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ABSTRACT

Tumors of kidney and renal pelvis are an important component of the overall cancer burden. Knowledge of causes of kidney and renal pelvis cancer is an area of interest both within the field of urological oncology and epidemiology. Although extensive research has been carried out on the topic, no single study exists which deploys whole national populations. Research on the subject has been mostly restricted to limited study populations, and its generalizability is in many cases problematic.

The aim of this thesis was to identify associations between occupational exposures and risk of kidney and renal pelvis cancer.

To accomplish the specific objectives of the thesis, in total, five studies were conducted (Studies I-V). First, cohort study design was applied to describe the occupational variation in the incidence of kidney cancer (Study I) and renal pelvis cancer (Study II) in the population of the Nordic countries. Next, the independent role of factors other than smoking was estimated, by adjusting with proxy of smoking, for kidney cancer (Study III) and renal pelvis cancer (Study IV). In Study V, nested case-control study design was adopted, to assess associations between occupational exposure to heavy metals (chromium (VI), iron, nickel, lead) and welding fumes, and the risk of kidney and renal pelvis cancer, and to describe other occupational exposures possibly associated with the risk of kidney cancer.

This research was conducted based on the data of the Nordic Occupational Cancer Study (NOCCA) encompassing five Nordic countries, namely, Denmark, Iceland, Finland, Norway, and Sweden. Its population included 14.9 million individuals (7.4 million males, and 7.5 million females). Data on occupation (exposure) were leveraged from national population censuses handled in 1960-1990. In Studies I-IV, occupational categories were considered as exposures. In Study V, for the purpose of the detailed exposure estimation, NOCCA Job-Exposure Matrix was used. Cancer incidence in the study population was followed-up until emigration, death, or December 31st of the following year: 2003 in Denmark and Norway, 2004 in Iceland, 2005 in Finland and Sweden. Data on mortality and emigration were retrieved from the Central Population Registries in each country. Data on cancer cases were obtained from the Nordic cancer registries.

For none of the countries, information about smoking habits on an individual level was provided. Therefore, in Studies I, II and V, no stratification regarding smoking was applied. However, to examine smoking-adjusted occupational variation in the incidence of kidney cancer, smoking prevalence by occupation was approximated using a model derived with linear regression from the standardized incidence ratio (SIR) of lung cancer, and used in adjustment for smoking (Studies III and IV).

In Study I, 85,940 cases of kidney cancer were identified. In Study II, 11,237 cases of the renal pelvis cancers were included. In Studies III and IV, analyses were conducted for males only. Females were not included since in different occupational categories smoking patterns were changing in such an irregular manner that it is hard to estimate the sum effect of the smoking habits in a given population. In Study III, 50,330 cases of kidney cancer were identified. In Study IV, 6,732 cases of renal pelvis cancer were identified. In Study V, there were 59,778 kidney and renal pelvis cancer cases for which 298,890 sex-, age-, and country-matched controls were identified. Study V was based on data from three countries, namely, Iceland, Finland, and Sweden. Norway and Denmark were excluded because of lack of access to the individual level records.

In Study III, the highest smoking-adjusted standardized incidence ratios (SIR_{adj}) of kidney cancer were observed among dentists (SIR_{adj} 1.32, 95% confidence interval (CI) 1.06-1.62), journalists (SIR_{adj} 1.20, 95%CI 1.00-1.42), and physicians (SIR_{adj} 1.19, 95%CI 1.03-1.36). The lowest SIR_{adj} was observed among forestry workers (SIR_{adj} 0.82, 95%CI 0.76-0.88).

In Study IV, the highest SIR_{adj} were observed among physicians (SIR_{adj} 1.63, 95%CI 1.16-2.23), artistic workers (SIR_{adj} 1.43, 95%CI 1.03-1.94), and public safety workers (SIR_{adj} 1.38, 95%CI 1.14-1.65). The lowest SIR_{adj} were observed among forestry workers (SIR_{adj} 0.51, 95%CI 0.38-0.66), farmers (SIR_{adj} 0.76, 95%CI 0.69-0.83), and unskilled construction workers (SIR_{adj} 0.78, 95%CI 0.68-0.90).

In Study V, in the analysis of odds ratio (OR)for both sexes and all age groups combined, for none of the studied agents (heavy metals and welding fumes), the dose-response trend was statistically significant. In the analysis with stratification by age at the index date (date of diagnosis of the case), in the group of <59 years, OR for the high exposure to nickel was significant (OR 1.49, 95%CI 1.03-2.17). In the group of 59-74 years ORs for the following were statistically significant: high exposure to iron (OR 1.41, 95%CI 1.07-1.85), moderate exposure to welding fumes (OR 1.27, 95%CI 1.02-1.56), and high exposure to welding fumes (OR 1.43, 95%CI 1.09-1.89). In conclusion, the results of this investigation show that there is an association between occupation and the risk of cancers of kidney and renal pelvis. Diverse prevalence of smoking among different occupational categories plays an important role in occupational variation in the incidence of both kidney cancer and renal pelvis cancer. The studies identified that the smoking-adjusted incidence of kidney and renal pelvis cancers is considerably increased among occupations with higher education and in public safety workers. One of the characteristics in many of these occupations is low physical workload. In the nested case-control study, there was no association between exposure to chromium (VI) or lead and the risk of kidney or renal pelvis cancer.

This thesis is so far the most comprehensive research project in terms of a number of observed cancer cases dealing with the association between the occupation and incidence of kidney and renal pelvis cancer. Moreover, it is the first project that benefits from data covering the entire national populations, making the presented results population-representative and generalizable.

TIIVISTELMÄ

Munuaisen ja munuaisaltaan kasvaimet ovat merkittävä osa kaikista syövistä. Sekä urologisen onkologian että epidemiologian tieteenaloilla kiinnostaa tietämys munuaissyövän ja munuaisaltaan syövän syistä. Vaikka aihetta on jo tutkittu laajasti, mikään aiemmista tutkimuksista ei ole kattanut kokonaisia väestöjä. Aihepiirin tutkimukset ovat pääasiassa tehty suppeissa tutkimusväestöissä, joten tulosten yleistettävyys on usein ongelmallista.

Tämän väitöskirjan tavoitteena oli tunnistaa yhteyksiä työperäisten altisteiden ja munuaissyövän ja munuaisaltaan syövän riskin välillä. Tutkimuksen yksityiskohtaisiin tavoitteisiin vastaamiseksi tehtiin yhteensä viisi tutkimusta (Osatyöt I-V). Ensin tehtiin kohorttitutkimukset, joissa kuvailtiin munuaissyövän (Osatyö I) ja munaisaltaan syövän (Osatyö II) ilmaantuvuuden vaihtelua eri ammattiryhmien välillä Pohjoismaiden väestöissä. Seuraavaksi tulokset vakioitiin tupakointia arvioivalla muuttujalla ja siten tutkittiin muiden tekijöiden kuin tupakan itsenäistä yhteyttä munuaissyövän (Osatyö III) ja munuaisaltaan syövän (Osatyö IV) riskiin. Osatyössä V asetelmana oli upotettu tapaus-verrokki -tutkimus ja siinä arvoitiin ensisijaisesti työperäisen raskasmetalleille (kromi (VI), rauta, nikkeli ja lyijy), hitsauskaasuille altistumisen ja toissijaisesti muiden työperäisten altisteiden mahdollista yhteyttä munuaisen ja munuaisaltaan syöpien riskiin.

Tässä tutkimuksessa käytettiin Nordic Occupational Cancer Study (NOCCA) -aineistoa kaikista viidestä Pohjoismaasta. Tutkimusväestöön kuului 14,9 miljoonaa henkilöä (7,4 miljoonaa miestä ja 7,5 miljoonaa naista). Ammattia koskevat tiedot saatiin kansallisista, vuosina 1960-1990 tehdyistä väestölaskennoista. Osatöissä I-IV altistemuuttujana oli ammattinimike. Osatyössä V altistumista arvioitiin tarkemmin NOCCA työaltistusmatriisin avulla. Syövän ilmaantumista tutkimusväestössä seurattiin maastamuuttoon, kuolemaan tai seuraavien vuosien joulukuun 31. päivään saakka: Tanskassa 2003, Islannissa 2004 ja Suomessa ja Ruotsissa 2005. Tiedot kuolemista ja maasta muutosta saatiin kunkin maan väestörekisteristä ja tiedot syöpätapauksista kunkin maan syöpärekisteristä.

Mistään näistä maista ei ollut saatavilla yksilötason tietoa tupakointitottumuksista, mutta osatöitä III ja IV varten arvioitiin lineaarisella regressiomallilla tupakoinnin

yleisyyttä kussakin ammattiryhmässä NOCCA-aineiston keuhkosyövän vakioidun ilmaantuvuussuhteen (*standardized incidence ratio*, SIR) perusteella.

Osatyössä I oli mukana 85 940 munuaissyöpätapausta. Osatyössä II oli mukana 11 237 munaisaltaan syövän tapausta. Osatöissä III ja IV analyyseihin otettiin mukaan vain miehet. Naisia ei otettu mukaan, koska tupakointitottumukset muuttuivat eri ammattiryhmissä niin epäsäännöllisellä tavalla, että oli vaikeaa arvioida tupakointitapojen kokonaisvaikutusta tietyssä väestössä. Osatyön III aineistossa löydettiin 50 330 munuaissyöpätapausta. Osatyön IV aineistossa löydettiin 6732 munaisaltaan syövän tapausta. Osatyössä V oli mukana 59 778 munaissyövän ja munuaisaltaan syövän tapausta ja 298 890 heille valittua sukupuolen, iän ja maan mukaan kaltaistettua verrokkia. Osatyö V perustui kolmen maan – Islannin, Suomen ja Ruotsin – aineistoon. Norjaa ja Tanskaa ei otettu mukaan, koska yksilötason tietoja ei ollut saatavilla.

Osatyössä III havaittiin korkeimmat tupakointivakioidut munuaissyövän ilmaantuvuussuhteet (SIR_{vak}) hammaslääkäreillä (SIR_{vak} 1.32, 95 %:n luottamusväli *[confidence interval, 95%CI]* 1.06-1.62), toimittajilla (SIR_{vak} 1.20, 95%CI 1.00-1.42) ja lääkäreillä (SIR_{vak} 1.19, 95%CI 1.03-1.36). Matalin SIR_{vak} havaittiin metsureilla (SIR_{vak} 0.82, 95%CI 0.76-0.88).

Osatyössä IV havaittiin korkeimmat SIR_{vak} -luvut lääkäreillä (SIR_{vak} 1.63, 95%CI 1.16-2.23), taitelijoilla (SIR_{vak} 1.43, 95%CI 1.03-1.94) ja turvallisuusalan työntekijöillä (SIR_{vak} 1.38, 95%CI 1.14-1.65). Matalimmat SIR_{vak} luvut havaittiin metsureilla (SIR_{vak} 0.51, 95%CI 0.38-0.66), maanviljelijöillä (SIR_{vak} 0.76, 95%CI 0.69-0.83) ja kouluttamattomilla rakennusalan työntekijöillä (SIR_{vak} 0.78, 95%CI 0.68-0.90).

Osatyössä V millään tutkituista tekijöistä (raskasmetallit ja hitsauskaasut) ei ollut tilastollisesti merkitsevää annos-vastesuhdetta, kun analysoitiin molemmat sukupuolet ja kaikki ikäryhmät yhdessä. Kun analyysi ositettiin diagnoosi-iällä, alle 59-vuotiaiden ryhmässä havaittiin tilastollisesti merkitsevä riski (*odds ratio*, OR) suurelle nikkelialtistukselle (OR 1.49, 95%CI 1.03-2.17). Lisäksi 59-74-vuotiaiden ryhmässä havaittiin tilastollisesti merkitsevä OR suurelle altistukselle raudalle (OR 1.41, 95%CI 1.07-1.85), kohtalaiselle altistukselle hitsauskaasuille (OR 1.27, 95%CI 1.02-1.56) ja suurelle altistukselle hitsauskaasuille (OR 1.43, 95%CI 1.09-1.89).

Yhteenvetona voidaan todeta, että tämän tutkimuksen tulosten mukaan ammatti on yhteydessä munuaissyövän ja munuaisaltaan syövän riskiin. Tupakoimisen yleisyys vaihtelee suuresti ammattiryhmien välillä, mikä selittää paljon ammattiryhmittäistä vaihtelua sekä munuaissyövän että munuaisen altaan syövän ilmaantuvuudessa. Tupakoinnilla vakioitu munuaissyövän ja munuaisen syövän ilmaantuvuus on merkittävästi suurentunut monissa korkean koulutuksen vaativissa ammateissa ja turvallisuusalan työntekijöillä, joiden yhteinen piirre on työn alhainen fyysinen rasittavuus. Raskasmetalleille ja hitsauskaasuille altistumisen ja munaissyövän tai munuaisaltaan syövän välillä ei havaittu mainittavaa yhteyttä.

Tämä väitöskirja on toistaiseksi eniten syöpätapauksia sisältävä tutkimusprojekti ammatin yhteydestä munuaissyövän ja munuaisenaltaan syövän ilmaantuvuuteen. Lisäksi se on ensimmäinen projekti, joka hyödyntää kokonaisia väestöjä kattavaa aineistoa, joten tulokset edustavat koko väestöä ja ovat yleistettäviä.

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ABBREVIATIONS

ASR	age-standardized rate
BMI	body mass index
CI	confidence interval
DALYs	disability-adjusted life years
ccRCC	clear cell renal cell carcinomas
ESRD	end-stage renal disease
FINJEM	Finnish Information System on Occupational Exposures
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases for Oncology
ISCO	International Standard Classification of Occupations
NOCCA	Nordic Occupational Cancer Study
NOCCA-JEM	NOCCA Job-Exposure Matrix
OR	odds ratio
pRCC	papillary renal cell carcinoma
RR	risk ratio
RCC	renal cell carcinoma
SD	standard deviation
SIR	standardized incidence ratio
SMOR	standardized morbidity odds ratio
SMR	standardized mortality ratio
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
UV	ultraviolet radiation
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

I. Michalek, I.M., Martinsen, J.I., Weiderpass, E., Kjaerheim, K., Lynge, E., Sparen, P., Tryggvadottir, L., Pukkala, E. (2019). Occupation and risk of kidney cancer in Nordic countries. *Journal of Occupational and Environmental Medicine,* 61(1):41-46.

II. Michalek, I.M., Martinsen, J.I., Weiderpass, E., Kjaerheim, K., Lynge, E., Sparen, P., Tryggvadottir, L., Pukkala, E. (2019). Occupation and risk of cancer of the renal pelvis in Nordic countries. *BJU International*, 123(2):233-238.

III. Michalek, I.M., Kinnunen, T. I., Kjaerheim, K., Lynge, E., Martinsen, J.I., Sparen, P., Tryggvadottir, L., Weiderpass, L., Pukkala, E. Smoking-adjusted risk of kidney cancer and occupation - cohort study of Nordic males [submitted]

IV. Michalek, I.M., Kjaerheim, K., Martinsen, J.I., Sparen, P., Tryggvadottir, L., Weiderpass, L., Pukkala, E., Lynge, E. (2019). Smoking-adjusted risk of renal pelvis cancer and occupation - cohort study of Nordic males. *Acta Oncologica*, 20:1-4.

V. Michalek, I.M., Martinsen, J.I., Weiderpass, E., Hansen. J., Sparen, P., Tryggvadottir, L., Pukkala, E. (2019). Heavy metals, welding fumes, and other occupational exposures, and the risk of kidney cancer: A population-based nested case-control study in three Nordic countries. *Environmental Research*, 173:117-123.

The above-listed publications are referred to in the text by their Roman numerals.

1 INTRODUCTION

High-risk occupational categories like chimney sweeps formed practically the only known risk factors for human cancer until the discovery of cancer-causing effects of tobacco smoking in the 1950s (Siemiatycki, 2014; Thun, 2010). Since then, due to the evolution of contemporary epidemiological and toxicological methods, and due to systematic and extensive efforts, many more cancer risk factors were identified, in both occupational and non-occupational settings (IARC, 2014).

Countries that are currently regarded as high-resource settings were the epicenter of the heyday of dirty industrial workplaces in the first half of the 20th century. However, during the last 70 years, due to social, economic, and technological transformations, both the number of blue-collar workers and concentration levels of pollutants in regular workplaces decreased (Hashino et al., 2016). Notwithstanding, occupational carcinogens still constitute an important portion of all known human carcinogens.

Currently, a similar pattern of industrial development is observed in low-resource settings. Unfortunately, in countries where industrial pursuits undergo accelerated growth, the absence of essential occupational hygiene control measures is common (Siemiatycki, 2014). Moreover, in those countries, there is no infrastructure to investigate risks potentially associated with work in such conditions. Further lack of comprehensive regulations may cause a notable increase in occupational cancer in those countries.

To be able to conclude as to whether a substance causes cancer in human beings, one needs to perform observations in human populations. Since one cannot ethically or practically randomize people to exposure to a suspected carcinogen, one is dependent on non-randomized observations, such as those made in case-control and cohort studies. Such non-randomized experiments can take advantage of groups of people who have been exposed for non-research purposes, such as occupational cohorts in specific industries.

Finding of occupational carcinogenic agents provides not only an instant tool for preventing occupational cancer. Its potential profit goes beyond the occupational health as most agents are observed also in the non-occupational environment and consumer goods, oftentimes at concentrations as high as those found in the workplace. Moreover, investigation of occupational agents can contribute valuable data for evaluating hazards incurred at levels found in the general environment.

Currently, the known risk factors for kidney cancer include tobacco smoking, obesity, family or individual history of kidney cancer, history of von Hippel-Lindau disease, and chronic dialysis (Moch et al., 2016). Moreover, according to the International Agency for Research on Cancer (IARC), exposure to trichloroethylene, cadmium, and arsenic are carcinogenic to the human kidney (IARC, 2019b). Recognized risk factors for renal pelvis cancer include aristolochic acid, phenacetin, and tobacco smoking (IARC, 2019b). As there are no clinically useful biomarkers of kidney cancer, the importance of its prevention is even greater. There remains a need for comprehensive research on the association between occupational exposures and risk of kidney and renal pelvis cancer.

2 REVIEW OF LITERATURE

2.1 Classification of kidney and renal pelvis cancer

For the last four decades, new cases of cancers were coded deploying the International Classification of Diseases (ICD) published and regularly updated by the World Health Organization (WHO) (WHO, 2019). Currently, the ICD for Oncology (ICD-O) is becoming more and more common, generally accepted classification of tumors (IARC, 2019a). The classification provides a uniform nomenclature of human cancers, that is used worldwide by pathologists and oncologists. Within this classification, there are two modes of coding - by topography (primary anatomical site of cancer) or by morphology (histological type of cancer).

2.1.1 Topographical classification

The current topographical cancer coding system is described in Chapter II of the 10^{th} revision of the ICD (version from 2016) (WHO, 2016). The code C64 denotes the malignant neoplasm of kidney, except renal pelvis. The code C65 indicates the malignant neoplasm of the renal pelvis. Both renal calyces and pelviureteric junction are covered by code C65. The codes corresponding to the C64 and C65 in previous ICD classifications are presented in Table 1.

Table 1. Coding systems of malignant neoplasm of kidney except renal pelvis, and malignant neoplasm of the renal pelvis, according to International Classification of Diseases (ICD) revisions (WHO, 2016).

ICD revision	Code	Definition
ICD-7	180.0	malignant neoplasm of kidney, except pelvis
	180.1	malignant neoplasm of renal pelvis
ICD-8	189.0	malignant neoplasm of kidney, except pelvis
	189.1	malignant neoplasm of renal pelvis
ICD-9	189.0	malignant neoplasm of kidney, except pelvis
	189.1	malignant neoplasm of renal pelvis
ICD-10	C64	malignant neoplasm of kidney, except renal pelvis
	C65	malignant neoplasm of renal pelvis

2.1.2 Morphological classification

Identifying the subtype of tumor has real importance regarding prognosis and therapeutic approach. Over time, many histological subtypes of tumors have been distinguished. Currently, the morphological terminology used for coding cancer cases is based mainly on dominant histological characteristics of the tumors (e.g., clear cell or papillary), resemblance to embryological structures (e.g., metanephric), or anatomical location (e.g., collecting duct) (IARC, 2016).

The current 4th edition of *WHO Classification of Tumours of the Urinary System and Male Genital Organs* was published in 2016. The most recent update was caused by the emergence of new knowledge about the pathology, epidemiology, and genetics of these cancers (Humphrey et al., 2016). In this classification, neoplasms of the kidney are part of the *tumors of the kidney*, and neoplasms of the renal pelvis are part of the *tumors of the urothelial tract*.

2.1.2.1 Morphological classification of tumors of the kidney

Currently, eight major morphological types of kidney cancer are distinguished - renal cell tumors, metanephric tumors, nephroblastic and cystic tumors occurring mainly in children, mesenchymal tumors, mixed epithelial and stromal tumor family, neuroendocrine tumors, miscellaneous tumors, and metastatic tumors (IARC, 2016) (Table 2). Among adults, the most common subtypes of kidney malignancies are renal cell tumors, mesenchymal tumors occurring mainly in adults, and metastatic tumors.

Table 2. World Health Organization (WHO) classification of tumors of the kidney. Adapted from the 4th edition of *WHO Classification of Tumours of the Urinary System and Male Genital Organs* (IARC, 2016).

WHO classification of tumors of the kidney	
Renal cell tumors	**Mesenchymal tumors occurring mainly in adults**
Clear cell renal cell carcinoma	Leiomysarcoma
Multilocular cystic renal neoplasm of low malignant potentialhe	Angiosarcoma
Papillary renal cell carcinoma	Rhabdomyosarcoma
Hereditary leiomyomatosis and renal cell carcinoma – associated renal cell carcinoma	Osteosarcoma
Chromophobe renal cell carcinoma	Synovial sarcoma
Collecting duct carcinoma	Ewing sarcoma
Renal medullary carcinoma	Angiomyolipoma
MiT family translocation renal cell carcinomas	Epithelioid angiomyolipoma
Succinate dehydrogenase-deficient renal carcinoma	Leiomyoma
Mucinous tubular and spindle cell carcinoma	Haemangioma
Tubulocystic renal cell carcinoma	Lymphangioma
Acquired cystic disease-associated renal cell carcinoma	Haemangioblastoma
Clear cell papillary renal cell carcinoma	Juxtaglomerular cell tumor
Renal cell carcinoma, unclassified	Renomedullary interstitial cell tumor
Papillary adenoma	Schwannoma
Oncocytoma	Solitary fibrous tumor
Metanephric tumors	**Mixed epithelial and stromal tumor family**
Metanephric adenoma	Cystic nephroma
Metanephric adenofibroma	Mixed epithelial and stromal tumor
Metanephric stromal tumors	
	Neuroendocrine tumors
Nephroblastic and cystic tumors occurring mainly in children	Well-differentiated neuroendocrine tumor
Nephrogenic rests	Large cell neuroendocrine carcinoma
Nephroblastoma	Small cell neuroendocrine carcinoma
Cystic partially differentiated nephroblastoma	Phaeochromocytoma
Pediatric cystic nephroma	
	Miscellaneous tumors
Mesenchymal tumor	Renal haemotopoeiteic neoplasms
	Germ cell tumors
Mesenchymal tumors occurring mainly in children	
Clear cell sarcoma	**Metastatic tumors**
Rhabdoid tumor	
Congenital mesoblastic nephroma	
Ossifying renal tumor of infancy	

Renal cell tumors

According to the European Association of Urology, renal cell carcinoma (RCC) makes up to 90% of all kidney tumors (EAU, 2019). The most prevalent renal cell tumors are clear cell renal cell carcinoma (ccRCC) and papillary renal cell carcinoma (pRCC).

According to IARC, ccRCC is the most common kidney tumor (IARC, 2016). Accounting for 65-70% of all cases of this disease, ccRCC occurs mainly sporadically. However, some familial cancer syndromes are mentioned in the literature, e.g., von Hippel-Lindau syndrome and constitutional chromosome 3 translocations (IARC, 2016). Between 60% and 80% of ccRCCs are found incidentally. The most common symptoms are haematuria and flank pain. Metastases can occur in many organs, mainly in lungs, liver, and bones (IARC, 2016).

The second most common subtype of renal cell tumors is pRCC, making up to 19% of this group (IARC, 2016). For this cancer, no specific etiological factors are known. However, pRCC is diagnosed more often in individuals suffering from end-stage renal disease or acquired cystic kidney disease (IARC, 2016). The most common genetic syndromes connected with increased risk of pRCC are hereditary pRCC, hereditary leiomyomatosis and RCC, and familial papillary thyroid carcinoma. Half of the pRCC cases remain asymptomatic. Typical triad of symptoms (abdominal mass, flank pain, and haematuria) is rare, occurring in 5-10% of cases (IARC, 2016).

Around 5-9% of all renal cell tumors are oncocytomas (IARC, 2016). Most of them are asymptomatic and detected incidentally. Rarely, patients report haematuria, flank pain, or dysuria. Chromophobe RCCs constitute 5-7% of the group of all renal cell tumors (IARC, 2016). They are mostly sporadic. Patients do not present any unique symptoms and are usually diagnosed incidentally.

Mesenchymal tumors occurring mainly in adults

Angiomyolipoma is the most common type of mesenchymal tumors primarily occurring in adults, yielding up to 1% of all surgically removed kidney malignancies (IARC, 2016). It may develop sporadically as well as in connection with tuberous sclerosis. The etiology of this entity remains unclear. Usually, symptoms reported by patients with angiomyolipoma of sporadic origin include flank pain and hematuria. Patients diagnosed with tuberous sclerosis usually do not indicate any signs of a kidney tumor. Other subtypes of mesenchymal tumors occurring mainly in adults are very rare (IARC, 2016).

Metastatic tumors

Metastases in kidney rarely happen, making up about 11% of fine-needle aspirates interrogating renal masses (IARC, 2016). Here also typically presented symptoms are flank pain and hematuria. The most common primary tumors are lung, breast, gynecological tract, and head and neck tumors. Notwithstanding, most frequently, renal tumors found in patients suffering from other malignancies are not metastases, but synchronous primary tumors (IARC, 2016).

2.1.2.2 Morphological classification of tumors of the urothelial tract

Currently, ten major morphological groups of the tumors of the urothelial tract are distinguished: urothelial tumors, squamous cell neoplasms, glandular neoplasms, urachal carcinoma, tumors of Müllerian type, neuroendocrine tumors, melanocytic tumors, mesenchymal tumors, urothelial tract hematopoietic and lymphoid tumors, and miscellaneous tumors (Table 3). Urothelial tumors are the most common morphological subtype of cancer in this group (IARC, 2016).

Table 3. World Health Organization (WHO) classification of tumors of the urothelial tract. Adapted from the 4th edition of *WHO Classification of Tumours of the Urinary System and Male Genital Organs* (IARC, 2016).

WHO classification of tumors of the urothelial tract

Urothelial tumors

Infiltrating urothelial carcinoma
- Nested, including large nested
- Microcystic
- Micropapillary
- Lymphoepithelioma-like
- Plasmacytoid/ signet ring cell / diffuse
- Sarcomatoid
- Giant cell
- Poorly differentiated
- Lipid-rich
- Clear cell

Non-invasive urothelial neoplasms
- Urothelial carcinoma in situ
- Non-invasive papillary urothelial carcinoma, low-grade
- Non-invasive papillary urothelial carcinoma, high-grade
- Papillary urothelial neoplasm of low malignant potential
- Urothelial papilloma
- Inverted urothelial papilloma
- Urothelial proliferation of uncertain malignant potential
- Urothelial dysplasia

Squamous cell neoplasms
- Pure squamous cell carcinoma
- Verrucous carcinoma
- Squamous cell papilloma

Glandular neoplasms
- Adenocarcinoma, NOS
  - Enteric
  - Mucinous
  - Mixed
- Villous adenoma

Urachal carcinoma

Tumors of Müllerian type
- Clear cell carcinoma
- Endometrioid carcinoma

Neuroendocrine tumors
- Small cell neuroendocrine carcinoma
- Large cell neuroendocrine carcinoma
- Well-differentiated neuroendocrine tumor
- Paraganglioma

Melanocytic tumor
- Malignant melanoma
- Naevus
- Melanosis

Mesenchymal tumors
- Rhabdomyosarcoma
- Leiomyosarcoma
- Angiosarcoma
- Inflammatory myofibroblastic tumor
- Perivascular epithelioid cell tumor
  - Benign
  - Malignant
- Solitary fibrous tumor
- Leiomyoma
- Haemangioma
- Granular cell tumor
- Neurofibroma

Urothelial tract hematopoietic and lymphoid tumors

Miscellaneous tumors
- Carcinoma of Skene, Cowper, and Littre glands
- Metastatic tumors and tumors extending from other organs
- Epithelial tumors of the upper urinary tract
- Tumors arising in a bladder diverticulum
- Urothelial tumors of the urethra

Whereas more than 90% of urothelial tumors occur in the urinary bladder, 5-10% develop in the upper urinary tract, including the renal pelvis (IARC, 2016). The severity of symptoms reported by patients depends highly on the tumor stage. Most often signs include hematuria, urgency, nocturia, and dysuria. Women tend to present dysuria more often, which can result in misdiagnosis as urinary tract infection and delayed diagnosis of the tumor. The late stages of the disease may manifest as urinary obstructive symptoms, palpable mass in the abdomen, or edema of lower extremities. Metastases occur commonly, mainly in liver, lungs, and bones, and demonstrate with weight loss, and/or osseous pain (IARC, 2016).

2.2 Epidemiology of kidney cancer

2.2.1 Global statistics

According to IARC, in 2018, kidney cancer was the 10^{th} most common cancer in men and 14^{th} most common in women worldwide (IARC, 2018). The estimated age-standardized (World) incidence in 2018 ranged from 16.8 per 100,000 in Belarus to <0.50 per 100,000 in some countries of Sub-Saharan Africa (Figure 1). In the dominant majority of WHO Member States, in which kidney cancer incidence in both sexes is known, kidney cancer is much more common in men than in women (153 out of 177 Member States). In 2018, the highest estimated male:female ratio of kidney cancer incidence was 12.2 and was observed in Suriname (IARC, 2018).

According to IARC, in 2018, kidney cancer was the 13^{th} and 16^{th} most common cause of death from cancer worldwide, among men and women, respectively (IARC, 2018). The age-standardized (World) mortality rates ranged from 6.5 to 0.1 per 100,000 in Belarus and Equatorial Guinea, respectively (Figure 2). In the majority of WHO Member States, in which estimated mortality of kidney cancer was known, mortality among men was higher than among women (157 out of 169 Member States).

A note of caution is due here. Such global statistics may be somewhat limited by different access to healthcare and medical imaging modalities (possible underdiagnoses of cases) and a different level of accuracy of cancer registrations.

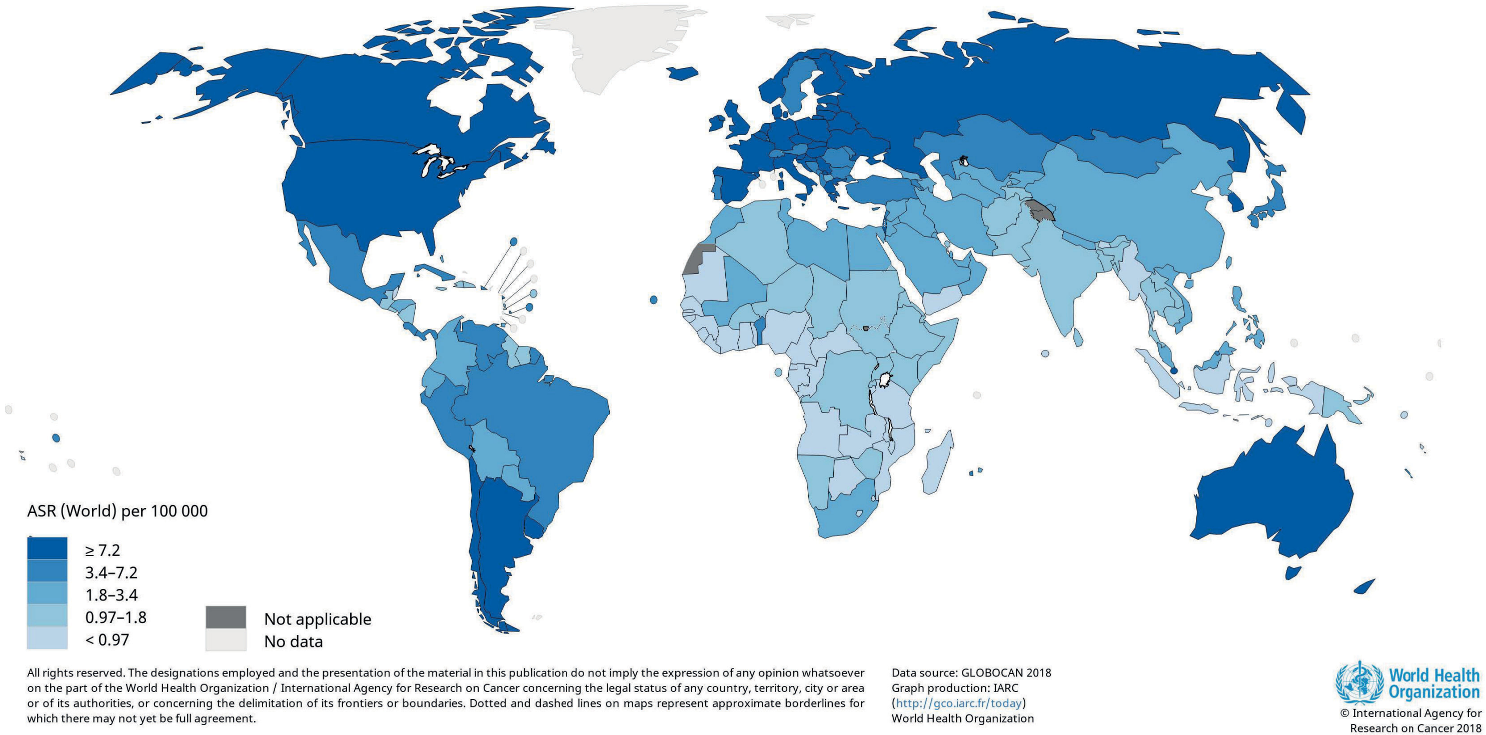


Figure 1. Estimated age-standardized incidence rates (ASR) in 2018, kidney cancer, both sexes, all ages. Source: (IARC, 2018).

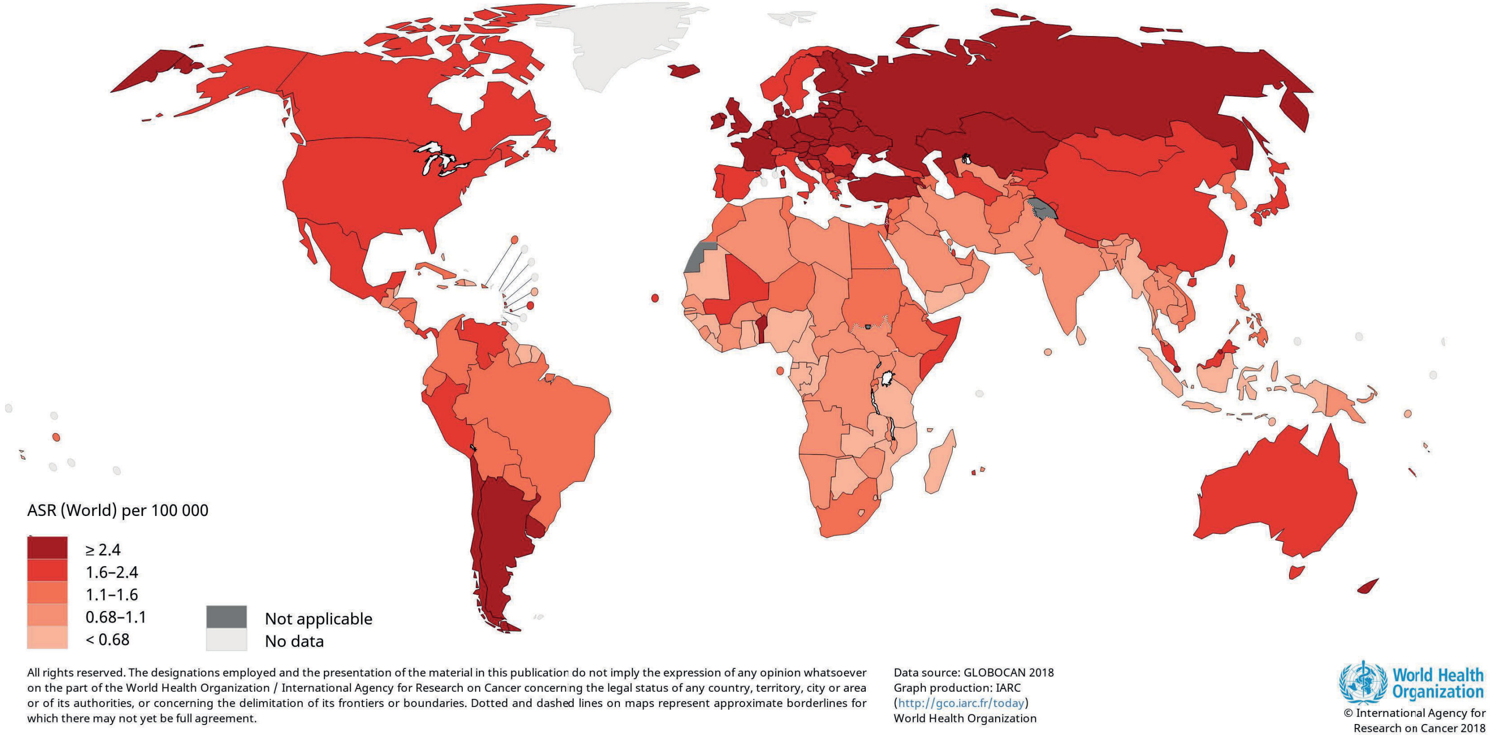


Figure 2. Estimated age-standardized mortality rates (ASR) in 2018, kidney cancer, both sexes, all ages. Source: (IARC, 2018).

2.2.2 Nordic statistics

More detailed data on the epidemiology of kidney cancer in Northern Europe are provided by the Association of the Nordic Cancer Registries in the NORDCAN database. The database encompasses regularly updated data from national cancer registries of the five Nordic countries (Finland, Sweden, Norway, Denmark, and Iceland).

According to NORDCAN, in 2012-2016, in the Nordic countries approximately 2,487 and 1,430 new cases of kidney cancer per year were diagnosed among males and females, respectively (Table 4) (Danckert et al., 2019). The cases constituted 2.4%-4.4% of all cancers among males and 1.6%-2.8% among females. The lowest age-standardized (World) incidence rates were observed in Sweden and amounted 8.4 and 4.6 per 100,000 in men and women, respectively. The highest age-standardized (World) incidence rates were found in Iceland and were 14.2 and 8.0 per 100,000 in males and females, respectively (Figures 3 and 4). The estimated annual change in the latest ten years ranged between -1.4% in Icelandic women to +2.9% in Norwegian men (Figures 5 and 6).

The estimated number of deaths per year due to kidney cancer in 2012-2016 in Nordic countries was 1,471 (Table 4) (Danckert et al., 2019). The highest age-standardized (World) mortality rates were observed among Icelandic men (4.7 per 100,000), and the lowest among Norwegian women (1.3 per 100,000). There was a downward trend of mortality in the latest ten years in all groups, except Icelandic men (Figures 7 and 8).

In 2012-2016, 1-year relative survival ranged from 90% in Swedish men to 78% in Icelandic men (Table 4). During the same period, 5-year relative survival varied from 74% in Swedish and Norwegian women to 63% in Icelandic men.

Table 4. Epidemiology of kidney cancer in Nordic countries in 2012-2016. Based on NORDCAN (Danckert et al., 2019).

	Nordic region		Finland		Sweden		Norway		Denmark		Iceland	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
Mean number of new cases per year	2,487	1,430	547	393	756	436	562	262	585	316	35	21
Proportion of all cancers (%)	2.9	1.8	3.3	2.5	2.4	1.6	3.3	1.8	2.8	1.6	4.4	2.8
Risk of getting the disease before age of 75 years (%)	1.3	0.6	1.2	0.7	1.0	0.5	1.6	0.7	1.4	0.7	1.8	0.9
Age-standardized incidence rate (World) per 100,000	10.5	5.4	10.6	6.1	8.4	4.6	13.3	5.8	11.7	5.6	14.2	8.0
Annual change in the last 10 years (%)	+2.4	+1.3	+2.0	+0.3	+2.0	+1.3	+2.9	+0.6	+2.9	+2.8	-0.1	-1.4
Mean number of deaths per year	896	575	209	156	315	212	168	90	189	107	14	8
Proportion of all cancer deaths (%)	2.7	2.0	3.2	2.7	2.7	1.4	2.9	1.8	2.3	1.4	4.4	2.7
Risk of dying from the disease before the age of 75 years (%)	0.3	0.2	0.4	0.2	0.3	0.1	0.4	0.1	0.4	0.2	0.5	0.2
Age-standardized mortality rate (World) per 100,000	3.1	1.5	3.5	1.7	2.7	1.4	3.4	1.3	3.3	1.4	4.7	2.1
Annual change in the last 10 years (%)	-1.5	-2.7	-0.2	-0.9	-2.5	-4.3	-2.0	-2.6	-0.7	-2.2	+0.5	-2.1
Relative 1-year survival (%)	.	.	79	82	90	89	85	86	83	84	78	84
Relative 5-year survival (%)	.	.	64	68	72	74	70	74	64	65	63	66

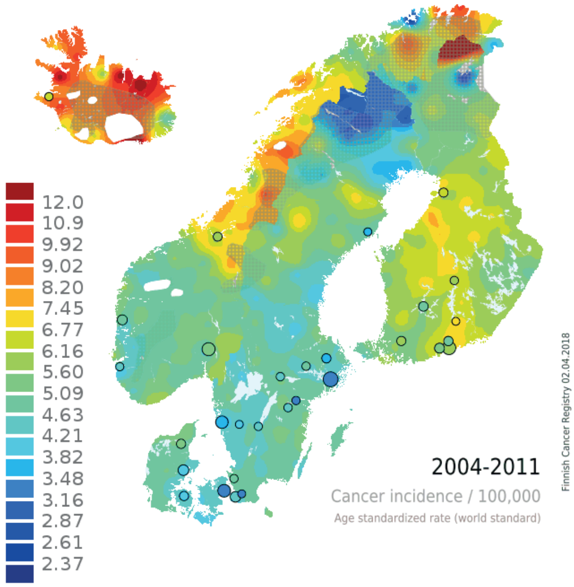


Figure 3. Map of kidney cancer incidence in Nordic females in 2004-2011 (Danckert et al., 2019).

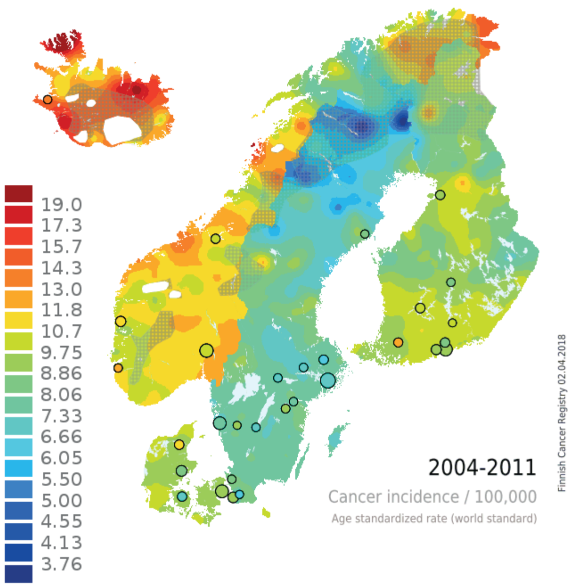


Figure 4. Map of kidney cancer incidence in Nordic males in 2004-2011 (Danckert et al., 2019).

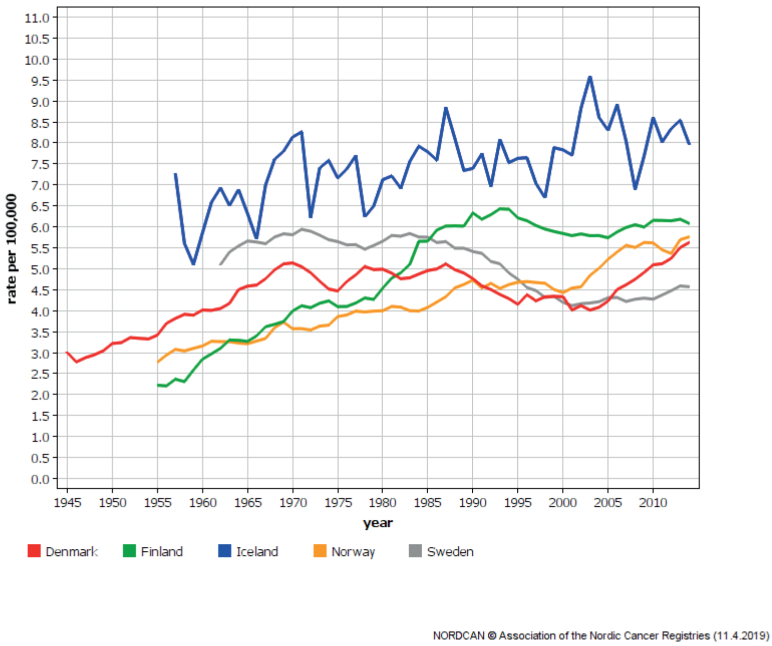


Figure 5. Age-standardized (World) incidence rates in 1945-2015, kidney cancer, females (Danckert et al., 2019).

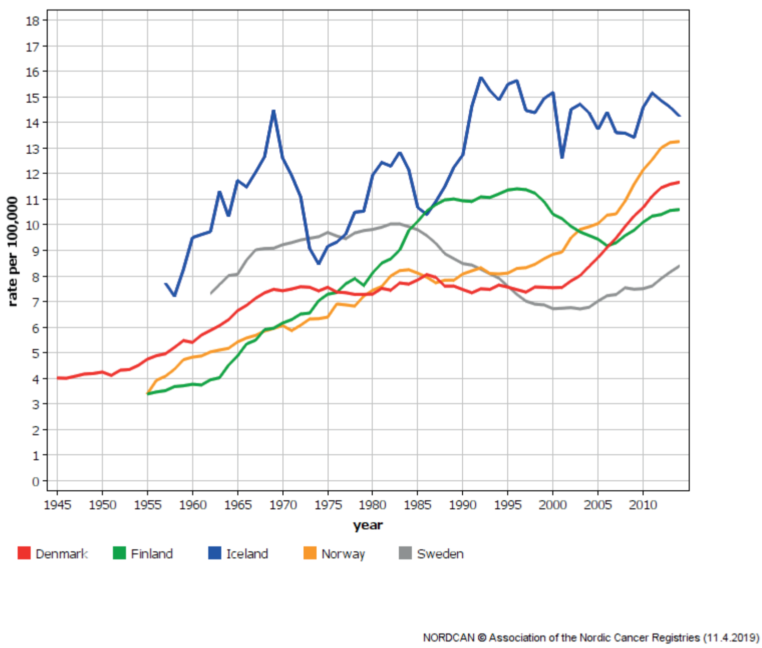


Figure 6. Age-standardized (World) incidence rates in 1945-2015, kidney cancer, males (Danckert et al., 2019).

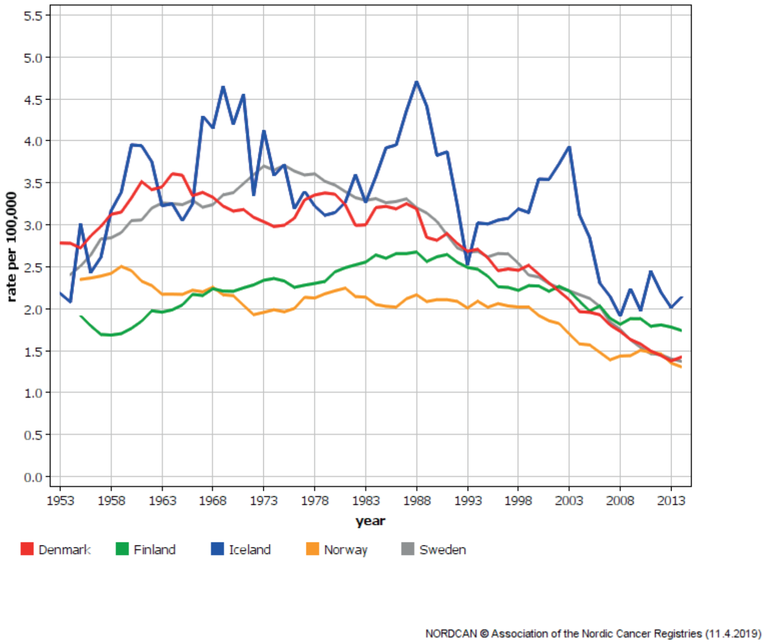


Figure 7. Age-standardized (World) mortality rates in 1945-2015, kidney cancer, females (Danckert et al., 2019).

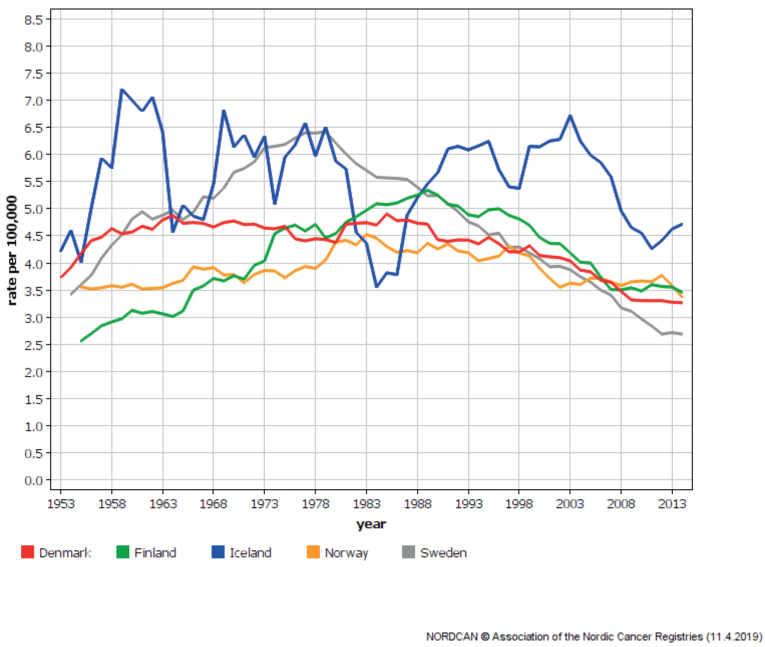


Figure 8. Age-standardized (World) mortality rates in 1945-2015, kidney cancer, males (Danckert et al., 2019).

2.2.3 Global burden of disease

The burden of disease is primarily measured with disability-adjusted life years (DALYs). DALYs denote years of life lost due to premature mortality and years of life lost due to time lived in states of less than full health.

According to the Institute for Health Metrics and Evaluation, in 2017, DALYs due to kidney cancer ranged between 0.02% (95% confidence interval (CI) 0.01%-0.03%) of total DALYs in the Central African Republic to 0.74% (95%CI 0.63%-0.87%) in Iceland (Figure 9) (IHME, 2017). The DALYs rate per 100,000 varied between 8.59 (95%CI 6.20-10.97) in Kenya to 220.75 (95%CI 185.91-241.00) in Czechia (Figure 10) (IHME, 2017).

2.3 Epidemiology of renal pelvis cancer

While the epidemiology of kidney cancer is reported comprehensively, little is known about the epidemiology of renal pelvis cancer. Usually, such tumors are reported together with bladder cancer or in the category of "other cancers" combined with other rare neoplasms. Heretofore, the distribution of the neoplasms within the urinary tract has not been comprehensively investigated.

Based on the data from the Finnish Cancer Registry, in 2015, renal pelvis cancer was the second most frequent cancer of the urinary tract among men, with age-standardized rates (ASR) (World) of 0.61 per 100,000. Also for women, the second highest ASR was observed for the renal pelvis cancer, which, in 2015, was 0.17 per 100,000. The male:female ratio was 2.3:1.0. In 2015, mortality due to renal pelvis cancers was about 0.10 per 100,000 and 0.06 per 100,000, among men and women, respectively.

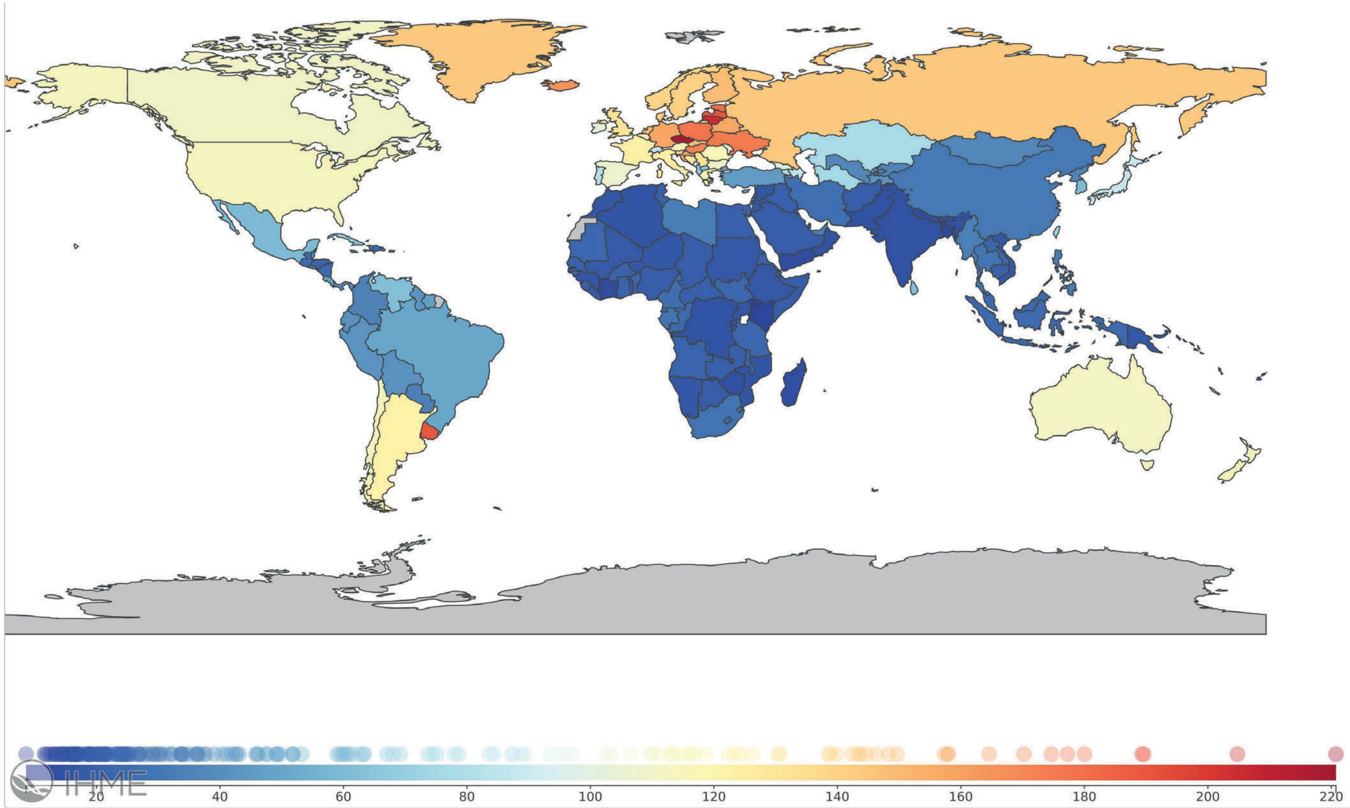


Figure 9. Disability-adjusted life years due to kidney cancer (per 100,000), both sexes, all ages, 2017 (IHME, 2017).

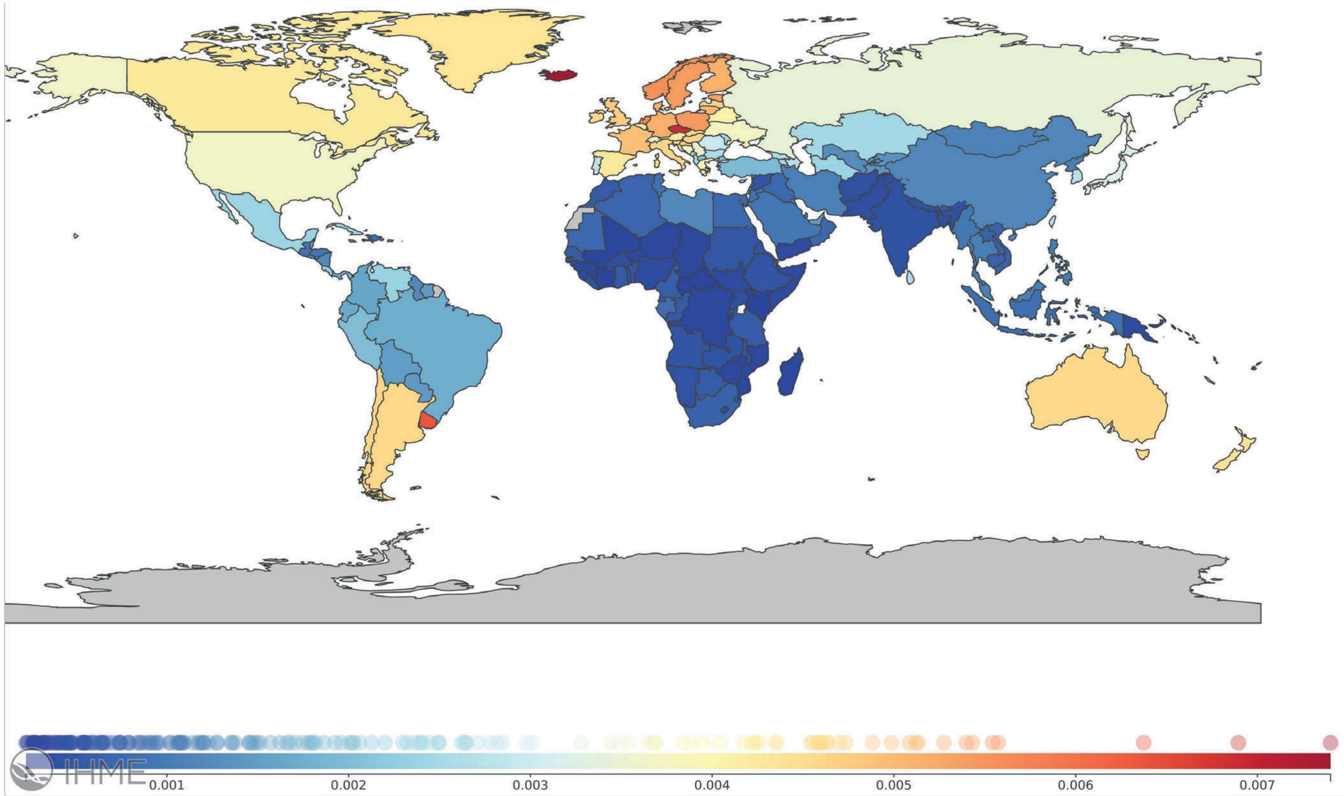


Figure 10. Disability-adjusted life years (DALYs) due to kidney cancer (percent of total DALYs), both sexes, all ages, 2017 (IHME, 2017).

2.4 Risk factors for kidney and renal pelvis cancer

For almost five decades IARC has been publishing *Monographs on the Identification of Carcinogenic Hazards to Humans*. These *Monographs* provide a sound systemized list of occupational carcinogens. The following three levels of evidence are distinguished: Group 1 - carcinogenic to humans; Group 2 - probably carcinogenic to humans; and Group 3 - not classifiable as to its carcinogenicity to humans (IARC, 2019b). The term "agent" denotes "any chemical, physical, or biological entity or exposure circumstance for which evidence on the carcinogenicity is evaluated". Apart from agents recognized in the IARC *Monographs* (Table 5), some other occupational exposures, obesity, hypertension, and end-stage renal disease can be associated with increased risk of developing kidney cancer (IARC, 2016). Moreover, 2-4% of renal cell tumors are hereditary, related to several genetic disorders (IARC, 2016). Other risk factors for renal pelvis cancer remain unclear.

Table 5. Agents classified by the International Agency for Research on Cancer in *Monographs on the Identification of Carcinogenic Hazards to Humans*, Volumes 1-123, by site (IARC, 2019b).

Cancer site	Carcinogenic agents with sufficient evidence in humans	Agents with limited evidence in humans
Kidney	– Tobacco smoking – Trichloroethylene – X-radiation, gamma-radiation	– Arsenic and inorganic arsenic compounds – Cadmium and cadmium compounds – Perfluorooctanoic acid – Printing processes – Welding fumes
Renal pelvis	– Aristolochic acid, plants containing – Phenacetin – Phenacetin, analgesic mixtures containing – Tobacco smoking	– Aristolochic acid

2.4.1 Tobacco smoking

Hunt et al., conducted a meta-analysis of 24 publications on the association between cigarette smoking and risk of RCC (Hunt et al., 2005). In the final analysis, 19 case-control studies (altogether 8,032 cases and 13,800 controls) and five cohort studies (total sample size of 1,457,754 individuals) were included. According to the authors of the meta-analysis, cigarette smoking was strongly associated with RCC. The pooled risk ratio (RR) of RCC for ever smokers, compared to non-smokers was 1.38 (95%CI 1.27-1.50). The RR was higher among males (RR 1.54, 95%CI 1.42-1.68) than females (RR 1.22, 95%CI 1.09-1.36). Furthermore, in both sexes, strong dose-dependency with number of cigarettes smoked was observed. Finally, smoke cessation resulted in a substantial reduction of the RR.

2.4.2 Obesity

Renehan et al. conducted a meta-analysis of prospective observational studies on the association of body mass index (BMI) and the incidence of different subtypes of cancer (Renehan et al. 2008). They analyzed 17 datasets concerning kidney cancer, which total sample size was 5,473,638 individuals. Elevated BMI was strongly linked with renal tumors in both sexes. The estimated pooled RR associated with every 5 kg/m^2 increase in BMI was 1.24 (95%CI 1.15-1.34, $p<0.0001$) and 1.34 (1.25-1.43, $p<0.0001$) in men and women, respectively. Another study by Renehan et al., based on observations from 30 European countries in 2002, reported that the population attributable risk for renal cancer, per every 5 kg/m^2 increase in BMI, was 11% (95%CI 6.5%-16%) in men and 17% (14%-20%) in women (Renehan et al., 2010).

2.4.3 Hypertension

Weikert et al. investigated the association between blood pressure and RCC, deploying a large European population of 296,638 individuals (Weikert et al., 2008). According to the authors, blood pressure was independently associated with the risk of RCC. The reported RR for the highest vs. the lowest blood pressure categories were 2.48 (95%CI 1.53-4.02) and 2.34 (1.54-3.55) for systolic and diastolic blood pressures, respectively. No significant difference regarding sex or antihypertensive medications use was observed. Moreover, individuals taking antihypertensive drugs, with well-controlled blood pressure had no increase of RR of RCC.

2.4.4 End-stage renal disease

Prevalence of renal adenoma and RCC in pre-transplant end-stage renal disease patients was investigated by Denton et al., who retrospectively reviewed 262 nephrectomy reports (Denton et al., 2002). RCC was found in 4.2% of cases. The authors reported higher prevalence of renal tumors in pre-transplant end-stage renal disease patients, than in previous studies, that were based on radiological diagnosis only.

2.4.5 Hereditary tumors

The authors of the *WHO Classification of Tumours of the Urinary System and Male Genital Organs* mention eight types of hereditary renal cell tumors (IARC, 2016). The most common, von Hippel-Lindau syndrome, is connected with multiple bilateral ccRCC. Other manifestations of the syndrome can be haemangioblastoma of the retina and central nervous system, phaeochromocytoma, pancreatic and renal cysts, and neuroendocrine tumors. Other hereditary renal cell tumors include hereditary papillary RCC, hereditary leiomyomatosis and RCC, familial papillary thyroid carcinoma, hyperparathyroidism-jaw tumor syndrome, Birt-Hogg-Dubé syndrome, tuberous sclerosis, and constitutional chromosome 3 translocations.

2.4.6 Occupational exposures

There are many publications on specific occupational agents that are possibly connected with an elevated or decreased risk of kidney cancer. In cases, in which the causative agent remains unclear, the risk among occupational categories is reported. Notwithstanding, occupation does not in itself confer a carcinogenic hazard, but the condition of work or some occupational exposures may confer a risk (IARC, 2014).

The following section of the thesis, describing occupational exposures possibly connected with the risk of kidney and renal pelvis cancer, is a summary of findings of a systematic review of the literature conducted by the author of the thesis. A detailed protocol of the systematic review can be found in PROSPERO repository (CRD42018106954) (Appendix 1). Summary of literature on occupational exposure by occupational agents is presented in Table 6.

2.4.6.1 Heavy metals

Arsenic and arsenic compounds

According to IARC, arsenic and inorganic arsenic compounds are carcinogenic to the human kidney (IARC, 2019b). However, it was underlined that although the data are suggestive of a relationship with exposure to arsenic in drinking-water, a chance of bias cannot be ruled out.

Regarding occupational exposures, Boffetta et al. examined the association between risk of RCC and occupational exposure to arsenic dust and fumes (Boffetta et al., 2011). The odds ratio (OR) of RCC for individuals ever exposed to arsenic, adjusted for sex, age, center, residence, tobacco smoking, BMI, and hypertension, was 0.96 (95%CI 0.45-2.04).

Cadmium and cadmium compounds

High exposure to cadmium is observed in zinc smelter, foundry-workers, welders or solders of cadmium plated materials, cadmium plant workers, and workers of other manufacturers of cadmium compounds. IARC classified exposure to cadmium and its compounds as carcinogenic to humans (IARC, 2019b).

According to Boffetta et al., who conducted a case-control study, the OR of RCC in individuals ever exposed to cadmium was 1.40 (95%CI 0.69-2.85) (Boffetta et al., 2011). However, according to the authors, there was no dose-risk relationship, and confounding due to lead exposure was possible. Pesch et al. (Pesch et al., 2000), who conducted a German, multicenter case-control study, found elevated OR both in men (OR 1.4, 95%CI 1.1-1.8) and in women (OR 2.5, 95%CI 1.2-5.3), who were at high occupational exposure to cadmium.

Chromium

Chromium (III) compounds are used in printing, tanning, for waterproofing, and as corrosion inhibitors. Chromium (VI) compounds have a variety of uses, including oil purification, pickling, leather tanning, photography, production of synthetic perfumes, lithography, process engraving, pyrotechnics, inhibition of corrosion, production of automobiles, and wood preservation.

While chromium (VI) compounds are classified as carcinogenic to humans by IARC (IARC, 2019b), chromium (III) compounds are not. According to Boffetta et al., the OR of RCC in the population ever exposed to chromium (III) and chromium (VI) was 1.21 (95%CI 0.61-2.41) and 0.95 (95%CI 0.50-1.81), respectively (Boffetta et al., 2011).

Lead

High exposure to lead is observed among jobs entailing processing lead, alloy, or brass foundries, secondary smelting, torch cutting of scrap metal or lead painted parts, welding of galvanized parts, hot tinning, ammunition manufacturing, indoor firing with unjacketed bullets, manufacturing of lead salts or alkyds, kiln work in pottery, work in ceramic or glass factories, spraying of high lead paints or pottery glazes, indoor hand scraping of lead paints, grinding or blasting of lead painted parts, manual typography, dry cleaning of lead-contaminated areas, sandblasting, and lead-acid battery production.

IARC does not recognize lead as the cause of kidney cancer. However, according to Boffetta et al., the OR of kidney cancer in the population ever exposed to lead was 1.55 (95%CI 1.09-2.21) (Boffetta et al., 2011). There was no clear trend in either the duration of exposure-outcome or cumulative exposure-outcome relation. Nevertheless, the OR in the group with the highest cumulative exposure was significantly elevated (OR 2.25, 95%CI 1.21-4.19).

Nickel and its compounds

Due to its qualities, nickel is mainly used in the production of stainless steel, nonferrous alloys, superalloys, electroplating, as a catalyst, in the manufacture of alkaline batteries, coins, welding products, pigments, and electronic products.

According to IARC, there is no association between exposure to nickel and its mixtures and developing kidney cancer (IARC, 2019b). Accordingly, Boffetta et al. reported the OR of RCC in the population ever occupationally exposed to nickel at 0.51 (95%CI 0.27-0.94) (Boffetta et al., 2011).

Iron and its compounds

Due to large exploitation of iron ores worldwide, iron is the most widely used of all metals in the metallurgical industry. It is also used in the production of ammonia, fuels, and lubricants. Moreover, its compounds are deployed in water purification, sewage treatment, textile industry, printing, and manufacture of paints. No literature was found on the question of exposures to iron and the risk of kidney cancer.

2.4.6.2 Petroleum derived liquids

IARC classified occupational exposure to petroleum refining as probably carcinogenic to humans (IARC, 2019b). However, petroleum solvents are labeled as unclassifiable as to its carcinogenicity to humans.

Siemiatycki et al. examined associations between several sites of cancers and twelve petroleum-derived liquids (Siemiatycki et al., 1987). They reported a significantly increased OR of kidney cancer among individuals exposed to aviation gasoline (OR 2.6, 90%CI 1.2-5.8), and jet fuel (OR 2.5, 90%CI 1.1-5.4). The occupations exposed to aviation gasoline and jet fuel were aircraft mechanics and repairmen. According to the authors, it was hard to distinguish the effects of aviation gasoline and jet fuel on kidney cancer, but they ascribed a more significant role to aviation gasoline. Another study, conducted on a cohort of Finnish oil refining workers, reported elevated OR of kidney cancer among individuals occupationally exposed to crude oil hydrocarbons (OR 3.12, 95%CI 1.09-8.90) (Anttila et al., 2015).

2.4.6.3 Diesel or gasoline engine exhaust

IARC classified gasoline, gasoline engine exhaust, and diesel marine fuel as possibly carcinogenic to humans (IARC, 2019b). Moreover, exposure to diesel engine exhaust was classified as carcinogenic to humans.

Lynge et al. examined a relationship between occupational exposure to gasoline vapors and the risk of developing cancer (Lynge et al., 1997). Among male workers, the reported standardized incidence ratio (SIR) was 1.3 (95%CI 1.0-1.7) and 2.0 (95%CI 1.0-3.7), for kidney cancer and renal pelvis cancer, respectively. Among female employees, only four cases of kidney cancer were reported, with SIR 1.2 (95%CI 0.3-3.0). A Finnish study (Lohi et al., 2008) found no significant RRs of renal cancer neither among males nor females exposed occupationally to gasoline.

In a large cohort study, Boffetta et al. examined the association between occupational exposure to diesel engine emissions and the risk of cancer in Swedish males and females (Boffetta et al., 2001). The reported SIRs of kidney cancer were 1.06 (95%CI 1.02-1.11) and 0.82 (0.57-1.16), among men and women, respectively.

Guo et al. examined the association between occupational exposure to diesel and gasoline engine exhaust and developing kidney cancer in Finland (Guo et al., 2004). Slightly elevated SIRs were observed among bus drivers (SIR 1.39, 95%CI 1.06-1.79) and among road-building machine operators (SIR 1.65, 95%CI 1.11-2.36). Decreased SIR was observed in mining and quarry workers (SIR 0.15, 95%CI 0.00-0.89).

2.4.6.4 Solvents

Lohi et al., who studied the association between occupational exposure to solvents and risk kidney cancer, found no significantly increased or decreased RRs among individuals exposed to chlorinated hydrocarbon solvents, aliphatic hydrocarbon solvents, aromatic hydrocarbon solvents, and other organic solvents (Lohi et al., 2008).

Pesch et al. (Pesch et al., 2000), found elevated OR of being exposed to benzene among both males and females diagnosed with kidney cancer. Moreover, the team identified elevated OR for males exposed to carbon tetrachloride, chlorinated solvents, polycyclic aromatic hydrocarbons, tetrachloroethylene, trichloroethylene, and other solvents.

Table 6. Summary of studies on occupational exposures and risk of kidney cancer; by occupational exposure agents.

Authors and year of the publication	Study design	Study population (size; sex)	Follow-up period	Cases of kidney cancer (n)	Type of measure of association	Measure of association (95%CI)
METALS AND FUMES						
Arsenic and arsenic compounds						
Boffetta et al. (2011)	Case-control	1,097 CA; M&F 1,476 CO; M&F	1999-2003	1,097	OR^{P}	0.96 (0.45-2.04)
Cadmium and cadmium compounds						
Boffetta et al. (2011)	Case-control	1,097 CA; M&F 1,476 CO; M&F	1999-2003	1,097	OR^{P}	1.40 (0.69-2.85)
Pesch et al. (2000)	Case-control	935 CA; M&F 4,298 CO; M&F	1991-1995	935	OR^{P}	M: 1.4 (1.1.-1.8)** F: 2.5 (1.2-5.3)**
Chromium (III) and its compounds						
Boffetta et al. (2011)	Case-control	1,097 CA; M&F 1,476 CO; M&F	1999-2003	1,097	OR^{P}	1.21 (0.61-2.41)
Chromium (VI) and its compounds						
Boffetta et al. (2011)	Case-control	1,097 CA; M&F 1,476 CO; M&F	1999-2003	1,097	OR^{P}	0.95 (0.50-1.81)
Lead and its compounds						
Boffetta et al. (2011)	Case-control	1,097 CA; M&F 1,476 CO; M&F	1999-2003	1,097	OR^{P}	1.55 (1.09-2.21)
Mattioli et al. (2002)	Case-control	249 CA; M&F 238 CO ;M&F	1987-1994	249	OR^{P}	0.13 (0.02-0.73)
Pesch et al. (2000)	Case-control	935 CA; M&F 4,298 CO; M&F	1991-1995	935	OR^{P}	M: 1.2 (1.0-1.6)** M: 1.5 (1.0-2.3)*** F: 2.6 (1.2-5.5)***

Authors and year of the publication	Study design	Study population (size; sex)	Follow-up period	Cases of kidney cancer (n)	Type of measure of association	Measure of association (95%CI)
Nickel and its compounds						
Boffetta et al. (2011)	Case-control	1,097 CA; M&F 1,476 CO; M&F	1999-2003	1,097	OR[P]	0.51 (0.27-0.94)
Solder fumes						
Pesch et al. (2000)	Case-control	935 CA; M&F 4,298 CO; M&F	1991-1995	935	OR[P]	M: 1.5 (1.0-2.4)[***] F: 1.9 (1.0-3.8)[**]
PETROLEUM-DERIVED LIQUIDS; GASOLINE VAPORS; ENGINE EXHAUST						
Automotive gasoline						
Guo et al. (2004)	Cohort	7,366; .	1971-1995	7,366	SIR[N]	0.85 (0.58–1.25) 1.13 (0.98–1.31) 1.08 (0.98–1.19)
Lynge et al. (1997)	Cohort	16,524; M	1971-1991	53	SIR[B]	1.3 (1.0-1.7)
				10	SIR[C]	2.0 (1.0-3.7)
		2,445; F	1971-1991	4	SIR[B]	1.2 (0.3-3.0)
Mellemgaard et al. (1994)	Case-control	368 CA; M&F 396 CO; M&F	1989-1992	368	OR[P]	M: 2.1 (1.1-4.1)
Partanen et al. (1991)	Case-control	408 CA; M&F 819 CO; M&F	1977-1978	408	OR[P]	1.72 (1.03-2.87)
Siemiatycki et al. (1987)	Case-control	181 CA; M 2,196 CO; M	1979-1985	181	OR[N]	1.2 (0.8-1.6)[#]
Aviation gasoline						
Parent et al. (2000)	Case-control	142 CA; M 2,433 CO; M	1979-1985	142	OR[P]	3.5 (1.4-8.6)[†]
Siemiatycki et al. (1987)	Case-control	181 CA; M 2,196 CO; M	1979-1985	181	OR[N]	2.6 (1.2-5.8)[#]

Authors and year of the publication	Study design	Study population (size; sex)	Follow-up period	Cases of kidney cancer (n)	Type of measure of association	Measure of association (95%CI)
Crude oil						
Siemiatycki et al. (1987)	Case-control	181 CA; M 2,196 CO; M	1979-1985	181	OR[N]	1.2 (0.2-6.3)[#]
Anttila et al. (2015)	Nested case-control	30 CA;. 81 CO;.	1971-1996	30	OR[J]	3.12 (1.09-8.90)
Cutting fluids						
Mellemgaard et al. (1994)	Case-control	368 CA; M&F 396 CO; M&F	1989-1992	368	OR[P]	M: 2.1 (1.0-4.3)
Pesch et al. (2000)	Case-control	935 CA; M&F 4,298 CO; M&F	1991-1995	935	OR[P]	M: 1.3 (1.0-1.8)* F: 1.9 (1.0-3.6)* F: 3.1 (1.1-8.2)***
Siemiatycki et al. (1987)	Case-control	181 CA; M 2,196 CO; M	1979-1985	181	OR[N]	1.0 (0.7-1.5)[#]
Diesel fuel/Diesel engine exhaust						
Boffetta et al. (2001)	Cohort	.	1971-1989	2,243; M 33;F	SIR[A] SIR[A]	1.06 (1.02-1.11) 0.82 (0.57-1.16)
Guo et al. (2004)	Cohort	7,366; .	1971-1995	7,366	SIR[N]	1.06 (0.82–1.36) 1.08 (0.92–1.26) 1.17 (1.05–1.30)
Siemiatycki et al. (1987)	Case-control	181 CA; M 2,196 CO; M	1979-1985	181	OR[N]	1.4 (0.8-2.3)[#]
Heating oil						
Siemiatycki et al. (1987)	Case-control	181 CA; M 2,196 CO; M	1979-1985	181	OR[N]	1.1 (0.6-2.1)[#]
Jet fuel						
Parent et al. (2000)	Case-control	142 CA; M 2,433 CO; M	1979-1985	142	OR[P]	3.5 (1.4-8.7)[†]

Authors and year of the publication	Study design	Study population (size; sex)	Follow-up period	Cases of kidney cancer (n)	Type of measure of association	Measure of association (95%CI)
Siemiatycki et al. (1987)	Case-control	181 CA; M 2,196 CO; M	1979-1985	181	OR[N]	2.5 (1.1-5.4)[#]
Kerosene						
Siemiatycki et al. (1987)	Case-control	181 CA; M 2,196 CO; M	1979-1985	181	OR[N]	1.3 (0.8-2.1)[#]
Mineral spirits						
Siemiatycki et al. (1987)	Case-control	181 CA; M 2,196 CO; M	1979-1985	181	OR[N]	1.1 (0.8-1.4)[#]
Hydraulic fluids						
Siemiatycki et al. (1987)	Case-control	181 CA; M 2,196 CO; M	1979-1985	181	OR[N]	1.1 (0.6-2.0)[#]
Lubricating oils						
Siemiatycki et al. (1987)	Case-control	181 CA; M 2,196 CO; M	1979-1985	181	OR[N]	1.2 (0.9-1.5)[#]
Other mineral oils						
Pesch et al. (2000)	Case-control	935 CA; M&F 4,298 CO; M&F	1991-1995	935	OR[P]	M: 1.3 (1.0-1.8)[*]
Siemiatycki et al. (1987)	Case-control	181 CA; M 2,196 CO; M	1979-1985	181	OR[N]	1.3 (0.7-2.2)[#]
SOLVENTS						
Benzene						
Anttila et al. (2015)	Nested case-control	30 CA;. 81 CO;.	1971-1996	30	OR[J]	2.11 (0.87–5.13)
Pesch et al.(2000)	Case-control	935 CA; M&F 4,298 CO; M&F	1991-1995	935	OR[P]	M: 1.2 (1.0-1.5)[*] F: 1.4 (1.0-1.9)[*] M: 1.2 (1.0-1.6)[**] F: 1.3 (1.0-1.8)[**]

Authors and year of the publication	Study design	Study population (size; sex)	Follow-up period	Cases of kidney cancer (n)	Type of measure of association	Measure of association (95%CI)
Carbon tetrachloride						
Pesch et al. (2000)	Case-control	935 CA; M&F 4,298 CO; M&F	1991-1995	935	OR^{P}	M: 1.2 (1.0-1.6)**
Chlorinated solvents						
Pesch et al. (2000)	Case-control	935 CA; M&F 4,298 CO; M&F	1991-1995	935	OR^{P}	M: 1.4 (1.1-1.9)*
Other organic solvents						
Pesch et al. (2000)	Case-control	935 CA; M&F 4,298 CO; M&F	1991-1995	935	OR^{P}	M: 1.6 (1.1-2.3)***
Other solvents						
Mellemgaard et al. (1994)	Case-control	368 CA; M&F 396 CO; M&F	1989-1992	368	OR^{P}	F: 6.4 (1.8-23)
Pesch et al. (2000)	Case-control	935 CA; M&F 4,298 CO; M&F	1991-1995	935	OR^{P}	M: 1.3 (1.0-1.7)* M: 1.5 (1.0-2.3)*** F: 2.1 (1.0-4.4)***
Polycyclic aromatic hydrocarbons						
Pesch et al. (2000)	Case-control	935 CA; M&F 4,298 CO; M&F	1991-1995	935	OR^{P}	M: 1.3 (1.0-1.6)**
Tetrachloroethylene						
Pesch et al. (2000)	Case-control	935 CA; M&F 4,298 CO; M&F	1991-1995	935	OR^{P}	M: 1.4 (1.1-1.7)*
Trichloroethylene						
Pesch et al. (2000)	Case-control	935 CA; M&F 4,298 CO; M&F	1991-1995	935	OR^{P}	M: 1.3 (1.0-1.8)*

Authors and year of the publication	Study design	Study population (size; sex)	Follow-up period	Cases of kidney cancer (n)	Type of measure of association	Measure of association (95%CI)
OTHER AGENTS						
Asbestos						
Anttila et al. (2015)	Nested case-control	30 CA;. 81 CO;.	1971-1996	30	OR[J]	0.97 (0.59-1.58)
Mattioli et al. (2002)	Case-control	249 CA; M&F 238 CO ;M&F	1987-1994	249	OR[P]	7.11 (1.46-34.51)
McCredie et al. (1993)	Case-control	636 CA; M&F 523 CO; M&F	1989-1990	636	RR[H]	1.62 (1.04-2.53)
Pesch et al. (2000)	Case-control	935 CA; M&F 4,298 CO; M&F	1991-1995	935	OR[P]	M: 1.3 (1.0-1.7)**
Felt dust						
Parent et al. (2000)	Case-control	142 CA; M 2,433 CO; M	1979-1985	142	OR[P]	3.6 (1.0-13.0)†
Inks / Paints and pigments						
Parent et al. (2000)	Case-control	142 CA; M 2,433 CO; M	1979-1985	142	OR[P]	2.5 (1.0-6.2)***
Pesch et al. (2000)	Case-control	935 CA; M&F 4,298 CO; M&F	1991-1995	935	OR[P]	M: 1.6 (1.1-2.5)***
Ozone						
Parent et al. (2000)	Case-control	142 CA; M 2,433 CO; M	1979-1985	142	OR[P]	1.8 (1.0-3.2)†

- M-males; F-females. CA-cases; CO-controls.
- OR-odds ratio; RR-relative risk; SIR-standardized incidence ratio.
- A-ICD-7 180; B-ICD-7 180.0; C-ICD-7 180.1; J-ICD-10 C64; H-ICD-9 189.0; N-unspecified kidney cancer; P-renal cell carcinoma.
- *-medium exposure, ** high exposure, *** - substantial exposure, † - any exposure
- #-90%CI

2.4.6.5 Specific occupations

In this section, the literature on the risk of kidney cancer in particular occupational categories has been arranged according to the International Standard Classification of Occupations (ISCO). ISCO was developed by the International Labour Organization and is a tool for organizing jobs into a defined set of groups according to the tasks and duties undertaken in the position (ILO, 2012).

Summary of literature on occupational exposure, by occupational categories, is presented in Table 7.

Metal processing and finishing plant operators (ISCO unit groups 8121- 8122)

The biggest number of studies presenting statistically significant findings on the association between occupation and the risk of kidney cancer concerned metal processing and finishing plant operators.

Ferrochromium, ferrosilicon, and silicon plant workers. Hobbesland et al. conducted a study on Norwegian employees of ferrosilicon and silicon metal plants (Hobbesland et al., 1999). The reported SIRs were 1.33 (95%CI 0.66-2.38) and 1.67 (1.03-2.55) in furnace workers and non-furnace workers, respectively. In a detailed analysis of the non-furnace workers, significantly elevated risk of kidney cancer was found only among mechanics (SIR 2.92, 95%CI 1.33-5.54). However, in a further analysis, no association between risk of kidney cancer and duration of work was found. Huvinen et al., who investigated a cohort of Finnish ferrochromium and stainless steel production workers, reported contradictory results (Huvinen et al., 2013). Risk of kidney cancer in this population was significantly decreased (SIR 0.38, 95% 0.14-0.82).

Aluminum plant workers. According to Romundstad et al., SIR of kidney cancer in a population of Norwegian aluminum plant workers was 1.1 (95%CI 0.8-1.4) (Romundstad et al., 2000). Among employees most heavily exposed to polycyclic aromatic hydrocarbons, the risk was increased significantly (SIR 2.8, 95%CI 1.1-7.4). Spinelli et al. reported SIR of kidney cancer among Canadian aluminum reduction plant workers at 1.00 (95%CI 0.62-1.52) (Spinelli et al., 2006). The risk was statistically significant in employees with high exposure to coal tar pitch volatiles.

Lead smelting plant workers. Cocco et al. investigated the risk of kidney cancer in a population of Italian male lead smelters (Cocco et al., 1997). The reported standardized mortality ratio (SMR) for kidney cancer was 142 (95%CI 46-333). In further stratification, the risk was elevated only among laborers (SMR 337, 95%CI 70-985). The dose-response relationship trend was statistically significant.

Chemical products plant and machine operators (ISCO unit group 8313)

Petroleum refinery workers. Many authors studied the association between work in the petroleum industry and kidney cancers. Schnatter et al. examined mortality of renal malignancies among Canadian petroleum marketing and distribution workers (Schnatter et al., 1993). They reported nine cases of kidney cancer in this cohort, yielding SMR of 1.35 (95%CI 0.62-2.57). According to the authors, the SMR among workers exposed to hydrocarbons was 1.58 (95%CI 0.63-3.25). Wong et al. conducted a similar study on a cohort of American distribution workers (Wong et al., 1993). The SMR of kidney cancer was 65.4 (95%CI 33.7-114.1) and 83.7 (95%CI 45.8-140.5) among land-based and marine workers, respectively. Pukkala reported SIR 1.97 (95%CI 1.29-2.88) among Finnish oil refinery workers (Pukkala, 1998). In the male subpopulation, SIR was 2.13 (95%CI 1.38-3.13). Moreover, SIR was higher in oil refineries than in other departments of the company. Two studies conducted by American researchers examined mortality of kidney cancer among refinery/petrochemical plant active and terminated workers (Gamble et al., 2000; Lewis et al., 2000). In the first study, SMR was 144 (95%CI 100-200) and in the latter one, 140 (95%CI 90-206) (Gamble et al., 2000; Lewis et al., 2000). In another Canadian study, SMR among male workers was 0.96 (95%CI 0.69-1.30) (Lewis et al. 2000).

Vitamin A and E synthesis workers. Richard et al. were the first to report on the association between work in a chemical plant producing vitamin A and E (Richard et al., 2004). They found SIR of kidney cancer at 13.1 (95%CI 6.28-24.10). All of the cases occurred among male workers, most of whom worked in a position dealing with fabrication for many years (range 10-35). Iwatsubo et al. conducted a similar study on a population employed by production of vitamin A and reported SMR at

1.10 (95%CI 0.30-2.82) and 5.31 (1.09-15.1), among males and females, respectively (Iwatsubo et al., 2014). Subsequently, the authors reported a dose-response relation between cumulative exposure to chloracetal C5 and kidney cancer.

Tetrafluoroethylene synthesis and polymerization workers. Consonni et al. conducted a cohort study assessing the risk of kidney cancers among tetrafluoroethylene synthesis workers in five countries (Germany, Netherlands, Italy, UK, and USA) (Consonni et al., 2013). They reported SMR of renal tumor at 1.44 (95%CI 0.69-2.65).

Firefighters (ISCO unit group 5411)

Kang et al. reported a standardized morbidity odds ratio (SMOR) at 1.34 (95%CI 0.90-2.01) among firefighters for kidney cancer (Kang et al., 2008). According to Ide, the incidence rate among Scottish firefighters was 9.1 per 100,000 (standard deviation (SD) 18.7), while the incidence rate in the population of Scotland was 4.4 per 100,000 (SD 1.2) (Ide, 2014). The mortality rates were 6.5 per 100,000 (SD 16.3) and 1.9 per 100,000 (SD 0.5), respectively. Baris et al. reported SMR of kidney cancer at 1.07 (95%CI 0.61-1.88) (Baris et al., 2001). Glass et al. reported a lower risk of kidney cancer among male volunteer firefighters (SIR 0.82, 95%CI 0.71-0.94) than among paid firefighters (SIR 1.08, 95%CI 0.81-1.41) (Glass et al., 2017; Glass et al., 2016). For volunteer firefighters, the risk of kidney cancer was higher with increased attendance at fires, particularly structural ones. Finally, Pukkala et al. reported SIR of 0.94 (95%CI 0.75-1.17) in the Nordic countries (Pukkala et al., 2014).

Mining and quarrying laborers (ISCO unit group 9311)

Black coal miners. In Czechia, the risk of kidney cancer among black coal miners was lower than in the national male population (SIR 0.66, 95%CI 0.43-0.97), which according to the authors could be attributed to "healthy worker effect" (Tomaskova et al., 2012). However, the average age of the miners at the beginning of observation was 44.1 (SD 6.2), and the follow-up period was 12 years. Knowing that the peak incidence of kidney cancer is between 60 and 70 years of age (EAU, 2019), it is possible that the observation time in this study did not allow for the latency of kidney cancer.

Copper miners. Seidler et al., who conducted a case-cohort study in German copper miners' population, found no elevation of kidney cancer incidence (SIR 1.01, 95%CI

0.79-1.27) (Seidler et al., 2014). There was slightly increased risk among individuals with prolonged exposure to dinitrotoluene, but statistically insignificant. A limitation of the study was a relatively young median age at the end of follow-up (54 years), which limited the latency period for kidney cancer.

Mercury miners. According to Boffetta et al., who conducted a cohort study in four European countries (Spain, Italy, Slovenia, and Ukraine), the mortality from kidney cancer was decreased among mercury miners in comparison to the general population (SMR 0.59, 95%CI 0.22-1.28) (Boffetta et al., 1998; Gomez et al., 2007). However, the authors provided no data on the average age of the miners.

Granite workers. Attfield et al., who investigated American granite workers, found that mortality due to kidney cancer was higher with increasing exposure to respirable free silica, reaching maximum SMR at 3.12 ($p<0.05$) (Attfield et al., 2004). According to the authors, the studied granite workers were almost exclusively exposed to silica.

Table 7. Summary of studies on occupational exposures and risk of kidney cancer; by occupational category, arranged according to the International Standard Classification of Occupations.

Authors and year of the publication	Study design	Study population (size; sex)	Follow-up period	Cases of kidney cancer (n)	Type of measure of association	Measure of association (95%CI)
Building architects (2161) / Landscape architects (2162)						
Heck et al. (2010)	Case-control	992 CA; M&F 1,459 CO; M&F	1999-2003	992	OR^{P}	M&F: 1.89 (1.35-2.65) M: 1.59 (1.07-2.35) F: 3.66 (1.75-7.65)
Mechanical engineers (2144) / Mechanical engineering technicians (3155)						
Heck et al. (2010)	Case-control	992 CA; M&F 1,459 CO; M&F	1999-2003	992	OR^{P}	M&F: 1.71 (1.03-2.84)
Pharmacists (2262)						
Wilson et al. (2008)	Cohort	. ; M&F	1971-1989	1,374	SIR^{C}	F: 7.23 (1.45-21.12)
Accountants (2411)						
Zhang et al. (2004)	Case-control	406 CA; M&F 2,434 CO; M&F	1985-1987	406	OR^{P}	M: 2.7 (1.0-7.6)
Lawyers (2611) / Judges (2612) / Legal professionals not elsewhere classified (2619)						
Wilson et al. (2008)	Cohort	. ; M&F	1971-1989	1,374	SIR^{C}	M: 6.06 (1.95-14.13)
Authors and related writers (2641) / Journalists (2642)						
Wilson et al. (2008)	Cohort	. ; M&F	1971-1989	1,374	SIR^{C}	F: 5.10 (1.03-14.91)
Incinerator and water treatment plant operator (3132)						
Friis et al. (1993)	Cohort	656; M	1965-1987	3	SMR^{B}	2.39 (0.49-6.99)
Metal production process controllers (3135)						
Karami et al. (2012)	Case-control	1,217CA; M&F	2002-2007	1,217	OR^{P}	0.5 (0.3-1.0)
Athletes and sports players (3421)						
Pukkala et al. (2000)	Cohort	2,269; M	1967-1995	6	SIR^{N}	0.43 (0.16-0.93)
Sormunen et al. (2014)	Cohort	2,448; M	1986-2010	4	$SIR^{N,O}$	0.23 (0.06-0.57)

Authors and year of the publication	Study design	Study population (size; sex)	Follow-up period	Cases of kidney cancer (n)	Type of measure of association	Measure of association (95%CI)
General office clerks (411)						
Heck et al (2010)	Case-control	992 CA; M&F 1,459 CO; M&F	1999-2003	992	OR[P]	M: 0.72 (0.52-0.99)
Wilson et al. (2008)	Cohort	. ; M&F	1971-1989	1,374	SIR[C]	M; 3.40 (1.24-7.39)
Sales workers (52)						
Auperin et al. (1994)	Case-control	196 CA; M&F 347 CO; M&F	1987-1991	196	OR[P]	2.1 (1.2-4.0)
Heck et al. (2010)	Case-control	992 CA; M&F 1,459 CO; M&F	1999-2003	992	OR[P]	M: 1.63 (1.02-2.61)
Ji et al. (2005)	Cohort	.; M&F	1961-2000	16,912	SIR[A,B,C]	M: 1.09 (1.01-1.16)[A] M: 1.09 (1.01-1.17)[B]
Zhang et al. (2004)	Case-control	406 CA; M&F 2,434 CO; M&F	1985-1987	406	OR[P]	M: 1.8 (1.0-3.3) F: 2.2 (1.0-4.7) F: 3.1 (1.0-9.6)
Firefighters (5411)						
Baris et al. (2001)	Cohort	7,789; M&F	1925-1989	12	SMR[G]	1.07 (0.61-1.88)
Glass et al. (2017)	Cohort	163,094; M	1998-2010	196	SIR[J]	0.82 (0.71-0.94)
Glass et al. (2016)	Cohort	29,014; M	1982-2010	52	SIR[J]	1.08 (0.81-1.41)
Ide (2014)	Cohort	. ; M	1984-2005	4	IR[N] MR[N]	9.1 vs. 4.4, (2.4-6.7) 6.5 vs 1.9, (2.8-6.4)
Kang et al. (2008)	Case-control	258,964; M	1987-2003	64	SMOR[M]	1.34 (0.90-2.01)
Pukkala et al. (2014)	Cohort	16,422; M	1961-2005	84	SIR[J, K]	0.94 (0.75-1.17)
Skilled agricultural, forestry, and fishery workers (6) / Agricultural, forestry, and fishery laborers (921)						
Heck et al. (2010)	Case-control	992 CA; M&F 1,459 CO; M&F	1999-2003	992	OR[P]	M&F: 1.43 (1.05-1.93) F: 1.79 (1.07-2.99) F: 2.73 (1.05-7.13)

Authors and year of the publication	Study design	Study population (size; sex)	Follow-up period	Cases of kidney cancer (n)	Type of measure of association	Measure of association (95%CI)
Karami et al.(2012)	Case-control	1,217CA; M&F	2002-2007	1,217	OR[P]	2.1(1.0-4.5) 3.2 (1.0-10.1)
Partanen et al. (1991)	Case-control	408 CA; M&F 819 CO; M&F	1977-1978	408	OR[P]	M: 0.63 (0.42-0.94)
Wilson et al. (2008)	Cohort	. ; M&F	1971-1989	1,374	SIR[C]	F: 0.46 (0.21-0.88) M: 0.58 (0.46-0.73) M: 0.58 (0.45-0.74)
Zhang et al. (2004)	Case-control	406 CA; M&F 2,434 CO; M&F	1985-1987	406	OR[P]	M: 1.9 (1.0-3.7)
Field crop and vegetable growers (6111) / Crop farm laborers (9211)						
Forastiere et al. (1993)	Case-control	1,579 CA;. 462 CO;.	1953-1985	26	OR[N]	1.39 (0.75-2.64)*
Karami et al. (2012)	Case-control	1,217CA; M&F	2002-2007	1,217	OR[P]	3.3 (1.0-11.5)
Gardeners, horticultural and nursery workers (6113) / Garden and horticultural laborers (9214)						
Parent et al. (2000)	Case-control	142 CA; M 2,433 CO; M	1979-1985	142	OR[P]	4.1 (1.7-10.3) 1.6 (1.0-2.6)
Forestry and related jobs (6210) / Mobile forestry plant operators (8341) / Forestry laborers (9215)						
Alavanja et al. (1989)	Cohort	1,411; M	1970-1979	18	PMR[D]	2.1 (1.2-3.3)
Wilson et al. (2008)	Cohort	. ; M&F	1971-1989	1,374	SIR[C]	M: 0.51 (0.30-0.81)
Plumbers and pipe fitters (7126)						
Mellemgaard et al. (1994)	Case-control	368 CA; M&F 396 CO; M&F	1989-1992	368	OR[P]	8.5 (1.1-66)
Painters and related workers (7131)						
Mariusdottir et al. (2016)	Cohort	18,840 CA; M&F 1,235 CO; M&F	1971-2005	225	HR[P]	2.97 (1.31-6.74)

Authors and year of the publication	Study design	Study population (size; sex)	Follow-up period	Cases of kidney cancer (n)	Type of measure of association	Measure of association (95%CI)
Blacksmiths, hammersmiths, and forging press workers (7221)						
McCredie et al. (1993)	Case-control	636 CA; M&F 523 CO; M&F	1989-1990	636	RR[H,I]	2.13 (1.04-4.39)[I]
Motor vehicle mechanics and repairers (7231)						
Zhang et al. (2004)	Case-control	406 CA; M&F 2,434 CO; M&F	1985-1987	406	OR[P]	M: 2.0 (1.1-3.5) M: 2.9 (1.5-5.8) M: 4.0 (1.3-12.2)
Aircraft engine mechanics and repairers (7232)						
Mariusdottir et al. (2016)	Cohort	18,840 CA; M&F 1,235 CO; M&F	1971-2005	225	HR[P]	4.51 (1.11-18.28)
Parent et al. (2000)	Case-control	142 CA; M 2,433 CO; M	1979-1985	142	OR[P]	2.8 (1.0-8.4)
Potters and related workers (7314)						
Birk et al. (2009)	Cohort	8,288; M	1985-2005	11	SMR[J,K, L]	0.65 (0.32-1.16)
		9,356; F	1985-2005	5	SMR[J,K, L]	0.67 (0.22-1.56)
Glass makers, cutters, grinders and finishers (7315)						
Shannon et al. (2005)	Cohort	2,557; M	1950-1997	14	SIR[G] SMR[G]	192 (105-321) 146 (30-427)
Printers (7322)						
Ilychova et al. (2012)	Cohort	3,120; F 1,423; M	1979-2003	7 6	SMR[J]	F: 1.42 (0.57-2.93) M: 1.26 (0.46-2.75)
Parent et al. (2000)	Case-control	142 CA; M 2,433 CO; M	1979-1985	142	OR[P]	3.0 (1.2-7.5)
Food processing and related trades workers (751) / Food and related products machine operators (8160)						
Ji et al. (2005)	Cohort	.; M&F	1961-2000	16,912	SIR[A,B,C]	M: 1.51 (1.02-2.10)[C]
Laakkonen et al. (2006)	Cohort	29,557; .	1971-1995	-	SIR[N]	M: 1.51 (1.16-1.94)

Authors and year of the publication	Study design	Study population (size; sex)	Follow-up period	Cases of kidney cancer (n)	Type of measure of association	Measure of association (95%CI)
Wilson et al. (2008)	Cohort	. ; M&F	1971-1989	1,374	SIR[C]	F: 2.73 (1.59-4.37) M: 1.65 (1.12-2.35) F: 4.53 (1.81-9.33) M: 4.49 (1.45-10.49) M: 2.22 (1.11-3.98)
Pelt dressers, tanners, fellmongers (7535)						
Veyalkin et al. (2003)	Cohort	3,500; M&F	1953-2000	3 M [F,G] 5 F [F,G]	PMR[F,G]	M: 0.45(0.1-1.3) F: 1.7 (0.5-3.9)
Shoemakers and related workers (7536)						
Bulbulyan et al. (1998)	Cohort	4,569; F 616; M	1979-1993	7 3	SMR[G]	1.6 (0.6-3.2) 3.2 (0.7-9.4)
Fu et al. (1996)	Cohort	4,215; M	1939-1991	8	SMR[G]	66 (28-129)
		1,005; M 1,003; F	1950-1990	4	SMR[G]	222 (61-569)
Ji et al.(2005)	Cohort	.; M&F	1961-2000	16,912	SIR[A,B,C]	F: 3.85 (1.00-8.54)[C]
Metal processing and finishing plant operators (8121, 8122)						
Cocco et al. (1997)	Cohort	1,388; M	1950-1992	5	SMR[G]	142 (46-333)
Heck et al. (2010)	Case-control	992 CA; M&F 1,459 CO; M&F	1999-2003	992	OR[P]	M&F: 0.43 (0.24-0.78) M: 0.41 (0.21-0.80)
Hobbesland et al. (1999)	Cohort	2,534; M	1953-1991	11	SIR[A]	1.33 (0.66-2.38)
		3,384; M	1953-1991	21	SIR[A]	1.67 (1.03-2.55)
Huvinen et al. (2013)	Cohort	8,146; M&F	1974-2011	6	SIR[N]	0.38 (0.14-0.82)
Romundstad et al. (2000)	Cohort	11,103; M	1953-1996	55	SIR[A]	1.1 (0.8-1.4)
Spinelli et al. (2006)	Cohort	6,423; M	1957-1999	21	SIR[G] SMR[G]	1.00 (0.62-1.52) 0.74 (0.30-1.52)

Authors and year of the publication	Study design	Study population (size; sex)	Follow-up period	Cases of kidney cancer (n)	Type of measure of association	Measure of association (95%CI)
Laundry machine operators (8157) / Hand launderers and pressers (9121)						
Blair et al.(2003)	Cohort	4,049; F 1,320; M	1948-1993	5 3	SMR[D]	1.0 (0.4-2.0)
Ji et al. (2005)	Cohort	.; M&F	1961-2000	16,912	SIR[A,B,C]	F: 1.41 (1.13-1.71)[A] F: 1.45 (1.15-1.79)[B]
Lynge et al. (1995)	Nested case-control	10,600; .	1970-1987	16	RR[P]	0.7 (0.2-2.6)
McCredie et al. (1993)	Case-control	636 CA; M&F 523 CO; M&F	1989-1990	636	RR[H,I]	2.49 (0.97-6.35)[H] 4.68 (1.32-16.56)[I]
Mechanical machinery assembler (8211)						
Boice et al. (2006)	Cohort	41,351; M&F	1948-1999	74	SMR[G]	1.06 (0.33-1.33)
Marsh et al. (2008)	Cohort	223,894; M&F	1952-2004	492	SMR[N]	0.96 (0.88-1.05)
Electrical and electronic equipment assemblers (8212)						
Pesch et al. (2000)	Case-control	935 CA; M&F 4,298 CO; M&F	1991-1995	935	OR[P]	M: 3.2 (1.0-10.3)
Clapp (2006)	Cohort	27,272; M	1969-2001	265	PMR[N] PCMR[N]	146.4 (129.9-164.9) 136.1 (120.9-153.2)
		4,669; F	1969-2001	31	PMR[N] PCMR[N]	135.3 (95.4-192.0) 120.1 (84.7-170.2)
Chemical products plant and machine operators (8313) Petroleum refinery workers						
Gamble et al. (2000)	Cohort	6,238; M&F	1970-1992	25	SMR[G]	140 (90-206)
Lewis et al. (2000)	Cohort	17,025; M	1970-1992	25	SMR[G]	144 (100-200)
Lewis et al. (2000)	Cohort	26,322; M	1964-1994	41	SMR[D]	0.96 (0.69-1.30)
		8, 238; F	1964-1994	3	-	-
Pukkala (1998)	Cohort	9,524; M&F	1971-1994	26	SIR[N]	1.97 (1.29-2.88)
		7,512; M	1971-1994	25	SIR[N]	2.13 (1.38-313)
Schnatter et al. (1993)	Cohort	6,672; M	1964-1983	9	SMR[N]	1.35 (0.62-2.57)

Authors and year of the publication	Study design	Study population (size; sex)	Follow-up period	Cases of kidney cancer (n)	Type of measure of association	Measure of association (95%CI)
Wong et al. (1993)	Cohort	9,026; .	1947-1989	12	SMR[D]	65.4 (33.7-114.1)
		9,109; .	1947-1989	12	SMR[D]	83.7 (45.8-140.5)
Vitamin A&E production						
Iwatsubo et al. (2014)	Cohort	2,522; M&F	1968-2006	7	SMR[N]	M: 1.10 (0.30-2.82) F: 5.31 (1.09-15.1)
Richard et al. (2004)	Cohort	.; M&F	1994-2003	10	SIR[P]	13.1 (6.28-24.10)
Tetrafluoroethylene production						
Consonni et al. (2013)	Cohort	5,879; M	1950-2008	10	SMR[G]	1.44 (0.69-2.65)
Car, taxi and van drivers (8322) / Heavy truck and lorry drivers (8332)						
Brownson (1988)	Case-control	326 CA; M&F 978 CO; M&F	1984-1986	326	OR[P]	M: 3.1 (1.1-8.5)
Mellemgaard et al. (1994)	Case-control	368 CA; M&F 396 CO; M&F	1989-1992	368	OR[P]	3.1 (1.3-7.7)
Rafnsson et al. (1991)	Cohort	868; M	1951-1988	6	SMR[A]	1.77 (0.65-3.85)
		726; M	1951-1988	4	SMR[A]	1.97 (0.54-5.05)
Bus and tram drivers (8331)						
Soll-Johanning et al. (1998)	Cohort	16,203; M	1943- 1992	83	SIR[A]	1.6 (1.3-2.0)
Earthmoving and related plant operators (8342) Asphalt workers						
Boffetta et al. (2003)	Cohort	29,820; M	1953-2000	26	SMR[G]	0.76 (0.50-1.11)
Randem et al. (2003)	Cohort	8,763; M	1970-1997	14	SIR[A]	0.9 (0.5-1.5)
Randem et al. (2004)	Cohort	22,363; M	1925-1992	44	SIR[G]	0.82 (0.60-1.11)
Domestic cleaners and helpers (9111) / Cleaner and helpers in offices, hotels, and other establishments (9112)						
Pesch et al. (2000)	Case-control	935 CA; M&F 4,298 CO; M&F	1991-1995	935	OR[P]	F: 1.9 (1.2-3.1)
Wilson et al. (2008)	Cohort	. ; M&F	1971-1989	1,374	SIR[C]	M: 2.27 (1.04-4.31)

Authors and year of the publication	Study design	Study population (size; sex)	Follow-up period	Cases of kidney cancer (n)	Type of measure of association	Measure of association (95%CI)
Mining and quarrying laborers (9311)						
Black coal miners						
Tomaskova et al. (2012)	Cohort	6,705; M	1992-2006	24	SIR[J]	0.66 (0.43-0.97)
		2,158; M	1992-2006	12	SIR[J]	1.07 (0.58-1.82)
Copper miners						
Seidler et al. (2014)	Case-cohort	16,441; .	1961-2005	74 [J] 3[K]	SIR[J] SIR[K]	1.01 (0.79-1.27) 0.98 (0.32-3.06)
Mercury miners						
Boffetta et al. (1998)	Cohort	6,784; M 265; F	1950-1995	6	SMR[G]	0.59 (0.22-1.28)
Granite workers						
Attfield et al. (2004)	Cohort	5,414;M	1982-1994	.	SMR[N]	1.37 (.)

- M-males; F-females. CA-cases; CO-controls.
- IR-incidence rate; MR-morbidity rate; OR-odds ratio; PCMR-proportionate cancer mortality ratio; PMR-proportionate mortality ratio; RR-relative risk; SIR-standardized incidence ratio, SMR-standardized mortality ratio; SMOR-standardized morbidity odds ratio.
- [A] ICD-7 180; [B] ICD-7 180.0; [C] ICD-7 180.1; [D] ICD-8-189; [F] ICD-9 188; [G] ICD-9 189; [J] ICD-10 C64; [K] ICD-10 C65; [L] ICD-10 C66; [M] ICD-O-3 649 kidney cancer; [N] unspecified kidney cancer; [O] unspecified renal pelvis cancer; [P] renal cell carcinoma.
- *-CI 90%.

2.5 Assessment of quality of the existing literature

A considerable amount of research has been published on occupational exposures and risk of kidney cancer (35 identified articles) or mixed kidney and renal pelvis cancer (27 identified articles), while the literature on the risk of renal pelvis cancer in particular remains sparse (4 identified articles). Most of the identified studies (Tables 6 and 7) applied a cohort study design (49 out of 66). The rest of the studies used a case-control design (17 out of 66).

The Newcastle-Ottawa scale is a statistical tool designed to systematically assess the quality of non-randomized studies to be included in the systematic reviews of the literature (Wells et al., 2013). It determines eight characteristics of each study. For each out of the eight components, one star can be awarded as a symbol of high quality. Star system provides a quick, reader-friendly visual assessment of the quality of the studies. Two different tools were created, one designed for cohort studies, and the other one for case-control studies. The characteristics constitute three principal groups of features: selection, comparability, and outcome (for cohort studies) or exposure (for case-control studies). The author of the thesis assessed the quality of the identified studies (Table 6 and 7) using the Newcastle-Ottawa scale (Appendix 2; Table 1 and 2).

The vast majority of the identified cohort studies used non-representative exposed cohorts. Only about 25% of the deployed cohorts were truly representative for the average exposure in the community, and 2% were somewhat representative. Moreover, only about 33% of cohort studies demonstrated that the outcome of interest (kidney or renal pelvis cancer) was not present at the start of the study. Furthermore, the majority of the cohort studies failed to provide comparability of cohorts based on the design or analysis. Only 8% of the identified studies controlled for tobacco smoking, which is the most important possible confounding factor that should be taken into consideration. About 27% of the studies controlled for additional factors, of less potential for confounding (e.g., sex, age, and BMI). While none of the studies provided an independent blind assessment of the outcome, 65% deployed record linkage. However, it should be noted that many of these were mortality studies, that is using death records. Such studies are not suitable for investigating neoplasms with reduced lethality. For such neoplasms, incidence studies should be carried out, that is studies using data from cancer registries collecting data from cancer cases. Finally, only about 53% of the studies provided adequate follow-up, that is either complete follow-up of all subjects accounted for, follow up > 60%, or description of the lost cases.

Regarding the quality of identified case-control studies, their flaw was ascertainment of exposure, which was neither secure record, nor structured interview blind to case/control status (12 out of 17 studies). Moreover, in about 47% of the studies, the non-response rate was the same for both cases and controls. In general, the comparability of cases and controls based on the design or analysis was better than in cohort studies (12 out of 17 studies controlled for tobacco smoking, and 11 out of 17 controlled for additional factors of less potential for confounding (e.g., sex, age, and BMI)). However, it should be noted that none of them addressed the possible problem of recall bias (e.g., by choosing an appropriate data collection method) that is of particular concern in retrospective studies.

The identified studies have several other limitations that are not assessed by the Newcastle-Ottawa scale. Firstly, most of the analyzed studies have only been carried out in small study populations. Moreover, only a few studies benefited from data covering the entire national populations, making the presented results population-representative and generalizable. Furthermore, most of the research either concerned only the male population (28 studies), or mixed male-female population (21 studies). Only 11 studies reported association for men and women separately. Six studies did not report the sex of the study participants. In most of the studies, the female population was too small to observe statistically significant results. The inclusion of sex in the data analysis in the case of urinary tract cancers is of considerable importance since until now the higher incidence of these tumors among men is unclear.

Regarding the quality of data on exposure, the majority of the identified studies did not control for the duration of employment. Moreover, only a few studies provided stratification by calendar years of employment, which is of particular importance in case of studies examining the association between performed occupation and risk of cancer, not between occupational agent and risk of cancer. Studies should account for calendar years of employment since the legislation and jurisprudence on the work conditions have changed over time, as also has the availability of various personal protective equipment. Additionally, many studies in which the measure of exposure was based on employer-administered records, did not provide information on the exact occupational category. Hence there was a risk of exposure misclassification, that could bias the observed effect towards null.

In most of the studies, the information concerning the quality of the source of data on outcome was sparse. In the case of studies deploying data from cancer registries, information on the degree of completeness and coverage of the registry in question was mostly unavailable. Moreover, the majority of studies did not provide information on equality of access to the healthcare system regardless of socioeconomic status, which means that the presented data could be socioeconomically biased.

Regarding the analytical and statistical methods deployed, majority of the studies did not allow for the latency of the kidney or renal pelvis cancer for all of the study participants, which might bias the results towards null. Moreover, in most of the studies deploying multivariable regression models, the problem of the omitted-variable bias was not addressed. Furthermore, the issue of possible overfitting of the model and generation of numerically unstable estimates was not addressed. Finally, no procedure was applied to evaluate the robustness of the inferences.

3 JUSTIFICATION OF THE CURRENT STUDY

Despite the rich literature on the topic of associations of occupational exposures with the risk of kidney cancer, there remains a paucity of evidence on similar associations with the risk of renal pelvis cancer. Moreover, in the existing literature on kidney cancer, chance, bias, and confounding could not be reasonably excluded. Some results were not statistically significant, most of the studies deployed a small number of exposed cases, and there was sparse evidence of an exposure-response association.

Based on the review of the existing literature, there are some important gaps in the current knowledge and methodology of the studies that should be addressed.

First of all, there remains a need to deploy a cohort that is representative of the average exposure in the community, and the non-exposed cohort is drawn from the same community as exposed cohorts. There also remains a need for a demonstration that the outcome of interest had not been present at the start of the study. Moreover, population-representativeness should be provided, e.g., by including all of the cases of cancer identified in the chosen period in the whole population. Additionally, there is a need for studies, maximally reducing the problem of the no-response individuals, e.g., by censuses to obtain the data on exposure. There also remains a need for controlling for exposure to the most important potential confounding factor that should be taken into consideration, i.e., tobacco smoking. Furthermore, there is a need for accounting for changes in working conditions over time, either by stratification by calendar years of employment or calculating cumulative exposure to an occupational agent on the individual level. Also, there remains a need to perform analysis allowing for the latency between exposures and outcome, while calculating the cumulative exposures to occupational agents on the individual level.

Finally, while performing analysis of the results, there is a need of a study addressing the problem of the omitted-variable bias, e.g. by using multiple cumulative exposure variables; avoiding the issue of possible overfitting of the model and generation of numerically unstable estimates, e.g., by creating the final multivariable logistic model using a purposeful selection of variables; and evaluating the robustness of the inferences, e.g. by a posthoc conservative Bonferroni procedure for multiple analyses.

4 AIMS OF THE STUDY

The overarching aim of the thesis was to assess the association between occupational exposures and risk of kidney and renal pelvis cancer.

The specific objectives of the research were as follows:

1. to describe the occupational variation in the incidence of kidney cancer in the population of the Nordic countries (Study I)

2. to describe the occupational variation in the incidence of cancer of the renal pelvis in the population of the Nordic countries (Study II)

3. to examine the smoking-adjusted occupational variation in the incidence of kidney cancer in the population of Nordic males (Study III)

4. to examine the smoking-adjusted occupational variation in the incidence of renal pelvis cancer in the population of Nordic males (Study IV)

5. to assess associations between occupational exposure to heavy metals (chromium (VI), iron, nickel, lead) and welding fumes, and the risk of kidney and renal pelvis cancer (Study V)

6. to describe other occupational exposures possibly associated with the risk of kidney and renal pelvis cancer (Study V)

5 MATERIALS AND METHODS

5.1 Source population

This research was conducted leveraging data from the NOCCA study. NOCCA is a cohort study based on data from five Nordic countries, namely, Denmark, Iceland, Finland, Norway, and Sweden. Its population included 14.9 million individuals (7.4 million males, and 7.5 million females). The study was described in detail by Pukkala et al. (2009).

5.2 Study design

In this doctoral research, in total, five studies were conducted (Studies I-V) (Table 8). In the first four studies (I-IV), population cohort study design was applied to describe the occupational variation in the incidence of kidney cancer (Study I), renal pelvis cancer (Study II), smoking-adjusted incidence of kidney cancer (Study III), and smoking-adjusted incidence of renal pelvis cancer (Study IV), in the population of the Nordic countries. In Study V, nested case-control study design was adopted, to assess associations between occupational exposure to heavy metals (chromium (VI), iron, nickel, lead) and welding fumes, and the risk of kidney cancer and to describe other occupational exposures possibly associated with the risk of kidney cancer.

Table 8. Summary of materials and methods used in Studies I-V.

	STUDY I	STUDY II	STUDY III	STUDY IV	STUDY V
Study design	Population cohort study	Population cohort study	Population cohort study	Population cohort study	Nested case-control study
Countries included	Denmark Iceland Finland Norway Sweden	Denmark Iceland Finland Norway Sweden	Denmark Iceland Finland Norway Sweden	Denmark Iceland Finland Norway Sweden	Iceland Finland Sweden
Measure of effect	SIR	SIR	SIR, SIR_{adj}	SIR, SIR_{adj}	OR
Sex of participants	males and females	males and females	males	males	males and females
Cancer site included	kidney	renal pelvis	kidney	renal pelvis	kidney and renal pelvis
Occupation included	first recorded	first recorded	first recorded	first recorded	all recorded

OR-odds ratio, SIR-standardized incidence ratio; SIR_{adj}-SIR adjusted for tobacco-smoking

5.3 Study population

The majority of the presented doctoral research was based on data from five countries - Denmark, Iceland, Finland, Norway, and Sweden (Studies I-IV). Study V was based on data from three countries - Iceland, Finland, and Sweden. Norway and Denmark were excluded because of lack of access to the individual level records.

Analyses in Studies I, II, and V, were conducted for both sexes. In Studies III and IV, analyses were conducted for males only. Females were not included since in different occupational categories smoking patterns were changing in such an irregular manner that it is hard to estimate the sum effect of the smoking habits in a given population. For example, in Finland, in earlier decades, women with high socioeconomic status smoked most, and then the smoking increased rapidly in low socioeconomic status and decreased in high socioeconomic status women (Pukkala et al., 2005).

5.4 Information on exposure

In the NOCCA study, data on occupation (exposure) were leveraged from national population censuses handled in 1960-1990. In all Nordic countries, participation in censuses was mandatory. During censuses, participants were asked to declare their occupation through free-text in self-administered questionnaires. Subsequently, the data collected through surveys were digitalized and centrally encoded by respective national statistical offices, using unique personal identity codes. All original national occupation codes were converted to Nordisk Yrkesklassifisering (NYK), a Nordic adaptation of the ISCO from 1958. NYK comprises 53 distinct occupational categories and an additional class of economically inactive persons that were described in details elsewhere (Pukkala et al., 2009).The censuses included in this research were held in Sweden in 1960, 1970, 1980, 1990; in Norway in 1960, 1970, 1980; in Finland in 1970, 1980, 1990; in Iceland in 1981; and Denmark in 1970. All individuals, who were aged 30-64 years on January 1st of the year of the respective census, composed the NOCCA cohort.

In Studies I-IV, occupational categories were considered as exposures. For individuals participating in more than one census, the first registered occupation was used.

In Study V, for the purpose of the detailed exposure estimation, NOCCA Job-Exposure Matrix (NOCCA-JEM) was used (described in detail by Kauppinen et al. (2009)). The matrix converses NYK codes to quantitative estimates of exposure to 29 substances potentially related to cancer risk (Table 9). For each occupational category, it provides two variables for each agent: the probability of being exposed (P) and the average exposure level (L), among the exposed persons. Time of exposure (T), was assessed individually, starting at the age of 20 (typical age to start work in non-academic occupations), and ending on the index date (date of diagnosis of the case) or age of 65 (typical age at retirement), whichever occurred first.

Table 9. Occupational exposure agents investigated in Study V.

Abbreviation	Occupational exposure agents	Unit
ALHC	Aliphatic and alicyclic hydrocarbon solvents	ppm
ANIM	Animal-borne dust	mg/m^3
ARHC	Aromatic hydrocarbon solvents	ppm
ASB	Asbestos	f/cm^3
BAP	Benzo(a)pyrene	µg/m^3
BENZ	Benzene	ppm
BITU	Bitumen fumes	mg/m^3
CHC	Chlorinated hydrocarbon solvents	ppm
CR	Chromium	µg/m^3
DEEX	Diesel engine exhaust	mg/m^3
FE	Iron	mg/m^3
FORM	Formaldehyde	ppm
GASO	Gasoline	ppm
IRAD	Ionizing radiation	mSv
MCH	Methylene chloride	ppm
NI	Nickel	µg/m^3
NIGH	Nightwork	none
OSOL	Other organic solvents	ppm
PB	Lead	µmol/l
PER	Perchloroethylene	ppm
PPWL	Perceived physical workload	score [a]
QUAR	Quartz dust	mg/m^3
SO2	Sulphur dioxide	ppm
TCE	1,1,1-Trichloroethane	ppm
TOLU	Toluene	ppm
TRI	Trichloroethylene	ppm
UV	Ultraviolet radiation	J/m^2
WELD	Welding fumes	mg/m^3
WOOD	Wood dust	mg/m^3

[a] Score of workers reporting heavy or rather heavy physical work in national Finnish “Quality of Work Life Survey”, Finland 1990 ("Quality of Work Life Surveys,").

For each individual, information from all available censuses was included. Cumulative occupational exposures (CE) to 29 agents, defined as P×L×T, were calculated for all cases and controls. The occupation reported during the first census in which the individual took part was considered an occupation performed by this individual from the age of 20 years. When more than one occupational code was assigned to one person in different censuses, it was assumed that the change of work occurred in the middle of the period between the polls. For these individuals, cumulative exposure was a sum of all P×L×T, calculated for each separate occupational period. All cumulative exposures were calculated for three different lags of 0, 10, and 20 years, to allow for a cancer latency period. The results for lag

10 and lag 20 were similar, and therefore only findings for the lag of 10 years are presented in this thesis.

5.5 Data on other exposures - smoking prevalence and SIR of lung cancer

For none of the countries, information about smoking habits on an individual level was provided. Therefore, in Studies I, II and V, no stratification regarding smoking was conducted. However, to examine smoking-adjusted occupational variation in the incidence of kidney cancer, a simple linear regression model was created, in which a proxy of smoking prevalence by occupation in the Nordic countries was determined using SIR of lung cancer (Studies III and IV).

To create the model, data on survey-based tobacco smoking prevalence in Finnish males from the Finnish Information System on Occupational Exposures (FINJEM) (Kauppinen et al., 2009) were used. Information on smoking prevalence in 512 FINJEM categories was converted to 54 NYK categories (Table 10). No similar data from other Nordic countries were available. Furthermore, data on the occupational category- and country-specific SIRs of lung cancer among males, that came from the publication of Pukkala et al. (2009), were used.

Table 10. Smoking prevalence among Finnish males, by occupational categories. Based on Finnish Information System on Occupational Exposures (Kauppinen et al., 2009).

Occupational category	Smoking prevalence
Administrators	25.8%
Artistic workers	38.5%
Assistant nurses	25.1%
Beverage workers	37.9%
Bricklayers	40.8%
Building caretakers	32.5%
Chemical process workers	34.1%
Chimney sweeps	32.6%
Clerical workers	30.6%
Cooks and stewards	53.3%
Dentists	25.1%
Drivers	42.0%
Electrical workers	34.1%
Engine operators	42.2%
Farmers	22.0%
Fishermen	42.7%
Food workers	38.1%
Forestry workers	38.0%
Gardeners	28.5%
Glass makers	41.2%
Journalists	27.0%
Laboratory assistants	33.0%
Launderers	34.6%
Mechanics	38.6%
Military personnel	24.9%
Miners and quarry workers	50.2%
Nurses	25.1%
Other construction workers	53.6%
Other health workers	29.6%
Other workers	45.1%
Packers	38.8%
Painters	43.0%
Physicians	21.0%
Plumbers	35.0%
Postal workers	40.6%
Printers	35.6%
Public safety workers	32.6%
Religious workers	26.4%
Sales agents	39.8%
Seamen	44.1%
Shoe and leather workers	42.9%
Shop workers	37.0%
Smelting workers	48.2%

Occupational category	Smoking prevalence
Teachers	19.7%
Technical workers	26.9%
Textile workers	35.9%
Transport workers	36.4%
Waiters	43.9%
Welders	44.0%
Wood workers	37.4%

5.6 Information on outcome

The study population was followed-up until emigration, death, or December 31st of the following year: 2003 in Denmark and Norway, 2004 in Iceland, 2005 in Finland and Sweden. Data on mortality and emigration were retrieved from the Central Population Registries in each country. Data on cancer cases were obtained from the respective Nordic cancer registries.

In Studies I and III, cases of kidney cancer (180.0 according to ICD-7) were included. In Studies II and IV, cases of renal pelvis cancer were included (180.1 according to ICD-7). In Study V, both cases of kidney cancer and renal pelvis cancer were included (180.0 and 180.1 according to ICD-7).

Finally, unique personal identity codes were used to perform linkage of the information on occupations from censuses, cancer cases from cancer registries, and death and emigration from national population registries. Only participants with a minimum age of 20 at the index date and having information from at least one census prior to index date were included in this study.

5.7 Case and control definitions (Study V)

In Study V (nested case-control study), the cases were defined as all individuals diagnosed with cancer of the kidney or the renal pelvis between 1961-2005 in Sweden, 1971-2005 in Finland, and 1982-2004 in Iceland. For each case, five controls were selected randomly from the NOCCA individuals, who were alive and free from kidney or renal pelvis cancer on the date of diagnosis of the case (henceforth the "index date" for the case-control set). Controls were matched individually to cases on birth date, sex, and country. Both cases and controls could have a history of any other comorbid cancer.

5.8 Statistical analysis

5.8.1 Studies I and II

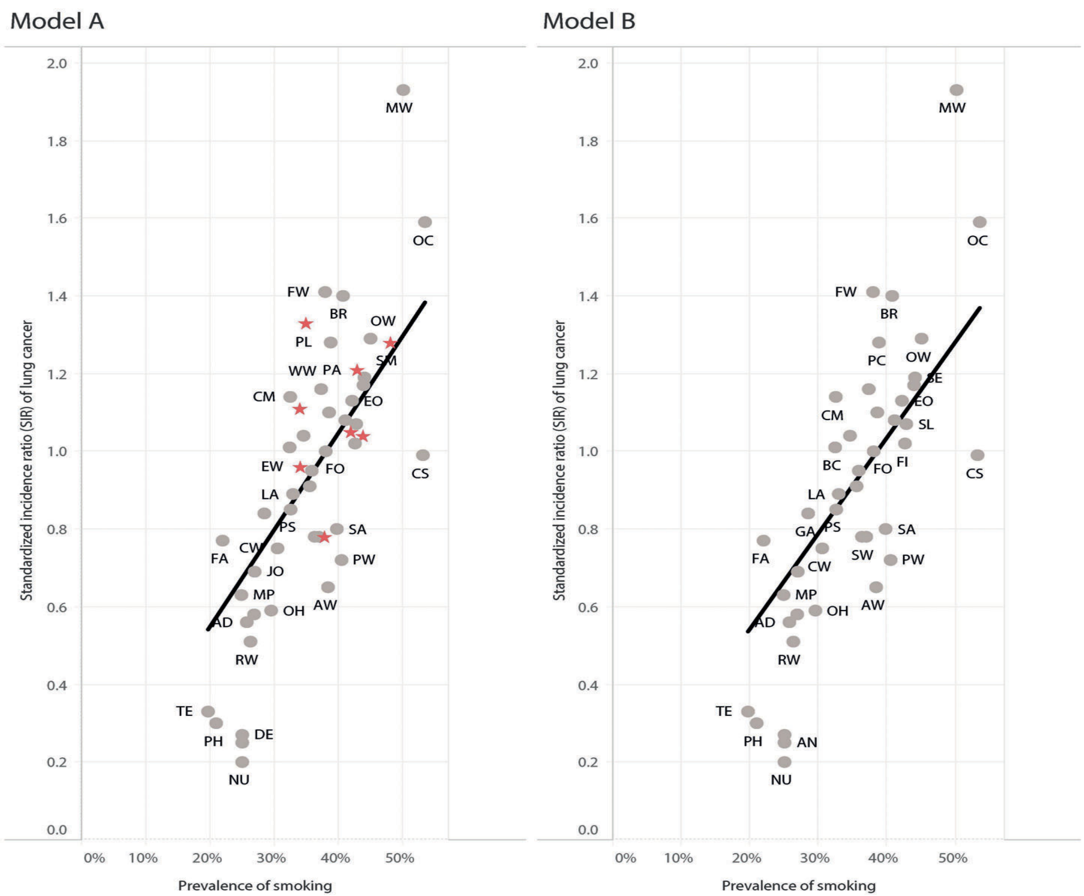
For each occupational category, the ratios of observed to expected number of cases, denoted as SIRs, were calculated. They were based on the first occupation recorded in the census, that is at the time of entry into the study population. The national incidence rates were used as a reference. For each occupation category, the 95%CIs were calculated assuming the Poisson distribution of the observed number of cases. Occupational categories were further stratified by year of diagnosis, age at follow-up, sex, and country. Although SIR calculations were based on 5-year categories of both calendar periods and age, here, they were combined into 15-year periods (1961-1975; 1976-1990; and 1991-2005), and broad age groups (30-49, 50-69, and ≥70 years). More detailed data are shown only for occupational categories with the highest (≥1.15) and the lowest (≤0.85) SIRs. To assess the significance of time trends of the SIRs, Poisson regression trend test was performed.

5.8.2 Studies III and IV

Simple linear regression analysis was used to examine the linear relationship between survey-based smoking prevalence in Finnish males and SIR of lung cancers in Finnish males (Model A). The following occupational categories were not included in the model, due to missing data on the prevalence of smoking: domestic assistants, economically inactive, hairdressers, and tobacco workers. Mean smoking prevalence (explanatory variable) was 35.9% (SD 8.2%). Mean SIR of lung cancer was 0.93 (SD 0.35). The assumptions of the simple linear regression analysis were met. To account for the risk of lung cancer observed in non-smokers, the intercept was defined *a priori* at 0.05. The regression line was described by the equation Y=0.05+2.48X (r_2=0.57; Figure 11 Model A), where Y denoted SIR of lung cancers in Finnish males, and X denoted smoking prevalence in Finnish males. The model was validated using a jackknife resampling (Efron et al., 1981).

Additionally, to assess whether the presence of occupational categories characterized by other risk factors for lung cancer than smoking affects the above linear trend, Model B was created. Occupational categories that should be excluded were determined on the basis of the literature (Haldorsen et al., 2017). The following categories (with the SIR of lung cancer >1.15) were not included in the regression equation: drivers (exposed to diesel exhaust (Haldorsen et al., 2004; Kjaerheim et al., 2010)); painters (exposed to polycyclic aromatic hydrocarbons (Haldorsen et al., 2004)); plumbers (exposed to asbestos (Kjaerheim et al., 2010)), beverage workers, chemical process workers, electrical workers, smelting workers, tobacco workers, and waiters. Besides, domestic assistants, economically inactive, and hairdressers were excluded, due to missing data. The assumptions of the simple linear regression analysis were met. As in Model A, to account for the risk of lung cancer observed in non-smokers, the intercept was set *a priori* at 0.05. The regression line was described by the equation Y=0.05+2.46X (r^2=0.58; Figure 11 Model B), where Y denoted SIR of lung cancers in Finnish males, and X denoted smoking prevalence in Finnish males. The model was validated using a jackknife resampling (Efron et al., 1981).

Subsequently, the above models were used to predict the smoking prevalence by occupation among Nordic males. It was assumed that the relationship between the prevalence of smoking and the risk of lung cancer for different occupational categories should be similar in all Nordic countries. The findings were reported using both models to indicate their effect on the results.



Standardized incidence ratio (SIR) of lung cancer dependence of smoking in Finnish males.
Model A. SIR L = 2.4878 S - 0.05;
Model B. SIR L = 2.4612 S - 0.05;
where: SIR L - standardized incidence ratio of lung cancer; S - prevalence of smoking.

The data is filtered on smoking prevalence in NOCCA occupational groups, which keeps non-null values only. Variables appearing only in model A are marked with a star symbol. The marks are labeled by the following NOCCA occupational groups: AD - administrators; AN - assistant nurses; AW - artistic workers; BC - building caretakers; BE - beverage workers; BR - bricklayers; CH - chemical process workers; CM - chimney sweeps; CS - cooks and stewards; CW - clerical workers; DE - dentists; DR - drivers; EO - engine operators; EW - electrical workers; FA - farmers; FI - fishermen; FO - food workers; FW - forestry workers; GA - gardeners; GM - glass makers etc.; JO - journalists; LA - laboratory assistants; LD - launderers; ME - mechanics; MP - military personnel; MW - miners and quarry workers; NU - nurses; OC - other construction workers; OH - other health workers; OW - other workers; PA - painters; PC - packers; PH - physicians; PL - plumbers; PR - printers; PS - public safety workers; PW - postal workers; RW - religious workers etc.; SA - sales agents; SE - seamen; SL - shoe and leather workers; SM - smelting workers; SW - shop workers; TE - teachers; TR - transport workers; TW - technical workers, etc.; TX - textile workers; WA - waiters; WE - welders; WW - woodworkers.

Figure 11. Correlation of standardized incidence ratio (SIR) of lung cancer and prevalence of smoking in Finnish males .

To calculate smoking-adjusted SIR (SIR_{adj}), adjustment of the expected number of cases was performed by summing the expected number of cases and the product of the expected number of cases, and the difference between the smoking prevalence in a given occupational category and the smoking prevalence in the entire national population. The 95%CIs were calculated assuming a Poisson distribution.

Since the results for both models were extremely close, only results for the Model B are presented in this thesis, as Model B was characterized by a higher coefficient of determination.

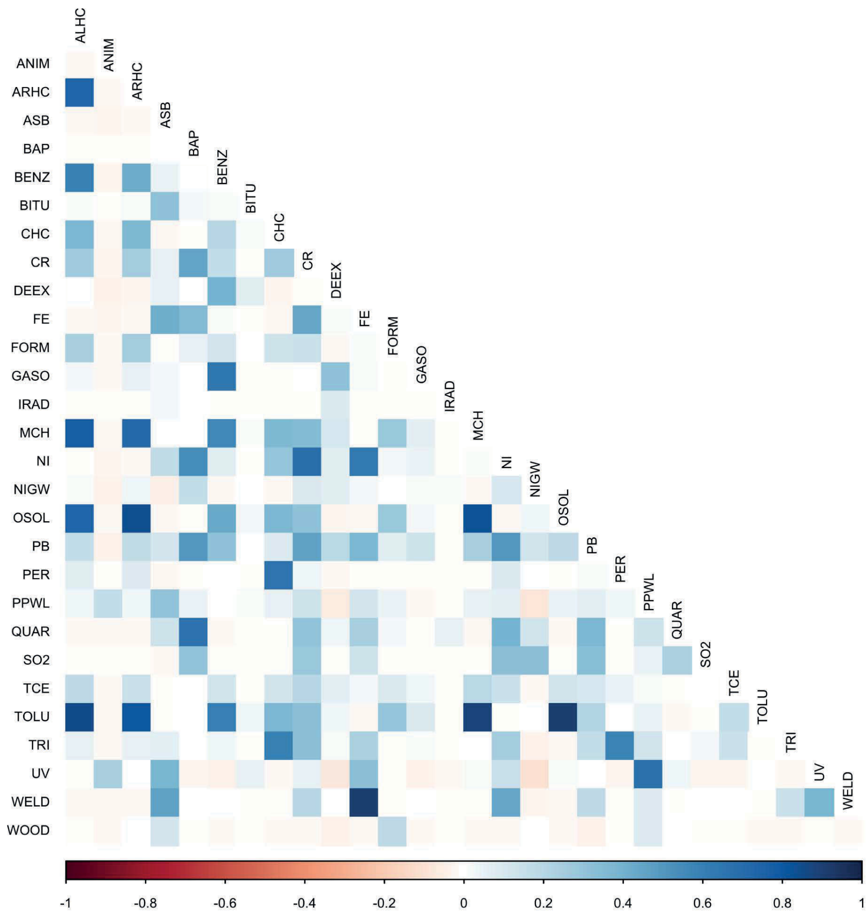
5.8.3 Study V

Conditional logistic regression was used to generate ORs and 95%CIs, testing the hypothesis that exposure to heavy metals (chromium (VI), iron, lead, and nickel) and welding fumes is associated with increased risk of kidney or renal pelvis cancer.

The final main effect model was created using the purposeful selection of variables (explained in detail by Bursac et al. (2008). The choice of this method of creating the model allowed avoiding "overfitting" of the model and generation of numerically unstable estimates.

In the first step, the univariable logistic regression model for each independent CE variable available in the NOCCA-JEM was fitted. Subsequently, a first multivariable logistic model was created in which all of the covariates, for which *p*-value of its Wald statistic was <0.25 in the univariable logistic model, were fitted. The significance level of 0.25 was recommended by Mickey et al. (1989). Variables describing heavy metal exposures were forced in the model as *a priori* selected variables of interest in this study. Next, the significance of each variable from the multivariable model was assessed using the Wald statistic. Covariates not contributing at the traditional significance level of $p<0.05$ were gradually eliminated. For each reduction, the difference between the values of the estimated coefficients, $\Delta\beta$, was calculated. Excluded variables for which $\Delta\beta > 20\%$ were added back into the model. Subsequently, the fit of the first multivariable logistic model was compared with the final one, deploying a likelihood ratio test.

The algorithm denoted aliphatic and alicyclic hydrocarbon solvents, asbestos, chlorinated hydrocarbon solvents, diesel engine exhaust, perceived physical workload, quartz dust, trichloroethylene, ultraviolet radiation, and wood dust, as significant/confounding covariates. Subsequently, correlation check between these agents was performed (Figure 12). Iron and welding fumes were highly correlated, and therefore they were not used in the same model. The final models were as follows: 1) ALHC + ASB + CHC + CR + DEEX + NI + PB + PPWL + QUAR + TRI + UV + WELD + WOOD; 2) ALHC + ASB + CHC + CR + DEEX + FE + NI + PB + PPWL + QUAR + TRI + UV + WOOD.



ALHC	Aliphatic and alicyclic hydrocarbon solvents	NI	Nickel
ANIM	Animal-borne dust	NIGW	Nightwork
ARHC	Aromatic hydrocarbon solvents	OSOL	Other organic solvents
ASB	Asbestos	PB	Lead
BAP	Benzo(a)pyrene	PER	Perchloroethylene
BENZ	Benzene	PPWL	Perceived physical workload
BITU	Bitumen fumes	QUAR	Quartz dust
CHC	Chlorinated hydrocarbon solvents	SO2	Sulphur dioxide
CR	Chromium	TCE	1,1,1-Trichloroethane
DEEX	Diesel engine exhaust	TOLU	Toluene
FE	Iron	TRI	Trichloroethylene
FORM	Formaldehyde	UV	Ultraviolet radiation
GASO	Gasoline	WELD	Welding fumes
IRAD	Ionizing radiation	WOOD	Wood dust
MCH	Methylene chloride		

Figure 12. Correlation of cumulative exposures calculated up to the index date minus ten years (in case-control set for Study V).

Each occupational agent was analyzed as a three-category exposure, including low (<50 percentile), moderate (≥50 percentile and <90 percentile), and high (≥ 90 percentile). Individuals with no exposure (defined as PxLxT=0) constituted a reference category. Subsequently, to assess a dose-response relationship between exposure to heavy metals (chromium (VI), iron, lead, and nickel) and welding fumes, and kidney or renal cancer, Pearson's chi-squared test for linear trend was performed. Unexposed individuals were excluded from the analysis of the trend test. To evaluate the robustness of the inferences *a posthoc* conservative Bonferroni procedure was adopted for multiple analyses (Dunn, 1961). The Bonferroni-corrected significance threshold was 0.004 (that is 0.05/13 variables). A *p*-value <0.004 was deemed as significant evidence for a causal association when assessing the significance of the trend test.

To explore possible effect modifiers, analyses were later stratified by sex and age group at diagnosis (<59, 59-74, >74). Age groups were *a priori* determined based on quartile distribution (that is <Q1, Q1-Q3, >Q3).

5.9 Software

Data management and statistical analyses for Studies I-IV were performed using Stata/IC 15.0 for Mac (StataCorp LP, College Station, TX, USA), and for Study V using R studio 1.1.442 with packages corrplot, dosresmeta, Epi, lmtest, readxl, ResourceSelection, survival, and xlsx.

5.10 Ethical issues

All of the studies presented in this thesis were scientific register-based studies conducted without direct contact to participating individuals. The studies consisted part of the NOCCA project. The NOCCA study has received approvals from all respective country-specific ethical committees. In the NOCCA project, individual-level data were used solely for scientific purposes, in accordance with legal regulations on privacy applicable in countries participating in NOCCA. The NOCCA project obeys strict rules to secure complete confidentiality and protection of the individuals.

The studies presented in this thesis were conducted according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines (Vandenbroucke et al., 2007).

6 RESULTS

6.1 Characteristics of the study population

6.1.1 Studies I and II

In Studies I and II, the whole NOCCA population (both males and females) was included (Table 11). The population encompassed 14.9 million individuals: 0.1 million from Iceland, 2.0 million from Denmark, 2.6 million from Norway, 3.4 million from Finland, and 6.8 million from Sweden, that contributed, in total, 385 million person-years of observation in follow-up.

In Study I, 85,940 cases of kidney cancer were identified (50,330 among males and 35,610 among females). In Study II, 11,237 cases of the renal pelvis cancers were identified (6,732 among males and 4,505 among females).

6.1.2 Studies III and IV

In Studies III and IV, only men from the NOCCA population were included (Table 11). The study population encompassed 7.4 million people: 0.1 million from Iceland, 1.0 million from Denmark, 1.3 million from Norway, 1.7 million from Finland, and 3.4 million from Sweden, who contributed, in total, 185 million person-years of observation in follow-up.

In Study III, 50,330 cases of kidney cancer were identified. In Study IV, 6,732 cases of renal pelvis cancer were identified.

6.1.3 Study V

In Study V, there were 59,778 kidney and renal pelvis cancer cases (34,856 males and 24,922 females) from Iceland, Finland, and Sweden (Table 11). For these cases, 298,890 sex-, age-, and country-matched controls were identified.

Table 11. Number of study participants, by study, country, sex, and age category.

	STUDY I	STUDY II	STUDY III	STUDY IV	STUDY V
Study population	14,902,573	14,902,573	7,447,726	7,447,726	358,668
Denmark	2,013,346	2,013,346	995,576	995,576	-
Iceland	120,995	120,995	61,439	61,439	3,528
Finland	3,404,800	3,404,800	1,670,815	1,670,815	105,882
Norway	2,562,674	2,562,674	1,286,261	1,286,261	-
Sweden	6,800,758	6,800,758	3,433,635	3,433,635	249,258
Number of cases	85,940	11,237	50,330	6,732	59,778
Male cases	50,330	6,732	50,330	6,732	34,856
Female cases	35,610	4,505	-	-	24,922

6.2 Standardized incidence ratios by occupational categories

6.2.1 Kidney cancer

In Study I, the highest (≥1.15) statistically significant SIRs of kidney cancer, for both sexes combined, were observed in welders (SIR 1.24, 95%CI 1.14-1.35), public safety workers (SIR 1.16, 95%CI 1.08-1.25), and seamen (SIR 1.16, 95%CI 1.07-1.26) (Table 12). The lowest (≤0.85) statistically significant SIRs were found in laboratory assistants (SIR 0.76, 95%CI 0.60-0.94) and forestry workers (SIR 0.77, 95%CI 0.72-0.83).

When stratified by sex, none of the above occupations was at a significantly elevated risk of developing kidney tumors among females (Table 12). However, elevated SIR was observed among female building caretakers (SIR 1.11, 95%CI 1.06-1.17) and economically inactive females (SIR 1.02, 95%CI 1.01-1.04). The lowest significant risk was observed in female dentists (SIR 0.57, 95%CI 0.33-0.91), technical workers (SIR 0.71, 95%CI 0.57-0.87), and laboratory assistants (SIR 0.72, 95%CI 0.51-0.97). The highest statistically significant SIRs in males were found in waiters (SIR 1.26, 95%CI 1.02-1.53), welders (SIR 1.25, 95%CI 1.14-1.36), cooks and stewards (SIR 1.23, 95%CI 1.05-1.44), seamen (SIR 1.16, 95%CI 1.07-1.26), and public safety workers (SIR 1.16, 95%CI 1.08-1.25). The lowest significant SIRs were observed in forestry workers (SIR 0.77, 95%CI 0.72-0.83) and farmers (SIR 0.78, 95%CI 0.75-0.80).

A statistically significant upward time trend of SIR, over the 45 years of follow-up, was observed among seamen and farmers. A statistically significant downward trend of SIR was observed among public safety workers. When stratified by age at the time of diagnosis, a statistically significant increase in SIR among farmers was observed. A significant decrease in SIR was observed among seamen.

Among the analyzed occupational categories, there were no statistically significant differences in SIR between the Nordic countries.

Table 12. The observed number of cases (Obs) and standardized incidence ratios (SIR) of kidney cancer in the Nordic Countries, by occupational category and sex.

Occupational category	Both sexes			Males			Females		
	Obs	SIR	95%CI	Obs	SIR	95%CI	Obs	SIR	95%CI
Administrators	2,453	1.06	1.02-1.11	2,300	1.08	1.04-1.13	153	0.84	0.71-0.99
Artistic workers	312	1.02	0.91-1.14	256	1.06	0.93-1.20	56	0.88	0.66-1.14
Assistant nurses	610	0.92	0.85-1.00	59	1.10	0.84-1.42	551	0.91	0.83-0.98
Beverage workers	70	1.07	0.84-1.36	52	1.13	0.84-1.48	18	0.95	0.56-1.49
Bricklayers	385	1.00	0.90-1.10	385	1.00	0.90-1.10	-	-	-
Building caretakers	2,343	1.09	1.05-1.14	531	1.02	0.93-1.11	1,812	1.11	1.06-1.17
Chemical process workers	643	0.93	0.86-1.01	570	0.93	0.85-1.01	73	0.98	0.77-1.23
Chimney sweeps	42	1.17	0.84-1.58	42	1.18	0.85-1.59	-	-	-
Clerical workers	4,366	0.99	0.96-1.02	1,810	1.06	1.01-1.11	2,556	0.94	0.90-0.98
Cooks and stewards	563	1.08	0.99-1.17	155	1.23	1.05-1.44	408	1.03	0.93-1.13
Dentists	106	0.91	0.75-1.11	89	1.04	0.83-1.28	17	0.57	0.33-0.91
Domestic assistants	871	0.95	0.89-1.01	4	0.72	0.20-1.84	867	0.95	0.89-1.02
Drivers	2,791	1.13	1.08-1.17	2,747	1.13	1.09-1.17	44	0.87	0.63-1.17
Economically inactive	21,174	1.02	1.01-1.04	2,575	1.03	0.99-1.07	18,599	1.02	1.01-1.04
Electrical workers	1,403	1.02	0.97-1.08	1,289	1.02	0.96-1.08	114	1.06	0.87-1.27
Engine operators	1,165	1.07	1.01-1.14	1,142	1.08	1.02-1.14	23	0.93	0.59-1.40
Farmers	5,263	0.80	0.78-0.83	4,458	0.78	0.75-0.80	805	1.00	0.93-1.07
Fishermen	575	1.08	0.99-1.17	572	1.08	1.00-1.18	3	0.53	0.11-1.56
Food workers	1,169	1.07	1.01-1.13	812	1.10	1.02-1.17	357	1.02	0.91-1.13
Forestry workers	858	0.77	0.72-0.83	849	0.77	0.72-0.83	9	0.86	0.39-1.63
Gardeners	2,320	0.91	0.87-0.94	1,233	0.84	0.80-0.89	1,087	0.99	0.93-1.05
Glassmakers	765	0.94	0.87-1.01	596	0.94	0.87-1.02	169	0.92	0.78-1.06
Hairdressers	268	1.03	0.91-1.16	119	1.11	0.92-1.33	149	0.97	0.82-1.14
Journalists	155	1.10	0.93-1.28	132	1.17	0.98-1.38	23	0.81	0.51-1.22
Laboratory assistants	83	0.76	0.60-0.94	42	0.80	0.58-1.09	41	0.72	0.51-0.97
Launderers	263	0.94	0.83-1.07	62	0.89	0.68-1.14	201	0.96	0.83-1.10
Mechanics	3,839	1.06	1.03-1.09	3,669	1.06	1.02-1.09	170	1.13	0.96-1.31
Military personnel	419	1.13	1.02-1.24	417	1.12	1.02-1.24	2	2.44	0.30-8.82
Miners and quarry workers	279	1.07	0.95-1.20	278	1.07	0.95-1.21	1	0.42	0.01-2.35
Nurses	422	0.87	0.79-0.96	7	0.72	0.29-1.49	415	0.87	0.79-0.96
Other construction workers	1,527	0.97	0.92-1.02	1,488	0.96	0.92-1.01	39	1.39	0.99-1.90
Other health workers	464	0.94	0.86-1.03	159	0.98	0.83-1.15	305	0.92	0.82-1.03
Other workers	2,338	0.99	0.95-1.03	1,671	0.97	0.93-1.02	667	1.03	0.96-1.12
Packers	1,594	1.07	1.02-1.13	1,264	1.06	1.01-1.13	330	1.11	0.99-1.24
Painters	679	0.95	0.88-1.03	671	0.96	0.89-1.04	8	0.61	0.26-1.20
Physicians	224	0.91	0.80-1.04	202	0.95	0.82-1.09	22	0.69	0.43-1.05
Plumbers	470	1.11	1.01-1.21	470	1.11	1.01-1.21	-	-	-
Postal workers	930	1.03	0.96-1.10	460	0.99	0.90-1.08	470	1.07	0.98-1.18
Printers	493	1.02	0.93-1.12	395	1.01	0.91-1.12	98	1.06	0.86-1.29
Public safety workers	793	1.16	1.08-1.25	768	1.16	1.08-1.25	25	1.22	0.79-1.80
Religious workers	995	0.95	0.89-1.01	751	0.98	0.91-1.05	244	0.87	0.76-0.99

Occupational category	Both sexes			Males			Females		
	Obs	SIR	95%CI	Obs	SIR	95%CI	Obs	SIR	95%CI
Sales agents	2,737	1.09	1.05-1.13	2,398	1.11	1.07-1.16	339	0.98	0.87-1.08
Seamen	628	1.16	1.07-1.26	628	1.16	1.07-1.26	-	-	-
Shoe and leather workers	269	1.01	0.89-1.14	186	1.03	0.89-1.19	83	0.97	0.77-1.20
Shop workers	3,166	1.04	1.00-1.08	1,347	1.13	1.07-1.19	1,819	0.98	0.94-1.03
Smelting workers	832	1.06	0.99-1.14	813	1.07	0.99-1.14	19	1.00	0.60-1.56
Teachers	1,872	0.87	0.83-0.91	1,088	0.88	0.83-0.93	784	0.86	0.80-0.92
Technical workers	3,734	1.03	1.00-1.06	3,646	1.04	1.01-1.08	88	0.71	0.57-0.87
Textile workers	1,462	1.01	0.96-1.06	475	1.01	0.92-1.11	987	1.01	0.95-1.07
Tobacco workers	34	1.25	0.87-1.75	12	1.47	0.76-2.56	22	1.16	0.73-1.75
Transport workers	997	1.09	1.03-1.16	956	1.09	1.02-1.16	41	1.23	0.88-1.67
Waiters	495	1.04	0.95-1.14	95	1.26	1.02-1.53	400	1.00	0.90-1.10
Welders	540	1.24	1.14-1.35	533	1.25	1.14-1.36	7	1.12	0.45-2.31
Woodworkers	2,692	0.93	0.90-0.97	2,602	0.93	0.89-0.97	90	0.96	0.77-1.18

CI - confidence interval.

6.2.2 Renal pelvis cancer

In Study II, the highest (≥1.15) statistically significant SIRs for renal pelvis cancer, for both sexes combined, were found among seamen (SIR 1.51, 95%CI 1.23-1.82), printers (SIR 1.39, 95%CI 1.11-1.71), welders (SIR 1.37, 95%CI 1.03-1.78), public safety workers (SIR 1.35, 95%CI 1.12-1.62), packers (SIR 1.23, 95%CI 1.07-1.41), textile workers (SIR 1.22, 95%CI 1.06-1.39), painters (SIR 1.22, 95%CI 1.00-1.46), transport workers (SIR 1.20, 95%CI 1.01-1.42), clerical workers (SIR 1.18, 95%CI 1.09-1.27), electrical workers (SIR 1.18, 95%CI 1.02-1.36), and food workers (SIR 1.16, 95%CI 1.01-1.34) (Table 13). The lowest (≤0.85) statistically significant SIRs were observed among forestry workers (SIR 0.47, 95%CI 0.35-0.62), gardeners (SIR 0.72, 95%CI 0.62-0.83), and woodworkers (SIR 0.81, 95%CI 0.72-0.91).

When stratified by sex, the highest SIRs were observed in seamen (SIR 1.51, 95%CI 1.23-1.82) and clerical workers (SIR 1.19, 95%CI 1.08-1.31) among males and females, respectively (Table 13). The lowest SIRs were found in forestry workers (SIR 0.48, 95%CI 0.36-0.62) in men, and religious workers (SIR 0.53, 95%CI 0.29-0.89) in women. All 95%CIs, calculated for both sexes separately, overlapped.

An ascending trend of the SIRs over the whole period of the follow-up was found among public safety workers. A descending tendency in the SIR was observed among food workers and packers. In the occupational categories stratified by age at the time of diagnosis, statistically significantly elevated SIRs were observed among printers and transport workers. A significant decline of SIRs was found in food workers.

No significant differences in SIRs were observed when stratified by countries.

Table 13. The observed number of cases (Obs) and standardized incidence ratios (SIR) of renal pelvis cancer in the Nordic Countries, by occupational category and sex.

Occupational category	Both sexes			Males			Females		
	Obs	SIR	95%CI	Obs	SIR	95%CI	Obs	SIR	95%CI
Administrators	399	1.09	0.98-1.20	365	1.08	0.97-1.19	34	1.20	0.83-1.68
Artistic workers	49	1.31	0.97-1.74	41	1.37	0.99-1.86	8	1.08	0.46-2.12
Assistant nurses	84	1.07	0.85-1.32	9	1.10	0.50-2.09	75	1.06	0.83-1.33
Beverage workers	15	1.05	0.59-1.73	8	0.75	0.32-1.47	7	1.94	0.78-3.99
Bricklayers	65	1.03	0.79-1.31	65	1.03	0.79-1.31	-	-	-
Building caretakers	301	0.97	0.87-1.09	76	1.02	0.80-1.28	225	0.96	0.84-1.09
Chemical process workers	95	1.09	0.88-1.33	81	1.06	0.84-1.32	14	1.30	0.71-2.17
Chimney sweeps	7	1.73	0.70-3.57	7	1.75	0.70-3.60	-	-	-
Clerical workers	684	1.18	1.09-1.27	262	1.15	1.02-1.30	422	1.19	1.08-1.31
Cooks and stewards	40	0.81	0.58-1.10	10	0.69	0.33-1.27	30	0.86	0.58-1.23
Dentists	17	1.13	0.66-1.80	15	1.31	0.73-2.16	2	0.55	0.07-2.00
Domestic assistants	109	0.94	0.77-1.13	-	-	-	109	0.94	0.77-1.13
Drivers	336	1.01	0.91-1.13	329	1.01	0.91-1.13	7	1.06	0.43-2.18
Economically inactive	2,578	0.97	0.93-1.00	335	1.08	0.97-1.20	2243	0.95	0.91-0.99
Electrical workers	191	1.18	1.02-1.36	169	1.16	0.99-1.35	22	1.33	0.83-2.01
Engine operators	106	0.85	0.70-1.03	104	0.85	0.69-1.03	2	1.24	0.15-4.48
Farmers	571	0.61	0.56-0.66	496	0.62	0.56-0.67	75	0.59	0.46-0.73
Fishermen	59	0.84	0.64-1.08	58	0.83	0.63-1.07	1	1.28	0.03-7.11
Food workers	203	1.16	1.01-1.34	145	1.18	0.99-1.38	58	1.14	0.86-1.47
Forestry workers	53	0.47	0.35-0.62	53	0.48	0.36-0.62	-	-	-
Gardeners	195	0.72	0.62-0.83	137	0.75	0.63-0.89	58	0.66	0.50-0.86
Glass makers.	120	1.08	0.90-1.29	100	1.10	0.90-1.34	20	0.97	0.59-1.50
Hairdressers	44	1.19	0.86-1.60	18	0.98	0.58-1.55	26	1.39	0.91-2.04
Journalists	19	1.15	0.69-1.80	13	0.94	0.50-1.61	6	2.26	0.83-4.91
Laboratory assistants	17	1.20	0.70-1.92	9	1.27	0.58-2.41	8	1.13	0.49-2.23
Launderers	40	0.99	0.70-1.34	7	0.65	0.26-1.34	33	1.11	0.76-1.56
Mechanics	521	1.13	1.04-1.24	494	1.12	1.02-1.22	27	1.47	0.97-2.14
Military personnel	49	1.00	0.74-1.32	49	1.00	0.74-1.32	-	-	-
Miners and quarry workers	28	1.02	0.68. 1.47	28	1.03	0.68-1.48	-	-	-
Nurses	68	1.05	0.81-1.33	2	2.20	0.27-7.93	66	1.03	0.80-1.31
Other construction workers	207	0.88	0.76-1.01	205	0.88	0.76-1.01	2	1.22	0.15-4.41
Other health workers	76	1.17	0.92-1.47	31	1.30	0.89-1.85	45	1.09	0.80-1.46
Other workers	371	1.09	0.98-1.21	278	1.09	0.97-1.23	93	1.09	0.88-1.34
Packers	208	1.23	1.07-1.41	177	1.24	1.06-1.44	31	1.17	0.80-1.66
Painters	112	1.22	1.00-1.46	111	1.22	1.00-1.47	1	0.99	0.03-5.51
Physicians	42	1.24	0.90-1.68	39	1.30	0.93-1.78	3	0.77	0.16-2.26
Plumbers	62	1.26	0.97-1.62	62	1.26	0.97-1.62	-	-	-
Postal workers	109	1.02	0.84-1.23	56	0.88	0.67-1.15	53	1.23	0.92-1.60
Printers	89	1.39	1.11-1.71	74	1.37	1.08-1.73	15	1.46	0.82-2.41
Public safety workers	118	1.35	1.12-1.62	115	1.35	1.11-1.62	3	1.44	0.30-4.20
Religious workers	106	0.88	0.72-1.07	92	0.98	0.79-1.20	14	0.53	0.29-0.89
Sales agents	302	1.10	0.98-1.24	267	1.10	0.97-1.24	35	1.13	0.78-1.57
Seamen	105	1.51	1.23-1.82	105	1.51	1.23-1.82	-	-	-
Shoe and leather workers	40	1.26	0.90-1.72	25	1.11	0.72-1.64	15	1.63	0.91-2.69
Shop workers	561	1.12	1.03-1.22	268	1.07	0.94-1.20	293	1.17	1.04-1.31
Smelting workers	131	1.13	0.94-1.34	129	1.13	0.94-1.34	2	0.99	0.12-3.57
Teachers	260	0.95	0.84-1.07	148	0.88	0.75-1.04	112	1.05	0.86-1.26
Technical workers	508	1.09	1.00-1.19	490	1.08	0.99-1.18	18	1.27	0.75-2.00
Textile workers	219	1.22	1.06-1.39	84	1.30	1.04-1.61	135	1.18	0.99-1.39
Tobacco workers	8	1.28	0.55-2.53	3	1.66	0.34-4.84	5	1.13	0.37-2.64

Occupational category	Both sexes			Males			Females		
	Obs	SIR	95%CI	Obs	SIR	95%CI	Obs	SIR	95%CI
Transport workers	142	1.20	1.01-1.42	140	1.21	1.02-1.43	2	0.79	0.10-2.87
Waiters	57	1.07	0.81-1.39	11	0.94	0.47-1.69	46	1.11	0.81-1.48
Welders	56	1.37	1.03-1.78	56	1.39	1.05-1.80	-	-	-
Woodworkers	285	0.81	0.72-0.91	281	0.82	0.72-0.92	4	0.48	0.13-1.22

CI - confidence interval.

6.3 Smoking-adjusted standardized incidence ratios by occupational categories

6.3.1 Prevalence of smoking

Prevalence of smoking among Nordic males, calculated using a simple regression model, is presented in Figure 13. The highest prevalence of smoking was estimated for the waiters (75.2%), tobacco workers (70.7%), and seamen (63.8%). The lowest prevalence of smoking was estimated for nurses (14.2%), teachers (17.9%), and dentists (18.3%).

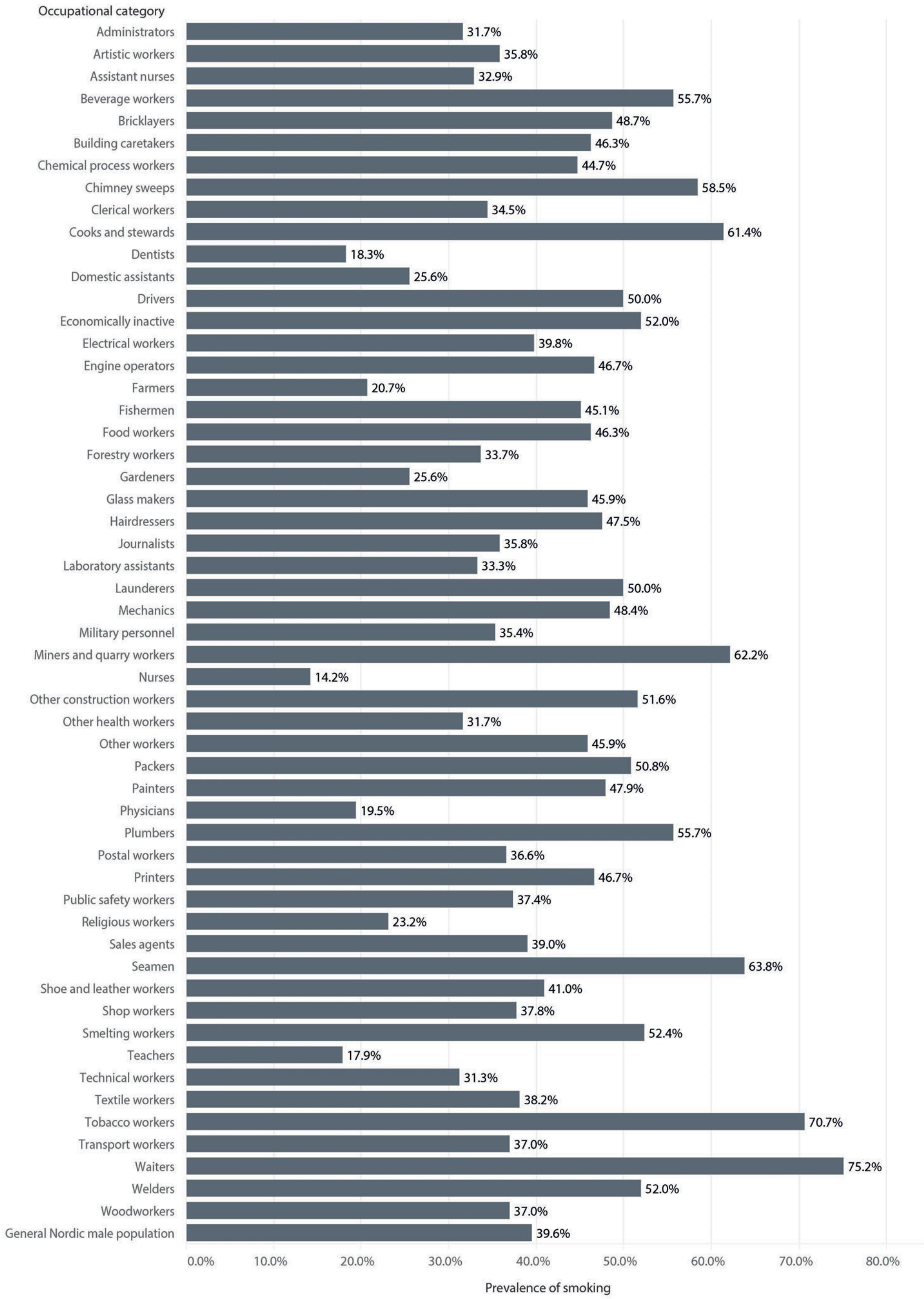


Figure 13. Prevalence of smoking among Nordic males estimated based on SIR of lung cancer (calculations based on Model B, Studies III and IV).

6.3.2 Kidney cancer

In Study III, SIR_{adj} estimates ≥1.15 were observed among dentists (SIR_{adj} 1.32, 95%CI 1.06-1.62), journalists (SIR_{adj} 1.20, 95%CI 1.00-1.42), physicians (SIR_{adj} 1.19, 95%CI 1.03-1.36), public safety workers (SIR_{adj} 1.18, 95%CI 1.10-1.26), administrators (SIR_{adj} 1.17, 95%CI 1.13-1.22), military personnel (SIR_{adj} 1.16, 95%CI 1.05-1.28), and religious workers (SIR_{adj} 1.17, 95%CI 1.09-1.26). The lowest smoking-adjusted SIR_{adj} (≤0.85) was observed among forestry workers (SIR_{adj} 0.82, 95%CI 0.76-0.88).

In most occupational categories, SIR_{adj} was closer to 1.0 than the non-adjusted SIR (34 of 54 occupational categories) (Figure 14). In the case of 18 occupational categories, the SIR shifted towards 1.0. The most notable changes in SIR resulting from the smoking-adjustment were observed among tobacco workers, waiters, dentists, nurses, teachers, physicians, seamen, and cooks and stewards.

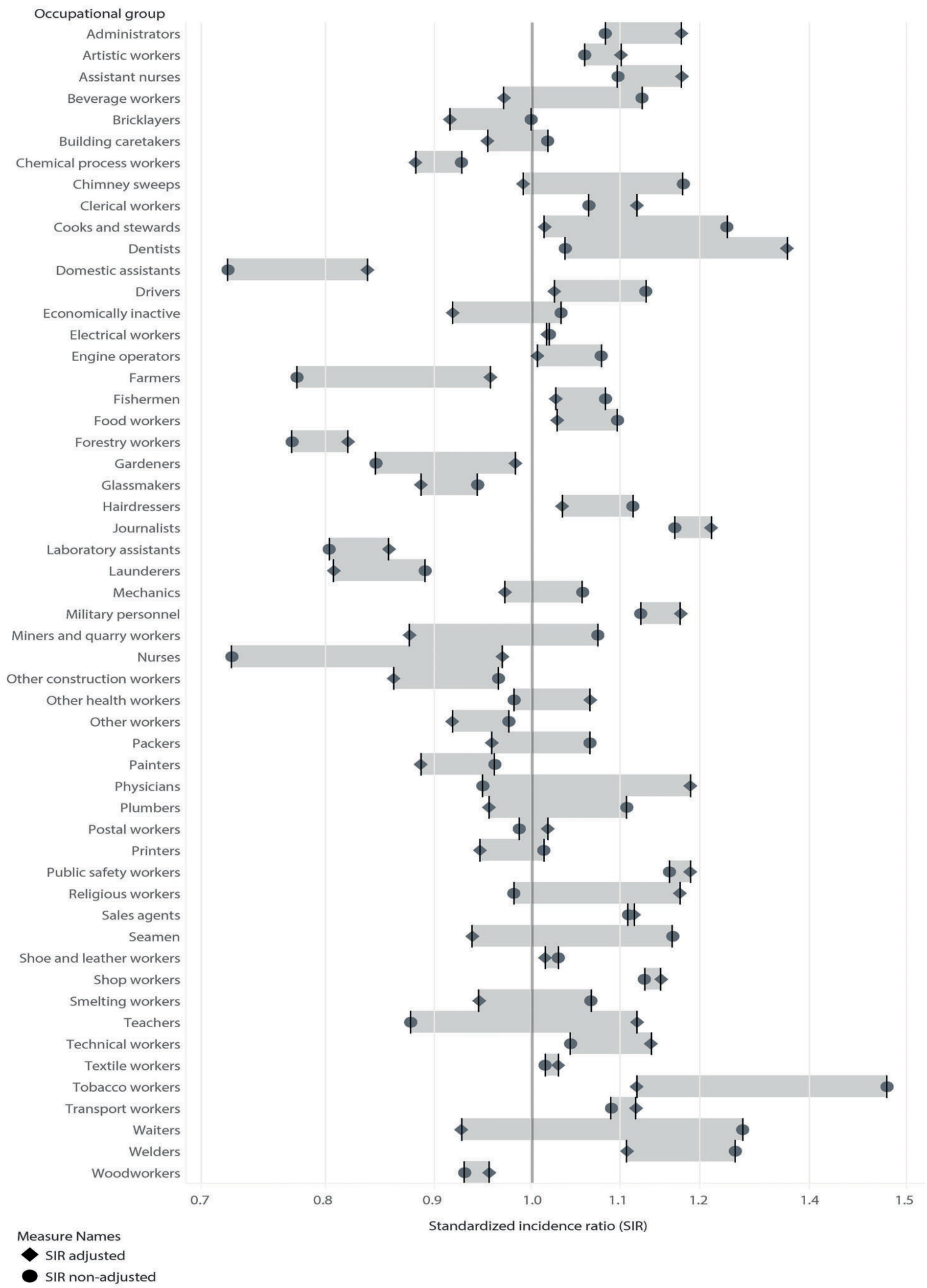


Figure 14. Non-adjusted and smoking-adjusted standardized incidence ratios (SIR) for kidney cancer, plotted for 53 occupational categories and one group of economically inactive among Nordic males (results for Model B).

6.3.3 Renal pelvis cancer

In Study IV, statistically significant SIR_{adj} estimates ≥1.15 were observed among physicians (SIR_{adj} 1.63, 95%CI 1.16-2.23), artistic workers (SIR_{adj} 1.43, 95%CI 1.03-1.94), public safety workers (SIR_{adj} 1.38, 95%CI 1.14-1.65), textile workers (SIR_{adj} 1.32, 95%CI 1.05-1.63), printers (SIR_{adj} 1.28, 95%CI 1.01-1.61), transport workers (SIR_{adj} 1.24, 95%CI 1.05-1.47), clerical workers (SIR_{adj} 1.21, 95%CI 1.07-1.37), technical workers (SIR_{adj} 1.18, 95%CI 1.08-1.29), and administrators (SIR_{adj} 1.17 1.05-1.30). The lowest smoking-adjusted SIR_{adj} (≤0.85) were observed among forestry workers (SIR_{adj} 0.51, 95%CI 0.38-0.66), farmers (SIR_{adj} 0.76, 95%CI 0.69-0.83), other construction workers (SIR_{adj} 0.78, 95%CI 0.68-0.90), engine operators (SIR_{adj} 0.79, 95%CI 0.65-0.96), and woodworkers (SIR_{adj} 0.84, 95%CI 0.74-0.94).

In the case of 22 out of 54 occupational categories, SIR_{adj} was closer to 1.0 than the non-adjusted SIR (Figure 15). In the case of eight occupational categories, the SIR shifted towards 1.0. The most notable changes in SIR resulting from the smoking-adjustment were observed among nurses, tobacco workers, dentists, physicians, seamen, chimney sweeps, waiters, and teachers.

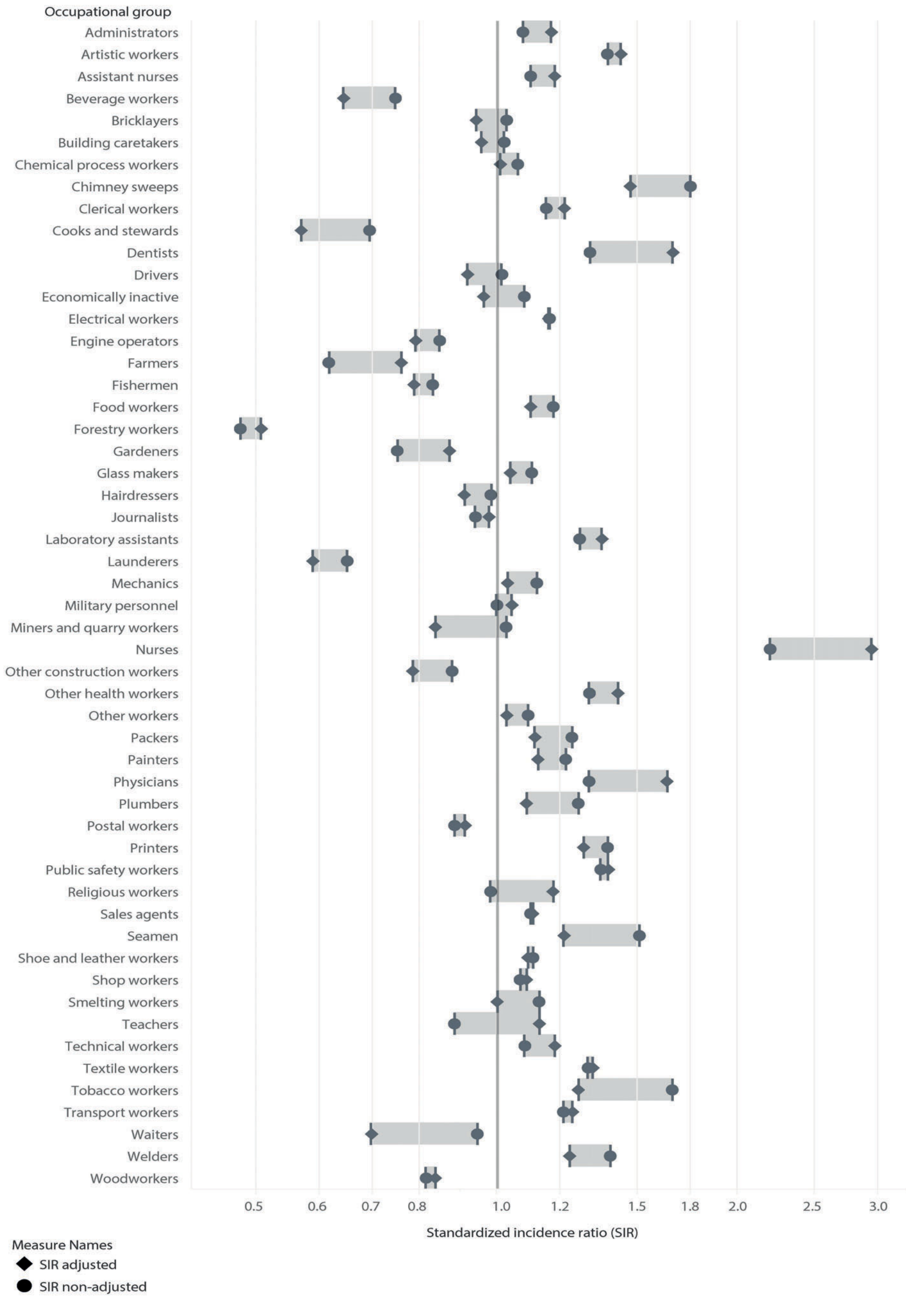


Figure 15. Non-adjusted and smoking-adjusted standardized incidence ratios (SIR) for renal pelvis cancer, plotted for 53 occupational categories and one group of economically inactive among Nordic males (results for Model B).

6.4 Exposure to heavy metals and welding fumes

In Study V, in the analysis of ORs for both sexes and all age groups combined, for none of the studied agents (heavy metals and welding fumes), the dose-response trend was statistically significant.

It was observed that the ORs in women were frequently higher than in men, although based on a much smaller number of cases (Figure 16). Moreover, moderate and high exposures to welding fumes were associated with excess risk in men. This may still not indicate that the absolute excess risk due to the exposure would be higher in women because the reference incidence level of kidney and renal pelvis cancer is much lower in women.

In the analysis with stratification by age at the index date (Figure 17), in the group of <59 years, OR for the high exposure to nickel was significant (OR 1.49, 95%CI 1.03-2.17). In the group of 59-74 years ORs for the following were statistically significant: high exposure to iron (OR 1.41, 95%CI 1.07-1.85), moderate exposure to welding fumes (OR 1.27, 95%CI 1.02-1.56), and high exposure to welding fumes (OR 1.43, 95%CI 1.09-1.89).

Males

Agent	Category of exposure	Cases	Controls
Chromium	low	3,004	14,314
	moderate	2,462	11,467
	high	585	3,011
Iron	low	2,607	11,956
	moderate	2,101	9,935
	high	570	2,544
Lead	low	3,427	15,978
	moderate	2,860	13,455
	high	672	3,432
Nickel	low	2,620	12,210
	moderate	2,149	10,054
	high	560	2,563
Welding fumes	low	2,485	11,877
	moderate	2,211	10,014
	high	581	2,540

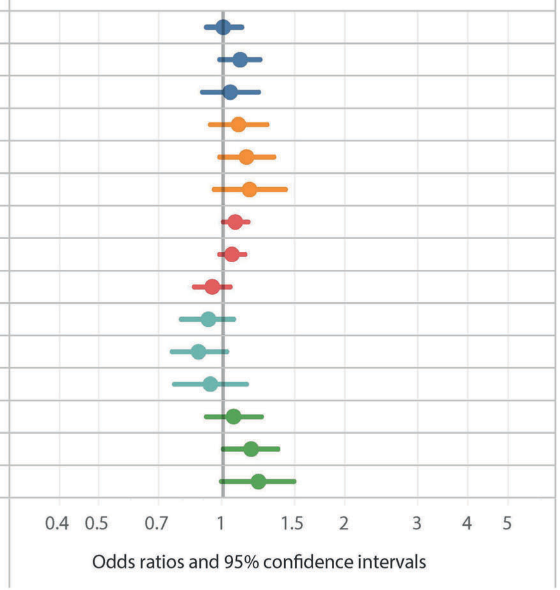


Figure 16a. Sex-specific odds ratios (OR) and 95% confidence intervals of kidney and renal pelvis cancer associated with exposures to heavy metals and welding fumes. (Chromium, iron, lead, nickel - OR estimates calculated using Model 2; Welding fumes - OR estimates calculated using Model 1).

Females

Agent	Category of exposure	Cases	Controls
Chromium	low	244	1,065
	moderate	185	786
	high	26	104
Iron	low	234	931
	moderate	105	442
	high	8	24
Lead	low	447	1,798
	moderate	180	821
	high	38	188
Nickel	low	239	1,017
	moderate	117	449
	high	19	65
Welding fumes	low	271	1,093
	moderate	70	286
	high	6	18

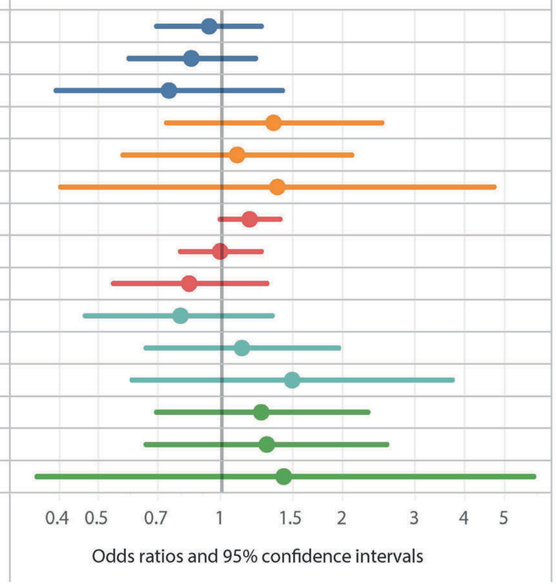


Figure 16b. Sex-specific odds ratios (OR) and 95% confidence intervals of kidney and renal pelvis cancer associated with exposures to heavy metals and welding fumes. (Chromium, iron, lead, nickel - OR estimates calculated using Model 2; Welding fumes - OR estimates calculated using Model 1).

Age at index date <59 years

Agent	Category of exposure	Cases	Controls
Chromium	low	1,183	5,365
	moderate	827	3,862
	high	79	387
Iron	low	1,125	4,958
	moderate	623	2,940
	high	72	323
Lead	low	1,683	7,722
	moderate	690	3,211
	high	79	366
Nickel	low	1,246	5,549
	moderate	485	2,329
	high	127	518
Welding fumes	low	1,086	4,975
	moderate	622	2,757
	high	112	489

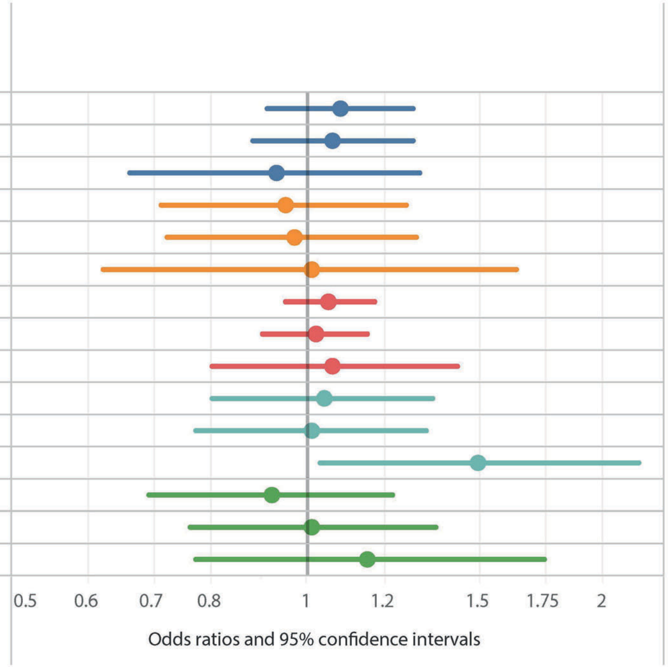


Figure 17a. Odds ratios (OR) and 95% confidence intervals of kidney and renal pelvis cancer associated with exposures to heavy metals and welding fumes, by age at the index date. (Chromium, iron, lead, nickel - OR estimates calculated using Model 2; Welding fumes - OR estimates calculated using Model 1)

Age at index date 59-74 years

Agent	Category of exposure	Cases	Controls
Chromium	low	1,474	7,187
	moderate	1,313	6,063
	high	297	1,569
Iron	low	1,297	6,047
	moderate	1,026	4,855
	high	335	1,511
Lead	low	1,624	7,524
	moderate	1,652	7,889
	high	330	1,664
Nickel	low	1,196	5,741
	moderate	1,187	5,455
	high	300	1,461
Welding fumes	low	1,200	5,767
	moderate	1,133	5,190
	high	324	1,454

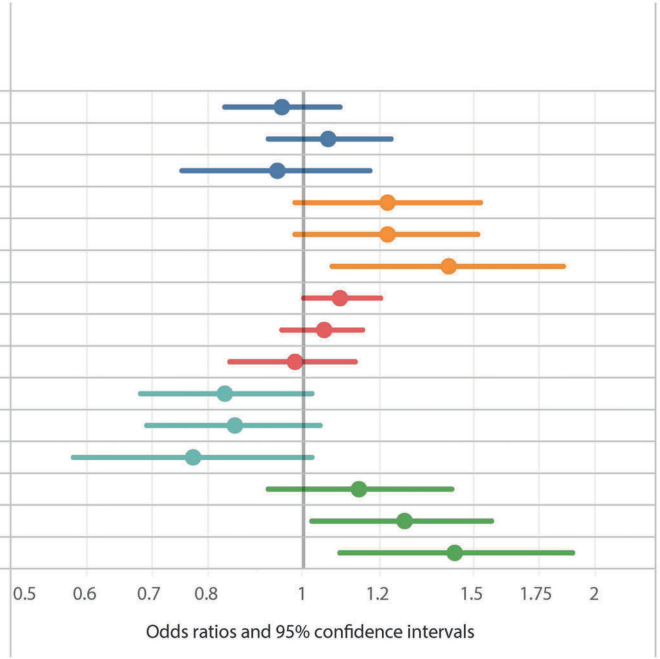


Figure 17b. Odds ratios (OR) and 95% confidence intervals of kidney and renal pelvis cancer associated with exposures to heavy metals and welding fumes, by age at the index date. (Chromium, iron, lead, nickel - OR estimates calculated using Model 2; Welding fumes - OR estimates calculated using Model 1)

Age at index date >74 years

Agent	Category of exposure	Cases	Controls
Chromium	low	591	2,827
	moderate	507	2,328
	high	235	1,159
Iron	low	419	1,882
	moderate	557	2,582
	high	171	734
Lead	low	567	2,530
	moderate	698	3,176
	high	301	1,590
Nickel	low	417	1,937
	moderate	594	2,719
	high	152	649
Welding fumes	low	470	2,228
	moderate	526	2,353
	high	151	615

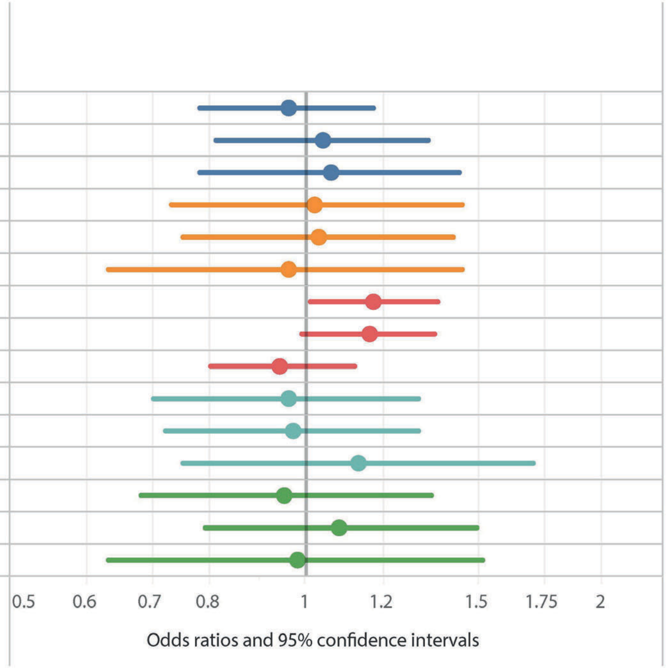


Figure 17c. Odds ratios (OR) and 95% confidence intervals of kidney and renal pelvis cancer associated with exposures to heavy metals and welding fumes, by age at the index date. (Chromium, iron, lead, nickel - OR estimates calculated using Model 2; Welding fumes - OR estimates calculated using Model 1)

6.5 Other occupational exposures

In Study V, further analysis of covariates revealed a statistically significant increase, more than 10%, of OR for high exposure to asbestos (OR 1.19, 95%CI 1.08-1.31) (Figure 18). Statistically significant, more than 10%, decrease of OR was observed among individuals characterized by high exposure to aliphatic and alicyclic hydrocarbon solvents (OR 0.81, 95%CI 0.69-0.95); high exposure to perceived physical workload (OR 0.86, 95%CI 0.82-0.91); moderate (OR 0.85, 95%CI 0.81-0.88), and high exposure (OR 0.85, 95%CI 0.79-0.92) to ultraviolet radiation (UV); and high (OR 0.82, 95%CI 0.71-0.94) exposure to wood dust. Dose-response test for trend was statistically significant for exposure to ultraviolet (p<0.001).

Agent	Category of exposure	Cases	Controls
Aliphatic and alicyclic hydrocarbon solvents	low	1,628	7,316
	moderate	1,223	5,931
	high	248	1,541
Asbestos	low	4,486	22,513
	moderate	3,646	17,947
	high	953	4,448
Chlorinated hydrocarbon solvents	low	702	3,344
	moderate	490	2,746
	high	125	684
Diesel engine exhaust	low	3,692	16,869
	moderate	2,863	12,931
	high	736	3,304
Perceived physical workload	low	17,375	84,989
	moderate	13,151	68,740
	high	2,932	17,541
Quartz dust	low	1,932	9,967
	moderate	1,567	7,952
	high	374	2,006
Trichloroethylene	low	1,760	8,118
	moderate	1,347	6,560
	high	355	1,619
Ultraviolet radiation	low	7,140	37,124
	moderate	5,213	30,198
	high	1,348	7,504
Wood dust	low	1,334	7,082
	moderate	1,062	5,670
	high	244	1,440

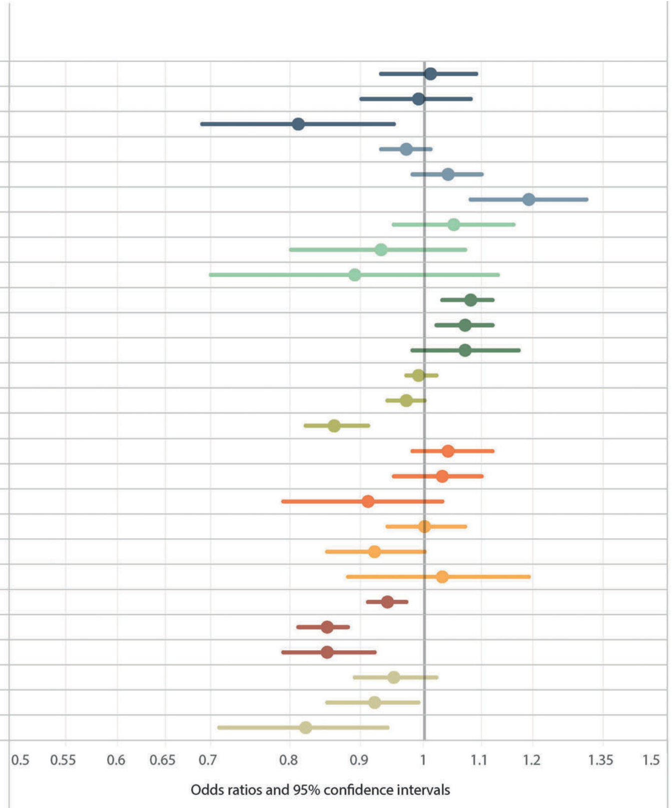


Figure 18. Odds ratios (OR) and 95% confidence intervals of kidney and renal pelvis cancer associated with other occupational exposures. (OR estimates calculated using Model 1).

7 DISCUSSION

7.1 Main findings of the research

7.1.1 Occupational variation and kidney cancer

Among the occupational categories that were covered by Study I, smoking non-adjusted risk of kidney cancer among both sexes was significantly elevated among welders, seamen, and public safety workers. Laboratory assistants, forestry workers, and farmers were at the lowest risk of the disease.

In Study III, where smoking-adjusted SIRs for the population of Nordic males were calculated, the highest SIR_{adj} of kidney cancer was observed among dentists, journalists, physicians, public safety workers, administrators, military personnel, and religious workers. The lowest smoking-adjusted risk was observed among forestry workers.

Study III provided an important opportunity to advance the understanding of how adjustment for smoking influences the distribution of SIR of kidney cancer. The most significant changes were observed among tobacco workers, waiters, dentists, nurses, teachers, physicians, seamen, and cooks and stewards. All of the above categories were characterized by the smoking frequency significantly different from the national average. In the case of waiters, seamen, and cooks and stewards, the change was fundamental because the SIR ceased to be statistically significant. Contrarily, in the case of dentists and physicians, after adjustment, SIR became statistically significant. The biggest change was observed for the teachers, who after smoking adjustment turned from decreased to increased risk of kidney cancer.

7.1.2 Occupational variation and renal pelvis cancer

In Study II, the highest smoking non-adjusted risk of developing renal pelvis cancer, for both sexes, was observed among seamen, printers, welders, public safety workers, packers, textile workers, painters, transport workers, clerical workers, electrical workers, and food workers. The lowest risk was found in forestry workers, gardeners, and woodworkers.

In Study IV, where smoking-adjusted SIRs for the population of Nordic males were calculated, the highest SIR_{adj} of renal pelvis cancer was observed among physicians, artistic workers, public safety workers, textile workers, printers, transport workers, clerical workers, technical workers, and administrators. The lowest smoking-adjusted risk was observed in forestry workers, farmers, other construction workers, engine operators, and woodworkers.

Study IV, like study III, provided an important opportunity to advance the understanding of how adjustment for smoking influences the SIR of renal pelvis cancer. The most significant changes were observed among nurses, tobacco workers, dentists, physicians, seamen, and chimney sweeps. All of the above categories were characterized by the smoking frequency significantly different from the national average. In the case of welders, seamen, packers, painters, mechanics, and gardeners the change was fundamental because the SIR ceased to be statistically significant. Contrarily, in the case of physicians, artistic workers, technical workers, administrators, engine operators, and other construction workers, after adjustment SIR became statistically significant.

7.1.3 Heavy metals and welding fumes

Study V was unable to demonstrate any significant, dose-dependent relationship between exposures to chromium (VI), iron, nickel, lead, and welding fumes and the risk of developing kidney or renal pelvis cancer.

Among individuals diagnosed under the age of 59 years, a link may exist between exposure to nickel and the risk of kidney or renal pelvis cancer.

The value of ORs among the individuals diagnosed between the age of 59 and 74, and characterized by moderate and high cumulative exposures to welding fumes, and high cumulative exposures to iron, suggests that a weak link may exist between exposure to welding fumes or iron and risk of developing kidney or renal pelvis cancer. Concurrent exposure to iron and welding fumes hinders understanding of their independent roles as risk factors.

In the case of the other ORs identified in the study (low cumulative exposure to lead), the possibility of chance findings cannot be excluded.

7.1.4 Other covariates

The results of Study V indicate that there is a positive association between exposures to asbestos and diesel engine exhaust and the risk of kidney or renal pelvis cancer. Furthermore, the exposures to physical workload, wood dust, and UV were found to be associated with a lower risk of kidney or renal pelvis cancer.

7.2 Possible explanations for the findings and comparison with the previous literature

7.2.1 Occupational variation

Physicians and dentists

An unexpected finding is the elevated and statistically significant smoking-adjusted SIR of kidney cancer (Study III) among dentists and physicians and elevated and statistically significant smoking-adjusted SIR of renal pelvis cancer (Study IV) among physicians. To the author's knowledge, these are the first studies reporting an elevated risk of developing kidney and renal pelvis cancer among above occupational categories.

Previously, some studies indicated an elevated risk of oral cancer (Tarvainen et al., 2017) and cutaneous squamous cell carcinoma (Alfonso et al., 2016) among dentists, and a higher risk of developing breast cancer (Katuwal et al., 2018) and seminoma (Ylonen et al., 2018) among physicians.

Health care providers can be exposed both to X-radiation and gamma radiation, that are electromagnetic radiations, distinguished by their origin. They are used not only while applying some of the techniques of medical imaging *sensu stricto*, but also while performing surgical procedures and in catheterization labs. Up to now, there is no literature on the association of exposure to X-radiation or gamma radiation and risk of kidney or renal pelvis cancer among health care providers. However, according to the IARC, they are carcinogenic agents to the kidney with sufficient evidence in humans (IARC, 2019b).

Furthermore, in the past, in their clinical practice health care providers used trichloroethylene. This nonflammable liquid is currently best known for its use as a solvent. However, previously, it was very popular as a volatile general anesthetic medium and self-administered anesthesia during childbirth. The introduction of halothane in 1956 greatly diminished its use, and until the 1980s, it was abandoned by most of the developed countries. Trichloroethylene was recognized as the cause of kidney cancer by the IARC (IARC, 2019b). Nevertheless, no studies on elevated exposure to trichloroethylene and carcinogenic risk among health care providers were published. There was one study reporting an increased risk of miscarriages among nurses exposed to unspecified concentrations of trichloroethylene in operating rooms (Corbett et al., 1974). However, due to limitations of the study, including possible bias due to concomitant exposure to other chemicals, the risk of miscarriages could not be conclusively attributed to exposure to trichloroethylene.

One more possible cause of elevated risk of renal pelvis cancer among healthcare providers is exposure to phenacetin. Phenacetin is an analgesic and antipyretic drug that, in the past, was extensively used for medical purposes. However, its implication in nephropathy and methemoglobinemia led to its withdrawal from the market in the 1980s. According to IARC, phenacetin is carcinogenic to human renal pelvis (IARC, 2019b). However, there are no studies on healthcare providers being at elevated exposure to phenacetin. The literature on addiction to analgesic drugs being prevalent among healthcare providers is sparse (Oyler, 1986). Hence suggesting, that phenacetin misuse would be common to such an extent to influence the general risk of renal pelvis cancer in the whole occupational category, would be groundless and speculative.

Above-mentioned exposures might be partially an explanation of an elevated SIR_{adj} of kidney cancer or renal pelvis cancer among healthcare provider. However, to obtain a full understanding of these findings, they should be scrutinized in future research.

Journalists and artistic workers

Another unexpected finding was an elevated smoking-adjusted risk of kidney cancer among journalists (Study III), and smoking-adjusted risk of renal pelvis among artistic workers (Study IV). According to the author’s knowledge, this is the first study reporting such findings. Previously, Tarvainen et al. (2008; 2017) described an increased risk of mouth and pharynx cancer among journalists and artists. The sedentary nature of the work might be essential to the increase of cancer risk in these occupational categories.

Public safety workers

Both in the case of the kidney (Study III) and renal pelvis cancer (Study IV) elevated smoking-adjusted SIR was observed among public safety workers. The category included workers who protect individuals and property against hazards and enforcers, i.e., firefighters, police officers, detectives, customs officers, and guards.

Unlike in the case of journalists and artists, literature regarding public safety workers and the risk of kidney cancer is extensive (Baris et al., 2001; Glass et al., 2017; Glass et al., 2016; Ide, 2014; Kang et al., 2008; Kleinman et al., 2015; Ma et al., 1998; Tsai et al., 2015). Glass et al., observed SIR 0.82 (95%CI 0.71-0.94) for volunteer firefighters (Glass et al., 2017), and SIR 1.08 (95%CI 0.81-1.41) for paid firefighters (Glass et al., 2016). However, they reported an upward trend of the relation of the risk of developing kidney cancer to employment duration. Such results may be partly attributed to the "healthy worker effect". Firefighters are exposed to volatile organic compounds and polycyclic aromatic hydrocarbons, both due to firefighting and using personal protective equipment (Baxter et al., 2014; Driscoll et al., 2016; Harrison et al., 2018; Lacey et al., 2014; Stec et al., 2018). Besides, increased exposures to asbestos, hydrogen chloride, and cyanide were reported in this occupational category (Melius, 2001). None of these compounds have been recognized by the IARC as factors associated with an increased risk of kidney cancer (IARC, 2019b).

Occupational category and physical activity

It is noteworthy that according to FINJEM (Kauppinen et al., 2009), most of the occupational categories, in which elevated smoking-adjusted SIR of kidney cancer or renal pelvis cancer was identified (dentists, journalists, physicians, administrators, artistic workers, and religious workers) are characterized by the lack of perceived physical workload. Low level of physical effort or sedentary work may be associated with an increased BMI which, according to IARC, is a risk factor of kidney cancer (Moch et al., 2016).

Based on data from annual surveys of the Finnish Public Health Institute (Helakorpi et al., 2002), the proportion of people whose BMI was 25 or higher was in the highest quartile for journalists, military personnel, religious workers, and some of the public safety workers (police officers, guards, customs officers). Notwithstanding, in the case of dentists, physicians, and firefighters in Finland, the proportion of those in the occupation whose BMI was 25 or higher was in the lowest quartile. No similar data from the other Nordic countries were available.

7.2.2 Exposure to heavy metals and welding fumes

Welding fumes

In Study V, the weak association between exposure to welding fumes and the risk of kidney cancer was observed. These results corroborate the findings presented in Studies I and II, and those of MacLeod et al. (2017). Furthermore, they are in accordance with the position of the IARC (2019b).

In Studies I-V, the definition of welders included individuals who join and cut metal parts using flame, electric arc and other sources of heat to melt and cut or fuse metal. It should be noted, that the exposures of welders may vary depending on their actual job. Hence, it would be beneficial if the NOCCA-JEM, similarly to its Finnish equivalent FINJEM, would combine exposure estimates for occupation and industry (e.g., "welder in stainless steel industry"; see (Kauppinen et al., 1998)). Unfortunately, there was no access to industry codes for all Nordic countries.

The known occupational exposures among welders are fumes, gases, UV radiation, electromagnetic fields, and co-exposure to asbestos and solvents (Guha et al., 2017). In future research it is needed to determine what is their association with the risk of kidney and renal pelvis cancer.

Iron

The higher OR among females exposed to iron and welding fumes, reported in Study V, might imply possible higher biological susceptibility of the female kidney to metals. Such hypothesis was already suggested in the literature (Johnson et al., 2003). Nevertheless, due to the very few women ever employed in metal industry, it is challenging to confirm sex differences even in such a large study. One should also avoid direct comparison of the relative risk estimates between sexes because the incidence of kidney cancer in unexposed women used as the reference is much lower than in men.

Lead

Previously, researchers noted the significance of exposure to lead as a possible risk factor for kidney or renal pelvis cancer (Boffetta et al., 2011; Ilychova et al., 2012). However, in Study V such association does not appear to be the case. There are many plausible interpretations of this discrepancy. One of them might be the fact that the previous studies were based on small study populations. This inconsistency may also be caused by the fact that the regression models in the earlier studies included lower number of variables of interest. It could be argued that the positive results of those studies were caused by the fact that no covariates were included.

For the purpose of the discussion, one more set of two conditional logistic regression models was created, in which only heavy metals and welding fumes were included, i.e., S1) CR + NI + PB + WELD, and S2) CR + FE + NI + PB. These experiments were designed to estimate what effect heavy metals and welding fumes would have on ORs, if they were the only occupational exposure factors included in the final multivariable model, that is, data for only five occupational agents instead of 29 would be available. These experiments confirmed that for smaller models that do not include other covariates, ORs are mostly higher (Table 14).

Table 14. Odds ratios (OR) and 95% confidence intervals (95%CI) of kidney and renal pelvis cancer associated with exposures to heavy metals and welding fumes, based on regression models with no additional covariates.

Agent (unit)	Cumulative exposure	Cases	Controls	OR_a	95%CI	OR_b	95%CI
Chromium b (µg/m3-years)	unexposed	53,272	268,143	1.00	Ref	1.00	Ref
	low	3,248	15,379	0.99	0.91-1.09	0.91	0.84-0.98
	moderate	2,647	12,253	1.07	0.96-1.18	0.91	0.84-0.99
	high	611	3,115	0.99	0.86-1.15	0.81	0.72-0.92
Iron b (mg/m3-years)	unexposed	54,153	273,058	1.00	Ref	1.00	Ref
	low	2,841	12,887	1.09	0.94-1.27	1.22	1.06-1.41
	moderate	2,206	10,377	1.10	0.95-1.28	1.16	1.01-1.34
	high	578	2,568	1.15	0.94-1.39	1.21	1.03-1.44
Nickel b (µg/m3-years)	unexposed	54,074	272,532	1.00	Ref	1.00	Ref
	low	2,859	13,227	0.92	0.80-1.06	0.93	0.82-1.07
	moderate	2,266	10,503	0.90	0.78-1.04	0.98	0.86-1.12
	high	579	2,628	0.99	0.82-1.20	1.06	0.89-1.26
Lead b (µmol/l-years)	unexposed	52,154	263,218	1.00	Ref	1.00	Ref
	low	3,874	17,776	1.09	1.03-1.16	1.10	1.04-1.17
	moderate	3,040	14,276	1.06	0.99-1.13	1.06	1.00-1.12
	high	710	3,620	0.95	0.86-1.05	0.97	0.88-1.06
Welding fumes a (mg/m3-years)	unexposed	54,154	273,062	1.00	Ref	1.00	Ref
	low	2,756	12,970	1.05	0.90-1.22	1.15	1.00-1.33
	moderate	2,281	10,300	1.14	0.98-1.33	1.21	1.05-1.39
	high	587	2,558	1.20	0.99-1.46	1.21	1.02-1.43

a OR estimates calculated using Model 1 (welding fumes) and Model 2 (chromium, iron, nickel, and lead).
b OR estimates calculated using Model S1 (welding fumes) and Model S2 (chromium, iron, nickel, and lead).

Chromium (VI) and Nickel

Observations on lack of association between the exposure to chromium (VI) and the risk of kidney or renal pelvis cancer are consistent with the literature (Boffetta et al., 2011).

In Study V it was observed that among individuals diagnosed under the age of 59 years, a link may exist between exposure to nickel and the risk of kidney or renal pelvis cancer. These findings are somewhat opposing to Boffetta et al., who reported the OR of RCC in the population ever occupationally exposed to nickel at 0.51 (95%CI 0.27-0.94) (Boffetta et al., 2011).

Cadmium

The link between cadmium, kidney toxicity, and estrogens was previously described in the literature (Johnson et al., 2003) in the connection with the estrogenic features of the kidney (Maric, 2009). Unfortunately, in Study V, examining the possible association between occupational exposure to this metal and risk of kidney cancer was impossible, since estimates for cadmium exposure are not incorporated in the NOCCA-JEM.

7.2.3 Other covariates

The findings of Study V indicate a positive association between exposure to asbestos and the risk of kidney cancer. Similar observations were reported in the earlier research (Peters et al., 2018; Sali et al., 2000). Moreover, an elevated risk of kidney or renal pelvis cancer among individuals exposed to diesel engine exhaust was found. This findings are consistent with that of Peters et al. (2018) and Boffetta et al. (2001).

Furthermore, in Study V, the physical workload was found to be connected with a decreased risk of kidney or renal pelvis cancer. Such results are likely to be related to the findings, that obesity is associated with a higher risk of kidney cancer (Ildaphonse et al., 2009; Mathew et al., 2009; Sawada et al., 2010).

Moreover, exposure to wood dust was found to be associated with a decreased risk of developing kidney cancer. Although lower SIR of kidney cancer among woodworkers was already reported in the literature(Pukkala et al., 2009), a full understanding of how exposure to wood dust contributes to the risk of kidney cancer is still missing. The above results need to be interpreted with caution as there is a positive correlation between exposure to wood dust and exposure to perceived physical workload (Figure 12).

Eventually, an unanticipated observation of Study V was that exposure to UV radiation was associated with a lower risk of kidney cancer. The test for trend confirmed a dose-response effect. A plausible explanation for this might be an increased level of vitamin D due to sunlight exposure. These results might support the conceptions of Darling et al. (Darling et al., 2016). Here, again, a note of caution is due since a positive correlation between exposure to UV radiation and exposure to perceived physical workload exists (Figure 12).

7.3 Strengths of the studies

To the knowledge of the author, the presented set of studies is so far the most extensive research project in terms of a number of observed cancer cases dealing with the association between the occupation and incidence of kidney and renal pelvis cancer. The large sample size is the main strength of the presented research. Moreover, these are the only studies so far that benefit from data covering the entire national populations, making the presented results population-representative and generalizable.

Another important strength of the presented studies is precise coding of occupation in all Nordic countries. Furthermore, all linkages between the census data, the mortality and emigration data, were based on the unique personal identity codes which guarantees a match close to accurate (Pukkala, 2011). The method of the linkage, by definition, ensured a complete ascertainment of relevant events.

Further, a significant advantage of the presented investigation is a high-quality standard maintained by all Nordic Cancer Registries regarding the completeness and accuracy of the registered data (Pukkala et al., 2018). Close to 100% coverage of incident cases has been reported in each of the registries.

7.4 Limitations of the studies

A major limitation of Studies I and II was the lack of data stratification regarding smoking. Due to the lack of data on smoking at the individual level, simple regression models were created, in which the proxy of smoking prevalence by occupation in the Nordic countries was determined using SIR of lung cancer (Studies III and IV). It was assumed that the relationship between smoking prevalence and lung cancer would be similar in a given occupational category for all Nordic countries. The models were characterized by satisfactory coefficients of determination (Model A $r2=0.57$; Model B $r2=0.58$). Results of Studies III and IV support clarification that the differing smoking patterns do not justify all the occupational variation in risk.

Another limitation of presented studies was no stratification regarding BMI, which is likely to affect the results to some extent. Other known risk factors for renal cancer not taken into consideration in the presented research are hereditary tumors, such as von Hippel-Lindau syndrome, Birt-Hogg-Dubé syndrome, tuberous sclerosis, and constitutional chromosome 3 translocations. Since the above conditions are rare and not associated with any of the professions, possible confounding of the results is unlikely.

In Studies I-IV broad professional categories may conceal the association between individual occupational exposures and risk of disease. However, in those studies, it was aimed to assess occupational variation in the incidence of kidney and renal pelvis cancers, not to evaluate specific occupational exposures.

In Studies I-IV, since the occupational categories were based on the data from the first available census, there is a possibility of exposure misclassification, which could bias the observed effect towards the null. However, such dilution is probably rather small due to high occupational stability in the Nordic countries (Notkola et al., 1997).

In Study V, due to the limited data on professional history, which was assessed only during censuses, it was assumed that there were no changes between the age of 20 years and the earliest known census occupation, nor between the latest known census occupation and age of 65 years.

7.5 Implications for the field of knowledge and suggestions for future research

The presented findings contribute in several ways to our knowledge of risk factors for kidney and renal pelvis cancer and provide a basis for further future investigation of some of them.

The present study appears to be the first one to compare the occupational variation in the incidence of kidney, and renal pelvis cancers prior and post adjustment for smoking. It confirmed that different prevalence of smoking among different professional categories plays a pivotal role in such variation.

Furthermore, this doctoral project adds to the growing body of research that indicates there is a positive association between exposure to welding fumes, iron, nickel, diesel engine exhaust, and asbestos and increased risk of kidney or renal pelvis cancer.

Further research should focus on determining the possible implications of the presented and similar studies for policymaking and clinical practice. There is a need to combine the results from multiple studies to increase power and to resolve ambiguity when reports oppose. Such an effort should be undertaken by a multidisciplinary group of scientists, including epidemiologists, statisticians, occupational hygienists, and clinicians.

After conducting such a comprehensive meta-analysis, several questions still should be answered. The research in the field of health economics should aim to garner some useful insights on in case of which occupations it would be profitable to implement routine screening for renal tumors. Policymakers should implement legislation that enforces the reduction of exposure to agents possibly hazardous to workers' health, alternatively provides access to protection measures reducing such exposure.

8 CONCLUSIONS

The overall goal of the thesis was to assess the association between occupational exposures and risk of kidney and renal pelvis cancer. The results of this investigation show that there is an association between occupation and the risk of these diseases.

Multifarious prevalence of smoking among different occupational categories plays an important role in occupational variation in the incidence of both kidney cancer and renal pelvis cancer. This confirms an essential role of tobacco smoking as a risk factor for the above malignancies. Nevertheless, the results of the presented research support clarification that the differing smoking patterns do not justify all the occupational variation in the risk.

The studies identified that the smoking-adjusted incidence of kidney and renal pelvis cancers is considerably higher among occupations with higher education and in public safety workers. One of the characteristics in many of these occupations is a low physical workload.

In the nested case-control study, there was no association between exposure to chromium (VI) or lead and the risk of kidney or renal pelvis cancer. Multiple regression analysis revealed that there is an elevated risk of kidney or renal pelvis cancer under the age of 59 in individuals with high exposure to nickel. Moreover, among individuals diagnosed with kidney or renal pelvis cancer at the age of 59-74, the risk was elevated for high exposure to iron, and moderate and high exposure to welding fumes. Concurrent exposure to the later agents may hinder interpretation of their roles as independent risk factors.

The results of the analysis of covariates in the above study indicate that there is a positive association between exposures to asbestos and diesel engine exhaust and the risk of kidney or renal pelvis cancer. Furthermore, the exposures to physical workload, wood dust, and UV were found to be associated with a lower risk of kidney or renal pelvis cancer.

This thesis has provided a deeper insight into the association between occupational exposures and risk of kidney and renal pelvis cancer. It lays the groundwork for future research into risk factors for kidney and renal pelvis cancer.

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APPENDIX
I

Protocol for a systematic review of the literature

Occupational exposures associated with kidney cancer: a systematic review

Irmina Michalek, Florentino Luciano Caetano dos Santos

Citation

Irmina Michalek, Florentino Luciano Caetano dos Santos. Occupational exposures associated with kidney cancer: a systematic review. PROSPERO 2018 CRD42018106954 Available from:
https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018106954

Review question

To analyse available evidence from epidemiological studies to examine occupational exposures associated to kidney cancer

Searches

The authors will carry out a systematic review of publications indexed in an electronic medical database - PubMed.

The literature search strategy will include MeSH terms such as „Kidney neoplasms"[MeSH], „Environmental exposure"[MeSH], „Occupational exposure"[MeSH], „Maternal exposure"[MeSH], „Paternal exposure"[MeSH], and „Risk factors"[MeSH].

The database mentioned above will be searched from its inception date to the 1st of September 2018. Additionally, the lists of references in identified publications will be manually searched.

When searching for literature, no language, regional, or temporal restrictions will be applied.

Types of study to be included

Inclusion criteria: Case-control studies, cohort studies, population studies, or cross-sectional studies.

Exclusion criteria: Editorials, reviews, case reports, or case series.

Condition or domain being studied

Kidney cancer

Participants/population

Adult, economically active individuals

Intervention(s), exposure(s)

Occupational exposures in adulthood

Comparator(s)/control

Not applicable

Context

Main outcome(s)

Occupational exposures associated with kidney cancer

Additional outcome(s)

Not applicable

Data extraction (selection and coding)

Risk of bias (quality) assessment

Two reviewers (IMM and FLCS) will independently assess the quality of included studies and the potential for risk of bias will be evaluated. The "Newcastle-Ottawa Quality Assessment Scale" will be used for assessing the methodological quality of the included studies. Discrepancies will be resolved by discussion.

Strategy for data synthesis

Based on pilot study, methodological and statistical heterogeneity across studies is expected. Hence, conducting meta-analyses of the evidence base might be challenging. Thus, a narrative synthesis will be employed to synthesise the data. However, the possibility of meta-analysis using random-effects modelling will be reconsidered after completing data extraction.

Analysis of subgroups or subsets

Where possible, we will conduct subgroup analyses based on the age groups, gender, and location of the tumor (kidney, renal pelvis, both).

Contact details for further information

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Type and method of review

Systematic review

Anticipated or actual start date

01 July 2018

Anticipated completion date

31 December 2018

Funding sources/sponsors

None

Conflicts of interest

Language

English

Country

Finland

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Humans; Kidney Neoplasms; Occupational Exposure

Date of registration in PROSPERO

30 August 2018

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26 September 2018

Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions

30 August 2018
26 September 2018

APPENDIX II

Description of cohort studies included in the chapter “2.4.6 Occupational exposures” and assessment of their quality according to the Newcastle-Ottawa Scale

Table 1. Description of cohort studies included in the chapter "2.4.6 Occupational exposures" and assessment of their quality (selection, comparability, outcome) according to the Newcastle-Ottawa scale.

Reference	Country	Measurement of exposure	Measure of association was adjusted for	Measure of association was stratified by	Selection						Comparability		Outcome				
					A		B	C		D	E		F		G	H	
Attfield et al. (2004)	USA	Self-reported during health surveillance program	-	-	-	-	★	-	★	-	-	-	-	★	-	-	-
Birk et al. (2009)	Germany	Employer-administered records	-	Sex	-	-	★	★	-	-	-	★	-	★	★	-	-
Baris et al. (2001)	USA	Employer-administered records	-	Duration of employment	-	-	★	★	-	-	-	-	-	-	★	-	-
Blair et al. (2003)	USA	Employer-administered records	-	Race Sex	-	-	★	★	-	-	-	-	-	★	★	-	-
Boice et al. (2006)	USA	Employer-administered records	Year of birth Year of hire	Time since first exposure	-	-	★	★	-	-	-	-	-	-	★	-	-
Boffetta et al. (1998)	Italy Slovenia Spain Ukraine	Employer-administered records	Age Country Calendar period Time since first exposure Estimated cumulative exposure	-	-	-	★	★	-	-	★	★	-	★	★	-	-
Boffetta et al. (2001)	Sweden	Self-reported during the national census	-	-	★	-	★	-	-	-	-	-	-	★	★	★	-
Boffetta et al. (2003)	Denmark Finland France Germany Israel Netherlands Norway Sweden	Self-administered questionnaire	Age Calendar period Country Duration of employment	-	-	-	★	★	-	★	-	★	-	★	★	-	★
Bulbulyan et al. (1998)	Russia	Employer-administered records	-	Duration of exposure Duration of employment	-	-	★	-	-	★	-	-	-	★	-	-	★

Reference	Country	Measurement of exposure	Measure of association was adjusted for	Measure of association was stratified by	Selection						Comparability		Outcome				
					A		B	C		D	E		F		G	H	
				Age at first exposure Gender Age Calendar year of follow-up													
Clapp (2006)	USA	Employer-administered records	-	Sex	-	-	★	★	-	-	-	★	-	-	★	-	-
Cocco et al. (1997)	Italy	Employer-administered records	-	-	-	-	★	-	-	-	-	-	-	★	★	-	★
Consonni et al. (2013)	Germany Great Britain Italy Netherlands USA	Employer-administered records	-	Time since first exposure	-	-	★	★	-	-	-	-	-	-	★	★	-
Fu et al. (1996)	Great Britain Italy	Self-reported during the national census (Great Britain) Employer-administered records (Italy)	-	Country	-	-	★	-	-	-	-	-	-	-	★	-	-
Friis et al. (1993)	Sweden	Employer-administered records	-	-	-	-	★	★	-	-	-	-	-	★	★	-	-
Gamble et al. (2000)	USA	-	National and state region Age	-	★	-	-	★	-	★	-	-	-	★	★	★	-
Glass et al. (2016)	Australia	Employer-administered records	Age Calendar period	Type of fire (structural, landscape, or vehicle)	-	-	★	★	-	-	-	★	-	★	★	-	-
Glass et al. (2017)	Australia	Employer-administered records	Age Calendar period	Type of fire (structural, landscape, or vehicle)	-	-	★	★	-	-	-	★	-	★	★	-	-
Guo et al. (2004)	Finland	Self-reported during the national census	-	-	★	-	★	-	-	★	-	-	-	★	★	★	-

Reference	Country	Measurement of exposure	Measure of association was adjusted for	Measure of association was stratified by	Selection						Comparability		Outcome				
					A		B	C		D	E		F		G	H	
Hobbesland et al. (1999)	Norway	Employer-administered records	Duration of work Year of first employment Time since start of work Age	-	★	-	★	★	-	-	-	-	-	★	★	-	-
Huvinen et al. (2013)	Finland	Employer-administered records	-	-	-	-	★	★	-	★	-	-	-	★	★	★	-
Ide at al. (2014)	Great Britain	Self-administered questionnaire	Age at diagnosis Length of service Region	-	★	-	★	★	-	★	-	-	-	★	-	★	-
Ilychova et al. (2012)	Russia	Employer-administered records	-	Sex	-	-	★	★	-	-	-	★	-	★	★	-	★
Iwatsubo et al. (2013)	France	Employer-administered records	-	-	-	-	-	-	★	-	-	-	-	★	★	-	-
Ji et al. (2005)	Sweden	Self-reported during the national census	-	-	★	-	★	-	-	★	-	-	-	★	★	★	-
Lewis, Schnatter et al. (2000)	Canada	Employer-administered records	Occupation Duration of employment Latency Time period Sex	-	-	-	★	★	-	-	-	★	-	★	★	-	-
Lewis, Gable et al. (2000)	USA	Employer-administered records	-	Location	-	-	★	★	-	-	-	-	-	★	★	-	-
Laakkonen et al. (2006)	Finland	Self-reported during the national census	-	Sex	★	-	★	-	-	★	-	★	-	★	★	★	-
Lynge et al. (1997)	Denmark Finland Norway Sweden	Self-reported during the national census	-	-	-	-	★	-	-	★	-	-	-	★	★	★	-
Kang et al. (2008)	USA	Cancer-registry administered questionnaire	Age Tobacco smoking	Age	-	★	-	-	★	-	★	★	-	★	★	★	-
Mariusdottir et al. (2016)	Iceland	Author-administered questionnaire	Age Sex BMI	-	★	-	★	-	★	★	★	★	-	★	★	★	-

Reference	Country	Measurement of exposure	Measure of association was adjusted for	Measure of association was stratified by	Selection						Comparability		Outcome				
					A		B	C		D	E		F		G	H	
			Tobacco smoking Diabetes type II History of kidney disease Hypertension														
Marsh et al. (2008)	USA	Employer-administered records	-	-	-	-	★	★	-	-	-	-	-	★	★	-	-
Pukkala (1998)	Finland	Employer-administered records	-	-	-	-	★	★	-	★	-	-	-	★	★	★	-
Pukkala et al. (2000)	Finland	Self-reported during the national census	-	-	-	-	★	-	-	★	-	-	-	★	★	★	-
Pukkala et al. (2014)	Denmark Finland Iceland Norway Sweden	Self-reported during the national census	-	Country Age Period of follow-up	-	-	★	-	-	★	-	★	-	★	★	★	-
Rafnsson et al. (1991)	Iceland	Trade union administered questionnaire	-	-	-	-	★	★	-	-	-	-	-	★	★	★	-
Randem et al. (2003)	Norway	Employer-administered records	-	Duration of employment	-	-	★	★	-	-	-	-	-	★	★	★	-
Randem et al. (2004)	Denmark Finland Norway Sweden	Employer-administered records (Denmark, Finland, Norway, Sweden) Self-reported during health surveillance program (Sweden)	-	Country	-	-	★	★	-	-	-	-	-	★	★	★	-
Richard et al. (2004)	France	Employer-administered records	-	-	★	-	★	★	-	-	-	-	-	-	-	-	-
Romundstad et al. (2000)	Norway	Employer-administered records	PAH exposure Fluoride exposure Tobacco smoking Age Calendar year	Time from hire	★	-	★	★	-	★	★	-	-	★	★	★	-
Schnatter et al. (1993)	Canada	Employer-administered records	-	-	-	-	★	-	-	-	-	-	-	★	★	-	-

Reference	Country	Measurement of exposure	Measure of association was adjusted for	Measure of association was stratified by	Selection						Comparability		Outcome				
					A		B	C		D	E		F		G	H	
Seidler et al. (2014)	Germany	Employer-administered records	-	-	-	-	★	★	-	-	-	-	-	★	★	-	-
Shannon et al. (2005)	Canada	Employer-administered records	-	-	-	-	★	★	-	-	-	-	-	★	★	-	-
Soll-Johanning et al. (1998)	Denmark	Employer-administered records	-	-	-	-	★	★	-	-	-	-	-	★	★	★	-
Sormunen et al. (2014)	Finland	Self-reported during the national census	-	-	-	-	★	★	-	-	-	-	-	★	★	★	-
Spinelli et al. (2006)	Canada	Employer-administered records	-	-	-	-	★	★	-	-	-	-	-	★	★	-	-
Tomaskova et al. (2012)	Czechia	-	Age Exposure years Severity of coal workers pneumoconiosis		-	-	-	-	-	★	-	-	-	★	-	-	-
Wilson et al. (2008)	Sweden	Self-reported during the national census	-	Tobacco smoking (by "smoking" occupational groups)	★	-	★	-	-	-	-	-	-	★	★	★	-
Wong et al. (1993)	USA	Employer-administered records	-	-	-	-	★	-	★	-	-	-	-	★	★	-	-
Veyalkin et al. (2003)	Belarus	Employer-administered records	Sex	-	★	-	★	-	-	★	-	★	-	★	★	★	-

A study can be awarded a maximum of one star (★) for each numbered item within the Selection (A-D) and Outcome categories (F-G). A maximum of two stars can be given for Comparability (E). Failure to meet the conditions described in brackets is marked with a hyphen (-).

A - Representativeness of the exposed cohort (truly representative of the average exposure in the community/ somewhat representative of the average exposure in the community)
B - Selection of the non-exposed cohort (drawn from the same community as the exposed cohort)
C - Ascertainment of exposure (secure record, structured interview)
D - Demonstration that outcome of interest was not present at start of the study (yes)
E - Comparability of cohorts on the basis of the design or analysis (study controls for tobacco smoking, study controls for additional factors (e.g. age, sex, BMI)
F - Assessment of outcome (independent blind assessment, record linkage)
G - Follow-up long enough for outcomes to occur (yes)
H - Adequacy of follow-up of cohorts (complete follow up, subjects lost to follow-up unlikely to introduce bias - small number lost - > 60% of follow-up, or description provided of those lost)

Table 2. Description of case-control studies included in the chapter "2.4.6 Occupational exposures" and assessment of their quality (selection, comparability, exposure) according to the Newcastle-Ottawa scale.

Reference	Country	Measurement of exposure	Measure of association was adjusted for	Measure of association was stratified by	Selection				Comparability		Exposure			
					A	B	C	D	E		F		G	H
Anttila et al. (2015)	Finland	Employer-administered records	-	-	-	★	★	★	-	-	★	-	★	★
Aupérin et al. (1994)	France	Self-administered questionnaire and Author-administered questionnaire	Sex Age Interviewer Educational level Tobacco smoking Occupation	-	★	★	-	★	★	★	★	-	-	★
Alavanja et al. (1989)	USA	-	Age Occupation Duration of employment Professional subspecialty Salary level	-	★	★	★	-	-	-	★	-	★	★
Boffetta et al. (2011)	Czechia Poland Romania Russia	Self-administered questionnaires	Age (5-year categories) Sex Study center Place of residence (rural/urban) Tobacco smoking BMI Hypertension	-	★	★	★	★	★	★	-	-	★	-
Brownson (1998)	USA	Cancer-registry administered questionnaire	Age Sex Tobacco smoking Alcohol consumption	-	-	★	-	★	★	★	-	-	★	-
Forastiere et al. (1993)	Italy	Self-administered questionnaire	Duration of occupation Type of crop Age License for the usage of pesticides	-	★	★	★	★	-	-	★	-	★	★
Heck et al. (2010)	Czechia Poland	Author-administered questionnaire	Age Sex	-	★	★	-	★	★	★	-	-	★	-

Reference	Country	Measurement of exposure	Measure of association was adjusted for	Measure of association was stratified by	Selection				Comparability		Exposure			
					A	B	C	D	E		F		G	H
	Romania Russia		Education Study center Tobacco smoking BMI Hypertension											
Karami et al. (2012)	USA	Author-administered questionnaire	Tobacco smoking Hypertension BMI Sex Age Family history of cancer Study center	-	-	★	★	-	★	★	-	-	★	-
Lynge et al. (1995)	Denmark	Self-reported during the national census	-	-	-	★	★	★	-	-	-	-	★	★
Mattioli et al. (2002)	Italy	Self-administered questionnaire and Author-administered questionnaire	BMI Tobacco smoking Consumption of coffee Alcohol Phenacetin and/or diuretics Meat consumption	-	★	★	-	★	★	-	★	-	★	★
Mellemgaard et al. (1994)	Denmark	Author-administered questionnaire	Age BMI Tobacco smoking	Sex	★	★	★	-	★	★	-	-	★	★
McCredie et al. (1993)	Australia	Author-administered questionnaire and Self-administered questionnaire	Age Sex Method of interview Education	-	-	-	★		-	-	-	-	★	-
Parent et al. (2000)	Canada	Self-administered questionnaire	Age Tobacco smoking BMI Occupational confounders: Aviation gasoline - none Jet fuel - hydrogen sulphide Felt dust - hair dust, styrene Inks - chromium (VI) Ozone - chromium (VI)	-	★	-	★	★	★	★	-	-	★	-

Reference	Country	Measurement of exposure	Measure of association was adjusted for	Measure of association was stratified by	Selection				Comparability		Exposure			
					A	B	C	D	E		F		G	H
			Gardeners - none Aircraft engine mechanics - none Printers - none											
Partanen et al. (1991)	Finland	Self-administered questionnaire	Obesity Tobacco smoking Coffee consumption	-	-	★	★	★	★	★	-	-	★	★
Pesch et al. (2000)	Germany	Author-administered questionnaire	Age Study center Tobacco smoking	Sex	★	★	★	★	★	★	-	-	★	-
Siemiatycki et al. (1997)	Canada	Author-administered questionnaire	Age Socioeconomic status Ethnic group Tobacco smoking Blue-/white collar job history	-	-	-	-	★	★	★	-	-	★	-
Zhang et al. (2004)	USA	Author-administered questionnaire and Self-administered questionnaire	Age BMI Tobacco smoking Type of respondent Red meat consumption Fruit consumption History of kidney cancer in the family	Sex	★	★	★	★	★	★	-	-	★	-

In none of the studies

A study can be awarded a maximum of one star (★) for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability. Failure to meet the conditions described in brackets is marked with a hyphen (-).

A - Adequate case definition (yes, with independent validation)
B - Representativeness of the cases (consecutive or obviously representative series of cases)
C - Selection of controls (community controls)
D - Definition of controls (no history of disease at the endpoint)
E - Comparability of cases and controls on the basis of the design and analysis (study controls for tobacco smoking, study controls for any additional factor, e.g. age, sex, BMI)
F - Ascertainment of exposure (secure record, structured interview blind to case/control status)
G - Same method of ascertainment for cases and controls
H - Non-response rate (same rate for both groups)

PUBLICATION
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Occupation and risk of kidney cancer in Nordic countries

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Occupation and Risk of Kidney Cancer in Nordic Countries

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Objective: The aim of this study was to describe the occupational variation in the incidence of kidney cancer in the Nordic population. **Methods:** The population comprised of 14.9 million individuals included in censuses between 1960 and 1990. Standardized incidence ratios (SIRs) were calculated for each occupational group. **Results:** Significantly increased SIRs were observed in welders [1.24, 95% confidence interval (95% CI) 1.14 to 1.35], public safety workers (1.16, 95% CI 1.08 to 1.25), and seamen (1.16, 95% CI 1.07 to 1.26). Significantly decreased SIRs were found in laboratory assistants (0.76, 95% CI 0.60 to 0.94) and forestry workers (0.77, 95% CI 0.72 to 0.83). **Conclusion:** A relatively small variation in the incidence of malignancies of the kidney between occupational groups was found in the cohort. There is abundant room for further progress in determining the effect of smoking in particular occupational groups.

Keywords: kidney neoplasms, Nordic countries epidemiology, occupation, occupational groups, risk

In 2012, kidney cancer was the ninth and fourteenth most common cancer worldwide among males and females, respectively.[1] It was the most common in the North American and European populations, with the World age-standardized rates (ASRs) 11.7 and 8.8 per 100,000 persons at risk per year, respectively. In the Nordic countries, the estimated annual change in ASR in the latest 10 years was +2.5% and +1.3% for men and women, respectively.[2,3] The highest ASR in the Nordic countries was observed in Iceland and the lowest in Sweden.

The risk of developing kidney cancer is higher among men, and it increases with age.[3] The other known risk factors for the disease are obesity, cigarette smoking, hypertension, and the end-stage renal disease.[4] In addition, according to the International Agency for Research on Cancer (IARC), there is sufficient evidence of a relationship between exposure to X-ray radiation, gamma radiation, and trichloroethylene, and the increased risk of renal tumors.[5]

Several studies conducted in recent years have focused on occupational risk factors for developing kidney malignancies.[6–13] Furthermore, few researchers have addressed the problem of increased risk among some specific professional groups.[14–19] However, the results of the studies mentioned above are mostly inconsistent. There remains a need for research based on data covering the entire national population.

The purpose of this study is to describe the occupational variation in the incidence of the malignant neoplasm of the kidney (excluding malignant neoplasm of the renal pelvis) in the population of the Nordic countries.

METHODS

The current investigation is part of the Nordic Occupational Cancer Study (NOCCA). The NOCCA is a cohort study based on data from five Nordic countries: Finland, Sweden, Norway, Denmark, and Iceland.[20]

Data on exposure (occupational category) were obtained through population censuses conducted between 1960 and 1990. The censuses included in the present study were held in Sweden in 1960, 1970, 1980, 1990; in Norway in 1960, 1970, 1980; in Finland in 1970, 1980, 1990; in Iceland in 1981; and in Denmark in 1970. All individuals aged 30 to 64 years on January 1 of the year of the respective census were included in the study. The data were collected through questionnaires, computerized, and centrally coded using unique personal identity codes, by respective national statistical offices. All original national occupation codes were converted to NYK - standard classification comprising 53 distinct occupational groups, and an additional class of economically inactive persons. NYK is a Nordic adaptation of the International Standard Classification of Occupations (ISCO) from 1958. No information about smoking habits was provided, and therefore, we did not conduct stratification regarding smoking.

The follow-up was performed until emigration, death, or December 31 of the following year: 2003 in Denmark and Norway, 2004 in Iceland, 2005 in Finland and Sweden. Data on mortality and emigration were obtained from the Central Population Registries in respective countries. Data on the outcome, that is, cases of malignancies of the kidney (ICD-7 180), excluding malignancies of the renal pelvis, were collected from national cancer registries in respective countries.

For each occupational group, the standardized incidence ratio (SIR) was calculated. The SIR was defined as the index of the observed to the expected number of cases, with national incidence rates as a reference. For each occupation category, the 95% confidence intervals (95% CIs) were calculated assuming the Poisson distribution of the observed number of cases. More detailed data (stratified by year of diagnosis, age at follow-up, sex, and country) are shown only for occupational groups with the highest ($\geq$1.15) and the lowest ($\leq$0.85) SIRs. Poisson regression trend test was performed to evaluate the significance of SIR secular trends. Statistical analysis was conducted with Stata/IC 15.0 for Mac (StataCorp LP, Texas).

RESULTS

The population of the NOCCA included 14.9 million people: 0.1 million from Iceland, 2.0 million from Denmark, 2.6 million from Norway, 3.4 million from Finland, and 6.8 million from Sweden. In total, they contributed 385 million person-years of observation in a follow-up until 2005. In this cohort, 85,940 cases

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TABLE 1. The Observed Number of Cases and Standardized Incidence Ratios of Kidney Malignancies in the Nordic Countries, by Occupational Category

Occupational Category	Obs	SIR	95% CI Lower	95% CI Upper
Administrators	2,453	**1.06**	**1.02**	**1.11**
Artistic workers	312	1.02	0.91	1.14
Assistant nurses	610	**0.92**	**0.85**	**1.00**
Beverage workers	70	1.07	0.84	1.36
Bricklayers	385	1.00	0.90	1.10
Building caretakers	2,343	**1.09**	**1.05**	**1.14**
Chemical process workers	643	0.93	0.86	1.01
Chimney sweeps	42	1.17	0.84	1.58
Clerical workers	4,366	0.99	0.96	1.02
Cooks and stewards	563	1.08	0.99	1.17
Dentists	106	0.91	0.75	1.11
Domestic assistants	871	0.95	0.89	1.01
Drivers	2,791	**1.13**	**1.08**	**1.17**
Economically inactive	21,174	**1.02**	**1.01**	**1.04**
Electrical workers	1,403	1.02	0.97	1.08
Engine operators	1,165	**1.07**	**1.01**	**1.14**
Farmers	5,263	**0.80**	**0.78**	**0.83**
Fishermen	575	1.08	0.99	1.17
Food workers	1,169	**1.07**	**1.01**	**1.13**
Forestry workers	858	**0.77**	**0.72**	**0.83**
Gardeners	2,320	**0.91**	**0.87**	**0.94**
Glassmakers, etc	765	0.94	0.87	1.01
Hairdressers	268	1.03	0.91	1.16
Journalists	155	1.10	0.93	1.28
Laboratory assistants	83	**0.76**	**0.60**	**0.94**
Launderers	263	0.94	0.83	1.07
Mechanics	3,839	**1.06**	**1.03**	**1.09**
Military personnel	419	**1.13**	**1.02**	**1.24**
Miners and quarry workers	279	1.07	0.95	1.20
Nurses	422	**0.87**	**0.79**	**0.96**
Other construction workers	1,527	0.97	0.92	1.02
Other health workers	464	0.94	0.86	1.03
Other workers	2,338	0.99	0.95	1.03
Packers	1,594	**1.07**	**1.02**	**1.13**
Painters	679	0.95	0.88	1.03
Physicians	224	0.91	0.80	1.04
Plumbers	470	**1.11**	**1.01**	**1.21**
Postal workers	930	1.03	0.96	1.10
Printers	493	1.02	0.93	1.12
Public safety workers	793	**1.16**	**1.08**	**1.25**
Religious workers, etc	995	0.95	0.89	1.01
Sales agents	2,737	**1.09**	**1.05**	**1.13**
Seamen	628	**1.16**	**1.07**	**1.26**
Shoe and leather workers	269	1.01	0.89	1.14
Shop workers	3,166	**1.04**	**1.00**	**1.08**
Smelting workers	832	1.06	0.99	1.14
Teachers	1,872	**0.87**	**0.83**	**0.91**
Technical workers, etc.	3,734	1.03	1.00	1.06
Textile workers	1,462	1.01	0.96	1.06
Tobacco workers	34	1.25	0.87	1.75
Transport workers	997	**1.09**	**1.03**	**1.16**
Waiters	495	1.04	0.95	1.14
Welders	540	**1.24**	**1.14**	**1.35**
Woodworkers	2,692	**0.93**	**0.90**	**0.97**

The data given in bold indicate significant estimates.
CI, confidence interval; Obs, observed number of cases; SIR, standardized incidence ratio.

of the malignant neoplasm of the kidney were identified (50,330 among males and 35,610 among females).

The highest ($\geq$1.15) statistically significant SIRs for malignancies of the kidney for both genders combined were observed in welders [1.24, 95% confidence interval (95% CI) 1.14 to 1.35], public safety workers (1.16, 95% CI 1.08 to 1.25), and seamen (1.16, 95% CI 1.07 to 1.26) (Table 1). The lowest ($\leq$0.85) statistically significant SIRs were found in laboratory assistants (0.76, 95% CI 0.60 to 0.94) and forestry workers (0.77, 95% CI 0.72 to 0.83).

TABLE 2. The Observed Number of Cases and Standardized Incidence Ratios of Kidney Malignancies in Nordic Countries in Selected Occupational Categories, by Year of Diagnosis

	1961–1975				1976–1990				1991–2005				
			95% CI				95% CI				95% CI		
Occupational Category	Obs	SIR	Lower	Upper	Obs	SIR	Lower	Upper	Obs	SIR	Lower	Upper	P*
Farmers	1,806	0.73	0.70	0.77	4,552	0.78	0.75	0.80	4,168	0.87	0.84	0.90	<0.001
Forestry workers	374	0.82	0.74	0.91	710	0.75	0.70	0.81	632	0.77	0.71	0.83	0.389
Laboratory assistants	2	0.17	0.02	0.62	52	0.80	0.60	1.05	112	0.78	0.65	0.94	0.162
Public safety workers	240	1.24	1.09	1.41	658	1.26	1.16	1.36	688	1.06	0.98	1.14	0.004
Seamen	148	0.89	0.75	1.04	516	1.20	1.10	1.31	592	1.22	1.13	1.33	0.003
Welders	116	1.17	0.97	1.40	374	1.21	1.09	1.34	590	1.28	1.18	1.39	0.256

CI, confidence interval; Obs, observed number of cases; SIR, standardized incidence ratio.
*Poisson linear test for trend.

The SIR showed a statistically significant upward time trend over the 45 years of follow-up among seamen and farmers (Table 2). A statistically significant downward trend in the SIR was observed among public safety workers. When stratified by age at the time of diagnosis, a statistically significant increase in SIR among farmers was observed (Table 3). A significant decrease in SIR was observed among seamen.

In professional groups stratified by sex, none of the occupations was at the significantly elevated risk of developing kidney tumors among females (Table 4). The lowest significant risk was observed in female laboratory assistants (0.72, 95% CI 0.51 to 0.97). The highest statistically significant SIRs of malignancies of the kidney in males were found in welders (1.25, 95% CI 1.14 to 1.36), seamen (1.16, 95% CI 1.07 to 1.26), and public safety workers (1.16, 95% CI 1.08 to 1.25). The lowest significant SIRs were observed in forestry workers (0.77, 95% CI 0.72 to 0.83) and farmers (0.78, 95% CI 0.75 to 0.80). Among the analyzed professional groups, there were no statistically significant differences in SIR between the Nordic countries (Table 5).

DISCUSSION

To the knowledge of the authors, the present study is the largest one in terms of a number of observed cancer cases dealing with the association between the profession and incidence of malignancies in the kidney so far. Among the 53 professional groups that were covered by our study, the risk of this cancer was significantly elevated among welders, seamen, and public safety workers. Laboratory assistants, forestry workers, and farmers had the lowest risk of the disease.

The highest risk was observed among welders (SIR = 1.24, 95% CI 1.14 to 1.35). This category included individuals involved in cutting and joining metal parts using flame, electric arcs, and other sources of heat.[20] The Danish welders were included in the category of mechanic workers. Similar results were reported by MacLeod et al,[21] who observed an increased risk of kidney cancer among Canadian welders (hazard ratio 1.30, 95% CI: 1.01 to 1.67). Welders of stainless steel are known to be exposed to solid aerosols of hexavalent chromium and nickel, generated from elemental compounds.[22] Moreover, elevated urinary cadmium levels, associated with renal tubular dysfunction, were reported in this occupational group.[23] In addition, high levels of chromium, copper, manganese, and zinc were found in the renal tissue of mice exposed to ARC-stainless steel welding fumes.[24] According to the IARC, there is limited evidence of a relationship between exposure to cadmium, cadmium compounds, and welding fumes and elevated risk of malignancies of the kidney.[5]

Another occupational category in which we observed the statistically significant elevation of SIR are seamen (SIR = 1.16, 95% CI 1.07 to 1.26). This group includes both sailors working on deck and in engine rooms. Similar results were reported in other Nordic studies.[25,26] Other researchers found an increased risk of developing lung cancer, mesothelioma, esophageal adenocarcinoma and squamous cell carcinoma, leukemia, and urinary bladder in this occupational class.[27–30] Seamen and marine engineers working on

TABLE 3. The Observed Number of Cases and Standardized Incidence Ratios of Kidney Malignancies in Nordic Countries in Selected Occupational Categories, by Age at Diagnosis

	30–49				50–69				70+				
			95% CI				95% CI				95% CI		
Occupational Category	Obs	SIR	Lower	Upper	Obs	SIR	Lower	Upper	Obs	SIR	Lower	Upper	P*
Farmers	400	0.74	0.67	0.82	4,894	0.79	0.76	0.81	5,232	0.82	0.80	0.85	0.005
Forestry workers	102	0.73	0.60	0.89	866	0.74	0.69	0.79	748	0.82	0.76	0.88	0.050
Laboratory assistants	14	0.39	0.22	0.66	118	0.89	0.74	1.07	34	0.66	0.46	0.93	0.318
Public safety workers	154	1.15	0.97	1.34	840	1.11	1.04	1.19	592	1.25	1.15	1.35	0.089
Seamen	116	1.24	1.02	1.48	764	1.23	1.14	1.32	376	1.03	0.93	1.14	0.011
Welders	144	1.30	1.10	1.53	622	1.19	1.10	1.29	314	1.33	1.19	1.49	0.468

CI, confidence interval; Obs, observed number of cases; SIR, standardized incidence ratio.
*Poisson linear test for trend.

TABLE 4. The Observed Number of Cases and Standardized Incidence Ratios of Kidney Malignancies in Nordic Countries in Selected Occupational Categories, by Sex

	Males				Females			
			95% CI				95% CI	
Occupational Category	Obs	SIR	Lower	Upper	Obs	SIR	Lower	Upper
Farmers	4,458	0.78	0.75	0.80	805	1.00	0.93	1.07
Forestry workers	849	0.77	0.72	0.83	9	0.86	0.39	1.63
Laboratory assistants	42	0.80	0.58	1.09	41	0.72	0.51	0.97
Public safety workers	768	1.16	1.08	1.25	25	1.22	0.79	1.80
Seamen	628	1.16	1.07	1.26	0	0.00	0.00	4.16
Welders	533	1.25	1.14	1.36	7	1.12	0.45	2.31

CI, confidence interval; Obs, observed number of cases; SIR, standardized incidence ratio.

merchant ships are exposed to asbestos while performing intermittent repair and maintenance tasks.[31] Moreover, asbestos used in gaskets, pipes, valves, and machinery can be released into the environment at the time of ship motion and vibration.[32] Moen et al[33] reported that workers working for more than 24 hours in the engine room had significantly higher 1-hydroxypyrene urine levels than unexposed seamen. So far, both asbestos and 1-hydroxypyrene have not been included by the IARC into the List of Classifications as a risk factor for kidney cancer.[5]

The third highest SIR in our study was observed in public safety workers (SIR = 1.16, 95% CI 1.08 to 1.25). The group included workers who protect individuals and property against hazards and enforcers, that is, firefighters, police officers, detectives, customs officers, and guards.[20] Similar results were reported for American firefighters (SIR = 1.27, 95% CI 1.09 to 1.48).[34] Contradictory results were reported by Glass et al,[35,36] who observed SIR = 0.82 (95% CI 0.71 to 0.94) for volunteer firefighters, and SIR = 1.08 (95% CI 0.81 to 1.41) for paid firefighters. However, an upward trend of the relation of the risk of developing renal malignancies to employment duration was reported by the authors. Such results may be partly attributed to the "healthy worker effect." Other studies reported nonsignificant SIRs in this group.[37–39] Firefighters are exposed to volatile organic compounds and polycyclic aromatic hydrocarbons, both due to firefighting and using personal protective equipment.[40–44] Besides, increased exposure to asbestos, hydrogen chloride, and cyanide was reported in this professional group.[45] None of these compounds have been recognized by the IARC as a factor associated with an increased risk of kidney cancer.[5]

Not all associations between professional categories and kidney cancer found in the study are exclusive repercussions of exposures at the workplace. Occupational categories differ in their exposures to tobacco smoking. Haldorsen et al[46] conducted a study on the smoking-adjusted incidence of lung cancer by occupation in Norwegian men. According to the authors, in most of the groups that were occupationally exposed to lung carcinogens, SIRs before adjustment were above 1.00. Postadjustment SIRs were further elevated, which indicated an effect of occupational exposure. Au contraire, the SIRs for waiters and cooks, originally considerably raised, were lowered to unity subsequently to smoking-adjustment, suggesting smoking to be the primary justification for the elevated risk. The above results support clarification that the differing smoking patterns do not justify all the occupational variation in risk.

Major strengths of our study are the large sample size and precise coding of occupation in all Nordic countries. Another significant advantage of our investigation is a high-quality standard maintained by all Nordic Cancer Registries regarding the completeness and accuracy of the registered data.[47] Furthermore, all linkages between the census data, the mortality, and emigration data were based on the unique personal identity codes, which guarantee a

TABLE 5. The Observed Number of Cases and Standardized Incidence Ratios of Kidney Malignancies in Nordic Countries in Selected Occupational Categories, by Country

	Denmark				Finland				Iceland				Norway				Sweden			
			95% CI				95% CI				95% CI				95% CI				95% CI	
Occupational Category	Obs	SIR	Lower	Upper	Obs	SIR	Lower	Upper	Obs	SIR	Lower	Upper	Obs	SIR	Lower	Upper	Obs	SIR	Lower	Upper
Farmers	736	0.70	0.65	0.76	1,482	0.83	0.78	0.87	45	1.00	0.73	1.34	1,179	0.85	0.80	0.90	1,821	0.80	0.76	0.84
Forestry workers	7	0.38	0.15	0.79	194	0.69	0.60	0.79	0	0.00	0.00	14.96	157	0.76	0.64	0.89	500	0.83	0.76	0.90
Laboratory assistants	12	0.65	0.34	1.14	32	0.88	0.60	1.24	3	1.17	0.24	3.41	18	0.66	0.39	1.04	18	0.72	0.43	1.14
Public safety workers	91	1.13	0.91	1.38	185	1.13	0.98	1.31	9	1.12	0.51	2.12	151	1.27	1.08	1.49	357	1.14	1.03	1.27
Seamen	59	1.24	0.94	1.60	83	1.38	1.10	1.71	8	1.44	0.62	2.84	339	1.14	1.03	1.27	139	1.06	0.89	1.26
Welders	—	—	—	—	116	1.21	1.00	1.45	2	2.03	0.25	7.33	105	1.32	1.08	1.60	317	1.23	1.10	1.37

CI, confidence interval; Obs, observed number of cases; SIR, standardized incidence ratio.

match close to accurate.[48] Finally, this is the only study so far that benefits from data covering the entire national populations.

The limitation of our study is the lack of data stratification regarding smoking and body mass index, which is likely to affect our results to some extent. Other known risk factors for renal cancer not taken into consideration in our research are hereditary tumors, such as von Hippel–Lindau syndrome, Birt–Hogg–Dubé syndrome, tuberous sclerosis, and constitutional chromosome 3 translocations. As the above conditions are rare and not associated with any of the professions, we do not think that they could confound our results. Too broad professional categories may conceal the association between individual occupational exposures and risk of disease. However, in our study, we aimed to assess occupational variation in the incidence of the malignant neoplasm of the kidney, not to evaluate specific occupational exposures.

CONCLUSION

The purpose of the current study was to determine the occupational variation in the incidence of the malignant neoplasm of the kidney in the population of the Nordic countries. This study has identified a relatively small variation in the incidence of malignancies of the kidney between occupational groups. The highest SIRs for both genders combined were observed in welders, public safety workers, and seamen. The lowest SIRs were found in laboratory assistants and forestry workers. Future studies, which take effect of smoking into account, will need to be undertaken.

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Occupation and risk of cancer of the renal pelvis in Nordic countries

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Epidemiology

Occupation and risk of cancer of the renal pelvis in Nordic countries

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Objectives

To evaluate occupational variation in the incidence of the malignant neoplasm of the renal pelvis in the population of the Nordic countries: Denmark, Iceland, Finland, Norway and Sweden.

Materials and Methods

The study cohort comprised 14.9 million individuals. Data on occupational history were obtained from national censuses. Standardized incidence ratios (SIRs) were calculated for each occupation.

Results

The highest SIRs were found in seamen (1.51, 95% confidence interval [CI] 1.23–1.82), printers (1.39, 95% CI 1.11–1.71), welders (1.37, 95% CI 1.03–1.78), and public safety workers (1.35, 95% CI 1.12–1.62). The lowest SIRs were observed in forestry workers (0.47, 95% CI 0.35–0.62), gardeners (0.72, 95% CI 0.62–0.83) and woodworkers (0.81, 95% CI 0.72–0.91).

Conclusions

The study suggests that there is an association between profession and risk of malignancy of the renal pelvis. The possible associations between exposure to asbestos, heavy metals and welding fumes, and risk of developing the disease should be studied further.

Keywords

renal pelvis cancer, urothelial carcinoma, occupational groups, occupation, risk, Nordic countries epidemiology

Introduction

Upper tract urothelial carcinoma is a rare malignancy that is not included as a separate entity in reports from national cancer registries. Little is known about the epidemiology of this disease. While data on ureteral cancers are included in the group ‘other cancers’, data on tumours of the renal pelvis are usually presented together with data on kidney tumours.

According to the International Agency for Research on Cancer (IARC), carcinogenic agents with sufficient evidence in humans that can be associated with malignancies of the renal pelvis are tobacco smoking, plants containing aristolochic acid, phenacetin and analgesic mixtures containing phenacetin [1]. Additionally, the IARC has recognized aristolochic acid as an agent connected with a higher risk of developing the disease, with limited evidence in humans.

Much research in recent years has focused on occupational exposures and risk of cancer, but few publications on this issue have been devoted to malignancies of the renal pelvis [2,3]. Moreover, the data presented in previous papers are limited and statistically insignificant. By contrast, new publications on urothelial cancers of the lower urinary tract have emerged [4]. There remains a need, therefore, for further research in the field of occupational exposures and risk of tumours of the renal pelvis.

The aim of the present study was to describe the occupational variation in the incidence of malignant neoplasm of the renal pelvis in the population of the Nordic countries.

Materials and Methods

This research is part of the Nordic Occupational Cancer Study (NOCCA), a cohort study based on data from all Nordic countries, namely, Denmark, Iceland, Finland, Norway and Sweden [5].

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Data on occupation (exposure) were collected during population censuses handled in the period 1960–1990. All individuals aged 30–64 years at the time of any of the censuses composed the population of the NOCCA study. Respective national statistical offices were responsible for compiling data from questionnaires, digitalization, and central coding by unique personal identity codes. The original national occupation codes were converted to a standard Nordic classification, NYK, which is an adaptation of the International Standard Classification of Occupations from 1958. The classification includes 53 specific professional groups and an extra additional category of economically inactive persons.

The endpoints of the follow-up were established as emigration, death or 31 December of the following year: 2003 in Denmark and Norway, 2004 in Iceland, 2005 in Finland and Sweden. Central Population Registries in each country were used to retrieve data on mortality and migration. Data on the cases of malignancy of the renal pelvis (outcome) identified by International Classification of Diseases-7 code 180.1, were obtained from the respective Nordic cancer registries.

The ratios of observed to expected number of cases, denoted as standardized incidence ratios (SIRs), were calculated for each of the professional groups, based on the first occupation noted in the census at time of entry into the study population. The national incidence rates were used as a reference. The 95% confidence intervals (CI) were calculated assuming the Poisson distribution. Occupational categories with SIRs ≥1.15 and ≤0.85 were further stratified by year of diagnosis, age at follow-up, sex and country. Although SIR calculations were based on 5-year categories of both calendar periods and age, we have here combined the results into 15-year periods (1961–1975; 1976–1990; and 1991–2005), and broad age groups (30–49, 50–69, and ≥70 years). A Poisson regression trend test was conducted to assess the significance of time trends of the SIRs. Statistical analysis was performed with Stata/IC 15.0 for Mac (StataCorp LP, College Station, TX, USA).

Results

The NOCCA dataset was assembled with the data of 14.9 million individuals, contributing to a total of 385 million person-years of observation until the end of the follow-up. The population comprised the 6.8 million entities from Sweden, 3.4 million from Finland, 2.6 from Norway, 2.0 million from Denmark, and 0.1 million from Iceland. Within this cohort, 11 237 cases of malignancy of the renal pelvis were identified (4 505 among women and 6 732 among men).

The highest (≥1.15) statistically significant SIRs for malignancy of the renal pelvis for both genders combined were found in seamen (1.51, 95% CI 1.23–1.82), printers (1.39, 95% CI 1.11–1.71), welders (1.37, 95% CI 1.03–1.78), public safety workers (1.35, 95% CI 1.12–1.62), packers (1.23, 95% CI 1.07–1.41), textile workers (1.22, 95% CI 1.06–1.39), painters (1.22, 95% CI 1.00–1.46), transport workers (1.20, 95% CI 1.01–1.42), clerical workers (1.18, 95% CI 1.09–1.27), electrical workers (1.18, 95% CI 1.02–1.36) and food workers

Table 1 Observed number of cases and standardized incidence ratios of kidney malignancies in the Nordic countries, by occupational category.

Occupational category	Number of cases observed	SIR	95% CI	
			Lower	Upper
Administrators	399	1.09	0.98	1.20
Artistic workers	49	1.31	0.97	1.74
Assistant nurses	84	1.07	0.85	1.32
Beverage workers	15	1.05	0.59	1.73
Bricklayers	65	1.03	0.79	1.31
Building caretakers	301	0.97	0.87	1.09
Chemical process workers	95	1.09	0.88	1.33
Chimney sweeps	7	1.73	0.70	3.57
Clerical workers	684	**1.18**	**1.09**	**1.27**
Cooks and stewards	40	0.81	0.58	1.10
Dentists	17	1.13	0.66	1.80
Domestic assistants	109	0.94	0.77	1.13
Drivers	336	1.01	0.91	1.13
Economically inactive	2 578	0.97	0.93	1.00
Electrical workers	191	**1.18**	**1.02**	**1.36**
Engine operators	106	0.85	0.70	1.03
Farmers	571	**0.61**	**0.56**	**0.66**
Fishermen	59	0.84	0.64	1.08
Food workers	203	**1.16**	**1.01**	**1.34**
Forestry workers	53	**0.47**	**0.35**	**0.62**
Gardeners	195	**0.72**	**0.62**	**0.83**
Glass makers etc.	120	1.08	0.90	1.29
Hairdressers	44	1.19	0.86	1.60
Journalists	19	1.15	0.69	1.80
Laboratory assistants	17	1.20	0.70	1.92
Launderers	40	0.99	0.70	1.34
Mechanics	521	**1.13**	**1.04**	**1.24**
Military personnel	49	1.00	0.74	1.32
Miners and quarry workers	28	1.02	0.68	1.47
Nurses	68	1.05	0.81	1.33
Other construction workers	207	0.88	0.76	1.01
Other health workers	76	1.17	0.92	1.47
Other workers	371	1.09	0.98	1.21
Packers	208	**1.23**	**1.07**	**1.41**
Painters	112	**1.22**	**1.00**	**1.46**
Physicians	42	1.24	0.90	1.68
Plumbers	62	1.26	0.97	1.62
Postal workers	109	1.02	0.84	1.23
Printers	89	**1.39**	**1.11**	**1.71**
Public safety workers	118	**1.35**	**1.12**	**1.62**
Religious workers etc.	106	0.88	0.72	1.07
Sales agents	302	1.10	0.98	1.24
Seamen	105	**1.51**	**1.23**	**1.82**
Shoe and leather workers	40	1.26	0.90	1.72
Shop workers	561	**1.12**	**1.03**	**1.22**
Smelting workers	131	1.13	0.94	1.34
Teachers	260	0.95	0.84	1.07
Technical workers, etc.	508	**1.09**	**1.00**	**1.19**
Textile workers	219	**1.22**	**1.06**	**1.39**
Tobacco workers	8	1.28	0.55	2.53
Transport workers	142	**1.20**	**1.01**	**1.42**
Waiters	57	1.07	0.81	1.39
Welders	56	**1.37**	**1.03**	**1.78**
Woodworkers	285	**0.81**	**0.72**	**0.91**

SIR, standardized incidence ratio. Data given in bold indicate significant estimates.

(1.16, 95% CI 1.01–1.34; Table 1). The lowest (≤0.85) statistically significant SIRs were observed in forestry workers (0.47, 95% CI 0.35–0.62), gardeners (0.72, 95% CI 0.62–0.83) and wood workers (0.81, 95% CI 0.72–0.91).

An ascending trend in SIRs over the whole period of the follow-up was found among public safety workers (Table 2). A descending tendency in the SIR was observed among food workers and packers. Statistically significantly elevated SIRs were observed among printers and transport workers, in professional categories stratified by age at the time of diagnosis (Table 3). A significant decline in SIRs was found in food workers and packers.

When stratified by sex, the highest SIRs were observed in seamen (1.51, 95% CI 1.23–1.82), and clerical workers (1.19,

Table 2 Observed number of cases and standardized incidence ratios of kidney malignancies in Nordic Countries in selected occupational categories, by year of diagnosis.

Occupational category	Year of diagnosis												P*
	1961–1975				1976–1990				1991–2005				
	Number of cases	SIR	95% CI		Number of cases	SIR	95% CI		Number of cases	SIR	95% CI		
			Lower	Upper			Lower	Upper			Lower	Upper	
Clerical workers	118	1.18	0.97	1.41	552	1.24	1.14	1.35	698	1.13	1.05	1.22	0.259
Electrical workers	42	1.23	0.88	1.66	132	1.07	0.90	1.27	208	1.25	1.09	1.43	0.433
Food workers	62	1.64	1.26	2.10	184	1.20	1.03	1.39	160	1.02	0.86	1.19	0.002
Forestry workers	12	0.30	0.15	0.52	58	0.59	0.45	0.76	36	0.42	0.30	0.59	0.690
Gardeners	52	0.72	0.54	0.95	146	0.63	0.53	0.74	192	0.81	0.70	0.93	0.132
Packers	82	1.52	1.21	1.88	194	1.30	1.13	1.50	140	1.03	0.87	1.22	0.004
Painters	22	0.84	0.53	1.28	100	1.25	1.01	1.52	102	1.31	1.07	1.59	0.108
Printers	20	1.36	0.83	2.11	70	1.36	1.06	1.71	88	1.42	1.14	1.75	0.790
Public safety workers	12	0.61	0.31	1.06	100	1.39	1.13	1.69	124	1.49	1.24	1.78	0.011
Seamen	24	1.58	1.02	2.36	94	1.65	1.33	2.02	92	1.36	1.10	1.67	0.274
Textile workers	52	1.17	0.88	1.54	194	1.22	1.06	1.41	192	1.23	1.07	1.42	0.775
Transport workers	30	1.18	0.80	1.69	114	1.17	0.97	1.41	140	1.23	1.04	1.45	0.737
Welders	8	0.95	0.41	1.86	42	1.44	1.04	1.95	62	1.40	1.07	1.80	0.484
Woodworkers	78	0.77	0.61	0.96	236	0.77	0.67	0.87	256	0.86	0.76	0.98	0.211

*SIR, standardized incidence ratio. *Poisson linear test for trend.*

Table 3 Observed number of cases and standardized incidence ratios of kidney malignancies in Nordic Countries in selected occupational categories, by age at diagnosis.

Occupational category	Age at diagnosis												P*
	30–49 years				50–69 years				≥70 years				
	Number of cases	SIR	95% CI		Number of cases	SIR	95% CI		Number of cases	SIR	95% CI		
			Lower	Upper			Lower	Upper			Lower	Upper	
Clerical workers	66	0.97	0.75	1.23	718	1.17	1.08	1.26	584	1.22	1.12	1.32	0.118
Electrical workers	24	0.98	0.63	1.46	204	1.15	1.00	1.32	154	1.26	1.07	1.48	0.205
Food workers	16	1.18	0.68	1.92	232	1.30	1.14	1.47	158	1.01	0.86	1.18	0.034
Gardeners	20	1.13	0.69	1.75	178	0.73	0.62	0.84	192	0.69	0.60	0.80	0.156
Forestry workers	6	0.62	0.23	1.34	38	0.36	0.26	0.50	62	0.56	0.43	0.72	0.155
Packers	26	1.72	1.12	2.52	208	1.27	1.10	1.45	182	1.14	0.98	1.32	0.070
Painters	12	1.30	0.67	2.28	128	1.35	1.13	1.61	84	1.04	0.83	1.29	0.093
Printers	4	0.49	0.13	1.27	94	1.35	1.09	1.66	80	1.58	1.25	1.96	0.033
Public safety workers	8	0.76	0.33	1.50	124	1.38	1.14	1.64	104	1.40	1.15	1.70	0.271
Seamen	14	1.75	0.96	2.94	120	1.57	1.30	1.87	76	1.38	1.09	1.73	0.303
Textile workers	10	0.89	0.43	1.64	200	1.22	1.06	1.40	228	1.24	1.09	1.42	0.503
Transport workers	10	0.87	0.42	1.61	112	0.93	0.76	1.12	162	1.55	1.32	1.81	<0.001
Welders	12	1.54	0.80	2.70	60	1.31	1.00	1.68	40	1.42	1.02	1.94	0.986
Woodworkers	28	0.89	0.59	1.28	252	0.74	0.65	0.83	290	0.87	0.78	0.98	0.162

*SIR, standardized incidence ratio. *Poisson linear test for trend.*

Table 4 Observed number of cases and standardized incidence ratios of kidney malignancies in Nordic Countries in selected occupational categories, by sex.

Occupational category	Men				Women			
	Number of cases	SIR	95% CI		Number of cases	SIR	95% CI	
			Lower	Upper			Lower	Upper
Clerical workers	262	1.15	1.02	1.30	422	1.19	1.08	1.31
Electrical workers	169	1.16	0.99	1.35	22	1.33	0.83	2.01
Food workers	145	1.18	0.99	1.38	58	1.14	0.86	1.47
Forestry workers	53	0.48	0.36	0.62	0	0.00	0.00	3.60
Gardeners	137	0.75	0.63	0.89	58	0.66	0.50	0.86
Packers	177	1.24	1.06	1.44	31	1.17	0.80	1.66
Painters	111	1.22	1.00	1.47	1	0.99	0.03	5.51
Printers	74	1.37	1.08	1.73	15	1.46	0.82	2.41
Public safety workers	115	1.35	1.11	1.62	3	1.44	0.30	4.20
Seamen	105	1.51	1.23	1.82	0	0.00	0.00	51.05
Textile workers	84	1.30	1.04	1.61	135	1.18	0.99	1.39
Transport workers	140	1.21	1.02	1.43	2	0.79	0.10	2.87
Welders	56	1.39	1.05	1.80	0	0.00	0.00	7.63
Woodworkers	281	0.82	0.72	0.92	4	0.48	0.13	1.22

SIR, standardized incidence ratio.

95% CI 1.08–1.31), among males and females respectively (Table 4). All 95% CIs, calculated for both sexes separately, overlapped. The lowest SIRs were found in forestry workers (0.48, 95% CI 0.36–0.62) in men, and gardeners (0.66, 95% CI 0.50–0.86) in women. No significant differences in SIRs were observed when stratified by country (Table 5).

Discussion

In the present study, the highest risk of developing malignant neoplasms of the renal pelvis was observed among seamen, printers, welders, public safety workers, packers, textile workers, painters, transport workers, clerical workers, electrical workers and food workers. The lowest risk was found in forestry workers, gardeners and woodworkers. The above pattern is similar to that reported for cancer of the urinary bladder [4]; however, a more substantial relative excess was observed in malignancy of the renal pelvis.

The professional group characterized by the most significant risk of tumours of the renal pelvis were seamen (SIR 1.51, 95% CI 1.23–1.82). This group included both sailors working on deck and in engine rooms [5]. Similarly, other studies conducted on the NOCCA population reported an increased risk of developing kidney [5] and urinary bladder [4] tumours in this occupational group. The risk may be associated with increased exposure to asbestos fibres, which are gradually released from pipes, gaskets and other insulating materials, along with ship movements [6]. Moreover, high exposure to asbestos was observed among marine employees performing all conservation works [7]. Asbestos has not been recognized by the IARC as a carcinogen associated with an increased risk of malignancy of the renal pelvis [1].

Printers were another group in which we observed a significantly increased risk of renal pelvis cancer (SIR 1.39, 95% CI 1.11–1.71). According to the previously adopted definition, the group included people who composed type, cast and engraved printing plates and operated printing presses to print text and illustrations, that is, setters, non-textile printers and bookbinders [5]. Similar results were observed for urinary bladder tumours [4]; however, for the same occupational group in the same population, the risk of malignancies of the kidney (excluding the renal pelvis) was not significantly increased (unpublished). This finding may be related to the different histological composition of the above anatomical structures. In contrast to the kidney, urothelial epithelium dominates in the renal pelvis as well as in the urinary bladder. Printers are exposed to inks and solvent fumes. Elevated concentration of many polycyclic aromatic hydrocarbons, including benzo[a]pyrene, has also been reported in the atmosphere of rotary letterpress machine rooms [8,9]. While the printing process was recognized by the IARC as a carcinogenic agent with limited evidence in humans regarding kidney and urinary bladder malignancies, it is still not recognized as a carcinogen associated with renal pelvis malignancy [1].

Welders were characterized by the third highest SIR (1.37, 95% CI 1.03–1.78). This professional group included people who join and cut metal parts using flame, electric arc and other sources of heat to melt and cut or fuse metal. The Danish welders were included in another occupational category, mechanic workers. Similar SIRs in the group of welders were obtained for malignancies of the kidney, excluding the renal pelvis (unpublished), but a lower SIR was observed for bladder tumours [4]. Welders are exposed to solid aerosols of hexavalent chromium and nickel, generated from elemental compounds [10]. Elevated cadmium levels in the urine were also reported in this group [11]. Furthermore, rodents exposed to ARC-stainless steel welding fumes have

Table 5 Observed number of cases and standardized incidence ratios of kidney malignancies in Nordic Countries in selected occupational categories, by country.

Occupational category	Denmark				Finland				Iceland				Norway				Sweden			
	Number of cases	SIR	95% CI		Number of cases	SIR	95% CI		Number of cases	SIR	95% CI		Number of cases	SIR	95% CI		Number of cases	SIR	95% CI	
			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper
Clerical workers	262	1.11	0.98	1.25	57	1.28	0.97	1.65	3	0.98	0.20	2.86	111	1.19	0.98	1.43	251	1.23	1.08	1.39
Electrical workers	52	1.25	0.94	1.64	18	1.20	0.71	1.90	1	1.96	0.05	10.91	34	1.08	0.75	1.50	86	1.17	0.94	1.45
Food workers	96	1.04	0.84	1.27	3	0.35	0.07	1.01	4	1.56	0.43	4.00	39	1.38	0.98	1.89	61	1.42	1.09	1.83
Forestry workers	5	0.68	0.22	1.60	10	0.58	0.28	1.07	0	0.00	0.00	299.68	11	0.45	0.23	0.81	27	0.43	0.28	0.62
Gardeners	46	0.79	0.58	1.05	28	0.54	0.36	0.78	0	0.00	0.00	36.37	44	0.83	0.61	1.12	77	0.72	0.57	0.90
Packers	57	1.56	1.18	2.02	21	1.17	0.72	1.78	0	0.00	0.00	5.54	36	1.00	0.70	1.38	94	1.21	0.98	1.48
Painters	36	1.16	0.81	1.60	9	1.11	0.51	2.11	1	4.69	0.12	26.14	19	1.44	0.87	2.25	47	1.19	0.87	1.58
Printers	39	1.56	1.11	2.13	6	1.22	0.45	2.66	0	0.00	0.00	15.91	14	1.53	0.84	2.58	30	1.21	0.82	1.73
Public safety workers	48	1.53	1.13	2.03	12	1.22	0.63	2.12	0	0.00	0.00	7.90	15	1.10	0.61	1.81	43	1.34	0.97	1.81
Seamen	25	1.37	0.89	2.02	6	1.66	0.61	3.62	1	3.26	0.08	18.14	54	1.58	1.19	2.07	19	1.41	0.85	2.20
Textile workers	88	1.47	1.18	1.81	21	1.27	0.79	1.94	0	0.00	0.00	2.96	36	1.32	0.92	1.82	74	1.00	0.78	1.25
Transport workers	41	1.03	0.74	1.40	18	1.52	0.90	2.40	1	1.44	0.04	8.04	26	1.41	0.92	2.06	56	1.18	0.89	1.53
Welders	–*	–*	–*	–*	11	2.08	1.04	3.73	0	0.00	0.00	81.40	14	1.54	0.84	2.58	31	1.17	0.79	1.66
Woodworkers	82	0.86	0.68	1.06	41	1.01	0.72	1.37	0	0.00	0.00	7.09	63	0.79	0.61	1.01	99	0.73	0.59	0.88

*SIR, standardized incidence ratio. *Danish welders were included in the category of mechanic workers (the separate category of welders did not exist).*

been found to have high levels of chromium, copper, manganese and zinc in their renal tissue [12]. While welding fumes have been recognized by the IARC as carcinogenic agents with limited evidence in humans for kidney tumours, they have not yet been accepted as factors related to renal pelvis cancer [1].

Public safety workers were another group in which we observed an elevated SIR (1.35, 95% CI 1.12–1.62). The category included people who protect individuals and property against hazards and enforce the law, that is, firefighters, police officers, detectives, customs officers and security guards [5]. Similar SIRs were observed for kidney (unpublished) and urinary bladder tumours [4]. Volatile organic compounds and polycyclic aromatic hydrocarbons are known occupational exposures in this professional category [13–17]. Exposures to asbestos, hydrogen chloride and cyanide were also reported in this category [18]. None of these compounds has been recognized by the IARC as a factor associated with the increased risk of cancer of the renal pelvis [1].

Because there is limited research on the topic of occupational exposure and risk of malignancy of the renal pelvis, it is not possible to compare our results with the current literature. To our knowledge, this is the first study on the relationship between occupational affiliation and risk of renal pelvis cancer characterized by such a large study population and based on data from the entire population.

The main strengths of the present study include the large sample size, the large number of cases of cancer of the renal pelvis and the completeness of their registration. Linkage based on unique personal identity numbers and accuracy of occupational coding are additional key advantages of this research. The lack of consideration of tobacco smoking as a potential confounding factor is a limitation of the study, while exposure to other recognized carcinogens associated with renal pelvis tumours, namely, aristolochic acid and phenacetin, are so rare that they could be considered irrelevant in the present study.
In conclusion, the results of the present study suggest that there is an association between occupation and risk of malignancy of the renal pelvis. Additional studies that take into account the effect of smoking are necessary. Further research should focus on the possible associations between exposure to asbestos, heavy metals and welding fumes and the risk of developing malignancy of the renal pelvis.

Conflict of Interest

None declared.

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Abbreviations: IARC, International Agency for Research on Cancer; SIR, standardized incidence ratio.

PUBLICATION
III

Smoking-adjusted risk of kidney cancer and occupation
- cohort study of Nordic males

Michalek, I.M., Kinnunen, T. I., Kjaerheim, K., Lynge, E., Martinsen, J.I.,
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IV

Smoking-adjusted risk of renal pelvis cancer and occupation
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LETTER TO THE EDITOR

Smoking-adjusted risk of renal pelvis cancer by occupation: a population-based cohort study of Nordic men

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Introduction

Knowledge of possible causes of renal pelvis malignancies is an important area of attention both within the field of urological oncology and epidemiology. The International Agency for Research on Cancer (IARC) classified the following agents as carcinogenic to human renal pelvis: aristolochic acid, phenacetin and tobacco smoking [1]. Although extensive research has been carried out on the matter, no single study exists deploying entire national populations and reporting analysis adjusted for the prevalence of tobacco smoking.

The objective of this study was to describe the smoking-adjusted occupational variation in the incidence of renal pelvis cancer in the male population of the Nordic countries.

Material and methods

The source population for this study was the Nordic Occupational Cancer Study (NOCCA). NOCCA is a cohort study based on data from five Nordic countries, namely, Denmark, Iceland, Finland, Norway and Sweden. Its population included 14.9 million individuals (7.4 million males and 7.5 million females). The NOCCA study was described in detail by Pukkala et al. [2].

In the present study, analyses were conducted for men only. Women were not included because in various occupational categories, smoking patterns changed irregularly, and it is hard to estimate the sum effect of the smoking habits in a given population.

Data on occupation were obtained from national population censuses. The censuses included in this research were held in Sweden in 1960, 1970, 1980 and 1990; in Norway in 1960, 1970 and 1980; in Finland in 1970, 1980 and 1990; in Iceland in 1981; and in Denmark in 1970. For individuals participating in more than one census, the first registered occupation was used. All individuals aged 30–64 years on 1 January of the year of the respective census composed the study cohort. The data collected through the censuses were digitalized and centrally encoded by the respective national statistical offices. The original national exact occupation codes were converted to 53 distinct occupational categories. One of them (domestic workers) was too small to be included in this study.

The above-described population was followed-up until emigration, death, or 31 December of the following year: 2003 in Denmark and Norway, 2004 in Iceland, 2005 in Finland and Sweden. Data on mortality and emigration were retrieved from the Central Population Registries in each country. Data on cancer cases were obtained from the respective Nordic cancer registries. Linkages were performed using unique personal identity codes. In this study, cases of renal pelvis cancer coded as 180.1, according to ICD-7, were included.

Data on survey-based occupation-specific tobacco smoking prevalence in Finnish males (1978–1995) were obtained from the Finnish Information System on Occupational Exposures (FINJEM) [3]. No comparable data from other Nordic countries were available. Data on the occupational category-specific standardized incidence ratio (SIR) of lung cancer among males (1960–2005) came from the publication of Pukkala et al. [2].

Simple linear regression analysis was used to examine the linear relationship between survey-based smoking prevalence in Finnish males and SIR of lung cancers in Finnish males. The following occupational categories were not included in the model, due to missing data on the prevalence of smoking: domestic assistants, economically inactive, hairdressers and tobacco workers. Additionally, to account for the occupational categories characterized by risk factors for lung cancer other than smoking, possibly affecting the above linear trend [4], the following categories (with the SIR of lung cancer >1.15) were not included in the regression equation:

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drivers (exposed to diesel exhaust [5,6]); painters (exposed to polycyclic aromatic hydrocarbons [6]); plumbers (exposed to asbestos [5]), beverage workers, chemical process workers, electrical workers, smelting workers and waiters. Mean smoking prevalence (explanatory variable) was 35.9% (standard deviation (SD) 8.2%). Mean SIR of lung cancer was 0.93 (SD 0.35). The assumptions of the simple linear regression analysis were met. To account for the risk of lung cancer observed in nonsmokers, the intercept was defined *a priori* at 0.05. The regression line was described by the equation $Y = 0.05 + 2.46X$ (r^2=0.58), where Y denoted SIR of lung cancers in Finnish males, and X denoted smoking prevalence in Finnish males. The model was validated using a jackknife resampling [7].

Subsequently, the above model was used to predict the smoking prevalence by occupation among Nordic males. It was assumed that the relationship between the prevalence of smoking and the risk of lung cancer for different occupational categories should be similar in all Nordic countries. Smoking-adjusted SIR was calculated as a sum of the expected number of cases in the occupational category and the product of the expected number of cases in this category and difference between smoking prevalence in the category and the smoking prevalence in the entire population. The 95% confidence intervals (95%CI) were calculated assuming a Poisson distribution.

Data management and statistical analyses were performed using Stata/IC 15.0 for Mac (StataCorp LP, College Station, TX, USA).

All studies presented in this thesis were register-based studies conducted without direct contact with participating individuals. The studies were part of the NOCCA project. The NOCCA study was according to the legal requirements in each of the Nordic studies contributing data, and individual-level data were used solely for scientific purposes in accordance with the respective permissions. The NOCCA project obeys strict rules to secure complete confidentiality and protection of the individuals.

Results

The study population encompassed 7.4 million men: 0.1 million from Iceland, 1.0 million from Denmark, 1.3 million from Norway, 1.7 million from Finland and 3.4 million from Sweden, who contributed, in total, 185 million person-years of observation in the follow-up. Among the study population, 6732 cases of renal pelvis cancer were identified.

The highest statistically significant smoking-adjusted SIRs were observed for physicians, artistic workers and public safety workers and the lowest ones for forestry workers, farmers and unskilled construction workers (Table 1). In 21 out of 52 occupational categories, the smoking-adjusted SIR was closer to 1.0 than the non-adjusted SIR.

Discussion

An unexpected finding of this study is the elevated and statistically significant smoking-adjusted SIR of renal pelvis cancer among physicians, which to our knowledge has not been reported in earlier studies. Elevated, although not statistically significant, risks were also found for dentists and other health workers.

A possible cause of the elevated risk of renal pelvis cancer among physicians that should be considered is exposure to phenacetin. Phenacetin is an analgesic and antipyretic drug that was extensively used in the past. According to IARC, phenacetin is carcinogenic to the renal pelvis [1]. However, there is no study on healthcare providers being at elevated exposure to phenacetin. Also, the literature is too sparse to suggest that addiction to analgesic drugs is prevalent in this group [8]. Nevertheless, the observation of excess risk of renal pelvis cancer among physicians, a professional group with easy access to this drug, is noteworthy.

Another possible explanation of our findings is that the physicians can be exposed both to X-radiation and gamma radiation. These agents have been previously classified by IARC as carcinogenic to the human urinary bladder, but not to the renal pelvis [1]. However, as both the urinary bladder and the renal pelvis is lined chiefly with transitional epithelium, we hypothesize that there might be an association between exposure to X-radiation or gamma radiation and elevated risk of renal pelvis cancer among physicians. Notwithstanding, the study by Hadkhale et al. [9] did not report on the increased risk of bladder cancer among physicians. Further studies need to be carried out to validate our assumption.

Finally, regarding the findings of elevated risk or renal pelvis cancer among physicians, it is important to bear in mind a possible surveillance bias. Symptoms of this cancer, like dysuria, hematuria and urgency, can remain unnoticed or dissimulated in the general population. Hence, clinicians may have a higher probability of having renal pelvis cancer detected due to increased surveillance.

Another unexpected finding was an elevated smoking-adjusted risk among artistic workers. According to the authors' knowledge, this is the first study reporting such a result. Previously, Tarvainen et al. [10,11] described an increased risk of mouth and pharynx cancer among artists. The interpretation of our findings is challenging, as the literature on occupational exposures among artistic workers is sparse.

An elevated smoking-adjusted SIR was also observed among public safety workers. The category included workers who protect individuals and property against hazards and enforcers, namely, firefighters, police officers, detectives, customs officers and guards. These findings are consistent with our previous study, where we presented non-adjusted SIRs of the renal pelvis cancer [12]. From the tabulations made for paper Pukkala et al. [13], we know that the SIR for renal pelvis cancer among Nordic firefighters is 1.04 (95%CI 0.50–1.91), suggesting that the increased risk in the category of public safety workers is not driven by exceptionally high risk among firefighters.

None of the agents recognized by IARC as carcinogenic to renal pelvis is specific to public safety workers. However, among agents recognized as carcinogenic to the human

Table 1. The observed number of cases (Obs) and standardized incidence ratios (SIRs) of renal pelvis cancer in Nordic males in occupational categories with either non-adjusted smoking-adjusted SIR >1.15 or <0.85 and Obs >5, sorted according to the smoking-adjusted SIR.

Occupational category	Obs	Smoking prevalence	Non-adjusted		Adjusted	
			SIR	95%CI	SIR	95%CI
Dentists	15	18.3%	1.31	0.73–2.16	1.66	0.93–2.74
Physicians	39	19.5%	1.30	0.93–1.78	1.63	1.16–2.23
Chimney sweeps	7	58.5%	1.75	0.70–3.60	1.47	0.59–3.02
Artistic workers	41	35.8%	1.37	0.99–1.86	1.43	1.03–1.94
Other health workers	31	31.7%	1.30	0.89–1.85	1.42	0.96–2.01
Public safety workers	115	37.4%	1.35	1.11–1.62	1.38	1.14–1.65
Laboratory assistants	9	33.3%	1.27	0.58–2.41	1.35	0.62–2.57
Textile workers	84	38.2%	1.30	1.04–1.61	1.32	1.05–1.63
Printers	74	46.7%	1.37	1.08–1.73	1.28	1.01–1.61
Transport workers	140	37.0%	1.21	1.02–1.43	1.24	1.05–1.47
Welders	56	52.0%	1.39	1.05–1.80	1.23	0.93–1.60
Clerical workers	262	34.5%	1.15	1.02–1.30	1.21	1.07–1.37
Seamen	105	63.8%	1.51	1.23–1.82	1.21	0.99–1.47
Assistant nurses	9	32.9%	1.10	0.50–2.09	1.18	0.54–2.24
Technical workers	490	31.3%	1.08	0.99–1.18	1.18	1.08–1.29
Administrators	365	31.7%	1.08	0.97–1.19	1.17	1.05–1.30
Religious workers	92	23.2%	0.98	0.79–1.20	1.17	0.95–1.44
Electrical workers	169	39.8%	1.16	0.99–1.35	1.16	0.99–1.35
Plumbers	62	55.7%	1.26	0.97–1.62	1.09	0.83–1.40
Packers	177	50.8%	1.24	1.06–1.44	1.12	0.96–1.29
Painters	111	47.9%	1.22	1.00–1.47	1.12	0.92–1.35
Food workers	145	46.3%	1.18	0.99–1.38	1.10	0.93–1.30
Gardeners	137	25.6%	0.75	0.63–0.89	0.87	0.73–1.03
Miners and quarry workers	28	62.2%	1.03	0.68–1.48	0.84	0.56–1.21
Woodworkers	281	37.0%	0.82	0.72–0.92	0.84	0.74–0.94
Engine operators	104	46.7%	0.85	0.69–1.03	0.79	0.65–0.96
Fishermen	58	45.1%	0.83	0.63–1.07	0.79	0.60–1.02
Unskilled construction workers	205	51.6%	0.88	0.76–1.01	0.78	0.68–0.90
Farmers	496	20.7%	0.62	0.56–0.67	0.76	0.69–0.83
Waiters	11	75.2%	0.94	0.47–1.69	0.70	0.35–1.25
Beverage workers	8	55.7%	0.75	0.32–1.47	0.64	0.28–1.27
Launderers	7	50.0%	0.65	0.26–1.34	0.59	0.24–1.21
Cooks and stewards	10	61.4%	0.69	0.33–1.27	0.57	0.27–1.05
Forestry workers	53	33.7%	0.48	0.36–0.62	0.51	0.38–0.66

urinary bladder [1], there are some, to which particular groups of public safety workers are occupationally exposed, like arsenic (firefighters) or diesel engine exhaust (police officers and firefighters). The study by Hadkhale et al. [9] also reported on the increased risk of bladder cancer among public safety workers. Based on the similar morphology of the above organs, we postulate that there may be an association between exposure to arsenic and diesel engine exhaust and the risk of renal pelvis cancer. These postulates are supported by our previous study, in which we observed that exposure to diesel engine exhaust was connected with higher risk of renal and renal pelvis cancer [14]. Further studies on this topic would be worthwhile.

The lowest statistically significant smoking-adjusted SIRs were observed among forestry workers and farmers. These observations are consistent with our previous study, where we reported on non-adjusted SIRs of the renal pelvis cancer [12]. They can be partially explained by the fact that the above occupational categories are characterized by high exposure to perceived physical workload, which is connected with lower body mass index (BMI). A positive association between BMI and risk of urothelial tumors has been previously postulated by Bae et al. [15].

Main strengths of this research are the large sample size and the fact that the study benefits from data covering the entire national populations. Other important advantages are precise coding of occupation in all Nordic countries and a high-quality standard maintained by all Nordic Cancer Registries regarding the completeness and accuracy of the registered data [16].

A limitation of the presented study is that occupational categories were based on the data from the first available census. Hence, there is a possibility of exposure misclassification, which could bias the observed effect towards the null. However, such dilution is probably rather small because occupational stability in the Nordic countries has been high [17].

It might be considered as another limitation of the study that the deployed smoking prevalence data are from the period 1978 to 1991 and hence cannot as such interfere on the causation of cancers diagnosed before that period. However, the time trends in smoking among Finnish men decreased rather parallelly in most population subgroups [18], and therefore the relative difference between the occupation in smoking prevalence are similar irrespective of which cross-sectional information we use.

In conclusion, the results of this investigation show that there is an association between occupation and the risk of renal pelvis cancer. Moreover, the diverse prevalence of smoking among different occupational categories plays an important role in occupational variation in the incidence of renal pelvis cancer. Finally, the study identified that the smoking-adjusted incidence of renal pelvis cancers is increased in physicians, artists, public safety workers, textile workers, printers and transport workers.

Disclosure statement

The authors report no conflicts of interest. Since 1 January 2019, Elisabete Weiderpass has been a staff member of the International Agency for Research on Cancer. Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

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Heavy metals, welding fumes, and other occupational exposures, and the risk of kidney cancer: A population-based nested case-control study in three Nordic countries

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Heavy metals, welding fumes, and other occupational exposures, and the risk of kidney cancer: A population-based nested case-control study in three Nordic countries

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ABSTRACT

Objectives: To determine whether occupational exposure to heavy metals (chromium (VI), iron, nickel, lead) and welding fumes is associated with the risk of kidney cancer and to describe whether other occupational exposures included in the Job Exposure Matrix of the Nordic Occupational Cancer (NOCCA) study are associated with the risk.

Materials and methods: Nested case-control study among individuals registered in population censuses in Finland, Iceland, and Sweden in 1960–1990. A total of 59,778 kidney cancer cases, and 298,890 controls matched on sex, age, and country. Cumulative occupational exposures to metals (chromium (VI), iron, nickel, lead), welding fumes, and 24 other occupational exposure covariates, lagged 0, 10, and 20 years.

Results: Overall, there was no or very little association between kidney cancer and exposures studied. The risk was elevated in individuals with high exposure to asbestos (OR 1.19, 95%CI 1.08–1.31). The risk was significantly decreased for individuals characterized with high perceived physical workload (OR 0.86, 95%CI 0.82–0.91), high exposure to ultraviolet radiation (OR 0.85, 95%CI 0.79–0.92), and high exposure to wood dust (OR 0.82, 95%CI 0.71–0.94). The risk of kidney cancer under the age of 59 was elevated in individuals with high exposure to nickel (OR 1.49, 95%CI 1.03–2.17). The risk of kidney cancer in age 59–74 years was elevated for individuals with high exposure to iron (OR 1.41, 95%CI 1.07–1.85), and high exposure to welding fumes (OR 1.43, 95%CI 1.09–1.89).

Conclusions: The only markedly elevated risks of kidney cancer were seen for the highest exposures of nickel and iron/welding fumes in specific age strata.

1. Introduction

Studies over the past three decades have provided valuable information on kidney cancer risk factors. Existing research recognizes the critical role played by tobacco smoking and obesity (Moch et al., 2016). Moreover, the important role of trichloroethylene and gamma radiation as carcinogenic agents that increase the risk of kidney cancer has been recognized by the International Agency for Research on Cancer (IARC) (IARC, 2006). Other agents that IARC identified as potential carcinogens connected with kidney cancer are perfluorooctanoic acid, printing process, arsenic, and cadmium (IARC, 2006).

Effects of exposure to toxic heavy metals, apart from arsenic, have not been comprehensively examined. There is little published data on chromium and nickel (Boffetta et al., 2011; Ilychova and Zaridze, 2012; Langard, 1994; Rashidi and Alavipanah, 2016; Southard et al., 2012). Moreover, Pesch et al. (2000) demonstrated that occupational

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Abbreviations

CE	Cumulative exposures
CI	Confidence intervals
IARC	International Agency for Research on Cancer
NOCCA	Nordic Occupational Cancer Study
NOCCA-JEM	Nordic Occupational Cancer Study Job Exposure Matrix
NYK	Nordisk Yrkesklassifisering
OR	Odds ratio
UV	Ultraviolet

exposures to cadmium, lead, welding fumes, and soldering fumes was connected with an elevated risk of kidney cancer in a German population. Pukkala et al. (2009) presented welders as one of the occupations characterized with the highest risk of developing kidney cancer in Nordic males. Recently, the IARC paid attention to associations between exposure to welding fumes and risk of cancer, though bias, chance, and confounding could not be reasonably excluded (Guha et al., 2017). There remains a paucity of evidence on the association between exposure to iron and risk of kidney cancer.

Debate continues about the relative importance of exposure to asbestos, some organic solvents, and pesticides and the risk of kidney cancer (Goodman et al., 1999; Jones et al., 2015; Kleinman et al., 2015; Messing et al., 1994; Ron et al., 1999; Sali and Boffetta, 2000; Wong, 1987; Xie et al., 2016). Recently, elevated risk of kidney cancer was connected with exposures to some types of dusts like glass fibers, mineral wool fibers, and brick dust (Karami et al., 2011). Other causal factors leading to kidney cancer remain speculative.

The primary objective of this study was to assess associations between occupational exposure to heavy metals (chromium (VI), iron, nickel, lead) and welding fumes, and the risk of kidney cancer. The secondary aim was to describe other occupational exposures possibly associated with the risk of kidney cancer.

2. Materials and methods

A nested case-control study of individuals from three Nordic countries (Finland, Iceland, and Sweden), who developed kidney cancer from 1961 to 2005, was performed.

2.1. Source population

The project was based on the Nordic Occupational Cancer Study (NOCCA) cohort which comprised 14.9 million individuals from five Nordic countries. NOCCA study was described in detail by Pukkala et al. (2009). The study has received approvals from country-specific ethical committees.

2.2. Study design and participants

Both cases and controls were extracted from the NOCCA study. The participants in this study were recruited from Finland, Iceland, and Sweden. Norway and Denmark were excluded because of lack of access to the individual level records.

The cases were defined as all individuals diagnosed with cancer of the kidney or the renal pelvis (7th International Classification of Diseases 180) between 1961-2005 in Sweden, 1971-2005 in Finland, and 1982-2004 in Iceland. For each case, five controls were randomly selected from the NOCCA individuals, who were alive and free from kidney cancer on the date of diagnosis of the case (henceforth the “index date” for the case-control set). Controls were individually matched to cases on birth date, sex, and country. Both cancers and controls could have a history of any other comorbid cancer.

2.3. Source of data on exposure and outcome

Data on exposure were obtained through population censuses, in which participants were asked to indicate their occupation through free text, using self-administered questionnaires. The following censuses contained information on occupation and were included in the study: Sweden - 1960, 1970, 1980, 1990; Finland - 1970, 1980, 1990; and Iceland - 1981. Participation in the census was mandatory. Subsequently, the data were digitalized and encoded using Nordisk Yrkesklassifisering (NYK), a Nordic adaptation of the International Standard Classification of Occupations from 1958. Data on outcome were acquired from national cancer registers in the respective Nordic countries. Finally, unique personal identity codes were used to perform linkage of the information on occupations from censuses, cancer cases from cancer registries, and death and emigration from national population registries. Only participants with a minimum age of 20 at the index date and having information from at least one census prior to index date were included in this study.

For the purpose of the detailed exposure estimation, NOCCA Job Exposure Matrix (NOCCA-JEM) was used (described in detail by Kauppinen et al. (2009)). The matrix converses NYK codes to quantitative estimates of exposure to 29 substances potentially related to cancer risk (Table 1). For each occupational category, it provides two variables for each agent: the probability of being exposed (P) and the average exposure level (L) among the exposed persons. Time of exposure (T), was assessed individually, starting at the age of 20 (typical age to start work in non-academic occupations), and index date or age of 65 (typical age at retirement), whichever occurred first.

Cumulative occupational exposures (CE) to 29 agents, defined as $P \times L \times T$, were calculated for all cases and controls. The occupation reported during the first census in which the individual took part was considered an occupation performed by this individual from the age of 20 years. When more than one occupational code was assigned to one person in different censuses, it was assumed that the change of work

Table 1
Occupational exposure agents taken into account in the study.

Abbreviation	Occupational exposure agents	Unit
ALHC	Aliphatic and alicyclic hydrocarbon solvents	ppm
ANIM	Animal-borne dust	mg/m^3
ARHC	Aromatic hydrocarbon solvents	ppm
ASB	Asbestos	f/cm^3
BAP	Benzo(a)pyrene	$\mu g/m^3$
BENZ	Benzene	ppm
BITU	Bitumen fumes	mg/m^3
CHC	Chlorinated hydrocarbon solvents	ppm
CR	Chromium	$\mu g/m^3$
DEEX	Diesel engine exhaust	mg/m^3
FE	Iron	mg/m^3
FORM	Formaldehyde	ppm
GASO	Gasoline	ppm
IRAD	Ionizing radiation	mSv
MCH	Methylene chloride	ppm
NI	Nickel	$\mu g/m^3$
NIGH	Nightwork	none
OSOL	Other organic solvents	ppm
PB	Lead	µmol/l
PER	Perchloroethylene	ppm
PPWL	Perceived physical workload	score [a]
QUAR	Quartz dust	mg/m^3
SO2	Sulphur dioxide	ppm
TCE	1,1,1-Trichloroethane	ppm
TOLU	Toluene	ppm
TRI	Trichloroethylene	ppm
UV	Ultraviolet radiation	J/m^2
WELD	Welding fumes	mg/m^3
WOOD	Wood dust	mg/m^3

[a] Score of workers reporting heavy or rather heavy physical work in national Finnish “Quality of Work Life Survey”, Finland 1990 (Statistics Finland, 2018).

occurred in the middle of the period between the censuses. For these individuals, CE was a sum of all $P \times L \times T$, calculated for each separate occupational period. All cumulative exposures were calculated for three different lags of 0, 10, and 20 years, to allow for a cancer latency period. The results for lag 10 and lag 20 were similar, and we therefore only present findings for the lag of 10 years.

2.4. Statistical analysis

Conditional logistic regression was used to generate odds ratios (OR) and 95% confidence intervals (CI), testing the hypothesis that exposure to heavy metals (chromium (VI), iron, lead, and nickel) and welding fumes is associated with increased risk of kidney cancer.

The final main effect model was created using the purposeful selection of variables (explained in detail by Bursac et al. (2008)). The choice of this method of creating the model allows avoiding "over-fitting" of the model and generation of numerically unstable estimates.

In the first step, we fitted the univariable logistic regression model for each independent CE variable. Subsequently, we created a first multivariable logistic model in which we fitted all of the covariates for which *p*-value of its Wald statistic was < 0.25 in the univariable logistic model. The significance level of 0.25 was recommended by Mickey (Mickey and Greenland, 1989). Variables describing heavy metal exposures were forced in the model as *a priori* selected variables of interest in this study. Next, we assessed the significance of each variable from the multivariable model using the Wald statistic. We gradually eliminated covariates not contributing at the traditional significance level of $p < 0.05$. For each reduction, we calculated the difference between the values of the estimated coefficients, $\Delta\beta$. Excluded variables for which $\Delta\beta > 20\%$ were added back into the model. Subsequently, we compared the fit of the first multivariable logistic model with the final one, deploying a likelihood ratio test.

The algorithm denoted aliphatic and alicyclic hydrocarbon solvents, asbestos, chlorinated hydrocarbon solvents, diesel engine exhaust, perceived physical workload, quartz dust, trichloroethylene, ultraviolet radiation, and wood dust, as significant/confounding covariates. Subsequently, correlation check between these agents was performed (Supplemental Fig. 1). Iron and welding fumes were highly correlated, and therefore they were not used in the same model. The final models were as follows: 1) ALHC + ASB + CHC + CR + DEEX + NI + PB + PPWL + QUAR + TRI + UV + WELD + WOOD; 2) ALHC + ASB + CHC + CR + DEEX + FE + NI + PB + PPWL + QUAR + TRI + UV + WOOD.

Each occupational agent was analyzed as a three-category exposure, including low (< 50 percentile), moderate (≥50 percentile and < 90 percentile), and high (≥90 percentile). Individuals with no exposure (defined as $P \times L \times T = 0$) constituted a reference category. Subsequently, to assess a dose-response relationship between exposure to heavy metals (chromium (VI), iron, lead, and nickel) and welding fumes, and kidney cancer, Pearson's chi-squared test for linear trend was performed. Unexposed individuals were excluded from the analysis for the trend test. To evaluate the robustness of our inferences a posthoc conservative Bonferroni procedure was adopted for multiple analyses. The Bonferroni-corrected significance threshold was 0.004 (i.e., 0.05/13 variables) (Dunn, 1961). We deemed a *p*-value < 0.004 as significant evidence for a causal association when assessing the significance of trend test.

To explore possible effect modifiers, analyses were later stratified by sex and age group at diagnosis (< 59, 59–74, > 74). Age groups were *a priori* determined based on quartile distribution (that is < Q1, Q1-Q3, > Q3).

Data management and all analyses were performed using R studio 1.1.442, using packages corrplot, dosresmeta, Epi, lmtest, readxl, ResourceSelection, survival, and xlsx.

Table 2
Demographic characteristics of the study population.

Characteristic		Cases		Controls		Total	
		N	%	N	%	N	%
Total		59,778	100.0	298,890	100.0	358,668	100.0
Sex	Male	34,856	58.3	174,280	58.3	209,136	58.3
	Female	24,922	41.7	124,610	41.7	149,532	41.7
Country	Finland	17,647	29.5	88,235	29.5	105,882	29.5
	Iceland	588	1.0	2940	1.0	3528	1.0
	Sweden	41,543	69.5	207,715	69.5	249,258	69.5
Year of birth	≤1910	8992	15.0	44,960	15.0	53,952	15.0
	1911–1920	14,660	24.5	73,300	24.5	87,960	24.5
	1921–1930	16,656	27.9	83,280	27.9	99,936	27.9
	1931–1940	10,745	18.0	53,725	18.0	64,470	18.0
	1941–1950	5998	10.0	29,990	10.0	35,988	10.0
	1951–1960	2399	4.0	11,995	4.0	14,394	4.0
	≥1961	328	0.5	1640	0.5	1968	0.5
Age at index date	20–29	94	0.2	474	0.2	568	0.2
	30–39	792	1.3	3971	1.3	4763	1.3
	40–49	4257	7.1	21,296	7.1	25,553	7.1
	50–59	11,756	19.7	58,749	19.7	70,505	19.7
	60–69	18,499	30.9	92,338	30.9	110,837	30.9
	70–79	17,846	29.9	89,276	29.9	107,122	29.9
	≥80	6534	10.9	32,786	11.0	39,320	11.0

3. Results

In the study, 59,778 kidney cancer cases, and 298,890 sex-, age-, and country-matched controls were identified (Table 2). Males accounted for 58.3% of study participants, and females for 41.7%. Most individuals were born before 1940. The mean age at the diagnosis was 66 years (median 67 years).

3.1. Heavy metals and welding fumes

In the OR analysis for both sexes and all age groups (Table 3), for none of the studied agents, the dose-response trend was statistically significant. It was observed that ORs in women were frequently higher than in men although based on a much smaller number of cases (Table 4). Moreover, moderate and high exposures to welding fumes were associated with excess risk in men. This may still not indicate that the absolute excess risk due to the exposure would be higher in women because the reference incidence level of kidney cancer is much lower in women. In the analysis with stratification by age at the index date (Table 5), in the group of < 59 years, OR for high exposure to nickel was significant (OR 1.49, 95%CI 1.03–2.17). In the group of 59–74 years, ORs for the following were statistically significant: high exposure to iron (OR 1.41, 95%CI 1.07–1.85), moderate exposure to welding fumes (OR 1.27, 95%CI 1.02–1.56), and high exposure to welding fumes (OR 1.43, 95%CI 1.09–1.89).

3.2. Other exposures

Further analysis of covariates revealed a statistically significant increase of OR for high exposure to asbestos (OR 1.19, 95%CI 1.08–1.31). Statistically significant (more than 10%) decrease of OR was observed among individuals characterized with high exposure to aliphatic and alicyclic hydrocarbon solvents (OR 0.81, 95%CI 0.69–0.95); high exposure to perceived physical workload (OR 0.86, 95%CI 0.82–0.91); moderate (OR 0.85, 95%CI 0.81–0.88), and high exposure (OR 0.85, 95%CI 0.79–0.92) to ultraviolet (UV) radiation; and high (OR 0.82, 95%CI 0.71–0.94) exposure to wood dust. Dose-response test for trend was statistically significant for exposure to UV ($p < 0.001$).

Table 3
Odds ratios (OR) and 95% Confidence intervals (95% CI) of kidney cancer associated with occupational exposures.

Agent (unit)	Cumulative exposure	Cases	Controls	OR	95% CI	*p*-value for trend
Heavy metals and welding fumes						
Chromium [b] (μg/m^3-years)	unexposed	53,272	268,143	1.00	Ref	0.78
	< 1331.05	3248	15,379	0.99	0.91–1.09	
	1331.05–13,611.17	2647	12,253	1.07	0.96–1.18	
	> 13,611.17	611	3115	0.99	0.86–1.15	
Iron [b] (mg/m^3-years)	unexposed	54,153	273,058	1.00	Ref	0.36
	< 410.84	2841	12,887	1.09	0.94–1.27	
	410.84–4899.30	2206	10,377	1.10	0.95–1.28	
	> 4899.30	578	2568	1.15	0.94–1.39	
Nickel [b] (μg/m^3-years)	unexposed	54,074	272,532	1.00	Ref	0.57
	< 992.80	2859	13,227	0.92	0.80–1.06	
	992.80–5624.32	2266	10,503	0.90	0.78–1.04	
	> 5624.32	579	2628	0.99	0.82–1.20	
Lead [b] (μmol/l-years)	unexposed	52,154	263,218	1.00	Ref	0.58
	< 369.53	3874	17,776	1.09	1.03–1.16	
	369.53–1151.97	3040	14,276	1.06	0.99–1.13	
	> 1151.97	710	3620	0.95	0.86–1.05	
Welding fumes [a] (mg/m^3-years)	unexposed	54,154	273,062	1.00	Ref	0.27
	< 254.00	2756	12,970	1.05	0.90–1.22	
	254.00–12,281.40	2281	10,300	1.14	0.98–1.33	
	> 12,281.40	587	2558	1.20	0.99–1.46	
Other exposures						
Aliphatic and alicyclic hydrocarbon solvents [b] (ppm-years)	unexposed	56,679	284,102	1.00	Ref	0.50
	< 1740.45	1628	7316	1.01	0.93–1.09	
	1740.45–30,000.62	1223	5931	0.99	0.90–1.08	
	> 30,000.62	248	1541	0.81	0.69–0.95	
Asbestos [b] (f/cm^3-years)	unexposed	50,693	253,982	1.00	Ref	0.36
	< 192.41	4486	22,513	0.97	0.93–1.01	
	192.41–1628.47	3646	17,947	1.04	0.98–1.10	
	> 1628.47	953	4448	1.19	1.08–1.31	
Chlorinated hydrocarbon solvents [b] (ppm-years)	unexposed	58,461	292,116	1.00	Ref	0.71
	< 2233.27	702	3344	1.05	0.95–1.16	
	2233.27–5779.19	490	2746	0.93	0.80–1.07	
	> 5779.19	125	684	0.89	0.70–1.13	
Diesel engine exhaust [b] (mg/m^3-years)	unexposed	52,487	265,786	1.00	Ref	0.07
	< 66.00	3692	16,869	1.08	1.03–1.12	
	66.00–197.39	2863	12,931	1.07	1.02–1.12	
	> 197.39	736	3304	1.07	0.98–1.17	
Perceived physical workload [b] (score[c]-years)	unexposed	26,320	127,620	1.00	Ref	0.06
	< 418.66	17,375	84,989	0.99	0.97–1.02	
	418.66–1600.14	13,151	68,740	0.97	0.94–1.00	
	> 1600.14	2932	17,541	0.86	0.82–0.91	
Quartz dust [b] (mg/m^3-years)	unexposed	55,905	278,965	1.00	Ref	0.98
	< 126.85	1932	9967	1.04	0.98–1.12	
	126.85–640.53	1567	7952	1.03	0.95–1.10	
	> 640.53	374	2006	0.91	0.79–1.03	
Trichloroethylene [b] (ppm-years)	unexposed	56,316	282,593	1.00	Ref	0.61
	< 3192.54	1760	8118	1.00	0.94–1.07	
	3192.54–12785.08	1347	6560	0.92	0.85–1.00	
	> 12,785.08	355	1619	1.03	0.88–1.19	
Ultraviolet radiation [b] (J/m^2-years)	unexposed	46,077	224,064	1.00	Ref	< 0.001
	< 464,202.10	7140	37,124	0.94	0.91–0.97	
	464,202.10–860,940.90	5213	30,198	0.85	0.81–0.88	
	> 860,940.90	1348	7504	0.85	0.79–0.92	
Wood dust [b] (mg/m^3-years)	unexposed	57,138	284,698	1.00	Ref	0.10
	< 923.70	1334	7082	0.95	0.89–1.02	
	923.70–3675.15	1062	5670	0.92	0.85–0.99	
	> 3675.15	244	1440	0.82	0.71–0.94	

[a] OR estimates calculated using Model 2.
[b] OR estimates calculated using Model 1.
[c] Score of workers reporting heavy or rather heavy physical work in national Finnish "Quality of Work Life Survey", Finland 1990 (Statistics Finland, 2018).

4. Discussion

4.1. Heavy metals and welding fumes

This study was unable to demonstrate any significant dose-dependent relationship between exposures to chromium (VI), iron, nickel, lead, and welding fumes and the risk of developing kidney cancer. Among individuals diagnosed under the age of 59 years, a link may exist between exposure to nickel and risk of kidney cancer. The value of ORs among the individuals diagnosed between the age of 59 and 74, and characterized by moderate and high CE to welding fumes, and high CE to iron, suggests that a weak link may exist between exposure to welding fumes or iron, and risk of developing kidney cancer. Concurrent exposure to iron and welding fumes hinders understanding of their independent roles as risk factors. In the case of the other ORs identified in the study (low CE to lead), we cannot exclude the possibility of chance findings.

One of the issues that emerge from the findings of the present study

Table 4
Sex-specific odds ratios (OR) and 95% Confidence intervals (95% CI) of kidney cancer associated with exposures to heavy metals and welding fumes.

Agent (unit)	Cumulative exposure	Males					Females				
		Cases	Controls	OR	95% CI	*p*-value for trend	Cases	Controls	OR	95% CI	*p*-value for trend
Chromium [b] (μg/m^3-years)	unexposed	28,805	145,488	1.00	Ref	0.55	24,467	122,655	1.00	Ref	0.55
	< 1331.05	3004	14,314	1.00	0.91–1.11		244	1065	0.93	0.69–1.25	
	1331.05–13,611.17	2462	11,467	1.10	0.98–1.23		185	786	0.84	0.59–1.21	
	> 13,611.17	585	3011	1.04	0.89–1.22		26	104	0.74	0.39–1.41	
Iron [b] (mg/m^3-years)	unexposed	29,578	149,845	1.00	Ref	0.31	24,575	123,213	1.00	Ref	0.72
	< 410.84	2607	11,956	1.09	0.93–1.28		234	931	1.34	0.73–2.48	
	410.84–4899.30	2101	9935	1.14	0.98–1.33		105	442	1.09	0.57–2.09	
	> 4899.30	570	2544	1.16	0.95–1.42		8	24	1.37	0.40–4.69	
Nickel [b] (μg/m^3-years)	unexposed	29,527	149,453	1.00	Ref	0.42	24,547	123,079	1.00	Ref	0.82
	< 992.80	2620	12,210	0.92	0.79–1.06		239	1017	0.79	0.46–1.33	
	992.80–5624.32	2149	10,054	0.87	0.75–1.02		117	449	1.12	0.65–1.94	
	> 5624.32	560	2563	0.93	0.76–1.14		19	65	1.49	0.60–3.70	
Lead [b] (μmol/l-years)	unexposed	27,897	141,415	1.00	Ref	0.78	24,257	121,803	1.00	Ref	0.87
	< 369.53	3427	15,978	1.07	1.00–1.15		447	1798	1.17	0.99–1.39	
	369.53–1151.97	2860	13,455	1.05	0.98–1.13		180	821	0.99	0.79–1.25	
	> 1151.97	672	3432	0.94	0.85–1.04		38	188	0.83	0.54–1.29	
Welding fumes [a] (mg/m^3-years)	unexposed	29,579	149,849	1.00	Ref	0.24	24,575	123,213	1.00	Ref	0.63
	< 254.00	2485	11,877	1.06	0.91–1.24		271	1093	1.25	0.69–2.29	
	254.00–12,281.40	2211	10,014	1.17	1.00–1.36		70	286	1.29	0.65–2.55	
	> 12,281.40	581	2540	1.22	0.99–1.49		6	18	1.42	0.35–5.87	

[a] OR estimates calculated using Model 2.
[b] OR estimates calculated using Model 1.

is the weak association between exposure to welding fumes and the risk of kidney cancer. This accords both with our earlier observations (Michalek et al., 2018a, 2018b) and those of MacLeod et al. (2017). Furthermore, this finding is in line with the position of the IARC (IARC, 2006). In our study, the definition of welders encompassed individuals who join and cut metal parts using flame, electric arc, and other sources of heat to melt and cut or fuse metal. Exposures of welders may differ depending on their actual work.Therefore, it would be good if the NOCCA-JEM, like its Finnish equivalent FINJEM, would include exposure estimates for combinations of occupation and industry (e.g. “welder in stainless steel industry”; see Kauppinen et al., 1998). Unfortunately, we did not have access to industry codes for all Nordic countries. The known occupational exposures among welders are fumes, gases, UV radiation, electromagnetic fields, and coexposure to asbestos and solvents (Guha et al., 2017). Further studies, which take these variables into account, will need to be undertaken.

The observed higher ORs among females exposed to iron and welding fumes might suggest possible higher biological susceptibility of the female kidney to metals, which was already suggested in the literature (Johnson et al., 2003). However, it is challenging to demonstrate sound sex differences even in such a large study due to the very few women ever employed as a welder, smelter, furnacemen, plumbers, and other metal industry workers. We should also avoid direct comparison of the relative risk estimates between sexes as the incidence of kidney cancer in unexposed women used as the reference is much lower than in men.

Prior studies noted the importance of exposure to lead (Boffetta et al., 2011; Ilychova and Zaridze, 2012). However, the findings of the current study do not support the previous research. There are several possible explanations for this inconsistency. One of them might be the fact that the previous studies were based on small study populations. This inconsistency may also be due to the fact that the regression models in the previous studies included a little number of variables of interest. It could be argued that the positive results in those studies were caused by the fact that no covariates were included.

For the purpose of the discussion, we created one more set of two conditional logistic regression models in which we included only heavy metals and welding fumes, i.e., S1) CR + NI + PB + WELD, and S2) CR + FE + NI + PB. These experiments were designed to estimate what effect heavy metals and welding fumes would have on ORs if they were the only occupational exposure factors included in the final multivariable model, that is, data for only five occupational agents instead of 29 would be available. These experiments confirmed that for smaller models that do not include other covariates, ORs are mostly higher (Supplemental Table 1).

Findings on no association between the exposure to chromium (VI) and the risk of kidney cancer are consistent with the literature (Boffetta et al., 2011; Langard, 1994). Very little was found in the literature on the question of exposures to iron or nickel and the risk of kidney cancer.

In our study, we were unable to examine the possible association between occupational exposure to cadmium and risk of kidney cancer because estimates for cadmium exposure are not included in the NOCCA-JEM. The importance of this metal regarding kidney toxicity due to its estrogenic nature was broadly discussed in the literature (Johnson et al., 2003) in the context of the estrogenic features of the kidney (Maric, 2009).

4.2. Other covariates

The results of this study indicate that there is a positive association between exposure to asbestos and the risk of kidney cancer. This study supports evidence from previous observations (Peters et al., 2018a, b; Sali and Boffetta, 2000). Furthermore, we found an increased risk of developing kidney cancer among individuals exposed to diesel engine exhaust. This finding was also reported by Peters et al. (Peters et al., 2018a, b) and Boffetta et al. (2001).

In this study, the physical workload was found to be associated with a lower risk of kidney cancer. These results are likely to be related to findings, that obesity may be associated with a higher risk of kidney malignancies (Ildaphonse et al., 2009; Mathew et al., 2009; Sawada et al., 2010).

Exposure to wood dust was found to be associated with a decreased risk of developing kidney cancer. Full understanding of how wood dust contributes to the risk of kidney cancer is still lacking. It was reported that the standardized incidence ratio was lower among woodworkers (Pukkala et al., 2009). However, these results need to be interpreted with caution as there is a positive correlation between exposure to wood dust and exposure to perceived physical workload (Supplemental Fig. 1), which is inversely correlated with the risk of obesity, that is a recognized risk factor of kidney cancer.

Table 5
Odds ratios (OR) and 95% Confidence intervals (95% CI) of kidney cancer associated with exposures to heavy metals and welding fumes, by age at index date.

Agent (unit)	Cumulative exposure	Cases	Controls	OR	95% CI	*p*-value for trend
Age at index date < 59 years						
Chromium [b] (μg/m^3-years)		13,239	66,963	1.00	Ref	0.83
	< 1331.05	1183	5365	1.08	0.91–1.28	
	1331.05–13,611.17	827	3862	1.06	0.88–1.28	
	> 13,611.17	79	387	0.93	0.66–1.30	
Iron [b] (mg/m^3-years)	unexposed	13,508	68,356	1.00	Ref	0.91
	< 410.84	1125	4958	0.95	0.71–1.26	
	410.84–4899.30	623	2940	0.97	0.72–1.29	
	> 4899.30	72	323	1.01	0.62–1.63	
Nickel [b] (μg/m^3-years)	unexposed	13,470	68,181	1.00	Ref	0.50
	< 992.80	1246	5549	1.04	0.80–1.34	
	992.80–5624.32	485	2329	1.01	0.77–1.32	
	> 5624.32	127	518	1.49	1.03–2.17	
Lead [b] (μmol/l-years)	unexposed	12,876	65,278	1.00	Ref	0.74
	< 369.53	1683	7722	1.05	0.95–1.17	
	369.53–1151.97	690	3211	1.02	0.90–1.15	
	> 1151.97	79	366	1.06	0.80–1.42	
Welding fumes [a] (mg/m^3-years)	unexposed	13,508	68,356	1.00	Ref	0.88
	< 254.00	1086	4975	0.92	0.69–1.22	
	254.00–12,281.40	622	2757	1.01	0.76–1.35	
	> 12,281.40	112	489	1.15	0.77–1.74	
Age at index date 59–74 years						
Chromium [b] (μg/m^3-years)	unexposed	24,892	125,119	1.00	Ref	0.96
	< 1331.05	1474	7187	0.95	0.83–1.09	
	1331.05–13,611.17	1313	6063	1.06	0.92–1.23	
	> 13,611.17	297	1569	0.94	0.75–1.17	
Iron [b] (mg/m^3-years)	unexposed	25,318	127,525	1.00	Ref	0.15
	< 410.84	1297	6047	1.22	0.98–1.52	
	410.84–4899.30	1026	4855	1.22	0.98–1.51	
	> 4899.30	335	1511	1.41	1.07–1.85	
Nickel [b] (μg/m^3-years)	unexposed	25,293	127,281	1.00	Ref	0.23
	< 992.80	1196	5741	0.83	0.68–1.02	
	992.80–5624.32	1187	5455	0.85	0.69–1.04	
	> 5624.32	300	1461	0.77	0.58–1.02	
Lead [b] (μmol/l-years)	unexposed	24,370	122,861	1.00	Ref	0.67
	< 369.53	1624	7524	1.09	1.00–1.20	
	369.53–1151.97	1652	7889	1.05	0.95–1.15	
	> 1151.97	330	1664	0.98	0.84–1.13	
Welding fumes [a] (mg/m^3-years)	unexposed	25,319	127,527	1.00	Ref	0.13
	< 254.00	1200	5767	1.14	0.92–1.42	
	254.00–12,281.40	1133	5190	1.27	1.02–1.56	
	> 12,281.40	324	1454	1.43	1.09–1.89	
Age at index date > 74 years						
Chromium [b] (μg/m^3-years)	unexposed	15,141	76,061	1.00	Ref	0.89
	< 1331.05	591	2827	0.96	0.78–1.17	
	1331.05–13,611.17	507	2328	1.04	0.81–1.33	
	> 13,611.17	235	1159	1.06	0.78–1.43	
Iron [b] (mg/m^3-years)	unexposed	15,327	77,177	1.00	Ref	1.00
	< 410.84	419	1882	1.02	0.73–1.44	
	410.84–4899.30	557	2582	1.03	0.75–1.41	
	> 4899.30	171	734	0.96	0.63–1.44	
Nickel [b] (μg/m^3-years)	unexposed	15,311	77,070	1.00	Ref	0.94
	< 992.80	417	1937	0.96	0.70–1.30	
	992.80–5624.32	594	2719	0.97	0.72–1.30	
	> 5624.32	152	649	1.13	0.75–1.70	
Lead [b] (μmol/l-years)	unexposed	14,908	75,079	1.00	Ref	0.67
	< 369.53	567	2530	1.17	1.01–1.36	
	369.53–1151.97	698	3176	1.16	0.99–1.35	
	> 1151.97	301	1590	0.94	0.80–1.12	
Welding fumes [a] (mg/m^3-years)	unexposed	15,327	77,179	1.00	Ref	0.95
	< 254.00	470	2228	0.95	0.68–1.34	
	254.00–12,281.40	526	2353	1.08	0.79–1.49	
	> 12,281.40	151	615	0.98	0.63–1.51	

[a] OR estimates calculated using Model 2.
[b] OR estimates calculated using Model 1.

Finally, an unanticipated finding was that exposure to UV radiation was associated with a lower risk of kidney malignancies. A dose-response effect was confirmed with the test for trend. A possible explanation for this might be an increased level of vitamin D due to sunlight exposure. These results corroborate ideas of Darling et al. (2016). Here, again, a note of caution is due since a positive correlation between exposure to UV radiation and exposure to perceived physical workload exists (Supplemental Fig. 1). Physical activity decreases the risk of obesity, that is one of the recognized risk factors of kidney cancer.

4.3. Strengths and limitations of the study

To the knowledge of the authors, this is the first study to assess the relationship between exposure to heavy metals and welding fumes deploying whole national populations. The high number of kidney cancer cases (59,778) is the main strength of our study.

Additional advantages are the linkage based on unique personal identity codes and the accuracy of occupational coding. The method of the linkage, by definition, ensured a complete ascertainment of relevant events. Moreover, according to Pukkala et al. (2018), close to 100% coverage of incident cases has been reported in each of the registries.

Findings of our study may be somewhat limited by the lack of data regarding tobacco smoking. However, a study adjusting the incidence of lung cancer for smoking (Haldorsen et al., 2004) supported clarification that the differing smoking patterns do not explain all the occupational variation in risk. Other known risk factors for renal cancer not taken into consideration in our research are hereditary tumors, such as von Hippel-Lindau syndrome.

Another source of uncertainty is limited data on professional history which was assessed only during censuses. We had to assume that there were no changes between the age of 20 years and the earliest known census occupation, nor between the latest known census occupation and age of 65 years.

5. Conclusions

In conclusion, in our study, there was no association between exposure to chromium (VI) or lead and the risk of kidney cancer. Multiple regression analysis revealed that there is an elevated risk of kidney cancer under the age of 59 in individuals with high exposure to nickel. Moreover, among individuals diagnosed with kidney cancer at the age of 59–74, the risk was elevated for high exposure to iron, and moderate and high exposure to welding fumes. Concurrent exposure to the latter agents may hinder interpretation of their roles as independent risk factors.

Conflicts of interest

The authors declare they have no actual or potential competing financial interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2019.03.023.

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