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Occupational heat exposure and prostate cancer risk: A pooled analysis of case-control studies

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ABSTRACT

Background: Heat exposures occur in many occupations. Heat has been linked to key carcinogenic processes, however, evidence for associations with cancer risk is sparse. We examined potential associations between occupational heat exposure and prostate cancer risk in a multi-country study.

Methods: We analysed a large, pooled dataset of 3142 histologically confirmed prostate cancer cases and 3512 frequency-matched controls from three countries: Canada, France, and Spain. Three exposure indices: ever exposure, lifetime cumulative exposure and duration of exposure, were developed using the Finnish Job-Exposure Matrix, FINJEM, applied to the lifetime occupational history of participants. We estimated odds ratios (ORs) and 95% confidence intervals (CIs), using conditional logistic regression models stratified by 5-year age groups and study, adjusting for potential confounders. Potential interactions with exposure to other occupational agents were also explored.

Results: Overall, we found no association for ever occupational heat exposure (OR 0.97; 95% CI 0.87, 1.09), nor in the highest categories of lifetime cumulative exposure (OR 1.04; 95% CI 0.89, 1.23) or duration (OR 1.03; 95% CI 0.88, 1.22). When using only the Spanish case-control study and a Spanish Job Exposure Matrix (JEM), some weakly elevated ORs were observed.

Conclusions: Findings from this study provide no clear evidence for an association between occupational heat exposure and prostate cancer risk.

1. Introduction

With more than half the global population currently employed, occupational exposures are of great public health importance (Kühn, 2019). Heat exposures occur frequently in many occupations, including in both indoor and outdoor workers such as chefs, factory workers, and farmers (NIOSH, 2016). These workers regularly contend with conditions involving high air temperatures, radiant heat from direct sunlight or machinery, potentially elevated humidity, and low wind speeds/air flow. This puts them at risk of heat stress; the body's thermoregulatory

Abbreviations: BMI, Body Mass Index; CI, Confidence Intervals; JEM, Job Exposure Matrix; OR, Odds Ratio; PAH, polycyclic aromatic hydrocarbon; PSA, prostatic specific antigen; SES, socioeconomic status.

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system becomes overwhelmed and can no longer maintain an optimal temperature (Cramer and Jay, 2016). Increased metabolic heat production during physical activity and the use of personal protective equipment further contribute to the risk of heat stress amongst workers (Cramer and Jay, 2016). A variety of personal and lifestyle factors can also influence a worker's exposure to heat and vulnerability to heat stress, including age, race/ethnicity, sex, BMI, acclimatisation and smoking habits (Acharya et al., 2018). The number of workers exposed to heat is expected to rise in the coming years due to global warming (Gao et al., 2018).

The global burden of prostate cancer is growing. In 2020 there were 1,414,259 new prostate cancer cases diagnosed globally and 375,304 deaths (Global Cancer Observatory, 2022). However, the aetiology of prostate cancer is still poorly understood. Currently, the only established risk factors are older age, African ancestry, and positive family history of prostate cancer (Pernar et al., 2018). Other suspected risk factors that have been investigated include obesity, cigarette smoking, diet, alcohol, and pesticide exposure (Rawla, 2019). The International Agency for Research on Cancer has also classified various occupational agents as possible prostate carcinogens, including cadmium (IARC, 2022) and x- and gamma-radiation exposures (IARC, 2022a) for example, as well as firefighting (Demers et al., 2022), and night shift work (IARC, 2020b), although the evidence is limited.

Studies have shown heat stress displays some key characteristics of human carcinogens (Smith et al., 2020). Direct heat exposure to cells causes DNA strand breaks, leading to genetic alterations (Kantidze et al., 2016). An increased production of reactive oxygen species caused by heat stress induces oxidative stress in cells and subsequently results in oxidative DNA damage (Gharibi et al., 2020). Heat stress can also cause a sustained inflammatory environment within the cells, further contributing to oxidative stress and DNA damage (Heled et al., 2013). The disruption of cell proliferation and apoptosis by heat stress allows DNA damaged cells to survive and continue replication (Venugopal et al., 2018). Heat stress also interferes with cell DNA repair pathways, causing elevations in mutagenesis and genomic instability (Venugopal et al., 2018; Roti Roti, 2008).

Many workers at risk of heat stress are also regularly exposed to an array of chemicals, including for example metals, pesticides, or polycyclic aromatic hydrocarbons (PAHs). Heat exposure has been shown to exacerbate chemical absorption and toxicity through increased skin permeability and respiration rate as part of the thermoregulatory response, making heat exposed workers even more vulnerable to potential health problems (Leon, 2008).

Previous studies investigating the role of heat on other male androgen-related cancers have had mixed results. One study (Zhang et al., 1995) identified 250 testicular cancer cases from the New York State Tumour Registry and 250 frequency-matched population controls and observed a positive association between self-reported low (<60 °F) (odds ratio (OR) 1.84; 95% confidence interval (CI) 1.25, 2.72) and high (>80 °F) (OR 1.68; 95% CI 1.18, 2.40) temperature exposure at work and testicular cancer risk. Another study (Rosenbaum et al., 1994) recruited 71 male breast cancer cases from the New York State Tumour Registry and 256 controls from a voluntary cancer screening clinic located in the same area and used city directories and questionnaires to obtain occupational history. Occupational heat exposure estimates were assigned based on a schema which detailed selected characteristics of each occupation. The study observed an elevated risk of male breast cancer for those ever-having occupational heat exposure compared to those never exposed (OR 2.5; 95% CI 1.02, 6.0). In contrast, another study (Cocco et al., 1998) observed no association between the probability and intensity of occupational heat exposure and male breast cancer risk. The study, also undertaken in the United States, selected 178 male breast cancer deaths and 1041 controls from all other causes of death. Information was collected from proxy respondents on the longest held job and a job exposure matrix (JEM) was used to assign occupational heat exposure estimates.

A recent Spanish study investigated occupational heat exposure and female breast cancer (Hinchliffe et al., 2021), which is shown to be related to prostate cancer (De Silva and Alcorn, 2022). The study observed positive associations for ever occupational heat exposure (OR 1.22; 95% CI 1.01, 1.46), and found those with higher lifetime cumulative exposures and durations were at even greater risk.

Several other studies have had mixed results in investigations of occupational heat exposure and various cancer types including nasopharyngeal (Armstrong et al., 2000), pancreatic (Kauppinen et al., 1995; Alguacil et al., 2000), oesophageal (Santibañez et al., 2008), liver (Rønneberg and Andersen, 1995), kidney (Weiderpass et al., 2003; Rønneberg et al., 1999), and stomach cancer (Santibañez et al., 2012). Differing methodologies and limitations, including small sample sizes and low heat exposure prevalence likely contributed to such disparities in the findings.

This study is among the first to examine associations between occupational heat exposure and prostate cancer risk. Here we analyse potential associations between occupational heat exposure and prostate cancer risk in a large, pooled dataset of histologically confirmed prostate cancer cases and frequency-matched controls from three different countries. We also investigated possible interactions between occupational heat exposure and other occupational agents.

2. Study population & methods

2.1. Study data

This study uses data from three large population-based case-control studies of prostate cancer risk undertaken around a similar time period: PROtEuS (Barul and Parent, 2021; Barul et al., 2019), MCC-Spain (Castaño-Vinyals et al., 2015) (www.mccspain.org), and EPICAP (Menegaux et al., 2014).

PROtEuS (Prostate Cancer & Environment Study) was conducted in Montreal, Canada between 2005 and 2012 and was specifically designed to study occupational exposures in prostate cancer. Eligible cases and controls were Canadian citizens registered on the provincial electoral list, residents of the Montreal metropolitan area and aged <76 years at diagnosis or interview. Histologically confirmed prostate cancer cases were actively recruited from hospitals in the study area. Controls, frequency matched by age, were randomly selected from the electoral list among men residing in the same geographical area as cases and without a history of prostate cancer. Overall, 79% of cases (n = 1937) and 56% of eligible controls (n = 1994) agreed to participate in the study.

MCC-Spain is a Spanish multicentre study undertaken between 2008 and 2013 to study incident histologically confirmed prostate, breast, colorectal and gastric cancer, as well as prevalent chronic lymphocytic leukaemia, using a common set of controls, frequency matched by age, sex, and region for all cancer cases combined. Incident prostate cancer cases were recruited in seven regions. Prostate controls were randomly selected from primary health care centres located within the same catchment area as the corresponding recruiting hospitals in these areas. Controls with a personal history of prostate cancer were excluded, along with those more than 5 years younger than the youngest prostate cancer case in each region. All participants were aged 40–85 years, had resided in the catchment area for at least 6 months prior to recruitment and were capable of answering the epidemiological questionnaire. A total of 1112 prostate cancer cases and 1493 controls were included, with response rates of 74% and 54%, respectively.

EPICAP (Epidemiological Study of Prostate Cancer) is a French study carried out between 2012 and 2014. Eligible cases were patients newly diagnosed with prostate cancer in 2012–2013, <75 years old and resident in the Hérault region at diagnosis. Cases were recruited by clinical research nurses from all public and private cancer care centres. Controls, frequency-matched by age, were selected among the general population of cancer free men, resident in the Hérault region at the time of the cases' diagnoses. Quotas on socioeconomic status (SES), calculated from

the census data of the region, were applied *a priori* to controls for potential selection bias arising from differential participation rates across SES categories. Overall, 819 cases and 879 controls were included, representing a participation rate of 75% and 79%, respectively.

2.2. Data collection

Data was collected in face-to-face interviews conducted by trained personnel. A wide range of information was collected on sociodemographic, environmental, lifestyle, and medical factors including personal and family history of cancer, and screening history by prostatic specific antigen (PSA) tests. Detailed occupational information (job titles, tasks, and work schedules) was also collected for the full employment history in each study, for each job held for more than 6 months (EPICAP) or at least one year (MCC-Spain and PROtEuS). Tumour Gleason scores, indicating cell differentiation at diagnosis, were used to define aggressive cancers.

2.3. Occupational heat exposure assessment

Occupations in MCC-Spain and EPICAP required translation to ISCO88 from CNO-94 and ISCO68 job codes respectively, using pre-existing crosswalks (INE, 2022; Turner et al., 2014). An occupational hygienist evaluated CNO-94 and ISCO68 job codes that translated to multiple ISCO88 codes and assigned the most appropriate code. In situations where multiple job codes were considered appropriate, the job code with the highest occupational heat exposure was assigned. In PROtEuS, occupations were directly coded by hygienists into ISCO88.

The FISCO88-FINJEM 2019 version of the Finnish JEM, FINJEM, translated to standard 4-digit ISCO88 codes, was subsequently applied (Sallmén and Uuksulainen, 2019) to the job histories of participants in each study. This JEM contains 390 major occupational groups and covers the calendar period 1995 to 2009, divided into five sub-periods of three years. Occupational heat exposure is defined in the FINJEM as heat from natural or artificial sources continuously exceeding 28 °C or reference values of the WGBT-index (Wet Bulb Globe Temperature-index) (Budd, 2008). For occupational heat exposure, an estimate of the proportion of workers exposed in that occupation (prevalence (P)) and an estimate of exposure intensity, denoted as the proportion of annual working time spent in heat (level (L)), is provided for three different time periods: 1995–1997, 1998–2000 and 2001–2003. Heat exposures did not vary greatly across the three time periods, so we applied the average heat exposure estimates here.

Using these estimates in combination with *a priori* knowledge, we defined ever occupational heat exposure as having ever held at least one job with a P $\geq$ 25% for a duration of at least one year. We deemed participants who had ever held a job with a P between 5% and 25% or with occupational heat exposure for less than one year to have uncertain exposure and to balance sensitivity and specificity we excluded them from the analysis (n = 463 cases and 465 controls). We implemented an *a priori* lag period of 5 years in all analyses, to allow for a potential prostate cancer latency period. All exposures occurring in the 5 years before diagnosis date for cases and interview date for controls were therefore not included in the main analysis. Participants only exposed in the 5 years before diagnosis/interview date were considered unexposed.

Participants who had only done voluntary work were excluded from the analysis (n = 17), as were participants who had worked exclusively in the military (n = 1), due to uncertain exposure. Participants with any missing occupational information, including missing occupational codes or missing start/finish years, were also excluded (n = 203 cases and 198 controls). Among participants excluded with missing occupational information, the average age was 65 years. The percentage of participants with missing occupational information ranged from 4% in EPICAP to 6% in MCC-Spain. Across all studies, the total number of included prostate cancer cases was 3142 and there were 3512 controls.

As part of a sensitivity analysis based on MCC-Spain only, we also applied heat estimates using a Spanish JEM, MatEmEsp, constructed based on FINJEM exposure estimates. Estimates were adapted by an expert panel of local industrial hygienists with extensive experience in company-based industrial hygiene measurements in Spain (Garcia et al., 2013). Occupational heat exposure in MatEmEsp is defined in the same way as in the FINJEM.

2.4. Statistical analysis

Variables were harmonised across the three participating studies (Appendix 1). The distributions of prostate cancer risk factors and occupational heat exposure were evaluated using one-way ANOVA and chi-squared tests. We calculated ORs using multivariate conditional logistic regression models stratified by 5-year age groups and study (country) and adjusted for potential confounders. Three different occupational heat exposure indices were developed: ever, and lifetime cumulative exposure and duration of exposure. Lifetime cumulative exposure was calculated as the sum of the product of P, L, and duration of occupational heat exposure for each job and was categorised into tertiles according to the distribution among exposed controls overall. Duration was calculated as the sum of the duration of occupational heat exposure for each job and categorised into >0- <10 years, ≥10-<25 years and ≥25 years, based on approximate tertiles according to the distribution amongst exposed controls. Overlapping jobs held during the same time period were considered part-time, so duration of these jobs was split. The reference group for all analyses was never occupational heat exposure. A directed acyclic graph in combination with *a priori* knowledge was used to identify potential confounders and select adjustment variables. Minimally-adjusted models were stratified by 5-year age groups and study, without adjustment for any other variables. Fully-adjusted models were further adjusted for education (less than primary, primary (6–16 years old), secondary (16–18 years old), university), family history of prostate cancer in a first degree relative (yes/no/missing), body mass index (BMI (kg/m^2)) within last two years before diagnosis/interview date (underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9), obesity (≥30)), cigarette smoking (never smoker, ex-smoker, and current smoker), and race/ethnicity (White/Caucasian, Other). We excluded participants with missing information on any of these variables (n = 19 cases and 45 controls).

We also assessed the impact of adjusting models for other potential confounders, including physical activity in free time (not very active, moderately active, very active, don't know) (Acharya et al., 2018), alcohol consumption (ever vs. never drinking alcohol at least once a month for at least 1 year) (Nunfam et al., 2019), and night shift work (ever vs. never night shift work) (IARC, 2020; Wendeu-Foyet et al., 2018; Papantoniou et al., 2015; Barul et al., 2019). We conducted sensitivity analyses restricting controls to only those screened for prostate cancer in the last 2 years to reduce the likelihood of undiagnosed prostate cancers among controls and potential confounding by screening history. Further analyses were conducted according to different strata of Gleason score (low grade prostate cancer (6 or 7 (3 + 4)) or high grade prostate cancer (≥ 8 or 7 (4 + 3))). We also analysed separately those who had done farm work <5 years and those who had done farm work 5+ years, to consider potential occupational pesticide exposures. Time window analyses were conducted to investigate the impact of the last heat exposure being ≥5 & <10 years, ≥10 & <20 years and ≥20 years before the diagnosis/interview date. We additionally evaluated separately indoor and outdoor heat exposed workers in EPICAP, where specific data was available on work location.

We also investigated other common occupational co-exposures: cadmium, lead, detergents (cleaning or washing agents containing surfactants), and PAHs. Positive associations with occupational detergent exposure were found in an MCC-Spain study of female breast cancer risk (Hinchliffe et al., 2021), although there is a lack of evidence in the literature regarding an association with prostate cancer. Cadmium, lead, and PAH exposures have previously been associated with an increased

prostate cancer risk in some studies (Mullins and Loeb, 2012; Rybicki et al., 2006; Barul and Parent, 2021). Separate analyses were conducted to compare associations between occupational heat exposure and prostate cancer risk in those never and those ever exposed to cadmium, lead, detergents or PAHs and potential interactions were explored. Exposure to these other occupational agents was also assigned using the FINJEM. Due to low exposure prevalence, ever exposure for all other occupational exposures was defined as having ever held at least one job with a P $\geq$ 5% for a duration of at least one year (as was occupational heat exposure for this specific analysis) (Appendix 2). The occupational co-exposures investigated were those contained in the FISCO88-FINJEM 2019 version of the Finnish job exposure matrix and for which there were sufficient numbers of participants exposed to heat and the other occupational exposure to perform the analysis.

For comparison with other work (Hinchliffe et al., 2021), and to assess the impact of using a Finnish JEM applied to a Spanish study population, we additionally analysed associations between occupational heat exposure and prostate cancer risk in MCC-Spain using a Spanish JEM, MatEmEsp (Garcia et al., 2013). Models for MCC-Spain alone were further stratified by Spanish regions.

Finally, to explore the impact of the *a priori* ever occupational heat exposure definition on the results, we performed sensitivity analyses using additional prevalence thresholds of $\geq$5% and $\geq$50%, lag years of 1 and 10 and an exposure duration threshold of 5 years.

All analyses were conducted using Stata 17 (StataCorp, 2021).

3. Results

Selected characteristics of the study subjects are presented in Table 1. Among the 6654 participants, the mean (±SD) age was 65 (7.1) years and ranged from 64 (6.8) years in PROtEuS to 66 (8.0) years in MCC-Spain. Participants in MCC-Spain were less educated than those in PROtEuS and EPICAP and were more often current smokers. The mean (SD) BMI across all studies was 27.3 (4.0) kg/m^2. Participants were predominantly White/Caucasian. Characteristics of controls ever (n = 1195) and never (n = 2317) having occupational heat exposure are presented in Appendix 3. Controls ever having occupational heat exposure were generally older, less educated and had a higher BMI.

The most common jobs in all studies included technical and commercial sales representatives, but other common jobs differed slightly across studies (Appendix 4). The most common heat-exposed jobs across all studies included machine-tool operators, field crop and vegetable growers, welders and flame cutters, cooks, and plumbers and pipe fitters. MCC-Spain had the highest proportion of participants who had ever done farm work (11.6%), followed by EPICAP (9.6%) and PROtEuS (3.9%). Across all three studies, occupations with the highest heat exposure (level (L)) included firefighters, metal workers and the occupational group of architects, engineers, and related professionals not elsewhere classified (eg. production engineers, industrial efficiency engineers, quantity surveyors, textiles technologists).

Overall, 34% of cases and 34% of controls were classified as being ever occupationally exposed to heat. MCC-Spain had the highest proportion of participants who were ever exposed (39%) compared to EPICAP (33%) and PROtEuS (31%). Mean (±SD) duration of heat exposure amongst the exposed was slightly higher in MCC-Spain (20 years (15.5)) compared to EPICAP (19 years (14.6)) and PROtEuS (18 years (14.4)). MCC-Spain had the highest mean lifetime cumulative exposure at 37.9 (P*L*duration in years), compared to EPICAP (35.9) and PROtEuS (32.3). The mean (±SD) number of jobs per participant was higher in EPICAP (5.9 (3.1)) compared to PROtEuS (5.2 (2.5)) and MCC-Spain (3.4 (2.1)).

In the minimally-adjusted models, using conditional logistic regression models stratified by 5-year age group and study only, slightly raised ORs were observed for ever occupational heat exposure (OR 1.06; 95% CI 0.95, 1.17) and in the highest categories of lifetime cumulative exposure and duration (Table 2). In the fully-adjusted models, we found no evidence for an association between ever occupational heat exposure and prostate cancer (OR 0.97; 95% CI 0.87, 1.09). There was also no evidence for an association in the highest categories of lifetime cumulative exposure or duration of exposure, and there was no evidence for an exposure-response trend. Findings were also similar in analysis of the individual studies separately. When adjusting models for other potential confounding factors, including physical activity in free time, alcohol consumption, night shift work and other occupational chemical exposures, associations remained largely unaltered (results not shown). Results were also similar when restricting controls in the analysis to only

Table 1
Distributions of risk factors among cases and controls in the three studies.

	MCC-Spain		PROtEuS		EPICAP		p-values[a]
	Controls N (%)	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)	Cases N (%)	
Total participants	1217 (56.3)	944 (43.7)	1569 (51.3)	1517 (48.7)	726 (51.6)	681 (48.4)	
Age; Mean (SD) Years	66.2 (8.5)	66.0 (7.3)	64.9 (6.8)	63.6 (6.8)	65.1 (6.1)	64.9 (5.8)	<0.001
Education							
Less than primary	203 (16.7)	211 (22.4)	48 (3.0)	29 (1.9)	53 (7.3)	55 (8.1)	
Primary (6–16 years old)	389 (32.0)	362 (38.4)	696 (43.6)	721 (47.5)	350 (48.2)	302 (44.4)	
Secondary (16–18 years old)	348 (28.6)	219 (23.2)	309 (19.4)	248 (16.4)	96 (13.2)	98 (14.4)	
University	277 (22.8)	152 (16.1)	543 (34.0)	519 (34.2)	227 (31.3)	226 (33.2)	<0.001
Smoking							
Never smoker	332 (27.3)	275 (29.1)	451 (28.3)	435 (28.7)	215 (29.6)	195 (28.6)	
Ex-smoker	637 (52.3)	490 (51.9)	856 (53.6)	830 (54.7)	398 (54.8)	383 (56.2)	
Current smoker	248 (20.4)	179 (19.0)	289 (18.1)	252 (16.6)	113 (15.6)	103 (15.1)	0.02
Family history of prostate cancer							
No	1079 (88.7)	752 (80.0)	1400 (87.7)	1116 (73.6)	602 (82.9)	467 (68.6)	
Yes	76 (6.2)	154 (16.3)	161 (10.1)	363 (23.9)	64 (8.8)	153 (22.5)	
Missing	62 (5.1)	38 (4.0)	35 (2.2)	38 (2.5)	60 (8.3)	61 (9.0)	<0.001
Body Mass Index (kg/cm2)							
Underweight (<18.5)	6 (0.5)	2 (0.2)	12 (0.8)	11 (0.7)	5 (0.7)	2 (0.3)	
Normal weight (18.5-24.9)	297 (24.4)	241 (25.5)	466 (29.2)	497 (32.8)	195 (26.9)	190 (27.9)	
Overweight (25.0-29.9)	628 (51.6)	477 (50.5)	766 (48.0)	732 (48.3)	352 (48.5)	339 (49.8)	
Obesity (≥30)	286 (23.5)	224 (23.7)	352 (22.1)	277 (18.3)	174 (24.0)	150 (22.0)	<0.001
Race/Ethnicity							
White/Caucasian	1210 (99.4)	929 (98.4)	1368 (85.7)	1350 (89.0)	646 (89.0)	597 (87.7)	
Other	7 (0.6)	15 (1.6)	228 (14.3)	167 (11.0)	80 (11.0)	84 (12.3)	<0.001

One-way ANOVA for continuous and chi-square for categorical.
SD: standard deviation.
[a] p-values for all studies combined.

Table 2
Associations between occupational heat exposure and prostate cancer risk (OR: Odds Ratio; 95% CI: 95% Confidence Interval).

	Pooled Analysis			MCC-Spain		PROtEus		EPICAP	
	Control/Cases (N)	OR (95% CI)[a]	OR (95% C[a])[b]	Control/Cases (N)	OR (95% CI)[c]	Control/Cases (N)	OR (95% CI)[c]	Control/Cases (N)	OR (95% CI)[c]
Never heat exposure	2317/2057	1 (ref)	1 (ref)	764/547	1 (ref)	1076/1048	1 (ref)	477/462	1 (ref)
Ever heat exposure	1195/1085	1.06 (0.95, 1.17)	0.97 (0.87, 1.09)	453/397	0.98 (0.80, 1.19)	493/469	1.01 (0.85, 1.19)	249/219	0.89 (0.70, 1.13)
Lifetime Cumulative Exposure[d]									
Low	401/340	0.95 (0.82, 1.12)	0.90 (0.77, 1.06)	128/97	0.92 (0.68, 1.25)	181/170	0.95 (0.75, 1.21)	93/73	0.80 (0.56, 1.13)
Medium	397/361	1.07 (0.91, 1.25)	0.98 (0.83, 1.15)	173/155	0.95 (0.73, 1.23)	162/154	1.03 (0.80, 1.32)	61/52	0.88 (0.59, 1.33)
High	397/384	1.15 (0.99, 1.35)	1.04 (0.89, 1.23)	152/145	1.07 (0.81, 1.41)	150/145	1.06 (0.82, 1.37)	95/94	0.98 (0.70, 1.36)
P-trend		0.08	0.85		0.87		0.70		0.68
Duration (Years)[e]									
>0 - <10	467/411	1.01 (0.87, 1.17)	0.93 (0.80, 1.09)	171/147	0.97 (0.75, 1.26)	192/180	0.94 (0.75, 1.19)	104/84	0.80 (0.57, 1.11)
≥ 10 - <25	313/276	1.03 (0.86, 1.22)	0.95 (0.79, 1.14)	131/100	0.81 (0.59, 1.10)	135/130	1.05 (0.80, 1.38)	47/46	1.06 (0.68, 1.65)
≥25	415/398	1.13 (0.97, 1.31)	1.03 (0.88, 1.22)	151/150	1.13 (0.86, 1.48)	166/159	1.06 (0.82, 1.36)	98/89	0.90 (0.64, 1.26)
P-trend		0.15	0.94		0.80		0.66		0.57

[a] Minimally-adjusted ORs (conditional logistic regression models stratified by age group (5-year) and study only).
[b] Fully-adjusted ORs (conditional logistic regression models stratified by age group (5-year) and study and adjusted for education, family history of prostate cancer, body mass index (kg/cm2), cigarette smoking, and race/ethnicity).
[c] Fully-adjusted ORs (conditional logistic regression models stratified by age group (5-year) and adjusted for education, family history of prostate cancer, body mass index (kg/cm2), cigarette smoking, and race/ethnicity).
[d] P*L*duration in years, cut points for all analyses: low (>0 - <9.43), medium (≥9.43 - <31.3), and high (≥31.3).
[e] Based on approximate tertiles according to the distribution amongst exposed controls.

those screened for prostate cancer in the last 2 years (results not shown). In time window analyses, findings were generally unchanged when stratified by time since last heat exposure (Appendix 5).

Table 3
Associations between occupational heat exposure and prostate cancer risk for high and low grade Gleason scores (OR: Odds Ratio; 95% CI: 95% Confidence Interval).

	Low grade prostate cancer (6 or 7 (3 + 4))		High grade prostate cancer (≥ 8 or 7 (4 + 3))	
	Control/ Cases (N)	OR (95% CI)	Control/ Cases (N)	OR (95% CI)
Never heat exposure	2317/1567	1 (ref)	2297/458	1 (ref)
Ever heat exposure	1195/796	0.96 (0.85, 1.09)	1192/280	1.03 (0.86, 1.23)
Lifetime Cumulative Exposure[a]				
Low	402/254	0.90 (0.75, 1.07)	401/86	0.99 (0.76, 1.28)
Medium	396/259	0.95 (0.79, 1.14)	394/98	1.09 (0.84, 1.40)
High	397/283	1.06 (0.88, 1.26)	397/96	1.02 (0.79, 1.33)
P-trend		0.89		0.70
Duration (Years)[b]				
> 0 - < 10	467/302	0.91 (0.77, 1.08)	466/108	1.05 (0.82, 1.33)
≥ 10 - < 25	313/204	0.97 (0.79, 1.18)	311/69	0.95 (0.71, 1.28)
≥ 25	415/290	1.03 (0.86, 1.23)	415/103	1.07 (0.83, 1.38)
P-trend		0.99		0.71

Fully-adjusted ORs (conditional logistic regression models stratified by age group (5-year) and study and adjusted for education, family history of prostate cancer, body mass index (kg/cm2), cigarette smoking, and race/ethnicity).
Overall p-value for heterogeneity (ever vs. never exposure) = 0.38.
[a] P*L*duration in years, cut points based on those of the controls overall.
[b] Based on approximate tertiles according to the distribution amongst exposed controls.

In analyses according to low and high Gleason scores (Table 3), no associations emerged. We also conducted additional analyses comparing associations in farm workers <5 years and those with longer farm work, with no evidence of associations in either category, nor of effect modification (results not shown).

Among the heat exposed workers in EPICAP, 38% had exclusively indoor heat exposed jobs, 28% had exclusively outdoor heat exposed jobs and 34% had a mix of indoor and outdoor heat exposed jobs. In an analysis comparing associations in indoor and outdoor heat exposed workers in EPICAP we found no associations between ever occupational heat exposure and prostate cancer in any category (results not shown).

When stratifying by other occupational exposures, there were also no associations observed among participants never or ever exposed to detergents (Appendix 6) or cadmium (Appendix 7). Slightly higher ORs were found among participants ever exposed to lead, but there was no evidence of an interaction between occupational heat and lead exposure (Appendix 8). In an analysis of participants ever exposed to PAHs, there were positive associations observed in the highest categories of lifetime cumulative heat exposure and duration of heat exposure, with evidence of exposure-response trends (Appendix 9), along with some evidence of an interaction between occupational heat exposure and occupational PAH exposure.

In the analysis of MCC-Spain using the Spanish JEM, MatEmEsp, (Table 4), ORs were slightly elevated for ever occupational heat exposure (OR 1.17; 95% CI 0.92, 1.47) and in the medium and high categories of lifetime cumulative exposure (ORs 1.27 95% CI 0.94, 1.72 and 1.20; 95% CI 0.87, 1.64; p-trend = 0.17 respectively) and duration (ORs 1.38; 95% CI 0.98, 1.95 and 1.24; 95% CI 0.94, 1.62; p-trend = 0.07 respectively).

In sensitivity analyses using different P-thresholds, exposure durations and lag years, results were generally unchanged (Appendix 10-12).

4. Discussion

In this large, pooled dataset, we assessed the potential association

Table 4
Association between occupational heat exposure and prostate cancer risk in the MCC-Spain study using a Spanish JEM (OR: Odds Ratio; 95% CI: 95% Confidence Interval).

	Controls/Cases (N)	OR (95% CI)
Never heat exposure	509/323	1 (ref)
Ever heat exposure	518/472	1.17 (0.92, 1.47)
Lifetime Cumulative Exposure[a]		
Low	173/130	1.08 (0.80, 1.44)
Medium	173/168	1.27 (0.94, 1.72)
High	172/174	1.20 (0.87, 1.64)
P-trend		0.17
Duration (Years)[b]		
> 0 - < 10	126/86	0.91 (0.65, 1.28)
≥ 10 - < 25	110/102	1.38 (0.98, 1.95)
≥ 25	282/284	1.24 (0.94, 1.62)
P-trend		0.07

Fully-adjusted ORs (conditional logistic regression models stratified by age group (5-year) and region and adjusted for education, family history of prostate cancer, body mass index (kg/cm2), cigarette smoking, and race/ethnicity).

[a] P*L*duration in years, cut points: low (>0 - <257), medium (≥257 - <727), and high (≥727).

[b] Based on approximate tertiles according to the distribution amongst exposed controls.

between occupational heat exposure and prostate cancer risk. In the overall analyses, we found no evidence to support our hypothesis.

When using the Spanish JEM instead of FINJEM to assign heat exposure estimates to MCC-Spain participants, some weak evidence for elevated ORs was observed, although CIs were wide, and there was no clear evidence for an exposure-response trend. There are a few possible explanations for the somewhat higher ORs observed when using a Spanish JEM with the MCC-Spain data. With MatEmEsp heat estimates applied to MCC-Spain, the five most common jobs among participants included three heat-exposed jobs, and occupations with the highest heat exposure were all plant and machine operators. In comparison, when applying FINJEM heat estimates, only one of the five most common jobs among participants was heat-exposed, and the most highly exposed jobs included firefighters and bakers, alongside plant and machine operator occupations. The average level of heat exposure was also greater when MatEmEsp heat estimates were applied in comparison to using the FINJEM (32.5 vs. 2 (L) (%)). Transformation of the original job codes to ISCO88 job codes for the pooled analysis could also have caused some misclassification errors.

The use of a JEM allowed us to identify details of concomitant chemical and physical exposures, a common occurrence in many occupations. We attempted to investigate possible interactions with some common occupational exposures, to gain insight into the effects of concomitant chemical and physical exposures. However, due to a low prevalence of exposure to other occupational agents, we had limited power. Stronger associations were observed here among participants ever occupationally exposed to PAHs, and there was some evidence of an interaction with occupational heat exposure. In total, 1000 (13%) participants were ever occupationally exposed to both heat and PAHs, comprising 32% of those ever occupationally exposed to heat. Occupations with both heat and PAH exposures included machine-tool operators, welders and flame cutters, miners and quarry workers, and ore and metal furnace operators. However, it is worth noting the majority of exposure to PAHs was from occupations with uncertain exposure (P of 5–25%). While we cannot speculate as to potential mechanisms underlying such an association, there is some evidence in the literature linking PAH exposure to prostate cancer (Rybicki et al., 2006) and future research could be useful.

There is as yet no consistent evidence linking occupational heat exposure to cancer risk. Although there are some studies of different cancer sites with divergent findings (Zhang et al., 1995; Cocco et al., 1998; Hinchliffe et al., 2021; Armstrong et al., 2000; Kauppinen et al., 1995; Alguacil et al., 2000; Santibañez et al., 2008, 2012; Rønneberg and Andersen, 1995; Weiderpass et al., 2003; Rønneberg et al., 1999). The present study largely documents the absence of an association with prostate cancer.

5. Strengths and limitations

Through the pooling of individual datasets, we were able to analyse a large number of histologically confirmed prostate cancer cases and frequency-matched controls with a relatively high occupational heat exposure prevalence. The study also benefited from the availability of Gleason scores and prostate cancer screening patterns, allowing us to explore factors that can influence the associations under study. We were able to adjust our analyses for the potential confounding effects of several other factors due to the availability of extensive information on sociodemographic and lifestyle characteristics on each participant. Participants were from the general population across multiple countries, and held a diverse range of occupations, reducing the likelihood for strong occupational related confounding and improving generalisability of the results.

However, as alluded to earlier, the use of a Finnish JEM to assign heat exposure estimates to participants in warmer climates may have resulted in some misclassification of heat exposure estimates and an attenuation of results. By applying standard occupational heat exposure estimates across the three countries, we were unable to consider possible differences in occupational heat exposure prevalence and intensity between countries, which could have introduced some misclassification errors (Lavoué et al., 2012). However, it is worth noting that all three countries are high income countries, which may make occupational heat exposures more comparable. The Finnish JEM, FINJEM, has also previously been applied successfully in epidemiological studies undertaken across many different countries (Kaupinnen et al., 2014).

In addition, the Finnish JEM estimates only covered the years 1995–2003, and exposures outside this period could have been misclassified to a greater extent. Some of the job titles in the JEM are non-specific and apply the same exposure estimates to each worker, despite potential differences in job tasks and environments. This could have caused further misclassification errors. Berkson errors could have arisen from assigning these group-based JEM exposures estimates instead of assigning individual level exposures (Oraby et al., 2018). However, the use of a JEM is favourable over self-reported exposures in some previous studies (above), as participants are assigned standardised exposure estimates which are less likely to be affected by recall bias.

Some of our results could have occurred by chance, as we have made multiple comparisons without adjusting sensitivity due to the exploratory nature of the analyses. Non-differential misclassification bias could also have affected the results due to our *a priori* definition of ever exposure to occupational heat exposure and the construction of multiple exposure indices. However, this appears to have had little influence, as sensitivity analyses with a variety of categories gave us similar results. The exclusion of a moderate number of participants here could have caused some selection bias. However, lifestyle characteristics of excluded participants were similar to those of included participants, so this is unlikely to have had a large impact. EPICAP had a higher control participation rate than the other two studies. This could have been due to differences in the recruitment process, as EPICAP used a survey institute specialised in population selection to recruit controls. Nevertheless, there were only marginal differences in census-based characteristics between participants and non-participants in PROtEuS, reassuring against selection bias in this study. Our exploratory analysis of ever and never farm work should be interpreted with caution. Pesticide exposure from farm work has previously been linked to various cancers including that of the prostate (Pluth et al., 2019) and pesticide exposure could also potentially be in the causal pathway between occupational heat exposure and prostate cancer risk. In harmonising the race/ethnicity variable, we were limited by the homogeneity of

race/ethnicity in MCC-Spain and EPICAP. However, we assessed the independent impact of adjusting for race/ethnicity in PROtEuS alone, which had a somewhat more heterogenous population, and results were unchanged. Education categories differed slightly between study populations, however access to the individual study data allowed us to harmonise these to the greatest extent possible. In MCC-Spain, due to differences in education level between cases and controls, we conducted an additional analysis stratified by low (less than primary or primary) and high (secondary or university) education using Spanish JEM heat estimates due to the substantially higher level of education among participating controls than among cases. Among those with a higher education level, somewhat higher ORs were observed in the highest categories of lifetime cumulative exposure and duration (Appendix 13). This is possibly due to differences in occupations between the groups. Participants with a lower education were more likely to have a heat exposed occupation. The five most common jobs among participants with a lower education were all heat exposed, whereas none of the five most common jobs among participants with a higher education were heat exposed. Participants with a lower education also had a higher proportion of the most highly heat exposed jobs compared to participants with a higher education.

6. Conclusions

Findings from this large-scale multi-country population-based study show little evidence for an association between occupational heat exposure and prostate cancer risk. Future studies focusing on the most highly exposed workers and based on individual assessments of exposure to heat considering differences in job characteristics may help uncover associations.

Author contributions

Alice Hinchliffe: Designed the study, conducted the analysis, and wrote the paper; **Juan Alguacil, Wendy Bijoux, Manolis Kogevinas, Florence Menegaux, Marie-Elise Parent, Beatriz Pérez Gomez:** Collected the data, participated in study design and preparation and review of the manuscript; **Sanni Uuksulainen:** Participated in exposure assessment and preparation and review of the manuscript; **Michelle Turner:** Designed the study, and wrote the paper. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

Ethics approval and consent to participate

All studies followed national and international directives on ethics and data protection [declaration of Helsinki and Spanish law on confidentiality of data (Ley Organica 15/1999 de 13 Diciembre de Proteccion de Datos de carácter personal LOPD)]. All subjects who agreed to participate and met the eligibility criteria signed an informed consent form before participating in the study. The protocols of each of the studies were approved by the Ethics committees of all participating institutions.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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References

Acharya, P., Boggess, B., Zhang, K., 2018. Assessing heat stress and health among construction workers in a changing climate: a review. Int. J. Environ. Res. Publ. Health 15 (2), 247.

Alguacil, J., Kauppinen, T., Porta, M., Partanen, T., Malats, N., Kogevinas, M., et al., 2000. Risk of pancreatic cancer and occupational exposures in Spain. PANKRAS II Study Group. Ann. Occup. Hyg. 44 (5), 391–403. Aug.

Armstrong, R.W., Imrey, P.B., Lye, M.S., Armstrong, M.J., Yu, M.C., Sani, S., 2000. Nasopharyngeal carcinoma in Malaysian Chinese: occupational exposures to particles, formaldehyde and heat. Int. J. Epidemiol. 29 (6), 991–998. Dec 1.

Barul, C., Parent, M.E., 2021. Occupational exposure to polycyclic aromatic hydrocarbons and risk of prostate cancer. Environ. Health 20 (1), 71. https://doi.org/10.1186/s12940-021-00751-w. PMID: 34154586; PMCID: PMC8218525.

Barul, C., Richard, H., Parent, M.-E., 2019. Night-shift work and risk of prostate cancer: results from a Canadian case-control study, the prostate cancer and environment study. Am. J. Epidemiol. 188 (10), 1801–1811. Oct 1.

Budd, G.M., 2008. Wet-bulb globe temperature (WBGT)—its history and its limitations. J. Sci. Med. Sport 11 (1), 20–32. Jan 1.

Castaño-Vinyals, G., Aragonés, N., Pérez-Gómez, B., Martín, V., Llorca, J., Moreno, V., et al., 2015. Population-based multicase-control study in common tumors in Spain (MCC-Spain): rationale and study design. Gac. Sanit. 29 (4), 308–315. Aug.

Cocco, P., Figgs, L., Dosemeci, M., Hayes, R., Linet, M.S., Hsing, A.W., 1998. Case-control study of occupational exposures and male breast cancer. Occup. Environ. Med. 55 (9), 599–604. Sep.

Cramer, M.N., Jay, O., 2016. Biophysical aspects of human thermoregulation during heat stress. Auton. Neurosci. 196, 3–13. Apr.

NIOSH, 2016. NIOSH criteria for a recommended standard: occupational exposure to heat and hot environments. By Jacklitsch B, Williams WJ, Musolin K, Coca A, Kim J-H, Turner N. Cincinnati. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication 2016-10, OH.

De Silva, F., Alcorn, J., 2022. A tale of two cancers: a current concise overview of breast and prostate cancer. Cancers 14 (12), 2954. Jan.

Demers, P.A., DeMarini, D.M., Fent, K.W., Glass, D.C., Hansen, J., Adetona, O., Andersen, M.H., Freeman, L.E.B., Caban-Martinez, A.J., Daniels, R.D., Driscoll, T.R., Goodrich, J.M., Graber, J.M., Kirkham, T.L., Kjaerheim, K., et al., 2022. Carcinogenicity of occupational exposure as a firefighter. Lancet Oncol. 23 (8), 985–986. Aug 1.

Gao, C., Kuklane, K., Östergren, P.-O., Kjellstrom, T., 2018. Occupational heat stress assessment and protective strategies in the context of climate change. Int. J. Biometeorol. 62 (3), 359–371. Mar.

Garcia, A., González-Galarzo, M.C., Kauppinen, T., Delclos, G., Benavides, F., 2013. A job-exposure matrix for research and surveillance of occupational health and safety in Spanish workers: MatEmESp. Am. J. Ind. Med. 56. Oct 1.

Gharibi, V., Khanjani, N., Heidari, H., Ebrahimi, M.H., Hosseinabadi, M.B., 2020. The effect of heat stress on hematological parameters and oxidative stress among bakery workers. Toxicol. Ind. Health 36 (1), 1–10. Jan 1.

Kühn, S., 2022. Global Cancer Observatory [Internet]. [cited, 2022 May 30]. Available from: https://gco.iarc.fr/.

Kühn, S., 2019. Global employment and social trends. World Employ. Soc Outlook 2019 (1), 5–24.

Heled, Y., Fleischmann, C., Epstein, Y., 2013. Cytokines and their role in hyperthermia and heat stroke. J. Basic Clin. Physiol. Pharmacol. 24 (2), 85–96.

Hinchliffe, A., Kogevinas, M., Pérez-Gómez, B., Ardanaz, E., Amiano, P., Marcos-Delgado, A., et al., 2021. Occupational heat exposure and breast cancer risk in the MCC-Spain study. Cancer Epidemiol. Biomarkers Prev. 30 (2), 364–372. Feb.

IARC (International Agency for Research on Cancer), 2020. Night Shift Work. IARC Monogr Identif Carcinog Hazards Hum 124, 1–371.

IARC (International Agency for Research on Cancer), 2012. Arsenic, Metals, Fibres, and Dusts. IARC Monogr Identif Carcinog Hazards Hum 100c, 1–527.

IARC (International Agency for Research on Cancer), 2012c. Radiation. IARC Monogr Eval Carcinog Risks Hum 100D, 7–303.

INE, 2022. Instituto Nacional de Estadística. INE [Internet]. [cited 2022 Mar 30]. Available from. https://www.ine.es/index.htm.

Kantidze, O.L., Velichko, A.K., Luzhin, A.V., Razin, S.V., 2016. Heat stress-induced DNA damage. Acta Naturae 8 (2), 75–78.

Kaupinnen, T., Uuksulainen, S., Saalo, A., Mäkinen, I., Pukkala, E., 2014. Use of the Finnish information system on occupational exposure (FINJEM) in epidemiologic, surveillance, and other applications. Ann. Occup. Hyg. 58 (3), 380–396. Jan 8.

Kauppinen, T., Partanen, T., Degerth, R., Ojajärvi, A., 1995. Pancreatic cancer and occupational exposures. Epidemiology 6 (5), 498–502. Sep.

Lavoué, J., Pintos, J., Van Tongeren, M., Kincl, L., Richardson, L., Kauppinen, T., Cardis, E., Siemiatycki, J., 2012. Comparison of exposure estimates in the Finnish job-exposure matrix FINJEM with a JEM derived from expert assessments performed in Montreal. Occup. Environ. Med. 69 (7), 465–471. Jul.

Leon, L.R., 2008. Thermoregulatory responses to environmental toxicants: the interaction of thermal stress and toxicant exposure. Toxicol. Appl. Pharmacol. 233 (1), 146–161. Nov 15.

Menegaux, F., Anger, A., Randrianasolo, H., Mulot, C., Laurent-Puig, P., Iborra, F., et al., 2014. Epidemiological study of prostate cancer (EPICAP): a population-based case-control study in France. BMC Cancer 14, 106. Feb 19.

Mullins, J.K., Loeb, S., 2012. Environmental exposures and prostate cancer. Urol. Oncol. 30 (2), 216–219. Apr.

Nunfam, V.F., Van Etten, E.J., Oosthuizen, J., Adusei-Asante, K., Frimpong, K., 2019. Climate change and occupational heat stress risks and adaptation strategies of mining workers: perspectives of supervisors and other stakeholders in Ghana. Environ. Res. 169, 147–155. Feb 1.

Oraby, T., Sivaganesan, S., Bowman, J.D., Kincl, L., Richardson, L., McBride, M., et al., 2018. Berkson error adjustment and other exposure surrogates in occupational case-control studies, with application to the Canadian INTEROCC study. J. Expo. Sci. Environ. Epidemiol. 28 (3), 251–258. May.

Papantoniou, K., Castaño-Vinyals, G., Espinosa, A., Aragonés, N., Pérez-Gómez, B., Burgos, J., et al., 2015. Night shift work, chronotype and prostate cancer risk in the MCC-Spain case-control study. Int. J. Cancer 137 (5), 1147–1157. Sep 1.

Pernar, C.H., Ebot, E.M., Wilson, K.M., Mucci, L.A., 2018 Jan. The epidemiology of prostate cancer. Cold Spring Harb Perspect Med (12), 8, 12 a030361.

Pluth, T.B., Zanini, L.A.G., Battisti, I.D.E., 2019. Pesticide exposure and cancer: an integrative literature review. Saúde debate 43 (122), 906–924. Sep.

Rawla, P., 2019. Epidemiology of prostate cancer. World J. Oncol. 10 (2), 63–89. Apr.

Rønneberg, A., Andersen, A., 1995. Mortality and cancer morbidity in workers from an aluminium smelter with prebaked carbon anodes–Part II: cancer morbidity. Occup. Environ. Med. 52 (4), 250–254. Apr.

Rønneberg, A., Haldorsen, T., Romundstad, P., Andersen, A., 1999. Occupational exposure and cancer incidence among workers from an aluminum smelter in western Norway. Scand. J. Work. Environ. Health 25 (3), 207–214. Jun.

Rosenbaum, P.F., Vena, J.E., Zielezny, M.A., Michalek, A.M., 1994. Occupational exposures associated with male breast cancer. Am. J. Epidemiol. 139 (1), 30–36. Jan 1.

Roti Roti, J.L., 2008. Cellular responses to hyperthermia (40–46 ° C): cell killing and molecular events. Int. J. Hyperther. 24 (1), 3–15. Jan.

Rybicki, B.A., Neslund-Dudas, C., Nock, N.L., Schultz, L.R., Eklund, L., Rosbolt, J., et al., 2006. Prostate cancer risk from occupational exposure to polycyclic aromatic hydrocarbons interacting with the GSTP1 Ile105Val polymorphism. Cancer Detect. Prev. 30 (5), 412–422. Jan 1.

Sallmén, M., Uuksulainen, S., 2019. O5D.5 Construction of Finnish ISCO-88 job exposure matrix: examination of dataset with two different classification of occupations in consecutive censuses. Occup. Environ. Med. 76 (Suppl. 1), A48–A49. Apr 1.

Santibañez, M., Vioque, J., Alguacil, J., Barber, X., 2008. García de la Hera M, Kauppinen T, PANESOES Study Group. Occupational exposures and risk of oesophageal cancer by histological type: a case-control study in eastern Spain. Occup. Environ. Med. 65 (11), 774–781. Nov.

Santibañez, M., Alguacil, J., de la Hera, M.G., Navarrete-Muñoz, E.M., Llorca, J., Aragonés, N., et al., 2012. Occupational exposures and risk of stomach cancer by histological type. Occup. Environ. Med. 69 (4), 268–275. Apr.

Smith, M.T., Guyton, K.Z., Kleinstreuer, N., Borrel, A., Cardenas, A., Chiu, W.A., et al., 2020. The key characteristics of carcinogens: relationship to the hallmarks of cancer, relevant biomarkers, and assays to measure them. Cancer Epidemiol. Biomarkers Prev. 29 (10), 1887–1903. Oct.

StataCorp, 2021. Stata Statistical Software: Release 17. StataCorp LLC, College Station, TX.

Turner, M.C., Benke, G., Bowman, J.D., Figuerola, J., Fleming, S., Hours, M., et al., 2014. Occupational exposure to extremely low-frequency magnetic fields and brain tumor risks in the INTEROCC study. Cancer Epidemiol. Biomarkers Prev. 23 (9), 1863–1872. Sep.

Venugopal, V., Krishnamoorthy, M., Venkatesan, V., Jaganathan, V., Occupational Heat Stress, S.F.D.P., Dna damage, Shock, Heat, 2018. Protein - A Review. Medical Research Archives (1), 6. Jan 15.

Weiderpass, E., Vainio, H., Kauppinen, T., Vasama-Neuvonen, K., Partanen, T., Pukkala, E., 2003. Occupational exposures and gastrointestinal cancers among Finnish women. J. Occup. Environ. Med. 45 (3), 305–315. Mar.

Wendeu-Foyet, M.G., Bayon, V., Cénée, S., Trétarre, B., Rébillard, X., Cancel-Tassin, G., et al., 2018. Night work and prostate cancer risk: results from the EPICAP Study. Occup. Environ. Med. 75 (8), 573–581. Aug 1.

Zhang, Z.F., Vena, J.E., Zielezny, M., Graham, S., Haughey, B.P., Brasure, J., et al., 1995. Occupational exposure to extreme temperature and risk of testicular cancer. Arch. Environ. Health 50 (1), 13–18. Feb.