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Original papers

Prostate cancer: an occupational hazard in Romania?

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Abstract

Several occupational carcinogens (arsenic, cadmium) and industries (rubber production) have been associated with prostate cancer risk but most of the data are from studies conducted on screened populations. Here we explored this association in Romanian men, a population with low PSA screening test coverage. We have analyzed 468 prostate cancer cases pathologically confirmed and 495 non-cancer hospital controls, recruited in the ROMCAN project. Personal information, including occupational activity, was collected through interview. Two experts classified jobs and activities into 15 economic sectors with similar patterns of exposure. Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between ever employed in each economic sector and prostate cancer risk. We observed a higher non adjusted risk for employment in electricity, gas, steam and air conditioning supply activities (OR=3.95, p=0.029), manufacturing–light industry (OR=1.88, p=0.039), financial, insurance and gambling (OR=1.44, p=0.046) and a lower risk for employment in construction industry (OR=0.62, p=0.010). After adjusting for potential confounders, only the low risk in construction workers was maintained (OR=0.55, p=0.004). Our study provides some evidence on the role of occupational factors on the prostate cancer risk but further assessments are needed. Healthy lifestyle promotion and prevention should be reinforced at workplaces.

Keywords: *prostate cancer; PSA screening; occupation; economic sectors; construction workers*

Introduction

Prostate cancer is the third cancer type in Romanian males (after lung and colorectal cancer) with estimated incidence and mortality age-standardized rates (using the European standard population) of 47.2 and 18.4 respectively in 2018. Although incidence rate is much lower than in Europe, the mortality rate is nearly

nearly equal (92.5 and 19.4 respectively) [1]. Prostate cancer mortality rates have been declining in most Western European countries [2]; in Romania, the rates are trending upward, from an estimated rate of 18.83 in 2008 to 25.2 deaths per 100,000 inhabitants in 2017 (https://vizhub.healthdata.org/gbd-compare/). The observed differences of mortality rates and trends may be more affected by differences in risk factors prevalence and treatment practices than by diagnostic practices [2, 3].

The most well-established non-modifiable risk factors are age, family history of prostate cancer, and ethnicity. Prostate cancer is more common in men over the age of 50, but in recent years, it has been diagnosed with increased frequency in younger men and professional active groups [4] leading to more years lived with disability caused by health status impairment. In Romania, the burden of the disease increased over the last ten years. Prostate cancer in men aged 15-49 caused 12.31 DALYs (disability-adjusted life years) per 100,000 in 2017 compared with 9.77 in 2008 (https://vizhub.healthdata.org/gbd-compare/). These data stimulate efforts to search for modifiable risk factors, essential for designing and implementing preventive and surveillance strategies to reduce the burden to the society and to avoid the death caused by this disease.

Lifestyle (diet, obesity, smoking, sexual behavior, sexually transmitted diseases), physical activity are important preventable risk factors although there is a mixed evidence of the effect of such factors [5, 6]. The occupational risk factors are not well established yet and seem to explain only a small proportion of cases. Several associations with certain occupations or activities have been observed: agriculture occupations, firefighting occupations, shift work, and whole-body vibrations [7–9]. Other data showed associations with rubber industry, metal workers and repairmen, and farming [10–12]. Particular occupational exposures have been related to the risk, such as pesticide, diesel exhaust, hexavalent chromium, arsenic, cadmium, polycyclic aromatic hydrocarbons, particulate matter, and shift working [13, 14]. Some of these chemicals have been identified as endocrine disruptors and humans can be exposed to them through environmental pollution also [15].

These studies have mostly been conducted in Western Europe and North America, in countries with high prevalence of PSA screening, resulting in detection biases and also greater proportion of indolent cases with benign prognosis [16]. Screening in Romania is not a usual practice and published data are scarce. There are no reports on PSA testing in men with symptoms originating from primary care. Some data from local screening initiative in Western Romania are available; CLOSER program showed a prevalence of PSA testing of 4.3% in the male population over the age of 50 [17].

In this study we aim at exploring potential associations between employment and prostate cancer, among a Romanian population with low PSA screening rates, using the data from the ROMCAN project.

Materials and Methods

The ROMCAN project is a hospital based case-control study, conducted in "Carol Davila" University clinics in Bucharest, and aimed to investigate genetic and non-genetic determinants of five major cancer types (colorectal, prostate, breast and lung). Details are described elsewhere [18–20].

All consecutive prostate cancer cases pathologically confirmed, hospitalized between 2014 and 2017, were invited to participate in the study. The control group consisted of patients hospitalized in the same clinic for acute urological diseases. All subjects gave written informed consent prior to enter the study and the study was approved by the ethic commission of The National College of Romanian Physicians.

The medical data were abstracted from the medical records. Lifestyle and occupational data were collected through direct interview by trained investigators, using standardized questionnaires. The anthropometric data (height and weight) at the moment of diagnosis and 2 years before were self-declared.

The main occupational activity was reported by each individual. The economic activities were codified according to CAEN (Classification of National Economic Activities, 2018, 2nd revision), two digits. CAEN, 2nd revision is the national version of NACE 2nd revision (Statistical Classification of Economic Activities in the European Community). Two occupational health specialists evaluated the exposures associated with each economic activity, based on known major occupational hazards. The considered exposures were: heavy and toxic metals (arsenic, cadmium, chromium, lead, nickel) occurring in various economic domains (manufacture and industry, agriculture, water and energy, constructions, health and social work, services, transportation), ergonomic factors (including inconvenient and difficult work postures, manual handling of burdens, occupational physical activity, sedentary work and standing work), physical and environmental factors (radiation, electro-magnetic fields). Then, the economic activities were grouped in 15 main sectors with similar exposure profiles.

We estimated crude odds ratios (OR) and 95 % confidence intervals (95 % CI) for those ever employed in each economic sector (the exposed group) against all the subjects never employed in those particular activities (the reference group). We restricted our analysis only to the occupational active patients (up to 65 years). Using logistic regression, models were adjusted for two recognized non-modifiable risk factors: age (as a continuous variable), first-degree family history of cancer (yes, no; all cancer types). We assumed statistical significance for $P<0.05$. For multiple comparisons we applied Bonferroni correction. Analyses were conducted using STATA/MP 13.0 software (College Station, TX).

Results

The study population included 468 cancer cases and 495 non-cancer controls. A detailed description of the cases and controls is presented in Table 1.

Controls were younger than cases. The mean age significantly differed between cases and controls by certain activity groups (agriculture, forestry and fishing, light industry, manufacture of basic metals, metal products, computer, electronic, electrical and optical products, construction, wholesale and retail, transporting and storage, financial and insurance activities, health, defence). Subjects living in urban area, widowed or divorced, educated at university level, were more likely to be cases. As expected, the familial history of cancer was a strong risk factor in our study (OR=2.47; CI=1.82-3.35; $P<0.001$). Body mass index (BMI) 2 years before diagnosis differed; controls were more likely to be obese than cases (OR=0.59, CI=0.45-0.77; $P<0.001$). Ever smokers have a slightly elevated but non-significant risk, compared to never smokers (OR=1.13; CI=0.88-1.46; P=0.338). The majority of cases (62.2%) were staged TNM II reflecting low screening practice.

The subjects held jobs classified in 74 CAEN activities. The activities were clustered into 15 economic sectors with similar patterns of exposure. The distribution of cases and controls according to the activity categories is presented in Table 2.

Three sectors of activities were associated with statistically elevated ORs for ever-employment in at least one CAEN category: manufacturing – light industry (OR=1.88, CI=1.00-3.62, P=0.039); electricity, gas, steam and air conditioning supply (OR=3.95, CI=1.03-22.14, P=0.029); financial and insurance activities, gambling and betting, real estate, rental and leasing, accommodation and food services, professional, scientific and technical activities and education (OR=1.44, CI=1.01-2.07, P=0.046). The high risk for prostate cancer associated with these work activities proved to attenuate and became non-significant after adjustment for age and family history of cancer.

Regarding decreased risk of prostate cancer, an inverse association was found for construction activities (CAEN codes 41-43) with OR= 0.62 (CI=0.42-0.89, P=0.010).

Decreased prostate cancer risk associated with employment in constructions remained robust after adjustment for age and family history of cancer (OR=0.55, CI=0.37-0.83, P=0.004).

Discussion

In this study we have explored the association between prostate cancer risk and employment in various economic activities using data from the self-reported occupational histories of approximately 1000 Romanian subjects recruited in the ROMCAN project.

We found positive associations for several economic sectors: light industry, electricity, gas, steam and air conditioning supply, and "white-collar" indoor occupations.

Employment in manufacture – light industry (food and beverages industry, manufacture of tobacco products, textiles, wearing apparel, leather and related products, wood and of products of wood, paper and paper products, printing) strongly associated with elevated prostate cancer risk but didn't remain significant following adjustment for non-occupational risk factors (family history of cancer, and age). Employment in these activities entails exposure to a large spectrum of chemicals, qualitatively different and time sensitive given that processes, materials and exposures change over time [21]; so far, only arsenic (and inorganic arsenic compounds) and cadmium (and cadmium compounds) showed limited evidence of association with prostate cancer, based on The International Agency for Research on Cancer (IARC) Monograph series of reviews [22].

In our study, subjects ever employed in electricity, gas, steam and air conditioning supply activities have a high risk of prostate cancer. These findings are similar with those reported in previous case-control studies for electrical power erecting, installing and repairing operators, and hydroelectric power plants [23, 24].

Table 1. Description of the study groups

Characteristics	Prostate cancer cases N= 468	Non-cancer controls N =495	P value
Age (years)			
Mean ± SD	60.7±3.8	56.0±6.6	<0.0001[a]
Median(range)	61(44-65)	58(42-65)	
Living area, N(%)			
Urban	372 (79.5)	350(70.7)	0.002[b]
Rural	95(20.3)	144(29.1)	
Missing	1(0.2)	1(0.2)	
Marital status, N(%)			
Married	415(88.7)	439(88.7)	0.03[b]
Unmarried	10(2.2)	14(2.8)	
Widowed	18(3.8)	10(2.0)	
Divorced	18(3.8)	8(1.6)	
Other	7(1.5)	24(4.9)	
Educational level, N(%)			
Less than primary (0-4 years)	7(1.5)	17(3.4)	0.001[b]
Primary (4-8 years)	41(8.8)	61(12.3)	
Secondary (8-13 years)	203(43.3)	234(47.3)	
College & University (>13 years)	216(46.2)	163(32.9)	
Missing	1(0.2)	20(4.1)	
Current smoking, N(%)			
No	364(77.8)	364(73.5)	0.126[b]
Yes	104(22.2)	131(26.5)	
Ever smoking, N(%)			
No	189(40.4)	215(43.4)	0.338[b]
Yes	279(59.6)	280(56.6)	
Body Mass Index (kg/m²)			
2 years before enrolment	N=444	N=434	
Mean ± SD	27.7±4.2	28.9±8.8	0.009[a]
Median(range)	27.5(16.9-43.8)	27.7(16.5-142.8)	
BMI categories			
normal	334(75.2)	295(67.9)	
obese (BMI≥30 kg/m2)	110(24.8)	139(32.1)	<0.001[b]
Familial cancer history			
no	327(69.9)	432(87.3)	<0.001[b]
yes	134(28.6)	56(11.3)	
do not know	7(1.5)	7(1.4)	
TNM staging (cases only), N(%)			
Stage I	1(0.2)	n/a	
Stage II	291(62.2)	n/a	
Stage III	70(15.0)	n/a	
Stage IV	104(22.2)	n/a	
Missing	2(0.4)	n/a	

[a]*Student t-test;* [b]*Chi2 test*

Table 2. Associations between economic sectors of activity and risk of prostate cancer

Economic sector (CAEN 2digits code)	Never employed Cases/Controls	Ever employed Cases/Controls	OR[a] (95% CI)	P[a]	OR[b] (95% CI)	P[b]
Agriculture, forestry and fishing, landscape services (01, 02, 03, 81)	436/460	32/35	0.96 (0.59-1.58)	0.887	1.14 (0.65-2.01)	0.640
Mining and quarrying (06, 07, 09)	465/486	3/9	0.35 (0.09-1.29)	0.115	0.28 (0.07-1.14)	0.075
Manufacturing – light industry (10-19)	437/477	31/18	1.88 (1.00-3.62)	0.039	1.88 (0.97-3.63)	0.059
Manufacturing – heavy industry (20-23)	452/488	16/7	2.47 (0.95-7.15)	0.055	2.14 (0.78-5.84)	0.138
Manufacture of metal products, computer, electronic, electrical and optical products, including installation and repair (24-33, 96)	327/343	141/152	0.97 (0.74-1.28)	0.845	0.96 (0.70-1.31)	0.804
Electricity, gas, steam and air conditioning supply (35)	457/492	11/3	3.95 (1.03-22.14)	0.029	3.68 (0.74-17.30)	0.112
Water supply, sewerage, waste management and remediation (36-39)	465/493	3/2	1.59 (0.18-19.11)	0.680	1.44 (0.21-9.83)	0.705
Construction (41-43)	415/410	53/85	0.62 (0.42-0.89)	0.010	0.55 (0.37-0.83)	0.004
Wholesale and retail trade (45-47)	457/482	11/13	0.89 (0.39-2.01)	0.784	0.92 (0.37-2.28)	0.864
Transporting and storage (49-53)	418/427	50/68	0.75 (0.51-1.11)	0.150	0.76 (0.49-1.19)	0.232
Telecommunications including repair services (61-63, 95)	460/489	8/6	1.42 (0.49-4.12)	0.521	1.44 (0.44-4.65)	0.543
Financial and insurance; Gambling, betting; Real estate, accommodation; Education, scientific and technical activities (55, 56, 64-66, 68-74, 77, 79, 82, 85, 94, 99)	389/434	79/61	1.44 (1.01-2.07)	0.046	1.33 (0.88-2.00)	0.168
Health (human and veterinary), social work and well-being (75, 86, 87, 88, 96)	459/488	9/7	1.37 (0.50-3.70)	0.538	1.74 (0.53-5.67)	0.359
Security and investigation; Public administration and defence (80, 84)	452/471	16/24	0.69 (0.36-1.32)	0.269	1.30 (0.60-2.77)	0.504
Arts; Publishing; Entertainment, sport and recreation; Travel services (58, 79, 90, 91, 93)	463/490	5/5	1.06 (0.30-3.68)	0.929	1.08 (0.25-4.59)	0.918

[a]crude OR; [b]OR adjusted with age and familial history of cancer (all cancers)

Potential exposures in these activities includes chemicals but also night-shift work, which has been associated with prostate cancer in the literature [8].

We have found suggestive trends of prostate cancer risk in several "white-collar" occupations, including financial and insurance activities, gambling and betting, real estate, rental and leasing, accommodation and food services, professional, scientific and technical activities and education. The associations become non-significant after adjustment for age and family history of cancer. These activities typically entail few chemical exposures and low physical activities. Long sitting period has been associated with a slightly elevated, but non-significant, increased risk of aggressive prostate cancer amongst obese men [25]. The results can also be interpreted in the context of prostate cancer-related diagnostic and screening activity observed for occupations that are related to higher social status and thus presumably better access to health care [5]. However, our study was designed for hospitalized subjects with equal access to hospital facilities suggesting that medical care is less probable to alter the relationship observed. There is also other data indicating that enhanced access to health may not drive the observed risk [16].

Significantly reduced prostate cancer risk was found for employment in constructions activities. There are inconsistent findings reported on the prostate cancer risk of constructors. A previous study on a large Swedish constructors cohorts reported positive association of fatal cases with increased BMI [26]. Other case-control study [27] reported significant negative association between cancer of the prostate and employment in the construction industry (OR = 0.76, 95% CI = 0.65-0.89). Similar, a recent case-control study conducted on a low screened population found a similar lower risk of prostate cancer in construction trades [16]. Several factors could explain these observations. First, these occupations entail mainly outdoors activities and workers may be exposed to high levels of ultraviolet radiation and vitamin D production in the skin which may have a protective effect on prostate cancer development [28]. However, employment in agriculture, forestry and fishing, landscape services, with long duration of exposure to solar radiation, was not likely to associate with low risk of prostate cancer in our study. Second, working in constructions is associated with intense physical activity and low prevalence of obesity, a well-recognized risk factor. Adjusting for obesity in our model didn't changed the association (OR=0.57; CI=0.38-0.85; P=0.006). Lastly, it may well be that our findings reflect under-detection of prostate cancer in our constructors' group, relative to other occupational groups, which was not fully captured through our consideration of screening practices in the questionnaire.

Our study features several strengths, the first being that it relied on symptomatic cases (with lower urinary tract symptoms) and histologically confirmed. Since in Romania there is no systematic screening program in place we were not able to estimate screening behavior that can be influenced by a number of factors, including lifestyle and those offered in the workplace, and thus can potentially confound an occupational association. Consequently, we could not adjust our models for screening patterns.

Second, to the best of our knowledge, this is the first case-control study conducted on Romanian subjects to investigate the role of occupational circumstances in prostate cancer risk. Our case–control design allowed examination of a broad range of exposure levels, though the prevalence of exposure to most agents was likely to be low. The questionnaires offered the opportunity to enumerate several non-occupational exposures, throughout a subject's lifetime, as well as medical and lifestyle factors that may confound or modify an exposure–disease association.

However, there were limitations that may possibly have influenced our observed associations. The occupational activities were derived from information provided by the subjects about their occupations and work sector. This is not likely to modify the results, as validity studies have generally shown high concordance between historical records of employment and self-reports [29]. Assignment of occupational CAEN codes and grouping study subjects for analysis, based on similarities in exposure, was conducted by experienced occupational health specialists blinded to the subjects' case/control status. By assigning subjects the mean exposure of their group the misclassification bias is attenuated [19] but the method might have entailed errors due to the lack of details on tasks and hazards. The coding of activities up to the 2-digits level of the CAEN classification is also likely to be problematic in terms of validity and reliability of qualitative exposure assessment. The data collected were restricted to the longest held occupational activity; therefore, the stratified analysis by duration of employment was not possible. In the absence of more specific methods (case-by case assessment, specific questionnaire, job-exposure matrix, others) we were not able to refine our analysis for particular occupational hazards.

The study size has limited our power to detect effects among certain activities. We adjusted our models for age and familial history, but were unable to adjust for other confounders, and therefore our adjustment may be incomplete. Due to the relatively large number of occupations tested, we cannot rule out the possibility that some of our findings might be due to chance. Applying the Bonferroni correction for multiple comparison none of the associations remained significant (P>0.003).

Conclusions

This study provides the first insight into occupational risk factors for prostate cancer in a Romanian sample of non-screened men. Our results do not allow concluding on existence of an elevated prostate cancer risk associated with a particular economic activity. However, in the economic sectors that showed an initial positive association (light industry, electricity, gas, steam and air conditioning supply, and "white-collar" indoor occupations), awareness and preventive programs should be reinforced.

An inverse association with construction activities has been found but it is unclear how much is the weight of the occupational related factors among other non-occupational characteristics. With the construction sector being the fourth larger Romanian occupational domain, the investigation of this complex working environment is far from sufficient. Future larger studies would benefit from use of more accurate and comprehensive assessment of occupational hazards.

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