

# Smoking as a Confounder in Case-Control Studies of Occupational Bladder Cancer in Women

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**Background:** In studies in men, risk estimates on occupation and bladder cancer are distorted by about 10% when not adjusting for smoking. We examined the degree to which occupational risk estimates for bladder cancer in women are confounded by smoking, and the degree of residual confounding by inadequate control of this effect.

**Methods:** Primary data of 11 case-control studies on occupation and bladder cancer from Denmark, France, Germany, Greece, Italy, and Spain were pooled. Information for smoking and lifetime occupational history for 700 female cases and 2,425 female controls ages 30-79 was abstracted and recoded. Logistic regression was used to calculate odds ratios (OR) by occupation, applying five models which differed in their degree of adjustment for smoking.

**Results:** In major occupational groups, risk estimates were distorted by less than 10% when not adjusting for smoking. A statistically significant excess risk for bladder cancer was found in 13 specific occupations and industries. In most occupations, adjustment for smoking led the ORs towards the null value, but all statistically significant associations were maintained after adjustment. In three occupations (lathe operators, field crop workers, and wood manufacturers), a statistically significant excess risk was masked when not adjusting for smoking. In six occupations, estimates were distorted by more than 10% (-22% up to +40%). In occupations where smoking acted as a positive confounder, the proportion of confounding removed using a dichotomous smoking variable (ever/never) was around 60%. In one occupation (buyers), controlling for smoking status (ever, never) led to over-adjustment, because the percentage of smokers was high but the quantity smoked was low.

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*Conclusions: Tobacco smoking was not found to be a major confounder for the association between occupation and bladder cancer in women. Most of this confounding effect could be removed by adjustment by smoking status (ever/never), without consideration of amount or duration of smoking. Am. J. Ind. Med. 36:75-82, 1999. © 1999 Wiley-Liss, Inc.*

**KEY WORDS:** *confounding factors; smoking; occupational exposure; bladder neoplasms; women*

## INTRODUCTION

Information on smoking is usually available in case-control studies examining occupational exposures, and adjustment for the potential confounding effect of smoking is, therefore, easily done. The magnitude of confounding by smoking has, however, rarely been quantified. This makes it difficult to evaluate to what extent risk estimates are confounded by smoking in occupational studies where smoking information is not available, such as industry-based studies or studies based on cancer incidence or mortality statistics. In the absence of smoking data, methods for sensitivity analyses and external confounding adjustment have been described, enabling a rough estimate of the potential confounding by smoking [Axelson and Steenland, 1988; Gail et al., 1988; Greenland, 1996]. Although such evaluations on a theoretical basis are useful, they have also been qualified as "educated guessing" [Greenland, 1996]. The confounding effect of smoking in women has not been studied, although it could be different from that in men because of differences in smoking habits and employment characteristics between genders.

Confounding by smoking in studies examining occupational exposures can either be negative (smoking rate in occupation is relatively low, resulting in an underestimation of the RR) or positive (smoking rate is relatively high, resulting in an overestimation of the RR). In many countries, smoking behavior varies considerably by occupation [Stellman et al., 1988; Brackbill et al., 1988]. In the US, the percentage of women having ever smoked regularly ranged from 59.4% in waitresses to 21.3% in farmers. Smoking rates also appear to be significantly higher in groups exposed to occupational hazards compared to groups less exposed [Stellman et al., 1988].

The degree of potential confounding depends on the difference in smoking habits between risk and reference group and on the strength of the association of the disease in question with smoking. Population surveys indicate that there is a wide range in occupation-specific smoking rates in both men and women of industrialized countries, suggesting that confounding by smoking might be considerable in specific diseases. The confounding effect of smoking on the RR for lung cancer has typically been found to be more important than that for bladder [Axelson and Steenland,

1988; Siemiatycki et al., 1988; Blair et al., 1988; Scherg, 1995; Chiaze et al., 1995; Greenland, 1996]. An empirical investigation in a case-control study in Montreal [Siemiatycki et al., 1988] looked at the degree of confounding bias related to smoking for bladder and lung cancer. For lung cancer, considerable distortions of unadjusted odds ratios (ORs) were found. For bladder cancer, the differences between adjusted and unadjusted ORs were not larger than 10% in 23 of 25 occupations. A higher than 20% distortion was seen in only one occupation (teachers). The difference between bladder and lung cancer can be attributed to the weaker association with smoking for bladder compared to lung cancer. Even for bladder cancer, however, the risks for smoking are higher than those typically found for occupation. The residual confounding by smoking that can be caused by using a restrictively categorized variable for smoking (i.e., "without taking into account quantity and duration of smoking") has been found to be limited [Cordier et al., 1993; Siemiatycki et al., 1988].

In this study, we quantified the magnitude to which the occupational risk estimates for bladder cancer are confounded by smoking in women using a large pooled dataset of 11 case-control studies with detailed occupational and smoking information. We also estimated the degree of residual confounding when limited rather than detailed information on smoking is available.

## MATERIAL AND METHODS

We performed a pooled analysis of case-control studies on bladder cancer that were conducted in European countries between 1976 and 1996 (Mannetje et al., in press). A total of 11 studies were identified using as criteria the availability of detailed occupational and smoking information and the accessibility of the primary data. Three additional European studies with detailed information on occupation were identified, one each from the UK [Cartwright, 1982], Sweden [Steineck et al., 1990], and Finland [Tola et al., 1980] but for various reasons it was not possible to incorporate them in the pooled analysis. The pooled file comprises data from three studies from Germany [Claude et al., 1988; Bolm-Audorff et al., 1993; Greiser and Molzahn, 1997], two each from France [Cordier et al., 1993; Hours et al., 1994], Italy [Vineis and Magnani, 1985; Porru et al., 1996], and Spain [González et al., 1989] (Serra, unpub-

TABLE I. Case-Control Studies of Bladder Cancer

| All                 | Country | Mean year<br>of enrollment | Cases |      | Controls |      | (n(hospital)/<br>n(population)) |
|---------------------|---------|----------------------------|-------|------|----------|------|---------------------------------|
|                     |         |                            | n     | %    | n        | %    |                                 |
|                     |         |                            | 700   |      | 2,425    |      | (761/1,664)                     |
| Jensen et al.       | Denmark | 1980                       | 96    | 13.7 | 193      | 8.0  | (0/193)                         |
| Claude et al.       | Germany | 1980                       | 95    | 13.6 | 120      | 4.9  | (120/0)                         |
| Rebelakos et al.    | Greece  | 1982                       | 47    | 6.7  | 44       | 1.8  | (44/0)                          |
| Vineis et al.       | Italy   | 1982                       | 39    | 5.6  | 183      | 7.5  | (183/0)                         |
| Cordier et al.      | France  | 1985                       | 83    | 11.9 | 101      | 4.2  | (101/0)                         |
| Gonzalez et al.     | Spain   | 1986                       | 49    | 7.0  | 120      | 4.9  | (57/163)                        |
| Hours et al.        | France  | 1986                       | 19    | 2.7  | 38       | 1.6  | (38/0)                          |
| Bolm-Audorff et al. | Germany | 1991                       | 51    | 7.3  | 55       | 2.3  | (55/10)                         |
| Porru et al.        | Italy   | 1992                       | 30    | 4.3  | 163      | 6.7  | (163/10)                        |
| Greiser et al.      | Germany | 1993                       | 176   | 25.1 | 1390     | 57.3 | (0/1390)                        |
| Serra (unp.)        | Spain   | 1995                       | 15    | 2.1  | 18       | 0.7  | (0/18)                          |
| Age                 |         |                            |       |      |          |      |                                 |
| 30-39 years         |         |                            | 12    | 1.7  | 109      | 4.5  | (72/37)                         |
| 40-49 years         |         |                            | 26    | 3.7  | 240      | 9.9  | (105/135)                       |
| 50-59 years         |         |                            | 119   | 17.0 | 573      | 23.6 | (152/421)                       |
| 60-69 years         |         |                            | 253   | 36.1 | 760      | 31.3 | (221/539)                       |
| 70-79 years         |         |                            | 290   | 41.4 | 743      | 30.6 | (211/532)                       |
| Smoking             |         |                            |       |      |          |      |                                 |
| Nonsmokers          |         |                            | 383   | 55.1 | 1649     | 68.2 | (608/1041)                      |
| Ex-smokers          |         |                            | 111   | 16.0 | 322      | 13.3 | (49/273)                        |
| Current smokers     |         |                            | 201   | 28.9 | 446      | 18.5 | (103/343)                       |
| 1-10,000 packs      |         |                            | 111   | 16.0 | 316      | 13.1 | (86/230)                        |
| 10,000-15,000 packs |         |                            | 46    | 6.6  | 81       | 3.4  | (11/70)                         |
| >15,000 packs       |         |                            | 44    | 6.3  | 49       | 2.0  | (6/43)                          |

Participating studies with number of female cases and controls, age distribution, and smoking habits.

lished) and one each from Greece [Rebelakos et al., 1985] and Denmark [Jensen et al., 1987].

**Primary** data from these 11 studies were combined using common coding and classification schemes for all variables. Originally used occupational codes were recoded to 5-digit ISCO (International Standard Classification of Occupations) 1968 codes [ILO, 1969] and industry codes to ISIC (International Standard Industrial Classification of All Economic Activities) revision-2 codes [Statistical Office of the United Nations, 1971]. All studies recorded the occupational and industry code of every job done more than 6 months and year of starting and end of each job, except for one study [Rebelakos et al., 1985], for which only information for the longest held job was available. All studies included detailed smoking information, including duration and quantity smoked. We limited the analysis to cases and controls within the age range 30 up to 79 years and excluded subjects outside this age range ( $n_{\text{cases}} = 161$ ,  $n_{\text{controls}} = 357$ ) and also prevalent cases ( $n_{\text{cases}} = 92$ ), defined as those with

more than 2 years time between diagnosis and interview. This final pooled dataset comprised 700 cases and 2,425 hospital or population controls. Controls were individually or frequency matched to cases on age (within 5 years) and geographic area (Table I). The case-control ratio differed per study, ranging from 1:1 to 1:8, with Germany forming the largest national component for cases as well as controls (Table I).

Unconditional logistic regression was applied, since most studies used frequency matched controls. ORs were calculated for major occupations and industries (one-digit ISCO and ISIC codes), and for those specific occupations and industries showing a statistically significant excess risk for women (Mannetje et al., in press). Five alternative models were used, differing in their degree of adjustment for smoking:

Model 1. (Crude OR), no adjustment for smoking.

Model 2. Smoking adjusted as a binary variable (never/ever).

- Model 3. Smoking adjusted as a 3-category variable (never/ex/current).
- Model 4. Smoking adjusted as a 5-category variable (never/ex/current stratified in three groups by cumulative tobacco consumption).
- Model 5. Smoking adjusted as three variables, of which two binary (smoker/nonsmoker; current/not current), and one continuous variable ( $\ln(\text{lifetime consumption in packs} + 1)$ ).

In addition, all ORs were adjusted for age (5-year age groups) and study. The large multicenter study in Germany [Greiser and Molzahn, 1997], was considered as three separate study areas (former East and West Germany and Berlin). The interaction term between center and age (continuous) was found to be statistically significant and therefore was also included in all models.

Confounding risk ratios [Axelson and Steenland, 1988], were calculated dividing the crude OR (for bladder cancer due to occupation) without adjustment for smoking (Model 1), by the "true" OR fully adjusted for smoking (estimated by Model 5).

Residual confounding was quantified by calculating the percent adjustment obtained in each model [Savitz and Barón, 1989]:

$$\text{Percent Adjustment} = \frac{\text{OR}_c(e) - \text{OR}_{pa}(e)}{\text{OR}_c(e) - \text{OR}_{ca}(e)} \times 100$$

$\text{OR}_c(e)$  = crude OR for exposure and disease ( $c$  = crude)

$\text{OR}_{pa}(e)$  = OR adjusted with the misclassified confounder ( $pa$  = partially adjusted)

$\text{OR}_{ca}(e)$  = OR adjusted with the correctly classified confounder (estimated by model 5)

The percent adjustment reflects the percentage of confounding removed by using a smoking variable in the model, which partially adjusts for smoking (i.e., does not sufficiently take the variation in tobacco smoking into account), compared to full adjustment. In this case, we calculated the percent adjustment achieved by using Models 2, 3, and 4, assuming that the use of Model 5 yielded to complete confounding adjustment. The percent adjustment was not calculated when the confounding by smoking was smaller than 10% and when partial and complete adjustment showed different confounding directions.

## RESULTS

### Smoking

Compared to never smokers, current smokers had more than a 3-fold risk for bladder cancer (OR = 3.61, 95% CI 2.80–4.65) and ex-smokers had an OR of 2.52 (95% CI 1.90–3.36). The ORs for "ever" smoking ranged between

studies from 1.42 to 8.07, but the interaction term between smoking and study was not statistically significant.

### Major Occupational and Industry Groups (One-Digit ISCO and ISIC Codes)

The prevalence of women having ever smoked for 1 year or more was 45% among cases and 32% among controls. Prevalence of smoking in the main occupational groups ranged from 22–59% in cases and between 18–48% in controls (Table 11). Smoking prevalence was lowest in agricultural workers (ISCO 6) and highest in administrative/managerial workers and clerical workers (ISCO 2 and 3). A similar pattern was observed for the main industry groups, although extreme smoking prevalences were seen for two industry groups (miners, electricity workers) including only a few cases. These high prevalences were not found in the larger control groups, indicating they were due to sampling variation because of small numbers rather than due to job characteristics.

Crude ORs (Model 1), smoking-adjusted ORs (Models 2–5), and the confounding RR (Model 1 divided by Model 5) for the major occupational and industry groups are shown in Table II. Smoking appears to be a positive confounder in most major occupation groups, although in nearly all groups the confounding effect was not more than 10%. Higher confounder RRs were seen for major industry groups, particularly mining (confounder RR = 1.24), transport (confounder RR = 1.10) and finance (confounder RR = 1.17). Among these major occupations and industries, agricultural workers and those in community, social, and personal services had a statistically significant lower risk for cancer of the bladder. Only the association of agricultural workers (ISCO 6, ISIC 1) and bladder cancer appeared to be negatively confounded by smoking (confounder RR around 0.90).

The percentage of positive confounding removed by using basic smoking information was high for those occupations and industries most confounded by smoking. For these major occupation and industry groups, at least 78% of confounding was removed by using Model 2 (i.e., smoking entered in the model as a dummy variable, never/ever).

### High-Risk Occupations and Industries

In the specific occupations and industries showing statistically significant excess risk ( $P < 0.05$ ), the confounding effect of smoking was more substantial (Table 11). The deviations in crude ORs (Model 1) compared to adjusted ORs (Model 5) ranged between –22% and +40% (confounder RR 0.78–1.40). In approximately half of these occupations and industries, the confounding effect was positive. In the three occupations negatively confounded by

TABLE II. Risk for Bladder Cancer in Major Occupations and Industries. Adjustment for Smoking in Four Different Ways<sup>1,2</sup>

|                                                                                         | Cases<br>N <sub>(ever smoked)</sub> /<br>N <sub>(never smoked)</sub><br>(% ever smoked) | Controls<br>N <sub>(ever smoked)</sub> /<br>N <sub>(never smoked)</sub><br>(% ever smoked) | Model 1<br>Crude OR<br>(95%CI) | Model 2<br>Adjusted OR<br>(95%CI) | Model 3<br>Adjusted OR<br>(95%CI) | Model 4<br>Adjusted OR<br>(95%CI) | Model 5<br>Adjusted OR<br>(95%CI) | Confounding<br>RR<br>OR <sub>(1)</sub> /OR <sub>(5)</sub> |
|-----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|--------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------------------------------|
| <b>Occupations</b>                                                                      |                                                                                         |                                                                                            |                                |                                   |                                   |                                   |                                   |                                                           |
| ISC01 Professional, technical,<br>and related                                           | 35135<br>(50%)                                                                          | 1771283<br>(38%)                                                                           | 0.81<br>(0.60-1.08)            | 0.80<br>(0.59-1.08)               | 0.81<br>(0.60-1.09)               | 0.80<br>(0.59-1.08)               | 0.81<br>(0.60-1.10)               | 1.00                                                      |
| ISC02 Administrative and<br>managerial workers                                          | 716<br>(54%)                                                                            | 23125<br>(48%)                                                                             | 1.07<br>(0.54-2.11)            | 0.98<br>(0.49-1.98)               | 1.01<br>(0.50-2.03)               | 1.00<br>(0.49-2.01)               | 1.04<br>(0.52-2.09)               | 1.03                                                      |
| ISC03 Clerical and related                                                              | 106/75<br>(59%)                                                                         | 3301497<br>(40%)                                                                           | 1.15<br>(0.92-1.44)            | 1.05<br>(0.84-1.33)               | 1.06<br>(0.84-1.33)               | 1.06<br>(0.84-1.33)               | 1.06<br>(0.84-1.33)               | 1.08                                                      |
| ISC04 Sales workers                                                                     | 78/81<br>(49%)                                                                          | 2231343<br>(39%)                                                                           | 1.17<br>(0.93-1.46)            | 1.14<br>(0.91-1.44)               | 1.16<br>(0.92-1.46)               | 1.16<br>(0.92-1.46)               | 1.16<br>(0.92-1.46)               | 1.01                                                      |
| ISC05 Serviceworkers                                                                    | 1231109<br>(53%)                                                                        | 3031566<br>(35%)                                                                           | 0.97<br>(0.79-1.19)            | 0.92<br>(0.75-1.13)               | 0.92<br>(0.74-1.13)               | 0.92<br>(0.74-1.13)               | 0.91<br>(0.74-1.13)               | 1.07                                                      |
| ISC06 Agricultural, animal<br>husbandry, forestry<br>workers, fishermen,<br>and hunters | 20/73<br>(22%)                                                                          | 571262<br>(18%)                                                                            | 0.86<br>(0.65-1.14)            | 0.96<br>(0.72-1.28)               | 0.96<br>(0.72-1.28)               | 0.95<br>(0.72-1.27)               | 0.96<br>(0.72-1.27)               | 0.90                                                      |
| ISC09 Production and related<br>workers                                                 | 1231132<br>(48%)                                                                        | 3071587<br>(34%)                                                                           | 1.14<br>(0.94-1.39)            | 1.10<br>(0.90-1.34)               | 1.09<br>(0.89-1.34)               | 1.10<br>(0.90-1.34)               | 1.08<br>(0.88-1.33)               | 1.06                                                      |
| <b>Industries</b>                                                                       |                                                                                         |                                                                                            |                                |                                   |                                   |                                   |                                   |                                                           |
| ISIC1 Agriculture, hunting,<br>forestry, and fishing                                    | 14135<br>(29%)                                                                          | 571242<br>(19%)                                                                            | 0.59<br>(0.42-0.85)            | 0.64<br>(0.45-0.92)               | 0.64<br>(0.45-0.91)               | 0.64<br>(0.44-0.91)               | 0.64<br>(0.45-0.92)               | 0.92                                                      |
| ISIC2 Mining and quarrying                                                              | 2/0<br>(100%)                                                                           | 6114<br>(30%)                                                                              | 0.92<br>(0.18-4.60)            | 0.74<br>(0.14-3.99)               | 0.73<br>(0.13-3.99)               | 0.77<br>(0.14-4.16)               | 0.74<br>(0.13-4.13)               | 1.24                                                      |
| ISIC3 Manufacturing                                                                     | 146/137<br>(52%)                                                                        | 384/712<br>(35%)                                                                           | 1.25<br>(1.02-1.53)            | 1.20<br>(0.97-1.48)               | 1.20<br>(0.97-1.48)               | 1.21<br>(0.98-1.49)               | 1.20<br>(0.97-1.48)               | 1.04                                                      |
| ISIC4 Electricity, gas, and<br>water                                                    | 411<br>(80%)                                                                            | 8115<br>(35%)                                                                              | 1.46<br>(0.50-4.22)            | 1.37<br>(0.47-4.00)               | 1.39<br>(0.48-4.00)               | 1.41<br>(0.49-4.07)               | 1.44<br>(0.50-4.19)               | 1.01                                                      |
| ISIC5 Construction                                                                      | 816<br>(57%)                                                                            | 22/39<br>(36%)                                                                             | 1.43<br>(0.76-2.71)            | 1.34<br>(0.69-2.59)               | 1.37<br>(0.71-2.66)               | 1.38<br>(0.71-2.68)               | 1.35<br>(0.69-2.62)               | 1.06                                                      |
| ISIC6 Wholesale and retail<br>trade, restaurants, hotels                                | 93/78<br>(54%)                                                                          | 2841447<br>(39%)                                                                           | 1.00<br>(0.80-1.25)            | 0.97<br>(0.77-1.22)               | 0.98<br>(0.78-1.23)               | 0.97<br>(0.77-1.22)               | 0.96<br>(0.76-1.21)               | 1.04                                                      |
| ISIC7 Transport, storage,<br>communications                                             | 18/10<br>(64%)                                                                          | 69186<br>(45%)                                                                             | 1.01<br>(0.64-1.58)            | 0.91<br>(0.57-1.44)               | 0.90<br>(0.57-1.43)               | 0.90<br>(0.57-1.44)               | 0.92<br>(0.58-1.47)               | 1.10                                                      |
| ISIC8 Finance, insurance, real<br>estate, business services                             | 25111<br>(69%)                                                                          | 84191<br>(48%)                                                                             | 0.83<br>(0.56-1.25)            | 0.73<br>(0.48-1.10)               | 0.71<br>(0.47-1.08)               | 0.71<br>(0.47-1.09)               | 0.71<br>(0.47-1.08)               | 1.17                                                      |
| ISIC9 Community, social, and<br>personal services                                       | 140/117<br>(54%)                                                                        | 441/779<br>(36%)                                                                           | 0.78<br>(0.63-0.96)            | 0.74<br>(0.59-0.91)               | 0.74<br>(0.60-0.91)               | 0.73<br>(0.59-0.91)               | 0.75<br>(0.61-0.93)               | 1.04                                                      |

<sup>1</sup>Subjects having worked for more than 6 months in a job. Subjects may contribute to more than one occupation or industry.

<sup>2</sup>Model 1: Crude OR, No adjustment for smoking; Model 2: Smoking adjusted as a binary variable (never/ever); Model 3: Smoking adjusted as a 3-category variable (never/ex/current); Model 4: Smoking adjusted as a 5-category variable (never/ex/current stratified in three groups by cumulative tobacco consumption); Model 5: Smoking adjusted as three variables of which two binary (smoker/non-smoker; current/not current), and one continuous variable (ln (lifetime consumption in packs + 1)).

smoking (lathe operators, field crop workers, and wood manufacturers), a statistically significant excess risk was masked when not adjusting for smoking. The widest differences between crude and adjusted ORs were mostly seen for occupations and industries with a small number of cases. For

the-high risk occupations with 20 cases or more, the deviation in OR was not found to be more than 10%, with the exception of the relatively large group of field crop workers ( $n_{\text{(cases)}} = 33$ ), which showed a negative confounding of -17%.

TABLE III. Occupations and industries With a Statistically Significant High Risk for Bladder Cancer<sup>1,2</sup>; Adjustment for Smoking in Four Different Ways<sup>3</sup>

|                                                                                                                 | Cases<br>N <sub>(ever smoked)</sub> /<br>N <sub>(never smoked)</sub><br>(% ever smoked) | Controls<br>N <sub>(ever smoked)</sub> /<br>N <sub>(never smoked)</sub><br>(% ever smoked) | Model 1<br>Crude OR<br>(95%CI) | Model 2<br>Adjusted OR<br>(95%CI) | Model 3<br>Adjusted OR<br>(95%CI) | Model 4<br>Adjusted OR<br>(95%CI) | Model 5<br>Adjusted OR<br>(95%CI) | Confounding<br>RR<br>OR <sub>(1)</sub> /OR <sub>(5)</sub> |
|-----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|--------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------------------------------|
| Occupations                                                                                                     |                                                                                         |                                                                                            |                                |                                   |                                   |                                   |                                   |                                                           |
| ISCO83 Blacksmiths, tool-<br>makers, and machine-<br>tool operators                                             | 9111<br>45%                                                                             | 17/34<br>33%                                                                               | 2.05<br>(1.13-3.70)            | 1.96<br>(1.07-3.59)               | 1.91<br>(1.04-3.51)               | 1.94<br>(1.06-3.57)               | 1.87<br>(1.02-3.45)               | 1.10                                                      |
| ISCO83420 Lathe operator                                                                                        | 013<br>0%                                                                               | 236<br>25%                                                                                 | 3.42<br>(0.83-14.0)            | 4.55<br>(1.08-19.2)               | 4.57<br>(1.09-19.1)               | 4.61<br>(1.11-19.2)               | 4.36<br>(1.02-18.6)               | 0.78                                                      |
| ISCO622 Field crop and veg-<br>etable farm workers                                                              | 1/32<br>3%                                                                              | 3/38<br>7%                                                                                 | 1.48<br>(0.87-2.53)            | 1.42<br>(1.05-3.14)               | 1.80<br>(1.04-3.12)               | 1.78<br>(1.03-3.08)               | 1.78<br>(1.03-3.08)               | 0.83                                                      |
| ISCO78 Tobacco preparers and<br>tobacco product<br>makers                                                       | 5/3<br>63%                                                                              | 315<br>38%                                                                                 | 3.81<br>(1.25-11.7)            | 3.35<br>(1.11-10.1)               | 3.26<br>(1.09-9.78)               | 3.12<br>(1.05-9.28)               | 3.08<br>(1.03-9.22)               | 1.24                                                      |
| ISCO791 Tailors and dress-<br>makers                                                                            | 30/30<br>50%                                                                            | 57/90<br>39%                                                                               | 1.47<br>(1.04-2.08)            | 1.42<br>(1.00-2.03)               | 1.42<br>(0.99-2.02)               | 1.44<br>(1.01-2.06)               | 1.43<br>(1.00-2.04)               | 1.03                                                      |
| ISCO45190 Other salesmen,<br>shop assistants,<br>and demonstrators                                              | 3/4<br>43%                                                                              | 10111<br>48%                                                                               | 2.74<br>(1.06-7.06)            | 2.58<br>(0.99-6.74)               | 2.65<br>(1.02-6.89)               | 2.63<br>(1.01-6.85)               | 2.51<br>(0.95-6.61)               | 1.09                                                      |
| ISCO37020 Mail sorting clerk                                                                                    | 410<br>100%                                                                             | 1/5<br>17%                                                                                 | 5.56<br>(1.39-22.2)            | 4.75<br>(1.10-20.5)               | 4.72<br>(1.09-20.4)               | 4.43<br>(1.01-19.5)               | 4.35<br>(0.99-19.1)               | 1.28                                                      |
| ISCO422 Buyers                                                                                                  | 311<br>75%                                                                              | 5/3<br>63%                                                                                 | 5.54<br>(1.31-23.4)            | 4.08<br>(0.89-18.6)               | 4.49<br>(0.96-20.9)               | 4.56<br>(1.00-20.9)               | 5.03<br>(1.12-22.5)               | 1.10                                                      |
| Industries                                                                                                      |                                                                                         |                                                                                            |                                |                                   |                                   |                                   |                                   |                                                           |
| ISIC314 Tobacco manufacture                                                                                     | 515<br>50%                                                                              | 5/10<br>33%                                                                                | 2.96<br>(1.20-7.29)            | 3.12<br>(1.25-7.75)               | 3.09<br>(1.24-7.67)               | 2.98<br>(1.20-7.36)               | 2.92<br>(1.18-7.25)               | 1.01                                                      |
| ISIC369 Manufacture of other<br>non-metallic mineral<br>products, except prod-<br>ucts of petroleum and<br>coal | 5/3<br>63%                                                                              | 6/6<br>50%                                                                                 | 4.78<br>(1.63-14.0)            | 3.47<br>(1.15-10.5)               | 3.48<br>(1.16-10.5)               | 3.55<br>(1.18-10.7)               | 3.41<br>(1.12-10.3)               | 1.40                                                      |
| ISIC331 Manufacture of wood<br>and wood products,<br>except furniture                                           | 234<br>33%                                                                              | 1/8<br>11%                                                                                 | 3.28<br>(0.97-11.1)            | 3.54<br>(1.02-12.3)               | 3.38<br>(0.98-11.7)               | 3.52<br>(1.02-12.1)               | 3.53<br>(1.02-12.2)               | 0.93                                                      |
| ISIC3 Manufacturing                                                                                             | 146/137<br>52%                                                                          | 384/1712<br>35%                                                                            | 1.25<br>(1.02-1.53)            | 1.20<br>(0.97-1.48)               | 1.20<br>(0.97-1.48)               | 1.21<br>(0.98-1.49)               | 1.20<br>(0.97-1.48)               | 1.04                                                      |
| ISIC371 Iron and steel basic<br>industries                                                                      | 412<br>67%                                                                              | 513<br>63%                                                                                 | 3.93<br>(1.11-13.9)            | 2.78<br>(0.80-9.69)               | 2.90<br>(0.83-10.2)               | 3.00<br>(0.85-10.5)               | 3.01<br>(0.83-11.0)               | 1.31                                                      |

<sup>1</sup>All occupations and industries (ISCO 1968 and ISIC-rev2 codes) with statistically significant high risk ( $P$ -value < 0.05).

<sup>2</sup>Subjects having worked for more than 6 months in a job. Subjects may contribute to more than one occupation or industry.

<sup>3</sup>Model 1: Crude OR, No adjustment for smoking; Model 2: Smoking adjusted as a binary variable (never/ever); Model 3: Smoking adjusted as a 3-category variable (never/ex/current); Model 4: Smoking adjusted as a 5-category variable (never/ex/current stratified in three groups by cumulative tobacco consumption); Model 5: Smoking adjusted as three variables of which two binary (smoked/non-smoker/current/not current), and one continuous variable (ln (lifetime consumption in packs + 1)).

In most high-risk occupations/industries, adjustment for smoking using detailed information did not lead to important changes in the crude ORs (Table III). In some occupations, however, residual smoking confounding was observed when

using a dichotomous (never/ever) smoking variable, particularly for tobacco workers (ISCO 78) and mail sorting clerks (ISCO 37020). In these two occupations, the proportion of confounding removed using a dichotomous smoking vari-

able (never/ever) was around 60% (63% and 67%, respectively). When ex- and current smokers were separately classified (Model 3), the proportion of confounding removed was 76% and 69%, respectively, while using a 5-category smoking variable (Model 4) it was 95% and 93%. Using a dichotomous smoking variable (never/ever) caused an over-adjustment of the risk in several occupations/industries. This bias was more pronounced in buyers (ISCO 422). In this occupation, adjustment for smoking as a dichotomous variable led to a lower OR, though full adjustment led again to a higher one. This occurred because the percentage of "ever smokers" among buyers was high, while the amount of cigarettes they smoked was low.

## DISCUSSION

Various criteria have been proposed regarding confounding selection policies, particularly in situations where it is not known a priori whether an exposure may confound another exposure-effect estimate [Maldonado and Greenland, 1993; Breslow and Day, 1980; Rothman and Greenland, 1998]. Often, a variable is retained in a model only if its inclusion seems to make an "important difference" in the exposure-effect estimate, "important" having sometimes been defined as a bigger than 10% change in the rate ratio of interest [Maldonado and Greenland, 1993]. The results presented here show that the crude ORs deviate from the smoking adjusted ORs by more than 10% in approximately half the occupations/industries statistically significantly associated with bladder cancer. Although the results of our analyses refer to the specific population examined in the case-control studies, they seem to have a wide applicability since this population included women living in several European countries and having been exposed during long time periods.

Two mechanisms underlie the variation in crude and adjusted ORs [Siemiatycki et al., 1988]: 1) the variation in smoking rates between the occupation under study and the reference population, due to job-specific differences in smoking habits, in which case smoking is associated with disease and occupation; 2) the variation in smoking rates between the occupation under study and the reference population, due to sampling variations, in which case smoking is not necessarily associated with occupation. When studying large occupational groups for their bladder cancer risk, the effect of the second mechanism is negligible and this study showed that the true confounding effect is mostly limited to a deviation in crude ORs of less than 10%. This is in concordance with findings from other studies on confounding by smoking on occupation-bladder cancer associations. When studying small occupational groups (which is mostly the case of high-risk occupations, particularly in women, where the number of subjects exposed is often small), it is not possible to separate the two effects.

Deviations of more than 10% were, however, mainly found for occupations and industries with less than 20 cases, suggesting an effect of sampling variation.

Residual confounding can arise in various ways: because of error in the measurement of the confounder, or due to less than optimal stratification or modeling of the confounder [Siemiatycki et al., 1988]. In this study, we were only able to look at the latter using different degrees of smoking information. In most occupations/industries, residual confounding was limited when adjusting for smoking using a dichotomous variable. It would, however, be recommendable to incorporate additional information including the quantity and duration of smoking, since under- as well as over-adjustment can occur when this information is not taken into account. For two high-risk occupations, ORs were not sufficiently adjusted for smoking when using only smoking status in the model (residual confounding of 40%) and for one occupation (buyers) the OR was clearly over-adjusted when the quantity smoked was not taken into account. Using pack-years as a continuous variable together with smoking status variables did not appear to give better adjustment results than using pack-years in strata (in this case, three strata of cumulative exposure).

In most cases, the confounding effect appeared to be positive (10 out of 13 high-risk occupations and industries). This supports the notion that in most high-risk occupations the smoking prevalence is also higher [Stellman et al., 1988] and that in these cases positive confounding can be expected. In none of the occupations/industries showing a statistically significant excess risk for bladder cancer could this be due to confounding by smoking. Even if less frequent, negative confounding by smoking appears to be equally important as positive confounding, since it can mask the excess risk of specific occupations, as can be illustrated by the group of "field crop workers." This occupation would not have been selected as being a statistically significant high-risk occupation if adjustment for smoking had not been made.

In conclusion, tobacco smoking was not found to be a major confounder for the association between occupation and bladder cancer in women, although in a few occupations risk could be under- as well as overestimated by more than 20%. Although adjustment for smoking taking into account both smoking status and quantity and duration of smoking is preferable, it should be noted that most of the confounding effect could be removed by adjustment by smoking status (ever/never), without consideration of amount or duration of smoking.

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