New insights on occupational exposure and bladder cancer risk: a pooled analysis of two Italian case–control studies

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Abstract

Purpose

The main risk factor for bladder cancer (BC) is cigarette smoking, but also occupational exposure to carcinogens is relevant, causing about 4–10% of BC. We aimed at investigating the association between BC risk, occupations held in the past and exposure to occupational carcinogens, also assessing whether these associations were influenced by tumour grade.

Methods

We pooled data from two Italian case–control studies on male BC, analyzing 893 cases and 978 controls. Occupations were classified using the International Standard Classification of Occupations and exposure to carcinogens was assigned using a validated Job Exposure Matrix. Logistic regression approach was used as well as a semi-Bayesian model, based on a priori information on exposure.

Results

A significantly increased BC risk was found for chemical engineering technicians, postmen, and lathe operators, but only, for the latter, the association remained significant after Bayesian control for type I error. Among carcinogens, cadmium and trichloroethylene were associated with BC. When analyzing data by grade, exposure to these carcinogens was associated with low-grade BC only.

Conclusions

Our results suggest that monitoring workplaces to prevent exposure to carcinogenic agents is still an important task, which should be still given adequate importance in public health.

Introduction

Bladder cancer (BC) is the most common neoplasm of the genitourinary tract and it is the ninth most diffused cancer in the world, with 430,000 new cases every year (Stewart and Wild 2014). Among people of Caucasian origin, about 92–99% of BCs are urothelial and most of them develop in the bladder's wall, less frequently in the trigone, in the urothelial orifices, in the dome, and in the bladder neck (Schottenfeld and Fraumeni 2006).

In Italy, BC represents about 11% of the total cancer diagnoses among men and 3% among women (AIOM AIRTUM 2016), and data from cancer registries (2005–2009) reveal an age-standardized rate equal to 45.4 cases per 100,000 in men and 8.2 cases per 100,000 in women (ITACAN v2.0 2018).

Risk factors for bladder cancer are mostly known; among them, cigarette smoking is the leading causal factor, causing more than 40% men's BC (Van Osch et al. 2016). Other risk factors are:

urinary system chronic infections (Negri and La Vecchia 2001), ionizing radiations treatments (Weiss et al. 1994), disinfection byproducts in water (Hrudey et al.2015), diet poor in fruit and vegetables (Sacerdote et al. 2007), and the presence of arsenic in drinking water (Saint-Jacques et al. 2014). An increased risk of bladder cancer is also observed among atomic bomb survivors and workers of nuclear installations (McGeoghegan and Binks 2000).

Furthermore, in industrialized countries, the second most important cause of BC is the exposure to occupational carcinogens, causing about 4–10% bladder tumour cases (Kogevinas et al. 1998, 2003). From the '50s on, a series of studies have detected about 40 occupations associated with an increased risk of BC (Kogevinas et al. 1998, 2003; Case and Hosker 1954; Case et al. 1954; Samanic et al. 2008; Purdue et al. 2015). Among those, the International Agency for Research on Cancer (IARC) has classified several occupations as carcinogenic to humans—group 1 (painters, workers in the rubber industry, in aluminum production, and in the production of the dyes auramine and magenta), or as probably carcinogenic to humans—group 2A (hairdressers or barbers), or as possibly carcinogenic to humans—group 2B (workers employed in dry cleaning, in printing processes, and in textile manufacturing). Moreover, an increased risk is present in workers exposed to aromatic amines (Vineis and Pirastu 1997) and polycyclic aromatic hydrocarbons (Boffetta and Silverman 2001; Rota et al. 2014).

To our knowledge, all these studies investigated solely either occupations or exposure to carcinogens; moreover, the investigation of several determinants together could bring to spurious through statistically significant results, due to the risk of type I error.

For this reason, the objectives of our study are:

1. to analyze the association between past employment and BC risk, using a Job Exposure Matrix (JEM), to use a priori information about the supposed presence of carcinogens in the working environment;

2. to analyze the relation between exposure to selected occupational carcinogens and BC risk;

3. to assess whether the association with occupational exposure to carcinogens differs by BC tumour grade.

Materials and methods

Subjects

For this study, we pooled data from two existing case–control studies on male BC conducted in the metropolitan areas of Turin and Brescia, two highly industrialized cities located in Northern Italy.

Details of the two studies can be found elsewhere (Ricceri et al. 2010; Sacerdote et al. 2013; Porru et al. 1996). Within the Brescia study, Porru et al. (2014) have already examined the interaction of previous exposure to PAHs and aromatic amines with the presence of genetic polymorphisms of metabolic and DNA repair enzymes on BC risk. Briefly, in Turin, 603 cases and 681 hospital controls were recruited between 1993 and 2012. Cases were patients aged between 40 and 74 years, with a new diagnosis of BC (ICD-IX 188.XX), histologically confirmed and diagnosed at S. Giovanni Battista hospital and Cellini clinic in Turin. Controls were patients aged between 40 and 74 years, hospitalized in S. Giovanni Battista in Turin, not affected by neoplastic, metabolic, urologic, or smoking-related diseases. They were recruited in general medicine, otolaryngology, orthopedics, and cardiology departments, with each disease present in no more than 10% of controls. Response rate was higher than 97% both in cases and controls. In Brescia 295 cases and 302 controls were recruited in 1992 and 1993 and from 1997 to 2000. Cases were patients aged between 20 and 80 years with a new diagnosis of BC, histologically confirmed and diagnosed

in the urology departments of the two main hospitals of the city. Controls were selected in the same hospitals among patients hospitalized for urological non-neoplastic diseases and they were frequency-matched to cases by age (± 5 years), period (1992–1993 and 1997–2000), and hospital of admission. Response rate was 93% in cases and 97% in controls.

Tumour histology, site, TNM classification, and grading of the primary tumour were assessed through inspection of the patients' pathology and clinical records, in collaboration with the urologists. Tumour stage and grade were determined according to the European Association of Urology Guidelines on Non-Muscle-invasive Urothelial Carcinoma of the Bladder (Babjuk et al. 2013).

Occupational exposures

In both studies, all patients answered a detailed questionnaire about their working history and lifestyle, including smoking habit. We classified occupations based on the International Standard Classification of Occupations (ISCO-68) (International Labour Office 1968), using the first four digits, as usually done in similar contexts.

In agreement with the literature, we considered a latency period from exposure to BC of 10 years (Rushton et al. 2008). It means that we assumed that a carcinogen exposure should have occurred at least 10 years before the onset of BC to be involved in the pathogenetic mechanism of that BC. Therefore, only jobs and occupational exposures occurring more than 10 years before BC for cases and before recruitment for controls have been taken into account. For this reason, young subjects that had been working for less than 10 years were excluded from the analyses ($n = 10$, 0.53% of the overall recruited subjects), leaving a final sample composed of 602 cases and 680 controls in the Turin study and 291 cases and 298 controls in the Brescia study.

Carcinogenic agents

The IARC has identified five agents that are possibly involved in the carcinogenic process of BC or tumours of the urinary tract and that are classified as certainly carcinogenic for humans (IARC—group 1) (IARC 2012): arsenic (AS), benzo[a]pyrene (BAP), welding fumes (WELD), aromatic amines (AA: 4-aminobiphenyl, benzidine, 2-naphthylamine, Ortho-Toluidine), and chlorinated hydrocarbon solvents (CHC: trichloroethylene, 1,2-dichloropropane). Moreover, other 24 probable (IARC—group 2A) or possible (IARC—group 2B) carcinogens are suspected risk factors for BC incidence and/or for other cancers of the genitourinary system: aliphatic and alicyclic hydrocarbon solvents (ALHC), diesel engine exhausts (DEEX), aromatic hydrocarbon solvents (ARHC), benzene (BENZ), cadmium (CD), chromium (CR), detergents (DET), fungicides (FUNG), gasoline (GASO), gasoline engine exhaust (GEEX), herbicides (HERB), insecticides (INSC), ionizing radiation (IRAD), iron (FE), lead (PB), low-frequency magnetic fields (MF), methylene chloride (MCH), nickel (NI), oil mist (OIL), other organic solvents (OSOL), perchloroethylene (PER), toluene (TOLU), trichloroethane (TCE), and trichloroethylene (TRI) (IARC 2012; Supplementary Table 1).

For all agents except AA, the exposure was assigned using a Finnish Job Exposure Matrix (FINJEM) (Kauppinen et al. 2009). Exposure to AA, that was absent in the above-cited JEM, was assigned by one of the authors, expert in industrial hygiene (A. d'E.), based on information extracted from different occupational exposure databases (Boiano and Hull2001; Falcone et al. 2013) and from the last IARC monograph updating exposure to aromatic amines (IARC 2012), with consensus obtained from all the research group. The JEM intensity and probability of exposure measured during years 1960–1984 were used, since it was assumed that, in the study population, most of the relevant exposures occurred before mid-80's, given the collection period of the subjects and the long latency of BC.

Descriptive analyses

Data were described using means and standard deviations or frequencies and percentages, for continuous or categorical variables, respectively. Age differences between cases and controls were tested using the Wilcoxon rank-sum test, after ascertainment of non-normality of the distribution through Kolmogorov–Smirnov test, while differences between categorical variables were tested using the Chi-square test.

All statistical analyses were performed using SAS V 9.3 and R software V 3.3.1 and a two-tailed *p* value less than 0.05 was considered statistically significant.

Analyses on occupations

Occupational exposure was analyzed using two different approaches. First, we used a dichotomous variable for each profession, indicating if a subject had ever been employed in that occupation for at least 2 years in his life (even if not continuously); second, we considered another dichotomous variable for each profession, examining the longest occupation held during subject's working life. Only occupations with at least five cases were considered for the analysis.

In each of the two approaches, odds ratios (ORs) and 95% confidence intervals (95% CI) were obtained from multivariable logistic regression models, adjusted for age, smoking status, intensity of smoking, and study (Turin or Brescia). A semi-Bayesian hierarchical model was employed to control for multiple comparisons and to improve the plausibility and stability of estimates [theoretical details of this model can be found in Witte et al. (1994), Greenland (1994), and Corbin et al. (2012)].

Analyses on occupational exposure to carcinogens

To estimate the risk associated with exposure to carcinogenic agents, ORs and 95% CI were obtained using multivariable logistic regression models, adjusted for age, smoking status, intensity of smoking, and study (Turin or Brescia), considering two types of exposure. First, a never/ever (for at least 2 years) exposure was considered; second, a cumulative exposure was considered, as done in d'Errico et al. (2009), categorizing the probability of exposure to the agent in each profession (from JEM data) into "low" (less than 10% of probability to be exposed), "medium"(between 10 and 50%), and "high" (more than 50%), and the level of exposure, derived from the JEM, into "low", "medium", and "high", using tertiles of each agent distribution as cut-offs. A weight, taking into account intensity and probability of exposure, was assigned to the different combinations of probability and exposure levels, as shown in Supplementary Table 2. The cumulative exposure of each subject was then obtained multiplying the weight for the duration in years of each job, and summing up this product across the whole subject's working life. Finally, the cumulative exposure was categorized into three levels: "no exposure", if the values of exposure were zero, "low exposure", if the values were less than the median exposure in controls; "high exposure" otherwise.

Since, from exploratory analyses, heterogeneity of the associations by tumour grade was observed for some carcinogens, analyses by grading were also conducted.

To control for the risk of first type error due to multiple comparisons, the False Discovery Rates (FDR) technique was applied (Benjamini and Hochberg 1995).

Results

In Table 1, results from descriptive analyses are presented separately for each study. The study population was composed of 589 subjects (31.5% of the total sample; 291 cases and 298 controls) from Brescia and 1282 subjects (68.5% of the total sample; 602 cases and 680 controls) from

Turin. In the Turin study population, a significant difference in age by case status was found (cases: mean 63.6 years, standard deviation SD 7.8; controls: mean 59.9 years, SD 9.7; $p < 0.0001$), while no difference was found in the Brescia study, due to the matching (cases: mean 63.7 years, SD 10.2; controls: mean 63.7 years, SD 10.3, $p = 0.67$). Both studies revealed a significant difference in smoking status ($p < 0.0001$), with higher percentages of smokers among cases (43.8% in Turin; 45.4% in Brescia) than among controls (25.3% in Turin; 26.8% in Brescia). Interestingly, only a small percentage of never smokers were found among cases both in Turin (8.1%) and in Brescia (7.9%).

Results from Chi-square tests showed that cases' and controls' distributions of the occupations longest held in life, categorized in major groups through the first digit of ISCO, were not different (p value = 0.58, in Turin, and 0.92, in Brescia).

In Turin, 86.4% ($n = 520$) BCs were not invasive, 60.5% ($n = 364$) were low-grade, and 56.7% ($n = 342$) were Ta tumours. In Brescia, 83.5% ($n = 243$) BCs were not invasive, 63.6% ($n = 185$) were low grade, and 24.1% ($n = 70$) were Ta tumours.

Analyses on occupations

Using the first approach (occupations held for at least 2 years), a list of 128 occupations (described by the first four ISCO-68 digits) were analyzed. All results from the logistic models are presented in Supplementary Table 3 (fourth column). Significantly increased risks were observed for chemical engineering technicians (ISCO-68 0361), OR 12.65 (95% CI 1.30–107.12), for postmen (ISCO-68 3703), OR 5.48 (95% CI 1.12–26.83), for tool and die makers (ISCO-68 8322), OR 6.03 (95% CI 1.19–30.63), and for lathe operators (ISCO-68 8342), OR 1.77 (95% CI 1.09–2.89) (Table 2). Interestingly, there were some occupations that did not have controls, but pertained to an elevated number of cases: rubber and plastic workers (ISCO-68 9019) and spray painters (ISCO-68 9393), with, respectively, 7 and 9 cases and 0 controls for both. In this case, it was not possible to estimate an OR through a regression model, but there was a suggestion of a possible association with BC (p value for Fisher's exact test: 0.04 and 0.002 respectively). Moreover, when considering all occupations involved in rubber production as a whole (ISCO-68: 9012, 9013, 9014 and 9019), we observed an increased risk of developing BC (OR 3.25, 95% CI 1.07–9.83).

Performing the Semi-Bayesian second stage of analysis, to control for false-positive results, we found that only the excess risk for lathe operators (ISCO-68 8342) maintained its statistical significance (Supplementary Table 3).

Using the second approach for the occupational exposure analysis (longest occupations performed in life), a list of 50 occupations (described by the first four ISCO-68 digits) were analyzed. Results are reported in Supplementary Table 4, showing again an increased risk of BC for lathe operators in the first stage of analysis (OR 2.36, 95% CI 1.06–5.18), that is attenuated, but still statistically significant in the second stage.

Analyses on occupational exposure to carcinogens

Analyses for having ever been exposed to one of the 29 selected agents (Table 3) showed significantly increased risks for CD (OR 1.27, 95% CI 1.03–1.57), and borderline significant associations for BAP (OR 1.19, 95% CI 0.96–1.47), CR (OR 1.19, 95% CI 0.94–1.42), PAHs (OR 1.19 95% CI 0.97–1.47), TCE (OR 1.19, 95% CI 0.96–1.46), and TRI (OR 1.21, 95% CI 0.98–1.50).

Considering cumulative exposure, we observed a significantly increased risk of BC for low cumulative exposure to CD (OR 1.34, 95% CI 1.03–1.76), to TCE (OR 1.33, 95% CI 1.02–1.73), and TRI (OR 1.30, 95% CI 1.00–1.73) and a borderline significantly increased risk for low

cumulative exposure to BAP (OR 1.26, 95% CI 0.96–1.66), to PB (OR 1.25, 95% CI 0.98–1.61), to PAHs (OR 1.21, 95% CI 0.93–1.59), and to WELD (OR 1.21, 95% CI 0.94–1.56). Moreover, a borderline significantly increased risk was found for high exposure to CD (OR 1.20, 95% CI 0.92–1.56), to CR (OR 1.20, 95% CI 0.94–1.54), and to DET (OR 1.19, 95% CI 0.94–1.52).

Analyses conducted separately by tumour grade showed an involvement of exposure to carcinogens only for low-grade BC (Table 4), while no significant result was found for high-grade BC (Supplementary Table 5). If we consider a dichotomous exposure (ever/never been exposed), for low-grade BC, a significantly increased risk was observed for BAP (OR 1.26, 95% CI 1.00–1.61), CD (OR 1.37, 95% CI 1.09–1.73), PAHs (OR 1.29, 95% CI 1.02–1.63), and TRI (OR 1.28, 95% CI 1.01–1.63), while borderline significant results were obtained for CR (OR 1.18, 95% CI 0.94–1.48), DET (OR 1.25, 95% CI 0.99–1.57), FE (OR 1.15, 95% CI 0.92–1.46), PB (OR 1.1695% CI 0.92–1.46), and TCE (OR 1.23, 95% CI 0.97–1.55). Considering cumulative exposure, a significantly increased risk of developing low-grade BC was observed for low exposure to TRI (OR 1.38, 95% CI 1.01–1.87), for high and low exposure to CD (respectively: OR 1.34, 95% CI 1.00–1.79 and OR 1.41, 95% CI 1.04–1.91), while borderline significant results were obtained for low exposure to BAP (OR 1.33, 95% CI 0.98–1.81), DET (OR 1.26, 95% CI 0.96–1.66), to PB (OR 1.28, 95% CI 0.96–1.69), to PAHs (OR 1.25, 95% CI 0.92–1.69), to TCE (OR 1.31, 95% CI 0.97–1.76), and to WELD (OR 1.25, 95% CI 0.94–1.66).

Discussion

There is wide agreement in the literature that at least part of BCs share an occupational etiology. This was observed in several single studies (Kogevinas et al. 2003; Case et al. 1954; Samanic et al. 2008; Purdue et al. 2015; Colt et al. 2014; Lohi et al. 2008) and was confirmed by a recent meta-analysis (Cumberbatch et al. 2017). Most of the occupations that were found to increase the risk for BC in these studies were identified also in several other studies. However, some inconsistencies were present, due in part to the fact that the risk estimates were often computed on small numbers of exposed cases. In fact, several studies pointed out that, when the number of events per variable is less than 10, the regression coefficients are biased (Concato et al. 1995; Peduzzi et al. 1995, 1996), even if, in some cases, this rule could be relaxed (Vittinghoff and McCulloch 2007). Therefore, it is possible that some results reported in the literature are spurious and it appears difficult to identify possible false-positive findings among them.

In our study, we observed an excess risk of BC in chemical engineering technicians, postmen, lathe operators, tool and die makers, as well as an excess BC risk (even if it could not be estimated, due to absence of exposed controls) among rubber and plastic products makers and spray painters. As it was pointed out in the previous studies (Case et al. 1954; Boffetta and Silverman 2001; Vineis and Di Prima 1983; IARC 2010), workers in these occupations were potentially exposed to aromatic amines (mainly: benzidine, 4-aminobiphenyl, b-naphthylamine, and 4-chloro-*o*-toluidine) or to other substances, such as polycyclic aromatic hydrocarbons, diesel engine exhausts, cutting oils, chlorinated hydrocarbons, or other solvents, and it could be speculated that these exposures were causal agents in BC development. In particular, spray painters may have been exposed in the past to spray paints containing water-soluble azo dyes, which have been demonstrated to be metabolized in humans through azoreduction into carcinogenic aromatic amines (Golka et al. 2004a).

To provide a quantitative basis to these associations, we performed a control for false-positive results and an improvement on the estimates within a Bayesian framework, assessing the probability of exposure to carcinogens for each worker through a validated JEM (Kauppinen et al. 2009). After this adjustment, an excess risk of BC could be still observed only for lathe operators, supporting the hypothesis that this occupation, or more generally the work of machine-tool operator, may be an occupation encompassing a high risk for BC. Many studies observed an increased risk of BC for metal workers, and the causal mechanism seems to be related to their exposure to mineral oils that are used to cut, lubrificate, and refresh the metal parts wrought in the

processes (Colt et al. 2014; Figueroa et al. 2015). Mineral oils, in fact, contain both PAHs and nitrosamines, which are known as human carcinogens (IARC 1987,2000, 2010).

The second aim of our study was to focus the attention on carcinogens rather than on occupations. Therefore, we employed a validated JEM to assess the association of BC with having ever been exposed and with cumulative exposure to selected carcinogens, using information on subjects' jobs.

The strongest result obtained was a 37% increase in BC risk due to CD exposure (41% for low cumulative exposure). CD was shown to be carcinogenic in humans through four different main mechanisms: aberrant gene expression, inhibition of DNA damage repair, inhibition of apoptosis, and induction of oxidative stress (Joseph 2009; Waisberg et al. 2003); CD has been classified as carcinogenic to humans (group 1) by the IARC, which stated that there is sufficient evidence for a causal association with lung cancer, and limited evidence for prostate cancer and kidney cancer (IARC 2012). Only a few in vivo models (Waalkes et al. 2000; Talaska et al. 1990) have been developed to assess the carcinogenicity of CD for BC, with contrasting results. Moreover, in an ecological study performed in Belgium to identify a possible relationship between cancer incidence and cadmium emissions from zinc smelters, no association was found with bladder (and any other) cancer (Verhoeven et al. 2011). Nevertheless, Feki-Tounsi and Hamza-Caffai (Feki-Tounsi and Hamza-Chaffai 2014) published a review in which they concluded that results from in vitro studies (Sens et al.2004; Larson et al. 2010) and from previous epidemiological studies (Feki-Tounsi et al. 2013; Kellen et al. 2007) would suggest an association between CD exposure and BC development.

We also found an excess risk of BC in subjects with low cumulative exposure to PB and TRI, when compared to non-exposed subjects. In a Finnish study conducted by Lohi et al. (2008), exposure to Chlorinated Aliphatic Hydrocarbons (CHC), mainly TRI e TCE, was associated with an increased risk of BC, in particular for female laboratory assistants, chemical industry laborers and shoemakers, and for male transport operators like taxi and bus drivers. Moreover, many animal experiments confirmed TRI and PER to be carcinogenic agents for urological cancers (Golka et al. 2004b). Our results were less strong than those observed in the previous studies, possibly because the increase in risk awareness and the implementation of control measures have reduced considerably the level of exposure to solvents in the last decades [for example, exposure to tetrachlorethylene in dry cleaning has decreased from 350 to 700 mg/m^3 in the '70s to 70–350 mg/m^3 in '80s (IARC 1995)].

Regarding the association with PB exposure, a recent review from Assi et al. (2016) on the effects of PB on human and animal health showed that PB is a possible cause of urinary cancer development (in particular for the kidney).

We also analyzed the risk of BC due to carcinogenic exposure by tumour grade. We observed that the carcinogens considered had a higher effect on the risk of low-grade BC, while it seems that they had only a marginal role in the risk of high-grade BC. In fact, together with the already observed increased risk due to CD, TRI, TCE, PAHs, and PB exposure, a statistically or borderline-statistically significant increased risk of developing low-grade BC was found also for BAP, CR, and DET exposure, while no association was found for high-grade BC. As a partial rationale for this, a recent paper (Van Batavia et al. 2014) showed that low-grade BC arises mainly from intermediate cells, while Keratin5-expressing basal cells are likely progenitors of high-grade BC, more prone to undergo a *TP53* mutation. Therefore, it is not surprising that carcinogens have different effects on these two different types of cells. To our knowledge, no other studies investigated the effect of carcinogens on BC risk by tumour grade, except for an old study which considered the association between BC and having worked in occupations bearing a high a priori risk for this cancer, and did not find any difference in the association with respect to grade (about

50% risk excess in both categories) (Sturgeon et al. 1994). Therefore, new studies are needed to further investigate this topic.

The main limitation of the present study lies in the fact that it is based on a hospital case–control design; indeed, it could be difficult to judge how much controls reflected the distribution of the population that generated cases. For this reason, we tested, if a socio-economic difference between cases and controls was present evaluating the frequency distribution of ISCO-68 macro-classes in cases and controls and, since there was no difference, it is unlikely that the observed associations were due to a possible higher socio-economic status of controls. Moreover, the use of hospital controls could bring to a not adequate representation of the underlying study base that generated the cases, although the percentage of Italian employees by broad occupational groups in those years is similar to that presented in the controls (http://dati.istat.it).

Another limitation is the use of a JEM to assign occupational exposure to the study population, which implies higher non-differential misclassification of the exposure than more detailed information at the individual level, with the consequence of a risk attenuation. However, the use of a JEM can also be a strength, given that it reduces the possibility of differential misclassification due to recall bias, that is more severe, due to its differential nature, and may lead to under- or overestimation of the true risk. Recall bias was also reduced keeping into account only jobs lasted for at least 2 years during the lifetime.

The construction of the cumulative dose of exposure through intensity weighted by probability may have also led to an imperfect classification of the subjects in low- or high cumulative exposure, and in particular to an underestimation of the true cumulative exposure for subjects with low probability and high intensity. This fact could be partially explained why some associations were stronger in subjects with lower exposure than in highly exposed subjects.

A strength of the study is the multi-centre approach, that has increased not only the sample size, but also the representativeness of the results, describing two different industrial and then post-industrial environments. Conversely, the two studies had not exactly the same design and this could lead to some heterogeneity.

Moreover, with respect to the previous studies, we performed an improvement of the plausibility and robustness of the risk estimates and a rigorous control of type I error, which is always present when performing many independent tests, employing semi-Bayesian analyses. Finally, we studied both occupation and occupational exposure to carcinogens, to provide a more detailed picture of BC risk among workers.

In conclusion, our study showed that several occupations, especially those involving rubber, plastic, and mechanical work, may beat higher risk of developing BC, as well as occupational exposure to several carcinogens, such as cadmium, lead, and chlorinated aliphatic hydrocarbons, which are not yet officially recognized as carcinogens for BC. These findings suggest that monitoring workplaces to prevent exposure to carcinogenic agents is still a very important task, which should be still given adequate importance in public health policies.

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