

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:

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 of 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.

Funding

This research was supported by a Nordic Cancer Union Grant for the project "Work and cancer: in-depth studies initiated by the NOCCA project".

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