Tutkimuksessa havaittiin lisääntynyt riski korkean tason altistumiselle trikloorietyleenille HR 1.23 (95% CI 1.12-1.40), tolueenille HR 1.20 (95% CI 1.00-1.38), bentseenille HR 1.16 (95% CI 1.04-1.31), aromaattisille hiilivetyliuottimille HR 1.10 (95% CI 0.94-1.30) sekä alifaattisille ja alisyklisille hiilivetyliuottimille HR 1.08 (95% CI 1.00-1.23), ja lisäksi keskitason altistumiselle tetrakloorietyleenille HR 1.12 (95% CI 1.02-1.23).

Yllä esitettyjen tulosten perusteella tämä tutkimus tukee näkemystä, jonka mukaan ammatti on yhteydessä virtsarakon syövän riskiin mutta tupakointi on tärkein riskitekijä. Esimerkiksi liuotinaltisteilla näytti olevan merkittävä rooli. NOCCA on maailman suurin ammattikohtaista syöpäriskiä tarkasteleva tutkimus ja CanCHEC puolestaan suurin kanadalainen vastaavanlainen tutkimus. Suuri määrä virtsarakon syöpätapauksia yhdistettynä vuosikymmenien taakse ulottuviin työhistoriatietoihin sekä työaltistusmatriisin käyttö altistekohtaisten määrällisten altistusten arvioimiseksi ovat tämän väitöskirjatutkimuksen laadun merkittäviä kulmakiviä.

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II. Hadkhale, K., MacLeod, J., Demers, P. A., Martinsen, J. I., Weiderpass, E., Kjærheim, K., Lynge, E., Sparén, P., Tryggvadóttir, L., Anne Harris, M., Tiepkema, M., Peters, P.A., Pukkala, E. (2017). Occupational variation in incidence of bladder cancer: A comparison of population-representative cohorts from Nordic countries and Canada. *BMJ Open, 7*(8), e016538-2017-016538.

III. Hadkhale, K., Martinsen, J. I., Weiderpass, E., Kjærheim, K., Sparén, P., Tryggvadóttir, L., Lynge, E., Pukkala, E. (2018). Occupational variation in bladder cancer in Nordic males adjusted with approximated smoking prevalence. *Acta Oncologica, (Epub ahead of print DOI: 10.1080/0284186X.2018.1518591).*

IV. Hadkhale, K., Martinsen, J. I., Weiderpass, E., Kjærheim, K., Sparén, P., Tryggvadóttir, L., Lynge, E., Pukkala, E. (2017). Occupational exposure to solvents and bladder cancer: A population-based case control study in Nordic countries. *International Journal of Cancer, 140*(8), 1736-1746.

Publications listed here are referred in the text by their roman numerals.

ABBREVIATIONS

ALHC	Aliphatic and alicyclic hydrocarbon solvents
ARHC	Aromatic hydrocarbon solvents
ATSDR	Agency for Toxic Substances and Diseases Registry
BENZ	Benzene
CanCHEC	Canadian Census Health and Environment Cohort
CAREX	Carcinogen exposure database
CI	Confidence interval
DALY	Disability adjusted life years
DEEX	Diesel engine exhaust
ETS	Environmental tobacco smoke
EU	European Union
FINJEM	Finnish Job Exposure Matrix
GBD	Global Burden of Disease
GLOBOCAN	Global cancer statistics
HDI	Human development index
HR	Hazard ratio
IARC	International Agency for Research on Cancer
ICD 10	International Classification of Disease, 10^{th} version
ILO	International Labour Organization
JEM	Job exposure matrix
L	Mean level of exposure (in JEM)
mRR	Meta relative risk
NOCCA	Nordic Occupational Cancer study
NOCCA-JEM	Nordic Occupational Cancer Study Job Exposure Matrix
NORDCAN	Cancer statistics for the Nordic countries
OR	Odds ratio
OSOL	Other organic solvents
P	Proportion of exposed persons (in JEM)
PAH	Polycyclic aromatic hydrocarbons
PER	Perchloroethylene

RR	Relative risk
SHTS	Second hand tobacco smoke
SDI	Socio-demographic index
SMR	Standardised mortality ratio
SRR	Summary relative risk
SIR	Standardised incidence ratio
TOLU	Toluene
TRI	Trichloroethylene
WHO	World Health Organization
YLL	Years of life lost

IARC classification of groups based on exposure to carcinogenetic agents to humans. (Source: IARC, 2018 *last updated 30 July 2018*)

Group 1:	Carcinogenic to humans
Group 2A:	Probably carcinogenic to humans
Group 2B:	Possibly carcinogenic to humans
Group 3:	Not classifiable as to its carcinogenicity to humans
Group 4:	Probably not carcinogenic to humans

1 INTRODUCTION

Occupational exposures constitute a major part of environmental exposure. The International Agency for Research on Cancer (IARC) has identified about 100 workplace carcinogens and classified a similar number of additional workplace exposures as possible carcinogens to humans (Cogliano et al., 2011). Almost half of the recognised human carcinogens were discovered from workplaces more than a decade ago (Siemiatycki et al., 2004). According to the International Labour Organization (ILO) the global estimation of deaths due to occupational cancer (malignant neoplasm) in high-income countries accounted for 212,000 cases. This figure was based on World Health Organization (WHO) mortality data in 2011 (Takala 2015). In the European Union (EU-28), occupational cancer contributed about 102,500 deaths, which is equivalent to 53% of all "work related deaths" (Takala, 2014). According to the European Union carcinogen exposure database (EU CAREX), 1 in 5 workers are exposed to workplace carcinogens. It is equivalent to about 32 million workers of the total number employed in Europe (EU-15) who have experienced some exposures listed in CAREX 1990-1993 (Kauppinen, 2000) and the corresponding figure in Canada was 43% (Peters et al., 2015).

Global cancer statistics (GLOBOCAN) 2012 reports that bladder cancer was the 7th most common cancer in men and the 17th in women in the world in 2012, while in developed countries it was ranked 4th and 9th most common in men and women respectively (Burger et al., 2013, GLOBOCAN, 2012). It is relatively common in more developed regions of the world (Ferlay et al., 2015). According to the Global Burden of Disease (GBD) study, there were 541,000 incident cases and 188,000 deaths globally in 2015 due to bladder cancer. It caused 3.4 million "disability adjusted life years" (DALY) in 2015 (GBD, 2017). In the European region, more than 120,000 people were diagnosed with bladder cancer, and there are more than 40,000 deaths estimated annually (Leal et al., 2016). Bladder cancer cost up to 4.9 billion euros in 2012 with health care accounting for 2.9 billion and representing 5% of the total health care cancer costs in the EU. It also included lost productivity due to cancer attributable mortality and morbidity. The costs varied across the countries, and the Nordic countries are represented among the high expenditures (Leal et al., 2016). In Canada, the estimated total cost for bladder cancer for new cases due to occupational exposure alone was 131 million, with an average per case cost equivalent to 658,055 Canadian dollars according to 2011 figures (Jung et al., 2018).

Overall, the occupational cancer burden is increasing, mainly in industrialised countries. According to the Global Burden of Disease report, bladder cancer ranked in the 9th position for cancer incidence and the 13th positon for deaths globally in 2015 (GBD, 2017). Bladder cancer is 3 to 4 times more common in men than in women and increases with age (rare under the age of 40 years) (GLOBOCAN, 2012, Ferlay et al., 2015). In Europe and the United States, it accounts for up to 10% of all malignancies among men (Parkin et al., 2002).

According to the IARC, both incidence and mortality of bladder cancer is higher in developed countries as compared to developing countries. However, the incidence has largely increased in developing countries in recent years (GLOBOCAN, 2012). The latest report on Global Burden of Disease (GBD) in 2017 shows a high incidence of bladder cancer in North America, Northern and Western Europe, while lower in South East Asia and Oceania for both sexes. It is more common in men with 1 in 59 men diagnosed before the age of 79 years as compared to 1 in 239 in women (GBD, 2017). Between 2005 and 2015, "age standardised DALY" for both sexes decreased by 9% at the global level with the largest decrease (13%) in high-middle socio demographic index (SDI) countries and the largest increase (3%) in low SDI countries (GBD, 2017).

Occupation and smoking are recognized to be the most important risk factor on a population level and it accounts for as much as 20% of all bladder cancer cases (Kirkali et al., 2005, Wilcox et al., 2016). IARC monographs from 1971 through 2017 report that the number of recognised occupational carcinogens has increased over the decades, with lung cancer contributing highest among all cancers (23%) and bladder contributing 7% of the total due to workplace carcinogenic exposures (Loomis et al., 2018). Occupational exposure to chemicals such as aromatic amines, polycyclic aromatic hydrocarbons, benzidine, ortho-toluidine is associated with the risk of bladder cancer (Kogevinas et al., 2003, Wilcox et al., 2016). Despite the ban on production and use of carcinogenic substances, cancer due to carcinogenic exposures at work is still the biggest problem in many industrialized countries (Takala et al., 2015). Recent epidemiological data show that the total number of incident cases is rising (GBD, 2017), and there is a broad spectrum of professions with increased incidence and mortality of bladder cancer (Babjuk, 2017, Cumberbatch et al., 2015).

The aim of this study was to assess the association of work-related factors and risk of bladder cancer. First, we described the variation of bladder cancer incidence in occupational categories in the Nordic population and compared the similar occupations with the Canadian population. As smoking is one of the most important risk factors for bladder cancer, we further analysed the “smoking adjusted risk” of bladder cancer using proxy smoking prevalence from lung cancer incidence in the same occupational categories. Finally, we estimated the risk of bladder cancer related to quantitative exposure to solvents and other agents using a job exposure matrix (JEM). Information of demographic and other variables came from cancer registries, census records and population registries.

2 LITERATURE REVIEW

2.1 Brief history of occupational cancer

The origin of occupational medicine date back to the era of Hippocrates (470 to 410 BC), who is the father of medicine. He observed lead poisoning among miners. In the early 16th century, Gregorius Agricola reported lung cancer among ore mines in Germany. Bernardino Ramazzini (1633-1714) is the father of occupational medicine. His contributions on occupational diseases focused on protective measures for industry workers. In 1700, his book on occupational diseases and industrial hygiene was the first comprehensive book on occupational diseases that outlined health hazards due to exposure of chemicals, dust, metals, and others among industry workers (Pope et al., 2004). Some of the important dates in the history of occupational medicine are 1775 when Sir Percival Pott reported scrotal cancer in chimney sweep workers. Sir Thomas Marison Legge (1863-1932) investigated industrial skin cancer, anthrax, cataract and other diseases due to occupational exposure. His contribution included the introduction of occupational medicine in the medical study (Gochfeld, 2005, Guidotti, 2000).

Bladder cancer was recognised as an occupational disease in the late 19th century, when a German surgeon, Ludwig Rehn, reported an increased number of bladder tumour cases among workers exposed to aniline (Rehn, 1895). Exposure to certain agents such as aromatic amines was observed to be causally associated with bladder cancer, and therefore measures to reduce exposure in the workplace were started already in the 1960s (Dolin et al., 1992). Later studies from the United States, the United Kingdom and some other European countries observed an elevated risk of bladder cancer in different occupational categories (Blair et al., 1990, Cumberbatch et al., 2015, Dolin et al., 1992, Kogevinas et al., 1998, Pukkala et al., 2009, Vlaanderen et al., 2014). Since then, there has been better identification and assessment of risk for occupation related diseases.

Introduction of modern methods of epidemiology helped to detect the increasingly subtle risk and their documentation for conditions in the general population (Guidotti, 2000). However, the problem has not been solved yet. In addition, there have been changes in the nature of the jobs, and people are switching jobs, sometimes making it difficult to identify the occupational hazard at a particular workplace. Despite this, even in industrialised countries, working conditions are not ideal and still require more areas of improvement (Espina et al., 2015). To address this, a comprehensive surveillance mechanism that automatically updates about the changing risk may be attainable with further developments in health information technology (Guidotti, 2000).

2.2 Descriptive epidemiology of bladder cancer

The bladder is a part of the urinary system. It collects and stores urine from kidneys. Urine enters the bladder through the ureter and exits through urethra. The walls of the bladder have several layers and most bladder cancers start in the innermost layer. As the cancer grows into other layers, it turns into more advanced stage. Bladder cancer may grow outside the bladder, spreading to other nearby lymph nodes. In an advanced stage, it can spread to distant lymph nodes, the bones, lungs, or to the liver (American Cancer Society, 2017). There are different types of bladder cancer depending on stage, and these stages are important factors for treatment (Cancer Research UK, 2015). More than 90% of the bladder cancers are transitional cell bladder cancer (Figure 1). It becomes invasive if the cells grow into a deeper layer. Squamous cell bladder cancer is the second most common type (about 5%) (Cancer Research UK, 2015). Adenocarcinoma is the third type, and it is a very rare disease in bladder muscle. The survival from bladder cancer is fairly good, about 70% (Cancer Research UK, 2015).

Staging is another important factor for the treatment of bladder cancer. It helps to identify how big the cancer is and how far it has spread. The most common use of staging system is TNM. T (Tumour) describes the size of the tumour that has grown through the bladder wall. N (Nodes) describes any cancer spread to lymph nodes near the bladder and M (Metastasized) describes the cancer spread to distant sites away for the bladder (Cancer Research UK, 2015 and American Cancer Society, 2017). According to the 10th revision of the International Classification of Diseases (ICD-10), malignant neoplasm of the bladder is coded as C67 (WHO, 2010).

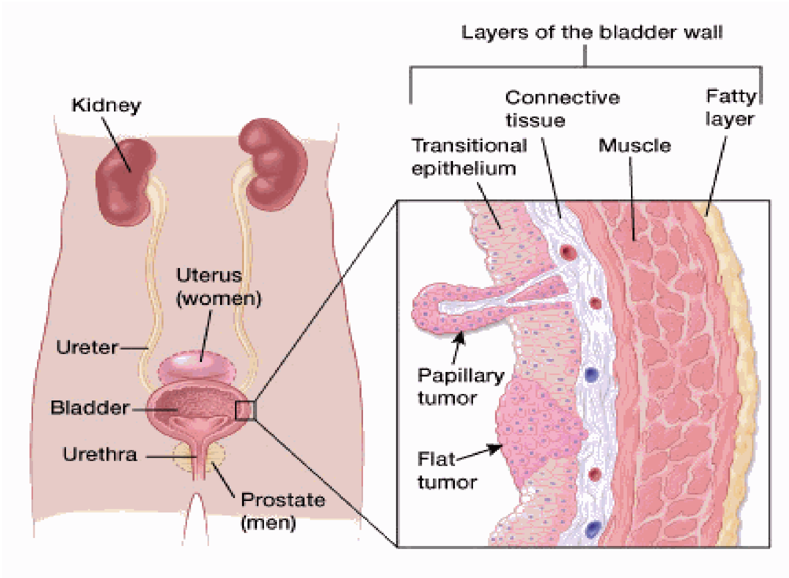

Figure 1. Transitional cell bladder cancer (© American Cancer Society 2013. Used with permission)

Bladder cancer is one of the most common tumours and significant cause of tumour related death worldwide (Babjuk et al., 2017). Incidence rates of bladder cancer is consistently higher in men as compared to women (3:1) and risk increases with age. Bladder cancer incidence varies worldwide with the highest overall incidence rates in Europe and the lowest rates in Africa (exceptionally among Egyptian men and Malawian women) (Antoni et al., 2017). According to the GBD study, age standardized incidence rates of bladder cancer diagnosed among men was the highest in Egypt and the lowest in Oceania (GBD, 2015). In the European region, southern European countries particularly Spain and Italy have highest incidence rates (Antoni et al., 2017). According to the GLOBOCAN report, a total of 55% of the bladder cancer cases occurs in 20% of the population living in very high human development index (HDI) countries (GLOBOCAN, 2012, Antoni et al., 2017). Globally, bladder cancer is now the 18th leading cause of cancer based on absolute years of life lost (YLL) in both sexes (GBD, 2015).

In the Nordic countries, bladder cancer ranks in the top five most commonly diagnosed cancer in males (GLOBOCAN, 2012). "Age standardised incidence rates" of bladder cancer in the Nordic countries increased until 1990 with the highest incidence in Denmark and the lowest in Finland (Figures 2 and 3). According to

NORDCAN, both age-standardised incidence and mortality rates in 1990- 2015 are highest in Denmark and lowest in Finland for both sexes (NORDCAN, 2018). In Canada, bladder cancer is the 4th most commonly diagnosed cancer in males and the 12th most common in females (Canadian cancer statistics, 2017). There has been little change in bladder cancer incidence in both males and females in the last decades (Figures 2 and 3). In 2012, 8900 Canadians were diagnosed with bladder cancer, and 2400 died due to this disease (Canadian cancer statistics, 2017) (Table 1). Incidence and mortality rates of bladder cancer were highest in Denmark and similarly lower in Canada and other Nordic countries in both sexes (Table 1). The lifetime probability of mortality due to bladder cancer at different ages is similar in Nordic and Canadian populations (Table 2).

Table 1. Estimated number of incident cases and deaths of bladder in Nordic countries and Canada in 2012.

Country	**Male**			**Female**		
	Number	Crude rate	ASR(W)	Number	Crude rate	ASR(W)
Incidence						
Denmark	1311	47.3	22.9	470	16.7	7.0
Finland	869	32.7	15.2	224	8.1	2.7
Iceland	50	30.2	17.7	17	10.4	6.0
Norway	1021	41.1	21.6	357	14.4	6.4
Sweden	1776	37.5	16.6	574	12.1	4.7
Canada	5972	34.7	18.4	2114	12.1	5.6
Mortality						
Denmark	375	13.5	5.9	183	6.5	2.3
Finland	205	7.7	3.1	71	2.6	0.7
Iceland	15	9.1	4.7	3	1.8	0.6
Norway	232	9.3	4.1	102	4.1	1.3
Sweden	486	10.3	3.8	199	4.2	1.3
Canada	1483	8.6	4.0	638	3.7	1.3

Source: GLOBOCAN 2012. Available at: CANCER TODAY, International Agency for Research on Cancer, World Health Organization, Lyon France.
Crude and age-standardised rate (ASR) per 100,000, W: World standard population.

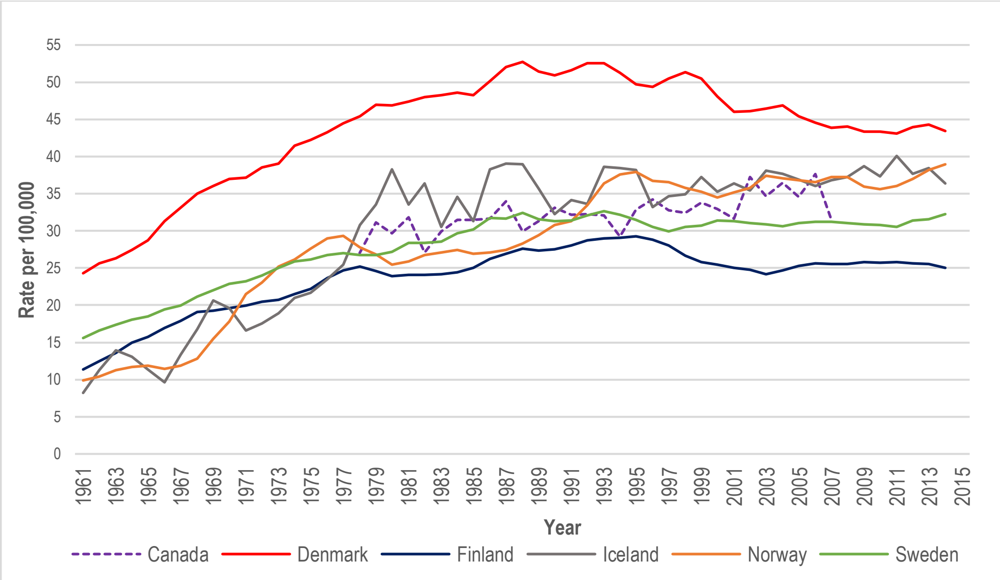

Figure 2. Age-standardised incidence (world) of bladder cancer in Nordic countries (1961-2015) and Canada (1978-2007), males.

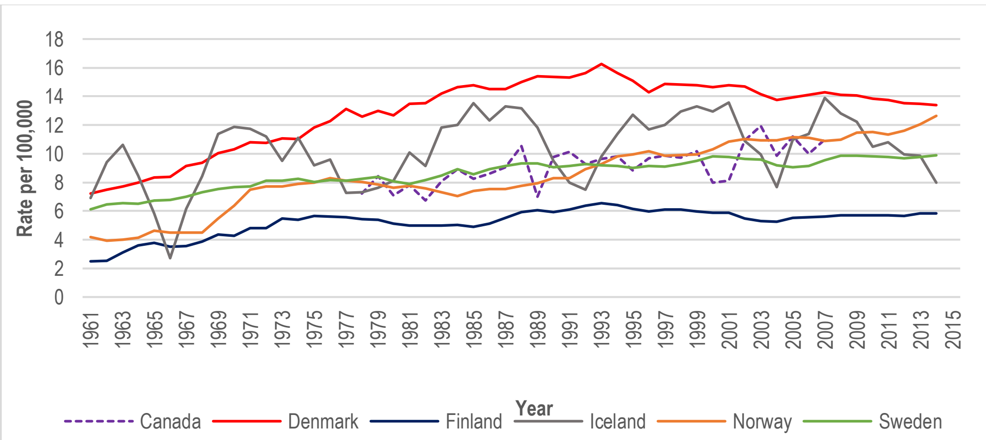

Figure 3. Age-standardised incidence (world) of bladder cancer among in Nordic countries (1961-2015) and Canada (1978-2007), females.

Sources: NORDCAN, 2018. Association of the Nordic cancer registries and Cancer incidence in five continents time trends, CI5 Plus. International Agency for Research on Cancer, Lyon France [Accessed 17th July 2018].

Table 2. Lifetime probability of dying from bladder cancer at selected ages, Nordic countries (2012-2015) and Canada, 2012.

Region Sex	Age		
	60 years	70 years	80 years
Nordic countries			
Male	0.11	0.38	1.07
Female	.	0.13	0.36
Canada			
Male	0.10	0.40	0.90
Female	.	0.10	0.30

Sources: NORDCAN, 2018 and Canadian Cancer Statistics, 2018 [Accessed: 28th June 2018].
(.) Information not available.

Survival of bladder cancer has increased over the years. According to the United States National Cancer Institute SEER project, age adjusted 5- year relative survival of urinary bladder cancer from 2008 -2014 is 78.1% in males and 72.9% in females in the United States (National Cancer Institute SEER Statistics, 2018). A review of articles published between 1975 and 2011 reported that bladder cancer survival was lower in females than in men (Fajkovic et al., 2011). Another study by Mungan and colleagues reported similar findings after adjustment for age and mortality (Mungan et al., 2000). According to the latest NORDCAN survival statistics from 2011-2015, a 5 year "age standardised relative survival" is highest in Finland and lowest in Denmark; men 79% (95% CI 78-81) versus 74% (95% CI 73-75) and women 75% (95% CI 72-78) versus 67% (95% CI 65-68) (NORDCAN, 2018). Likewise, in Canada survival has been consistently increasing for both males and females but rates are lower among females. "Five-year age standardised survival" in Canada from 2006-2008 for men is 74% (95% CI 72-75) and for women 71% (95% CI 69-74) (Canadian cancer statistics, 2017).

2.3 Occupational diseases

According to the World Health Organization (WHO), any disease contracted primarily because of an exposure to risk factors arising from work related activity is known as occupational disease (WHO, 2018). The International Labour Organization (ILO) listed out the following as occupational diseases (ILO, revised 2010).

1. Occupational diseases caused by exposure to agents arising from work activities such as chemical agents, physical agents, biological, parasitic or infectious agents.
2. Occupational disease by target organ system such as respiratory diseases, skin diseases, musculoskeletal disorders, mental and behavioural disorders
3. Occupational cancers on exposure to various agents such as asbestos, benzene, wood dust etc. and
4. Other diseases such as miners' nystagmus and diseases where a direct link is established scientifically or determined by methods appropriate to national conditions and practice, between the exposure arising from work activities and the diseases contracted by the worker.

The risk of cancer in this group is much higher than the general population due to exposure of different types of agents at workplaces (GLOBOCAN, 2012). Some of these agents include asbestos, wood dust, soot (PAH), benzo[a]pyrene, aromatic amines (4-aminobiphenyl, benzidine) organic solvents, radiation and exposure to other indoor pollutants such as tobacco smoking and formaldehyde (Yang et al., 2011). A recent study of the IARC monographs reported different occupational carcinogens, agents, occupations and the different sites involved (Loomis et al., 2018), including cancers of the lung, skin, bladder, leukaemia that are associated with various occupations and industries (Loomis et al., 2018, Yang et al., 2011).

2.4 Risk factors

There are different factors associated with the risk of bladder cancer. Some of them are avoidable and some are non-avoidable. The risk increases with age. Persons in the age group of 60 years and over are the highest risk group for bladder cancer. Smoking is the primary risk factor for bladder cancer. Studies have identified the population attributable risk for bladder cancer is highest due to smoking; both active and passive smokers (relatively lower among passive smokers). Occupation is the second highest risk (Silverman et al., 1989, Wilcox et al., 2016). Risk factors for bladder cancer are mainly differentiated into inherited genetic predispositions and external exposures such as environmental and life style related. As most bladder tumours are associated with smoking and the acquired carcinogen exposure, avoidance of exposure from smoking and carcinogens could be the primary prevention of decrease in the incidence of risk (Burger et al., 2013). Studies have shown a dose- response relationship of cigarette smoking and risk of bladder cancer (Doll et al., 1994, Dreyer et al., 1997). There is also good evidence that smoking cessation reduces the rate of recurrence of many cancers (Richardson et al., 1993). Some of the most important risk factors are described below.

2.4.1 Genetic factors

In the recent years, genome-wide association studies (GWAS) have identified genetic variants for different human diseases including cancer. However, most of the studies in cancer susceptibility loci identified the association with modest increase risk with odds ratio (OR) generally below 1.5 (Stadler et al., 2010), particularly for testicles, breast, colon and rectum and prostate cancers (Stadler et al., 2010). In relation to bladder cancer, studies have reported common genetic polymorphisms and complex diseases with an exception of association between NAT2 slow acetylation, GSTM1 null genotype and the risk of bladder cancer. Findings on associations between polymorphisms in other genes are inconsistent (Garcia-Closas et al., 2005). Epidemiological studies have identified two-fold higher risk in first-degree relatives in bladder cancer patients compared to other groups (Burger et al., 2013). Inherited genetic factors were also established as a risk factor. Studies have suggested that genetic disposition affected the individual susceptibility to extrinsic carcinogens and these carcinogens are mainly from smoking (Burger et al., 2013). Researches on other forms of genetic variation in human genome such as genomic structural changes and sequence variation has been slowly emerging (Stadler et al., 2010). Hence, further research on this topic is essential to identify the genetic risk factors for bladder cancer in the future.

2.4.2 Behavioural risk factors

Tobacco smoking is a well-known and the most important risk factor for bladder cancer. It accounts for about 50% of the risk of bladder cancer diagnosis (Burger et al., 2013, Dreyer et al., 1997, Letasiova et al., 2012). There are numerous studies on tobacco smoking including cigar and pipe and other environmental tobacco smoke and the risk of development of bladder cancer. A meta-analysis of 43 case control and cohort studies reported that there was about a three-fold higher risk of bladder cancer among current smokers as compared to non-smokers (Zeegers et al., 2000). Case control studies from six European countries (excluding Nordic) and the separate studies from Nordic countries reported an elevated risk with increased duration of smoking and number of cigarettes smoked per day (Brennan et al., 2000, Brennan et al., 2001, Dryer et al., 1997, Kuper et al., 2002). A positive dose response risk was observed both for duration of smoking and number of cigarettes smoked (Zeegers et al., 2002). The precise mechanism of cigarette smoking and bladder cancer risk is yet to be determined. The risk is most likely due to exposure to a large number of chemicals such as PAHs. Some of them are 2-naphthylamine and 4-aminobiphenyl substances that are the most toxicogenic substances present in the cigarettes that cause bladder carcinogens (Zeegers et al., 2002).

Some of the previous studies had suggested an increased risk of bladder cancer with consumption of alcohol and coffee. Most but not all of the studies were consistent with a small positive risk of bladder cancer. A meta-analysis based on 14 epidemiologic studies reported a slight increased risk of bladder cancer with coffee intake RR 1.2 (95% CI 1.0-1.4). However, this small positive association could possibly be due to confounding by smoking (Zeegers et al., 2001). In relation to alcohol consumption, studies have observed a slightly increased risk of bladder cancer, and yet the conclusions are still not clear if the association is also confounded due to smoking (Zeegers et al., 2001). A meta-analysis of 30 epidemiological studies reported a slight but statistically non-significant increased "smoking adjusted risk" for men RR 1.3 (95% CI 0.9-2.0). The risk among women remains unclear (Zeegers et al., 2001).

2.4.3 Non-occupational environmental factors

Despite smoking being a confirmed risk factor for bladder cancer, studies have not observed a direct association between second hand tobacco smoke (SHTS), also known as environmental tobacco smoke (ETS), and bladder cancer risk. A large prospective study from Japan observed a dose response with increased risk of lung cancer but no significant increased risk of bladder cancer among wives of husbands who are smokers (Hirayama, 1987). A population based case control study in Canada observed similar non-increased risk of bladder cancer in relation to environmental tobacco smoke exposure at home or at work (Lee et al., 2002). However, a Shanghai bladder cancer study reported an elevated risk of bladder cancer among lifelong non-smokers exposed to ETS compared to those with no ETS exposure (Tao et al., 2010). This study also reported higher risk among females as compared to their male counterparts (Tao et al., 2010). A systematic review of articles from 2000 to 2013 reported that a high concentration of arsenic in drinking water showed a higher risk of incidence and mortality of bladder cancer (Christoforidou et al., 2013, Letasiova et al., 2012). Most studies reported a significant increased risk with a concentration level of >300-500 μg/l with no increase at lower concentrations (Christoforidou et al., 2013, Mink et al., 2008). Likewise, high intake of fruits and vegetables, vitamins such as A, C, D as well as folate, green leafy vegetables, have shown protective effect for bladder cancer (Cancer Research UK, 2015, Ferris et al., 2013, Silberstein et al., 2010, Tang et al., 2014,). Other dietary intakes such as consumption of red meat, animal fats and cholesterols were observed as risk factors for bladder cancer (Ferris et al., 2013). Studies have observed lower risk of bladder cancer among those with high physical activity level but no association with being obese or overweight. However, recent studies indicated that overweight men are more at risk of developing bladder cancer compared to normal men, but these results could be due to smoking habits (Cancer Research UK, 2015, Ferris et al., 2013). Future studies are required to clarify this association.

2.4.4 Occupational factors

Occupational exposure has been identified as the most important risk factor for bladder cancer second to smoking. Increased risk of bladder cancer was reported among the persons employed in industries such as aluminium production, rubber production, textile, dye manufacturing, and chemical solvent industries (Cogliano et al., 2011, Kogevinas et al., 1998, Lynge et al., 2006, Rota et al., 2014, Silverman et al., 2006). These occupations include painters, printers, hairdressers, dry cleaners, waiters, chimney sweeps, transportation workers, plumbers, food and beverage workers etc. (Colt et al., 2011, Cordier et al., 1993, Engholm et al., 2010, Hogstedt et al., 2013, Kogevinas et al., 2003, Pukkala et al., 2009, Samanic et al., 2008, Zheng et al., 2002).

A meta-analysis of 15 case control and cohort studies from 1989 to 2011reported an increased risk of bladder cancer among dry cleaning workers with meta relative risk (mRR) of 1.47 (95% CI 1.16-1.85) (Vlaanderen et al., 2014). For the smoking adjusted studies, the risk was 1.50 (95% CI 0.80-2.84). Likewise, epidemiological studies published after the review by IARC in 1982 reported an excess risk of bladder cancer by more than 1.5-fold among rubber workers in more than half of the studies (Kogevinas et al., 1998). In this multicentre study, excess risk was reported in many countries indicating the possibility of causal association between the exposure and risk of bladder cancer among the industry workers (Kogevinas et al., 1998). Many epidemiological studies reported a 20-50% increased risk of bladder cancer among painters than the general population. The risk was higher for those having exposure history of more than 20 years (Ferris et al., 2013). Another meta-analysis in painters reported about 1.3-fold increased risk of bladder cancer among painters as compared to the unexposed groups (Guha et al., 2010). The risk increased with the duration of employment. IARC classified occupational exposure as a painter as 'Carcinogenic to humans', mainly based on the increased risk of lung and bladder cancer (Guha et al., 2010).

Increased risk of bladder cancer was also observed among printers. A meta-analysis of case-control studies in six European countries reported that occupations related to the printing industry had a 80% greater risk of bladder cancer compared to the general population OR 1.81 (95% CI 1.03-3.17) (Kogevinas et al., 2003). Other studies also observed similar risk among these population groups (Dryson et al., 2008, Samanic et al., 2008). Printers are exposed to printing inks consisting of pigments and a solvent (IARC, 1996). Both meta-analysis as well as individual studies have reported excess risk of bladder cancer among various other occupations. These occupations include drivers and transportation workers (Dolin et al., 1992, Golka et al., 2004, Khoubi et al., 2013, Kogevinas et al., 2003, Silverman et al., 1986), plumbers (Anton-Culver et al., 1992, Puntoni et al., 2001, Silverman et al., 1986, Zheng et al., 2002), waiters (Cassidy et al., 2009, Porru et al., 1996, Reijula et al., 2015), tobacco workers (Dolin et al., 1992, Pukkala et al., 2009).

Other occupations found to be at risk of bladder cancer include ship deck crews, seamen (Dolin et al., 1992, Pukkala et al., 1996, Rafnsson et al., 2003), chimney sweeps (Blair et al., 2007, Evanoff et al., 1993, Hogstedt et al., 2013). Although in the Finnish study, the overall SIR was not higher than 1.1 (95% CI 0.8-1.4), the category of probably most exposed to solvents (deck officers), the SIR was 1.4 (95%

CI 0.9-2.2). Decreased risk was observed among teachers, doctors and agricultural workers (Blair et al., 1992, Kogevinas et al., 2003, Pukkala et al., 2009, Samanic et al., 2008). This protective effect could be due to the low prevalence of smoking, high demand of physical activity in the workplace, intake of fresh food and vegetables and residence in the low air pollution areas (Blair et al., 1992). Despite this, studies have also reported increased risk for long-term agricultural workers (10 years and more) (Cassidy et al., 2009, Colt et al., 2011). Exposure to carcinogenic solvents in the pesticides and other inorganic dusts in farming contributes to the risk of bladder cancer in this occupation (Cassidy et al., 2009).

It is sometimes difficult to attribute excess risk in one occupational group to a particular agent because workers in the same occupation are often exposed to a diverse group of agents (solvents and cofactors). For example, painters, printers, transportation workers are exposed to benzene as well as other aromatic hydrocarbons solvents (Ferris et al., 2013, Guha et al., 2010, Kogevinas et al., 2003). Chimney sweeps are exposed to soot, asbestos and other polycyclic aromatic hydrocarbons (Evanoff et al., 1993, Hogstedt et al., 2013). Some of the occupational categories are heterogeneous and a risk estimate for a broader category may hide a risk related to a specific occupation.

Epidemiological studies have shown moderately increased risk of bladder cancer in some occupations. It is possible that the observed risk estimates are influenced by unmeasured confounding such as smoking, especially for those studies where smoking information was not available or taken into account. However, the studies with smoking adjustment have also shown significant increased risk of bladder cancer in some occupations such as painters, printers, hairdressers, launderers, chimney sweeps, waiters etc. (Guha et al., 2010, Hogstedt et al., 2013, IARC, 1996 Vol.65, Reulen et al., 2008, Takkouche et al., 2009). These studies reported that smoking is the most common risk factor of bladder cancer but there are other exposure agents responsible for the increased risk in addition to smoking. Hence, confounding due to smoking alone is not substantial (Blair et al., 2007). Besides that, in a large occupational cohort studies, either systematic or chance differences in unmeasured lifestyle factors, such as smoking, may not be able to entirely change the risk estimate (Kriebel et al., 2004).

2.4.4.1 Solvent exposure

Occupational exposures have been estimated to attribute for more than 20% of all bladder cancer cases in industrialized countries and exposure to carcinogenic solvents is the main risk factor (Kogevinas et al., 2003, Matic et al., 2014). However, occupational carcinogens potentially associated with the risk of bladder cancer are difficult to identify precisely due to multiple exposures to complex mixtures of various types of carcinogenic compounds, long latency period and genetic polymorphisms (Ferris et al., 2013). To date, many carcinogens associated with the increased risk of bladder cancer are known. Some of them identified as carcinogenic and others as probably carcinogenic to humans (IARC, 2018). Despite this, carcinogens associated with specific occupation and risk of bladder cancer has not yet been identified (Ferris et al., 2013). Some of the most important solvents observed as a risk of bladder are as follows.

2.4.4.1.1 Benzene

Benzene is an industrial chemical ubiquitous in the environment due to the emission from gasoline and combustion of hydrocarbons (Kim et al., 2006). It is a clear, colourless, volatile and highly flammable liquid and slightly soluble in water (IARC, 2012 100F). Historically, benzene has been used as a component of inks in the printing industries and later on in other chemical and drug industries to manufacture rubbers, lubricants, dyes, detergents, pesticides and as an additive to unleaded gasoline (ATSDR, 2007, NTP, 2005, Williams et al., 2008). Nowadays, it is use in the manufacture of organic chemicals. In Europe, benzene is primarily used in drugs, dyes, insecticides and plastics, while in United States it is primarily used for the production of ethylbenzene, which is used in turn in polystyrene and various other copolymers, latexes and resins (IARC, 2012 100F).

Occupational exposure to benzene occurs mainly through inhalation or absorption through the skin in different industries such as rubber, paint, crude oil refining and gasoline as well as among those involved in transportation industries (IARC, 2012 100F). Non-occupational exposures include inhalation of automobile exhaust mostly in urban areas in heavy motor vehicle traffic areas, gasoline filling stations, air tobacco smoke, drinking contaminated water or contaminated food etc. (IARC, 2012 100F). However, intake of benzene from food and water is comparatively lower than air (ATSDR, 1997, NTP, 2005). A high concentration of benzene affects the bone marrow, cell proliferation and leads to hematologic disorders (IARC, 2012 100F).

The broad category of aromatic hydrocarbon solvents includes benzene (as well as other solvents such as toluene, xylene). Hence, it is often difficult to disentangle the individual effects. Studies have reported strong association on occupational exposure to benzene and risk of leukaemia, but the association with bladder cancer is less strong (Cogliano et al., 2011, IARC, 2012 100F, Rushton et al., 2012, Siemiatycki et al., 2004). Despite this, individual studies have reported strong risk, while others reported lower or no risk. A population-based case referent study among males in Sweden during 1985- 1987 reported that exposure to benzene (any annual dose) had two-fold increased risk compared to the general population RR 2.0 (95% CI 1.0-3.8) and the highest risk was observed among those exposed to a high annual dose (Steineck et al., 1990). The study also observed the highest risk RR 5.1 (95% CI 0.6-43.6) among those exposed to both diesel and petrol exhausts. Increased risk of bladder cancer was observed in a French cohort study on a chlorine chemical plant where the workers were exposed to high levels of benzene and dioxin (Bonneterre et al., 2012). The risk was higher among those with the longest employment history, signifying that the exposure dose was higher among the long-term workers (Bonneterre et al., 2012). On the contrary, an Italian case control study observed no association with the risk of bladder cancer for those exposed to benzene (la Vecchia et al., 1990). Likewise, a Russian study among females in the printing industry observed only a suggestive risk of bladder cancer among these women exposed to benzene. In this industry, benzene was used as a bookbinding chemical (Bulbulyan et al., 1999). However, this estimation was based on a very small number of deaths among the workers exposed to benzene, which raises the risk of chance findings in the study. A Norwegian study observed significant increased risk of urinary bladder cancer among workers in a printing industry. However, this study was not able to identify the specific carcinogen in relation to bladder cancer risk among printers (Kvam et al., 2005). A death certificate study of bladder cancer patients in the United Kingdom showed an association of death among workers in printing industries, painters, rubber workers, dye stuff manufactures and other related occupations was due to high exposure to benzene (standardized mortality ratio, SMR 1.42 (95% CI 1.03-1.91) as estimated with a JEM (Dolin et al., 1992).

Based on the findings from these studies that includes meta-analysis, reviews and individual studies, we can conclude that benzene is carcinogenic solvent and exposure to benzene (both short term and long term) can be a risk factor for the development of bladder cancer. Additionally, long term (as well as the high dose) exposure resulted in elevated risk of bladder cancer. The most pronounced risk of bladder cancer due to exposure of benzene was found in occupations such as painters, printers, transportation workers, dyestuff workers and rubber workers.

2.4.4.1.2 Trichloroethylene

Trichloroethylene is a non-flammable liquid and its odour resembles the odour of chloroform. It is slightly soluble in water and best known for the use of cleaning and degreasing metal parts. It has had numerous other uses such as anaesthetic, heat transfer medium, extraction of fats and oils, production of chlorofluorocarbons and ingredients in industrial and consumer use (Doherty, 2000). It was first prepared on the reduction of hexachloroethane with hydrogen, and commercial production began in Germany in 1920 and the USA in 1925 (IARC, 2014). Due to environmental and health safety regulations, there has been significant reduction in the use and production of trichloroethylene in recent years. The EU has set regulations on human exposures at the industrial level. According to this legislation, individual exposure at a concentration of more than 0.1% is prohibited, and industries have to substitute other chemicals such as tetrachloroethylene, etc. (IARC, 2014).

A substantial number of epidemiological studies have reported the risk of different cancers on exposure to trichloroethylene. The biggest risk observed were kidney, liver, and non-Hodgkin lymphoma (IARC, 2014). In recent years, studies have also shown increased risk of bladder cancer on exposure to trichloroethylene. A German study observed increased risk of bladder cancer among those exposed to trichloroethylene among males (Pesch et al., 2000). In this study, the exposure level was estimated using the job exposure matrix. Likewise, another study from the United States observed increased risk among those exposed at the highest exposure category (Zhao et al., 2005). This study observed dose response relationship between exposure to trichloroethylene and risk of bladder cancer. It also reported that confounding due to smoking is very unlikely. Despite this, the association between the exposure and risk was not statistically significant (Zhao et al., 2005). Another individual study among aerospace workers exposed to trichloroethylene observed slightly increased but statistically insignificant risk of bladder cancer at medium and high exposure levels RR 1.41 (95% CI 0.53-3.81) in a four group category level from low to none (Morgan et al., 1998). The job exposure matrix measured the exposure estimates.

IARC has classified trichloroethylene as a group 1 carcinogen to humans mainly based on sufficient evidence on risk of kidney cancer and limited evidence on cancer of liver and non-Hodgkin's lymphoma (Guha et al., 2012). Many studies have observed exposure to trichloroethylene among dry cleaning workers. However, it should be noted that both trichloroethylene and tetrachloroethylene were used as dry cleaning substances before 1960, and due to the change in regulations trichloroethylene was replaced after 1960 (IARC, 2014). Hence, future studies specific to trichloroethylene exposure are required to see the clear association between the exposure agent(s) and risk of bladder cancer.

2.4.4.1.3 Tetrachloroethylene

Tetrachloroethylene is a colourless, non-flammable liquid slightly soluble in water and miscible with alcohol, ether, chloroform, benzene etc. (IARC, 2014). It was first prepared in 1821 using thermal decomposition of hexachloroethane (Doherty, 2000a). Around the 1950s, 80% of the tetrachloroethylene was used in dry cleaning and the rest in metal cleaning and vapour degreasing (Doherty, 2000a). However, by the 1980s, the pattern was changed due to environmental regulations and improved technology and hence about 50% was used in dry cleaning industries (Doherty, 2000a, Linak et al., 1992). The pattern again changed by the 1990s. After this change, more than 50% was used in intermediates and about 15% in dry cleaning (ATSDR, 1997a). These days tetrachloroethylene, which is also known as perchloroethylene, is mainly used as a raw material for the production of fluorocarbons and to a lesser extent in printing and textile industries (Guha et al., 2012, IARC, 2014). Occupational exposure to tetrachloroethylene was measured in various regions of the world to estimate its global effect. The National Institute of Occupational Safety and Health (NIOSH) in the USA and European CAREX in different European countries estimated the occupational exposure of tetrachloroethylene to be noticeable among a wide range of industry workers such as dry cleaning, textiles, metals, automotive, printing and cleaning industries (IARC, 2014). Workers in the dry cleaning industry were highly exposed to tetrachloroethylene but the number of exposed individuals has decreased markedly in recent years (von Grote et al., 2006).

Many epidemiological studies have shown increased risk of bladder cancer among workers exposed to tetrachloroethylene. Some of these studies have shown significant increased risk among workers in the dry cleaning industry. The most recent findings by Vlaaderen and colleagues in a review reported significant increased risk of bladder cancer of overall mRR of 1.47 (95% CI 1.16-1.85) and "smoking adjusted risk" 1.50 (95% CI 0.80-2.84) among dry cleaning workers (Vlaanderen et al., 2014). A cohort study by Ruder and colleagues (Ruder et al., 1994) observed significant excess risk of bladder cancer among dry cleaning workers in both males and females (combined SMR) 2.54 (95% CI 1.16-1.82), while a Swedish cohort study did not observe an excess risk of bladder cancer among dry cleaning and laundry workers (Selden et al., 2011). Nevertheless, the latter study reported some possible bias and confounding in the occupational history of the cohort members.

Another Nordic study observed excess risk of bladder cancer among dry cleaning workers during the period when tetrachloroethylene was the dominant solvent (Lynge et al., 2006). However, this study also reported differences in the level of exposure to tetrachloroethylene, and possible confounding effect in the study. This implies the overall evidence on bladder cancer among dry cleaners is equivocal (Lynge et al., 2006). Besides this, it is to be noted that there is a marked overlap between the populations in the study by Lynge and colleagues and the NOCCA study (Pukkala et al., 2009). A Canadian study observed increased but insignificant risk of bladder cancer among men, adjusted for smoking and other confounding factors (Gaertner et al., 2004). On the contrary, a later study from Montreal, Canada observed a decreased risk of bladder cancer among workers exposed to tetrachloroethylene adjusted for smoking and other covariates (Christensen et al., 2013). From these studies, we can conclude that observed evidence among dry-cleaners exposed to tetrachloroethylene and risk of bladder cancer is unclear. Future research is highly recommended to identify the role of tetrachloroethylene associated with the bladder cancer risk. According to IARC, exposure to tetrachloroethylene is possibly carcinogenic (group 2A) to humans (IARC, 2018).

2.4.4.2 Other exposures

2.4.4.2.1 Aromatic amines

Aromatic amines are a group of well-known bladder carcinogens. Exposure to aromatic amines has been causally associated with an increased risk of bladder cancer (Vineis et al., 1997). They were used as antioxidants and intermediates in the fabrication of rubber, cutting oils, azo dye manufacturing, pesticides and aluminium. The most common occupations exposed to these chemicals are leather workers, painters, hairdressers and barbers (Pira et al., 2010, Vineis et al., 1997). Exposure to aromatic amines has been decreasing in recent years mostly after EU regulations of workplace safety and health were introduced. Exposure to aromatic amines accounts for up to 25% of the bladder carcinogens in some industrialised countries, and the rate is even alarming in developing countries (Vineis et al., 1997). IARC has classified some of the arylamine as carcinogenic and some as probably carcinogenic to humans.

Epidemiological studies have observed the association of aromatic amines in relation to the risk of bladder cancer for a long time. The link between aromatic amines and bladder cancer was established in 1895 by the German physician, Ludwig Rehn, based on the bladder cancer cases reported from workers of dye factories relating with aniline compounds. In 1954, another study reported bladder cancer mortality rates from 10 to 50 times higher than expected among dye industry workers in England due to exposure to different forms of aromatic amines such as 2-naphthylamine, 4-chloro-o-toludine and 2-chloroaniline (Case et al., 1954). In a later study, Dolin observed increased risk of bladder as well as lung cancer among male textile workers in England and Wales 1969-1980 (Dolin et al., 1992). The study revealed the cause deaths was exposure of aromatic amines using a JEM (Dolin et al., 1992).

A French study among male farmers and farm labourers during 1984 to 1986 observed an increased relative risk (RR) of bladder cancer among those heavily exposed to pesticides RR 1.14 (95% CI 1.07-1.22). This study claims that this population group was exposed to herbicides that contained diuron contaminated by aromatic amines (Viel et al., 1995). Similarly, other studies have also reported increased risk when exposed to different forms of aromatic amines such as 2-naphthylamine, benzidine, and 4-aminobiphenyl (Vineis et al., 1997). However, not all studies were adjusted for smoking and some of these studies were based on very few numbers of cases.

Recent studies have reported risk among workers exposed to aromatic amines. E.g., an Italian follow up study, observed increased risk of bladder cancer among those exposed to aromatic amines (Pira et al., 2010). This study observed increased risk with increased duration of exposure SMR 1.50 (95% CI 1.36-1.66). Numerous epidemiological studies have demonstrated the risk of bladder cancer due to exposure to aromatic amines. Based on these studies, we can conclude there is a direct relationship of bladder cancer risk with long-term exposure. Studies also reported reduced risk observed after banning some aromatic amines such as 2-naphthylamine and benzidine, and SMR of bladder cancer increased with younger age at first exposure and increasing duration of exposure (Pira et al., 2010). In this case, the route to transmission is mainly transdermal and respiratory. Hence, the risk is higher among smokers associated with aromatic amines and other carcinogens in the cigarette (Ferris et al., 2013).

2.4.4.2.2 Polycyclic aromatic hydrocarbons

PAHs represent a group of chemicals that contain 2 or more benzene rings. They are produced as by-products of biomass of incomplete burning or pyrolysis of fossil fuels extraction, processing and consumption (Ferris et al., 2013). The IARC has classified benzo[a]anthracene and dibenzo[a,h]anthracene as probable human carcinogens and benzo[a]pyrene and soot as carcinogenic to humans. "The most common among these is benzo[a]pyrene, which is often used as a marker of PAH exposure." Humans are exposed to PAH through inhalation, ingestion and skin contact. Non-occupational exposure includes tobacco smoking, urban air, and ingestion of roasted or fried foods that are for some populations the main route of exposure. The main routes of occupational exposure are inhalation and skin exposure (Boffetta et al., 1997). It is often difficult to measure the cancer risk on exposure of PAH in humans because it depends on the composition of raw materials and the combustion circumstances and the estimation based on lag time (Boffetta et al., 1997, Burstyn et al., 2007).

Exposure to PAHs was observed in several occupations. The industries associated with it are, e.g., aluminium production, iron and steel industries, coal gasification, coke production, diesel engine exhaust, coal tar pitches, tar distillation, chimney sweeps, asphalt workers, carbon black, carbon and graphite electrode manufacture etc. Hence, exposure to PAHs was observed as a risk for many different types of cancers such as lung, larynx as well as skin, in addition to bladder cancer. Many epidemiological studies have observed a most consistent risk of lung cancer due to exposure of PAHs, while the risk of bladder cancer is less consistent (Boffetta et al., 1997). However, the studies have observed and identified the pattern of bladder cancer risk, indicating positive results in these occupations.

Epidemiological studies have observed exposure to PAH and risk of bladder cancer. Nevertheless, not all studies have consistent findings, and not all the studies have reported "smoking adjusted risk". A French hospital based case control study observed PAH exposure to the risk of bladder cancer OR 1.3 (95% CI 1.0-1.7) adjusted for smoking, coffee drinking and aromatic amines. This association was stronger among heavy smokers (Clavel et al., 1994). The findings from an Italian case-control study were also consistent with the French study, signifying PAH as one of the most important risk factors of bladder cancer OR 2.14 (95% CI 0.82-5.60) adjusted for smoking and aromatic amines (Bonassi et al., 1989). A Swedish cohort study estimated positive exposure response association among chimney sweep workers primarily exposed to PAH and risk of bladder cancer (Hogstedt et al., 2013).

A meta-analysis of cohort studies published between 2006 and 2014 reported an increased risk of bladder as well as respiratory tract cancers risk on exposures due to PAH at selected occupations. These studies reported a borderline increased risk of bladder cancer (Rota et al., 2014). Therefore, the risk for bladder cancer could not be ruled out if the observed excess risk estimate is due to possible bias or residual confounding (Boffetta et al., 2008). A historical cohort study among male asphalt workers employed in Denmark, Finland, Norway and Israel observed a slightly different result than the previous studies. In this study, cumulative exposure to PAH was not associated with the incidence of bladder cancer (Burstyn et al., 2007). The limitation of this study was the absence of control for possible sources of confounding. Hence, it was impossible to conclude if a link between exposures to PAH and risk of bladder cancer was established. Considering the lag time exposure of 15 years, there was an indication of exposure-response association with a two-fold increase in relative risk of bladder cancer in the higher exposure categories. Likewise, sensitivity analysis reported that confounding by smoking is unlikely for the observed exposure response trends (Burstyn et al., 2007). The most recent study among steel producing factories in France reported the risk of bladder cancer among these workers was likely due to exposure of carcinogenic agents such as PAH at the workplace (Colin et al., 2018).

2.4.4.2.3 Diesel engine exhaust

Diesel engine exhaust is a complex mixture of gases and fine particles of sulphates, nitrates and carcinogens such as PAHs, nitroarenes, phenols, and heterocyclic compounds (McClellan, 1987). Diesel engines emit gases such as oxides of carbon, nitrogen as well as low molecular weight hydrocarbons (Latifovic et al., 2015). In 2012, IARC classified diesel emissions as a group 1 carcinogenic to humans (revised from group 2A), primarily based on strong evidence for lung cancer and limited but positive association with bladder cancer on exposure to diesel engine exhaust (Latifovic et al., 2015). Exposure to diesel engine exhaust and occurrence of bladder cancer is plausible because metabolites of PAH present in diesel engine exhaust are concentrated in urine and may interact with the urothelium of the bladder cancer (Silverman et al., 1986).

Diesel engine exhaust belongs to the top 10 agent responsible for carcinogenic exposure at work in UK and interesting fact is that 85% of the occupational cancer cases come from top 10 chemical agents (Takala et al., 2015). Epidemiological studies have reported increased occupational risk of bladder cancer on exposure to diesel engine exhaust (Boffetta et al., 2001, Brown et al., 2011, Kogevinas et al., 2003, Silverman et al., 1986, Silverman et al., 2006). However, some other studies have observed the risk due to diesel engine exposure has been diminishing in the recent decades (Pukkala et al., 1992, Manju et al., 2009). The period specific stratified analysis in NOCCA (1991-2005) as well as in the Canadian study (1991-2010) also observed similar decreased risk of bladder cancer in some specific occupations such as drivers in Study II. Future research is highly recommended to see the clear association between exposure to diesel engine exhaust and risk of bladder cancer. The following table 3 shows IARC classification on exposure to carcinogenic agents and bladder cancer with sufficient and limited evidence in humans (volumes 1-122).

Table 3. IARC classification of exposure to carcinogenic agents and risk of urinary bladder cancer with sufficient and limited evidence in humans (volumes 1 to 122) (Source: IARC, 2018)

Carcinogenic agents with sufficient evidence in humans (Group 1)	Carcinogenic agents with limited evidence in humans (Group 2A / 2B)
Aluminium production	4-Chloro-ortho-toluidine
4-Aminobyphenyl	Coal-tar pitch
Arsenic and inorganic arsenic compounds	Dry cleaning
Auramine production	Engine exhaust, diesel
Benzidine	Hairdressers and barbers (Occupational exposure)
Chlornaphazine	2-mercaptobenzothiazole
Cyclophosphamide	Pioglitazone
Magenta production	Printing process
2-Naphthylamine	Soot
Painting	Textile manufacturing
Rubber production industry	Tetrachloroethylene
Schistosoma haematobium	
Tobacco smoking	
Ortho-Toluidine	
X-radiation, gamma radiation	

2.4.5 Changes in exposure to occupational carcinogens over time

IARC monographs have identified a number of recognized carcinogens over a period of 4 decades and evaluated more than 1000 agents based on carcinogens to humans (group 1, 2A, 2B, 3 and 4). During this period, some new carcinogens were identified, and some of the previously identified carcinogens were revised (upgraded/downgraded) to other groups based on the latest scientific evidence. For e.g. during the period of 23 years (1981-2004), 12 new previously unrecognized carcinogens were identified (Siemiatycki et al., 2004). Similarly, trichloroethylene, previously classified as probably carcinogenic to humans (group 2A), was moved to carcinogenic to humans (Group 1) (IARC, 2014). Along with the identification of occupational carcinogens, manufacturing and its use levelled up at a high rate (Wilson et al., 2009). As a result, the EU in 1980 banned the use of some carcinogenic substances such as aromatic amines in the workplace. Following this ban, similar bans were implemented in other industrialized countries such as the USA and Canada. Additionally, other preventive measures were introduced as a consequence of improved legislation, implementation of safety and hygiene programmes, elimination or decreased production of hazardous chemical substances that are classified as risk to human health, and substitution with less carcinogens (Creely et al., 2007). Due to this, some workplace carcinogenic exposures started to decrease from the early 1990s (Burstyn et al., 2000, Creely et al., 2007).

A substantial decrease in exposure to occupational carcinogens have been reported in the Nordic countries. According to the Finnish job exposure matrix (FINJEM), exposure to carcinogens such as benzene, benzo[a]pyrene, and asbestos have substantially decreased in Finland from 1950 to 2008 (Kauppinen et al., 2013). Similarly, a Danish study reported decreased exposure to trichloroethylene by 4% from 1947 to 1964 and by 15% from 1964 to 1989 (Raaschou-Nielsen et al., 2002). At present, risk due to some of the occupational carcinogens such as PAH, diesel engine exhaust is decreasing in some industrialized countries (Creely et al., 2007, Raaschou-Nielsen et al., 2002, Shen et al., 2013). However, the risk of cancer due to carcinogenic exposure at work is still the biggest individual threat in terms of the number of deaths in many industrialized countries (Takala et al., 2015). This risk is shifting towards developing countries, primarily due to the movement of industries from high income to low income countries (Blair et al., 2011).

2.5 Exposure assessment in occupational studies

In epidemiologic studies including occupational epidemiology, accurate exposure measurement is very important to estimate or measure the precise risk due to occupation. However, it remains one of the biggest challenges. Exposure measurement is performed to characterise the nature, dose (amount), time, and temporal pattern of exposure (Armstrong et al., 1992, Dos-Santos Silva, 1999). In population-based studies such as cohort, case control, and registry-based studies, it is very difficult to collect the measurement data from the participants' workplaces, and it is even difficult to collect from past workplaces. Hence, these studies have usually used the following three approaches (Dopart et al., 2017).

a) job exposure matrix (JEM) that links occupational groups to exposure estimates,
b) job by job expert review of questionnaires, or
c) expert opinion, based on expert judgement to provide the estimates of the probability, intensity, and frequency of exposure for the study subject.

An increasing number of studies have used measurement data for statistical modelling of available exposure measurements (Dopart et al., 2017). In any case, the information obtained should include the exact details of the nature of exposure, dose and its distribution over time are essential to observe the clear association between the exposed and outcome variable. For accuracy in measurement of exposure, the nature of exposure should be as clear as possible. For example, to measure carcinogenic exposure among drivers, it is essential to obtain the information on exposure to different forms of carcinogenic agents such as diesel engine exhaust, route of exposure and behaviour of exposure that may hide the risk of being exposed. Furthermore, it is also important to collect information on occupational history and, duration of the job performed in a single day/week or month. Smoking behaviour is also other important factor. In occupational cancer studies, any behaviour that may hide the risk of being exposed to hazards should be clear, e.g., the use of protective clothing among the field workers in outside sun. Additionally, exposure level is usually high at workplaces. Therefore, it is relatively easier to measure the exposure level at particular workplaces, e.g. miners working in the mining plants. Workplaces usually provide a more defined environment than the general outside environment (Nieuwenhuijsen, 2015).

Most exposure of interest variables are quantitative. They may reflect the total accumulated dose (cumulative exposure), rate (number of exposure episodes per day), peak exposure (the highest exposure level), or average exposure (the ratio of cumulative exposure to the duration of exposure). Each exposure should also be characterised by the distribution over time, i.e., continuous or periodic, because exposure duration determines cumulative exposure and a critical time window for many diseases. Inclusion of exposures outside of the critical time window into the exposure variable may lead to misclassification of exposure (Rothman, 1981). Data on the exposures of interest may be obtained through various methods such as personal interviews, self-administered questionnaires, diaries, records, biological measurements and measurements of the environments. If the subject is too ill or dead, it is also common to obtain the information from a proxy respondent such as member of their family. A proxy variable is often used in epidemiology if the exposure variable of interest is not directly measurable for example socioeconomic status.

2.5.1 Confounding and selection bias

Confounding refers to a spurious association between a given exposure and an outcome observed because of the influence of a third variable (Szklo et al., 2014). It is related to both exposure and outcome, but is not within the causal pathway. Confounding is more likely to occur in observational than in experimental studies. In experimental studies, randomisation reduces the likelihood of confounding (Szklo et al., 2014). In occupational epidemiology, exposed groups may be different from the general population in terms of overall death rates. This so-called "healthy worker effect". In occupational epidemiology, it is common because severely ill and chronically disabled are ordinarily disabled from employment (Li et al., 1999). It could be due to selection bias rather than confounding because bias can occur already from selecting the workers for employment. However, it could be both confounding as well as selection bias (Chowdhury et al., 2017). Besides this, workers are provided with improved access to healthcare services facilities as compared to the general population, they can choose to continue working or leave the work due to sickness, disability etc. Workers may also be physically active and have a better socio-economic status (Shah, 2009).

2.5.2 Assessment of causality

There are various methods of assessment of causality in epidemiological research. However, the estimate on the statistical association between exposure and disease is not necessarily a causal one. Studies are strengthened by the trend of increasing or decreasing incidence with increasing exposure, which is often an exposure–response relationship (Dos-Santos Silva, 1999). Widely accepted criteria for causation were proposed by Sir Bradford Hill in 1965 for chronic diseases (Rothman et al., 2005). Hill's viewpoints define the number of factors to assess the causality between the exposed and outcome variable: strength of the association, dose response effect, lack of temporal ambiguity, consistency of the findings, experiment, analogy, biological plausibility, coherence of the evidence, and specificity of the association. In occupational epidemiology, these criteria are widely accepted to access the causality. Nevertheless, causal assessment is an iterative process centred on measurement of the exposure-disease relationship. Therefore, it is very important to consider these things in generalising the study findings and to improve the validity of the study. Identifying the cause and applying the required tools is very essential to estimate the true association between the exposure variable and outcome of interest.

Summary of the literature review

The summary of the current literature review suggests that occupation is associated with increased risk of bladder cancer (Table 4). Some specific occupations are strongly associated with an increased risk of bladder cancer. A few of the occupations, such as agriculture workers, forestry workers, teachers and doctors, were observed as having reduced risk of bladder cancer in most of the studies. The risk depends on various factors such as the nature of job, employment history, duration of employment etc. Workplace exposure to carcinogenic substances is the second most important risk factor after smoking.

Among the workplace solvent exposure, the most consistent risk was observed on exposure to polycyclic aromatic hydrocarbons, aromatic amines, diesel engine exhaust, benzene and its derivatives. However, the quantitative exposure estimates were limited and variable within the studies. The strongest evidence was observed among chimney sweeps, painters, printers, transportation workers, miners, hairdressers, and dry-cleaners. Future studies on occupation-specific exposure to solvents and other agents and the risk of bladder cancer are required to see the clear association.

Table 4. Summary of the literature review on occupational exposure and risk of bladder cancer.

Reference, country	Study design	Country, length of follow up	Study population	Exposure assessment	Assessment of the outcome	Confounder adjustment	Method of risk estimation	Main findings
Al-Zalabani et al., 2016	Meta-analysis, 126 studies	1995 to 2015	Working age population	Occupational, lifestyle and environmental factors	Bladder cancer	yes / no	OR, HR, SIR, Effect size (ES)	Smoking is the key risk factor for smoking. With numerous modifiable risk factors, bladder cancer makes one of the most preventable diseases.
Andersen et al., 1999	Cohort	Nordic countries, 20 years	Working age from 25 to 64 years at the time of census	Occupational categories	Multiple cancers (35 cancer sites)		SIR	The risk of cancer, even under equity and equal access to health care depends on the person's position in society. Dyestuff industry and rubber workers are at high risk of BC.
Band et al., 2005	Matched case control	British Columbia, Canada	20 years and older population	Occupation and industry titles	Bladder cancer	Smoking, alcohol and educational level		Workplace exposure to chemical solvents (exposure to silica and electromagnetic fields in addition) may be risk to bladder carcinogens.
Blair et al., 2007	literature review			Occupational exposure		Tobacco and other occupational exposures.	Descriptive	It is rare to find substantial confounding in occupational studies, even by risk factors that are strongly related to the outcome of interest.
Blair et al., 1990	Cohort	United States	Dry cleaning union members	Dry cleaners	Multiple cancers	Age, sex, race, and calendar time.	SMR, SRR (Standardised rate ratio)	Risk of different cancers (including bladder but not kidney) among dry-cleaners showed a significant association with estimated cumulative exposure to dry cleaning solvents.
Blair et al., 1992	Meta-analysis		Farmers		Multiple cancers	yes/ no	MRR (meta relative risk)	Exposure to farming industry was observed as decreased risk among farmers.
Boffetta et al., 1997	Review	Multiple	Industrial workers	Polycyclic aromatic hydrocarbons	Multiple cancers	yes/ no	OR	Heavy occupational exposure to mixtures of PAH entitles a substantial risk of lung, skin, and bladder cancer. Bladder cancer risk was found mainly on exposures to PAH from coal tar's and pitches.
Boffeta et al., 2001	Meta-analysis, 35 studies	Multiple	All forms of transportation workers and maintenance	Job exposure matrix and others exposure to diesel exhaust.	Bladder neoplasms	yes/ no	OR, RR, SIR,	Exposure to diesel exhaust may increase the risk of bladder cancer. Confounding and other bias such as publication bias may affect the observed risk estimation.

Table 4 (continued)

Reference, country	Study design	Country, length of follow up	Study population	Exposure assessment	Assessment of the outcome	Confounder adjustment	Method of risk estimation	Main findings
Cassidy et al., 2009	Cases control	USA	Hospital patients	Occupation and Industry	Bladder neoplasms	Age, gender and smoking status	OR	Increased risk was observed in those with an employment history of 10 years or more including farmers and agricultural workers, contrary to many other studies.
Cogliano et al., 2011	Review	Multiple	Working age population	Occupation and Industry	Multiple cancers	yes / no		IARC classification based on carcinogenic risk to humans to multiple cancers.
Cumberbatch et al., 2015	Meta-analysis, 217 studies	Multiple	working age population in industry workers	Carcinogen exposure	Bladder cancer	Socioeconomic factors, smoking (yes/no)	RR	Exposure to aromatic amines at workplace was observed as highest incidence, while PAH and heavy metals have highest mortality of bladder cancer. The profile of at-risk occupations is changing and affecting women more than men.
Dolin et al., 1992	Cohort	United Kingdom	Death certificate study.	Using job exposure matrix	Bladder cancer		SMR	Exposure to paints, pigments, benzene and cutting oils were observed as high risk of bladder cancer.
Dryson et al., 2008	Case-control	New Zealand	Working population in between 25-70 years.	Industrial workers	Bladder cancer	Gender, age, smoking ethnicity and occupation	OR	The most pronounced risk of bladder cancer was observed among hairdressers and textile workers exposed to carcinogenic agents such as aromatic amines.
Ferris et al., 2013	Cohort	Review	Working age population	Occupational and constitutional factors	Bladder cancer	yes / no	RR, OR	The most significant constitutional risk factors are age, gender, race, ethnicity, geographic location, and genetic polymorphisms while risk factors due to occupation are related to aromatic amines and polycyclic aromatic hydrocarbons.
Gaertner et al., 2004	Case-control	Canada	Working age population aged 20-74 years.	Occupation and industry	Bladder cancer	Age, province, race, smoking status, fruits, and coffee consumption.	OR	Bladder cancer risk is common in many professions due to workplace carcinogenic exposure. Elevated risk was observed among male hairdressers, miners, primary metalworkers, and mechanics.

Table 4 (continued)

Reference, country	Study design	Country, length of follow up	Study population	Exposure assessment	Assessment of the outcome	Confounder adjustment	Method of risk estimation	Main findings
Gandini et al., 2008	Systematic meta-analysis, 254 studies	Multiple, 1961 to 2005	5 continents.	Current and former smokers.	13 cancer sites	yes/ no	SRR	Smoking is the biggest risk of lung cancer, but heterogeneity was higher among current smokers. Occupational risk was relatively higher for bladder cancer, and the pooled relative risk was higher among current male smokers.
Guha et al., 2012	IARC report	Multiple	Working age population	Trichloroethylene, tetrachloroethylene, chlorinates solvents and their metabolites	Multiple cancers	yes/ no		Exposure to tetrachloroethylene was a risk for many different cancers. However, consistent risk was observed for bladder. Drycleaners were observed as having increased risk with adjustment for smoking and some other factors.
Guha et al., 2010	Meta-analysis, 41 studies	Multiple	Painters	Exposures in painting industry	Bladder cancer deaths	Smoking	RR	Painters are causally associated with the risk of bladder cancer. Risk increases with increased duration of employment.
Haldorsen et al., 2017	Cohort	Norway	Working age population	Occupation	Multiple cancers	Smoking and alcohol	SIR	Effect of workplace exposures and cancers related to alcohol and tobacco are very important. It should be analysed with special precaution.
Harling et al., 2010	Meta-analysis, 42 studies	Multiple	Hairdressers	Hair dying chemicals	Bladder cancer		SRR	Study suggests significant increased risk of bladder cancer among hairdressers. Risk is higher with duration of employment.
Hogstedt et al., 2013	Cohort	Sweden, 1958 to 2006	Chimney sweeps	Hydroxypyrene in urine as a biomarker for PAH exposure.	Multiple cancers	Age and calender year	SIR	Chimney sweeps are at high risk of multiple cancer including bladder and lung cancers. Exposure to soot is the risk factor for bladder cancer in this occupation.
Jensen et al., 1987	Cohort	Denmark,	Transportation workers	Occupational exposure and occupational history	Bladder cancer	Tobacco smoking, age and sex	RR	Increased risk of bladder cancer was observed among those employed in transportation industries such as bus and truck drivers. Duration of employment was the important risk factor for the diseases occurrence.

Table 4 (continued)

Reference, country	Study design	Country, length of follow up	Study population	Exposure assessment	Assessment of the outcome	Confounder adjustment	Method of risk estimation	Main findings
Kauppinen et al., 2014	Review	Finland and other	Working age population	Chemical agents using Job exposure matrix	Quantitative estimates of exposure prevalence	Smoking, alcohol, diet, physical activity.	HR, RR etc.	FINJEM has been used as an exposure assessment tool in occupational epidemiology, mainly in large registry-based studies in different countries.
Kogevinas et al., 1998	Review, 90 studies	Multiple	Industry workers	Manufacture of tyre cable and other rubber products	Multiple cancers	yes/ no	OR, RR, SIR, SMR	Bladder cancer was observed as moderate but one of the most consistent risks among rubber industry workers.
Kriebel et al., 2004	Cohort	United States	Manufacturing workers of NHIS study	Smoking and alcohol drinking	Occupational cancers (tobacco and alcohol related)	yes	OR	It is unlikely that either systematic or chance differences in smoking and drinking habits will cause as much as a 20% change in the relative risk in large studies within the same working population.
Letasiova et al., 2012	Review	Multiple, 1998 to 2010	General population and working population	Occupational and environmental	Bladder cancer	yes/ no	OR, RR, SMR	After smoking, the highest risk of bladder cancer is due to exposure of aromatic amines at workplace. The other environmental risk factor includes arsenic in drinking water.
Lohi et al., 2008	Cohort	Finland, born 1906 to1945	Economically active	FINJEM	Bladder cancer	Smoking and obesity	RR	Exposure to some solvents at workplace can be risk of bladder cancer.
Lynge et al., 2006	Case-control	Nordic countries,	Dry cleaners (launderers)	Exposure to tetrachloroethylene	Multiple cancers	Smoking and alcohol	RR	The overall evidence in risk of bladder cancer in drycleaners is equivocal.
Olsen et al., 1997	Cohort	Nordic countries	Working age population	Occupational carcinogens	Multiple cancers		Population attributable risk percent	Risk in Nordic populations could be avoided by eliminating exposure to known carcinogens equivalent to 33% and 20% in men and women respectively. Smoking habits account for a little more than half of the observed avoidable cases.
Pukkala et al., 1992	Cohort	Finland	Hairdressers	Hairdressing chemicals	Multiple cancers		SIR	Reduction in exposure to hairdressing chemicals at salons could be due to improved working conditions and EU legislations over the use of such chemicals.

Table 4 (continued)

Reference, country	Study design	Country, length of follow up	Study population	Exposure assessment	Assessment of the outcome	Confounder adjustment	Method of risk estimation	Main findings
Pukkala et al., 2009	Cohort	Nordic countries	Working age population	Occupation	Multiple cancers	No information on alcohol and smoking habits	SIR	Occupation is a risk factor of many different cancers including bladder cancer.
Pukkala et al., 2017	Systematic review	Nordic countries	Nordic	Overview of the procedures and data comparability	Nordic cancer registries			Nordic cancer registries represent high quality standard in terms of completeness and accuracy of the registered data. However, there are numerous differences in registration routines, classification systems and inclusion of some tumours.
Reulen et al., 2008	Meta-analysis	Multiple, articles published from 1963 to 2008	Various	Occupational categories	Bladder cancer	yes/ no	SRR	Small but consistent risk of bladder cancer was observed in different occupations. Moreover, population health impact may be substantial considering the number of people in these occupations.
Richardson et al., 2007	Case control	Canada, from 1983 to 1990.	Various occupation	Job exposure matrix	Bladder cancer in males	smoking, alcohol, ethnicity, and questionnaire	OR	Several specific chemical agents, mainly the derivatives of combustion products of fossil fuels were significantly associated with the increased risk of bladder cancer.
Rota et al., 2014	Systematic review	Multiple, Published 2006 to 2014.	Multiple	PAH	Respiratory and urinary tract cancers.	yes/ no	RR, SMR	Occupational exposure to PAH was observed as increased risk of bladder and respiratory tract cancer in some occupations.
Rushton et al., 2012	Cohort	United Kingdom	Working age population	Occupational factors	Multiple cancers	Employment turnover period	Attributable fraction and attributable numbers.	Bladder and lung cancer are among the most important cancer cites for occupational attribution.
Samanic et al., 2008	Cases control	Spain, 1998 to 2000	Hospital patients	Occupational and residential history, dietary patterns, family history,	Bladder cancer	Age, smoking hospital region, and employment	OR	Significantly elevated bladder cancer risk was observed among printers, textile industry workers, transportation workers and hotel industry workers.

Table 4 (continued)

Reference, country	Study design	Country, length of follow up	Study population	Exposure assessment	Assessment of the outcome	Confounder adjustment	Method of risk estimation	Main findings
Siemiatycki et al., 1994	Case control	Canada	Working age population	Occupational history	Bladder cancer	Family income, ethnicity, age, smoking, coffee drinking	OR	Several of the occupations were associated with increased risk of bladder cancer including motor vehicle drivers and textile dyers.
Siemiatycki et al., 2004	Review	Multiple	Working age population	IARC classifications and other	Multiple cancers	yes/ no		The occupational environment has been most fruitful for investigating the aetiology of human cancer. IARC monograph has been indispensable component in this process. It has been useful for researchers in setting research priorities, understanding carcinogens and to prevent occupational cancers.
Silvermen et al., 1986	Case control	United States, 21 to 84 years	Drivers / Deliverymen	Motor exhaust emission	Bladder cancer	Age, smoking, coffee drinking, employment history and urinary tract infections.	RR	Statistically significant increased risk of bladder cancer was observed with duration of employment in truck drivers. Additionally, in truck drivers employed 25 years or more, 120% increased risk of bladder cancer was observed.
Takala et al., 2015	Report	Europe and global	Working age population	Occupation and workplace exposure to various agents	Multiple cancers		numerous methods	Occupation is the risk factor of many different cancers. Workplace exposure to the top 10 carcinogenic substances are responsible for 85% of all cancer cases.
Vineis et al., 1985	Case control, males only	Italy	Occupations	Job exposure matrix	Bladder cancer		RR	Risk was higher among leather industry workers, printing, dye stuff, and rubber industry workers. JEM observed risk of bladder cancer due to exposure of aromatic amines.

Table 4 (continued)

Reference, country	Study design	Country, length of follow up	Study population	Exposure assessment	Assessment of the outcome	Confounder adjustment	Method of risk estimation	Main findings
Vlaanderen et al., 2014	Meta-analysis	Multiple	Dry cleaners (Launderers)	Tetrachloroethylene	Bladder cancer	yes/ no	Meta relative risk (mRR)	Dry cleaners have increased risk of bladder cancer. Tetrachloethylene exposure at workplace could be the potential risk factor.
Wilcox et al., 2016	Cohort	USA	Occupations	Smoking and occupational exposures	Bladder cancer	Smoking, age, race, gender, BMI, history of other cancers.	HR	In addition to the known causal relationship between occupation and bladder cancer risk, occupation may be related to increased risk of recurrence.

3 PURPOSE OF THE STUDY

The overall aim of the study is to assess the association of work related factors and the risk of bladder cancer among the adult population. The specific objectives of the study are as follows. A summary of the study procedure and findings from each study is illustrated below (Figure 4).

1. To describe occupational variation in risk of bladder cancer in the Nordic countries (Study I)

2. Occupational variation in incidence of bladder cancer: comparison of population-representative cohorts from Nordic countries and Canada (Study II)

3. To assess occupational variation in bladder cancer in Nordic males adjusted with approximated smoking prevalence (Study III)

4. To assess the relationship between occupational exposure to solvents and the risk of bladder cancer (Study IV)

4 MATERIALS AND METHODS

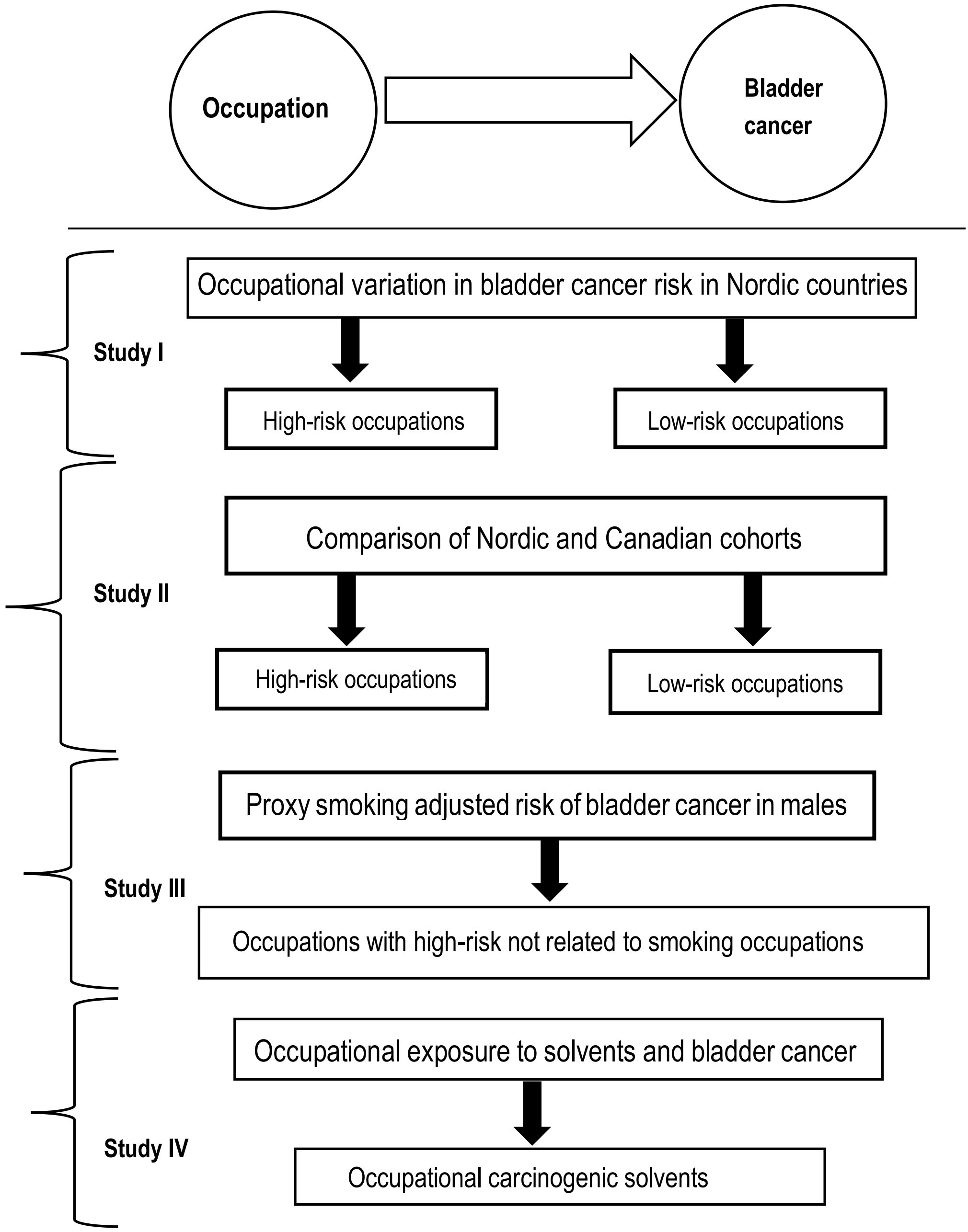

Figure 4. Operational framework of the study.

4.1 Nordic occupational cancer study (NOCCA)

The Nordic Occupational Cancer (NOCCA) project is a cohort of populations in Denmark, Finland, Iceland, Norway and Sweden. It is the source population from where study populations were drawn for each of the studies. A summary of the project is described here, while the details of the NOCCA study have been described elsewhere (Pukkala et al., 2009). The NOCCA cohort consists of individuals from all five Nordic countries who participated in one or more population censuses in 1960, 1970, 1980/1981 or 1990, were 30 to 64 years of age at the beginning of follow-up and lived in the country on January 1 after the census (Figure 5). There were 2.0 million such individuals from Denmark, 3.4 million from Finland, 0.1 million from Iceland, 2.6 million from Norway and 6.8 million from Sweden.

There were altogether 7,447,726 men and 7,454,847 women. Person-years of follow-up were calculated from the year following the first census record of the individual until the date of emigration, death or to December 31 of the following years: Denmark and Norway in 2003, Iceland in 2004, and Finland and Sweden in the year 2005.

The census records include questionnaire-based information on economic activity, occupation and industry, which were centrally coded and computerised in the national statistics offices. Occupations were coded into more than 300 categories according to the national adaptations of the International Standard Classification of Occupations from 1958 in three Nordic countries, Finland, Norway and Sweden. In Denmark, special national nomenclature was used with a separate category for self-employed persons, family workers, salaried employees, skilled workers and unskilled workers. In Iceland, occupations were coded according to the national adaptations of the International Standard Classification of occupations (ISCO-68). It was later again converted into ISCO-58 with instructions from International Labour organization (ILO). For the NOCCA study, the original national codes were converted according to the Nordic occupational classification (NYK) into 53 categories with one additional category of economically inactive persons. NYK is the Nordic adaptation of ISCO from 1958 (Details of the occupational categories are available at http://astra.cancer.fi/NOCCA/categories.html. Data on incident cancer cases were obtained from the national cancer registries in each of the Nordic countries. These registries get information from clinical and pathological departments, general practitioners, private clinics, and death registers that are almost similar in all Nordic countries. A system of giving unique personal identity codes to all the residents of the Nordic countries linked to the population registry, census records and cancer registry provided all the required information of exposures of all the participants. This personal identity code was useful in collecting information such as name, address, marital status, education, economic activity, occupation and industry that was recorded for each person. There are national differences between the data sources, but generally, the incidence data can be considered highly complete and accurate in international comparison. An important difference between the Nordic countries is the lack of a death certificate for cancers in Sweden, which was estimated to cause a loss of up to 4% of cancer cases (Mattsson et al., 1984). This study was undertaken with linkage of individual records based on unique personal identity codes used in all Nordic countries.

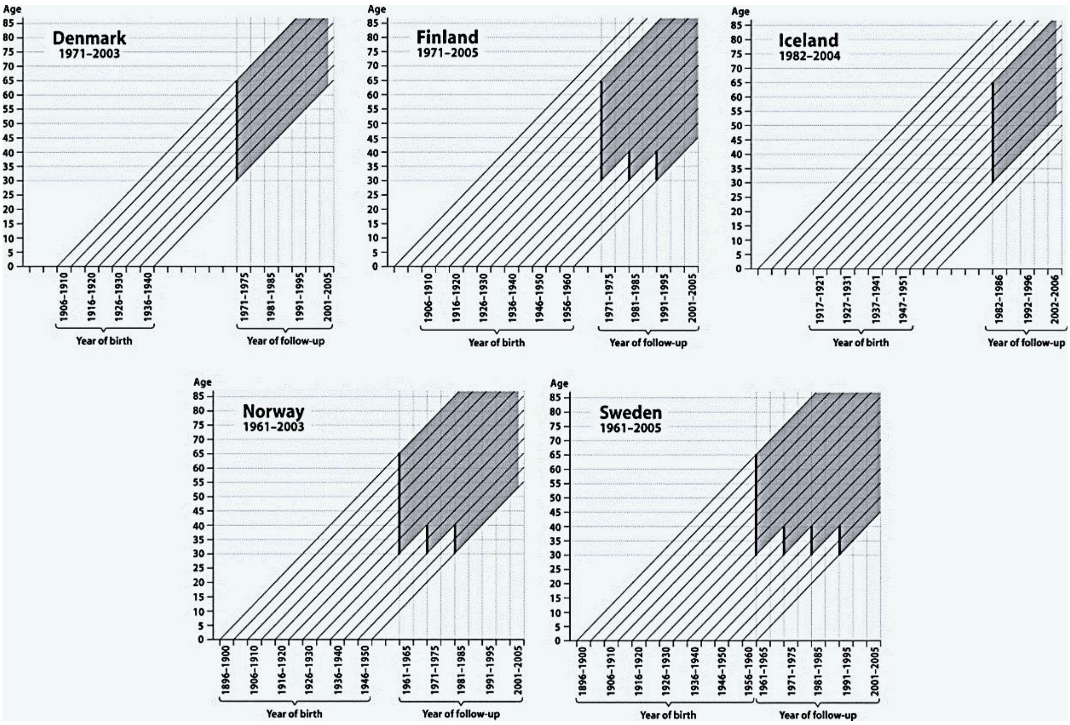

Figure 5. Follow up (grey area) of the study cohort defined by year of birth, age and country (Source: Pukkala et al., 2009).

4.2 Canadian Census Health and Environment Cohort (CanCHEC)

The CanCHEC cohort was derived from respondents to the 1991 Canadian Census who were included in the Canadian Census Mortality and Follow-Up Study (Peters et al., 2013). The present study utilises data from the linkage of the 1991 Canadian Census 2B (Long Form) with the Canadian Mortality Database (CMDB) (1991-2011), Canadian Cancer Registry (CCR) (1992-2010) and Historical Tax Summary Files (HTSF) (1984-2011). The nationally-representative cohort included 2,735,152 individuals representing 15% of the Canadian non-institutional resident population aged 25 years or older on census day (June 4, 1991), who were a usual resident of Canada and among the 20% of Canadian households selected to complete the long form census questionnaire (Peters et al., 2013). Occupation and socioeconomic characteristics were obtained from the census. For analytical purposes, occupation was classified into 42 mutually exclusive categories based on the 1991 Standard Occupational Classification (SOC-91). Follow-up of this cohort was expanded to include cancer morbidity through linkage to the Canadian Cancer Database (CCDB) through deterministic and probabilistic methods. Further methodological details about the cohort have been described elsewhere (Wilkins et al., 2008, Peters et al., 2013). In this study, to minimise the healthy worker effect (Soskolne et al., 2010), the analytical cohort was restricted to individuals with a valid entry for an occupation reported on census day and excluded individuals 75 years or older to minimise survival bias. Person-time at risk was counted from cohort entry on June 4, 1991 to the date of disease diagnosis, death, and loss to follow-up, or to the end of follow-up on December 31, 2010, whichever occurred first.

4.3 Study populations (I, II, III and IV)

Study I was a cohort study from all five Nordic countries. The study populations were both male and female of working age between 30-64 years of age. Occupational groups were classified into 54 categories including one group of economically inactive persons. For each country, gender and occupational category, the observed number of cancer cases and person years of observation were stratified into eight 5-year attained age categories; 30-34; 35-39; 40-44; 45-49; 50-54; 55-59; 60-64; 65-69; 70-74; 75-79; 80-85 years; and 5-year calendar periods. During the follow up of altogether 384.4 million person-years, 148,669 cases of bladder cancer were detected. There were altogether 111,458 men and 37,211 women bladder cancer cases in the study.

Study II is based on the cohort derived from the Nordic Occupational Cancer study (NOCCA) followed from 1961-2005 and the Canadian Census Health and Environment Cohort (CanCHEC) followed from 1991-2005 derived from the Canadian Census Mortality and Cancer Follow-up Study. The NOCCA cohort follow-up study was restricted to the period 1991-2005 to increase comparability with the CanCHEC study. In the NOCCA cohort, 73,653 cases of bladder cancer were diagnosed among 14,902,573 (50.0% male) individuals over the 1991-2005 follow-up period (141.6 million person-years). In the CanCHEC cohort, 8,170 cases of bladder cancer were diagnosed among 2,051,315 (54.0% male) individuals during the 1991-2010 follow up period (36.7 million person-years).

Study III utilises the NOCCA dataset for both bladder and lung cancer followed up from 1961-2005. Lung cancer cases were utilised to measure the proxy smoking prevalence of bladder cancer to see the "smoking adjusted risk" of bladder cancer. The study included 111,458 cases of bladder and 208,297 of lung cancer cases. The highest number of study population was from Sweden, and the least from Iceland. Likewise, proxy smoking prevalence was highest in Denmark and least in Sweden. We only considered the male population in the study, and occupational groups were classified to 53 categories, excluding one group of economically inactive persons.

Study IV also belongs to the NOCCA project. However, for this particular study, we did not have access to individual data records from Denmark. Hence, we had to restrict the study to Finland, Iceland, Norway and Sweden. This case control study included 113,343 cases and 566,715 controls. In this study, the Nordic Occupational Cancer Study Job Exposure Matrix (NOCCA-JEM) was used to quantitatively estimate the exposure to solvents and other agents. NOCCA-JEM was derived from the FINJEM. Three-fourths of the study subjects were male, and more than half were from Sweden. 56.8% of the cases and controls were born before 1920, and thus, were likely to have some employment and possible exposure before 1945, during periods for which NOCCA-JEM provides no exposure estimates. The proportion of exposed among the cases and controls was 17.5% and 82.5% respectively.

4.4 Information on exposure and study outcome

In this study, occupation was the exposure variable categorised into 54 broad occupational group including one group of economically inactive persons in the

NOCCA study while in CanCHEC, occupation was categorised into 42 groups. The outcome of the study was bladder cancer.

4.4.1 Occupational categories

For the NOCCA study, the original national codes were converted into a common classification of 53 broad categories with an additional category of economically inactive persons. Details of the occupational categories in the NOCCA study are available at http://astra.cancer.fi/NOCCA/categories.html. Likewise, for the CanCHEC, occupation was categorised into 42 groups. The majority of the occupational categories were comparable. However, some of the occupational categories such as chimney sweeps appeared only in NOCCA, while others such as waiters and tobacco workers that were not categorised in CanCHEC, were contained in a broader occupational group of food and beverage workers and food processing workers respectively in the CanCHEC study.

4.4.2 Occupational exposures in Nordic countries and Canada

The population of the Nordic countries included in this study was born between 1896 and 1960. People in the oldest cohorts started working in the period between 1910 and 1920, typically at the age of 15 years. However, in the later years with increasing durations of education, many persons in the youngest cohort started their working careers at the age of 25 years or higher. The normal time for retirement in the Nordic countries was between 65 to 70 years. It means that the persons included in this study have participated in the labour market before the First World War until the turn of millennium, with enormous change in the types of economic activities and the structure of the labour force, living and working conditions in the Nordic countries (Pukkala et al., 2009).

Likewise, the CanCHEC cohort was derived from the respondents to the 1991 Canadian census mortality and follow up study. There is not much information on occupational history documented before 1945 in Canada. The labour force survey was the first survey after 1945 that consisted of 1% of the population aged 14 and over. Hence, the occupational history of the Canadian population believed to have started much later than in Nordic countries. A summary of the study and data characteristics is described below (figure 6).

	NOCCA	CanCHEC
Countries	Denmark, Finland, Iceland, Norway and Sweden	Canada
Linkage datasets	Censuses, cancer registries and population registries	Canadian mortality database, cancer registry and tax summary files
Age at follow up	30 to 64 years	25 to 74 years
Follow up period	1961 to 2005. Restricted to 1991 - 2005	1991 to 2010
Cancer cases	73,653	8170
Occupational Categories	54	42

Figure 6. Study and data characteristics in NOCCA and CanCHEC cohorts in study II.

4.4.3 Smoking as a risk factor, proxy smoking and lung cancer

In general, effects from tobacco smoking on bladder cancer risk are substantial and exceed those from most occupational cancer studies (Haldorsen et al., 2017, Olsen et al., 1997). Both NOCCA and CanCHEC lack direct information on the smoking habits of the subjects. In many epidemiological studies, where there is no direct information on smoking habits, a proxy variable is used to estimate the approximate exposure. E.g., educational level and social class have been used as a proxy for smoking.

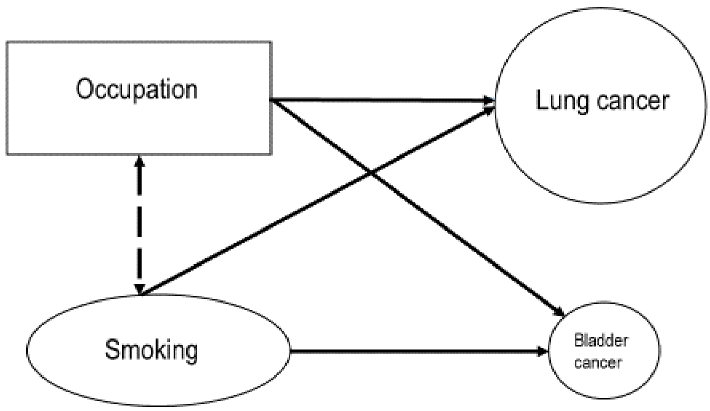

Figure 7. Directed acyclic graph (DAG) of the connection of occupation and smoking to risk of cancers of the bladder and lung.

Figure 7 explores the association between occupation and smoking habits, and risk of lung and bladder cancers. There is well-known and evidence-based association between smoking and risks of lung as well as bladder cancer. The relative risk of both lung as well as bladder cancer risk due to smoking was established a long time ago. Epidemiological studies have reported their association already in the early 1980s (Hakulinen et al., 1981). Dryer and colleagues observed a dose response pattern of smoking and the risk of bladder cancer in the Nordic population in a synthesis paper with a collection of dataset from earlier studies (Dreyer et al., 1997). The study observed a 1.5, 2, 3 and 5-fold risk of bladder cancer by increasing the number of cigarettes per day from 5, 10, 20, and 40 or more compared to never smokers corresponding to an excess relative risk of 0.10 per cigarette per day. Such relative risks (RRs) are usually measured for some duration of smoking.

Similarly, smoking is the most predominant factor of lung cancer, and industrial exposures to carcinogenic substances at the workplace are the other important risk factors for increased risk (Dreyer et al., 1997, Pukkala et al., 2009). Relative risk of lung cancer due to smoking is very high as compared to bladder cancer for the same number of cigarettes per day. By increasing the number of cigarettes per day from 5, 10, 20, and 40 or more, the relative risk increases by 5, 8, 16 and 30-fold respectively compared to never smokers (Dreyer et al., 1997). As the smoking habit is common in some occupations, the risk of lung cancer is also higher in those occupations. Occupations such as teachers, doctors and, agricultural workers tend to smoke less than the average population whereas tobacco workers, waiters, transportation workers, miners and quarry workers, etc. smoke more. This exposure was reflected in the occupational variation of lung cancer risk in a Norwegian survey (detail in Haldorsen et al., 2004) and in a Nordic study (figure 8). The prevalence of smoking in different occupations from 1978 to 1991 according to the Finnish survey (FINJEM) is shown below (Table 5).

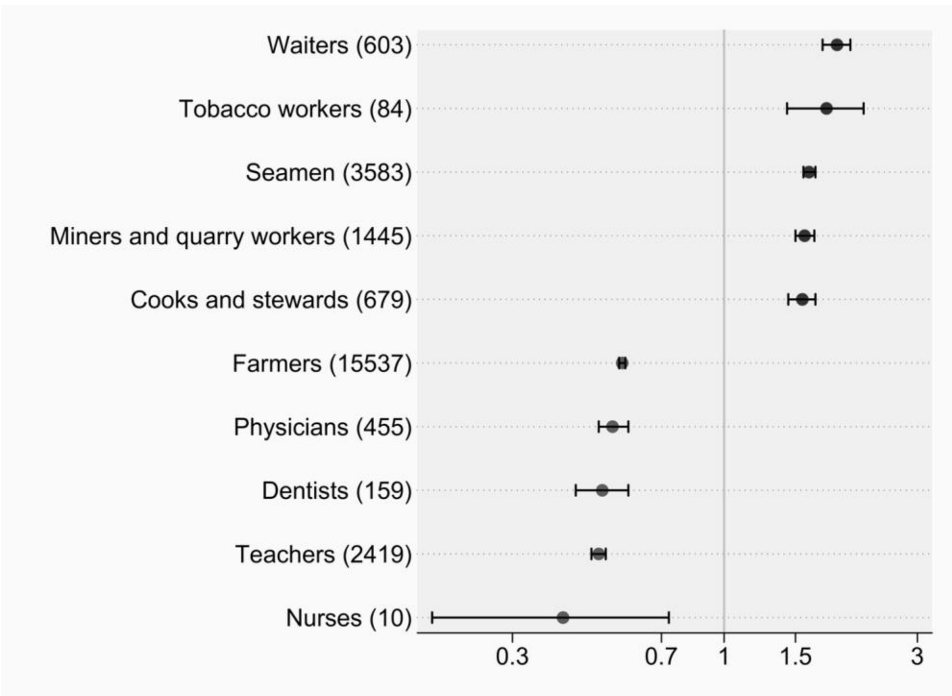

Figure 8. Highest and lowest SIRs of lung cancer in Nordic men (Source: Pukkala et al., 2009).

Table 5. Smoking prevalence in different occupations from FINJEM (1978-1991)

Occupations	Male	Female	Average (weighted)
Technical workers	0.26	0.17	0.25
Laboratory assistants	0.33	0.26	0.27
Physicians	0.17	0.09	0.17
Dentists	0.15	0.06	0.13
Nurses	0.18	0.22	0.22
Assistant Nurses	0.19	0.14	0.14
Other health workers	0.25	0.15	0.17
Teachers	0.18	0.16	0.18
Religious workers	0.24	0.14	0.17
Artistic workers	0.32	0.28	0.33
Journalists	0.27	0.40	0.33
Administrators	0.23	0.23	0.23
Clerical workers	0.31	0.23	0.24
Sales agents	0.33	0.27	0.31
Shop workers	0.31	0.22	0.28
Farmers	0.29	0.02	0.17
Gardeners	0.31	0.09	0.16
Fishermen	0.42	.	0.42
Forestry workers	0.36	0.05	0.32
Miners and quarry workers	0.46	.	0.46
Seamen	0.43	.	0.43
Transport workers	0.39	0.28	0.38
Drivers	0.40	0.38	0.40
Postal workers	0.34	0.22	0.27
Textile workers	0.36	0.19	0.20
Shoe and leather workers	0.41	0.20	0.27
Smelting workers	0.46	0.26	0.31
Mechanics	0.41	0.26	0.41
Plumbers	0.42	.	0.36
Welders	0.44	0.26	0.43
Electrical workers	0.34	0.28	0.35
Wood workers	0.39	0.32	0.34
Painters	0.39	0.35	0.42
Other construction workers	0.48	0.22	0.32
Bricklayers	0.41	.	0.39
Printers	0.33	0.24	0.31
Chemical process workers	0.37	0.18	0.33
Food workers	0.36	0.19	0.27
Beverage workers	0.28	0.20	0.20

Occupations	Male	Female	Average (weighted)
Tobacco workers	0.39	0.24	0.24
Glass makers etc.	0.37	0.26	0.26
Packers	0.38	0.24	0.29
Engine operators	0.30	0.30	0.28
Public safety workers	0.33	0.38	0.33
Cooks and stewards	0.52	0.19	0.20
Domestic assistants	0.36	0.18	0.23
Waiters	0.43	0.33	0.35
Building caretakers	0.27	0.22	0.22
Chimney sweeps	0.40	.	0.32
Hairdressers	0.23	0.23	0.23
Launderers	0.34	0.24	0.25
Military personnel	0.24	.	0.24
Other workers	0.38	0.24	0.34

4.4.4 Nordic Occupational Job Exposure Matrix (NOCCA-JEM)

JEM is used in occupational epidemiology to estimate level of exposure. This exposure estimate can be used to assess risk or burden of disease. JEMs were developed for estimating exposure agents in occupational studies. Nowadays, it is in use for the surveillance of workplace hazards and for prediction of future exposures from different chemical agents. In large census-based studies, a generic JEM covering all occupations in a national classification is often the only practical option to perform the required conversion of occupational titles to exposure estimates (Kauppinen et al., 2009). A valid JEM in an epidemiological study may be able to identify the agents causing the risk.

The Finnish Job exposure matrix (FINJEM) was used as a base matrix to construct NOCCA-JEMs for all the Nordic countries. This modified version of FINJEM was used in Study IV to convert job titles of the participants to specific occupational agents. FINJEM was constructed in the 1990s to use in a census based Finnish occupational studies on occupational cancer. FINJEM has three dimensions: agents, occupations and exposure periods. The agent includes over 80 chemical, physical, microbiological, ergonomic and psychological factors. The occupational dimension covers all occupations (311 categories) of the longitudinal occupational classification used in Finnish censuses. The time dimension covers the periods 1945-1959, 1960-1984, 1985-1994, 1995-1997, 1998-2000, 2001-2003, 2004-2006, 2007-

2009, and 2010-2012 (Kauppinen et al., 2009). The cells of this 3-dimensional matrix characterise occupational exposure in two measures. The proportion of exposed (P) and the mean level of exposure (L). Both P and L are based on exposure measurement data, which include over 4,000 measurements based on tens of thousands of samples (Kauppinen et al., 1998). The minimum level of exposure included is defined agent by agent. The level of exposure is expressed as long-term (one-year average during working hours) concentration of the agent in the working room air among the exposed workers (Figure 9). The FINJEM databases also includes documentation on the grounds of estimates, definitions of agents and measurement/ survey data (Kauppinen et al., 2009).

NOCCA-JEM was created by modifying FINJEM. Informations on exposed occupations and exposure prevalence (P) in NOCCA-JEM is based on knowledge of the Nordic experts and FINJEM prevalence estimates. NOCCA-JEM exposure intensity (L) was derived from FINJEM intensity estimates and exposure measurements data from the Nordic countries (Kauppinen et al., 2009). FINJEM estimates were directly adopted from Norway, Iceland, Sweden and Denmark if the differences between the country specific P and L values from these countries was within 50% and 150% of the corresponding FINJEM values. Otherwise, FINJEM values were modified for each country. If the prevalence of a chemical agent was less than 5% and the prevalence of a non-chemical agent was less than 10% for all the periods, such agents were not included in the NOCCA-JEM. Likewise, the FINJEM period 1960-84 was split into two NOCCA-JEM periods because it was believed that exposure levels and agents may have changed in the 1970s. FINJEM periods after 1995 were not assessed because their relevance in cancer studies may be small due to a long latency period required for the development of cancer after exposure (Kauppinen et al., 2009). NOCCA-JEM provides values for 28 chemical and non-chemical factors. It covers 4 periods: 1945-59, 1960-74, 1975-84, and 1985-94 for chemical and only the 1985-94 period for non-chemical agents. NOCCA-JEM includes 492 occupational categories for men and 447 for women in Denmark, 311 in Finland, 374 in Iceland, 322 in Norway, and 296 in Sweden (Kauppinen et al., 2009).

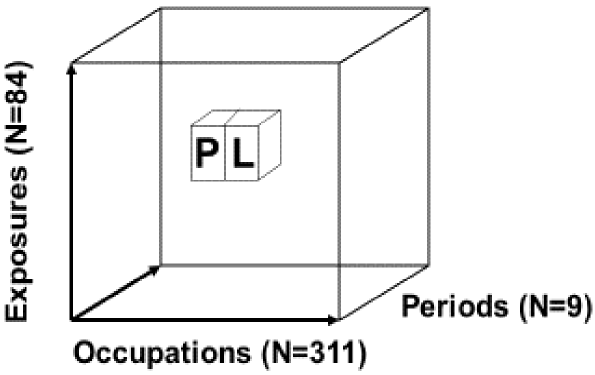

Figure 9. Finnish job exposure matrix (FINJEM) exposure information system. Exposure to each agent is characterized by the periods (1945-1959, 1960-1984,1985-1994, 1995-1997, 1998-2000, 2001-2003, 2004-2006, 2007-2009, and 2010-2012). Likewise, the exposure agents (n = 84) (Source: Kauppinen et al., 2014).

4.4.5 Solvent exposure and risk of bladder cancer

In Study IV, occupational solvent exposure was estimated using NOCCA-JEM by correctly linking occupational titles to NOCCA-JEM. All incident cases of bladder cancer were extracted from the NOCCA cohort. For each case, five controls were selected, matched by birth year and sex and were randomly selected from among individuals who were alive and free from bladder cancer at the date of diagnosis of the case. The date of diagnosis was also referred to as the index date. The inclusion criteria for participants in the study were having a minimum age of 20 years at the index date and having occupational information from at least one census. The following exposure solvents were considered for analysis: aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents, benzene, toluene, chlorinated hydrocarbon solvents, perchloroethylene, 1,1,1 trichloroethane, trichloroethylene and other organic solvents. We assumed that the solvent exposures before 1945 could be taken as zero. An occupational code was assigned for each cases and control based on the occupational codes recoded in the census. For each occupational code and year of exposure, the exposure estimate was calculated as the product of proportion and level of exposure (P * L) from NOCCA-JEM. These years specific values were then added up for the entire employment period (T).

Exposure was assumed to start at the age of 20 years and end at the index date or at age 65, whichever occurred first. If there were different occupational codes of an individual in the census records, we assume that the individual had changed occupations at the midpoint of two known census years. In that case, the exposure history of an individual consists of more than one P * L* T value. The cumulative exposures of these individuals were estimated by summing up all their P * L* T values over their entire working career. This procedure was repeated for all the exposure agents. For the purpose of analysis, cumulative exposures among the exposed cases and controls were categorised into three levels. From zero to the 50^{th} percentile as low exposure, between the 50^{th} and 90^{th} percentiles as medium exposure level and from above the 90^{th} percentile as high exposure level. Individuals with no exposure were used as the reference group.

4.5 Ethical considerations

Ethical committees and data inspection boards from each Nordic country approved the NOCCA study with participation of at least one author form each country in a role of co-author. The University of Toronto, Health Sciences research ethics board, approved the Canadian (CanCHEC) study. Prior approval was obtained therefore no additional approval was needed for this study.

4.6 Statistical analyses

Descriptive statistics were used in this study to describe basic features of the data in all four separate studies. Bladder cancer diagnoses from 1961-2005 in the Nordic countries were classified into 54 categories. SIRs of these occupations were stratified according to the countries, year of diagnosis and age at diagnosis. Likewise, Study II compared the similarity of both high and low risk occupational categories in the Nordic countries and Canada. In CanCHEC, HRs for bladder cancer were calculated for 42 occupational categories. Study III utilised the NOCCA dataset on both bladder and lung cancer cases in males. The results are presented as SIRs for both lung and bladder cancer cases. However, the lung cancer SIRs are used as a proxy for smoking prevalence in an occupational category. Both SIRs and smoking adjusted SIRs were estimated for 53 occupational categories, excluding a group of economically inactive persons. Study IV assesses the association exposure to solvents and risk of bladder cancer in four Nordic countries, excluding Denmark.

Census-based occupational titles of the cases and controls were lined with the job exposure matrix created for the NOCCA study (NOCCA-JEM) to estimate quantitative cumulative exposures.

4.6.1 Standardized incidence ratio and Hazard ratio

In Studies I, II and III, the SIR was used to measure cancer incidence rates with the entire national study populations used as reference rates. In these studies, the incidence of bladder cancer in 53 different occupational categories, in addition to one economically inactive group was compared with the corresponding incidence in the entire national study population. In Study II, we restricted the study population only from 1991-2005 to make it more consistent with the CanCHEC study. Likewise, in Study III, we excluded the economically inactive group of males and the complete female population for the purpose of analysis. Results are presented in SIRs. The SIR was counted as the ratio of the observed number of cases to the expected number of cases. Exact 95% confidence intervals (CI) were defined based on a Poisson distribution. For each country, gender and occupational category, the observed number of cancer cases and person years were stratified into eight 5-year attained age categories (30-34; 35-39…, 85+ years) and nine 5-year calendar periods (1961-1965, …, 2001-2005). The expected number of cases in each country, sex, 5-year age group, were calculated by multiplying the number of person-years in each stratum by the respective national incidence rate.

In Study III, we also calculated the "smoking adjusted risk" (SIR_{adj}). Hence, for SIR_{adj}, the expected number was corrected by multiplying the original expected number with the product of proxy smoking prevalence value and relative risk (RR) estimate of bladder cancer due to smoking in each occupational category (Armitage 1971, Carstensen et al., 1988). The estimation of smoking prevalence was based on linear regression ($Y = \alpha + \beta X$) where X is the SIR of lung cancer. Exact 95% confidence intervals (CIs) of the SIRs were defined based on the Poisson distribution of the observed number of cases. Analysis was stratified by age groups, calendar period, countries, time period from the first hired to the occupation and duration of employment to evaluate the consistency with the main results. The Poisson test for increasing/decreasing trend was done to assess the statistical significance of the observed trends across subgroups in stratified analysis. Analyses were performed in two different models. In model 1, we included all 53 occupational categories. However, in model 2, we excluded occupations with smoking-adjusted SIRs for lung cancer markedly higher than 1.0, according to an earlier Norwegian study (Haldorsen et al., 2004). These occupational groups include miners and quarry workers, drivers, smelting workers, mechanics, plumbers, welders, painters, bricklayers, printers, beverage workers, tobacco workers, glassmakers, packers, hairdressers, launderers and gardeners. These groups may reflect an increased risk of lung cancer due to other major risk factors in addition to smoking.

In Studies II and IV, Cox proportional hazards were used to calculate the HR and 95% CI. In Study II, Cox proportional hazards estimated risk of bladder cancer associated with employment according to the occupation at baseline. In absence of potential confounders such as lifestyle factors including smoking, physical activity and diet in the study, models were adjusted for age group, region and level of education. All person-years and counts are randomly rounded to base 5, and no counts < 5 were reported according to the Statistics Canada disclosure guidelines.

In Study IV, HR and 95% CI for each solvent were estimated using conditional logistic regression. A Person chi square test for linear trend was performed to assess the dose-response relationship between exposure variables and bladder cancer risk. Variables were selected using "purposeful selection of covariates". The univariate analysis of each variable with a significant univariate test was selected for further multivariate analysis based on the Wald test from logistic regression and $p \leq 0.25$. Benzene and toluene were highly correlated with aliphatic and alicyclic hydrocarbon solvents as well as with each other. Therefore, the analysis was performed in two different models. In model 1, both benzene and toluene were included but excluded aliphatic and alicyclic hydrocarbon solvents and in model 2, we included aliphatic and alicyclic hydrocarbon solvents but excluded benzene and toluene. All other solvents were included in both multivariate analyses. Results from both models were similar. Hence, we chose to present the results for aliphatic and alicyclic hydrocarbon solvents from model 2 and all other exposures from model 1. Age and sex specific analyses were performed to evaluate the effect modification of the main results with these (age and sex) variables. Analyses with various lag time assumptions 0 year (no lag time) 10 years and 20 years were repeated for the purpose of sensitivity analysis. The latency period is the interval of exposure and bladder cancer and the exposure during this latency period were unlikely to have an effect on the risk of bladder cancer. A lag time of 10 years was chosen as a main result in the study.

To determine the robustness of an assessment in the study, sensitivity analysis was performed. Analysis in the studies included various onset and end of working career that was determined from the age of 20 to 65 years. These methods included: stratification of the study population based on country, period and age of diagnosis (Study I), restriction of study cohort follow-up (Study II), exclusion of economically inactive persons, inclusion of a high-risk group (males only) and use of proxy variable to estimate the effect of unmeasured confounding (study III), estimation of exposure based on average intensities (L) and use of a lag time of 10 years (study IV). All the statistical analyses were done using statistical packages STATA and SPSS in addition to R in study III.

5 RESULTS

5.1 Characteristics of the study population

The study population in Study I, II and III comprises of participants from all five Nordic countries. Study II also includes the Canadian population. Study III was restricted to males only. Study IV excluded Denmark due to a data restriction policy. During the follow-up from 1961 to 2005, which is altogether 384.4 million person years, 148,669 bladder cancer cases were diagnosed. Two-thirds of the cases (111,458) were males, and the remaining one-third (37,221) were females. Altogether 208,297 lung cancer cases of males were observed during the same follow-up period. The highest number of participants for both bladder and lung cancer cases were from Sweden and the least from Iceland, and the majority of participants were older than 50 years of age.

Similarly, in Study II, participants were from the Nordic countries as well as Canada (all provinces). However, the number of participants as well as bladder cancer cases were comparatively higher in Nordic countries. Despite the restriction of the follow-up follow up (before 1991), we observed 73,653 bladder cancer cases in the Nordic countries, and 8,170 cases were observed in CanCHEC. An almost equal proportion of male and female cases were observed in both the NOCCA and CanCHEC studies (Table 6). In Study IV, 113,343 cases and 566,715 controls were diagnosed in four Nordic countries between 1961 and 2005. The proportion of those exposed among cases and controls were 17.5% and 82.5% respectively.

In all studies (except Study III), the proportion of bladder cancer cases was higher in males than in women. Likewise, bladder cancer cases were more common in ages 60 years and above. Using our own evidence as well as from other studies, we included only male bladder cancer cases for smoking adjusted effect on occupational risk of bladder cancer in Study III.

Table 6. Demographic characteristics of study population in four different studies.

	Study I	Study II	Study III	Study IV
Study design	Cohort	Cohort	Cohort	Case control
Risk estimate	SIR	SIR and HR	SIR	HR
Number of occupational categories	54	54 and 42	54	53
Number of bladder cancer cases				
Country				
Denmark	35,612	17,525	27,020	NA
Finland	17,998	11,109	13,716	18,521
Iceland	748	573	565	804
Norway	29,804	13,798	22,272	28,938
Sweden	64,507	30,648	47,885	65,080
Canada	NA	8,170	NA	NA
Sex				
Male	111,458	61,367	111,458	507,774
Female	372,11	20,456	excluded	172,284

SIR= standardized incidence ratio; HR= Hazard ratio; NA: no information available.

5.2 Risk of bladder cancer according to occupation

The most pronounced risk of bladder cancer (SIR > 1.40) in NOCCA was observed among tobacco workers, chimney sweeps and waiters. Statistically significant excess risk (SIR > 1.05) was observed among hairdressers, seamen, printers, and plumbers. Lower but statistically significant risk was also observed among sales agents, artistic workers, cooks and stewards, drivers, fishermen, clerical workers, military personnel, assistant nurses, shoe and leather workers, mechanics, public safety workers, administrators, shop workers, food workers, packers, building caretakers, transport workers, smelting workers, electrical workers, postal workers, textile workers, welders, chemical process workers, and engine operators (Table 7).

Table 7. Observed numbers (Obs), standardized incidence ratios (SIR) of most high-risk occupations (SIR > 1.05) of bladder cancer in Nordic countries in Study I

Occupation	Obs	SIR	95% CI
Tobacco workers	79	1.57	1.24-1.96
Chimney sweeps	105	1.48	1.21-1.80
Waiters	803	1.43	1.33-1.53
Hairdressers	550	1.28	1.18-1.40
Seamen	1478	1.22	1.16-1.30
Printers	1144	1.21	1.14-1.30
Plumbers	1020	1.20	1.13 -1.30
Sales agents	5500	1.16	1.13-1.20
Beverage workers	182	1.16	1.00-1.34
Artistic workers	665	1.16	1.08-1.26
Cooks and stewards	713	1.14	1.06-1.23
Drivers	6035	1.14	1.11-1.20
Fishermen	1453	1.13	1.07-1.20
Clerical workers	7385	1.12	1.09-1.14
Military personnel	916	1.12	1.05-1.20
Assistant nurses	812	1.11	1.04-1.20
Shoe and leather workers	521	1.10	1.00-1.20
Mechanics	8315	1.10	1.08-1.13
Public safety workers	1590	1.10	1.05-1.15
Launderers	434	1.09	1.00-1.20
Administrators	5872	1.09	1.06-1.11
Shop workers	5799	1.09	1.06-1.11
Food workers	2444	1.09	1.05-1.14
Packers	3013	1.09	1.05-1.13
Building caretakers	3221	1.09	1.05-1.13
Painters	1656	1.08	1.03-1.13
Transport workers	2138	1.08	1.04-1.13
Smelting workers	1943	1.08	1.03-1.13
Electrical workers	2879	1.08	1.04-1.12
Postal workers	1544	1.07	1.02-1.12
Textile workers	2182	1.06	1.02-1.10
Welders	826	1.06	1.00–1.13
Chemical process workers	1492	1.06	1.01-1.10
Engine operators	2234	1.06	1.01-1.10

CI = Confidence interval

Stratifying based on period, little temporal variation in the SIR was observed among the high-risk occupational categories. A slight increasing trend in the SIR was observed among drivers, tobacco workers and launderers in the high-risk occupational categories and among farmers, forestry workers and gardeners in low risk categories. Similarly, significant decreased risk was observed among painters, printers and waiters in this period. The highest SIR for the period of 1991-2005 was observed among tobacco workers, chimney sweeps, waiters and hairdressers (Table 8). Likewise, an increasing trend over the age observed among seamen, drivers, plumbers and, hairdressers in high-risk categories and among gardeners and forestry workers in low risk occupational categories. The SIR of tobacco workers and chimney sweeps were highest in the youngest group of 30 to 49 years (Table 9). The risk significantly remained elevated throughout the oldest age group of 70+ years. Stratification by sex observed painters, printers and tobacco workers were at high risk in women, but for other occupations men were at higher risk. Stratification by country observed similar risk across the Nordic countries in both high and low risk occupational categories.

Table 8. Observed numbers (Obs) and standardised incidence ratios (SIR) of bladder cancer among most high-risk occupations in Nordic countries, by period in Study I.

Occupation	**Year of diagnosis**								
	1961 - 1975			**1976 - 1990**			**1991 - 2005**		
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
Tobacco workers	6	1.24	0.45-2.70	34	1.55	1.07-2.16	39	1.65	1.17-2.26
Chimney sweeps	8	1.07	0.46-2.10	44	1.61	1.17-2.16	53	1.46	1.09-1.91
Waiters	100	1.76	1.43-2.13	313	1.47	1.31-1.64	390	1.33	1.20-1.47
Hairdressers	70	1.55	1.21-1.96	209	1.23	1.06-1.40	271	1.26	1.11-1.42
Seamen	162	1.37	1.16-1.59	554	1.18	1.08-1.28	762	1.22	1.13-1.30
Printers	142	1.45	1.22-1.71	428	1.23	1.11-1.35	574	1.15	1.05-1.24
Plumbers	108	1.30	1.06-1.56	359	1.17	1.05-1.30	553	1.20	1.10-1.30
Sales agents	704	1.28	1.19-1.38	2077	1.18	1.13-1.23	2719	1.12	1.07-1.16
Beverage workers	25	1.38	0.89-2.04	81	1.17	0.93-1.45	76	1.09	0.86-1.36
Artistic workers	82	1.60	1.27-1.98	239	1.19	1.04-1.35	344	1.08	0.96-1.19
Cooks and stewards	92	1.23	0.99-1.51	277	1.17	1.03-1.32	344	1.10	0.98-1.22
Drivers	497	1.03	0.93-1.12	2206	1.12	1.07-1.16	3332	1.18	1.14-1.22
Fishermen	162	0.97	0.83-1.13	648	1.16	1.07-1.25	643	1.16	1.06-1.24
Clerical workers	720	1.25	1.16-1.34	2624	1.15	1.10-1.19	4041	1.08	1.04-1.11

Table 8 (continued)

Occupation	Year of diagnosis								
	1961 - 1975			1976 - 1990			1991 - 2005		
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
Military personnel	58	1.09	0.83-1.41	291	1.10	0.98-1.23	567	1.14	1.04-1.23
Assistant nurses	61	1.24	0.94-1.59	250	1.14	1.00-1.28	501	1.09	0.99-1.18
Shoe and leather workers	89	1.15	0.92-1.41	230	1.13	0.99-1.28	202	1.04	0.90-1.19
Mechanics	872	1.16	1.09-1.24	3075	1.11	1.07-1.14	4368	1.09	1.05-1.11
Public safety workers	182	1.31	1.13-1.52	611	1.13	1.05-1.22	797	1.03	0.96-1.10
Launderers	46	0.97	0.71-1.29	177	1.08	0.92-1.25	211	1.12	0.97-1.28
Administrators	595	1.13	1.04-1.22	2436	1.16	1.11-1.21	2841	1.02	0.98-1.05
Shop workers	518	1.19	1.08-1.29	2207	1.08	1.03-1.12	3074	1.08	1.03-1.11
Food workers	270	1.13	1.00-1.27	973	1.07	1.00-1.13	1201	1.10	1.04-1.16
Packers	448	1.13	1.03-1.24	1247	1.10	1.03-1.15	1318	1.07	1.01-1.13
Building caretakers	304	0.99	0.88-1.11	1286	1.11	1.05-1.17	1631	1.09	1.03-1.14
Painters	219	1.17	1.02-1.33	676	1.09	1.01-1.18	761	1.05	0.97-1.12
Transport workers	188	1.09	0.93-1.25	793	1.09	1.01-1.16	1157	1.08	1.01-1.14
Smelting workers	230	1.04	0.90-1.17	802	1.09	1.01-1.17	911	1.08	1.01-1.15
Electrical workers	283	1.19	1.05-1.33	1005	1.09	1.02-1.16	1591	1.05	1.00-1.10
Postal workers	173	1.16	0.99-1.34	560	1.09	1.00-1.18	811	1.04	0.97-1.11
Textile workers	270	1.06	0.93-1.19	905	1.10	1.02-1.16	1007	1.04	0.97-1.10
Welders	64	1.09	0.83-1.38	277	1.11	0.98-1.24	485	1.02	0.93-1.11
Chemical process workers	186	0.94	0.81-1.08	655	1.12	1.03-1.20	651	1.05	0.97-1.13
Engine operators	237	1.11	0.97-1.25	802	1.05	0.97-1.12	1195	1.05	0.99-1.11

CI = Confidence interval

Table 9. Observed numbers (Obs) and standardised incidence ratios (SIR) of bladder cancer among most high-risk occupations in Nordic countries, by age at follow up in Study I.

Occupation	**Age**								
	30 - 49 years			**50 - 69 years**			**70 + years**		
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
Tobacco workers	5	3.50	1.13-8.16	36	1.51	1.05-2.08	38	1.52	1.07-2.08
Chimney sweeps	7	2.15	0.87-4.43	52	1.50	1.12-1.96	46	1.39	1.02-1.85
Waiters	33	1.39	0.95-1.95	380	1.50	1.35-1.66	390	1.36	1.23-1.50
Hairdressers	20	1.21	0.73-1.86	252	1.30	1.14-1.47	278	1.26	1.11-1.42
Seamen	60	1.17	0.89-1.50	737	1.22	1.13-1.31	681	1.22	1.12-1.31
Printers	67	1.41	1.09-1.79	578	1.23	1.13-1.33	499	1.17	1.06-1.27
Plumbers	37	0.87	0.61-1.20	513	1.21	1.10-1.31	470	1.23	1.12-1.34
Sales agents	234	1.09	0.95-1.23	2486	1.16	1.11-1.20	2780	1.17	1.13-1.21
Beverage workers	9	1.73	0.79-3.27	82	1.05	0.83-1.30	91	1.23	0.98-1.50
Artistic workers	34	1.07	0.73-1.48	320	1.17	1.04-1.30	311	1.17	1.04-1.31
Cooks and stewards	27	0.94	0.62-1.37	300	1.14	1.01-1.27	386	1.16	1.04-1.28
Drivers	255	1.03	0.90-1.06	3056	1.15	1.11-1.19	2724	1.15	1.10-1.19
Fishermen	33	0.99	0.68-1.39	635	1.18	1.09-1.28	785	1.10	1.02-1.18
Clerical workers	371	1.08	0.97-1.19	3526	1.11	1.07-1.14	3488	1.13	1.09-1.17
Military personnel	57	1.37	1.03-1.77	454	1.10	0.99-1.20	405	1.13	1.02-1.24
Assistant nurses	64	1.02	0.78-1.29	453	1.20	1.09-1.32	295	1.02	0.90-1.13
Shoe and leather workers	11	1.11	0.55-1.99	217	1.15	1.00-1.31	293	1.06	0.94-1.18
Mechanics	422	1.17	1.06-1.29	3978	1.09	1.05-1.12	3915	1.11	1.07-1.14
Public safety workers	69	1.04	0.80-1.31	756	1.12	1.03-1.19	765	1.09	1.01-1.16
Launderers	12	1.23	0.63-2.14	169	1.02	0.87-1.19	253	1.13	0.99-1.27
Administrators	226	1.11	0.97-1.26	2644	1.07	1.03-1.11	3002	1.10	1.05-1.13
Shop workers	206	1.04	0.90-1.19	2710	1.07	1.03-1.11	2883	1.11	1.06-1.14
Food workers	82	1.13	0.89-1.40	1127	1.09	1.02-1.15	1235	1.09	1.02-1.15
Packers	103	1.12	0.91-1.35	1327	1.10	1.04-1.16	1583	1.08	1.02-1.13
Building caretakers	132	1.22	1.02-1.44	1403	1.07	1.01-1.12	1686	1.10	1.04-1.15
Painters	67	1.20	0.93-1.53	721	1.04	0.96-1.11	868	1.11	1.03-1.18
Transport workers	61	0.91	0.69-1.17	988	1.12	1.05-1.18	1089	1.06	0.99-1.12
Smelting workers	69	1.10	0.85-1.39	951	1.13	1.05-1.20	923	1.04	0.97-1.10
Electrical workers	145	0.95	0.80-1.12	1438	1.07	1.02-1.03	1296	1.10	1.03-1.15
Postal workers	58	0.85	0.64-1.10	732	1.09	1.01-1.17	754	1.07	0.99-1.14

Table 9 (continued)

Occupation	Age								
	30 - 49 years			50 - 69 years			70 + years		
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
Textile workers	61	1.16	0.88-1.48	1.48	1.06	0.99-1.13	1231	1.06	1.00-1.12
Welders	55	1.08	0.81-1.40	414	1.01	0.91-1.11	357	1.11	0.99 -1.22
Chemical process workers	47	1.04	0.76-1.38	666	1.08	1.00-1.16	779	1.05	0.97 -1.12
Engine operators	122	1.13	0.93-1.34	1129	1.07	1.00-1.13	983	1.03	0.97-1.10

CI = Confidence interval

Comparing NOCCA and CanCHEC in Study II, we observed some similarity in the risk of bladder cancer. In the CanCHEC, the greatest statistically significant excess risk of bladder cancer (HR $\geq$ 1.40) was among hairdressers and welders in males and only among plumbers in females. Likewise, significant increased risk in males among administrators and managers were observed, as well as insignificant but increased risk in males among rubber and plastic workers, painters, chemical workers and miners. Furthermore, in females statistically insignificant but increased risk (HR $\geq$ 1.05) was observed among professional technical workers, metalworkers, wood workers, other service workers, construction workers, protective services workers, printers, dry cleaning workers, hairdressers, drivers and mobile plant workers, media workers, and food and beverage workers (Table 10). The significantly lowest risk was observed among gardeners, forestry workers and farmers in both NOCCA and CanCHEC cohorts.

Table 10. Observed number of cases and hazard ratios (HR) of bladder cancer in CanCHEC (1991-2010), by sex in Study I.

Occupation	Male			Female		
	Cases	HR	95% CI	Cases	HR	95% CI
Administrators and Managers	1,115	1.11	1.04-1.19	110	0.93	0.77-1.13
Agriculture	455	0.84	0.76-0.93	50	0.88	0.66-1.18
Artistic, media	70	0.77	0.61-0.98	25	1.09	0.73-1.63
Brick cement	55	1.08	0.83-1.42	<5	.	.
Chemicals	45	1.14	0.84-1.54	<5	.	.
Cleaners and janitors	295	0.97	0.86-1.09	100	1.00	0.82-1.23
Construction	410	0.95	0.86-1.06	10	1.25	0.63-2.51

Table 10 (continued)

Occupation	Male			Female		
	Cases	HR	95% CI	Cases	HR	95% CI
Dental	15	0.99	0.59-1.64	<5	.	.
Drivers & mobile Plant operators	520	0.95	0.87-1.04	10	1.09	0.64-1.85
Dry cleaning	5	0.46	0.22-0.97	15	1.11	0.65-1.88
Electrical	150	0.88	0.75-1.04	5	0.65	0.27-1.57
Firefighters	25	0.89	0.60-1.33	<5	.	.
Fishing and hunting	50	1.01	0.77-1.33	<5	.	.
Food and beverage	160	1.00	0.85-1.17	125	1.07	0.89-1.29
Food processing	60	0.77	0.59-1.01	15	0.59	0.35-0.98
Forestry	85	1.02	0.82-1.27	<5	.	.
Hairdressers	25	1.48	1.00-2.19	10	1.09	0.63-1.89
Lab workers	20	0.95	0.62-1.45	5	0.69	0.33-1.46
Machinery assemblers and operators	80	0.82	0.66-1.02	<5	.	.
Material handlers	100	0.94	0.77-1.14	10	0.72	0.36-1.44
Mechanics	330	1.01	0.90-1.13	<5	.	.
Metal workers	230	0.97	0.85-1.10	10	1.44	0.72-2.88
Miners	60	1.12	0.87-1.45	<5	.	.
Nursing	25	0.84	0.56-1.25	105	0.90	0.74 - 1.10
Office	660	1.03	0.95-1.12	575	1.09	0.99-1.21
Other health	30	0.96	0.68-1.34	15	0.85	0.51-1.41
Other professional	190	1.04	0.90-1.21	50	0.89	0.66-1.20
Other service workers	20	0.89	0.59-1.36	5	1.31	0.55-3.16
Painters	50	1.15	0.86-1.54	<5	.	.
Physicians	45	1.05	0.79-1.40	<5	.	.
Plumbers	90	0.95	0.77-1.16	5	2.90	1.20-6.98
Printers	40	1.04	0.77-1.41	10	1.21	0.63-2.34
Professional technical	400	1.03	0.93-1.14	15	1.45	0.90-2.35
Protective services	230	1.10	0.97-1.26	10	1.22	0.67-2.20
Rubber and plastics	30	1.22	0.84-1.78	<5	.	.
Sales	525	1.12	1.02-1.22	185	1.06	0.91-1.23
Teachers	230	0.87	0.76-1.00	125	0.91	0.75-1.11
Textiles	50	0.91	0.69-1.20	45	0.90	0.66-1.21
Travel and recreation	15	0.77	0.47-1.25	10	1.49	0.80-2.77
Veterinary	<5	.	.	<5	.	.
Welders	100	1.40	1.15-1.70	<5	.	.
Wood	260	1.00	0.88-1.13	5	1.34	0.56-3.23

HR = Hazard ratio; CI = Confidence interval (.) = Information not available. Numbers were rounded to nearest 5.
Counts < 5 are not reported.

Occupational categories in NOCCA were more comparable to CanCHEC (54 and 42). The majority of the occupation groupings were comparable between these two cohorts. However, some groups such as chimney sweeps appeared only in NOCCA while waiters were contained within a broader occupational category of food and beverage workers and tobacco workers in a broader group of food processing workers. Separately in two cohorts, we observed some similarity in the risk of bladder cancer. However, we identified the consistency in the risk only among sales workers. Risk of bladder cancer varied across the occupational categories in both cohorts.

5.3 Smoking adjusted risk of bladder cancer in Nordic males

In Study III, we estimated the "smoking adjusted risk" of bladder cancer in different occupations using proxy smoking prevalence from lung cancer incidence within the same cohort. Findings of this study reveal that smoking is the important risk factor of bladder cancer, and variation in bladder cancer risk observed between the occupational categories appears to be primarily due to smoking. We also observed that the smoking adjusted SIRs became closer to 1.0 for all occupations after adjustments. However, the adjustment did not change the direction of risk estimate, and those occupations that are observed to be high risk such as chimney sweeps, printers, hairdressers, waiters and cooks and stewards in earlier studies observed to be high risk even after proxy adjustments. Workplace exposure to solvents and other agents such as aromatic amines, polycyclic aromatic hydrocarbons, aromatic nitro compounds, benzidine, 4 amino biphenyl, tetrachloroethylene, diesel engine exhaust and other similar carcinogens are believed to be additional risk factors for bladder cancer. Hence, the study showed that occupation is evidently associated with the risk of bladder cancer. In addition to this, there are other risk increasing factors at the workplace associated with the risk of bladder cancer. This study included 111,458 cases of bladder and 208,297 of lung cancer cases in men in the Nordic countries. The smoking-adjusted SIR for virtually all of the occupations was closer to 1.00 compared to the unadjusted SIR (Figure 10). The highest smoking prevalence rates estimated from the lung cancer SIR in Nordic males were observed in Denmark in most of the occupational categories (Table 11).

The highest statistically significant smoking-adjusted SIRs were observed among chimney sweeps SIR 1.29 (95% CI 1.05-1.56), waiters 1.22 (1.07-1.38) hairdressers 1.14 (95% CI 1.02-1.26), cooks and stewards 1.12 (95% CI 1.01-1.25) and printers

1.11 (95% CI 1.04-1.18). Statistically significant increased SIRs were also observed among seamen 1.09 (95% CI 1.03-1.14) and drivers 1.08 (95% CI 1.05-1.10). The SIRs appeared to be similarly elevated across the Nordic countries for most of the occupations. However, for cooks and stewards and waiters, the adjusted SIRs were increased in some countries but decreased in others.

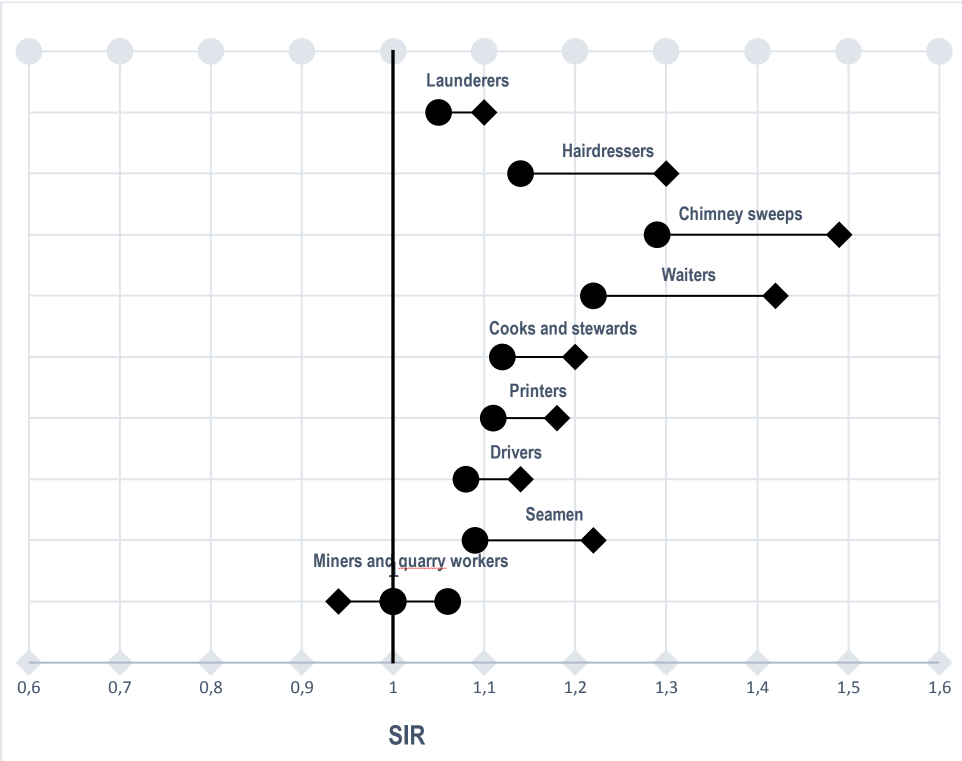

Figure 10. Original (square) and smoking adjusted (circle) standardised incidence ratios (SIR) for selected occupations (SIR > 1.05) in Nordic males in Study III.

Table 11. Smoking prevalence in Nordic males estimated from SIR of lung cancer in NOCCA study, by country in Study III.

Occupation	Denmark	Finland	Iceland	Norway	Sweden
Technical workers etc.	0.47	0.12	0.06	0.15	0.16
Laboratory assistants	0.55	0.17	0.09	0.20	0.05
Physicians	0.28	0.06	0.12	0.12	0.09
Dentists	0.23	0.06	0.00	0.19	0.08
Nurses	0.00	0.01	0.59	0.06	0.01
Assistant nurses	0.39	0.01	0.00	0.22	0.09
Other health workers	0.47	0.13	0.06	0.21	0.14
Teachers	0.28	0.09	0.08	0.10	0.09
Religious workers etc.	0.35	0.09	0.16	0.12	0.08
Artistic workers	0.41	0.15	0.21	0.26	0.18
Journalists	0.47	0.17	0.26	0.22	0.16
Administrators	0.50	0.16	0.21	0.23	0.19
Clerical workers	0.44	0.24	0.19	0.25	0.20
Sales agents	0.49	0.22	0.29	0.29	0.2
Shop workers	0.54	0.17	0.14	0.25	0.21
Farmers	0.31	0.42	0.12	0.17	0.12
Gardeners	0.48	0.3	0.26	0.21	0.16
Fishermen	0.65	0.43	0.16	0.39	0.24
Forestry workers	0.57	0.48	0.00	0.22	0.13
Miners and quarry workers	0.55	0.60	0.13	0.42	0.33
Seamen	0.61	0.35	0.23	0.47	0.33
Transport workers	0.61	0.29	0.28	0.32	0.23
Drivers	0.69	0.29	0.18	0.39	0.24
Postal workers	0.54	0.20	0.14	0.24	0.18
Textile workers	0.61	0.37	0.13	0.31	0.25
Shoe and leather workers	0.61	0.43	0.53	0.36	0.27
Smelting workers	0.66	0.44	0.22	0.45	0.27
Mechanics	0.62	0.28	0.13	0.36	0.23
Plumbers	0.74	0.33	0.18	0.40	0.26
Welders	.	0.21	0.09	0.36	0.22
Electrical workers	0.54	0.21	0.12	0.28	0.17
Wood workers	0.57	0.43	0.11	0.29	0.17
Painters	0.67	0.38	0.14	0.40	0.24

Occupation	Denmark	Finland	Iceland	Norway	Sweden
Other construction workers	0.67	0.56	0.13	0.37	0.25
Bricklayers	0.64	0.50	.	0.41	0.27
Printers	0.58	0.2	0.17	0.31	0.23
Chemical process workers	0.67	0.31	0.25	0.41	0.21
Food workers	0.64	0.29	0.19	0.38	0.25
Beverage workers	0.75	0.28	0.51	0.14	0.27
Tobacco workers	0.97	0.64	0.00	0.52	0.32
Glass makers etc.	0.66	0.29	0.16	0.39	0.22
Packers	0.64	0.40	0.16	0.42	0.26
Engine operators	0.59	0.29	0.12	0.34	0.22
Public safety workers	0.58	0.24	0.14	0.32	0.16
Cooks and stewards	0.63	0.13	0.22	0.35	0.18
Domestic assistants	0.48	0.00	0.00	0.3	0.02
Waiters	0.80	0.12	0.10	0.43	0.27
Building caretakers	0.72	0.33	0.28	0.37	0.18
Chimney sweeps	0.75	0.38	.	0.51	0.30
Hairdressers	0.64	0.21	0.22	0.39	0.31
Launderers	0.69	0.29	0.00	0.46	0.31
Military personnel	0.41	0.12	.	0.31	0.2
Other workers	0.61	0.39	0.21	0.34	0.23

5.4 Solvent exposure and risk of bladder cancer in adults

In study IV, we observed significant increased risk (HR > 1.10) for trichloroethylene 1.23 (95% CI 1.12-1.40), toluene 1.20 (95% CI 1.00-1.38) and benzene 1.16 (95% CI 1.04-1.31) at high exposure levels and perchloroethylene 1.12 (95% CI 1.02-1.23) at medium exposure levels. Exposure to ionising radiation 1.40 (95% CI 1.09-1.80) at high exposure levels and diesel engine exhaust at medium 1.21 (95% CI 1.09-1.16) and low 1.14 (95% CI 1.11-1.17) exposure levels was also observed among other cofactors. Lower but statistically significant (HR ≥ 1.05) increased risk was also observed for exposure to trichloroethylene at lower and medium exposure levels, aromatic hydrocarbon solvents at medium exposure level, aliphatic and alicyclic hydrocarbon solvents at medium exposure levels and benzene at medium exposure levels. Similarly, among other cofactors, asbestos at high 1.09 (95% CI 1.04-1.14) and low 1.07 (95% CI 1.04-1.10) exposure levels, diesel engine exhaust at high exposure levels 1.05 (95% CI 1.00-1.12), sulphur dioxide at medium 1.10 (95% CI 1.01 -1.20) and low 1.08 (95% CI 1.10-1.15) exposure levels was observed as a risk of bladder cancer. Risk by age category (< 50 years and ≥ 50 years) did not show any significant difference between the categories. The risk tended to be higher for cancers diagnosed at ages less than 50 years for aliphatic and alicyclic hydrocarbon solvents, benzene and toluene while for trichloroethylene, the risk was higher in older age component at high exposure levels. Stratification by sex did not observe any significant interactions indicating that the dose-response trend would be different in males and females.

6 DISCUSSION

6.1 Main findings

The main purpose of this thesis was to describe the variation in bladder cancer risk between occupations and identify the workplace carcinogenic solvents associated with it. Based on four separate studies, this study supports the findings from previous studies that occupation is evidently associated with the risk of bladder cancer. Smoking was observed as the important risk factor of bladder cancer in the study where a proxy smoking prevalence approximated from lung cancer risk was used in adjustment for smoking. After adjustment, the risk estimate was still high for some occupations, which indicates that there are other risk-increasing factors in addition to smoking. Study IV assessed the role of solvents as a cause of bladder cancer risk and provided evidence of an occupational exposure to trichloroethylene, perchloroethylene, aromatic hydrocarbon solvents, benzene, and toluene associated with the risk of bladder cancer. Further studies are needed to seek possible dose response associations between other occupational exposures and bladder cancer risk.

6.2 Comparison of findings from previous studies

In our study, we observed increased risk of bladder cancer in different occupations such as tobacco workers, chimney sweeps, waiters, printers, hairdressers, painters, dry cleaners etc. but risk varied between the occupational categories. Occupations associated with agricultural works and teachers were observed as low risk of bladder cancer. Our findings were in line with many other previous studies. A meta-analysis of studies published from 1995 to 2015 reported similar risk of bladder cancer in various occupations such as tobacco workers RR 1.72 (95% CI 1.37-2.15), dye workers RR 1.58 (95% CI 1.32-1.90), chimney sweeps RR 1.53 (95% CI 1.30-1.81), waiters RR 1.43 (95% CI 1.34-1.52), printers RR 1.23 (95% CI 1.17-1.30), transport workers RR (1.10, 1.06-1.13). Likewise, the lowest occupational risk categories were farmers RR 0.69 (95% CI 0.68-0.71), gardeners RR 0.78 (95% CI 0.75-0.81) and teachers RR 0.85 (95% CI 0.82-0.87) (Cumberbatch et al., 2015). Similarly, other individual studies also reported increased risk. For example, bladder cancer among male chimney sweeps in a Sweden was observed as elevated risk SIR 1.80 (95% CI 1.40-2.27) (Hogstedt et al., 2013). Meta-analysis of studies among painters RR 1.25 (95% CI 1.16-1.34) (Guha et al., 2010), dry cleaners RR 1.47 (95% CI 1.16-1.85) (Vlaanderen et al., 2014), drivers such as truck drivers RR 1.3 (95% CI 1.1-1.4), taxi drivers RR 1.6 (95% CI 1.2-2.2) reported increased risk of bladder cancer. Likewise, a case control study in western European men observed painters, miners, transportation workers, printers, metalworkers, rubber workers as some of the most high-risk occupations of bladder cancer (Kogevinas et al., 2003, Ferris et al., 2013). Parallel to our findings, Canadian studies also observed similar increased risk of bladder cancer among hairdressers, transportation workers, painters, metalworkers, insulation workers (Siemiatycki et al., 1994, Gaertner et al., 2004). Epidemiological studies have observed increased risk among those having an occupational history of at least 10 or more years (Cassidy et al., 2009, Ferris et al., 2013, Siemiatycki et al., 1994, Silverman et al., 1986). We observed a decreased trend of bladder cancer incidence among drivers in our study. Our finding was supported by meta- analysis and individual studies published in recent years (Colt et al., 2011, Dryson et al., 2008, Manju et al., 2009). However, not all studies were adjusted for smoking and some reported exposure misclassification in the study. Moreover, all these studies reported increased risk only in some occupations as described above but not in all occupational categories as observed in our Studies I and II.

Though many studies supported the findings of our study, not all studies were consistent. Contrary to the findings of our study, a case control study from United States observed a statistically significant increased risk of bladder cancer among agricultural workers (Cassidy et al., 2009). The risk was even significant and higher for those with long-term exposure of more than 10 years. Some studies observed borderline increased risk in some occupations such as painters OR 1.0 (95% CI 0.5-2.1), transportation workers OR 1.0 (95% CI 0.8-1.3), whereas others observed reduced risk such as printers OR 0.5 (95% CI 0.2-1.2) (Colt et al., 2011), painters OR 0.74 (95% CI 0.36-1.53) (Gaertner et al., 2004). A Nordic study among dry cleaning workers did not show any clear increased risk of bladder cancer (Lynge et al., 2006). Similarly, a New Zealand case control study did not observe increased, but instead decreased risk among miners, chemical processing workers, rubber and plastic workers and drivers. Some of the observed high-risk occupations such as sales workers, painters and printers reported statistically insignificant increased risk of bladder cancer (Dryson et al., 2008). This study was adjusted for age, sex, smoking and socioeconomic status.

Similar to the findings to our Study III, studies have reported smoking adjusted increased risk of bladder cancer. For e.g. meta-analysis study among drycleaners reported overall RR 1.47 (95% CI 1.16-1.85) and smoking adjusted RR 1.50 (0.80-2.84) (Vlaanderen et al., 2014), among painters overall RR 1.25 (1.16-1.34) and smoking adjusted RR 1.28 (1.15-1.43) (Guha et al., 2010). Some reported single "smoking adjusted risk" as a main analysis in their study (Colt et al., 2011, Hogstedt et al., 2013, Kogevinas et al., 2003, Reulen et al., 2008). All these studies observed smoking adjusted increased risk of bladder cancer in different occupational categories. Epidemiological studies have observed smoking as an important occupational risk factor for bladder cancer. However, adjustment with smoking alone did not completely changed the direction of the risk estimate (Blair et al., 2007, Kriebel et al., 2004). Studies have reported that either systematic or chance differences in unmeasured lifestyle factors such as smoking will not confound the risk by more than 20% (Blair et al., 2007, Kriebel et al., 2004). This effect was observed in our proxy smoking adjusted analysis where the observed risk estimate did not change the direction after adjustment of proxy smoking from lung cancer. This method is new in the field of occupational cancer epidemiology. Hence, future studies will shed more light on this topic. Despite all this, we cannot ignore the role of smoking in our study.

Solvent exposure and risk of bladder cancer was another interesting finding in our study. Some of our findings were in line with the previous studies. In our study, exposure to benzene was observed as increased risk of bladder cancer. Our findings on benzene exposure and the risk of bladder cancer was supported by other studies in the past (Steineck et al., 1990, la Vecchia et al., 1990). These studies reported occupational exposure to benzene was associated with significant increased risk of bladder cancer. However, many other epidemiological studies were consistent with exposure to benzene and risk of leukemia (Cogliano et al., 2011). Most studies supported our study on exposure to tetrachloroethylene, trichloroethylene and other agent such as diesel engine exhaust and risk of bladder cancer (IARC, 2018, Pesch et al., 2000, Ruder et al., 1994, Silverman et al., 2006, 2014, Zhao et al., 2005). Additionally, these studies also observed risk of other cancers such as lung and kidney on exposure to these agents.

6.3 Methodological considerations

6.3.1 Limitations of the study

In three NOCCA-based studies included in this doctoral thesis, occupational titles were combined from over 300 job specific titles into 54 occupational categories. This allowed a sufficient number of observed and expected number of cases in each occupational category. Some of the occupational categories are heterogeneous, and therefore, they may hide risk related to occupations that are more specific. E.g., rubber workers are categorised into the group of "glass ceramic and tile workers and others". If only small fraction of workers are exposed, then the effect may not be observed in the risk estimate of the entire occupational category. Exact occupational codes, rather than combined, were used to estimate the dose response risk of occupational solvent exposure (e.g. Study IV) and the broader occupational categories were only formed to describe the variation of bladder cancer risk between the occupational categories.

In the descriptive studies based on both NOCCA and CanCHEC, occupational categories were based on a single census at the age of 30 years (25 years in CanCHEC) or older at the time of census. This may not correctly identify the participants' occupational history because it does not consider changes in the workplace during the entire working career. Some of the persons in the non-exposed group in this study may actually have had exposures related to bladder carcinogens in other jobs during their working career. Hence, it would result in exposure misclassification and an attenuation of risk estimates. However, occupational stability was high in the early decades, and turnover was low in the older male population, e.g., in Finland (Notkola et al., 1997).

In CanCHEC, the 1991 census was limited to individuals over 25 years at the time of census that excluded institutional residents at the time of baseline. The study included historical tax summary files but excluded those who did not file taxes in 1990 or 1991 and also those not enumerated by the 1991 long-form census. The missing group might represent the minority groups. Nordic people have very long registered occupational histories as compared to Canadians. Hence, it was not possible to compare their working history directly in the NOCCA and CanCHEC studies. Similarly, some of the occupational categories in this study were not comparable. For example, occupations such as waiters and tobacco workers appeared as separate categories only in the Nordic study but were included in a broader occupational category of food and beverage workers and food processing workers respectively in the CanCHEC study. This limited our possibility of finding occupations with similarly elevated bladder cancer risk in the Nordic countries and Canada. Despite that the cohorts were large, the number of cases in some of the occupation categories were too few to measure the precise estimate, especially in the CanCHEC cohort.

There is slight variation in the registration of bladder cancer in the European and North American cancer registries. The major difference is that cases of bladder carcinoma in situ and pathological classification stage (pTa) transitional cell carcinoma are included in the North American cancer registries whereas it is not in European cancer registries (including Nordic countries) (Crow et al., 2003). The registration practices are fairly similar in all population-based cancer registries in Europe that are members of the European Network of Cancer Registries (ENCR) such as the Nordic ones. However, Denmark includes more urothelial tumours of the low grade and non-invasive lesions than the other Nordic cancer registries, which may partially explain the higher incidence of bladder cancer in Denmark (Pukkala et al., 2017).

A potential source of exposure misclassification is the limited information on job histories. Information on the job history of the NOCCA cohort members was available only from the censuses 1970 in Denmark, 1970, 1980 and 1990 in Finland, 1981 in Iceland, 1960, 1970 and 1980 in Norway, 1960, 1970, 1980 and 1990 in Sweden 1960, 1970, 1980, and 1990. Annual job histories for the entire working career were assigned assuming that the participants may have changed their occupation in the middle of two censuses but kept in same occupation before first and after the last census. This assumption holds very weak especially in cases from Denmark and Iceland. Because Denmark was not included in studies where individual occupational histories were needed and Icelandic participants were less than 1% in all studies, the problem of having occupational information from only one census should not have affected the overall risk estimates. However, there is only one census information available for the oldest and youngest birth cohorts in the dataset, also for the other Nordic countries. Fortunately, the occupational stability has been high in Nordic countries, particularly for the occupations with a high level of education (Pukkala et al., 2009; Notkola et al., 1997) and hence lack of complete occupational histories is not such a major weakness as it might be if people would have frequently changed their occupation.

One of the most important limitations is the lack of smoking information of the participants. Smoking is a well-established and strong potential confounder in studies on bladder cancer risk. We tried to address this issue using proxy smoking prevalence from lung cancer from the same dataset in Study III. Risk estimates for cancers of the bladder and lung among men in both the NOCCA and CanCHEC studies showed strong positive correlation. Those occupational groups at the highest risk of bladder cancer also had increased risk for lung cancer. This supports the hypothesis that at least some occupational variation in bladder cancer risk can be addressed by occupational difference in smoking. In CanCHEC, the level of education was adjusted in the analysis that indirectly controlled for occupational difference in smoking because smoking is correlated with education. However, in any case we could not rule out the possibility of residual confounding due to smoking in our study. Likewise, we were unable to control for other lifestyle related factors such as alcohol intake and family history. However, alcohol intake is not a clear risk factor of bladder cancer, and family history does not count to be the strong potential confounders that are likely to vary between occupational categories. Hence, smoking appeared to be the only strong confounding variable for the risk of bladder cancer. There could be some selection bias due to underreporting in this study. However, bias due to underreporting of cancer cases is very unlikely in Nordic cancer registries because registration is close to complete and possible small underreporting is not related to occupation (Pukkala et al., 2009).

In Study IV, only small proportions of the populations had considerable exposure to solvents that limits the cumulative exposure categorisation in our study. Hence, the threshold of highest exposure had to be set to a modest exposure level and modest exposure level to the low exposure level and so on. Similarly, we used an average exposure estimation for everyone in the occupational category due to variation of exposure levels within occupational categories. This could have over- or under-estimated the true exposure for some individuals in the study. Furthermore, we cannot ignore possible confounding due to occupational co-exposures to other bladder carcinogens that could be associated to solvent exposure, for example benzo[a]pyrene and chlorinated solvents in automobile mechanics and aromatic amines in printers.

There are some limitations on the use of NOCCA-JEM despite many advantages of the study. The JEM causes exposure misclassification because levels of exposure vary between the individuals. Even in the same occupation and exposure, prevalence is rarely 100% (Kauppinen et al., 2009). JEMs cannot account for such variation and assign group average estimates to all individuals within an occupational category

(Farioli et al., 2017). Using group-based exposure profile can lead to Berkson measurement error that results from random fluctuations in the actual exposure around the observed measurements (Heid et al., 2004). It can reduce the power of the study without diluting the risk estimates (Armstrong, 1998). A recent study in Finland observed that the proportion of localised-stage bladder is higher in some occupations with higher diagnostic activity (Noon et al., 2016). These occupations in our study are typically in the non-exposed group, indicating some surveillance bias in the study. Hence, this would increase the bladder cancer incidence in the reference (non-exposure) category consequently decreasing risk estimates in the exposed groups. Additionally, we were unable to analyse the risk of bladder cancer according to their subtypes in this study.

6.3.2 Strengths of the study

NOCCA is the largest cohort in studies on occupation-related cancer incidence in the whole world, and CanCHEC is the largest Canadian cohort to explore the association between work related factors and the risk of bladder cancer so far. Hence, this study was able to identify a large number of cases to estimate the risk, even in rare occupations. It covered virtually all working populations from all Nordic countries as well as in Canada, giving high statistical power for validity and generalisability of the study findings. Both NOCCA and CanCHEC cohorts were followed up for long period. This ensures good external validity of the study. Therefore, the study was able to identify the cases emerging after long lag times and possible to identify rare cancer.

Nordic cancer registries are famous for their accuracy in cancer registration (Pukkala et al., 2017). The existing registries captured virtually all cases of cancer incidence with high accuracy of occupational codes. The linkage between the census mortality and immigration and cancer incidence data were based on unique personal identity codes used in Nordic countries and through deterministic and probabilistic methods in CanCHEC that ensured a high probability of ascertaining relevant events for each participant.

Studies have also shown the completeness of cancer registration in Nordic countries. Denmark (95%), Finland (99%), Iceland (99%), and Norway (98%) (Pukkala et al., 2017). Unlike other Nordic cancer registries, the Swedish Cancer Registry does not use death certificates as a source of data (Mattsson et al., 1984, Pukkala et al., 2017). This has caused a loss of about 4% in all cancer cases and about

3% loss of cases of the urinary system (including bladder) (Mattsson et al., 1984). It is unlikely that it would have a major effect on the relative risk estimates because this underreporting is not related to occupation.

NOCCA-JEM was used to measure the exposure estimates of 29 exposure agents in four different calendar periods, providing estimates for more than 300 specific occupations. These quantitative exposure measurements were more specific than categorising into exposed and unexposed categories. FINJEM has been used widely in other countries such as the Netherlands, Australia, Spain and Germany (Kauppinen et al., 2014). It is also use as a hazard surveillance tool for assessment of risk in the prevention of hazards. This suggests that the occupational hazards estimated for Nordic circumstances can probably be generalised to many other countries.

6.3.3 Future implications of the research

Going forward, an interesting study would be to expand Study III and estimate occupational solvent exposure and risk of bladder cancer mainly among those occupations observed as high risk of bladder cancer after smoking adjustment. This would allow a wider possibility to observe exposure to different solvents among the high-risk occupations and risk of bladder cancer. It could bring out more evidence-based association of solvent(s) associated with the risk of bladder cancer in the specific occupation.

As smoking is the most important risk factor of bladder cancer, future studies with "smoking adjusted risk" would better explain the occupational cancer risk. Direct information on smoking habits is the better fit for the model adjustment. However, it is not always not possible, especially in register-based studies. In such cases, proxy adjustment can be another method to see the "smoking adjusted risk". Some of the most important variables are education, socioeconomic status depending on exposure variable(s) and outcome of interest. For e.g. educational level was a proxy variable in absence of individual level information on smoking (Winkleby et al., 1992) as well as socioeconomic status (Jankovic et al., 2014). Hence, an indirect adjustment could be assigned using proxy variables such as socioeconomic status in the absence of direct information.

In the Nordic countries, smoke free legislation was implemented for restaurants and other public places after 2005, which was the end of follow-up of this study (Reijula et al., 2015). Future follow up studies after this legislation would add knowledge in the current situation about occupational risk of bladder cancer (as well as other cancers such as lung cancer), especially among waiters and other restaurant workers. Likewise, exposures to carcinogenic chemicals at the workplace have been reduced in recent years, primarily following the ban of aromatic amines in the European Union and Canada after the 1980s. Follow-up studies are essential to observe the current trend of bladder cancer in different occupations such as hairdressers. Such follow-up studies would also address the issue of lag time in the development of bladder cancer.

The profile of risk occupations is changing due to more women being involved in the labour force in recent years (Cumberbatch et al., 2015). Future work would be essential to take care of the gender related risk, because current epidemiological studies show the risk of bladder cancer is mainly targeted towards men who have had a markedly higher incidence of balder cancer than women.

Occupational cancers are often preventable, as is so for bladder cancer. Cancer at work still is the biggest threat according to the number of deaths at work in many industrialised countries as well as in other parts of the world (Takala et al., 2015). The shift is changing towards developing countries. On the policy level, it is very essential to take action against the production of such carcinogenic substances that are clearly identified as carcinogenic risk to humans and probably carcinogenic risk to humans and to monitor and ban their use. This can help in the reduction and gradual elimination of hazardous exposures at work. Immediate measures are required among those identified as occupations with a high-risk of bladder cancer. To make this possible, extensive collaboration between industrial level stakeholders, policy makers and health specialists is required at the local, national and international levels (Takala et al., 2015). International organizations such as the EU, WHO, ILO and other related organisations can play a significant role for e.g. to promote an ambitious programme for 'zero work related cancer' in making hazard free workplaces in the future (Takala et al., 2015).

7 CONCLUSIONS

In this population-based follow up study in the Nordic countries and Canada, we observed that occupation was associated with bladder cancer risk. Further exploring individual studies, we observed some of the occupational categories at high risk and some occupations at low risk of bladder cancer. The comparative study of Nordic and Canadian observation identified a similarly increased risk only among sales workers and a decreased risk among teachers and agricultural workers, which suggests that other factors than occupational ones play a major role in cancer causation. Some of the occupational categories with elevated bladder cancer risk in the Nordic countries such as waiters, tobacco workers and chimney sweeps were not defined in a comparable way in CanCHEC.

Smoking in our study was strong risk factor of bladder cancer. This effect was clear when proxy smoking prevalence from lung cancer was adjusted with bladder cancer risk. However, we could also see some risk increasing factors in some specific occupations in addition to smoking. Workplace carcinogenic exposures appeared to be the risk factor for this increased risk. Further accessing the role of solvents as a cause of bladder cancer risk provided evidence of an occupational exposure to trichloroethylene, perchloroethylene, aromatic hydrocarbon solvents, benzene, and toluene associated with the risk of bladder cancer. Despite numerous limitations in the available data on exposure estimates and potential confounders, we can safely conclude that occupation is evidently associated with the risk of bladder cancer, but smoking is strong risk factor. Future researchers on solvents and other agent specific exposures among the high-risk occupations is highly recommended.

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Occupation and Risk of Bladder Cancer in Nordic Countries

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Objective: The purpose of the study was to describe the variation of bladder cancer incidence according to occupational categories in the Nordic countries. **Methods:** The study cohort comprised 15 million individuals older than 30 years who participated in one or more population censuses in 1960, 1970, 1980/1981, and/or 1990. Standardized incidence ratios (SIRs) were estimated for 53 occupational categories. **Results:** Significantly increased SIRs were observed among tobacco workers (1.57; 95% confidence interval [CI] 1.24 to 1.96), chimney sweeps (1.48; 95% CI 1.21 to 1.80), waiters (1.43; 95% CI 1.33 to 1.53), hairdressers (1.28; 95% CI 1.18 to 1.40), seamen (1.22; 95% CI 1.16 to 1.30), printers (1.21; 95% CI 1.14 to 1.30), and plumbers (1.20; 95% CI 1.13 to 1.30). A significantly decreased risk of bladder cancer was observed among gardeners (0.78, 0.75 to 0.80), forestry workers (0.74; 95% CI 0.70 to 0.78), and farmers (0.70; 95% CI 0.68 to 0.71). **Conclusions:** The SIR of bladder cancer was overall similar across the Nordic countries. The study suggests that occupation is evidently associated with bladder cancer risk.

Bladder cancer is the ninth most common cancer diagnosis and the most common urinary tract cancer in the world. Occupation has been identified as second most important risk factor of bladder cancer after smoking and it has been estimated that occupational exposures may account for about 20% of all bladder cancers in industrialized countries.[1] Bladder cancer is more common in men than in women and increases with age. In the Nordic countries, age standardized incidence rates of bladder cancer increased until 1990, with the highest incidence rate in Denmark and lowest in Finland.[2,3]

Although, cigarette smoking is the most common known etiological factor of bladder cancer so far, increased risk of bladder cancer has also been reported from workplace exposure to chemicals solvents such as polycyclic aromatic hydrocarbons from chimney soot,[4] tetrachloroethylene exposure among dry cleaners,[5] and exposure to o-toluidine among rubber industry workers.[6] Likewise, increased risk has also been reported among persons employed as painters, metal workers, hairdressers and barbers, miners, transportation workers, industrial workers.[7,8] Epidemiological studies have examined the association between occupation and risk of bladder cancer incidence in the past. However, the study findings are rather inconsistent.[9,10] Furthermore, the occupational risk for bladder cancer might have changed over time from one occupational risk group to another, signifying the need to identify more recent occupational risk groups for bladder cancer.[11,12] In this large population based study, we aimed at describing incidence rates of bladder cancer in different occupational categories in the Nordic countries.

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MATERIALS AND METHODS

The present study is based on the Nordic Occupational Cancer (NOCCA) project cohort of populations in Denmark, Finland, Iceland, Norway, and Sweden.[13] The NOCCA cohort consists of individuals from all five Nordic countries who participated in one or more population censuses in 1960, 1970, 1980/1981, or 1990, with 30 to 64 years age at the beginning of follow-up and living in the country on January 1 after the census. There were 2.0 million such individuals from Denmark, 3.4 million from Finland, 0.1 million from Iceland, 2.6 million from Norway, and 6.8 million from Sweden. There were altogether 7,447,726 men and 7,454,847 women. Person-years of follow-up were calculated from the year following the first census record of the individual until the date of emigration, death or to December 31 of the following years: Denmark and Norway in 2003, Iceland in 2004, and Finland and Sweden in the year 2005.

The census records include questionnaire-based information on economic activity, occupation, and industry, which were centrally coded and computerized in the national statistics offices. Occupations were coded into more than 300 categories according to the national adaptations of the International Standard Classification of Occupations from 1958 in three Nordic countries, Finland, Norway and Sweden. In Denmark, special national nomenclature was used for coding, and in Iceland, occupations were coded according to the national adaptations of the International Standard Classification of occupations (ISCO-68). For the NOCCA study, the original national codes were converted into 53 categories with one additional category of economically inactive persons.[13] Data on incident cancer cases were obtained from the national cancer registries in each of the Nordic countries. These registries get information from clinical and pathological departments, general practitioners, private clinics, and death registers that are fairly similar in all Nordic countries.[14] There are national differences between the data sources, but generally the incidence data can be considered highly complete and accurate in international comparison. The largest incomparability between the Nordic countries is the lack of a death certificate for induced cancers in Sweden that has been estimated to cause a loss of up to 4% of all cancer cases.[15]

Results are presented as standardized incidence ratios (SIRs), with the cancer incidence rates for the entire national study populations used as reference rates. The SIR is counted as the ratio of the observed number of cases to the expected number of cases. Exact 95% confidence intervals (CIs) were defined based on Poisson distribution. The expected number of cases in each country, sex, 5-year calendar period and 5-year age group, were calculated by multiplying the number of person- years in each stratum by the respective national incidence rate. The 95% CIs for SIR estimates were calculated by assuming Poisson distribution of the observed number of cases.

We choose to present in more detail by (time period, age, sex, and country) only for occupations statistically significant with overall SIR estimates of 1.20 or higher in our study, and the occupations that have previously been identified with an elevated bladder cancer risk listed by the International Agency for Research on Cancer (IARC).[16] A Poisson regression trend test was performed to access the significance of observed trends of SIR estimates across age and calendar periods.[17] The analyses were performed using stata version 13, StataCorp LP, College Station, TX. This study has been approved by the ethical committees and the data inspection boards in each of the Nordic countries.

RESULTS

During the follow up of altogether 384.4 million person years, 148,669 cases of bladder cancer were detected. There were altogether 111,458 men and 37,211 women bladder cancer cases in the study. Statistically significant SIRs for bladder cancer was highest ($SIR \geq 1.20$) among tobacco workers (1.57; 1.24 to 1.96), chimney sweeps (1.48; 95% CI 1.21 to 1.80), waiters (1.43; 95% CI 1.33 to 1.53), hairdressers (1.28; 95% CI 1.18 to 1.40), seamen (1.22; 95% CI 1.16 to 1.30), printers (1.21; 95% CI 1.14 to 1.30), plumbers (1.20; 95% CI 1.13 to 1.30). A significantly lowest ($SIR < 0.80$) risk was observed among gardeners (0.78; 95% CI 0.75 to 0.80), forestry workers (0.74; 95% CI 0.70 to 0.78), and farmers (0.70; 95% CI 0.68 to 0.71) (Table 1).

In general, little temporal variation during the study period of 45 years was observed in the SIRs among the high-risk occupational categories. A slight increasing trend in the SIR for bladder cancer was observed among drivers and launderers in high risk categories and among farmers, forestry workers, and gardeners in low-risk occupational categories of bladder cancer. Statistically insignificant increasing trends in SIR were also observed among tobacco workers in the study. Similarly, significant decreased risk was observed among painters, printers, and waiters over the periods. The highest SIR between the periods of 1991 and 2005 was observed among tobacco workers, chimney sweeps, waiters, and hairdressers (Table 2). Statistically significant increased trend over the age was observed among seamen, drivers, plumbers, hairdressers in high-risk occupational categories and among gardeners and forestry workers in low-risk categories. The SIRs of tobacco workers and chimney sweeps were highest in the youngest age group (30 to 49 years) and also remained significantly elevated up to the oldest age group (70+) (Table 3). The SIR of bladder cancer in women was observed higher than in men among painters, printers, and tobacco workers in our study (Table 4). The SIR for bladder cancer was similar across the Nordic countries in both high- and low-risk occupational categories (Table 5). Correlation of bladder cancer and lung cancer shows that smoking is positively associated with the risk of lung cancer in occupational risk categories. The correlation coefficient was higher in men ($r = 0.66$) than in women ($r = 0.20$) (Fig. 1).

DISCUSSION

This is the largest study to explore the association between occupation and bladder cancer risk so far. In this study, we observed tobacco workers, chimney sweeps, waiters, hairdressers, seamen, printers, and plumbers have the highest risk for bladder cancer among the 53 occupational groups. Gardeners, forestry workers, and farmers were observed as low-risk occupational groups. Higher SIR in women was observed among tobacco workers, painters, and printers.

Comparison of our results on high- and low-risk occupations of bladder cancer with respective results for lung cancer in NOCCA study[13] revealed a positive association in the SIRs. The SIR for bladder cancer tends to be lower for many of the occupations, which is expected because the relative risk because of smoking is lower in bladder cancer than in lung cancer.[13] In our study, we also observed some outliers in the graph. For example, occupations such as dentists, assistant nurses, postal workers among men and miners and quarry workers, technical workers, bricklayers among women. The observed higher SIR for bladder cancer than for lung cancer might indicate that there are other exposures in addition to smoking that may also contribute to the risk of bladder cancer (Fig. 1). Our study finding was also supported by other studies. A 40 years follow-up study among British physicians observed the lower risk of bladder cancer than lung cancer because of smoking as compared

TABLE 1. Observed Numbers (Obs) and Standardized Incidence Ratios (SIR) of Bladder Cancer in the Nordic Countries, by Occupational Category

Occupational Category	Obs	SIR	95% CI
Technical workers etc. (TW)	7,803	1.03	1.00–1.05
Laboratory assistants (LA)	182	1.09	0.93–1.26
Physicians (PH)	529	1.03	0.94–1.21
Dentists (DN)	235	1.06	0.92–1.20
Nurses (NU)	515	1.00	0.92–1.09
Assistant nurses (AN)	812	1.11	1.04–1.20
Other health workers (HW)	732	1.04	0.97–1.11
Teachers (TE)	3,107	0.86	0.83–0.90
Religious workers etc. (RW)	1,711	0.93	0.90–1.00
Artistic workers (AW)	665	1.16	1.08–1.26
Journalists (JO)	253	0.98	0.90–1.10
Administrators (AD)	5,872	1.09	1.06–1.11
Clerical workers (CW)	7,385	1.12	1.09–1.14
Sales agents (SA)	5,500	1.16	1.13–1.20
Shop workers (SW)	5,799	1.09	1.06–1.11
Farmers (FA)	10,096	0.70	0.68–0.71
Gardeners (GA)	3,162	0.78	0.75–0.80
Fishermen (FI)	1,453	1.13	1.07–1.20
Forestry workers (FW)	1,605	0.74	0.70–0.78
Miners and Quarry workers (MQ)	483	0.94	0.86–1.03
Seamen (SE)	1,478	1.22	1.16–1.30
Transport workers (TW)	2,138	1.08	1.04–1.13
Drivers (DR)	6,035	1.14	1.11–1.20
Postal workers (PW)	1,544	1.07	1.02–1.12
Textile workers (TX)	2,182	1.06	1.02–1.10
Shoe and leather workers (SL)	521	1.10	1.00–1.20
Smelting workers (SM)	1,943	1.08	1.03–1.13
Mechanics (ME)	8,315	1.10	1.08–1.13
Plumbers (PL)	1,020	1.20	1.13–1.30
Welders (WE)	826	1.06	1.00–1.13
Electrical workers (EW)	2,879	1.08	1.04–1.12
Wood workers (WW)	5,753	0.94	0.91–1.00
Painters (PA)	1,656	1.08	1.03–1.13
Other construction workers (OC)	3,606	1.01	1.00–1.04
Bricklayers (BR)	977	1.03	1.00–1.09
Printers (PR)	1,144	1.21	1.14–1.30
Chemical process workers (CP)	1,492	1.06	1.01–1.12
Food workers (FO)	2,444	1.09	1.05–1.14
Beverage workers (BW)	182	1.16	1.00–1.34
Tobacco workers (TO)	79	1.57	1.24–1.96
Glass makers etc. (GM)	1,687	1.05	1.00–1.10
Packers (PA)	3,013	1.09	1.05–1.13
Engine operators (EO)	2,234	1.06	1.01–1.10
Public safety workers (PS)	1,590	1.10	1.05–1.15
Cooks and stewards (CS)	713	1.14	1.06–1.23
Domestic assistants (DA)	1,043	1.05	1.00–1.11
Waiters (WA)	803	1.43	1.33–1.53
Building caretakers (BC)	3,221	1.09	1.05–1.13
Chimney sweeps (CH)	105	1.48	1.21–1.80
Hairdressers (HD)	550	1.28	1.18–1.40
Launderers (LA)	434	1.09	1.00–1.20
Military personnel (MP)	916	1.12	1.05–1.20
Other workers (OW)	4,824	1.01	1.00–1.04
Economically inactive (EI)	23,423	0.95	0.94–1.00

CI, confidence interval.

TABLE 2. Observed Numbers (Obs) and Standardized Incidence Ratios (SIR) of Bladder Cancer in Nordic Countries in Selected* Occupational Categories, by Period

	Year of Diagnosis									
	1961–1975			1976–1990			1991–2005			
Occupation	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI	p^{ϕ}
Tobacco workers	6	1.24	0.46–2.70	34	1.55	1.07–2.16	39	1.65	1.17–2.25	0.322
Chimney sweeps	8	1.07	0.50–2.10	44	1.61	1.17–2.17	53	1.46	1.09–1.91	0.258
Waiters	100	1.76	1.43–2.13	313	1.47	1.31–1.64	390	1.33	1.20–1.50	0.001
Hairdressers	70	1.55	1.21–1.96	209	1.23	1.07–1.40	271	1.26	1.11–1.42	0.009
Seamen	162	1.37	1.17–1.60	554	1.18	1.08–1.30	762	1.22	1.13–1.30	<0.001
Printers	142	1.45	1.22–1.71	428	1.23	1.11–1.35	574	1.15	1.05–1.24	<0.001
Plumbers	108	1.30	1.06–1.57	359	1.17	1.05–1.30	553	1.20	1.10–1.30	<0.001
Drivers	497	1.03	0.94–1.12	2,206	1.12	1.07–1.16	3,332	1.18	1.14–1.22	<0.001
Painters	219	1.17	1.02–1.33	676	1.09	1.01–1.18	761	1.05	0.97–1.12	<0.001
Launderers	46	0.97	0.71–1.30	177	1.08	0.93–1.25	211	1.12	0.97–1.30	0.020
Gardeners	372	0.74	0.67–0.82	1,211	0.75	0.70–0.79	1,579	0.81	0.77–0.85	<0.001
Forestry workers	181	0.60	0.50–0.66	658	0.74	0.70–0.80	766	0.80	0.74–0.90	<0.001
Farmers	1,090	0.59	0.56–0.62	4,308	0.64	0.62–0.66	4,698	0.74	0.72–0.76	<0.001

CI, confidence interval; p^{ϕ}, Poisson test for increasing/decreasing trend.
*Only occupations with significantly increased and decreased overall SIR are shown.

with non-smokers.[18] Later studies have also observed similar findings.[19,20] Hence, it shows that, even though the tobacco smoking is well established risk of bladder cancer, there is limited influence on the risk estimate.[21]

One of the high-risk occupations for bladder cancer in our study was tobacco workers. Active smoking is firmly established as a causal factor of bladder cancer.[3] Meta-analysis studies show two to seven times higher risk of developing bladder cancer among smokers than in non-smokers.[22] Tobacco workers have had easy access to tobacco because of which they are most likely to have high exposed to smoking. For example, we observed the profession with higher level of education (physicians, teachers), the risk of bladder cancer is decreased or insignificantly increased in our study (Table 1). This shows the occupational exposure to tobacco smoke (active or passive). Occupational exposure to tobacco during the processing might also have some carcinogenic risk.[23]

We also observed an elevated risk of bladder cancer among chimney sweeps in our study. They are most likely exposed to chimney soot rich in polycyclic aromatic hydrocarbons. IARC classified exposure to chimney soot as Group 1 carcinogens.[16] Similar to the findings of our study, increased risk of bladder cancer among those exposed to chimney sweeps was observed in a Swedish cohort study.[4,24] The studies observed positive exposure response association with bladder cancer. Besides bladder, study also observed the risk of other types of cancers such as lung esophagus, prostrate and haematolymphatic cancers. Chimney sweeps are also high exposed to smoking but there is very less likely that the potential confounding because of smoking alone is substantial.[21]

TABLE 3. Observed Numbers (Obs) and Standardized Incidence Ratios (SIR) of Bladder Cancer in Nordic Countries in Selected* Occupational Categories, by Age at Follow-Up

	Age at Diagnosis									
	30–49			50–69			70+			
Occupation	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI	p^{ϕ}
Tobacco workers	5	3.50	1.13–8.16	36	1.50	1.06–2.09	38	1.52	1.07–2.08	0.258
Chimney sweeps	7	2.15	0.90–4.43	52	1.50	1.12–1.97	46	1.40	1.02–1.86	0.190
Waiters	33	1.40	1.00–1.96	380	1.50	1.35–1.70	390	1.40	1.23–1.50	<0.001
Hairdressers	20	1.20	0.74–1.87	252	1.30	1.15–1.48	278	1.30	1.12–1.42	0.002
Seamen	60	1.17	0.90–1.50	737	1.22	1.14–1.32	681	1.22	1.13–1.31	<0.001
Printers	67	1.41	1.09–1.80	578	1.23	1.13–1.33	499	1.17	1.07–1.30	<0.001
Plumbers	37	0.87	0.61–1.20	513	1.21	1.10–1.32	470	1.23	1.22–1.35	<0.001
Drivers	255	1.03	0.91–1.16	3,056	1.15	1.11–1.20	2,724	1.15	1.10–1.20	<0.001
Painters	67	1.20	0.93–1.53	721	1.04	0.96–1.11	868	1.11	1.04–1.19	<0.001
Launderers	12	1.23	0.63–2.14	169	1.02	0.90–1.19	253	1.13	1.00–1.30	0.007
Gardeners	67	0.67	0.52–0.85	1,258	0.76	0.72–0.80	1,837	0.79	0.76–0.83	<0.001
Forestry workers	47	0.80	0.60–1.06	615	0.69	0.64–0.75	943	0.78	0.73–0.83	<0.001
Farmers	170	0.64	0.54–0.74	3,478	0.63	0.61–0.65	6,448	0.74	0.72–0.76	<0.001

CI, confidence interval; p^{ϕ}, Poisson test for increasing/decreasing trend.
*Only occupations with significantly increased and decreased overall SIR are shown.

TABLE 4. Observed Numbers (Obs) and Standardized Incidence Ratios (SIR) of Bladder Cancer in Nordic Countries in Selected* Occupational Categories, by Sex

	Male			Female		
Occupation	Obs	SIR	95% CI	Obs	SIR	95% CI
Tobacco workers	29	1.18	0.79–1.70	50	1.93	1.43–2.55
Chimney sweeps	105	1.49	1.21–1.80	0	0.00	0.00–15.6
Waiters	249	1.42	1.25–1.61	554	1.43	1.31–1.55
Hairdressers	357	1.30	1.17–1.45	193	1.24	1.07–1.43
Seamen	1,478	1.22	1.16–1.28	0	0.00	0.00–4.59
Printers	1,018	1.18	1.11–1.26	126	1.45	1.21–1.72
Plumbers	1,020	1.20	1.13–1.28	0	0.00	0.00–7.08
Drivers	5,971	1.14	1.11–1.17	64	1.20	0.92–1.53
Painters	1,641	1.08	1.03–1.13	15	1.51	0.85–2.50
Launderers	186	1.10	0.95–1.28	248	1.07	0.95–1.22
Gardeners	2,491	0.78	0.75–0.81	671	0.77	0.71–0.83
Forestry workers	1,599	0.74	0.71–0.78	6	0.59	0.22–1.28
Farmers	9,444	0.70	0.68–0.71	652	0.68	0.62–0.73

CI, confidence interval.
*Only occupations with significantly increased and decreased overall SIR are shown.

Waites were observed as one of the highest risk groups of bladder cancer in our study. The NOCCA results related to bladder cancer among waiters have been published in a separate paper on cancer among waiters,[25] which also concluded that Nordic waiters have an increased risk of all smoking and alcohol related cancers and among them Danish waiters have the highest incidence of bladder cancer in Nordic countries. Elevated risks of bladder cancer were observed among man waiters in a case control study from northern Italy[26] and a hospital based case control study from the USA.[27] Smoking was adjusted in both studies and controls were selected from hospital patients matched with age, sex, and ethnicity and with no history of any type of cancer.

Hairdressers are another high-risk occupation for bladder cancer among both men and women in our study. Slight decreased tendency of risk has been observed in the recent years but the decreased risk might be due banning the use of some aromatic amines as hair dying ingredients after 1980. In the 1950s and 1960s hairdressers extensively used brilliantine, a hair grooming oil product used to make hair smooth and shiny, especially among men. However, brilliantine use appears not be a major cause of bladder cancer among men.[28] A systematic review paper on bladder cancer observed hairdressers and barbers with occupational exposure to hair dyes experience an enhanced risk of bladder cancer.[10,29] The study also reports no difference in the risk of bladder cancer risk among the studies adjusted and non-adjusted to smoking. Duration of employment $\geq$10 years was observed as significantly increased risk of bladder cancer.[29] IARC classified these substances in group 2A as human carcinogens.[16]

Seamen include ship deck crews, officers, and engineers working on the deck and engine rooms. They are most likely to be exposed to oils, petroleum products, and chemicals. In our study, we observed an increased risk of bladder cancer among those occupationally exposed as seamen. An Icelandic cohort study among marine man engineers observed high incidence of urinary

TABLE 5. Observed Numbers (Obs) and Standardized Incidence Ratios (SIR) of Bladder Cancer in Nordic Countries in Selected* Occupational Categories, by Country

	Denmark			Finland			Iceland			Norway			Sweden		
Occupation	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
Tobacco workers	47	1.47	1.08–1.95	5	1.83	0.60–4.27	0	0.00	0.00-123	18	1.93	1.14–3.04	9	1.44	0.66–2.72
Chimney sweeps	16	1.66	0.95–2.70	16	1.16	0.66–1.90	–	–	–	15	1.11	0.62–1.83	58	1.71	1.30–2.20
Waiters	164	1.70	1.45–1.98	86	1.34	1.07–1.66	3	2.33	0.48–6.80	196	1.22	1.05–1.40	354	1.48	1.32–1.64
Hairdressers	183	1.30	1.11–1.50	30	1.27	0.86–1.80	1	0.72	0.02–4.00	90	1.35	1.09–1.66	246	1.25	1.10–1.41
Seamen	231	1.19	1.04–1.35	108	1.33	1.09–1.61	12	1.42	0.73–2.50	813	1.20	1.12–1.30	314	1.24	1.10–1.40
Printers	289	1.16	1.03–1.30	105	1.18	0.96–1.42	11	2.13	1.06–3.80	219	1.28	1.11–1.45	520	1.20	1.10–1.31
Plumbers	164	1.25	1.07–1.45	149	1.23	1.04–1.45	5	1.31	0.42–3.06	195	1.27	1.10–1.46	507	1.15	1.05–1.25
Drivers	1,642	1.17	1.11–1.22	824	1.09	1.02–1.17	33	1.36	0.93–1.90	1162	1.18	1.11–1.25	2,374	1.12	1.08–1.17
Painters	396	1.18	1.07–1.30	168	0.95	0.81–1.10	10	1.77	0.85–3.24	292	1.09	1.00–1.22	790	1.06	1.00–1.13
Launderers	115	0.98	0.80–1.17	26	1.11	0.72–1.62	2	0.73	0.09–2.62	78	1.17	0.92–1.46	213	1.13	1.00–1.30
Gardeners	469	0.80	0.73–0.90	604	0.81	0.75–0.90	1	0.51	0.01–2.83	641	0.71	0.65–0.76	1,447	0.79	0.75–0.83
Forestry workers	72	0.90	0.70–1.13	381	0.99	0.90–1.09	0	0.00	0.00–12.1	351	0.69	0.62–0.76	801	0.67	0.63–0.72
Farmers	2,483	0.61	0.60–0.63	2,266	0.84	0.80–0.90	34	0.53	0.40–0.74	2,294	0.73	0.70–0.76	3,019	0.67	0.64–0.70

CI, confidence interval.
*Only occupations with a significantly increased and decreased overall SIR are shown.

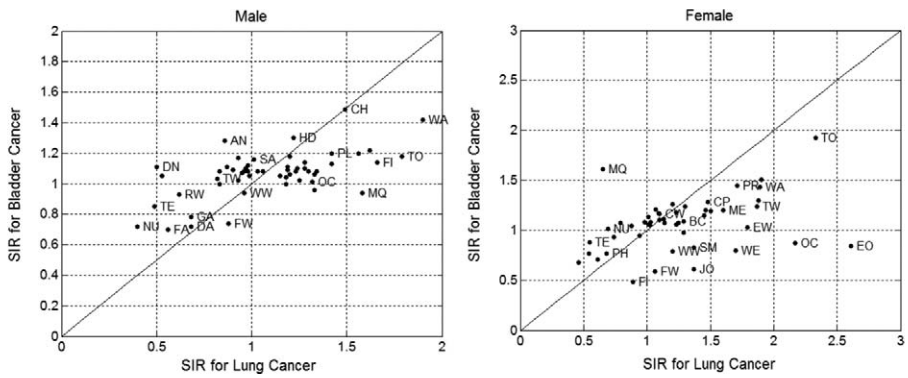

FIGURE 1. Correlation of SIR of bladder cancer and lung cancer in NOCCA study, by sex. NOCCA, Nordic Occupational Cancer; SIR, standardized incidence ratios.

bladder cancer.[30] The study also reports that bladder cancer is unlikely because of excessive smoking among the cohort as their smoking habits were similar to that of general man population. In line with our study findings, another study from United Kingdom also observed an elevated risk of bladder cancer mortality among the deck and engine room crew workers. Smoking habits of the participants were addressed using some proxy measures and other non-occupational factors in the study.[23]

We observed significantly increased risk of bladder cancer among printers in our study but the period specific incidence shows decreased risk over the period of 45 years. We also observed higher risk among women painters in our study. Previous studies conducted in some western European countries have also shown an elevated risk for bladder cancer in this occupational group.[8] A case-control study from Spain observed a high risk of bladder cancer among man printers, while no similar association was observed among women.[31] Smoking was adjusted in both the studies but the bladder cancer risk was reported to be same even after adjustment. IARC has classified occupational exposure in printing processes in group 2B as possibly carcinogenic to humans.[16]

Plumbers are exposed to chemical compounds such as chlorinated solvents, oils, etc. In our study, we observed statistically significant increased risk of bladder cancer among those who are occupationally exposed as plumbers. Similar increased risk of bladder cancer among plumbers was also observed in a study from Iowa, USA who were exposed for more than 10 years.[32] The study was adjusted with smoking and population controls were frequency matched for sex and age group. Other case controls studies have also reported similar increased risk.[33,34] The studies were adjusted for age and smoking. In contrast, Italian cohort study among ship yard workers did not observe bladder cancer risk among plumbers.[35] This study observed risks because of liver and pleural cancer among plumbers.

We observed a significantly elevated risk of bladder cancer among drivers. The trend increased significantly over the time period of 1961 to 2005. Our results were similar to the findings from other previous studies. A review of case control studies from western European countries observed the significant increased risk of bladder cancer among transportation operators.[8] In this review, lifetime smoking and occupational histories were examined. Similar increased risk of bladder cancer was also observed in a European and American study.[8,33] An Iranian study observed a very high significant risk of bladder cancer risk (OR 11.3, 95% CI 1.32 to 92.50) among the workers employed in the transportation industry.[36] Smoking was adjusted in all these studies. Drivers are likely to be exposed to chemicals, such as diesel exhaust fumes and smoke containing many aromatic nitro compounds. These substances create intermediaries, such as aromatic amines and polycyclic aromatic hydrocarbons that increase the risk of bladder cancer.[6]

Painters are mainly exposed to aromatic amines such as benzidine, 4-amino biphenyl, β-naphthylamine, and 4-chloro-o-tolouidine. Exposures to these substances are likely to increase the risk of bladder cancer.[37] Our observation of bladder cancer among painters was in line with the findings from other studies that observed increased risk of bladder cancer.[8,38] A meta-analysis of bladder cancer risk among painters observed that occupational exposure to painting are causally associated with the risk of bladder cancer. The study also reports that higher risk was observed among those exposed to longer duration of exposure.[7] The selected studies in this meta-analysis were adjusted for smoking and other occupational exposures. However, the association did not change significantly with adjustment.[7] IARC has classified the occupational exposure for painters as group 1—carcinogenic to humans.[16]

We observed an increased risk of bladder cancer incidence both in men and women launderers. Exposure to tetrachloroethylene is common in the dry cleaning industry, and that has been associated with a risk of bladder cancer.[5] Case control studies from Belgium and the USA observed a similar elevated risk of bladder cancer among laundry workers.[11,39] However the American study was limited to non-white men.[11] These studies were adjusted for smoking. A Nordic study has reported the risk of bladder cancer among launderers is equivocal signifying no clear association of bladder cancer risk in this occupational group.[40] In our study, we were not able to separate dry cleaners from other laundry workers and hence we used dry cleaners as a comparison group to launderers. However, the use of tetrachloroethylene was by far the dominant solvent among Nordic dry cleaners.[40] IARC has classified occupational exposure for dry cleaners in group 2B as possibly carcinogenic to humans.[16]

Significantly decreased risks were observed among gardeners, forestry workers, and farmers in our study. These occupational groups were observed as a low risk of all tobacco related cancers such as lung cancer in NOCCA study (Fig. 1). Other studies have also observed similar findings. A Spanish case control study observed decreased risks among farmers, forestry workers, and those involved in agricultural production and services.[31] The Finnish cohort study observed significantly low risks for most type of cancers, including bladder cancer, both in man and woman Finnish farmers.[41] Results of meta-analysis shows significantly reduced relative risk of bladder cancer among farmers.[42] This meta-analysis show decreased risk of cancer such as esophagus, lung, colon, and pancreas among those who are occupationally exposed as farmers. The conclusion of all these studies was farmers, gardeners, and forestry workers are most likely to have low risk not only for bladder cancer but for all tobacco related cancers. Hence, low smoking prevalence explains the finding. On contrary, a case control study from the USA observed statistically increased overall risk among farmers agricultural workers. The risk is even higher and significant with exposure for more than 10 years.[27]

According to NORDCAN, a Nordic tool for cancer information, planning, quality control, and research (www.ancr.nu), bladder cancer incidence was the highest in Denmark followed by Iceland, Norway, Sweden, and the lowest in Finland.[2] A decline in rates was observed from the 1990s in both the man and woman populations in Nordic countries. In our study, we observed an increase in period specific trend in SIR of bladder cancer among drivers, tobacco workers, and launderers (statistically insignificant among tobacco workers). The period specific variation in our study might also tell about the changes in occupational exposure levels and hence give a notion that there are more factors than exposure to smoking behind these differences. A higher SIR at a young age might tell that the exposure level at young age is exceptionally high among tobacco workers and chimney sweeps. However, the exposure levels are still high for these occupations at oldest age group. The recent changes in the legislations protecting the workplace carcinogenic exposure have been reduced in the recent years, for example, transportation workers.[43] After 2005, legislation for smoke free restaurants and other public places was implemented in Nordic countries.[25] Future studies are required to see the outcome after the smoking legislation. The current occupational safety and health legislation in Nordic countries is mainly based on European directives with minimum standards for safety and health in the workplace. It is binding and obligatory to transpose into the national legislation in each European Union (EU) member states. Hence, the occupational health legislation in each Nordic countries are mostly similar that are derived from EU directives. This directive concerns about health, safety, rights, safe working environment, working hours, and other conditions of employment. It also ensures technical safety requirements for manufacturers concerning the use of machinery and personal protective equipment in all Nordic countries.[44]

The aim of the study was to describe the variation in bladder cancer risk between occupations and not to identify specific occupational risk factors of bladder cancer. Some of the occupational categories are heterogeneous and may hide risks related to more specific occupations. Occupation at one point in time does not always correspond to the lifelong occupational history. Another limitation of the study is lack of information on smoking. In our study, we have observed the occupational exposure to smoking with lung cancer and bladder cancer risk and hence shows that potential confounding because of smoking alone is substantial. Therefore, we cannot ignore the effect of smoking. Individual work histories were based on census records at the time of the census, which is at the specific point of time. The data did not provide enough information of the number of times an individual has changed his job throughout the working history, type of job performed during the full working career. There are national differences between the data sources, but generally the incidence data can be considered highly complete and accurate in international comparison. In this type of study, with so many risk estimates, the likelihood of chance findings because of multiple comparisons is high. The consistency of the five independent country-specific risk estimates observations for a given occupation might help to separate true associations from chance findings.

The strengths of the study are the large number of bladder cancer cases, virtually full coverage of cancer cases in the Nordic cancer registries.[13,14] Another strength is the accuracy on the use of occupational codes.[13] Even if there would be some incompleteness in registration or some inaccuracy in diagnoses, they would not affect SIR estimates in so far as cancer diagnostics and registration follow similar procedures irrespective of the occupation of the person. The record linkages between the census data, the mortality and emigration data, and the cancer incidence data were based on the unique personal identity codes used in registries in all Nordic countries, which ensure a complete ascertainment of relevant events.[45]

CONCLUSION

The findings of this study show that occupations are evidently associated with the risk of bladder cancer. A further study is required to control for the effect of smoking, and to identify possible dose–response associations between bladder cancer risk and occupational exposure to chemical compounds such as chlorinated hydrocarbons, aromatic amines, polycyclic aromatic hydrocarbons, etc. that would explain the risk variation between occupational categories.

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Occupational variation in incidence of bladder cancer: a comparison of population-representative cohorts from Nordic countries and Canada

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ABSTRACT

Objectives The objective of this study was to compare occupational variation of the risk of bladder cancer in the Nordic countries and Canada.

Methods In the Nordic Occupational Cancer study (NOCCA), 73 653 bladder cancer cases were observed during follow-up of 141.6 million person-years. In the Canadian Census Health and Environment Cohort (CanCHEC), 8170 cases were observed during the follow-up of 36.7 million person-years. Standardised incidence ratios with 95% CI were estimated for 53 occupations in the NOCCA cohort and HR with 95% CIs were estimated for 42 occupations in the CanCHEC.

Results Elevated risks of bladder cancer were observed among hairdressers, printers, sales workers, plumbers, painters, miners and laundry workers. Teachers and agricultural workers had reduced risk of bladder cancer in both cohorts. Chimney-sweeps, tobacco workers and waiters had about 1.5-fold risk in the Nordic countries; no risk estimates for these categories were given from the CanCHEC cohort.

Conclusion We observed different occupational patterns in risk of bladder cancer in Nordic countries and Canada. The only occupation with similarly increased risk was observed among sales workers. Differences in smoking across occupational groups may explain some, but not all, of this variation.

Strengths and limitations of this study

- ► Only few countries have directly linked information on cancer and census data and this study provides in-depth analysis with high statistical power of population-level comparison using linkage data in Nordic countries and Canada.
- ► The availability of these two large cohorts and long duration of follow-up conducted in different areas of the world provided an opportunity to examine occupational variation of bladder cancer risk in different geographic regions.
- ► The lack of data on smoking information and workplace exposure to chemical solvents in this study would better explain the risk associated with bladder cancer.

INTRODUCTION

Bladder cancer is the ninth most common cancer in the world and occupation has been identified as the most important risk factor second to smoking.[1] It has been estimated that occupational exposure could account for as much as 20% of all bladder cancers diagnosed in industrialised countries.[1 2] In the Nordic countries, bladder cancer is the fifth most common cancer in men and 15th most common cancer in women.[3] Age-standardised incidence rates for bladder cancer increased until 1990, with the highest incidence in Denmark and lowest in Finland.[4] In Canada, bladder cancer is the fourth most common cancer in men and 12th most common cancer in women. There has been little to no change in bladder cancer incidence among both male and female Canadians in the last decade.[5]

Associations with bladder cancer have been observed for >40 occupations. While some findings have been consistent, others have been inconsistent or limited.[6 7] In-depth studies with high statistical power are required to establish clear associations of occupational risks of bladder cancer.[8] Furthermore, occupational bladder cancer risk factors may have changed over time, suggesting a need for more current evidence.[9 10] Outside of the Nordic countries, only few countries have directly linked information on cancer and census data. The availability of these two cohorts conducted in different areas of the world provided

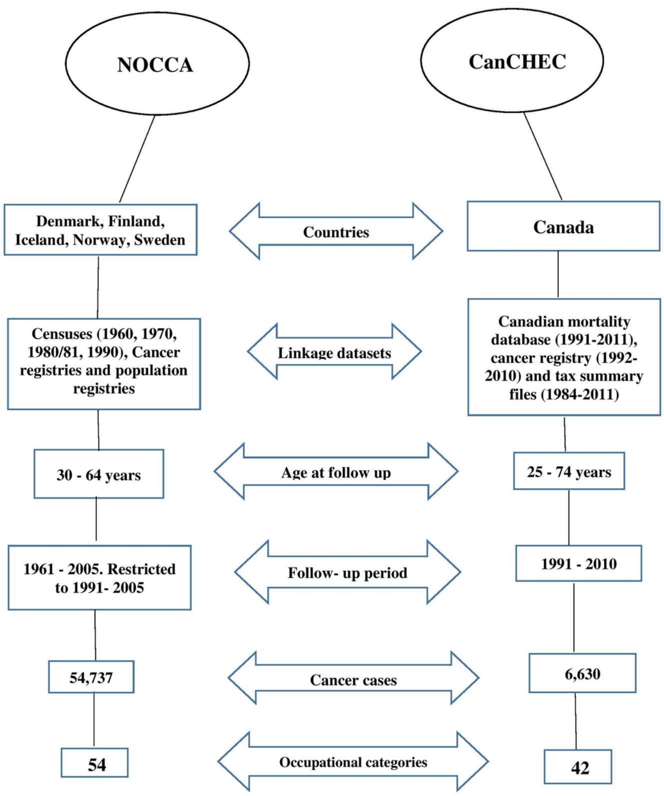

Figure 1 Flowchart of the methodological procedure in NOCCA cohort and CanCHECs. CanCHEC, the Canadian Census Health and Environment Cohort; NOCCA, the Nordic Occupational Cancer study.

an opportunity to examine occupational variation of bladder cancer risk in Nordic and Canadian population-based cohorts.

MATERIALS AND METHODS

The present study is based on the cohort derived from the Nordic Occupational Cancer study (NOCCA) followed up from 1961 to 2005 and the Canadian Census Health and Environment Cohort (CanCHEC) followed up from 1991 to 2005 derived from the Canadian Census Mortality and Cancer Follow-up Study (figure 1).

The NOCCA cohort comprises individuals in Denmark, Finland, Iceland, Norway and Sweden who participated in one or more population censuses in 1960, 1970, 1980–1981 or 1990, who were between the ages of 30 and 64 years and living in the country on 1 January after the census. The present study used the data from the cohort followed up only from the period 1991 to 2005 to increase comparability with the CanCHEC study. The census records include questionnaire-based information on economic activity, occupation and industry, which were centrally coded and computerised in the national statistics offices. Occupations were coded into >300 categories according to the national adaptations of the International Standard Classification of Occupations (ISCO) from 1958 in Finland, Norway and Sweden. In Denmark, special national nomenclature was used with a distinction from self-employed persons, family workers, salaried employees, skilled workers and unskilled workers. In Iceland, it was coded according to the ISCO-68 classification and later converted into ISCO-58 with instructions from International Labour Organisation. For the NOCCA study, the original national codes were converted according to the Nordic occupational classification (NYK) into 53 categories with 1 additional category of economically inactive persons. NYK is the Nordic adaptation of ISCO from 1958 (details of the occupational categories in NOCCA study are available at: http://astra.cancer.fi/NOCCA/categories.html).

Data on incident cancer cases were obtained from the national cancer registries in each of the Nordic countries. These registries capture information from clinical and pathological departments, general practitioners, private clinics and death registers that are fairly similar in all Nordic countries.[11] All the patients had bladder cancer at the age of diagnosis. Details of the NOCCA study have been described elsewhere.[12] NOCCA results are presented in standardised incidence ratios (SIRs) to estimate risks of bladder cancer across occupational groups with rates for the entire national study populations used as the reference rates. The SIR was calculated as the ratio of observed to expected cases. Exact 95% CIs were defined based on a Poisson distribution.

The CanCHEC cohort was derived from respondents to the 1991 Canadian Census who were included in the Canadian Census Mortality and Follow-Up Study.[13] The present study used data from the linkage of the 1991 Canadian Census 2B (long form) with the Canadian Mortality Database (1991–2011), Canadian Cancer Registry (1992–2010) and Historical Tax Summary Files (1984–2011). The nationally representative cohort included 2 735 152 individuals of the Canadian non-institutional resident population aged from 25 to 74 years on the census day (4 June 1991), who were residents of Canada and among the 20% of Canadian household selected to complete the long-form census questionnaire. Occupation, coded according to the 1991 Standard Occupational Classification (SOC-91), and socioeconomic characteristics were obtained from the census. The majority of the occupation groupings were comparable between CanCHEC and NOCCA. However, some groups such as chimney-sweeps appeared only in NOCCA while others, such as waiters, were contained within a broader occupational group of food and beverage workers and tobacco workers in a broader group of food processing workers. The CanCHEC was followed up for cancer morbidity through linkage to the Canadian Cancer Registry database through deterministic and probabilistic methods.

Person-time at risk was counted from the cohort entry on 4 June 1991 to date of disease diagnosis, death and loss to follow-up or end of follow-up on 31 December 2010, whichever occurred first. For the purpose of analyses, the first incident primary bladder cancer was considered and groups were re-coded based on the four-digit SOC codes. Details of the CanCHEC study have been

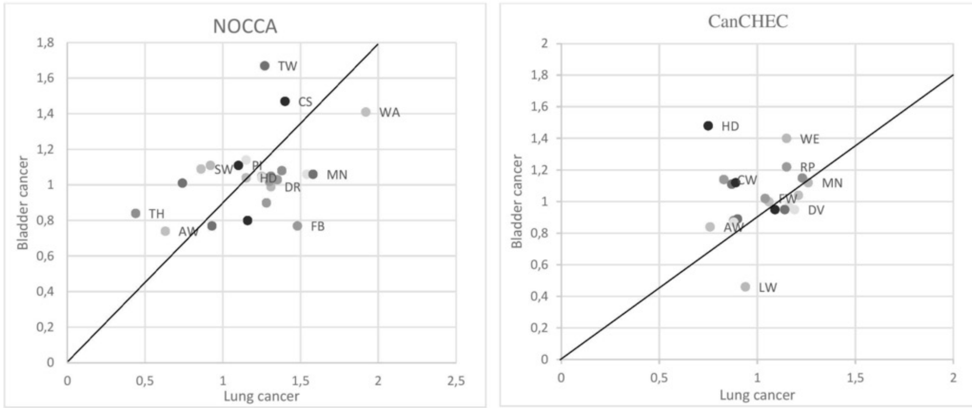

Figure 2 Correlation of bladder and lung cancer in men in NOCCA cohort and CanCHEC. AM, administrators and managers; AW, agriculture workers; CanCHEC, Canadian Census Health and Environment Cohort; CH, chemical workers; CS, chimney-sweeps; CW, construction workers; DV, drivers; EW, electrical workers; FB, food and beverage workers; FF, fire fighters; FP, food-processing workers; FW, forestry workers; HD, hairdressers; LW, laundry workers; MN, miners; MW, metal workers; NOCCA; Nordic Occupational Cancer study; PA, painters; PI, printers; PL, plumbers; RP, rubber and plastics workers; SIR, standardised incidence ratio; SW, sales workers; TH, teachers; TW, tobacco workers; WA, waiters; WE, welders.

described elsewhere.[13] Cox proportional HRs and 95% CIs were calculated using Cox proportional hazards disease-free survival analysis to estimate risks of bladder cancer associated with employment according to occupation at baseline. In the absence of information regarding potential confounders such as lifestyle factors, including smoking, physical activity and diet, models were adjusted for age group, region and level of education. In accordance with Statistics Canada disclosure guidelines, no counts <5 or corresponding model outputs are reported, and all person-years and counts are randomly rounded to base 5. Results may also be suppressed where counts <5 would be identified due to additivity across subgroups. STROBE guidelines was followed to report each sections, where applicable.

Demographic information and risk of bladder cancer by occupational category are presented by sex for the NOCCA cohort and the CanCHEC. Due to the absence of information on individual smoking behaviour, we also examined the risk of lung cancer and its relationship with the risk of bladder cancer in men across occupational groups (figure 2).

ETHICAL CONSIDERATIONS

Ethical committees and data inspection boards from each Nordic country approved the NOCCA study. The CanCHEC study was approved by the University of Toronto Health Sciences Research Ethics Board.

RESULTS

In the NOCCA cohort, 73 653 cases of bladder cancer were diagnosed among 14 902 573 (50.0% men) individuals over the 1991–2005 follow-up period (141.6 million person-years) (table 1). In the CanCHEC, 8170 cases of bladder cancer were diagnosed among 2 051 315 (54.0% men) individuals during the 1991–2010 follow-up period (36.7 million person-years).

The greatest statistically significant excess risks of bladder cancer for male workers in the NOCCA cohort were observed among tobacco workers (1.67), chimney-sweeps (1.47) and waiters (1.41), occupations that were not examined in CanCHEC (table 2). Lower but statistically significant elevated risks in NOCCA were also observed among sales workers, printers, metal workers and painters. Among them, only sales workers showed an elevated HR in CanCHEC. In turn, there were increased risks in the CanCHEC among hairdressers, welders and administrators and managers, while the SIRs for these occupations were close to 1.0 except for hairdressers in the NOCCA study (table 2). The correlation coefficient (r) of lung and bladder cancer in men in NOCCA and CanCHEC study was observed as 0.75 and 0.81, respectively (figure 2).

The greatest statistically significant excess risks for female workers in the NOCCA cohort were observed among tobacco workers (1.65), occupation that was not examined separately in CanCHEC (table 3). Statistically significant excess risk in CanCHEC was observed only among plumbers. Statistically significant elevated risks in NOCCA were also observed among printers, chemical workers, hairdressers, waiters, sales workers and administrative managers. While in CanCHEC, an insignificant increased risk was observed among printers, hairdresser and sales workers. Waiters were not examined separately in the CanCHEC study (table 3). Reduced risks were consistently observed for teachers and agriculture workers in both cohorts.

DISCUSSION

This comparison of results from two large cohort studies revealed occupational variation in bladder cancer risks.

Table 1 Demographic and other variables of the study population in Nordic countries (NOCCA) and Canada (CanCHEC) cohorts

	NOCCA		CanCHEC	
Variable	Category	Number (%)	Category	Number (%)
Population by country/province *NOCCA (1961–2005)* *CanCHEC (1991–2010)*	Denmark Finland Iceland Norway Sweden	2 013 346 (13.5%) 3 404 800 (22.8%) 120 995 (0.8%) 2 562 674 (17.2%) 6 800 758 (45.6%)	Atlantic Quebec Ontario Manitoba Saskatchewan Alberta British Columbia Yukon, NW Territory and Nunavut	162 135 (7.9%) 502 495 (24.5%) 756 295 (36.8%) 87 565 (4.3%) 77 855 (3.8%) 200 135 (9.7%) 243 735 (11.8%) 21 100 (1.2 %)
Population by sex	Male	7 447 726 (49.97%)	1 108 410 (54.03%)	
	Female	7 454 847 (50.03%)	942 905 (45.96%)	
Bladder cancer cases by country/province *NOCCA (1991–2005)* *CanCHEC (1991–2010)*	Denmark Finland Iceland Norway Sweden	17 525 (23.79%) 11 109 (15.08%) 573 (0.78%) 13 798 (18.73%) 30 648 (41.61%)	Atlantic Quebec Ontario Manitoba Saskatchewan Alberta British Columbia Yukon, NW territory and Nunavut	686 (8.4%) 2356 (28.8%) 2436 (29.8%) 350 (4.3%) 383 (4.7%) 839 (10.3%) 1082 (13.2%) 42 (0.5%)
Bladder cancer cases by age group (years)	30–34 35–44 45–54 55–64 65–74 75+	15 (0.02%) 506 (0.69%) 3546 (4.82%) 12 241 (16.62%) 25 258 (34.29%) 32 087 (43.56%)	25–34 35–44 45–54 55–64 65–74	396 (4.8%) 1365 (16.7%) 2558 (31.3%) 2972 (36.4) 879 (10.7%)
Bladder cancer cases by sex	Male	54 737 (74.32%)	6630 (81.1%)	
	Female	18 916 (25.68%)	1540 (18.8%)	

CanCHEC, Canadian Census Health and Environment Cohort; NOCCA, Nordic Occupational Cancer study.

Generally, the excesses in a given occupation seen in one cohort were not seen in the other. Male hairdressers in CanCHEC and female hairdressers in NOCCA showed a marked excess risk of bladder cancer while there was almost no indication of an excess risk among female hairdressers in CanCHEC and non-significant increased risk among male hairdressers in NOCCA. The finding of an excess risk is consistent with two different meta-analyses: (1) Harling and colleagues[14] reposted a summary risk ratio (SRR) of 1.70 (95% CI 1.10 to 2.88) and (2) Takkouche and colleagues,[15] a risk ratio (RR) of 1.30 (95% CI 1.20 to 1.42). Hairdressers are exposed to chemical compounds of aromatic amines such as benzidine, toluidine and aromatic nitrous compounds, and exposure to these chemical compounds has been linked to an increased risk of bladder cancer.[16] In particular, long-term exposure (≥10 years) as a hairdresser has been associated with greater risk of bladder cancer.[14 17]

Exposures to carcinogenic chemicals among hairdressers appear to have been diminishing in recent decades.[18] Following the ban on use of aromatic amines in the European Union in 1980s, thereafter a similar ban was also imposed in Canada. Some more recent studies that examined exposures after these bans have not reported excess risks of bladder cancer, but some studies have reported that banned substances are still in use, leading to the potential for ongoing exposure.[19] The period-specific stratified analysis of the NOCCA study from 1991 to 2005 also shows a similar decrease in risk among hairdressers over time in the Nordic countries and in Canada (results not shown). As our cohorts represent the follow-up from 1991, the highest risks observed in 1990s may have been due to the use of aromatic amines in dye products, which are not used any more.[19]

We observed some evidence of an association between bladder cancer and employment as a printer in this comparative study, with the greatest excess risk observed among Nordic women. A meta-analysis of case-control studies from six European countries observed that occupation related to printing had an up to 80% greater risk of bladder cancer than the general population (OR 1.81, 95% CI 1.03 to 3.17).[20] A Spanish study also observed a significantly elevated risk of bladder cancer among men in printing industry (OR 5.4, 95% CI 1.62 to 17.72).[21] Printers are mainly exposed to printing inks consisting of pigments and a solvent.[22] Exposures to chemical agents

Table 2 Bladder cancer risk in men by occupation in NOCCA and CanCHEC

Occupational category	NOCCA (n=54737)			CanCHEC* (n=6630)		
	Cases	SIR	95% CI	Cases	HR	95% CI
AM	2704	1.01	0.98 to 1.05	1115	**1.11**	**1.04 to 1.19**
AW	4356	*0.74*	*0.72 to 0.77*	455	*0.84*	*0.76 to 0.93*
CH	514	*0.90*	*0.81 to 0.97*	45	1.14	0.84 to 1.54
CS	53	**1.47**	**1.10 to 1.92**			
CW	1704	**1.06**	**1.01 to 1.10**	410	0.95	0.86 to 1.06
DV	2899	0.99	0.95 to 1.03	520	0.95	0.87 to 1.04
EW	1519	1.05	1.00 to 1.11	150	0.88	0.75 to 1.04
FF	581	*0.77*	*0.71 to 0.83*	25	0.89	0.60 to 1.33
FB	64	1.09	0.84 to 1.39	160	1.00	0.85 to 1.17
FP	683	*0.77*	*0.72 to 0.83*	60	0.77	0.59 to 1.01
FW	762	0.80	0.75 to 0.86	85	1.02	0.82 to 1.27
HD	140	1.14	0.96 to 1.35	25	**1.48**	**1.01 to 2.19**
LW	80	1.04	0.82 to 1.29	5	*0.46*	*0.22 to 0.97*
MW	901	**1.08**	**1.01 to 1.16**	230	0.97	0.85 to 1.10
MN	246	1.06	0.93 to 1.20	60	1.12	0.87 to 1.45
PA	753	**1.05**	**1.01 to 1.12**	50	1.15	0.86 to 1.54
PL	469	1.02	0.93 to 1.12	90	0.95	0.77 to 1.16
PI	502	**1.11**	**1.02 to 1.21**	40	1.04	0.77 to 1.41
RP	713	1.04	0.97 to 1.12	30	1.22	0.84 to 1.78
SW	2514	**1.11**	**1.07 to 1.15**	525	**1.12**	**1.02 to 1.22**
TH	1372	*0.84*	*0.80 to 0.90*	230	0.87	0.76 to 1.00
TW	17	**1.67**	**1.02 to 2.67**			
WA	122	**1.41**	**1.17 to 1.68**			
WE	484	1.03	0.94 to 1.12	100	**1.40**	**1.15 to 1.70**

Empty box indicates no information available. Bold indicates statistically significant inceased risk. Italics indicates statistically significant decreased risk.

*Model adjusted for age, sex, region and level of education.

AM, administrators and managers; AW, agriculture workers; CanCHEC, Canadian Census Health and Environment Cohort; CH, chemical workers; CS, chimney-sweeps; CW, construction workers; DV, drivers; EW, electrical workers; FB, food and beverage workers; FF, fire fighters; FP, food-processing workers; FW, forestry workers; HD, hairdressers; LW, laundry workers; MN, miners; MW, metal workers; NOCCA; Nordic Occupational Cancer study; PA, painters; PI, printers; PL, plumbers; RP, rubber and plastics workers; SIR, standardised incidence ratio; SW, sales workers; TH, teachers; TW, tobacco workers; WA, waiters; WE, welders.

in the printing industry have been associated with an increased risk of bladder cancer.[21]

Small yet consistent excess risks of bladder cancer were observed for sales workers of both sexes in the Canadian and Nordic cohorts. This association has been observed previously for men in a Swedish cohort study.[10] In the Swedish study, physical inactivity and sedentary work were suggested as the probable cause of increased risk of bladder cancer. The findings in this Swedish study and the present study are not independent due to marked overlap in the data between these studies. The meta-analysis by 't Mannetje and Pearce[23] reported a smoking-adjusted excess risk of bladder cancer among female sales workers. The study observed positive causal association with duration of employment among sales workers. Lower frequency of urination and reduced fluid intake were plausible explanations for the risk of bladder cancer in this group.[23]

Elevated risk of bladder cancer was observed among female, but not male, drivers in our comparative study. A meta-analysis of the occupational risk of bladder cancer study observed a significantly increased risk of bladder cancer among bus drivers with SRR of 1.29 (95% CI 1.08 to 1.53).[8] Similarly, a significant positive dose–response relationship between the duration of employment as a truck driver and the risk of bladder cancer was observed in a study by Silverman and colleagues.[7] This excess risk may be attributable to exposure to several air pollutants such as polycyclic aromatic hydrocarbons (PAH) and diesel engine exhausts, which may interact with the urothelium of the bladder.[7] However, a case–control study from the USA examined the lifetime occupational history of

Table 3 Bladder cancer risk in women by occupation in the NOCCA and CanCHEC

	NOCCA (n=18916)			CanCHEC* (n=1540)		
Occupational categories	**Cases**	**SIR**	**95% CI**	**Cases**	**HR**	**95% CI**
AM	137	**1.17**	**1.00 to 1.40**	110	0.93	0.77 to 1.13
AW	342	*0.70*	*0.60 to 0.74*	50	0.88	0.66 to 1.18
CH	63	**1.45**	**1.11 to 1.86**	<5	–	–
CS	0	–	0.00 to 52.7			
CW	11	1.00	0.50 to 1.80	10	1.25	0.63 to 2.51
DV	41	1.24	0.90 to 1.70	10	1.09	0.64 to 1.85
EW	72	1.00	0.79 to 1.26	5	0.65	0.27 to 1.57
FF	14	1.08	0.58 to 1.80	<5	–	–
FB	12	1.07	0.55 to 1.87	125	1.07	0.89 to 1.29
FP	212	1.02	0.88 to 1.16	15	*0.59*	*0.35 to 0.98*
FW	4	0.65	0.18 to 1.65	<5	–	–
HD	131	**1.42**	**1.20 to 1.68**	10	1.09	0.63 to 1.89
LW	131	1.18	0.98 to 1.40	15	1.11	0.65 to 1.88
MW	10	0.92	0.44 to 1.70	10	1.44	0.72 to 2.88
MN	2	1.75	0.21 to 6.34	<5	–	–
PA	8	1.29	0.56 to 2.54	<5	–	–
PL	0	–	0.00 to 21.7	5	**2.90**	**1.20 to 6.98**
PI	72	**1.47**	**1.15 to 1.85**	10	1.21	0.63 to 2.34
RP	101	1.01	0.82 to 1.22	<5	–	–
SW	205	**1.27**	**1.10 to 1.46**	185	1.06	0.91 to 1.23
TH	458	*0.81*	*0.73 to 0.90*	125	0.91	0.75 to 1.11
TW	22	**1.65**	**1.03 to 2.50**			
WA	268	**1.30**	**1.15 to 1.47**			
WE	4	1.08	0.30 to 2.77	<5	–	–

*Model adjusted for age, sex, region and level of education.
Bold indicates statistically significant increased risk. Italics indicate statistically significant decreased risk.
AM, administrators and managers; AW, agriculture workers; CanCHEC, Canadian Census Health and Environment Cohort; CH, chemical workers; CS, chimney-sweeps; CW, construction workers; DV, drivers; EW, electrical workers; FB, food and beverage workers; FF, fire fighters; FP, food-processing workers; FW, forestry workers; HD, hairdressers; LW, laundry workers; MN, miners; MW, metal workers; NOCCA; Nordic Occupational Cancer study; PA, painters; PI, printers; PL, plumbers; RP, rubber and plastics workers; SIR, standardised incidence ratio; SW, sales workers; TH, teachers; TW, tobacco workers; WA, waiters; WE, welders.

participants[24] and a nationwide case–control study from New Zealand[25] did not observed the clear increase in risk in these studies. The New Zealand study had observed some evidence for increased risks of bladder cancer among female drivers.[25] A meta-analysis[26] suggested that the occupational risk of bladder cancer among drivers has been reduced in recent years, which may be reflected in our findings for male drivers.

This comparative study also observed evidence of an association between the risk of bladder cancer and employment as a plumber. The excess risk in the CanCHEC cohort was observed among a small number of female plumbers in the study. Existing evidence has been similarly inconclusive. Studies in the USA have reported increased risks of bladder cancer in male plumbers[24 27] but this association was not observed among plumbers in an Italian case–control study.[28] Plumbers are exposed to many hazardous materials such as lead, welding fumes, tars and asbestos, which makes it difficult to identify the putative agents.[24 27]

Painters are commonly exposed to aromatic amines such as benzidine, 4-aminobiphenyl, β-naphthylamine and 4-chloro-*o*-toluidine and exposure to these substances has been linked to bladder cancer.[29] The International Agency for Research on Cancer (IARC) classified occupational exposure as a painter as carcinogenic to humans (group 1) mainly based on observed increased risks of lung cancer and bladder cancer. Although not reaching statistical significance, painters appeared to have an increased risk of bladder cancer in our comparative study. A meta-analysis reported a smoking-adjusted significant increased risk of bladder cancer among painters, which was consistently observed across 36 observational studies regardless of study design, sex and study location.[30]

Though the specific agents attributable for the risk of bladder cancer in painters have not been clearly identified, exposure to metal coatings, wood varnishes or stains that contain solvents, fillers and pigments are suggested risk factors.[30]

Miners appeared to be at increased risk of bladder cancer in our comparative study. This association was previously reported in studies from both Europe[8 20 21] and Canada.[8 31] Miners have known occupational exposures to chemical compounds such as PAH, which have been suggested as a strong risk factor in the aetiology of bladder cancer.[32] This increased risk could be due to a number of exposures in the mining setting. Miners can be exposed to relatively high levels of diesel exhaust, primarily among underground transportation workers, where excess risks of bladder cancer have previously been observed.[31]

Increased risk was observed among female dry cleaners in our comparative study, although risk estimates were not statistically significant. A recent meta-analysis of dry cleaning workers reported a significantly elevated risk of bladder cancer, and the excess risk did not appear to be confounded by smoking.[33] A case–control study from the USA also observed a similar increased risk of bladder cancer among dry cleaners, but this study was limited to non-white men.[9] In the NOCCA study, it was not possible to separate dry cleaners from other laundry workers and hence we used dry cleaners as a comparison group to launderers. Use of tetrachloroethylene was by far the dominant solvent among Nordic dry cleaners. Launderers can be exposed to tetrachloroethylene, which is a potential bladder carcinogen according to IARC (group 2A).[33]

Our study observed significantly elevated risk of bladder cancer associated with welding only among men in the CanCHEC cohort. An IARC working group had previously explored this association, and it was deemed limited and inconclusive.[34] Since the 1990 IARC evaluation, many studies have reported elevated risks of bladder cancer associated with welding. Several of these studies have, however, included small sample sizes or small numbers of cases. A hospital-based case–control study in France reported a sevenfold increased risk of bladder cancer in male welders compared with controls.[32] However, the association observed was not statistically significant. Excess risk of bladder cancer was also reported in the German-based study among welders who had worked for at least 6 months in this occupation at the time of first follow-up (standardised mortality ratio 3.04, 95% CI 1.14 to 8.10), but the risk estimate was observed to be non-statistically significant with extended follow-up.[35] While the strongest evidence of cancer risk in welders is lung cancer, the study suggests that occupational associations with bladder cancer are most probably due to exposures specific to welding fumes that may contribute to the risk of bladder cancer.[12]

Reduced risks of bladder cancer were associated with employment as a teacher and agricultural worker. These protective effects have been reported in a previous meta-analysis.[36] Consistently, lower risk of bladder cancer was observed among agricultural workers in Spanish studies.[20 21] Low prevalence of smoking, high physical demand of exercise in farming occupations, dietary factors such as high intake of fresh food and vegetables and residence in areas with little air pollution might account for the reduced risk of bladder cancer among farmers.[21 36] In contrast, a 2009 study from the USA reported long-term employment as an agricultural worker was associated with increased risk of bladder cancer.[37] The study suggested that long-term exposure to carcinogenic agents such as pesticides, solvents and other inorganic dusts could contribute to the increased risk of bladder cancer among agricultural workers.[37]

Smoking is the strongest known risk factor of bladder cancer and an important potential confounder in the studies of occupational bladder cancer.[38] The CanCHEC study allowed for adjustment for education, which aimed to indirectly control for occupational difference in smoking. Smoking has been shown to be strongly correlated with education levels and has been suggested as an appropriate proxy in model adjustment in the absence of individual-level smoking data.[39] The study also observed higher risk of smoking associated with lower education level. In our NOCCA–CanCHEC comparative study, those occupational groups at highest risk of bladder cancer were also commonly identified as at risk of lung cancer. Correlation of bladder and lung cancer in both the NOCCA and the CanCHEC studies in men suggests that smoking or some other shared risk factor(s) may be responsible for excess risks observed by occupations (figure 2). However, we also observed some outliers in the graph including dry cleaners, hairdressers and welders, which may indicate some occupation-specific risk factors for these groups.

Previous attempts to disentangle the effects of occupational exposures from smoking have indicated that smoking does not account for all of the excess risk of bladder cancer.[12 40] Although hairdressers have a higher prevalence of smoking compared with other workers and the general population,[16] Takkouche *et al* observed no difference in effect among this group with adjustment to smoking.[15] Adjustment for smoking also appeared to have little to no effect on risk estimates for painters,[30] hairdressers,[14] printers, transportation workers,[20] machine operators[21] and plumbers.[27] This supports the hypothesis that at least some occupational variation in bladder cancer risk can be explained by occupational difference in smoking.[12] However, we cannot rule out the possibility of residual confounding in our study.

This comparison of two large cohort studies conducted in different geographic regions aimed to describe variation in bladder cancer risk across occupations was unable to identify specific occupational patterns in risk of bladder cancer except for sales workers. Furthermore, Nordic peoples have long occupational history as compared with the Canadians. If we were unable to identify the specific risk of bladder cancer that would be similarly high in both geographic regions, one of the reasons may be that some of the risk estimates in one or both regions may be diluted towards unity. If only a small fraction of the workers are exposed, the effect may not be seen in the risk estimate of the entire occupational category. Additionally, occupation at one point in time does not necessarily correspond to lifelong occupational history. Some of the persons in non-exposed categories may actually have had exposure to bladder carcinogens in other jobs. This would result in misclassification and an attenuation of risk estimates.

Strengths of this study include the large cohort sizes, long duration of follow-up and large number of cases observed, although the NOCCA cohort was stronger in all of these aspects. However, the numbers of cases in some of the smaller occupational categories were too few to precisely measure associations. The use of existing registries captured virtually all incident cancer cases. The linkage between the census, mortality and immigration, and cancer incidence data were based on unique personal identity codes used in registries in all Nordic countries[12] and through deterministic and probabilistic methods in CanCHEC that ensures a high probability of ascertaining of relevant events. The use of existing data sources including the censuses and mortality and mobility records was an efficient approach for surveillance of large populations.

CONCLUSION

We observed different occupational patterns in risk of bladder cancer in Nordic countries and Canada. This comparative study identified consistency in risk only among sales workers. Risks of bladder cancer varied across occupational categories. Although exposure to carcinogens at work may contribute this variation, however, the present comparison of bladder cancer pattern in the Nordic countries and in Canada did not identify clues to the disease aetiology. The study illustrates that the possible effect of specific occupational exposure may be difficult to unravel in the datasets following people with work experiences from different time periods and categories into broad occupational groups.

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ORIGINAL ARTICLE

Occupational variation in bladder cancer in Nordic males adjusted with approximated smoking prevalence

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ABSTRACT

Background: Occupational exposure has been identified as the most important risk factor for bladder cancer second to smoking. The objective of this study was to estimate the occupational variation in risk of bladder cancer that is not attributable to smoking.

Material and methods: In the Nordic Occupational Cancer study (NOCCA), 111,458 cases of bladder cancer and 208,297 cases of lung cancer cases were observed among men in Denmark, Finland, Iceland, Norway and Sweden during 1961–2005. Relative smoking prevalence in an occupation was estimated based on standardized incidence ratio (SIR) for lung cancer in the given occupation. Crude and smoking-adjusted SIRs with 95% confidence intervals (CI) for bladder cancer were calculated for each occupation.

Results: The smoking-adjusted SIR for most of the occupations was closer to 1.00 than the unadjusted SIR. The highest statistically significant smoking-adjusted SIRs were observed among chimney sweeps (SIR 1.29, 95% CI 1.05–1.56), waiters (1.22, 1.07–1.38) hairdressers (1.14, 1.02–1.26), cooks and stewards (1.12, 1.01–1.25), printers (1.11, 1.04–1.18) and seamen (1.09, 1.03–1.14).

Conclusions: Smoking is a strong risk factor for bladder cancer but there may also be other factors in some specific occupations in addition to smoking. The occupational variation in risk of bladder cancer is small when adjusted for smoking, but risk increasing factors are indicated in some occupations.

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Introduction

Tobacco-smoking and occupational exposure, are the leading risk factors for bladder cancer. It has been estimated that occupational exposure may account for as many as 20% of all the bladder cancer cases in industrialized countries, and it is the second most important risk factor after smoking [1,2]. Workplace exposure to chemical carcinogens such as aromatic amines and polycyclic aromatic hydrocarbons (PAH) has been associated with increased risk of bladder cancer among painters, printers, drivers, hairdressers, launderers, and miners [2,3]. Bladder cancer is more common in men than in women, and the risk increases with age. In the Nordic countries, it is the fifth most common cancer in men. Age-standardized incidence rates increased until 1990, with the highest incidence in Denmark and the lowest in Finland [4]. There have been temporal changes in exposure to workplace carcinogens in the Nordic countries. According to the FINJEM, exposure to carcinogens such as benzene, benzo(a)-pyrene, and asbestos have substantially decreased in Finland from 1950 to 2008 [5]. Similarly, a Danish study reported decreased exposure to trichloroethylene by 4% from 1947 to 1964 and by 15% from 1964 to 1989 [6]. Another Danish study observed similar decreased trend of exposure to styrene, toluene and xylene over the period of 1955–1988 [7]. A Norwegian study reported a decreasing trend in exposure to polycyclic aromatic hydrocarbons among the Norwegian industry workers [8]. Overall, the carcinogenic exposures have decreased in last 20 years in the Nordic and in some other industrialized countries [9,10].

In the Nordic countries, Lung cancer incidence in Finnish men increased until 1970 and decreased sharply after that [4]. In Denmark and Sweden, the incidence started to decrease after 1980 and in Iceland and Norway after 2000 [4]. Smoking was assumed to be a crucial risk factor behind the occupational variations in both bladder and lung cancers [11,12]. However, the studies do not have information on occupation-specific smoking habits, and therefore we cannot separate the roles of smoking and occupational exposures. Methods for control for tobacco-smoking in the absence of individual-level smoking information have been discussed over a long period [13–17]. The suggested methods are based on combined information on smoking habits from

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numerous sources or from historical estimates of the effect of the confounders.

Epidemiological evidence of the causal association between cigarette-smoking and lung cancer was established around the 1950s. The International Agency for Research on Cancer (IARC) and an international working group of experts recognized the causal relationship between tobacco-smoking and lung cancer in 1985 [18]. Since then, a large number of studies have reported significant association between tobacco-smoking and the risk of lung cancer. Taking advantage of the convincing evidence of a strong association between smoking and lung cancer risk, we can consider the incidence of lung cancer in a specific occupational category to be a proxy for smoking prevalence in that occupation, unless there are other strong lung cancer carcinogens in the occupation. In our large population-based study, which included all working-age men in five Nordic countries, we assessed occupational variations in the risk of bladder cancer, adjusted with a proxy for smoking based on the incidence of lung cancer.

Material and methods

This study utilized the Nordic Occupational Cancer Study (NOCCA), comprising up to 45 years of cancer incidence data by occupational categories. The cohort consists of 14.9 million people from all five Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden), aged 30 to 64 years, who participated in one or more population censuses in 1960, 1970, 1980/81, or 1990 and were living in the country on 1 January after the census year. The census information on occupation for each individual was obtained through the questionnaires in the censuses, which were centrally coded and computerized in the national statistics offices. The original occupational codes were then reclassified into 53 different categories. Details of the NOCCA study have been described elsewhere [12]. Data on incident cancer cases were obtained from the national cancer registers in each of the Nordic countries. The follow-up started on 1 January after the earliest available census, and ended at death or at the end of the year 2003–2005 (Table 1). The registration of new cancer cases is based on the information from clinical and pathological departments, general practitioners, and private clinics. The largest incomparability between the Nordic countries is the absence of death certificates in Sweden, which has been estimated to cause a loss of up to 4% of all cancer cases [19]. Due to lack of information on smoking habits in all occupational categories in all Nordic countries over the study period, we estimated a proxy smoking prevalence in the occupational groups from the lung cancer incidence in the NOCCA data set. This study was undertaken with linkage of individual records based on the unique personal identity codes used in all the Nordic countries.

The results are presented as standardized incidence ratios (SIRs), i.e., ratios of observed to expected numbers of cases. In this study, we present SIRs for bladder cancer, while SIRs for lung cancer are used as proxies for smoking prevalence in an occupational category. For each country, gender, and occupational category, the observed number of cancer cases and person years was stratified into eight five-year attained age categories (30–34, 35–39 …, 85+ years) and nine five-year calendar periods (1961–1965 …, 2001–2005). For the SIRs for bladder cancer that were not adjusted for smoking, the expected number of cases in each country was calculated by multiplying the number of person years in each stratum by the respective national bladder cancer incidence rate.

For smoking-adjusted SIRs (SIR_{adj}), the expected number was corrected by multiplying the original expected number by the product of the proxy smoking prevalence value and the relative risk (RR) estimate for bladder cancer due to smoking in each occupational category [17,20]. For the purposes of analysis, we calculated the continuous RR based on smoking prevalence. Smoking prevalence was estimated based on the SIR for lung cancer (Figure 1). The estimation of smoking prevalence (Y) was based on linear regression ($Y = \alpha + \beta X$), where X is the SIR of lung cancer, $\alpha = Y -$ intercept value of smoking prevalence, and $\beta =$ slope of the line (Figure 1). From the figure, $\alpha = 0.4$ and the tangent function of regression line $\beta = 0.28$ approximately. The SIR for lung cancer is about 0.2 when smoking prevalence is zero, and about 1.8 when smoking prevalence is 0.5 (Line A in Figure 1). It shows the risk increases by nine times with a five time increase in smoking prevalence. Hence, if we assume that the RR for bladder cancer due to smoking is one third of lung cancer, the RR for bladder cancer increases by 0.18 with every 10% unit increase in smoking prevalence. Analyses were performed in two different models. In Model 1, we included all 53 occupational categories (Line A in Figure 1). In Model 2, we excluded occupations with smoking-adjusted SIRs for lung cancer markedly higher than 1.0 according to an earlier Norwegian study [14], i.e., miners and quarry workers, drivers, smelting workers, mechanics, plumbers, welders, painters, bricklayers, printers, beverage workers, tobacco workers, glass makers, packers, hairdressers, launderers and gardeners (Line B in Figure 1). The lung cancer rate for these occupations may reflect other major risk factors in addition to smoking. Exact 95% confidence

Table 1. Demographic variables of the study populations of bladder and lung cancer in Nordic countries.

			Males only		
Country	Base population (million)	Period of follow up	Person-years (million)	Bladder cancer cases	Lung cancer cases
Denmark	2.0	1971–2003	23.86	27 020	53 401
Finland	3.4	1971–2005	37.03	13 716	52 189
Iceland	0.1	1982–2004	1.18	565	996
Norway	2.6	1961–2003	34.94	22 272	37 334
Sweden	6.8	1961–2005	87.92	47 885	64 377
Total	14.9		184.93	111 458	208 297

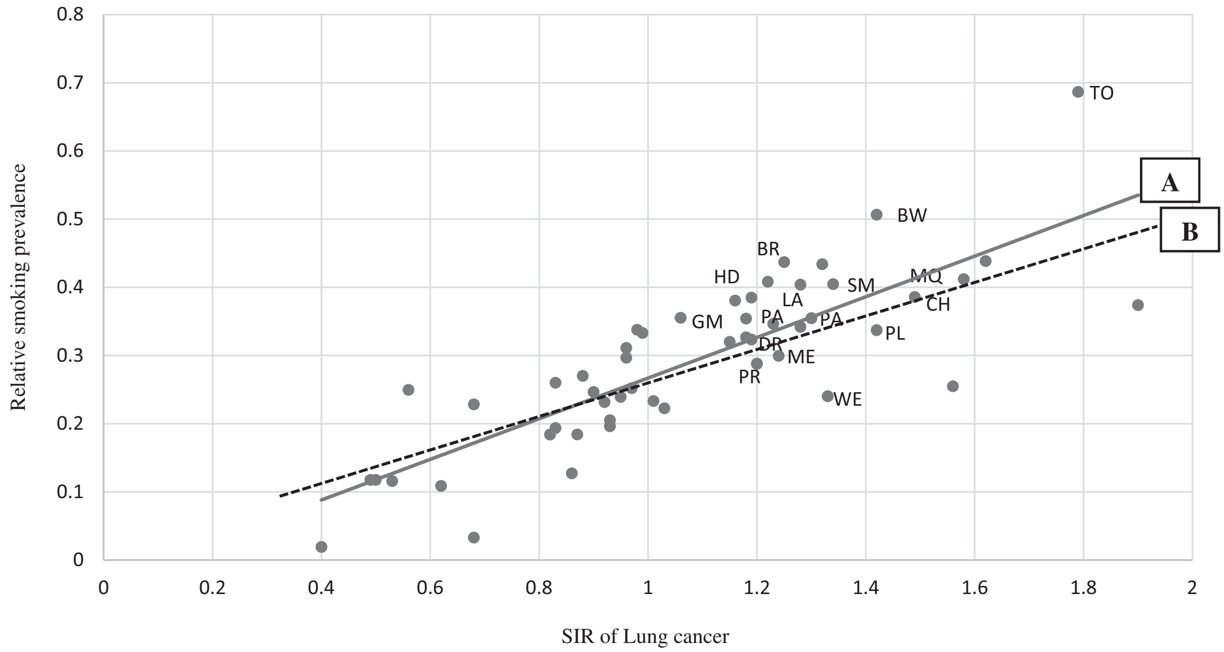

Figure 1. Smoking prevalence on the 53 occupational categories estimated based on standardized incidence ratios (SIR) of lung cancer in Nordic males. Regression line A: Estimation based on all 53 occupations ($y = \alpha + \beta x$). Regression line B: Estimation based only on 37 occupations excluding occupations with probable strong occupation-related risk factors other than smoking; miners and quarry workers, drivers, smelting workers, mechanics, plumbers, welders, painters, bricklayers, printers, beverage workers, tobacco workers, glass makers, packers, hairdressers launderers and gardeners ($y = \alpha + \beta x$).

intervals (CIs) of the SIRs were defined based on Poisson distribution. We used two-sided tests for a statistical significance level of 0.05. The ethical committees and data inspection boards in each of the Nordic countries approved the study.

Results

The study included 111,458 cases of bladder cancer and 208,297 cases of lung cancer, observed during a total follow-up time of 184.9 million person years (Table 1). The highest number of cases was from Sweden and the lowest from Iceland. The estimated smoking prevalence varied across the occupational categories. The correlation coefficient value ($r =$ 0.81, 0.78) shows the dose-response relationship of lung cancer incidence due to smoking (Figure 1).

The highest statistically significant unadjusted SIRs were observed for chimney sweeps (1.49, 1.21–1.80), waiters (1.42, 1.25–1.61), hairdressers (1.30, 1.17–1.45), cooks and stewards (1.20, 1.07–1.34), and printers (1.18, 1.11–1.26). The SIRs came closer to 1.00 for all occupations after adjustment with the proxy for smoking. The adjusted results from Models 1 and 2 were similar. Therefore, we chose to present the results from Model 1 (Figure 2 and Table 2).

SIR_{adj1} was >1.10 for chimney sweeps (1.29, 95% CI 1.05–1.56), waiters (1.22, 1.07–1.38), hairdressers (1.14, 1.02–1.26), cooks and stewards (1.12, 1.01–1.25), and printers (1.11, 1.04–1.18). A small but significant increased risk was also observed among seamen and drivers, while a similar non-significant risk was observed among laboratory assistants, miners and quarry workers, public safety workers, and launderers (Table 2). The SIR_{adj1} for bladder cancer appeared to be similarly elevated across the Nordic countries, e.g., for drivers, printers, and hairdressers. For cooks and stewards, waiters, and chimney sweeps, the SIR_{adj1} increased in some countries but decreased in others.

Discussion

This is the largest study to explore the association between occupation and risk of bladder cancer adjusted for smoking. Chimney sweeps, waiters, hairdressers, cooks and stewards and printers had the highest risk of bladder cancer after adjusting for smoking habits. The highest estimated prevalence of smoking was observed in Denmark and the lowest in Sweden (data not shown).

The most pronounced increased risk of bladder cancer in Nordic males was observed in chimney sweeps. A systematic review and meta-analysis of modifiable risk factors for the prevention of bladder cancer from 1995 to 2015 observed that chimney sweeps were among the occupations with the highest risk of bladder cancer (RR 1.53, 1.30–1.81) [21]. Another meta-analysis of 263 eligible articles published to June 2015 observed a similar high risk among chimney sweeps [22]. These studies observed that persons exposed to chemical solvents such as PAH and aromatic amines are at higher risk of bladder cancer. However, not all the studies included in this study were adjusted for smoking. Chimney sweeps are exposed to high levels of soot rich in PAH, which predominantly causes lung and bladder cancers [23–25].

Waiters were observed to be another high-risk group in our study. Similar risks were observed in different studies. A systematic review and meta-analysis observed that waiters had among the highest risks (RR 1.43, 1.34–1.52) of bladder cancer in occupational cancer studies after adjusting for

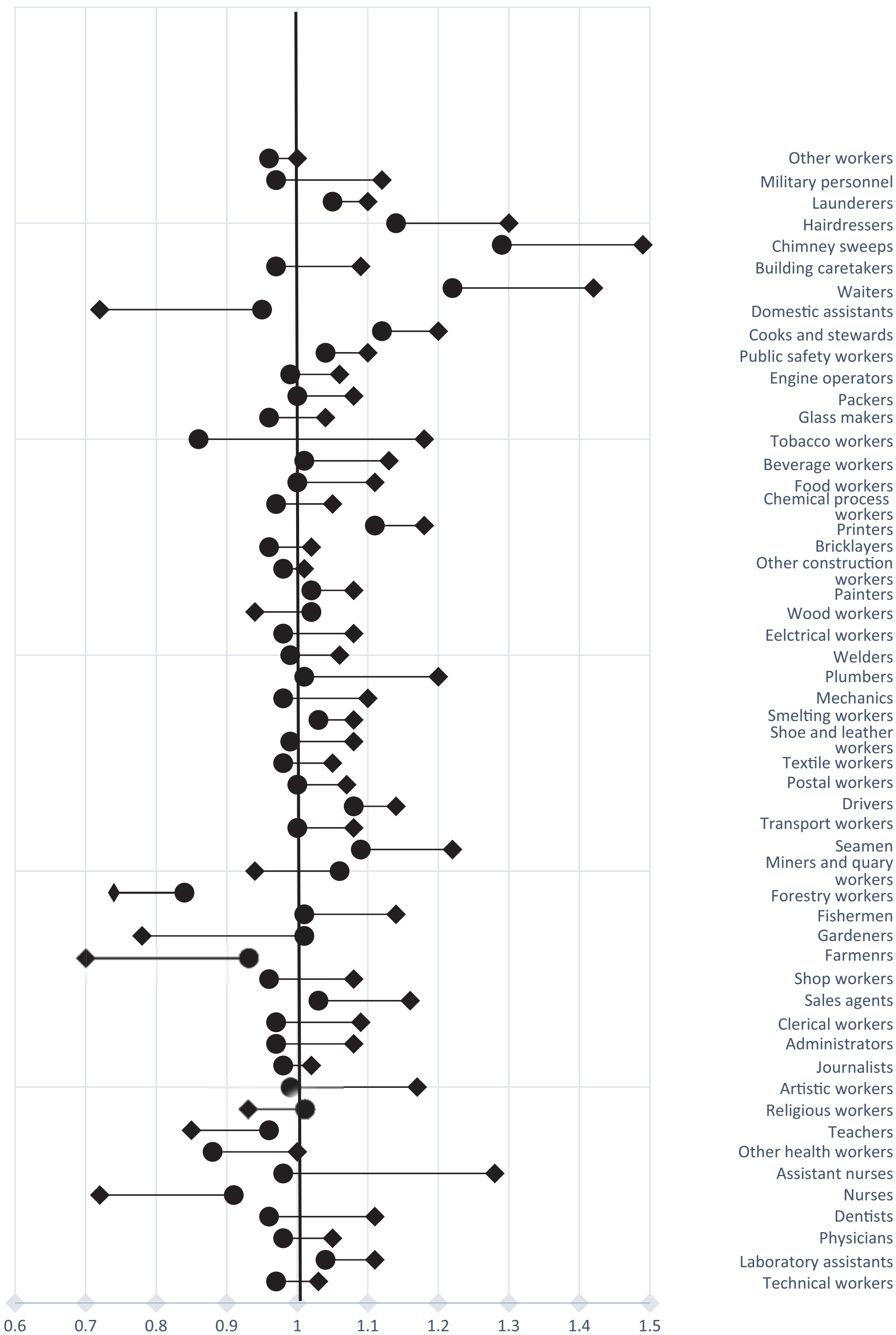

Figure 2. Original (square) and smoking adjusted (model 1, circle) standardized incidence ratios (SIR) for 53 occupational categories in Nordic males.

smoking status [22]. A case control study in the United States observed an overall (OR 2.84, 1.05–7.72) risk of bladder cancer following exposure for more than 10 years among those employed as waiters [26]. A case control study from Italy [27] and a cohort study from Sweden [28] observed similar increased risks. It should be noted that the data from the Swedish study markedly overlap with the data in our study. Waiters are mainly exposed to both active and passive smoking, and possibly to other workplace carcinogenic substances such as PAH [29]. Legislation regarding smoke-free

Table 2. Observed number of bladder cancer cases (Obs), standardized incidence ratio (SIR), 95% confidence interval (95% CI) with proxy smoking adjusted from lung cancer in occupations in Nordic males.

		Unadjusted		Adjusted			
				Model 1[a]		Model 2[b]	
Occupation	Obs	SIR	95% CI	SIR_{adj1}	95% CI	SIR_{adj2}	95% CI
Technical workers (TW)	7677	1.03	1.00–1.05	0.97	0.94–0.98	0.98	0.96–1.01
Laboratory assistants (LA)	124	1.11	0.92–1.32	1.04	0.86–1.24	1.06	0.88–1.27
Physicians (PH)	505	1.05	0.96–1.14	0.98	0.89–1.06	0.93	0.84–1.01
Dentists (DN)	214	1.11	0.96–1.27	0.96	0.83–1.09	0.98	0.85–1.12
Nurses (NU)	11	0.72	0.36–1.30	0.91	0.45–1.63	0.95	0.47–1.70
Assistant Nurses (AN)	159	1.28	1.09–1.50	0.98	0.83–1.14	1.00	0.86–1.17
Other health workers (HW)	370	1.00	0.90–1.11	0.88	0.79–0.98	0.92	0.82–1.01
Teachers (TE)	2297	0.85	0.81–0.88	0.96	0.92–1.00	0.83	0.79–0.86
Religious workers (RW)	1479	0.93	0.88–0.97	1.01	0.96–1.07	0.98	0.93–1.03
Artistic workers (AW)	593	1.17	1.08–1.27	0.99	0.91–1.06	1.02	0.94–1.10
Journalists (JO)	238	1.02	0.89–1.16	0.98	0.85–1.12	0.99	0.87–1.12
Administrators (AD)	5621	1.08	1.05–1.11	0.97	0.95–1.00	1.00	0.97–1.02
Clerical workers (CW)	4125	1.09	1.06–1.12	0.97	0.93–0.99	1.00	0.98–1.03
Sales agents (SA)	5095	1.16	1.12–1.19	1.03	1.00–1.06	1.03	1.00–1.05
Shop workers (SW)	3602	1.08	1.04–1.11	0.96	0.92–0.99	1.04	1.00–1.07
Farmers (FA)	9444	0.70	0.68–0.71	0.93	0.91–0.94	0.97	0.95–0.98
Gardeners (GA)	2491	0.78	0.75–0.81	1.01	0.97–1.05		
Fishermen (FI)	1450	1.14	1.08–1.20	1.01	0.96–1.07	1.05	1.00–1.10
Forestry workers (FW)	1599	0.74	0.71–0.78	0.84	0.79–0.87	0.96	0.91–1.01
Miners and quarry workers (MQ)	480	0.94	0.86–1.03	1.06	0.96–1.15		
Seamen (SE)	1478	1.22	1.16–1.28	1.09	1.03–1.14	1.11	1.05–1.16
Transport workers (TW)	2107	1.08	1.03–1.13	1.00	0.96–1.05	1.03	1.00–1.08
Drivers (DR)	5971	1.14	1.11–1.17	1.08	1.05–1.10		
Postal workers (PW)	1105	1.07	1.01–1.14	1.00	0.95–1.07	1.02	0.96–1.08
Textile workers (TX)	1133	1.05	0.99–1.12	0.98	0.92–1.04	0.95	0.90–1.01
Shoe and leather workers (SL)	428	1.08	0.98–1.19	0.99	0.90–1.09	1.02	0.93–1.12
Smelting workers (SM)	1929	1.08	1.04–1.13	1.03	0.98–1.07		
Mechanics (ME)	8135	1.10	1.08–1.12	0.98	0.96–1.00		
Plumbers (PL)	1020	1.20	1.13–1.28	1.01	0.95–1.07		
Welders (WE)	822	1.06	0.99–1.13	0.99	0.92–1.06		
Electrical workers (EW)	2756	1.08	1.04–1.12	0.98	0.95–1.02	1.03	0.99–1.06
Wood workers (WW)	5697	0.94	0.91–0.96	1.02	0.99–1.04	1.00	0.98–1.03
Painters (PA)	1641	1.08	1.03–1.13	1.02	0.97–1.07		
Other construction workers (OC)	3591	1.01	0.98–1.04	0.98	0.95–1.01	1.02	0.98–1.05
Bricklayers (BR)	975	1.02	0.96–1.09	0.96	0.90–1.02		
Printers (PR)	1018	1.18	1.11–1.26	1.11	1.04–1.18		
Chemical process workers (CP)	1389	1.05	1.00–1.11	0.97	0.91–1.01	1.01	0.96–1.06
Food workers (FO)	2066	1.11	1.06–1.16	1.00	0.95–1.04	1.03	0.98–1.07
Beverage workers (BW)	153	1.13	0.96–1.33	1.01	0.85–1.18		
Tobacco workers (TO)	29	1.18	0.79–1.70	0.86	0.57–1.23		
Glass makers etc. (GM)	1486	1.04	0.99–1.10	0.96	0.91–1.00		
Packers (PA)	2699	1.08	1.04–1.12	1.00	0.97–1.04		
Engine operators (EO)	2220	1.06	1.01–1.10	0.99	0.95–1.03	1.00	0.96–1.04
Public safety workers (PS)	1565	1.10	1.04–1.15	1.04	0.99–1.09	1.07	1.01–1.12
Cooks and stewards (CS)	309	1.20	1.07–1.34	1.12	1.00–1.25	1.13	1.01–1.27
Domestic assistants (DA)	7	0.72	0.29–1.48	0.95	0.38–1.95	0.97	0.38–1.99
Waiters (WA)	249	1.42	1.25–1.61	1.22	1.07–1.38	1.23	1.08–1.40
Building caretakers (BC)	1276	1.09	1.03–1.15	0.97	0.91–1.02	1.00	0.94–1.05
Chimney sweeps (CH)	105	1.49	1.21–1.80	1.29	1.05–1.56	1.31	1.07–1.58
Hairdressers (HD)	357	1.30	1.17–1.45	1.14	1.02–1.26		
Launderers (LA)	186	1.10	0.95–1.28	1.05	0.91–1.21		
Military personnel (MP)	915	1.12	1.05–1.20	0.97	0.91–1.03	1.00	0.94–1.07
Other workers (OW)	4079	1.00	0.97–1.03	0.96	0.93–0.99	0.97	0.94–1.00

[a]Model 1: Bladder cancer risk estimation based on all 53 occupational categories.
[b]Model 2: Bladder cancer risk estimation based only on 37 occupations excluding occupations with probable strong occupation-related risk factors other than smoking; miners and quarry workers, drivers, smelting workers, mechanics, plumbers, welders, painters, bricklayers, printers, beverage workers, tobacco workers, glass makers, packers, hairdressers launderers and gardeners.
Empty boxes in the model 2 shows the occupations excluded in the model due to probable strong occupation- related risk factor other than smoking.

restaurants and other public places was implemented in the Nordic countries after the period of our study, in 2005. Future studies are needed to show whether the small excess in the risk of bladder cancer will disappear.

In our study, hairdressers were at elevated risk of bladder cancer. In a meta-analysis by Harlings et al., a summary risk ratio (SRR) of 1.70 (95% CI 1.10–2.88) for bladder cancer was observed among hairdressers [30]. The study also observed an increase in SRR with an increase in the duration of employment, and observed no differences in the estimates of crude and smoking-adjusted risks. Another meta-analysis observed a pooled RR of 1.30 (95% CI 1.20–1.42) for bladder cancer among hairdressers [31]. The excess in this study was restricted to exposures before the ban in 1970 on the

Table 3. Observed number of bladder cancer, standardized incidence ratio (SIR), 95% confidence interval (95% CI) with proxy smoking adjusted from lung cancer in occupations with smoking-adjusted SIR from Model 1 (SIR_{adj1}) > 1.05 in Nordic males, by country.

	Denmark				Finland				Iceland				Norway				Sweden			
Occupation	Obs	SIR	SIR_{adj1}	95% CI	Obs	SIR	SIR_{adj1}	95% CI	Obs	SIR	SIR_{adj1}	95% CI	Obs	SIR	SIR_{adj1}	95% CI	Obs	SIR	SIR_{adj1}	95% CI
Sales agents	547	1.23	1.09	1.00–1.19	476	1.03	0.98	0.89–1.07	14	0.76	0.82	0.45–1.38	1054	1.11	1.02	0.96–1.08	3004	1.19	1.05	1.00–1.08
Miners & quarry workers	24	0.98	0.92	0.59–1.37	78	1.29	1.15	0.91–1.43	0	0.00	0.00	0.00–8.01	106	0.77	0.94	0.76–1.13	272	0.94	0.99	0.87–1.11
Seamen	231	1.19	1.08	0.94–1.23	108	1.34	1.09	0.89–1.32	12	1.42	1.15	0.59–2.01	813	1.21	1.03	0.96–1.10	314	1.24	1.06	0.94–1.18
Drivers	1619	1.16	1.04	0.98–1.08	822	1.10	1.03	0.96–1.10	32	1.32	1.15	0.78–1.62	1152	1.18	1.06	1.00–1.12	2346	1.12	1.04	1.00–1.08
Painters	394	1.18	1.11	1.00–1.23	160	0.93	0.98	0.83–1.14	10	1.78	1.48	0.70–2.72	291	1.09	1.05	0.93–1.17	786	1.06	1.02	0.95–1.09
Printers	260	1.12	1.04	0.91–1.17	81	1.13	1.07	0.85–1.33	8	1.80	1.44	0.62–2.84	198	1.27	1.07	0.92–1.22	471	1.19	1.07	0.97–1.16
Cooks and stewards	36	1.31	1.15	0.80–1.59	8	0.66	0.95	0.40–1.86	7	1.31	1.12	0.45–2.30	116	1.05	0.95	0.78–1.13	142	1.38	1.12	0.94–1.32
Waiters	103	1.69	1.22	0.98–1.48	11	1.00	0.86	0.43–1.54	2	3.59	2.27	0.27–8.21	50	1.03	0.94	0.69–1.23	83	1.54	1.28	1.02–1.58
Chimney sweeps	16	1.67	1.25	0.71–2.03	16	1.17	1.09	0.62–1.77	–	–	–	–	15	1.12	1.04	0.58–1.72	58	1.71	1.37	1.04–1.77
Hairdressers	140	1.31	1.17	0.98–1.38	5	1.34	1.20	0.39–2.80	1	1.28	1.11	0.02–6.19	53	1.37	1.10	0.82–1.44	158	1.27	1.10	0.93–1.28
Launderers	49	0.94	0.96	0.70–1.26	4	1.05	1.00	0.27–2.58	1	2.00	1.25	0.03–6.96	30	1.28	1.13	0.76–1.61	102	1.15	1.03	0.83–1.24

carcinogenic aromatic amines used in hair dyes. Hairdressers have historically been exposed to aromatic amines such as benzidine, toluidine and aromatic nitrous compounds, and exposure to these chemical compounds has been linked to an increased risk of bladder cancer [32]. Long-term exposure of >10 years has been associated with greater risk of bladder cancer [31,33]. A study among Finnish hairdressers showed that there was a marked overall excess risk of cancer until the mid-1970s, but almost no excess after that; this was interpreted as a consequence of a rapid decrease in exposure to carcinogenic agents [34]. Following the ban on carcinogenic substances in the European Union, some recent studies have reported an excess bladder cancer risk, but the risk is due to the use of such banned substances even after legislation, leading to the potential for ongoing exposure [35]. A separate NOCCA study on a period-specific stratified analysis from 1961 to 2005 observed a decreased risk among hairdressers [36].

Increased risk of bladder cancer was associated with employment as cooks and stewards in our study. These workers are commonly exposed to environmental tobacco smoke and other workplace chemical carcinogens associated with the risk of bladder cancer [22]. Two reviews, by Cumberbatch et al. and Al-Zalabani et al., reported the same statistically significant increased pooled relative risk (RR 1.15, 1.08–1.22) of bladder cancer among those exposed as cooks and stewards [21,22]. A higher relative excess was observed in males.

Printers were another high-risk group for bladder cancer observed in the study. A meta-analysis observed a significant pooled relative risk (RR 1.23, 1.17–1.30) among printers [22]. Another meta-analysis of case control studies from six European countries observed up to 80% greater risk of bladder cancer among those exposed as printers compared with the general population (OR 1.81, 95% CI 1.03–3.17) [3]. Printers are exposed to pigments and solvents (vehicles) that are carcinogenic with a risk of bladder cancer [37]. The IARC has classified occupational exposures in printing processes as possibly (group 2B) carcinogenic to humans [38].

In the absence of direct information on their occurrence or the magnitude of the population under study, it is possible to estimate the impact of confounding using indirect (proxy) measures [16]. In our study, we observed that the smoking-adjusted SIRs came closer to 1.0 for all occupations after adjustments with the proxy for smoking, but the adjustment did not change the direction of the risk estimate. This is in line with the findings of other studies that also observed that adjustment for smoking did not normally change the direction of the risk estimate [13–16,39]. Consistency across the country-specific risk estimate observations for a given occupation might help to separate true associations from chance findings. In this type of large cohort study, it has been estimated that either systematic or chance differences in unmeasured lifestyle factors such as smoking will not confound the risk by more than 20% [16,39], and we can safely conclude that the residual confounding due to smoking in our smoking-adjusted risk estimates is smaller. Hence, it is very unlikely that occupational variations in the risk of bladder cancer will affect the risk estimate due to smoking alone. Exposure to chemical agents, such as PAH, aromatic amines, and other workplace carcinogens is associated with the risk of bladder cancer [22].

In the Nordic countries, smoking prevalence corresponds well to the lung cancer incidence. This pattern of smoking prevalence and lung cancer incidence was reported in the national surveys separately in all the Nordic countries. According to the Norwegian national survey from 1965 to 1980, occupations with a high-risk of lung cancer had also a high level of smoking [14]. In this study, Haldorsen et al. estimated a 10% increase in the proportion of smoking to increase the lung cancer incidence by 26% in men. Similarly, data from Finnish national surveys (FINJEM) [40], Swedish national survey [17] and Norwegian national survey [14,41] estimated the occupation specific prevalence of smoking and other lifestyle factors in different occupational categories. In all these studies, smoking was positively associated with both lung and bladder cancer across different occupational categories [12]. Some of the most high-risk occupations included waiters, tobacco workers, seamen, miners and quarry workers, cooks and stewards, and transportation workers [12,14,41]. The surveys included information on sex, year of birth, age at smoking, smoking status (current smoking, former smoking) average number of cigarettes per day for cigarette smokers and the proportion of smoking a pipe among current smokers to describe their smoking habits [14,17,41]. These surveys had a high response rate and the validity of these data are considered to be of high standard [19].

Limitations of the study include exposure misclassification. As the individuals' occupational categories were based on occupations held in the year before the first available census, the data did not provide information on job changes across the entire working career. Misclassification of the exposure estimate would bias the observed effect towards null. However, occupational stability, e.g., in Finland, was high in the early decades, and turnover was low in the older male population [42]. Therefore, exposure misclassification in this NOCCA study should be relatively small. Nonetheless, we cannot rule out the possibility of residual confounding. The occupational titles were categorized into 53 broader categories to reach sufficient numbers of cancer cases in each category. Some of the occupational categories used in the study are heterogeneous and may hide more specific subcategories with occupation-specific risk factors. A similar limitation also concerns the use of smoking prevalence in an occupational category as a proxy for lifelong smoking habits for all men in that occupation. It is known from Finnish survey data that although the prevalence of smoking in men has decreased strongly in all socio-economic categories, the relative difference between categories has not changed [43,44]. If we assume that the latency time from smoking to cancer outcome is similar for lung cancer and bladder cancer, the use of SIRs for lung cancer to adjust bladder cancer SIRs for a similar period should take care of the complex lag-time issue.

The NOCCA study is the largest ever conducted on occupational cancer incidence, with virtually full coverage of cancer cases in the Nordic countries, and with large numbers of bladder and lung cancer cases. The occupational codes used are of high accuracy [12]. The completeness and accuracy of the Nordic cancer registers is of top quality in international rankings [19]; even if there were some incompleteness in registration or diagnosis, this would not affect SIR estimates as long as the cancer registration and diagnosis followed similar procedures irrespective of the person's occupation. The unique personal identity code, used for linkage between the census, vital status and cancer incidence data, is a highly reliable linkage tool [19].

This study suggests that smoking is not the only factor causing variation in bladder cancer incidence between the occupational categories but carcinogenic workplace exposures may also play a role in some specific occupations such as chimney sweeps, waiters, hairdressers, cooks and stewards, printers and seamen. Occupational exposure pattern has changed over the study period in all Nordic countries, primarily after following the ban on the use of some carcinogenic substances, e.g., aromatic amines, at workplaces after the 1980s in the European Union. Similarly, other preventive measures were introduced as a consequence of an improved legislation, implementation of safety and hygiene programs, elimination or decreased production of hazardous chemical substances that are classified as risk to human health, and substitution with few carcinogens are some of the remarkable measures for decreased risk [10]. Additionally, it is indeed a known fact that there is an increased risk of second smoking-related cancers in patients with first smoking-related cancer. In the NOCCA dataset also the second and higher primary malignancies are counted and therefore a person having e.g., head and neck cancer first and lung cancer later will contribute to lung cancer statistics.

Although there has been a decreasing trend in PAH exposure in the recent decades in the Nordic countries [45], it is still a problem causing lung and bladder cancer. PAHs are important workplace carcinogens that occur in various forms such as benzo[a]pyrene and soot. A Swedish study covering all male chimney sweeps observed increased risk of bladder and lung cancer due to PAH (soot) exposure [25]. Randem et al. reported similar increased risk of lung and bladder cancer due to PAH exposure among male asphalt industry workers in Denmark, Finland, Norway and Sweden [45]. Parallel to the findings of these studies, chimney sweeps in our study was observed as the highest risk of bladder cancer and workplace exposure to PAH could be an important factor for increased risk. Globally, workplace PAH exposure has been reduced after the peak in the mid-1990s [46]. The risk due to occupational carcinogens at workplace carcinogens such as PAH, asbestos, diesel engine exhaust is shifting towards the developing countries [47].

In summary, occupation is evidently associated with the risk of bladder cancer, but most of the variation in bladder cancer risk observed between occupational categories appears to be due to smoking. After adjustment with a proxy for smoking prevalence, we observed an evident excess in bladder cancer risk only in some occupational categories, most of which are suspected of facing occupational exposures to chemical carcinogens of such high levels that they could add to the risk of bladder cancer. The large size of our study made it possible to reveal significant findings in rare occupations such as chimney sweeps and male hairdressers. Future research on occupational exposures to chemical compounds would better explain the risk variation between occupational categories.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Occupational exposure to solvents and bladder cancer: A population-based case control study in Nordic countries

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The objective of the study was to assess the relationship between exposure to selected solvents and the risk of bladder cancer. This study is based on the Nordic Occupational Cancer (NOCCA) database and comprises 113,343 cases of bladder cancer diagnosed in Finland, Iceland, Norway and Sweden between 1961 and 2005 and 566,715 population controls matched according to country, sex and birth year. Census-based occupational titles of the cases and controls were linked with the job exposure matrix created by the NOCCA project to estimate quantitative cumulative occupational exposures. A conditional logistic regression model was used to estimate hazard ratios (HRs) and their 95% confidence intervals (95% CI). Increased risks were observed for trichloroethylene (HR 1.23, 95% CI 1.12–1.40), toluene (HR 1.20, 95% CI 1.00–1.38), benzene (HR 1.16, 95% CI 1.04–1.31), aromatic hydrocarbon solvents (HR 1.10, 95% CI 0.94–1.30) and aliphatic and alicyclic hydrocarbon solvents (HR 1.08, 95% CI 1.00–1.23) at high exposure level versus no exposure. The highest excess for perchloroethylene was observed at medium exposure level (HR 1.12, 95% CI 1.02–1.23). The study provides evidence of an association of occupational exposure to trichloroethylene, perchloroethylene, aromatic hydrocarbon solvents, benzene and toluene and the risk of bladder cancer.

The International Agency for Research on Cancer (IARC) has identified about 100 workplace carcinogens, and a similar number of additional workplace exposures have been classified as possible carcinogens.[1] Some epidemiological studies have demonstrated excess risks of certain cancers in relation to occupational exposure to some solvents. It is further estimated that as many as 20% of all bladder cancer incidence in industrialized countries may be attributable to occupational carcinogens.[2,3] There was sufficient evidence of carcinogenicity in humans for 4-amino biphenyl, aristolochic acid, benzidine, 2-napthylamine, o-toluidine, arsenic, x-radiation, gamma radiation, tobacco smoking, chlornaphazine and cyclophosphamide.[1] Excess risk of bladder cancer has been reported among several occupational groups such as painters, rubber industry workers, hairdressers and barbers, dry cleaners, transportation workers and printers.[1] These groups may be exposed to aromatic amines, polycyclic aromatic hydrocarbons, diesel exhaust and chlorinated hydrocarbons, and these chemicals have been implicated as the causative bladder carcinogens even if their exact role is debatable.[1,2,4–6] A study of painters suggests that the occupation-related risk of bladder cancer may be predominantly seen in the younger age categories.[7] While some study findings have been consistent, others have been inconsistent or limited.[1,6] In this large population-based study, we assess the relationship between occupational exposure to solvents (aliphatic and aromatic hydrocarbon solvents, aromatic hydrocarbon solvents, benzene, chlorinated hydrocarbon solvents, other organic solvents, perchloroethylene, trichloroethylene, 1,1,1 trichloroethane) and the risk of bladder cancer using a Nordic job exposure matrix (NOCCA-JEM).

Key words: aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents, benzene, job exposure matrix, risk, toluene, trichloroethylene, urothelial carcinoma

Abbreviations: FINJEM: Finnish job exposure matrix; HR: hazard ratio; IARC: International Agency for Research on Cancer; NOCCA: Nordic Occupational Cancer study;; NOCCA-JEM: Nordic occupational cancer study job exposure matrix; RR: relative risk

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What's new?
Evidence of the higher risk of bladder cancer among occupational groups remains limited. In this large population-based study, the authors assessed the relationship between occupational exposure to solvents (aliphatic and aromatic hydrocarbon solvents, aromatic hydrocarbon solvents, benzene, chlorinated hydrocarbon solvents, other organic solvents, perchloroethylene, trichloroethylene and 1,1,1-trichloroethane) and the risk of bladder cancer using a Nordic job exposure matrix. They found evidence of an association between occupational exposure to trichloroethylene, perchloroethylene, aliphatic and aromatic hydrocarbon solvents, benzene and toluene and bladder cancer risk. Among these solvents, only benzene and trichloroethylene are currently classified as Group 1 carcinogens to humans.

Material and Methods

The present study is based on the Nordic Occupational Cancer (NOCCA) project. The NOCCA cohort of 14.9 million individuals from Denmark, Finland, Iceland, Norway and Sweden consists of individuals from all five Nordic countries who participated in one or more population censuses in 1960, 1970, 1980/1981 and 1990. As we did not have access to individual data records from Denmark, we had to restrict the study to the remaining four Nordic countries. Occupational information was obtained from computerized census records from censuses 1960, 1970, 1980 and 1990 in Sweden, censuses 1960, 1970 and 1980 in Norway, censuses 1970, 1980 and 1990 in Finland and census 1981 in Iceland. Personal identity codes were used to link the census records with data from cancer registries and national population registries for information on cancer, death and emigration. Each person was followed until the date of emigration, death or end of the study, which was December 31 of the following years: 2003 in Norway, 2004 in Iceland, 2005 in Finland and Sweden. Details of the NOCCA study have been described previously.[8] Information on smoking, socioeconomic status and other non-occupational risk factors was not available. This study was approved by the ethical committee and the data inspection boards in each of the Nordic countries.

All incident cases of bladder cancer were extracted from the NOCCA cohort. For each case, five controls were selected, matched by birth year and sex, and were randomly selected from among individuals who were alive and free from bladder cancer at the date of diagnosis of the case (index date). Cases and controls could have a history of any cancer type other than bladder cancer. Persons with a minimum age of 20 years at index date and having occupational information from at least one census record before the index date were included in this study.

Exposure to solvents and other agents was quantitatively estimated based on linkage between occupational codes and NOCCA-JEM. NOCCA JEM was developed from the Finnish job exposure matrix (FINJEM). It covers >300 specific occupations as they are coded in the national census data, 29 exposure agents and 4 calendar periods: 1945–1959, 1960–1974, 1975–1984 and 1985–1994. Exposure agents are characterized by the proportion of exposed (P) and the mean level of exposure among the exposed persons (L) in a specific occupation and time period. Many prevalence and level estimates of FINJEM were modified to be in better accordance with measurement data available from the Nordic countries.[9] Eight new agents that were not included in FINJEM (six solvents and two other agents) were added to the NOCCA-JEM. FINJEM has been used to compare with many other JEMS.[9] We assumed that the solvent exposures before 1945 could be taken as zero. An occupational code was assigned for each case and control based on the occupational codes recorded in the censuses. For each occupational code and year of exposure, the exposure estimate was calculated as the product of proportion and level of exposure ($P \times L$) from NOCCA JEM. These year-specific values were then added up for the entire employment period (T).

Exposure was assumed to start at the age of 20 years and end at the index date or at 65 years, whichever occurred first. If there were different occupational codes in the census records for a given person, the individual was assumed to have changed occupations at the mid-point of two known census years. In that case, the exposure history of the person consisted of more than one $P \times L \times T$ value. The cumulative exposures of these individuals were estimated by summing up all their $P \times L \times T$ values over their entire working career. This procedure was repeated for all the exposure agents. Variables were selected using "purposeful selection of covariates." The univariate analysis of each variable with a significant univariate test was selected for further multivariate analysis based on the Wald test from logistic regression and $p \leq 0.25$.

In this study, we quantified exposure to the following individual solvents: aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents, benzene, toluene, chlorinated hydrocarbon solvents, perchloroethylene, 1,1,1 trichloroethane, trichloroethylene and other organic solvents. We also quantified exposures to ionizing radiation, asbestos, benzo[a]pyrene, diesel engine exhaust and sulfur dioxide, which, along with age and sex, were considered as potential confounders in our analysis. Benzene and toluene were highly correlated with aliphatic and alicyclic hydrocarbon solvents as well as with each other. We used, therefore, two main effect models (Models 1 and 2). In Model 1, we included benzene and toluene but excluded aliphatic and alicyclic hydrocarbon solvents, and in Model 2, we included aliphatic

Table 1. Demographic characteristics of bladder cancer cases and controls

Characteristics	Cases		Controls	
	N	%	*N*	%
Sex				
Male	84,629	74.7	423,145	74.7
Female	28,714	25.3	143,570	25.3
Country				
Finland	18,521	16.3	92,605	16.3
Iceland	804	0.7	4,020	0.7
Norway	28,938	25.5	144,690	25.6
Sweden	65,080	57.4	325,400	57.5
Year of birth				
≤1910	30,751	27.1	153,755	27.1
1911–1920	33,674	29.7	168,370	29.7
1921–1930	28,474	25.1	142,370	25.1
1931–1940	12,980	11.5	64,900	11.5
1941–1950	6,285	5.5	31,425	5.5
1951–1960	1,179	1.0	5,895	1.0
Age at index date[1]				
20–29	6,878	6.1	34,390	6.1
30–39	19,211	16.9	96,055	16.9
40–49	31,359	27.7	156,795	27.7
50–59	38,005	33.5	190,025	33.5
60+	17,890	15.8	89,450	15.8
Total	113,343	100	566,715	100

[1]Index date is defined as the date of diagnosis for the case in each case–control set.

and alicyclic hydrocarbon solvents but excluded benzene and toluene. All other solvents were included in both multivariate models.

Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for each solvent were estimated using conditional logistic regression. For the purpose of categorization, exposure values were defined as follows: below the 50th percentiles among the exposed cases and controls as low exposure level, between the 50th and 90th percentile inclusive as moderate and >90th percentile as high exposure level. Individuals with no exposure were used as reference. Pearson's χ^2 test for linear trend was performed to assess the dose–response relationship between exposure variables and bladder cancer risk. The unexposed group was excluded from the trend test. Analyses were repeated with different lag times of 0, 10 and 20 years. We present results with a 10-year lag, meaning that we did not count the exposures during the last 10 years before the index date. HRs are mutually adjusted for exposure to other solvents and chemicals.

Results

This study included 113,343 cases and 566,715 controls. Three fourths of the study subjects were male, and more than half were from Sweden. 56.8% of the cases and controls were born before 1920, and thus, likely to have some employment and possible exposure before 1945, during periods for which NOCCA-JEM provides no exposure estimate (Table 1). The proportion of exposed among the cases and controls was 17.5% and 82.5%, respectively. Table 2 shows the occupations with the highest solvent exposure with specific solvents based on NOCCA-JEM.

Statistically significant increased risks with $HR > 1.10$ were observed for trichloroethylene, toluene and benzene at high exposure level and perchloroethylene at medium exposure level. Although some of the HRs were statistically significant, the risk estimates were generally close to 1.0. The results from both models were similar. Hence, we chose to present the results for aliphatic and alicyclic hydrocarbon solvents from Model 2 and for all other exposures from Model 1 (Table 3).

The HRs tended to be higher for cancers diagnosed at ages <50 years for aliphatic and alicyclic hydrocarbon solvents, benzene and toluene, while for trichloroethylene, the HR was highest in the older age component at high exposure level (Table 4). We did not observe any significant interactions indicating that the dose–response trend patterns would be different in males and females (Table 5).

Table 2. Occupations with highest solvent exposures in NOCCA-JEM

Occupations	Exposures
Printers	Toluene
Painters	Toluene
Graphics	Toluene, other organic solvents
Plastic product workers	Aromatic hydrocarbons solvents
Rubber workers	Aliphatic and alicyclic hydrocarbons solvents, aromatic hydrocarbons solvents, toluene
Upholsterers	Aromatic hydrocarbons solvents, toluene
Laster and sole fitters	Aliphatic and alicyclic hydrocarbons solvents, benzene, other organic solvents, trichloroethylene
Chemical process workers	Aliphatic and alicyclic hydrocarbons solvents, aromatic hydrocarbons solvents, toluene
Refinery workers and others in chemical industry	Aliphatic and alicyclic hydrocarbons solvents, aromatic hydrocarbons solvents, toluene
Painters, lacquerers and floor layers	Aliphatic and alicyclic hydrocarbons solvents, aromatic hydrocarbons solvents, other organic solvents
Metal plating and coating work	Chlorinated hydrocarbons solvents, perchloroethylene, trichloroethylene, 1,1,1-trichloroethane
Wood workers	Trichloroethylene
Distillers	Toluene
Laundry workers	Aliphatic and alicyclic hydrocarbons solvents, aromatic hydrocarbons solvents, chlorinated hydrocarbon solvents, perchloroethylene, trichloroethylene
Crusher, grinders and calender operators	Other organic solvents
Paper and cardboard mill workers	Other organic solvents
Chemists	Aromatic hydrocarbons solvents, chlorinated hydrocarbon solvents
Footwear workers	Aliphatic and alicyclic hydrocarbons solvents, benzene, other organic solvents
Bookbinders	Other organic solvents
Machine and engine mechanics	Trichloroethylene
Maintenance crews and supervisors	Aromatic hydrocarbons solvents, toluene
Lithographers	Other organic solvents
Service station attendants	Benzene, toluene
Assemblers and other machine and metal ware occupations	Trichloroethylene
Electrical and electronic equipment assemblers	Trichloroethylene

Discussion

The findings of this study show a statistically significant increased risk of bladder cancer among individuals employed in occupations where exposures to solvents likely occur. Associations were estimated at different exposure levels for aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents, perchloroethylene, benzene, toluene and trichloroethylene.

IARC first classified trichloroethylene as probably carcinogenic to humans (Group 2A), but later it was re-evaluated as a Group 1 carcinogen.[10] In our study, the estimated exposure to trichloroethylene was significantly associated with an increased risk of bladder cancer, and the excess risk was observed at high exposure level. Dry cleaners and aircraft and aerospace workers were reported as highly exposed to trichloroethylene.[10] Similarly, perchloroethylene, which is commonly known as tetrachloroethylene, is mainly used in dry cleaning and to a lesser extent in the printing and textile industries.[10]

A German study observed an increased risk of bladder cancer among those exposed at a substantial exposure level of trichloroethylene [odds ratio (OR) 1.8, 95% CI 1.2–2.7] and tetrachloroethylene (OR 1.8, 95% CI 1.1–3.1) in males, using the job task exposure matrix.[11] Smoking was adjusted for in the analysis, and the substantial exposure level was similar to that of high exposure level in our study. Likewise, an American study observed an increased risk of bladder cancer among those exposed to trichloroethylene at the highest exposure level (risk ratio, 1.98, 95% CI 0.93–4.22). The study observed a dose–response relationship with exposure to

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Table 3. Hazard ratios (HRs) and 95% confidence interval (95% CI) of bladder cancer associated with exposure to solvents and other cofactors[1]

Agent[2] (unit)[3] Category (unit-years)	Cases	Controls	HR	95% CI	*p* for trend
Solvents					
Trichloroethylene (ppm)					
Unexposed	106,437	534,996	1.00	Reference	0.07
<32.80	3,433	15,884	1.07	1.02–1.12	
32.80–129.50	2,714	12,738	1.07	1.00–1.13	
>129.50	759	3,097	1.23	1.12–1.40	
Perchloroethylene (ppm)					
Unexposed	111,777	559,670	1.00	Reference	0.10
<13.60	747	3,560	1.00	0.92–1.09	
13.60–87.55	660	2,783	1.12	1.02–1.23	
>87.55	159	702	0.94	0.73–1.22	
Aliphatic and alicyclic hydrocarbon solvents (ppm)					
Unexposed	106,132	534,110	1.00	Reference	0.51
<18.73	3,648	16,276	1.00	0.94–1.05	
18.73–337.40	2,836	13,075	1.05	1.00–1.13	
>337.40	727	3,254	1.08	1.00–1.23	
Aromatic hydrocarbon solvents (ppm)					
Unexposed	107,281	537,691	1.00	Reference	0.02
<11.15	2,954	14,590	1.00	0.94–1.03	
11.15–298.93	2,469	11,565	1.06	1.00–1.14	
>298.93	639	2,869	1.10	0.94–1.30	
Benzene (ppm)					
Unexposed	105,363	530,478	1.00	Reference	0.07
<5.68	3,953	18,167	1.00	0.92–1.08	
5.68–15.04	3,172	14,510	1.05	1.00–1.15	
>15.04	855	3,560	1.16	1.04–1.31	
Toluene (ppm)					
Unexposed	105,139	529,444	1.00	Reference	0.68
<57.25	4,140	18,607	1.00	0.92–1.08	
57.25–707.50	3,230	14,952	1.00	0.91–1.07	
>707.50	834	3,712	1.20	1.00–1.38	
1,1,1–Trichloroethane (ppm)					
Unexposed	105,469	530,443	1.00	Reference	0.67
<5.60	6,011	27,807	0.98	0.93–1.02	
5.60–10.15	1,160	5,231	1.00	0.92–1.07	
>10.15	703	3,234	1.00	0.89–1.07	
Chlorinated hydrocarbon solvents (ppm)					
Unexposed	110,500	553,235	1.00	Reference	0.35
<27.58	1,416	6,746	1.00	0.92–1.09	
27.58–52.38	1,119	5,411	0.90	0.80–1.03	
>52.38	308	1,323	0.97	0.80–1.17	

Table 3. Hazard ratios (HRs) and 95% confidence interval (95% CI) of bladder cancer associated with exposure to solvents and other cofactors[1] (Continued)

Agent[2] (unit)[3] Category (unit-years)	Cases	Controls	HR	95% CI	*p* for trend
Other organic solvents (ppm)					
Unexposed	110,320	552,413	1.00	Reference	0.91
<105.55	1,529	7,137	1.02	0.96–1.09	
105.55–378.10	1,180	5,755	0.93	0.82–1.04	
>378.10	314	1,410	0.86	0.70–1.05	
Cofactors					
Asbestos (f/cm^3)					
Unexposed	91,112	461,009	1.00	Reference	0.10
<2.28	11,297	52,700	1.07	1.04–1.10	
2.28–16.78	8,684	42,478	1.02	1.00–1.04	
>16.78	2,250	10,528	1.09	1.04–1.14	
Benzo[a]pyrere (μg/m^3)					
Unexposed	103,657	521,657	1.00	Reference	0.59
<0.31	4,846	22,528	1.00	0.96–1.04	
0.31–7.25	3,910	18,042	1.01	1.00–1.06	
>7.25	930	4,488	1.00	0.92–1.09	
Diesel engine exhaust (mg/m^3)					
Unexposed	96,038	487,969	1.00	Reference	0.11
<0.70	8,973	40,447	1.14	1.11–1.17	
0.70–2.27	6,665	30,393	1.21	1.09–1.16	
>2.27	1,667	7,906	1.05	1.00–1.12	
Sulfur dioxide (ppm)					
Unexposed	111,109	556,478	1.00	Reference	0.05
<8.35	1,138	5,106	1.08	1.01–1.15	
8.35–45.70	908	4,072	1.10	1.01–1.20	
>45.70	188	1,059	0.90	0.75–1.04	
Ionizing radiation (mSv)					
Unexposed	112,736	563,671	1.00	Reference	0.03
<4.08	288	1,537	0.90	0.80–1.00	
4.08–8.91	241	1,220	0.92	0.80–1.07	
>8.91	78	287	1.40	1.09–1.80	

HR estimates for aliphatic and alicyclic hydrocarbon solvents are from Model 2 and other HR are from Model 1.
[1]In Model 1, we included benzene and toluene but excluded aliphatic and alicyclic hydrocarbon solvents and in Model 2, we included aliphatic and alicyclic hydrocarbon solvents but excluded benzene and toluene. All other solvents were included in both multivariate models.
[2]Occupationally unexposed individuals were used as a reference group.
[3]ppm, parts per million of agent; mg/m^3, milligram of agent in a cubic meter of workroom air; f/cm^3, fibers of asbestos in a cubic centimeter of workroom air; μg/m^3, microgram of agent in a cubic meter of workroom air and mSv, annual equivalent radiation dose in millisieverts.

trichloroethylene, and it also reports that confounding due to smoking was very small.[12]

In a Nordic study, excess risk of bladder cancer was observed among dry cleaning assistants exposed to tetrachloroethylene (rate ratio 1.44, 95% CI 1.07–1.93), regardless of the duration of employment.[13] In the Nordic countries, trichloroethylene was used mainly for degreasing metals and little in dry cleaning, whereas perchloroethylene was used extensively in dry cleaning.[14] Hence, the results for perchloroethylene in the Nordic dry cleaner study and the present study are not independent because of a marked overlap of the data in these two studies. A meta-analysis study of the exposure of tetrachloroethylene among dry cleaning workers observed the overall meta-RR of 1.47 (95% CI 1.16–1.85).[15] In our study, exposure to perchloroethylene was associated with a significantly increased risk of bladder cancer at

Table 4. Hazard ratios (HR) and 95% confidence intervals (95% CI) of bladder cancer associated with exposure to solvents, by age at diagnosis (ppm = parts per million)[1]

Agent[2] (unit)	<50 years					≥50 years				
Category (unit-years)	Cases	Controls	HR	95% CI	*p* for trend	Cases	Controls	HR	95% CI	*p* for trend
Trichloroethylene (ppm)										
Unexposed	54,713	275,139	1.00	Reference	0.44	51,724	259,857	1.00	Reference	0.40
<32.80	873	3,858	1.11	1.02–1.22		2,560	12,026	1.04	1.00–1.10	
32.80–129.50	1,293	5,868	1.12	1.03–1.21		1,421	6,870	1.01	0.94–1.09	
>129.50	569	2,375	1.24	1.10–1.40		190	722	1.27	1.02–1.60	
Perchloroethylene (ppm)										
Unexposed	56,843	284,627	1.00	Reference	0.98	54,934	275,043	1.00	Reference	0.07
<13.60	200	896	1.02	0.90–1.21		547	2,664	1.00	0.90–1.11	
13.60–87.55	337	1,390	1.11	1.00–1.30		323	1,393	1.13	1.00–1.30	
>87.55	68	327	0.90	0.60–1.30		91	375	1.00	0.70–1.38	
Aliphatic and alicyclic hydrocarbon solvents (ppm)										
Unexposed	54,462	274,116	1.00	Reference	0.50	51,670	259,994	1.00	Reference	0.06
<18.73	1,262	5,603	1.00	0.90–1.07		2,386	10,673	1.00	0.94–1.07	
18.73–337.40	1,291	5,685	1.12	1.00–1.27		1,545	7,390	1.00	0.90–1.10	
>337.40	433	1,836	1.23	1.00–1.50		294	1,418	1.00	0.81–1.16	
Aromatic hydrocarbon solvents (ppm)										
Unexposed	54,732	274,800	1.00	Reference	0.25	52,549	262,891	1.00	Reference	0.05
<11.15	1,277	5,955	1.03	0.95–1.11		1,677	8,635	0.95	0.90–1.01	
11.15–298.93	1,102	5,039	1.10	1.00–1.22		1,367	6,526	1.05	0.95–1.15	
>298.93	337	1,446	1.09	0.83–1.42		302	1,423	1.10	0.90–1.34	
Benzene (ppm)										
Unexposed	54,040	272,312	1.00	Reference	0.10	51,323	258,166	1.00	Reference	0.96
<5.68	1,191	5,297	1.00	0.90–1.20		2,762	12,870	1.00	0.90–1.09	
5.68–15.04	1,568	7,036	1.07	0.93–1.24		1,604	7,474	1.04	0.92–1.20	
>15.04	649	2,595	1.22	1.03–1.44		206	965	1.04	0.90–1.26	
Toluene (ppm)										
Unexposed	53,905	271,682	1.00	Reference	0.84	51,234	257,762	1.00	Reference	0.26
<57.25	1,341	5,814	1.00	0.90–1.15		2,799	12,793	1.00	0.90–1.09	
57.25–707.50	1,700	7,575	1.00	0.90–1.11		1,530	7,377	1.00	0.90–1.10	
>707.50	502	2,169	1.23	1.00–1.55		332	1,543	1.11	0.90–1.41	
1,1,1-Trichloroethane (ppm)										
Unexposed	54,167	272,587	1.00	Reference	0.12	51,302	257,856	1.00	Reference	0.06
<5.60	2,897	12,768	1.00	0.91–1.05		3,114	15,039	1.00	0.90–1.03	
5.60–10.15	283	1,413	0.85	0.73–1.00		877	3,818	1.08	1.00–1.20	
>10.15	101	472	0.90	0.70–1.11		602	2,762	1.03	0.92–1.14	
Chlorinated hydrocarbon solvents (ppm)										
Unexposed	56,234	281,693	1.00	Reference	0.47	54,266	279,475	1.00	Reference	0.15
<27.58	453	1,972	1.01	0.90–1.20		963	4,774	1.01	0.91–1.12	
27.58–52.38	605	2,877	0.83	0.70–1.01		514	2,534	1.00	0.81–1.20	
>52.38	156	698	0.91	0.70–1.21		152	625	1.03	0.80–1.35	

Table 4. Hazard ratios (HR) and 95% confidence intervals (95% CI) of bladder cancer associated with exposure to solvents, by age at diagnosis (ppm = parts per million) (Continued)

Agent[2] (unit) Category (unit-years)	<50 years Cases	Controls	HR	95% CI	p for trend	≥50 years Cases	Controls	HR	95% CI	p for trend
Other organic solvents (ppm)										
Unexposed	56,060	280,904	1.00	Reference	0.79	54,260	271,509	1.00	Reference	0.36
<105.55	587	2,644	1.05	0.94–1.16		942	4,493	1.00	0.92–1.10	
105.55–378.10	570	2,708	0.95	0.80–1.13		610	3,047	0.90	0.76–1.04	
>378.10	231	984	0.90	0.64–1.20		83	426	0.80	0.60–1.09	

[1]HR estimates for aliphatic and alicyclic hydrocarbon solvents are from Model 2 and all the other HR are from Model 1. In Model 1, we included benzene and toluene but excluded aliphatic and alicyclic hydrocarbon solvents and in Model 2, we included aliphatic and alicyclic hydrocarbon solvents but excluded benzene and toluene. All other solvents were included in both multivariate models.
[2]Occupationally unexposed individuals were used as a reference group in all analysis.

medium exposure level compared with no exposure. Trichloroethylene and perchloroethylene are the subcategories of chlorinated solvents. Hence, it is difficult to disentangle their individual effects. According to IARC, exposure to trichloroethylene was categorized as a Group 1 carcinogenic, whereas perchloroethylene (tetrachloroethylene) was categorized as probably carcinogenic to humans (Group 2A).

The broad category of aromatic hydrocarbon solvents includes benzene (as well as toluene, xylene and others) so that it becomes difficult, if not impossible to disentangle their effects. According to IARC, occupational exposure to benzene occurs through inhalation or dermal absorption of solvents in manufacturing industries such as for rubber and paint, crude oil refining, transport of crude oil and gasoline service stations.[16] In our study, we observed a dose–response risk of bladder cancer exposed to benzene, aliphatic and alicyclic hydrocarbon solvents and aromatic hydrocarbon solvents. Previous epidemiological studies have observed an elevated risk of bladder cancer among painters [relative risk (RR) 1.28, 95% CI 1.15–1.43], transportation workers (OR 1.6, 95% CI 1.1–2.6), gas and electrical services workers (OR 3.9, 95% CI 1.1–2.6), gasoline workers (OR 1.21, 95% CI 1.03–1.42) and rubber workers (OR 2.5, 95% CI 0.9–7.3).[2,17–19] These occupations are exposed to solvents such as benzene, toluene, aliphatic and alicyclic hydrocarbon solvents and aromatic hydrocarbon solvents, and hence the resultant outcome may be due to the combined effect of these solvents at the workplace.[1,20]

A Finnish study observed increased risk estimates of all exposure categories studied in bladder cancer exposed to solvents such as aliphatic and alicyclic hydrocarbon solvents and aromatic hydrocarbon solvents.[21] This effect could be due to benzene exposure and their chemical nature of combination. Smoking was adjusted for, and the observed association was true only among women in the study. In our study, we did not observe any significant differences in the risk estimates between males and females for exposure to any of the solvents such as aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents and benzene.

Exposure to toluene usually occurs among those occupationally exposed to painting, varnishing, cleaning chemicals, laboratories, transportation, chemical dyes, pharmaceuticals, detergents and explosives.[22] In our study, we observed a significantly increased risk of bladder cancer for those exposed to toluene at a high exposure level, but no effect was observed at low and medium exposure levels. Epidemiological studies have observed that exposure to toluene in painters is associated with a positive risk of bladder cancer,[7,17] but according to the IARC, the total evidence of the carcinogenicity in humans is inadequate.[23] The concurrent exposures of toluene to other solvents make it difficult to disentangle their specific effect. We observed that the HR for benzene and toluene at a high exposure level was especially elevated for bladder cancer in the younger age category. Our finding is in line with a study from New Zealand that observed a 2.3-fold statistically significant risk of bladder cancer among painters aged 20–59 years as compared to a 1.3-fold excess in the older age groups.[7]

Earlier studies have suggested an association between exposures to other agents such as asbestos, diesel engine exhaust, sulfur dioxide and ionizing radiation and an increased risk of bladder cancer.[24–26] In our study, exposures to asbestos (low and high exposure level), diesel engine exhaust (low and medium exposure levels), sulfur dioxide (low and medium exposure levels) and ionizing radiation (high exposure level) were observed as significant increased risks of bladder cancer.

Only small proportions of the populations of Norway, Finland, Sweden and Iceland had considerable exposure to solvents. This limited our choice of cumulative exposure categorization in our study. Therefore, the threshold of the highest exposure level had to be set to a modest exposure level. Variation in exposure levels within occupational categories means the use of average exposure estimates for everyone in the occupational category, and that may under- or overestimate the true exposure for some individuals. Such misclassification dilutes the contrast between the categories in this study. Individual work histories were based on census records

Table 5. Hazard ratios (HR) and 95% confidence intervals (95% CI) of bladder cancer associated with exposure to solvents, by sex (ppm = parts per million)[1]

Agent[2] (unit) Category (unit-years)	Males					Females				
	Cases	Controls	HR	95% CI	*p* for trend	Cases	Controls	HR	95% CI	*p* for trend
Trichloroethylene (ppm)										
Unexposed	78,288	393,919	1.00	Reference	0.03	28,149	141,077	1.00	Reference	0.67
<32.80	3,090	14,391	1.06	1.01–1.12		343	1,493	1.01	0.83–1.23	
32.80–129.50	2,588	12,179	1.07	1.02–1.14		126	559	0.96	0.71–1.30	
>129.50	663	2,656	1.25	1.13–1.40		96	441	0.93	0.50–1.74	
Perchloroethylene (ppm)										
Unexposed	83,408	417,517	1.00	Reference	0.05	28,369	142,153	1.00	Reference	0.48
<13.60	639	3,099	1.00	0.90–1.09		108	461	1.13	0.90–1.50	
13.60–87.55	516	2,274	1.07	1.00–1.20		144	509	1.30	1.00–1.71	
>87.55	66	255	1.09	0.80–1.53		93	447	0.90	0.51–1.53	
Aliphatic and alicyclic hydrocarbon solvents (ppm)										
Unexposed	77,843	392,332	1.00	Reference	0.62	28,289	141,778	1.00	Reference	0.27
<18.73	3,485	15,623	1.00	0.94–1.05		163	653	1.03	0.83–1.28	
18.73–337.40	2,589	12,024	1.08	1.00–1.17		247	1,051	0.90	0.70–1.20	
>337.40	712	3,166	1.13	1.00–1.29		15	88	0.70	0.40–1.30	
Aromatic hydrocarbon solvents (ppm)										
Unexposed	79,249	397,066	1.00	Reference	0.01	28,032	140,625	1.00	Reference	0.59
<11.15	2,598	13,021	1.00	0.93–1.03		356	1,569	1.00	0.80–1.30	
11.15–298.93	2,169	10,295	1.07	1.00–1.15		300	1,270	1.03	0.80–1.31	
>298.93	613	2,763	1.10	0.93–1.30		26	106	1.20	0.64–2.24	
Benzene (ppm)										
Unexposed	77,200	389,265	1.00	Reference	0.02	28,163	141,213	1.00	Reference	0.19
<5.68	3,488	16,210	1.00	0.90–1.05		465	1,957	1.21	0.95–1.55	
5.68–15.04	3,094	14,178	1.03	0.94–1.13		78	332	1.14	0.80–1.70	
>15.04	847	3,492	1.15	1.02–1.29		8	68	0.55	0.24–1.30	
Toluene (ppm)										
Unexposed	76,767	387,370	1.00	Reference	0.71	28,372	142,074	1.00	Reference	0.96
<57.25	3,880	17,474	1.02	0.94–1.11		260	1,133	0.91	0.70–1.20	
57.25–707.50	3,162	14,644	1.03	0.95–1.12		68	308	0.80	0.53–1.15	
>707.50	820	3,657	1.23	1.04–1.46		14	55	0.83	0.34–2.00	
1,1,1-Trichloroethane (ppm)										
Unexposed	77,107	388,347	1.00	Reference	0.60	28,362	142,096	1.00	Reference	0.98
<5.60	5,711	26,544	1.00	0.92–1.01		300	1,263	1.04	0.85–1.30	
5.60–10.15	1,120	5,078	1.00	0.91–1.07		40	153	1.15	0.80–1.70	
>10.15	691	3,176	1.00	0.90–1.07		12	58	1.11	0.58–2.20	
Chlorinated hydrocarbon solvents (ppm)										
Unexposed	82,184	411,328	1.00	Reference	0.12	28,316	141,907	1.00	Reference	0.30
<27.58	1,160	5,718	1.00	0.90–1.08		256	1,028	1.00	0.80–1.24	
27.58–52.38	1,080	5,249	0.90	0.80–1.04		39	162	0.90	0.60–1.44	
>52.38	205	850	1.00	0.81–1.21		103	473	1.02	0.50–2.08	
Other organic solvents (ppm)										
Unexposed	81,842	409,740	1.00	Reference	0.86	28,478	142,673	1.00	Reference	0.73
<105.55	1,356	6,455	1.00	0.93–1.07		173	682	1.30	1.05–1.50	
105.55–378.10	1,129	5,597	0.90	0.80–1.01		51	158	1.72	1.14–2.60	
>378.10	302	1,353	0.84	0.70–1.03		12	57	1.23	0.50–3.14	

[1]HR estimates for aliphatic and alicyclic hydrocarbon solvents are from Model 2 and all the other HR are from Model 1. In Model 1, we included benzene and toluene but excluded aliphatic and alicyclic hydrocarbon solvents and in Model 2, we included aliphatic and alicyclic hydrocarbon solvents but excluded benzene and toluene. All other solvents were included in both multivariate models.
[2]Occupationally unexposed individuals were used as a reference group in all analysis.

at one to four census dates. Hence, if persons changed occupation before, between or after the known census years, it may have caused further misclassification of the exposure estimate and biased the observed effect toward null.[27,28] We assumed no solvent exposure before 1945. In our study, 68.8% of both cases and controls were born before 1925 and hence had part of their estimated work career before 1945. According to a recent study on bladder cancer in Finland,[29] the proportion of localized-stage bladder cancers is higher in certain occupations that appear to be related to higher diagnostic activity. Such occupations in our study are typically in the non-exposed group, and therefore the possible surveillance bias would increase the bladder cancer incidence in the reference category, consequently decreasing the HR estimates in the exposed groups.

The confirmed association between smoking and bladder cancer makes it important to estimate the role of smoking as a potential confounder. We did not have direct information about smoking of the individuals of the NOCCA cohort, but the aggregate level information can be estimated, e.g., on the basis of lung cancer risk in each of the occupations.[8] If the risk of lung cancer in a given occupation is elevated and there are no other work-related exposures than smoking, then the risk of bladder cancer should also be elevated due to smoking, but not as much as for lung cancer (because the RR due to smoking is lower for bladder cancer than for lung cancer). The RRs for bladder cancer clearly differ from this pattern.[30] Those occupational groups at the highest risk of bladder cancer were also commonly identified as having an elevated risk of lung cancer, which lends support to the hypothesis that at least some occupational variation in bladder cancer risk can be explained by occupational differences in smoking. In earlier studies in populations with smoking patterns similar to the Nordic countries, the risk estimates for bladder cancer did not significantly change when adjusted with smoking.[11,12,20,21,31] Though smoking is a well-established risk factor for bladder cancer, occupational differences in bladder cancer risk do not appear to be solely due to smoking.[31]

This study is to our knowledge the largest study to explore the relationship between occupational solvents exposure and the risk of bladder cancer so far. The study covered the populations of four Nordic countries followed up for a long period of time. Due to the large number of cases and controls from different Nordic countries, this study presents a higher external validity. NOCCA-JEM has been used in the study, due to which we could generate quantitative exposure estimates for different solvents such as aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents, benzene, toluene, perchloroethylene, trichloroethylene and a number of potentially confounding exposures. In this study, we were able to control for exposure to multiple other agents and variation in exposure levels over time. In recent years, there have been changes in exposure levels with time in some of the occupations such as dry cleaning and the transportation industry. For example, the occupational safety limit for the use of tetrachloroethylene used in the dry cleaning industry was decreased in all Nordic countries after 1970.[13] Similarly, in the transportation industry, the qualities of fuel used in vehicles have been improved, showing a reduced risk of urinary bladder cancer among motor vehicle drivers.[32]

The study provides evidence of an association between occupational exposure to trichloroethylene, perchloroethylene, aliphatic and aromatic hydrocarbon solvents, benzene and toluene and bladder cancer risk. Among these solvents, only benzene and trichloroethylene are currently classified as Group 1 carcinogens. Future studies are required with high-quality quantitative exposure measurement to explore in more detail the association of agent-specific exposure and the risk of bladder cancer.

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