Occupational heat exposure and cancer risk

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ABSTRACT

Heat exposure is a well-known occupational health hazard prevalent in many workplaces. In recent years, it has become a growing concern for various workers around the world, as climate change causes global average temperatures to rise and there is an increased frequency and intensity of extreme weather events, such as heatwaves. Heat exposure has been linked to a number of key carcinogenic processes. Despite this, current epidemiological evidence on occupational heat exposure and cancer risk is limited, and potential risks have not been examined in detail.

The aim of this thesis was to evaluate associations between occupational heat exposure and the risk of female breast and colorectal cancer in a Spanish population-based multi-case-control study, as well as the risk of prostate cancer in a large international pooled case-control study. This thesis also aimed to examine potential interactions of exposure to occupational heat and other common occupational agents.

Occupational heat exposure was assessed using the lifetime occupational history of participants in combination with job exposure matrix (JEM) estimates. Three heat exposure indices were evaluated: ever, lifetime cumulative exposure and duration of exposure. The reference group for all analyses was never occupational heat exposure. Occupational heat exposure was associated with an increased risk of female breast cancer, particularly for hormone receptor positive tumours. There was no evidence of an association

between occupational heat exposure and the risk of prostate or colorectal cancer overall, though there were some positive associations among females for colorectal cancer. Differences in heat exposed occupations, variations in thermoregulatory response and uncontrolled confounding may partly explain these results. There was some evidence for potential interactions between exposure to occupational heat and some other common occupational exposures. There is a need for larger studies focussing on the most highly exposed workers, in order to further examine potential associations.

RESUMEN

La exposición al calor es un ampliamente conocido factor de riesgo para la salud laboral, frecuente en muchos lugares de trabajo. En los últimos años, se ha convertido en una preocupación creciente para numerosos trabajadores de todo el mundo, ya que el cambio climático provoca un aumento de las temperaturas medias globales y se observa una mayor frecuencia e intensidad de fenómenos meteorológicos extremos, como las olas de calor. La exposición al calor se ha relacionado con una serie de procesos cancerígenos clave. A pesar de ello, la evidencia epidemiológica actual sobre la exposición al calor en el trabajo y el riesgo de padecer cáncer es limitada, y los riesgos potenciales no se han examinado en detalle.

El objetivo de esta tesis fue evaluar las asociaciones entre la exposición laboral al calor y el riesgo de cáncer de mama y colorrectal en mujeres dentro de un estudio poblacional español casos-control, así mismo como el riesgo de cáncer de próstata en un gran estudio internacional caso-control. Esta tesis también pretendía examinar las posibles interacciones de la exposición laboral al calor y otros agentes laborales comunes.

La exposición laboral al calor se evaluó utilizando el historial laboral vital de los participantes en combinación con las estimaciones de la matriz de exposición laboral (JEM). Se evaluaron tres índices de exposición al calor: nunca, exposición acumulada a lo largo de la vida y duración de la exposición. El grupo de referencia para todos los análisis fueron aquellos que nunca sufrieron exposición laboral al calor. La exposición laboral al calor en el trabajo se asoció con un

mayor riesgo de cáncer de mama en mujeres, en particular para los tumores de tipo receptor hormonal positivo. No hubo muestras de una asociación global entre la exposición laboral al calor y el riesgo de cáncer de próstata o colorrectal, aunque en mujeres hubo algunas asociaciones positivas con el cáncer colorrectal. Diferencias en las ocupaciones laborales, variaciones en la respuesta termorreguladora y factores de confusión no controlados podrían explicar parcialmente estos resultados. Hubo algunos indicios de posibles interacciones entre la exposición al calor ocupacional y algunas otras exposiciones ocupacionales comunes. Es necesario llevar a cabo estudios de mayor tamaño centrados en los trabajadores más expuestos, con el fin de examinar más a fondo las posibles asociaciones.

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PREFACE

This thesis has been written at the Barcelona Institute for Global Health (ISGlobal), Barcelona, Spain between October 2018 and December 2022 under the supervision of Dr. Michelle C Turner. It includes a compilation of three scientific articles (2 published and 1 under review). The thesis complies with the procedures and regulations of the Doctoral Programme in Biomedicine of the Department of Medicine and Life Sciences of the Pompeu Fabra University, Barcelona, Spain.

The objective of the thesis was to investigate the association between occupational heat exposure and the risk of various cancers: female breast, prostate, and colorectal. The present thesis contributes to the limited current knowledge on occupational heat exposure and the risk of cancer. The thesis begins with an introductory chapter outlining what is currently known about cancer and occupational heat exposure. This is followed by a discussion of the gaps in the current knowledge as a rationale for the thesis objective. Subsequently, the 3 scientific articles are included, which all incorporate data from the MCC-Spain study: a large population-based multicase-control study. Finally, the thesis includes a general discussion of the findings and how they compare with existing evidence, strengths and limitations, and future research recommendations.

For this thesis, the PhD candidate has worked on multiple steps of epidemiological research including cleaning and preparation of data, data analysis, co-ordination of pooled studies, interpretation of

results, preparation of scientific articles for publication, and research dissemination at both national and international conferences. In addition to the 3 scientific articles included in this thesis, the PhD candidate has been working on another scientific article investigating the association between occupational heat exposure and the risk of stomach cancer in a large, multi-national pooled case-control study. The PhD candidate has also undertaken a research stay (March 2019) at Monash University, Department of Epidemiology and Preventive Medicine (Melbourne, Australia) under the supervision of Prof. Malcolm Sim and Dr. Deborah Glass.

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1. INTRODUCTION

1.1. Occupational Health Context

Research on occupational health, and the implementation of measures to protect the health of workers dates back centuries[1]. Occupational health risks were first recognised in ancient times but became a greater concern during the industrial revolution in 18th century Great Britain[2]. During this time, an increasing number of people began working in factories, mills, and mines, where dangerous machinery and exposure to chemicals caused a huge rise in work-related accidents and diseases[2]. In response, the first labour organisations were formed, and regulations were introduced to protect the health and safety of workers[1].

Since then, work environments and conditions have been continuously changing in both the developed and developing world due to globalisation, rapid technological innovation, and an altering demographic of workers[3,4], and new occupational health hazards continue to emerge[5]. Through extensive research, a wide range of occupational hazards have been identified, including exposures to a variety of chemical and biological agents, physical factors, and psychosocial risks. The International Labor Organization (ILO) and the World Health Organization (WHO) have developed standards and guidelines to promote occupational health and safety and improve working conditions[6]. However, occupational health strategies remain inadequate in many countries and working conditions for many workers do not meet the international standards[7].

Occupational hazards still contribute substantially to the global burden of disease. Globally, there are over 350 million non-fatal occupational accidents recorded each year, and an estimated 2.8 million people die annually from work-related causes, accounting for 5-7% of all global fatalities[8,9]. The major cause of work-related deaths across the world is occupational diseases, including circulatory and respiratory diseases and cancer[8,9]. It is estimated that around 32% of all work-related deaths worldwide are due to occupational cancer, and 2-8% of all cancers may be attributable to occupational exposures[10,11]. A large proportion of the agents currently classified by the International Agency for Research on Cancer (IARC) as human carcinogens are found in occupational settings[10,11].

1.2. Cancer Epidemiology

1.2.1. Breast Cancer

According to the World Health Organisation, breast cancer is currently the world's most prevalent cancer[12]. In 2020, 2.26 million new breast cancer cases were diagnosed globally and there were an estimated 0.7 million breast cancer attributable deaths. Among females, breast cancer accounts for 1 in 4 of all cancer cases and 1 in 6 cancer deaths. In Spain, it is estimated that nearly 30% of all new cancer cases (118,691) among females in 2020 were breast cancer[13]. The worldwide breast cancer burden is predicted to increase to approximately 3.2 million new cases and over 1 million deaths by 2040. The developed world has some of the highest incidence rates of breast cancer[13], but incidence rates are rapidly increasing in

developing countries. This increase is partly explained by a growing and aging population, lifestyle changes such as diet and physical inactivity, sociocultural changes including changes in reproductive factors, and an increase in the proportion of women in the industrial workforce[14].

Breast cancer has multiple biological and clinical subtypes. Hormone receptor positive luminal-like tumours, characterised by high genetic expression of the oestrogen receptor, are the most common breast cancer subtype, accounting for 60-70% of all breast cancers[15]. Less common breast cancer subtypes include human epidermal growth factor receptor-2 positive tumours and triple negative tumours, which generally have poorer clinical outcomes[15].

Breast cancer risk is multifactorial with established risk factors including age, family history, genetics, and hormonal and reproductive factors. Despite the extensive research on breast cancer aetiology, these established risk factors only explain <40% of the burden of disease[16]. The risk of developing breast cancer increases with age, with most breast cancers occurring in women over the age of 50 years[17]. Family history is known to be strongly related to breast cancer risk. Women with breast cancer in their first-degree family have around twice the risk of developing breast cancer compared to those with no family history of breast cancer in a first degree relative[18]. This gives strong evidence for the genetic link to the disease. Around 20-25% of hereditary breast cancers and 5-10% of all breast cancers are due to inherited genetic mutations of recognised breast cancer genes; mainly

BRCA1 (BReast CAncer gene one) and *BRCA2* (BReast CAncer gene two)[19,20].

Reproductive and hormonal factors have consistently been shown to be associated with breast cancer risk. An increased risk of developing breast cancer has been linked to early menarche, late menopause and nulliparity, along with the use of combined hormone therapy after menopause[17]. Current or recent use of hormonal contraceptives is also associated with an increased breast cancer risk, and the risk increases with the duration of use[21]. In contrast, a lower breast cancer risk is found for those with a higher parity and those with an early age of first full-term birth[22].

Lifestyle is considered an increasingly important contributing factor to breast cancer aetiology, with obesity, diet, physical inactivity, smoking, and alcohol consumption identified as potential risk factors. Obesity has been identified as a breast cancer risk factor in postmenopausal women and it is estimated that around 20% of all postmenopausal breast cancers may be attributable to obesity[23]. Obesity is also associated with poor prognosis and decreased survival rate in breast cancer patients[24]. However, a high BMI has been linked to a lower risk of breast cancer among premenopausal women[25]. It has been suggested that a high-fat, high-calorie intake could be linked to an increased risk of breast cancer, although no strong consistent association has been found[26]. Being physically active as an adult appears to reduce breast cancer risk, irrespective of BMI, with stronger evidence for postmenopausal than premenopausal breast cancer[27]. Evidence on the role of cigarette smoking in breast cancer

has been inconsistent, although more recent studies support a moderate positive association between breast cancer risk and duration and intensity of cigarette smoking[28]. Alcohol is known to be a strong risk factor for breast cancer and studies have reported a consistent dose–response effect of alcohol on the risk of breast cancer, even at lower levels of consumption[29].

The International Agency for Research on Cancer (IARC) has classified a number of occupational exposures as potential female breast cancer risk carcinogens, based on limited evidence in humans, including ethylene oxide, dieldrin (insecticide), polychlorinated biphenyls, and night shift work[30]. Other occupational factors that have also been linked to an elevated breast cancer risk include exposure to ionising radiation, solvents and sedentary work[31]. Exposure to X- and Gamma-radiation is an established breast cancer risk factor in humans[30].

1.2.2. Prostate Cancer

Prostate cancer is the second most frequent malignancy amongst males worldwide, with approximately 1.4 million new cases and almost 0.4 million deaths in 2020[13,32]. Among males, prostate cancer accounts for 1 in 5 of all cancer deaths globally[33]. In Spain, more than 20% of all new cancer cases (34,613) among males in 2020 were prostate cancer[13]. By 2040 the worldwide prostate cancer burden is expected to grow to almost 2.3 million new cases and 0.7 million deaths[34]. Approximately 12.5% of men will be diagnosed with prostate cancer at some point during their lifetime[35]. More than 90%

of diagnosed prostate cancers are acinar adenocarcinomas, which develop in the gland cells that line the prostate gland[36]. The remaining 5-10% of prostate cancers are non-acinar tumours, including various histological subtypes such as ductal adenocarcinoma, basal cell carcinoma and neuroendocrine tumours[36].

The aetiology of prostate cancer remains elusive and currently the only established risk factors are age, ethnicity, genetic factors, and family history. Prostate cancer is more common amongst older males, with a median age at diagnosis of 67 years[35]. Males of African descent are 2 to 3 times more likely to be diagnosed with prostate cancer than white males and are often diagnosed at a younger age[37]. Many studies have demonstrated prostate cancer is more frequent in men with a family history of prostate cancer. Hereditary factors account for up to 42% of the prostate cancer risk and numerous genes associated with prostate cancer have been identified[38]. Other proposed risk factors for prostate cancer include alcohol consumption, smoking, diet, physical inactivity and diabetes[39], but current evidence is inconclusive. IARC has also classified various other factors as possible prostate carcinogens[30], including cadmium, arsenic, night shift work, red meat consumption, firefighting, and work in the rubber manufacturing industry, although there is limited evidence in humans.

Internationally there are substantial disparities in prostate cancer incidence and mortality rates[40]. Among the regions with the highest incidence rates in 2020 were Northern/Western Europe and

Australia/New Zealand. The regions with the lowest rates were South America and Southern, Central and Eastern Europe[13]. This is likely a result of differences in genetic risks between ethnicities and differences in medical care, in particular early detection, and prostate cancer screening with prostate-specific antigen tests[41]. It could also reflect differences in socioeconomic, environmental and lifestyle factors[42].

Steroid hormones, particularly androgens, are also suspected to play a major role in human prostate carcinogenesis. Testosterone is the principle circulating androgen in males. Within the prostate, testosterone is metabolised to dihydrotestosterone (DHT), a more potent androgen[43]. The prostate is dependent on these androgens and androgen receptors for normal development and function. Research has shown androgens acting via androgen receptors are also critical for the growth and survival of prostate cancer cells[44], and due to the androgen dependency of the prostate, androgen deprivation therapies have emerged as the standard treatment for aggressive prostate cancer[45]. Despite this, there is still some debate about the precise relationship between androgens and prostate cancer[46].

1.2.3. Similarities between breast and prostate cancer

Breast and prostate cancer are the two most common cancers among males and females combined, and in 2020 they accounted for a fifth of all new cancer cases worldwide[13]. The aetiology of these cancers is complex and still not well understood but the highly correlated incidence rates in many countries suggests they may share similar

features and characteristics[47,48]. Sex steroid hormones (androgens in males and oestrogens in females) play a critical role in the development and progression of both breast and prostate carcinogenesis[49]. Both cancers also have a high heritability, estimated to be around 31% for breast cancer and 58% for prostate cancer, and have been linked to mutations in the BRCA1 and BRCA2 genes[50]. Evidence suggests they may also be influenced by similar environmental and lifestyle factors[51,52].

1.2.4. Colorectal Cancer

Colorectal cancer is the third most commonly diagnosed and the second most deadly cancer worldwide[13]. There were almost 2 million new colorectal cancer cases and 1 million colorectal cancer attributable deaths in 2020[13]. In Spain, nearly 15% (40,441) of all new cancer cases diagnosed in 2020 were colorectal cancer[13]. It is predicted that by 2040 the worldwide colon cancer burden will grow to nearly 2 million new cases and over 1 million deaths, and the rectal cancer burden will grow to approximately 1.2 million and more than 550,000 deaths[13]. Around two-thirds of all colorectal cancer cases occur in high-income regions such as Europe, Australia/New Zealand, and North America[53]. However, colorectal cancer incidence is rapidly rising in low- and middle-income countries, due to the adoption of an increasingly westernised lifestyle, including changes in diet and the prevalence of overweight and obesity[54].

The term colorectal cancer encompasses both colon and rectal cancers. These cancers are often merged as they share many

biological and clinical features[55]. The most common type of colorectal cancer are adenocarcinomas, which emerge in the glandular, epithelial cells of the colon and rectum. Other less common types include carcinoid tumours, gastrointestinal stroma tumours, lymphomas and sarcomas[56].

The majority of colorectal cancer is sporadic and largely attributable to modifiable risk factors[57] such as obesity, alcohol consumption, tobacco smoking, a sedentary lifestyle and poor diet, including high red and processed meat, low fibre, low whole grain and low calcium[57,58]. Other, non-modifiable factors associated with higher colorectal cancer risk include age, inflammatory bowel disease (IBD), and family history of colorectal cancer[57]. Colorectal cancer is more frequently diagnosed in the elderly. More than 50% of colorectal cancers are diagnosed after age 70, and only 10% are diagnosed before age 55[58]. However, over the last several decades there has been a rising incidence of early-onset colorectal cancer among individuals <50 years of age and by 2030 early-onset colorectal cancer is expected to rise by more than 140%[59]. People with IBDs, such as ulcerative colitis and Crohn's disease, are 2–6 times more likely to develop colorectal cancer than the general population due to sustained inflammation and oxidative stress[60]. Family history as a risk factor encompasses both shared environmental risk and genetic risk[61]. Around 2-5% of all colorectal cancers occur as a result of hereditary syndromes including hereditary nonpolyposis colorectal cancer (Lynch syndrome) and familial adenomatous polyposis (FAP), among others[62].

CRC incidence rates are approximately 30% higher in men than in women, while mortality rates are approximately 40% higher. These disparities are not fully understood but are thought to be a result of hormonal factors, testing rates and lifestyle and environmental exposures[63]. Colorectal cancer is also more common among African Americans, although research has shown this is predominantly due to differences in medical care such as screening uptake and treatment, and disparities in modifiable risk factors[57].

Various occupational factors have also been classified as colorectal cancer carcinogens by IARC. Based on sufficient evidence in humans, exposure to ionising radiation increases the risk of colon cancer. Additionally, there is limited evidence linking exposure to asbestos and night shift work, and work as a firefighter, to an increased colorectal cancer risk[30].

1.3. Heat exposure

1.3.1. Thermoregulation and heat stress

The human thermoregulatory system maintains normal core body temperature at around 37°C through a balance of endogenous heat production and heat dissipation to the surrounding environment[64]. The primary mechanisms for heat dissipation are cutaneous vasodilation and sweating. Cutaneous vasodilation increases skin blood flow, which boosts convective heat transfer from the core to the peripheral surface[65]. Sweating cools the skin through evaporation and increases the temperature gradient from the core to the skin to further promote heat transfer[66]. Under certain circumstances, the thermal load posed by the environment or by intense exercise can

overwhelm the thermoregulatory system. In these situations, heat balance cannot be achieved, and the core body temperature rises, leading to heat stress[67]. The health consequences of heat stress range from heat exhaustion and dehydration to cardiovascular and chronic kidney diseases[65,68,69]. In extreme cases, heat stress can lead to multiple organ dysfunction and progression to death[70].

1.3.2. Occupational heat exposure

Heat exposures and risks of heat stress can be a serious problem for workers. Outdoor occupations such as agriculture, construction, transport, tourism, and sports are particularly vulnerable, as they regularly contend with hot and humid climatic conditions while undertaking high levels of physical activity[65]. Workers in indoor settings near furnaces, ovens, and boilers, such as bakers and factory workers, are also at risk if temperature levels inside are not regulated properly with adequate air conditioning or proper ventilation[71]. Occupational heat exposures and heat stress is projected to intensify in the future as climate change is causing global average temperatures to rise and increasing the frequency and intensity of extreme weather events, such as heat waves[71,72]. This will affect both outdoor occupations and indoor occupations with inadequate temperature control[73]. Those who already work in hot environments in hot climates will be greater affected. Workers in large cities are also likely to be more impacted compared to rural workers due to the urban heat island effect (i.e., built-up areas releasing heat absorbed during the day and night)[74].

1.3.3. Occupational heat stress risks

Four key environmental factors contribute to occupational heat exposure and a worker's risk of heat stress: high air temperatures, radiant heat (e.g., from the sun or a furnace), elevated humidity, and low air movement[75]. Evaporation of sweat from the skin is the only method of heat loss from the body in ambient heat at or above 34-37°C[76]. When air humidity is high, and air movement is low, sweat evaporation is greatly reduced, causing the core body temperature to rise[77]. In many occupations, heat exposure is further compounded by high levels of physical exertion such as heavy lifting and manual labour, which produces metabolic heat, further contributing to the risk of heat stress[78]. In some occupations, the requirement to wear heavy semipermeable or impermeable protective clothing, causes further problems as it impedes heat loss through evaporation and convection[75].

A variety of personal factors can also increase the vulnerability of the individual worker to heat stress when exposed to heat. Workers over the age of 65 are at greater risk of heat stress due to a decrease in thermoregulatory ability caused by changes in sweating, blood flow to the skin and cardiovascular function[79]. Older workers are also more likely to have certain medical conditions, such as heart disease, and use prescription medications, which both contribute to inefficient thermoregulation and heat intolerance[80]. The hydration status of a worker also influences the risk of experiencing heat stress. In hot environments, workers can become dehydrated if they do not adequately replace body fluids lost through excess sweating[81].

Dehydration causes reductions in sweating function and cutaneous vasodilation, resulting in core temperature rises[82]. Workers who are more physically fit develop physiological adaptations (increased cardiac function, plasma volume, and microvascular function) which improve thermoregulatory and cardiovascular performance during exercise and heat stress[83]. Regularly performing physical activities also improves sweating function, contributing to enhanced thermoregulatory ability[84]. Individual characteristics, such as body fat content, body mass and surface area to mass ratio can also affect a person's thermoregulatory capability[67]. Fat tissue has different heat transfer properties compared with muscle and can potentially have an insulating effect[84]. A larger body mass allows for greater distribution of internal heat, making heavier people less vulnerable to developing heat stress[67]. Those with a higher surface area to mass ratio will experience more heat gain through convection and radiation when air temperature exceeds skin temperature[65,84].

Heat acclimatisation also greatly influences an individual workers physical response to heat and their ability to cope with heat exposures[85]. Heat acclimatisation refers to the complex process of physiological adaptations that occur due to repeated elevations in body temperature from either physical activity, high temperatures, or a combination of both[86]. These adaptations include improved thermoregulatory responses such as earlier onset of sweating, greater sweat production, reduced electrolyte loss in sweat and increased cutaneous vasodilation, along with increased blood volume and reduced cardiovascular strain[85]. In general, heat acclimatisation is obtained after exposure to heat for 10-14 days in succession[87]. Heat

acclimatised workers have lower core and skin temperatures and a reduced heart rate at the same work level and environmental temperatures, reducing their risk of developing heat stress[88].

1.3.4. Occupational heat assessment

To protect workers from the effects of heat exposure, heat stress indices and protective guidelines have been developed. To date, more than 45 heat stress indices have been developed, but no one single heat stress index has gained universal acceptance[89]. Examples of current heat stress indices are the effective temperature, the heat stress index, the predicted heat strain, the index of thermal stress and the wet bulb globe temperature (WBGT). WBGT is among the most widely used heat stress indices in occupational settings globally[90]. It incorporates air temperature, humidity, air speed, and radiant heat, all of which are important in understanding the heat exchange between a person and the environment. WBGT is estimated as a weighted average of the natural wet-bulb, black globe, and air temperatures[91]. It is generally measured using a heat stress monitor with specialised sensors but can also be estimated indirectly from models that calculate the required WBGT inputs from standard meteorological station measurements of air temperature, humidity, wind speed, barometric pressure, and, when available, radiant heat load[91,92].

The WBGT has been established as an international standard for the assessment of heat stress by the ISO (International Organization for Standardization), and it serves as the metric upon which the heat stress standard ISO 7243 for determining ergonomic effects of

thermal environments is based[93]. The ISO 7243 standard provides a simple convenient method to evaluate the degree of heat stress to which a person is exposed[94]. It provides WBGT reference values (exposure limits) for maximum occupational heat exposures. The WBGT value used in the standard is a weighted average, over time and space, and is measured over a period of maximum heat stress[95]. For time variations (e.g. in metabolic rate or WBGT) a time-weighted average is taken over a period of work/resting of one hour[94]. WBGT reference values in ISO 7243 vary based on different work intensities (metabolic rate measured in watts per unit skin area) and the acclimatisation status of the worker[91]. Standard WBGT reference values are based on workers wearing cotton clothing, with a low thermal insulation, but in the case of other clothing conditions, a correction clothing adjustment factor can be added[72]. When assessing occupational heat exposures, the WBGT value of the hot environment is compared to these WBGT reference values in the ISO 7243. If the levels exceed the reference values, the strain on the workers must be reduced and a more detailed analysis undertaken[94]. The WBGT thresholds for 'safe' hourly continuous work range from 31°C for light intensity work to 25.5°C for very heavy intensity work, although these values change slightly when different levels of rest time are required[96].

1.3.5. Occupational heat regulations in Spain

The Spanish National Institute for Occupational Safety and Health has developed specific legislation aimed at preventing heat-related occupational accidents and illnesses in Spain. In closed work

environments, the temperature should range between 17°C and 27°C for sedentary work and between 14°C and 25°C for light manual work, and relative humidity must be between 30-70%, except in places where there are risks due to static electricity, where the lower limit must be 50%[97]. No specific temperatures or guidelines are provided for heavier manual work indoors or for outdoor work, but it is expected that all employers take responsibility to provide a working environment that minimises health and safety risks to workers[97].

1.4. Heat exposure and cancer mechanisms

Several plausible mechanisms linking occupational heat exposure to cancer have been proposed. In continuation some of the main mechanisms will be discussed.

1.4.1. Key characteristics of human carcinogens

The existing epidemiologic evidence suggests heat stress displays some of the key characteristics of human carcinogens[98]. Firstly, heat stress is genotoxic and can act as a DNA damaging agent. Heat stress can directly induce both single-stranded (SSB) and double-stranded (DSB) DNA breaks in a cell cycle phase–dependent manner[99]. In the S phase of the cell cycle, heat stress leads to SSBs through inhibition of the DNA replication process. Heat stress induced DSBs occur primarily in non-S-phases of the cell cycle, although the mechanisms of their formation due to heat stress are still not clear[100,101]. Another key characteristic is the induction of oxidative stress. Heat stress causes a disproportionate increase of reactive oxygen species in cells

relative to the antioxidant capacity[102]. This oxidative imbalance can result in DNA mutation and oxidative DNA damage[103]. Both are key events in carcinogenesis. Heat stress has also been linked to chronic inflammation. The body's inflammatory response to heat stress causes an over-secretion of proinflammatory cytokines[104]. If sustained over a long period of time this can degenerate into chronic inflammation, which further contributes to oxidative stress and DNA damage[105]. Heat stress triggers the HSF1-mediated stress response which induces the expression of high levels of heat shock proteins (HSPs)[106]. This stress response and HSPs play important roles in protecting cells against damage[107]. However, HSPs are commonly overexpressed in tumour cells, and they have been shown to protect cells from apoptosis by interrupting cell death and inactivation pathways, ultimately inducing tumorigenesis[108]. Finally, heat stress has been shown to disrupt proteins involved in virtually all DNA repair pathways, resulting in the accumulation of damaged DNA. This causes increased mutagenesis and genomic instability, thereby promoting carcinogenesis[109].

1.4.2. Concomitant Exposures

An additional consideration when assessing the relationship between occupational heat exposure and cancer risk is the possibility that occupations involving exposures to high temperatures are likely to have concomitant chemical exposures[110]. Exposures to certain chemicals, such as lead and metallic oxides, can affect the human thermoregulatory system, making workers more susceptible to heat stress[111]. The physiological responses that occur during heat stress,

such as increased ventilation rate, sweating, and skin blood flow, can also impact the absorption, metabolism, and toxicity of chemicals[110]. The skin represents a primary route of exposure for environmental toxicants and the function of this organ is heavily altered during heat exposure[111]. An increased respiratory rate can also enhance the amount of chemicals that are inhaled and absorbed into the body. Dehydration, as a result of excess fluid loss through sweating, also affects the concentration of chemicals in the body which has a significant impact on chemical toxicity[111]. In addition, many workers who are exposed to high temperatures may remove protective clothing due to discomfort which puts them at further risk of chemical exposure and absorption[110]. Heat exposure has been shown to increase toxicity to several environmental toxicants including carbon monoxide, heavy metals (nickel, cadmium, lead), and organic solvents[111]. Some of these agents have previously been linked to an increased risk of multiple cancers including lung, stomach, prostate, and breast cancer[112,113].

1.4.3. Diet

Another plausible mechanism specific to gastrointestinal cancers involves diet. Those working under conditions of heat stress excrete large quantities of salt during excess sweating. To maintain the balance of salt in the body, heat exposed workers consume much greater quantities of salt than the WHO recommended safe daily level of 6g per person per day[114]. There is some limited evidence linking a high dietary salt intake with an increased risk of colorectal cancer[115,116].

1.5. Current Knowledge

There is limited evidence regarding occupational heat exposure and cancer risk. Previous studies investigating occupational heat exposure and various cancers have had mixed results.

1.5.1. Occupational heat exposure and female breast cancer risk

To the best of our knowledge, only one previous paper has investigated potential associations between occupational heat exposure and female breast cancer risk. Between 1971 and 1995 Weiderpass et al[117] carried out a cohort study, as part of the Women's Occupational Cancer Study in Finland, to evaluate associations between occupational exposures and the incidence of pre-menopausal (age less than 50 years at diagnosis) and postmenopausal (50 or more years) breast cancers in Finland. The study incorporated 892,591 women from the 1970 census of Finland who reported having an occupation considered to be their main source of income. The cohort was followed up for cancer incidence through emigration, death, or the end date of the study, whichever came first, through the Finnish Cancer Registry. Occupations recorded in the census were converted to job codes according to the Nordic Classification of Occupations and the International Classification of Occupations. A probability (estimated proportion of exposed) and mean level among exposed for 31 chemicals and 2 ergonomic agents, including heat, was subsequently applied to each occupation using the Finnish job exposure matrix (FINJEM). The study performed two separate analyses. The first considered occupations with a probability ≥ 20%

as exposed for each agent. In the second analysis, exposure to each agent was calculated as the product of level and probability and was divided into three categories: zero, low and medium/high. The study reported no association between occupational heat exposure and either pre-or post-menopausal breast cancer in the first analysis. In the second analysis, a significant inverse association between low and medium/high levels of occupational heat exposure and female breast cancer risk was found among pre-menopausal women, but no clear association was observed among post-menopausal women. A limitation of this study was the use of census data to obtain job-titles at one point in time, which could have introduced some misclassification errors. There was also insufficient adjustment for confounders.

1.5.2. Occupational heat exposure and prostate cancer risk

As far as we know, no previous studies have investigated the link between occupational heat exposure and prostate cancer. Studies on occupational heat exposure and other male androgen-related cancers have had mixed results.

In 1998 a case-control study[118] of 178 cases of male breast cancer and 1041 controls was undertaken in the United States with the aim of evaluating the role of various occupational exposures on male breast cancer. The study used data from the United States national mortality follow-back survey, which collected information on sociodemographic, lifestyle, and occupational factors (longest worked occupation and industry) from proxy respondents of a 1%

sample of all 1986 deaths among subjects aged 25–74 years. Estimates of the probability and intensity level of occupational heat exposure were applied to each occupation with a job exposure matrix based on occupation and industry codes from the United States 1980 census of population. The study found no associations between either the probability and intensity of occupational heat exposure and the risk of male breast cancer. However, the number of participants exposed to heat was small (14 cases; 101 controls) and the complete work histories of participants was not available which could have caused exposure misclassification.

In contrast, another case-control study of 71 male breast cancer cases and 256 controls undertaken in 1994[119] observed an elevated risk of male breast cancer for those ever-having occupational heat exposure compared to those never exposed (OR fully adjusted model 2.5; 95% CI 1.02, 6.0). This study recruited histologically confirmed male breast cancer cases from the New York State Tumour Registry. Controls, frequency matched by race, diagnosis/screening date, and 5-year age groups, were selected from a free, voluntary cancer screening clinic. Occupational data, including the usual occupation, company name and type of work done, was collected from the cancer registration card for cases and the screening clinic questionnaire for controls. Job title and employer name were also collected from city directories. Job titles were subsequently assigned using the Dictionary of Occupational Titles. Occupational heat exposure was assigned using a schema detailing selected characteristics of occupations and ever being exposed was defined as having held at least one job with “extremes of heat plus temperature change both

inside and outdoors". However, exposure assessment was quite crude and, again, the number of participants classified as heat exposed was small (9 cases; 20 controls).

Another case-control study of 250 pathologically confirmed testicular cancer cases and 250 controls undertaken in 1995[120] observed a positive association between high (≥80°F) (OR 1.68; 95% CI 1.18, 2.40) temperature exposure at work and testicular cancer risk. The study recruited pathologically confirmed testicular cancer cases from the New York State Tumour Registry. Controls, matched by 2- or 5-year age groups, were selected from the neighbourhood of residence of each case. Detailed interviews were conducted by trained personnel to collect information on sociodemographic, occupational, and other potential risk factors. Information on occupational heat exposure was collected by asking participants a series of questions, including if they were ever exposed to higher-than-normal temperatures at work (≥80°F), how often they were exposed, and for how long. The method of exposure assessment is an important limitation in this study, as it is difficult to assess the validity of self-reported occupational exposures.

1.5.3. Occupational heat exposure and gastrointestinal cancer risk

Previous studies have investigated occupational heat exposure and various gastrointestinal cancers.

The PANESOES project is a hospital-based case-control study designed to explore the influence of major lifestyles and diet on the risk of three gastrointestinal cancers: stomach, oesophageal and

pancreatic. The study aimed to recruit approximately 200 cases of oesophageal cancer, 200 cases of pancreatic cancer and 400 cases of stomach cancer, along with 400-450 controls. Cases and controls between 30-80 years old were recruited concurrently from participating hospitals. Controls, frequency matched to cases by age, sex, and province, were selected from diseases not related to the main exposures of interest. Information on sociodemographic, lifestyle and occupational factors (main occupation, job title, number of years worked) was collected in face-to-face interviews by trained interviewers. Occupational heat exposure estimates were assigned using the FINJEM, and exposure to heat was calculated as the product of probability and level of exposure and was categorised into high, low, and unexposed. No significant associations were observed between occupational heat exposure and the risk of stomach cancer[121], oesophageal cancer[122] or pancreatic cancer[123]. Limitations of these studies include consideration of only the main occupations (i.e., the longest held), low numbers of participants occupationally exposed to heat and the lack of relevant exposure information, such as duration, in the occupational heat exposure metric.

A cohort study of female workers in Finland, also undertaken as part of the Women's Occupational Cancer Study in Finland (above), observed no significant associations between low and medium/high levels of occupational heat exposure and oesophageal, stomach, colon, rectum, liver, gallbladder, or pancreatic cancer, although relative risks were elevated for liver cancer in the medium/high level of heat exposure[124].

Another Finnish study of 595 incident cases of pancreatic cancer and 1622 controls undertaken in 1995 found a positive though imprecise association of occupational heat stress and pancreatic cancer risk (OR 2.2; 95% CI 0.8, 6.6)[125]. The study identified deceased pancreatic cancer cases and deceased controls who had developed other forms of cancers (stomach, colon or rectal) from the Finnish Cancer Register. A postal questionnaire was sent to the next-of-kin to obtain information on participants' lifestyle factors and lifelong work histories. The first analysis was undertaken using occupational heat exposure estimates assigned to occupational histories by an experienced industrial hygienist. The second analysis assigned a probability (none/low/high) and level (none/low/high) of occupational heat exposure with a job exposure matrix (JEM) created in the United Kingdom. A limitation here is that occupational histories collected from the next-of-kin may not be entirely accurate which could lead to misclassification errors. Occupational heat exposure could also be linked to the other cancers that the controls had contracted, which may introduce bias into the study.

Another case-control study of 185 pancreatic cancer cases and 264 controls undertaken between 1992 and 1995 observed no significant association between occupational heat exposure and pancreatic cancer[126]. Cases and controls were recruited concurrently from five general hospitals in Spain. Controls were patients who had been admitted to the same hospitals as cases with pancreatitis, other benign pathologies, or other cancers. Trained personnel conducted interviews to collect information on participants' clinical history, lifestyle, and occupational history. Based on the occupational history,

the FINJEM was used to assign participants occupational heat exposure as either substantial, low, or unexposed. Some limitations of this study include the use of hospital controls, which can introduce selection bias and the problem of some controls having other forms of cancer, which could attenuate the results.

1.5.4. Occupations and cancer risk

Rather than evaluating exposure to specific occupational agents, such as heat, some previous studies have investigated potential associations between a range of occupational titles and different cancers. A population-based study of 1230 breast cancer cases and 1315 controls undertaken in France in 2011 observed an increased risk of breast cancer among some workers with a high risk of heat stress, including textile workers, rubber and plastic product makers, labourers, and manufacturing workers[127]. A study of 1937 prostate cancer cases and 1994 controls undertaken in Canada in 2016 found an excess risk of prostate cancer among workers in heat exposed occupations, including the paper products industry, wood industry, steel industry, forestry and logging and textile processing[128]. However, for other typically heat exposed jobs, including farmers and workers in the food and beverage service, such as cooks and waiters, no associations were observed. Another case-control study of 819 prostate cancer cases and 879 controls undertaken in France in 2022 also found no excess risk of prostate cancer for farmers and food and beverage service workers, along with other heat exposed occupations including firefighters, blacksmiths, machine-tool operators, and heavy and toxic metal workers[129]. A cohort study of

693,501 men and 231,858 women undertaken in Sweden in 2002 observed an increased risk of stomach cancer among engineers, miners and quarrymen, masonry and concrete workers, heavy labourers, metal processing workers, glass and ceramic workers, waiters, launderers and dry cleaners and firefighters, all occupations where heat exposures are common[130]. On the other hand, the study found no associations among farmers, a typically heat exposed occupation, although heat exposures among farmers in Sweden may be less common due to the milder climate. A case control study of 443 stomach cancer cases and 479 controls undertaken in Poland in 2005 found higher risks of stomach cancer in some heat exposed occupations including male fabricated metal products workers and workers in construction and leather goods industries[131]. In a large cohort study undertaken in five Nordic countries in 2009 associations between a wide range of occupations and various cancers were examined[132]. An increased risk of gastrointestinal cancers and breast cancer was found among a variety of heat exposed occupations including waiters and cooks, construction workers, smelter and metal foundry workers, construction workers and miners. The study did not observe any associations between heat exposed occupations and prostate cancer risk. There were also no associations found for any cancers among farmers or forestry workers, but again, heat exposures in these occupations may be less common in Nordic countries. Another study undertaken in Britain in 2010 also analysed the associations between occupations and cancer[133]. The study found a higher incidence of cancer in occupations with a greater risk of heat

stress including construction, metal working, mining, farming, and several manufacturing sectors.

2. RATIONALE FOR STUDY

Anthropogenic climate change has caused global average temperatures to rise rapidly over the past few decades. The last decade was the warmest on record, and temperatures are projected to continue rising over the coming years[134]. The frequency and intensity of extreme weather events, including heat waves, is also projected to increase[135]. Heat is a well-known occupational health hazard[72]. The effects of climate change will undoubtedly impact the prevalence, distribution, and severity of heat exposures in a range of workplaces[75], putting more workers at risk of developing heat stress[136].

Mechanisms have been proposed which could link heat stress to carcinogenesis, and there is some evidence in the literature that suggests occupational heat exposure might be associated with an increased risk of cancer. However, the current evidence is limited, and results have been inconsistent. In the majority of existing studies occupational heat exposure was not considered as the primary focus of the study. Instead, a range of occupational exposures were evaluated concurrently. Consequently, potential cancer risks from occupational heat exposure have not been examined or discussed in detail. Low occupational heat exposure prevalence is also a common limitation in many existing studies, which can reduce the power to detect an association[137]. No previous studies to our knowledge have examined possible interactions between occupational heat exposure and other occupational exposures, despite research showing heat exposures can increase chemical absorption and toxicity. In studies

examining only occupational titles and cancer risk, it is difficult to identify the relevant exposures in jobs with an increased risk, especially considering many jobs involve exposures to multiple agents. Furthermore, there is little current evidence on occupational heat exposure and the risk of cancer.

There is a need to update the evidence and add to the current limited knowledge on occupational heat exposure and cancer risk. Research needs to focus specifically on occupational heat exposure and examine associations with cancer in more depth to gain a clearer understanding. It is also important to investigate potential interactions between occupational heat exposure and other occupational exposures. The availability of a large general population dataset in Spain with detailed information on lifetime occupational history and a relatively high heat exposure prevalence, combined with access to a country-specific JEM gave us the opportunity to conduct further research on this topic and overcome many of the limitations of previous studies.

3. OBJECTIVES

The primary objective of this thesis was to assess the possible association between occupational heat exposure and the risk of three different types of cancer: breast, prostate, and colorectal. To evaluate this, the following specific objectives were developed:

- To investigate the association between occupational heat exposure and breast cancer risk among females in the MCC-Spain study (Paper I).

- To investigate the association between occupational heat exposure and prostate cancer risk in a large, pooled dataset of three studies across three different countries: Spain, France, and Canada (Paper II).

- To investigate the association between occupational heat exposure and colorectal cancer risk in the MCC-Spain Study (Paper III)

A fourth paper is in preparation to evaluate occupational heat exposure and stomach cancer risk in a large, pooled dataset. This work is not presented as part of the thesis here but has been part of the work undertaken by the candidate during the last few years and is nearing completion.

Hypothesis: Exposure to heat at work increases the risk of developing cancer.

4. METHODS

4.1. Studies

This chapter provides a summary of the datasets used in the three papers this thesis is based on. The MCC-Spain data was used across all three papers, but for Paper II, where there was an existing consortium for prostate cancer, data was pooled to increase sample size and the quality of the study.

4.1.1. The Multi-Case Control (MCC)-Spain Study

The MCC-Spain study[138] is a population-based multicase-control study undertaken between 2008 and 2013 in 23 collaborating hospitals across 12 Spanish provinces (Asturias, Barcelona, Cantabria, Girona, Granada, Gipuzkoa, Huelva, León, Madrid, Murcia, Navarra, and Valencia). The study aimed to assess the influence of environmental, lifestyle and genetic factors on common tumours (breast, prostate, gastric, colorectal, chronic lymphocytic leukaemia).

All newly diagnosed histologically confirmed cancer cases were recruited from collaborating hospitals and invited to participate through telephone contact. A common set of population controls, frequency matched to all cases by age, sex, and region, was randomly selected from primary care health centres located within the hospitals' catchment areas. To minimise non-participation, five potential participants were selected at random for each control needed. If the first person on the list could not be contacted after a minimum of 5 attempts at different times throughout the day, the next

person was contacted. All participants had to be between 20 and 85 years old, have resided in the catchment area for at least 6 months prior to recruitment and be able to answer the epidemiological questionnaire. On average, the response rate was 71% for breast cancer cases, 74% for prostate cancer cases and 68% for colorectal cancer cases. In controls, the mean response rate was 53%.

A structured computerised epidemiological questionnaire was administered by trained personnel in face-to-face interviews. Information was collected on socio-demographic and lifestyle factors, and lifetime occupational history for each participant. Occupational questions were included on specific job titles, tasks, exposures, and timing of each job. Jobs were subsequently coded by two experts following the Spanish National Classification of Occupations (CNO-94).

4.1.2. Prostate Cancer and Environment Study (PROtEus)

PROtEus[139,140] is a large population-based case-control study conducted in Montreal, Canada, between 2005 and 2012 to assess the role of environmental factors in prostate cancer risk. Newly diagnosed histologically confirmed prostate cancer cases, were selected from pathology departments across seven French hospitals in Montreal. Controls, frequency-matched to cases in 5-year age groups, were randomly recruited from the electoral list of French speaking men residing in the same districts as cases. Eligible subjects were men, aged ≤75 years at the time of diagnosis/recruitment, residents of the greater Montreal area, registered on Quebec's

permanent electoral list and Canadian citizens. Study participants represented 79.4% of eligible prostate cancer cases and 55.5% of eligible controls.

Face-to-face interviews were conducted to collect information on sociodemographic, lifestyle and medical factors and a complete occupational history for all participants. A detailed description of each job held for at least 2 years was collected including information on job tasks, timing, and use of specific products. Occupations were subsequently coded according to the 1971 Canadian Classification and Dictionary of Occupations.

4.1.3. Epidemiological study of prostate cancer (EPICAP)

EPICAP (Epidemiological study of prostate cancer)[141] is a French population-based case-control study conducted between 2012 and 2014. The study aimed to investigate the role of environmental, occupational, and genetic factors on the risk of prostate cancer. Eligible cases were patients newly diagnosed with histologically confirmed prostate cancer between 2012-2013, <75 years of age and resident in the department of Hérault at diagnosis. Cases were identified by clinical research nurses, recruited, and trained specifically for the study in all participating centres: 3 public hospitals and 3 private urology clinics. Controls, frequency matched by age, were selected from the general population of cancer free men who were resident in the department of Hérault at the time of the cases' diagnoses. Quotas by socioeconomic status (SES) were calculated from the census data available in each study area and set a

priori to control for potential selection bias arising from differential participation rates across SES categories. Participation rates were 75% for cases and 79% for controls.

Cases and controls were face-to-face interviewed by a specially trained, experienced clinical research nurse. Information was collected on sociodemographic characteristics, a full professional and residence history, lifestyle and leisure activities, and personal and family medical history. For each occupation of more than 6 months, information was gathered on starting and finishing dates, a description of the job and tasks involved, and the name and address of the company. For some specific jobs, a more detailed questionnaire was answered by participants. An industrial hygienist subsequently coded the job titles blinded to the subject's case/control status using the International Standard Classification of Occupations (ISCO) 1968.

4.2. Heat Exposure Assessment

Two different JEMs were used to assign occupational heat exposure to study participants. These JEMs are described in more detail below.

4.2.1. Matriz Empleo-Exposición Española (MatEmEsp)

MatEmEsp[142] is a Spanish JEM covering the period between 1996-2005. The JEM contains exposure estimates for a wide range of occupational agents and conditions (chemical, physical, and biological agents, ergonomic risk factors, psychosocial risk factors, safety hazards, employment conditions, and socio-demographic

characteristics). Occupations are coded according to the Spanish Classification of Occupations (CNO94). MatEmEsp was created through the adaptation of the FINJEM exposure estimates (below). A panel of five actively employed industrial hygienists with extensive experience in company-based industrial hygiene measurements in Spain revised exposure estimates from FINJEM to more accurately represent the levels of exposure for each job title amongst Spanish workers. MatEmEsp provides estimates of the proportion of workers exposed (P) and the levels of exposure (L) for each agent and job title. For heat, the level of exposure is considered as the average yearly proportion of working time with heat stress. Heat exposure is defined as continuous exposure or exposure for significant periods (e.g. certain times of the year) to heat from natural or artificial sources which exceeds the specific WBGT indices of ISO 7243. Heat exposure estimates are only provided for occupations where at least 5% of the workers had exposures to temperatures exceeding the WBGT thresholds.

4.2.2. Finnish Job Exposure Matrix (FINJEM)

The FINJEM is one of the most widely used JEMs of all currently available JEMs[143]. In our study the FISCO88-FINJEM 2019 version of the FINJEM was used. This JEM includes 390 major occupational groups and incorporates a range of chemical and physical exposures, including heat[144]. Exposure estimates in the FINJEM were derived by a team of over 20 experts from the Finnish Institute of Occupational Health. The JEM covers the period 1995-2009, with estimates divided into five sub-periods of three years. For each agent

and time period, two exposure metrics are provided: the proportion of exposed workers (P) (expressed as a percentage) and the level of exposure (L) among the exposed workers in the occupation (in agent specific units)[145]. For heat, the level of exposure is given as the proportion of annual working time spent in heat. Occupational heat exposure is considered as exposure to heat from natural or artificial sources continuously exceeding 28°C or reference values of the WBGT-index. In our study, an existing crosswalk was used to convert job codes from the original Finnish version of ISCO88 International Standard Classification of Occupations 1988 (FISCO88) of the JEM to standard 4-digit ISCO88 codes, before applying the JEM to participants' occupations.

4.3. Statistical Analysis

We estimated odds ratios (ORs) and 95% confidence intervals (CIs) for the association between each type of cancer and three different occupational heat exposure indices: ever, lifetime cumulative exposure and duration of exposure. Using JEM estimates in combination with *a priori* knowledge, ever occupational heat exposure was defined as ever having held at least one job with a $P \geq 25\%$ and with an exposure duration of at least one year. We deemed participants 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. To allow for a possible cancer latency period, an *a priori* lag of 5 years was applied to all analyses. 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. Those only exposed to occupational heat in the 5 years before interview/diagnosis date were considered unexposed. For each job with a P≥25% according to the above definition, lifetime cumulative exposure was calculated as the sum of the product of P, L, and duration. Duration was calculated as the sum of the duration of occupational heat exposure. Duration and lifetime cumulative exposure were then categorised into tertiles according to the distribution among exposed controls. 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. We evaluated the impact of adjusting for multiple potential confounding variables and conducted a variety of subgroup analyses. We also evaluated potential interactions between occupational heat exposure and exposure to a range of other occupational agents. Finally, we conducted sensitivity analyses to explore the effect of the *a priori* ever occupational heat exposure definition on the results.

5. RESULTS

5.1. Paper I

Occupational heat exposure and breast cancer risk in the MCC-Spain study

5.2. Paper II

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

5.3. Paper III

Occupational heat exposure and colorectal cancer risk in the MCC-Spain study

5.1. Paper I

Occupational Heat Exposure and Breast Cancer Risk in the MCC-Spain Study

Hinchliffe A, Kogevinas M, Pérez-Gómez B, Ardanaz E, Amiano P, Marcos-Delgado A, Castaño-Vinyals G, Llorca J, Moreno V, Alguacil J, Fernandez-Tardón G, Salas D, Marcos-Gragera R, Aragonés N, Guevara M, Gil L, Martin V, Benavente Y, Gomez-Acebo I, Santibáñez M, Ángel Alba M, García AM, Pollán M, Turner MC.

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Occupational Heat Exposure and Breast Cancer Risk in the MCC-Spain Study

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Background: Mechanisms linking occupational heat exposure with chronic diseases have been proposed. However, evidence on occupational heat exposure and cancer risk is limited.

Methods: We evaluated occupational heat exposure and female breast cancer risk in a large Spanish case–control study. We enrolled 1,738 breast cancer cases and 1,910 frequency-matched population controls. A Spanish job-exposure matrix, MatEmEsp, was used to assign estimates of the proportion of workers exposed ($P \geq 25\%$ for at least 1 year) and work time with heat stress (wet bulb globe temperature ISO 7243) for each occupation. We used three exposure indices: ever versus never exposed, lifetime cumulative exposure, and duration of exposure (years). We estimated ORs and 95% confidence intervals (CI), applying a lag period of 5 years and adjusting for potential confounders.

Results: Ever occupational heat exposure was associated with a moderate but statistically significant higher risk of breast cancer (OR 1.22; 95% CI, 1.01–1.46), with significant trends across categories of lifetime cumulative exposure and duration ($P_{trend} = 0.01$ and 0.03, respectively). Stronger associations were found for hormone receptor–positive disease (OR ever exposure = 1.38; 95% CI, 1.12–1.67). We found no confounding effects from multiple other common occupational exposures; however, results attenuated with adjustment for occupational detergent exposure.

Conclusions: This study provides some evidence of an association between occupational heat exposure and female breast cancer risk.

Impact: Our results contribute substantially to the scientific literature. Further investigations are needed considering multiple occupational exposures.

Introduction

The human thermoregulatory system maintains core body temperature at approximately 37°C. Excessive heat exposure increases body temperature, putting this system under stress (1). Heat stress can cause acute illnesses such as heat stroke (2). Heat stress can also cause DNA damage and inhibit the DNA repair system (3). This triggers the heat shock response, causing the release of heat shock proteins (HSP) designed to minimize cell damage (4). In certain conditions, HSPs protect cells from apoptosis by interrupting cell death and inactivation pathways (5). This may provide an enabling environment for cells with damaged DNA to survive and multiply, resulting in tumorigenesis (6, 7). Specific HSPs, such as HSP90, are thought to play a key role in breast tumorigenesis (8).

Heat exposures are prevalent in many occupations. Outdoor workers, such as farmers, face hot and humid climatic conditions (9), and

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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indoor workers, such as chefs, experience heat from equipment, and minimal air flow. In addition, workers contend with elevated metabolic heat production from physical activity and inhibited sweating from personal protective equipment (10, 11). Occupational heat exposures are predicted to rise due to climate change. Workers in countries already experiencing high temperatures, such as Spain, will likely be greater affected (12, 13).

Evidence on occupational heat exposure and cancer risk is limited. A cohort study by Weiderpass and colleagues (14) reported a significant inverse association between occupational heat exposure and female breast cancer risk in premenopausal women, but no clear association in postmenopausal women. However, job titles were recorded from a cross-section in time, and census data were used. Misclassification errors could have occurred. Other studies investigating different cancer types have conflicting results. Significant positive associations were reported between occupational heat exposure and nasopharyngeal (15), testicular (16), pancreatic (17), and male breast cancer (18), and nonsignificant positive associations were found for esophageal (19), kidney (20), and liver cancer (21). In contrast, no associations were observed for male breast (22), stomach (23), kidney (24), and pancreatic cancer (25) in other work. These studies have limitations such as small sample sizes, low exposure prevalence, and consideration of only the longest/most recent occupation. Current evidence is limited, and further studies are needed.

In this study, we analyzed associations between female breast cancer risk and ever occupational heat exposure, lifetime cumulative exposure, and duration of exposure in a large Spanish dataset, addressing key limitations of previous studies. Here, information on the lifetime cumulative exposure of a large number of female breast cancer cases and controls with a relatively high occupational heat exposure prevalence was obtained. We also explored possible interactions between occupational heat exposure and other occupational exposures, along with their potential confounding effects.

Materials and Methods

MCC-Spain study

The MCC-Spain study is a multicenter, population-based, case–control study undertaken between 2008 and 2013 (www.mccspain.org; ref. 26). Histologically confirmed cases of cancer of the breast, prostate, colorectum, stomach, and chronic lymphocytic leukemia, and population controls were recruited from 23 different hospitals across 12 regions of Spain.

Newly diagnosed female breast cancer cases, ages 23 to 85, were recruited from 18 hospitals in 10 regions of Spain. Controls, frequency matched by age, sex, and region, were identified from primary health care centres located in the same area as hospitals from which cases were recruited. Controls were invited to participate by telephone. All participants had to have resided in the area for at least 6 months prior to recruitment and be able to complete the epidemiologic questionnaire.

In total, 1,738 breast cancer cases and 1,910 controls were eligible and completed the questionnaire. The response rate was 71% for cases and 53% on average for controls. We excluded participants who were exclusively housewives, as housework was not included in the job exposure matrix (JEM; $N = 392$; 12.8% of controls, 9.0% of cases). We also excluded other participants who had missing occupational information ($N = 60$; 1.8% of controls, 1.5% of cases), and those with a previous personal history of cancer ($N = 126$; 4.1% of controls, 4.1% of cases).

The MCC-Spain study followed the 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 gave written informed consent before participating in the study. The protocol of MCC-Spain was approved by the ethics committees of all participating institutions.

Data collection

A computerized questionnaire was administered by trained personnel in face-to-face interviews. Detailed occupational information for all jobs held for at least 1 year was obtained, along with a thorough personal and family medical history and information on other risk factors such as age, education level, and reproductive and menstrual factors.

Occupational heat exposure assessment

Two experts coded job titles following the Spanish National Classification of Occupations (CNO94). Occupational heat exposure was subsequently assigned using the Spanish JEM, MatEmEsp (27), which provides estimates of the proportion (P) of workers exposed and level (L) of exposure for multiple occupational agents and conditions, including heat. In MatEmEsp, heat estimates were adapted from the Finnish JEM, FINJEM by an expert panel of local industrial hygienists. The level of exposure to heat is considered as the proportion of working time with heat stress, defined as exposure to heat above specific wet bulb globe temperature indices determined in ISO 7243, an international standard for the assessment of thermal environments. MatEmEsp covers the period from 1996 to 2005.

Statistical analysis

Wilcoxon rank-sum and χ^2 tests were used to compare distributions of risk factors for breast cancer between cases and controls and between participants never and ever exposed to occupational heat. We defined three main exposure indices for the analyses: ever versus never exposed, lifetime cumulative exposure, and total duration of exposure.

Duration of occupational heat exposure was defined as the sum of duration of exposure for each job with a $P \geq 25\%$, according to the below definition of ever occupational heat exposure. Duration years were rounded to the nearest half year. Overlapping jobs were considered part-time and duration was split equally between them. Duration was categorized *a priori* into 1 to 5 years, >5 to 10 years, and >10 years.

Ever occupational heat exposure was defined *a priori* as having held at least one job with a $P \geq 25\%$ and with an exposure duration of at least 1 year. To balance sensitivity and specificity, participants with a $P \geq 5\%$ and <25%, or who were exposed for less than 1 year were considered to have uncertain exposure and were excluded from the analysis (32 controls, 60 cases). To allow for a possible cancer latency period, an *a priori* lag of 5 years was applied to all analyses. Therefore, all exposures in the 5 years before interview date for controls and diagnosis date for cases were not considered. Those only exposed to occupational heat in the 5 years before interview/diagnosis date were considered unexposed.

Lifetime cumulative exposure was calculated as the sum of the product of P, L, and duration, for jobs with a $P \geq 25\%$ according to the above definition. Lifetime cumulative exposure was categorized into tertiles according to the distribution among exposed controls.

We estimated ORs and 95% confidence intervals (CI) for the association between the different occupational heat exposure indices

and breast cancer risk using two-tailed unconditional logistic regression models, with a significance level of 5%. The reference group for all analyses was participants never exposed to occupational heat. Basic models adjusted for age (as a continuous variable), region, and socioeconomic score (constructed using participants' education level, social class by occupation and parents' socioeconomic status, SES; ref. 26). A directed acyclic graph and a priori knowledge were used to identify other potential confounders. All models were also adjusted for cigarette smoking (never smoker, ex-smoker, and current smoker), family history of breast cancer in a first-degree relative (yes/no/missing), physical activity in free time (inactive, a little active, moderately active, and very active), body mass index (BMI), menopausal status, parity (no children, 1–2, and ≥3), oral contraceptive use (never vs. ever), and diabetes (yes/no). We created a missing indicator as a third category for family history of breast cancer to include participants with missing information. We excluded participants with missing information on any of the other variables (13 cases, 22 controls). Ordinal variables were taken as continuous to test for linear trends, using unexposed participants as the reference category.

We conducted a range of sensitivity analyses. We adjusted models for education level as an alternative to socioeconomic score, with little change in findings. We also considered alcohol and dietary variables, constructed of scores assigned according to adherence to the World Cancer Research Fund recommendations for cancer prevention (28). These variables made minimal difference to the results and had a high percentage of missing (11%), so were not included in the final models. We further adjusted models for other occupational exposures including physical activity at work (sedentary, a little active, moderately active, quite active, very active), night shift work (ever vs. never), and a range of other common occupational exposures (organic dusts, metals, inorganic mineral dusts, pesticides, polycyclic aromatic hydrocarbons, organic solvents, detergents, ionizing radiation, formaldehyde, sulfur gases, engine exhaust, toxic fumes). We conducted subgroup analyses by categories of menopausal status, cigarette smoking, socioeconomic score, age at first exposure, and breast cancer subtypes. Breast cancer cases were classified into three subtypes based on local pathology reports: (i) hormone receptor–positive: tumors with luminal human EGFR 2 negative ($Erb2^-$) and estrogen receptor positive (ER^+) or progesterone receptor positive (PR^+); (ii) Erb2 positive: tumors with luminal human EGFR 2 positive ($Erb2^+$) irrespective of estrogen or progesterone receptor results; (iii) triple negative: tumors with ER^-, PR^-, and $Erb2^-$. We also tested for interactions between occupational heat exposure and a range of factors including menopausal status, cigarette smoking, socioeconomic score, and common occupational exposures, according to the likelihood ratio test. Finally, we explored the effect of *a priori* decisions on the results. In addition to the default P of ≥25%, exposure duration of at least 1 year and lag period of 5 years, we analyzed alternative threshold combinations. We investigated P thresholds of ≥5% and ≥50%, an exposure duration of at least 5 years and lag periods of 1 and 10 years.

All statistical analyses were performed using Stata SE (version 16.1; ref. 29).

Data availability

The database was registered in the Spanish Agency for Data Protection, number 2102672171. Permission to use the database will be granted to researchers outside the study group after revision and approval of each request by the Steering Committee. More information can be found at https://www.mccspain.org/.

Results

Table 1 shows distributions of characteristics between the 1,389 cases and 1,434 controls retained for analysis. Controls were older than cases [57.2 years; standard deviation (SD) 12.8 vs. 54.9 years; SD 11.9], more frequently postmenopausal (67.0% vs. 61.6%) and had higher parity. More controls had never smoked (55.2% vs. 51.1%) and fewer reported a family history of breast cancer (8.9% vs. 15.5%).

Approximately 21.9% of controls and 26.7% of cases ever had occupational heat exposure (**Table 2**). Among those exposed, the average duration of exposure was 10.6 years (SD: 10.1) and the average lifetime cumulative exposure was 268 (P*L* duration in years; SD: 370). Operators of furnaces, mining laborers, launderers and ironers, and cooks and other food preparers were among the most highly exposed (Supplementary Table S1). Characteristics of controls ever ($N = 313$) and never ($N = 1121$) having occupational heat exposure are presented in Supplementary Table S2. Controls ever having occupational heat exposure had a lower category of socioeconomic score (51.1% vs. 21.7%), had a higher average BMI (26.6 kg/m^2 vs. 25.1 kg/m^2) and parity, were less likely to have ever taken oral contraceptives (45.7% vs. 56.0%), and more likely to have diabetes (8.8% vs. 6.3%).

Overall, ever occupational heat exposure was associated with a moderate but statistically significant higher risk of breast cancer (OR fully adjusted model 1.22; 95% CI, 1.01–1.46). ORs in the highest categories of lifetime cumulative exposure and duration were also elevated and there were statistically significant trends (ORs highest categories 1.40; 95% CI, 1.06–1.86; $P_{trend} = 0.01$ and 1.35; 95% CI, 1.02–1.79; $P_{trend} = 0.03$, respectively; **Table 2**).

Findings were generally unchanged when adjusting models for other occupational factors including physical activity at work, night shift work, and a range of other common occupational exposures, except for occupational detergent exposure, where findings were attenuated (**Table 3**). In total, 508 (18%) women were ever occupationally exposed to heat and detergents, representing 79% of those with ever occupational heat exposure. A total of 434 (16%) women had simultaneous heat and detergent exposures during the same occupation. Affected occupations included cooks, cleaners, and agricultural workers, among others. Among those never occupationally exposed to detergents, elevated ORs were observed for ever occupational heat exposure (OR 1.27; 95% CI, 0.87–1.85) and in the highest category of lifetime cumulative exposure (OR 1.99; 95% CI, 0.95–4.14; $P_{trend} = 0.14$) and duration (OR 1.40; 95% CI, 0.77–2.54; $P_{trend} = 0.25$); however, results were based on small numbers of participants and were not statistically significant (Supplementary Table S3).

Table 4 shows the association between occupational heat exposure and breast cancer risk by breast cancer subtypes. For hormone receptor–positive tumors, stronger associations were observed for ever occupational heat exposure (OR 1.38; 95% CI, 1.12–1.67), in the highest tertile of lifetime cumulative exposure (OR 1.59; 95% CI, 1.17–2.17; $P_{trend} = 0.001$) and for exposures longer than 10 years (OR 1.50; 95% CI, 1.10–2.05; $P_{trend} = 0.002$) than other types (overall P value for heterogeneity ever vs. never exposure 0.02).

ORs for ever occupational heat exposure tended to be larger in premenopausal women (OR 1.53; 95% CI, 1.11–2.10), and in the highest categories of lifetime cumulative exposure (OR 2.23; 95% CI, 1.26–3.96; $P_{trend} = 0.002$) and duration (OR 1.81; 95% CI, 1.04–3.13; $P_{trend} = 0.02$) though no significant interaction by menopausal status was observed ($P = 0.14$; **Table 5**).

We conducted further analyses by breast cancer subtypes for premenopausal and postmenopausal women separately. We found a stronger association between ever occupational heat exposure and hormone receptor–positive tumors among premenopausal women

Table 1. Distribution of participant characteristics among female breast cancer controls and cases.

	Controls ($N = 1{,}434$)[a] *N* (%)	Cases ($N = 1{,}389$)[a] *N* (%)	*P*[b]
Age (years), mean (SD)	57.2 (12.8)	54.9 (11.9)	<0.001
Region			
Madrid	320 (22.3)	294 (21.2)	
Barcelona	260 (18.1)	240 (17.3)	
Navarra	141 (9.8)	188 (13.5)	
Guipuzcoa	213 (14.9)	182 (13.1)	
Leon	124 (8.7)	152 (10.9)	
Asturias	84 (5.9)	57 (4.1)	
Huelva	49 (3.4)	72 (5.2)	
Cantabria	139 (9.7)	113 (8.1)	
Valencia	54 (3.8)	49 (3.5)	
Girona	50 (3.5)	42 (3.0)	0.002
Socioeconomic score			
Low	403 (28.1)	386 (27.8)	
Medium	750 (52.3)	767 (55.2)	
High	281 (19.6)	236 (17.0)	0.15
Cigarette smoking			
Never smoker	792 (55.2)	710 (51.1)	
Ex-smoker	333 (23.2)	403 (29.0)	
Current smoker	309 (21.6)	276 (19.9)	0.002
Family history of breast cancer			
No	1,258 (87.7)	1,140 (82.1)	
Yes	128 (8.9)	215 (15.5)	
Missing	48 (3.4)	34 (2.5)	<0.001
BMI (kg/cm^2), mean (SD)	25.5 (4.7)	25.8 (4.7)	0.02
Physical activity			
Inactive	538 (37.5)	582 (41.9)	
Mildly active	286 (19.9)	260 (18.7)	
Moderately active	186 (13.0)	178 (12.8)	
Very active	424 (29.6)	369 (26.6)	0.10
Menopausal status			
Postmenopause	961 (67.0)	856 (61.6)	
Premenopause	473 (33.0)	533 (38.4)	0.003
Parity			
Nulliparous	297 (20.7)	300 (21.6)	
1–2 children	805 (56.1)	821 (59.1)	
≥3 children	332 (23.2)	268 (19.3)	0.04
Ever oral contraceptives	771 (53.8)	706 (50.8)	0.12
Diabetes			
No	133 (93.0)	1,295 (93.2)	
Yes	101 (7.0)	94 (6.8)	0.77

Abbreviation: SD, standard deviation.
[a]The sum may differ due to missing values (13 cases/22 controls with missing data).
[b]Wilcoxon rank-sum test for continuous and χ^2 test for categorical variables.

(OR 1.74; 95% CI, 1.22–2.46), and in the highest categories of lifetime cumulative exposure (OR 2.43; 95% CI, 1.32–4.49; $P_{trend} = 0.001$) and duration (OR 1.90; 95% CI, 1.05–3.44; $P_{trend} = 0.006$; overall *P* value for heterogeneity ever vs. never exposure premenopausal women = 0.02; *P* value for heterogeneity postmenopausal women = 0.19; Supplementary Tables S4 and S5).

We observed stronger associations between occupational heat exposure and breast cancer risk among participants first exposed before 30 years old (Supplementary Table S6). We also observed somewhat stronger associations among ever cigarette smokers, although no significant interaction was found ($P = 0.47$; Supplementary Table S7). A significant interaction was observed between occupational heat exposure and socioeconomic score ($P = 0.03$). Participants with a middle or high socioeconomic score had larger ORs for ever occupational heat exposure (OR 1.42; 95% CI, 1.12–1.81) and in the highest categories of lifetime cumulative exposure (OR 2.08; 95% CI, 1.36–3.17; $P_{trend} = < 0.001$) and duration (OR 1.76; 95% CI, 1.18–2.62; $P_{trend} = 0.003$; Supplementary Table S8).

Using a P threshold of 25%, no significant interactions were observed between occupational heat exposure and other common occupational exposures, including detergents ($P_{interaction} > 0.05$). Because of the low exposure prevalence of some other occupational exposures (Supplementary Table S9), we also investigated interactions using a P threshold of 5% but found no significant interactions.

Results of additional sensitivity analyses are in Supplementary Tables S10–S12. Larger ORs for ever exposure and categories of cumulative exposure and duration were observed with a P threshold of 5%. Using a P threshold of 50%, results were not significant with

Table 2. Association of occupational heat exposure and female breast cancer risk by different exposure indices.

	Controls (N = 1,434) N (%)	Cases (N = 1,389) N (%)	OR (95% CI)[a]	OR (95% CI)[b]
Never heat exposure	1,121 (78.2)	1,018 (73.3)	1 (ref)	1 (ref)
Ever heat exposure	313 (21.9)	371 (26.7)	1.22 (1.01–1.46)	1.22 (1.01–1.46)
Lifetime cumulative exposure[c]				
Low (>0–<60)	105 (7.3)	114 (8.2)	1.04 (0.78–1.39)	1.07 (0.80–1.43)
Medium (≥60–<210)	104 (7.3)	119 (8.6)	1.23 (0.92–1.63)	1.20 (0.90–1.60)
High (≥210)	104 (7.3)	138 (9.9)	1.40 (1.06–1.85)	1.40 (1.06–1.86)
P_{trend}			0.01	0.01
Duration (years)				
1–5	125 (8.8)	143 (10.4)	1.14 (0.88–1.48)	1.15 (0.88–1.50)
>5–10	83 (5.8)	91 (6.6)	1.13 (0.83–1.55)	1.16 (0.84–1.60)
>10	104 (7.3)	134 (9.7)	1.38 (1.04–1.82)	1.35 (1.02–1.79)
P_{trend}			0.02	0.03

[a]Adjusted for age, region, and socioeconomic score.
[b]Adjusted for age, region, socioeconomic score, cigarette smoking, family history of breast cancer, physical activity in free time, BMI, menopausal status, parity, oral contraceptive use, and diabetes.
[c]P*L*duration in years.

lower numbers of exposed cases and controls. With lag periods of 1 or 10 years, results did not substantially change. Similar results were observed for exposures in 10 years before diagnosis/interview date (Supplementary Table S13).

Discussion

In this Spanish case–control study, having ever been occupationally exposed to heat was associated with a moderate but statistically significant higher risk of female breast cancer. A significant positive trend was observed by categories of lifetime cumulative exposure and duration. The association between occupational heat exposure and breast cancer risk was also stronger for hormone receptor–positive breast cancer.

Previous studies on occupational heat exposure and cancer risk have been inconsistent and encountered limitations. We identified only one other study that investigated associations between occupational heat exposure and female breast cancer risk. A large cohort study by Weiderpass and colleagues (14) in 1999 used census and registry data to follow up 892,591 Finnish women for breast cancer incidence. The

Table 3. Associations between occupational heat exposure, occupational detergent exposure, and female breast cancer risk.[a]

	Occupational heat exposure				Occupational detergent exposure			
	Controls (N = 1,403) N (%)	Cases (N = 1,355) N (%)	OR (95% CI)[b]	OR (95% CI)[c]	Controls (N = 1,403) N (%)	Cases (N = 1,355) N (%)	OR (95% CI)[b]	OR (95% CI)[d]
Never exposure	1,109 (79.0)	1,007 (74.3)	1 (ref)	1 (ref)	827 (59.0)	708 (52.3)	1 (ref)	1 (ref)
Ever exposure[a]	294 (21.0)	348 (25.7)	1.22 (1.01–1.48)	1.13 (0.93–1.38)	576 (41.1)	647 (47.8)	1.28 (1.09–1.52)	1.24 (1.04–1.48)
Lifetime cumulative exposure[b,e]								
Low	94 (6.7)	103 (7.6)	1.10 (0.81–1.49)	1.07 (0.78–1.48)	195 (13.9)	205 (15.1)	1.16 (0.93–1.46)	1.12 (0.88–1.42)
Medium	98 (7.0)	110 (8.1)	1.19 (0.88–1.60)	1.10 (0.81–1.50)	190 (13.5)	216 (15.9)	1.32 (1.05–1.66)	1.26 (1.00–1.60)
High	102 (7.3)	135 (10.0)	1.38 (1.04–1.84)	1.25 (0.93–1.68)	191 (13.6)	226 (16.7)	1.43 (1.10–1.85)	1.38 (1.06–1.79)
P_{trend}			0.02	0.13			0.001	0.007
Duration (years)[c]								
1–5	116 (8.3)	130 (9.6)	1.15 (0.87–1.51)	1.08 (0.81–1.44)	142 (10.1)	159 (11.7)	1.24 (0.96–1.61)	1.23 (0.94–1.61)
>5–10	78 (5.6)	89 (6.6)	1.21 (0.87–1.67)	1.10 (0.77–1.55)	124 (8.8)	142 (10.5)	1.29 (0.98–1.71)	1.25 (0.94–1.65)
>10	100 (7.1)	129 (9.5)	1.33 (1.00–1.78)	1.23 (0.91–1.67)	310 (22.1)	346 (25.5)	1.30 (1.06–1.59)	1.23 (1.00–1.52)
P_{trend}			0.03	0.16			0.01	0.04

[a]A total of 31 controls and 34 cases excluded because of uncertain detergent exposure.
[b]Adjusted for age, region, socioeconomic score, cigarette smoking, family history of breast cancer, physical activity in free time, BMI, menopausal status, parity, oral contraceptive use, and diabetes.
[c]Adjusted for age, region, socioeconomic score, cigarette smoking, family history of breast cancer, physical activity in free time, BMI, menopausal status, parity, oral contraceptive use, diabetes, and either ever detergent exposure/cumulative detergent exposure/or duration of detergent exposure.
[d]Adjusted for age, region, socioeconomic score, cigarette smoking, family history of breast cancer, physical activity in free time, BMI, menopausal status, parity, oral contraceptive use, diabetes, and either ever heat exposure/cumulative heat exposure/or duration of heat exposure.
[e]P*L*duration in years; cutoff points for heat based on those of the overall population, and cutoff points for detergent: low (≤140), medium (>140–≤510), and high (>510).

Table 4. Association of occupational heat exposure and female breast cancer risk stratified by breast cancer subtype.[a]

	Hormone receptor positive		Erb2 positive		Triple negative	
	Control/ cases (*N*)	OR (95% CI)[b]	Control/ cases (*N*)	OR (95% CI)[b]	Control/ cases (*N*)	OR (95% CI)[b]
Never heat exposure	1,121/7,648	1 (ref)	1,121/192	1 (ref)	1,121/81	1 (ref)
Ever heat exposure[c]	313/266	1.38 (1.12–1.67)	313/49	0.83 (0.57–1.19)	313/27	1.15 (0.71–1.87)
Lifetime cumulative exposure[d]						
Low (>0–<60)	105/75	1.11 (0.80–1.53)	105/13	0.59 (0.32–1.11)	105/14	1.94 (1.03–3.64)
Medium (≥60–≤210)	103/91	1.45 (1.06–1.99)	103/16	0.91 (0.51–1.62)	103/7	0.88 (0.39–2.02)
High (>210)	104/98	1.59 (1.17–2.17)	104/19	0.99 (0.57–1.73)	104/6	0.72 (0.30–1.75)
P_{trend}		0.001		0.65		0.72
Duration (years)						
1–5	126/100	1.25 (0.93–1.68)	126/19	0.79 (0.46–1.35)	126/12	1.28 (0.66–2.48)
>5–10	83/71	1.42 (1.01–2.01)	83/10	0.61 (0.30–1.23)	83/7	1.13 (0.49–2.59)
>10	104/95	1.50 (1.10–2.05)	104/20	0.62–1.83)	104/8	1.02 (0.47–2.26)
P_{trend}		0.002		0.57		0.77

[a]A total of 126 cases excluded because of missing subtype information.
[b]Adjusted for age, region, socioeconomic score, cigarette smoking, family history of breast cancer, physical activity in free time, BMI, menopausal status, parity, oral contraceptive use, and diabetes
[c]Overall *P* value for heterogeneity (ever vs. never exposure) = 0.02.
[d]P*L*duration in years; cutoff points based on those of the overall population.

study used the FINJEM to calculate occupational heat exposure as the product of exposure level and probability and categorized this into none, low, and medium/high. A decreased risk of breast cancer was found for premenopausal women in the medium/high category of exposure [standardized incidence ratio (SIR) 0.29; 95% CI, 0.04–2.06; $P_{trend} = 0.007$), though results were imprecise, and no clear association was found for postmenopausal women in the medium/high category of exposure (SIR 1.14; 95% CI, 0.66–1.96; $P_{trend} = 0.002$). These contrasting results could be due to differing study methods and limitations. The Finnish study only analyzed job titles from a cross-section of time. Participants who changed occupations could possibly have been misclassified. In addition, reproductive variables were taken as averages for each occupational group, and menopausal status was defined only by age.

Other studies have investigated associations between occupational heat exposure and male breast cancer risk. A case–control study in 1998 by Cocco and colleagues (22) analyzed 178 deceased male breast cancer cases and 1,041 deceased controls. Information on lifestyle factors and the longest held job was collected from proxy respondents. A JEM was used to assign estimates of intensity and probability of occupational heat exposure. Prevalence of exposure was approximately 8% in cases and 10% in controls. No clear association was reported for probability or intensity of occupational heat exposure and male breast cancer risk. In a case–control study undertaken in 1994 by Rosenbaum and colleagues (18), city directories and questionnaires were used to obtain occupational histories of 63 cases and 253 frequency-matched controls. Estimates of occupational heat exposure were assigned using the U.S. Dictionary of Occupational Titles (30),

Table 5. Association between occupational heat exposure and female breast cancer risk in premenopausal and postmenopausal women.

	Premenopause		Postmenopause	
	Control/ cases (*N*)	OR (95% CI)[a]	Control/ cases (*N*)	OR (95% CI)[a]
Never heat exposure	379/383	1 (ref)	742/635	1 (ref)
Ever heat exposure[b]	94/150	1.53 (1.11–2.10)	219/221	1.05 (0.83–1.32)
Lifetime cumulative exposure[c]				
Low (>0–<60)	44/54	1.15 (0.74–1.80)	61/58	1.02 (0.69–1.50)
Medium (≥60–≤210)	29/50	1.63 (0.98–2.71)	74/69	0.98 (0.68–1.41)
High (>210)	20/44	2.23 (1.26–3.96)	84/93	1.11 (0.79–1.55)
P_{trend}		0.002		0.65
Duration (years)				
1–5	40/66	1.63 (1.04–2.56)	86/77	0.96 (0.68–1.35)
>5–10	31/39	1.19 (0.71–2.01)	52/54	1.10 (0.73–1.67)
>10	23/45	1.81 (1.04–3.13)	81/90	1.11 (0.79–1.56)
P_{trend}		0.02		0.53

[a]Adjusted for age, region, socioeconomic score, cigarette smoking, family history of breast cancer, physical activity in free time, BMI, parity, oral contraceptive use, and diabetes.
[b]$P_{interaction}$ (ever vs. never exposure) = 0.14.
[c]P*L*duration in years; cutoff points based on those of the overall population.

which details characteristics of each occupation. Prevalence of exposure was 14% in cases and 8% in controls. The study reported an elevated risk of breast cancer for males ever exposed to occupational heat compared with those never exposed (OR 2.50; 95% CI, 1.02–6.00).

Inconsistent results have also been reported by other studies investigating other cancer types. Significant positive associations were observed between occupational heat exposure and nasopharyngeal (15), testicular (16), and pancreatic cancer (17). Positive associations were also found for esophageal (19), kidney (20), and liver cancer (21), although not significant. However, no significant associations were reported for stomach (23), kidney (24), and pancreatic cancer (25) in other work.

Evidence exists for the biological plausibility of an association between occupational heat exposure and breast cancer. Existing evidence indicates heat exposure can cause DNA damage (31) by disrupting proteins involved in crucial processes such as DNA replication and repair. DNA damage can cause genetic instability, which contributes to tumorigenesis and is a distinctive feature of cancer (3). A recent study found significant associations between occupational heat exposure and DNA damage in male steel workers (32), supporting the hypothesis that heat exposure is associated with DNA damage. Heat exposure also triggers the heat shock response, designed to protect cells from damage (33). The heat shock response activates heat shock transcription factor 1 (HSF1), which upregulates HSPs in cells (7). Multiple studies have linked HSF1 and HSPs to crucial steps in cancer formation (4–6). They can inhibit key signaling pathways involved in the surveillance of DNA damage and regulation of apoptosis, allowing DNA damaged cells to survive and undergo uncontrolled cell proliferation (5); an important event in the formation and progression of tumors (4). HSF1 and HSPs are commonly overexpressed in cancer cells and may help them to survive, supporting the idea that heat stress could be associated with cancer (4, 34). Additional evidence shows HSPs interact with key proteins involved in breast carcinogenesis, including estrogen receptors (8, 35). This could support the stronger associations we observed for hormone receptor positive breast cancer and in premenopausal women.

This study has some limitations. We were unable to assess potential confounding effects of specific other occupational exposures, rather we examined groups of occupational exposures, due to low exposure prevalence. With adjustment for occupational detergent exposure, results attenuated. The definition of detergent exposure in the JEM included exposure to any cleaning or washing agents containing surfactants. Although there is a lack of evidence in the literature regarding associations between breast cancer and detergents (36, 37), significant positive associations with occupational detergent exposure were observed here, and it is difficult to disentangle findings of occupational heat and detergent exposure in this study. Nevertheless, positive, though attenuated, and increasing associations with occupational heat exposure remained with adjustment for occupational detergent exposure. In addition, some of the results could have occurred by chance, as we applied multiple comparisons without adjustment due to the exploratory nature of this analysis. Controls had a lower socioeconomic score than cases. Occupations with greater chemical or physical hazards are usually associated with lower socioeconomic scores which may also interact with heat exposures, though there was no evidence for effect modification by other common occupational exposures here. Results from stratified analyses by SES support the internal validity of an effect for heat exposure. The definition used for ever occupational heat exposure, and construction of various exposure indices could have contributed to nondifferential misclassification bias; however, sensitivity analyses with a variety of categories produced similar results, showing this had little impact. The use of a 10-year lag period greatly reduced the sample size and therefore the statistical power of the study. In sensitivity analyses, findings were similar using different lag periods. Small numbers of cases and controls in some subgroup analyses also reduced statistical power. The use of the MatEmEsp JEM introduced various limitations. First, Berkson errors can occur using group-based JEM measurements instead of individual level exposures (38). Second, estimates only covered the period between 1996 and 2005. Exposures occurring outside this period could have misclassification errors, although working conditions and occupational heat exposure in many jobs is unlikely to have varied through more recent years. Finally, some of the job titles in MatEmEsp are nonspecific. This could have led to further misclassification errors.

These limitations are balanced by major strengths. We analyzed a large number of histologically confirmed female breast cancer cases and frequency-matched controls with relatively high occupational heat exposure prevalence. The availability of lifetime occupational history allowed us to capture the exposure of participants over the entire working life. The extensive amount of participant information collected enabled us to adjust models for multiple potential confounders. Data on breast cancer subtypes meant we were able to gain a deeper understanding of associations between occupational heat exposure and breast cancer. We recruited from the general population in multiple regions of Spain, including participants with a diverse range of occupations, making our results more generalizable. Occupational heat exposure estimates were adapted from existing estimates in the FINJEM by five actively employed industrial hygienists with extensive experience in industrial hygiene measurements in Spain, giving us a more relevant exposure assessment. The JEM also gave participants a standardized exposure, minimizing the possibility of recall and reporting bias.

With an increasing risk of occupational heat exposure and changing patterns of exposure expected because of climate change (39), it is essential that health effects of occupational heat exposure are understood. Therefore, further studies are needed. Future studies could attempt to capture and analyze occupational heat exposure with individual exposure assessments and further investigate effect modification by personal hormonal factors and other occupational exposures.

In summary, this study provides evidence of a potential link between occupational heat exposure and female breast cancer risk. A higher risk was identified for hormone receptor–positive breast cancer subtype. Further investigations are needed to separate different exposure effects and understand the possible mechanisms for these associations.

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Authors' Contributions

A. Hinchliffe: Conceptualization, formal analysis, writing–original draft, writing–review and editing. **M. Kogevinas:** Conceptualization, resources, supervision, writing–original draft, writing–review and editing. **B. Pérez-Gómez:** Resources, writing–review and editing. **E. Ardanaz:** Resources, writing–review and editing. **P. Amiano:** Resources, writing–review and editing. **A. Marcos-Delgado:** Resources, writing–review and editing. **G. Castaño-Vinyals:** Resources, project

administration, writing–review and editing. **J. Llorca:** Resources, writing–review and editing. **V. Moreno:** Resources, writing–review and editing. **J. Alguacil:** Resources, writing–review and editing. **G. Fernandez-Tardón:** Resources, writing–review and editing. **D. Salas:** Resources, writing–review and editing. **R. Marcos-Gragera:** Resources, writing–review and editing. **N. Aragonés:** Resources, writing–review and editing. **M. Guevara:** Resources, writing–review and editing. **L. Gil:** Resources, writing–review and editing. **V. Martin:** Resources, writing–review and editing. **Y. Benavente:** Resources, writing–review and editing. **I. Gomez-Acebo:** Resources, writing–review and editing. **M. Santibáñez:** Resources, writing–review and editing. **M.A. Alba:** Resources, writing–review and editing. **A.M. García:** Resources, writing–review and editing. **M. Pollán:** Resources, writing–review and editing. **M.C. Turner:** Conceptualization, resources, supervision, writing–original draft, writing–review and editing.

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Supplementary Material Paper I

Supplementary Table 1. Proportion and level of occupational heat exposure and proportion of all jobs for the ten most common heat exposed jobs and the ten most highly exposed jobs in the dataset

	CNO94	Proportion (%)	Level (%)	Proportion*Level (%)	Proportion of all jobs (N = 7076) (%)
Ten most common heat exposed jobs					
Waiters, bartenders and the like	5020	25	25	6.25	3.22
Cooks and other food preparers	5010	70	60	42	2.71
Pawns of manufacturing industries	9700	30	25	7.5	0.88
Skilled self-employed workers in agricultural activities, except in orchards, nurseries and gardens	6011	100	35	35	0.65
Transport laborers and unloaders	9800	30	25	7.5	0.50
Launderers, ironers and similar	9122	100	50	50	0.48
Skilled self-employed workers in livestock activities, including pet animals and valuable fur domestic animals	6111	90	25	22.5	0.48
Agricultural laborers	9410	100	25	25	0.47
Operators of machines for preparing fibres, spinning and winding	8361	30	50	15	0.45
Bakers, confectioners and confectioners	7802	50	70	35	0.37
Ten most highly exposed jobs					
Operators of ore furnaces and primary metal melting furnaces	8121	100	100	100	0.03
Operators of glass and ceramic furnaces and similar machines	8131	100	100	100	0.06
Operators of secondary melting furnaces, metal casting and moulding machines; operators of rolling mills	8122	100	100	100	0.03
Mining labourers	9500	100	80	80	0.01
Launderers, ironers and similar	9122	100	50	50	0.48
Operators of bleaching, dyeing, and cleaning machines	8364	70	70	49	0.24
Tanners and leather preparers	7941	70	70	49	0.01
Cooks and other food preparers	5010	70	60	42	2.71
Operators of machines for manufacturing rubber products	8331	50	80	40	0.13
Operators of machines to treat hides and skins	8365	50	70	35	0.01

Supplementary Table 2. Distribution of participant characteristics among female breast cancer controls ever exposed to heat and female breast cancer controls never exposed to heat

	Never heat (N=1121)[1]	Ever heat (N=313)[1]	*p*-value[2]
	N(%)	N(%)	
Age; mean (SD)	56.9 (12.7)	58.4 (12.9)	0.06
Region			
Madrid	273 (24.4)	47 (15.0)	
Barcelona	196 (17.5)	64 (20.5)	
Navarra	109 (9.7)	32 (10.2)	
Guipuzcoa	170 (15.2)	43 (13.7)	
Leon	90 (8.0)	34 (10.9)	
Asturias	65 (5.8)	19 (6.1)	
Huelva	35 (3.1)	14 (4.5)	
Cantabria	103 (9.2)	36 (11.5)	
Valencia	42 (3.8)	12 (3.8)	
Girona	38 (3.4)	12 (3.8)	0.06
Socioeconomic score			
Low	243 (21.7)	160 (51.1)	
Medium	617 (55.0)	133 (42.5)	
High	261 (23.3)	20 (6.4)	<0.001
Cigarette smoking			
Never smoker	608 (54.2)	184 (58.8)	
Ex-smoker	276 (24.6)	57 (18.2)	
Current smoker	237 (21.1)	72 (23.0)	0.06
Family history of breast cancer			
No	979 (87.3)	279 (89.1)	
Yes	105 (9.4)	23 (7.4)	
Missing	37 (3.3)	11 (3.5)	0.54
BMI (kg/cm^2); mean (SD)	25.1 (4.5)	26.6 (4.9)	<0.001
Physical activity			
Inactive	415 (37.0)	123 (39.3)	
Mildly active	226 (20.2)	60 (19.2)	
Moderately active	145 (12.9)	41 (13.1)	
Very active	335 (29.9)	89 (28.4)	0.89
Menopausal status			
Post-menopause	742 (66.2)	219 (70.0)	
Pre-menopause	379 (33.8)	94 (30.0)	0.21
Parity			
Nulliparous	247 (22.0)	50 (16.0)	
1-2 children	628 (56.0)	177 (56.6)	
≥ 3 children	246 (21.9)	86 (27.5)	0.02
Ever oral contraceptives	628 (56.0)	143 (45.7)	0.001
Diabetes			
No	2004 (93.7)	624 (91.2)	
Yes	135 (6.3)	60 (8.8)	0.03

[1]The sums may differ due to missing values (13 cases/22 controls with missing data); SD: standard deviation

[2]Wilcoxon rank-sum for continuous and chi-square for categorical variables

Supplementary Table 3. Association between occupational heat exposure and female breast cancer risk among participants never occupationally exposed to detergents

	Never occupational detergent exposure	
	Control/Cases *(N)*	**OR (95% CI)[1]**
Never heat exposure	762/639	1 (ref)
Ever heat exposure	65/69	1.27 (0.87, 1.85)
Lifetime cumulative exposure[2]		
Low (>0 - <60)	26/26	1.23 (0.70, 2.18)
Medium (≥60 - <210)	26/22	0.95 (0.52, 1.76)
High (≥210)	13/21	1.99 (0.95, 4.14)
P-trend		0.14
Duration (Years)		
1 - 5	29/31	1.31 (0.76, 2.26)
>5 - 10	13/12	0.97 (0.43, 2.21)
>10	23/26	1.40 (0.77, 2.54)
P-trend		0.25

[1]Adjusted for age, region, socioeconomic score, cigarette smoking, family history of breast cancer, physical activity in free time, BMI, menopausal status, parity, oral contraceptive use and diabetes

[2]P*L*duration in years, cut points based on those of the overall population

Supplementary Table 4. Association of occupational heat exposure and female breast cancer risk in pre-menopausal women stratified by breast cancer subtype (OR: odds ratio, 95% CI: 95% confidence interval)

	Hormone receptor positive		**Erb 2 positive**		**Triple Negative**	
	Control/Cases *(N)*	**OR (95% CI)[1]**	**Control/Cases *(N)***	**OR (95% CI)[1]**	**Control/Cases *(N)***	**OR (95% CI)[1]**
Never heat exposure	379/247	1 (ref)	379/75	1 (ref)	379/29	1 (ref)
Ever heat exposure[2]	94/109	1.74 (1.22, 2.46)	94/17	0.68 (0.35, 1.29)	94/13	2.02 (0.93, 4.39)
Lifetime cumulative exposure[3]						
Low (>0 - <60)	44/39	1.34 (0.82, 2.20)	44/4	0.37 (0.12, 1.11)	44/7	2.78 (1.03, 7.52)
Medium (≥60 - <210)	30/38	1.83 (1.07, 3.15)	30/7	0.88 (0.34, 2.29)	30/4	1.34 (0.40, 4.51)
High (≥210)	20/32	2.43 (1.32, 4.49)	20/6	1.08 (0.37, 3.20)	20/2	1.99 (0.39, 10.05)
P-trend		0.001		0.67		0.20
Duration (Years)						
1 - 5	40/47	1.84 (1.12, 3.03)	40/8	0.88 (0.37, 2.09)	40/4	1.48 (0.44, 4.98)
> 5 - 10	31/30	1.47 (0.84, 2.58)	31/2	0.17 (0.04, 0.82)	31/5	2.12 (0.67, 6.70)
> 10	23/32	1.90 (1.05, 3.44)	23/7	1.23 (0.45, 3.42)	23/4	2.87 (0.80, 10.37)
P-trend		0.006		0.34		0.05

[1]Adjusted for age, region, socioeconomic score, cigarette smoking, family history of breast cancer, physical activity in free time, BMI, menopausal status, parity, oral contraceptive use and diabetes

[2]P-value for heterogeneity (ever vs. never exposure) = 0.02

[3]P*L*duration in years, cut points based on those of the overall population

Supplementary Table 5. Association of occupational heat exposure and female breast cancer risk in post-menopausal women stratified by breast cancer subtype (OR: odds ratio, 95% CI: 95% confidence interval)

	Hormone receptor positive		Erb 2 positive		Triple Negative	
Factor	**Control/Cases *(N)***	**OR (95% CI)[1]**	**Control/Cases *(N)***	**OR (95% CI)[1]**	**Control/Cases *(N)***	**OR (95% CI)[1]**
Never heat exposure	742/401	1 (ref)	742/117	1 (ref)	742/52	1 (ref)
Ever heat exposure[2]	219/157	1.19 (0.92, 1.55)	219/32	0.85 (0.54, 1.34)	219/14	0.75 (0.39, 1.44)
Lifetime cumulative exposure[3]						
Low (>0 - <60)	61/37	1.04 (0.67, 1.62)	61/10	0.84 (0.40, 1.77)	61/7	1.74 (0.71, 4.27)
Medium (≥60 - <210)	74/53	1.24 (0.83, 1.83)	74/9	0.80 (0.38, 1.70)	74/3	0.48 (0.14, 1.65)
High (≥210)	84/67	1.28(0.88, 1.84)	84/13	0.90 (0.46, 1.78)	84/4	0.46 (0.15, 1.35)
P-trend		0.13		0.57		0.13
Duration (Years)						
1 - 5	86/53	1.05 (0.72, 1.54)	86/11	0.72 (0.36, 1.43)	86/8	1.17 (0.51, 2.66)
> 5 - 10	52/41	1.37 (0.88, 2.14)	52/8	0.96 (0.42, 2.19)	52/2	0.46 (0.10, 2.04)
> 10	81/63	1.24 (0.85, 1.80)	81/13	0.94 (0.48, 1.83)	81/4	0.53 (0.18, 1.58)
P-trend		0.13		0.73		0.19

[1]Adjusted for age, region, socioeconomic score, cigarette smoking, family history of breast cancer, physical activity in free time, BMI, menopausal status, parity, oral contraceptive use and diabetes

[2]P-value for heterogeneity (ever vs never exposure) = 0.19

[3]P*L*duration in years, cut points based on those of the overall population

Supplementary Table 6. Association of occupational heat exposure and female breast cancer risk stratified by age at first occupational heat exposure (OR: odds ratio, 95% CI: 95% confidence interval)

	10- < 20 years old at first exposure		≥ 20- < 30 years old at first exposure		≥ 30 years old at first exposure	
Factor	**Control/Cases *(N)***	**OR (95% CI)[1]**	**Control/Cases *(N)***	**OR (95% CI)[1]**	**Control/Cases *(N)***	**OR (95% CI)[1]**
Never heat exposure	1121/1018	1 (ref)	1121/1018	1 (ref)	1121/1018	1 (ref)
Ever heat exposure	147/180	1.34 (1.04, 1.73)	83/108	1.24 (0.91, 1.69)	83/83	0.98 (0.71, 1.37)
Lifetime cumulative exposure[2]						
Low (>0 - <60)	45/50	1.14 (0.74, 1.75)	33/33	0.94 (0.57, 1.56)	27/31	1.16 (0.68, 1.98)
Medium (≥60 - <210)	52/60	1.30 (0.87, 1.94)	23/39	1.66 (0.97, 2.85)	29/20	0.67 (0.37, 1.22)
High (≥210)	50/70	1.58 (1.07, 2.34)	27/36	1.25 (0.74, 2.12)	27/32	1.14 (0.67, 1.96)
P-trend		0.01		0.12		0.91
Duration (Years)						
1 - 5	58/68	1.25 (0.86, 1.83)	28/41	1.38 (0.84, 2.29)	40/34	0.85 (0.53, 1.37)
> 5 - 10	37/44	1.30 (0.82, 2.06)	24/25	0.98 (0.55, 1.76)	22/24	1.12 (0.61, 2.04)
> 10	52/68	1.48 (1.00, 2.18)	31/42	1.30 (0.80, 2.12)	21/25	1.09 (0.59, 2.02)
P-trend		0.02		0.25		0.84

[1]Adjusted for age, region, socioeconomic score, cigarette smoking, family history of breast cancer, physical activity in free time, BMI, menopausal status, parity, oral contraceptive use and diabetes

[2]P*L*duration in years, cut points based on those of the overall population

Supplementary Table 7. Association between occupational heat exposure and female breast cancer risk in never smokers and ever smokers (OR: odds ratio, 95% CI: 95% confidence interval)

	Never-smokers		**Ever-smokers**	
	Control/Cases *(N)*	**OR (95% CI)[1]**	**Control/Cases *(N)***	**OR (95% CI)[1]**
Never heat exposure	608/518	1 (ref)	513/500	1 (ref)
Ever heat exposure[2]	184/192	1.11 (0.86, 1.42)	129/179	1.38 (1.03, 1.83)
Lifetime cumulative exposure[3]				
Low (>0 - <60)	50/47	1.01 (0.66, 1.56)	55/65	1.10 (0.73, 1.64)
Medium (≥60 - <210)	62/64	1.06 (0.72, 1.57)	41/55	1.37 (0.87, 2.15)
High (≥210)	72/80	1.20 (0.84, 1.72)	32/57	1.94 (1.19, 3.17)
P-trend		0.33		0.006
Duration (Years)				
1 - 5	62/66	1.12 (0.76, 1.63)	64/77	1.18 (0.81, 1.73)
>5 - 10	52/51	1.03 (0.68, 1.56)	31/42	1.36 (0.82, 2.27)
>10	70/75	1.16 (0.80, 1.67)	34/60	1.76 (1.10, 2.80)
P-trend		0.43		0.01

[1]Adjusted for age, region, socioeconomic score, cigarette smoking, family history of breast cancer, physical activity in free time, BMI, menopausal status, parity, oral contraceptive use and diabetes

[2]P-value for interaction (ever vs. never exposure) = 0.47

[3]P*L*duration in years, cut points based on those of the overall population

Supplementary Table 8. Association between occupational heat exposure and female breast cancer risk stratified by socioeconomic status (OR: odds ratio, 95% CI: 95% confidence interval)

	Low socioeconomic score		**Middle & high socioeconomic score**	
	Control/Cases *(N)*	**OR (95% CI)[1]**	**Control/Cases *(N)***	**OR (95% CI)[1]**
Never heat exposure	243/231	1 (ref)	878/787	1 (ref)
Ever heat exposure[2]	160/155	0.99 (0.72, 1.34)	153/216	1.42 (1.12, 1.81)
Lifetime cumulative exposure[3]				
Low (>0 - <60)	37/35	0.99 (0.58, 1.68)	68/79	1.13 (0.80, 1.61)
Medium (≥60 - <210)	56/54	1.00 (0.64, 1.55)	48/65	1.35 (0.90, 2.01)
High (≥210)	67/66	0.97 (0.65, 1.47)	37/72	2.08 (1.36, 3.17)
P-trend		0.91		<0.001
Duration (Years)				
1 - 5	58/52	0.93 (0.60, 1.45)	68/91	1.33 (0.95, 1.88)
>5 - 10	42/43	1.06 (0.65, 1.73)	41/50	1.21 (0.78, 1.87)
>10	60/60	0.98 (0.64, 1.51)	44/75	1.76 (1.18, 2.62)
P-trend		0.99		0.003

[1]Adjusted for age, region, socioeconomic score, cigarette smoking, family history of breast cancer, physical activity in free time, BMI, menopausal status, parity, oral contraceptive use and diabetes

[2]P-value for interaction (ever vs. never exposure) = *0.03*

[3]P*L*duration in years, cut points based on those of the overall population

Supplementary Table 9. Exposure prevalence of other common occupational exposures using a P-threshold of 25%

	Controls[1]	Cases[1]
	N (%)	N (%)
Never organic dust	918 (81.5)	824 (78.8)
Ever organic dust	209 (18.5)	222 (21.2)
Never metal	1359 (99.1)	1322 (98.7)
Ever metal	12 (0.9)	17 (1.3)
Never inorganic mineral dust	1155 (96.9)	1070 (95.5)
Ever inorganic mineral dust	37 (3.1)	50 (4.5)
Never pesticide	1253 (99.5)	1180 (98.4)
Ever pesticide	6 (0.5)	19 (1.6)
Never polycyclic aromatic hydrocarbon	1461 (99.9)	1444 (99.8)
Ever polycyclic aromatic hydrocarbon	2 (0.1)	3 (0.2)
Never organic solvent	1139 (99.4)	1137 (98.4)
Ever organic solvent	7 (0.6)	19 (1.6)
Never detergent	842 (58.6)	730 (51.6)
Ever detergent	595 (41.4)	686 (48.5)
Never engine exhaust	1436 (99.2)	1419 (99.0)
Ever engine exhaust	12 (0.8)	14 (1.0)
Never ionising radiation	1464 (99.4)	1456 (99.5)
Ever ionising radiation	9 (0.6)	8 (0.6)
Never noise	0 (0)	0 (0)
Ever noise	1431 (100)	1425 (100)
Never formaldehyde	1439 (99.4)	1408 (99.3)
Ever formaldehyde	9 (0.6)	10 (0.7)
Never sulphur gas	1394 (96.1)	1373 (95.4)
Ever sulphur gas	57 (3.9)	66 (4.6)
Never toxic fume	1465 (99.7)	1453 (99.5)
Ever toxic fume	5 (0.3)	7 (0.5)
Never night shift	1229 (86.7)	1187 (86.2)
Ever night shift	189 (13.3)	190 (13.8)

[1]The sums may differ due to missing values

Supplementary Table 10. Association between occupational heat exposure and female breast cancer risk using different combinations of lag years, durations and proportion thresholds

	P-threshold 5 & duration at least 1 year & lag 1 year	P-threshold 5 & duration at least 5 years & lag 1 year	P-threshold 25 & duration at least 1 year & lag 1 year	P-threshold 25 & duration at least 5 years & lag 1 year	P-threshold 50 & duration at least 1 year & lag 1 year	P-threshold 50 & duration at least 5 years & lag 1 year
	OR (95% CI)[1]	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**
Controls/cases (N)	1477/1465	1229/1207	1450/1412	1213/1168	1297/1212	1119/1037
Never heat exposure	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Ever heat exposure	1.28 (1.07, 1.52)	1.37 (1.11, 1.69)	1.21 (1.01, 1.45)	1.28 (1.03, 1.58)	1.08 (0.85, 1.37)	1.15 (0.87, 1.52)
Lifetime Cumulative Exposure[2]						
Low (>0 - <60)	1.13 (0.86, 1.48)	1.21 (0.75, 1.95)	1.09 (0.81, 1.46)	1.14 (0.64, 2.02)	0.78 (0.45, 1.34)	0.25 (0.05, 1.21)
Medium (≥60 - <210)	1.20 (0.92, 1.57)	1.19 (0.87, 1.62)	1.14 (0.86, 1.50)	1.09 (0.79, 1.51)	1.03 (0.69, 1.54)	1.04 (0.59, 1.85)
High (≥210)	1.54 (1.17, 2.02)	1.59 (1.20, 2.09)	1.42 (1.07, 1.87)	1.46 (1.10, 1.93)	1.23 (0.90, 1.68)	1.28 (0.93, 1.75)
P-trend	0.001	0.001	0.01	0.01	0.27	0.18
Duration (Years)						
1 - 5	1.18 (0.92, 1.52)	1.57 (0.81, 3.04)	1.16 (0.89, 1.52)	1.51 (0.76, 3.01)	1.08 (0.75, 1.56)	1.87 (0.78, 4.48)
>5 - 10	1.19 (0.88, 1.62)	1.21 (0.89, 1.65)	1.19 (0.87, 1.64)	1.21 (0.87, 1.67)	1.00 (0.63, 1.60)	1.01 (0.63, 1.61)
>10	1.44 (1.12, 1.87)	1.46 (1.13, 1.90)	1.28 (0.98, 1.67)	1.30 (0.99, 1.70)	1.12 (0.80, 1.58)	1.14 (0.81, 1.61)
P-trend	0.003	0.003	0.04	0.04	0.51	0.43

[1]Adjusted for age, region, socioeconomic score, cigarette smoking, family history of breast cancer, physical activity in free time, BMI, menopausal status, parity, oral contraceptive use and diabetes

[2]P*L*duration in years, cut points based on those of the overall population

Supplementary Table 11. Association between occupational heat exposure and female breast cancer risk using different combinations of lag years, durations and proportion thresholds

	P-threshold 5 & duration at least 1 year & lag 5 years	**P-threshold 5 & duration at least 5 years & lag 5 years**	**P-threshold 25 & duration at least 5 years & lag 5 years**	**P-threshold 50 & duration at least 1 year & lag 5 years**	**P-threshold 50 & duration at least 5 years & lag 5 years**
	OR (95% CI)[1]	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**
Controls/cases (N)	1460/1440	1178/1157	1162/1120	1289/1198	1072/998
Never heat exposure	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Ever heat exposure	1.28 (1.07, 1.54)	1.34 (1.08, 1.67)	1.25 (1.00, 1.56)	1.08 (0.85, 1.37)	1.14 (0.85, 1.52)
Lifetime Cumulative Exposure[2]					
Low (>0 - <60)	1.11 (0.85, 1.45)	1.02 (0.64, 1.64)	0.95 (0.55, 1.65)	0.70 (0.41, 1.18)	0.22 (0.05, 1.03)
Medium (≥60 - <210)	1.27 (0.96, 1.68)	1.24 (0.89, 1.72)	1.14 (0.81, 1.61)	1.17 (0.77, 1.77)	1.25 (0.66, 2.35)
High (≥210)	1.53 (1.16, 2.02)	1.56 (1.17, 2.07)	1.42 (1.06, 1.90)	1.21 (0.88, 1.66)	1.23 (0.89, 1.70)
P-trend	0.001	0.002	0.02	0.26	0.23
Duration (Years)					
1 - 5	1.18 (0.91, 1.52)	1.41 (0.70, 2.81)	1.32 (0.64, 2.74)	1.03 (0.71, 1.48)	1.76 (0.69, 4.50)
>5 - 10	1.17 (0.86, 1.58)	1.14 (0.84, 1.56)	1.13 (0.82, 1.57)	1.01 (0.63, 1.61)	0.97 (0.61, 1.57)
>10	1.53 (1.17, 2.00)	1.51 (1.15, 1.99)	1.33 (1.00, 1.78)	1.18 (0.82, 1.69)	1.17 (0.81, 1.68)
P-trend	0.002	0.004	0.05	0.43	0.44

[1]Adjusted for age, region, socioeconomic score, cigarette smoking, family history of breast cancer, physical activity in free time, BMI, menopausal status, parity, oral contraceptive use and diabetes

[2]P*L*duration in years, cut points based on those of the overall population

Supplementary Table 12. Association between occupational heat exposure and female breast cancer risk using different combinations of lag years, durations and proportion thresholds

	P-threshold 5 & duration at least 1 year & lag 10 years	P-threshold 5 & duration at least 5 years & lag 10 years	P-threshold 25 & duration at least 1 year & lag 10 years	P-threshold 25 & duration at least 5 years & lag 10 years	P-threshold 50 & duration at least 1 year & lag 10 years	P-threshold 50 & duration at least 5 years & lag 10 years
	OR (95% CI)[1]	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**
Controls/cases (N)	1400/1388	1079/1092	1374/1341	1064/1058	1241/1164	990/949
Never heat exposure	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Ever heat exposure	1.28 (1.06, 1.54)	1.45 (1.16, 1.82)	1.22 (1.00, 1.48)	1.35 (1.07, 1.72)	1.08 (0.84, 1.39)	1.23 (0.91, 1.67)
Lifetime Cumulative Exposure[2]						
Low (>0 - <60)	1.09 (0.82, 1.44)	1.32 (0.79, 2.22)	1.06 (0.78, 1.43)	1.28 (0.68, 2.38)	0.71 (0.40, 1.25)	0.41 (0.10, 1.65)
Medium (≥60 - <210)	1.15 (0.86, 1.54)	1.20 (0.85, 1.70)	1.06 (0.79, 1.43)	1.08 (0.75, 1.55)	0.94 (0.61, 1.44)	1.17 (0.61, 2.23)
High (≥210)	1.73 (1.28, 2.33)	1.72 (1.27, 2.32)	1.61 (1.19, 2.18)	1.60 (1.17, 2.18)	1.37 (0.97, 1.92)	1.34 (0.95, 1.90)
P-trend	0.001	0.001	0.007	0.005	0.19	0.11
Duration (Years)						
1 - 5	1.06 (0.82, 1.38)	1.77 (0.83, 3.76)	1.04 (0.79, 1.36)	1.67 (0.76, 3.68)	0.92 (0.63, 1.35)	2.17 (0.83, 5.67)
>5 - 10	1.45 (1.05, 2.00)	1.43 (1.03, 1.98)	1.48 (1.06, 2.08)	1.45 (1.03, 2.05)	1.44 (0.88, 2.35)	1.39 (0.84, 2.28)
>10	1.47 (1.10, 1.95)	1.44 (1.07, 1.92)	1.28 (0.94, 1.73)	1.25 (0.92, 1.70)	1.08 (0.73, 1.58)	1.05 (0.71, 1.55)
P-trend	0.002	0.003	0.02	0.03	0.42	0.39

[1]Adjusted for age, region, socioeconomic score, cigarette smoking, family history of breast cancer, physical activity in free time, BMI, menopausal status, parity, oral contraceptive use and diabetes

[2]P*L*duration in years, cut points based on those of the overall population

Supplementary Table 13. Association between occupational heat exposure and female breast cancer risk more than ten years before diagnosis/ interview date and in the ten years before diagnosis/interview date

	Ten year lag		**Last ten years**	
	Control/Cases *(N)*	**OR (95% CI)[1]**	**Control/Cases *(N)***	**OR (95% CI)[1]**
Never heat exposure	1090/1001	1 (ref)	835/855	1 (ref)
Ever heat exposure	284/340	1.22 (1.00, 1.48)	132/179	1.16 (0.90, 1.50)
Lifetime Cumulative Exposure[2]				
Low (>0 - <60)	94/105	1.06 (0.78, 1.43)	54/64	1.03 (0.70, 1.52)
Medium (≥60 - <210)	104/105	1.06 (0.79, 1.43)	46/54	0.98 (0.64, 1.50)
High (≥210)	86/130	1.61 (1.19, 2.18)	32/61	1.65 (1.05, 2.59)
P-trend		0.007		0.09
Duration (Years)				
1 - 5	124/131	1.04 (0.79, 1.36)	69/78	1.00 (0.71, 1.42)
>5 - 10	66/95	1.48 (1.06, 2.08)	63/101	1.33 (0.95, 1.88)
>10	94/114	1.28 (0.94, 1.73)	(N/A)	(N/A)
P-trend		0.02		0.14

[1]Adjusted for age, region, socioeconomic score, cigarette smoking, family history of breast cancer, physical activity in free time, BMI, menopausal status, parity, oral contraceptive use and diabetes

[2]P*L*duration in years, cut points based on those of the overall population

5.2. Paper II

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

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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 ra-tios (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 occu- pational 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 condi-tions involving high air temperatures, radiant heat from direct sunlightor 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 ≥ 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 ≥5% and ≥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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Supplementary Material Paper II

Appendix 1: Variable Harmonisation

Variable	MCC-Spain	PROtEus	EPICAP	Harmonised
Age at diagnosis/interview	Date of birth	Age (years)	Age (years)	Age (years)
Education: highest level of study completed	1 - Less than primary 2 - Primary 3 - Secondary 4 - University	1. Less than primary 2. Primary 3. Secondary 4. University 5. Other 6. Don't know	1 = Less than primary 2 = Primary 3 = Secondary 4 = University	1. Less than primary 2. Primary (6-16 years old) 3. Secondary (16-18 years old) 4. University 9. Don't know
First-degree family history of prostate cancer	0 - No first degree relative prostate cancer 1 - First degree relative prostate cancer 9 - Missing	0 - No first-degree relative with prostate cancer 1 - First-degree relative with prostate cancer 9 - Don't know	0 = No 1 = Yes . = Don't know	0 - No first degree relative prostate cancer 1 - First degree relative prostate cancer 9 - Don't know
BMI	BMI one year ago (Kg/m2)	BMI two years ago (Kg/m2)	BMI calculated from weight two years before and current height (Kg/m2)	BMI within the last two years before diagnosis/interview date (Kg/m2)
Have you ever smoked (cigarettes)?	0= Never smoker 1= Former smoker 2= Current smoker	1. Never smoker 2. Ex-smoker 3. Current smoker 999. DK	0 = Never smoker 1 = Ex-smoker 2 = Current smoker . = Don't know	0 = Never smoker 1 = Ex-smoker 2 = Current smoker 9 = Don't know
What ethnicity or race do you belong to?	1 - White/caucasian 2 - Maghrebi 3- Other african 4 - Asian 5 - Gypsy 6 - Other 9 - Don't know	1. European 2. Black 3. Asian 10. Other 999. Don't know	1 = Caucasian 2 = French (Overseas) 3 = Maghrebi 4 = Other African 5 = Other (Asian and Near and Middle East inhabitants)	1. White/Caucasian 2. Other 9. Don't know
Gleason score	0=Controls 1=Low-grade PCa (gleason <=6 , and gleason=7 with 3+4) 2=High-grade PCa (gleason >=8 , and gleason=7 with 4+3) 9=Don't know	0=Controls 1=Low-grade PCa (gleason <=6 , and gleason=7 with 3+4) 2=High-grade PCa (gleason >=8 , and gleason=7 with 4+3) 999=DK	0=Controls 1=Low-grade PCa (gleason <=6 , and gleason=7 with 3+4) 2=High-grade PCa (gleason >=8 , and gleason=7 with 4+3) 9=Don't know	0=Controls 1=Low-grade PCa (gleason <=6 , and gleason=7 with 3+4) 2=High-grade PCa (gleason >=8 , and gleason=7 with 4+3) 9=DK
Number of years since last prostate cancer screening?	1 – Less than 6 months 2 – 6 and < 12 months 3 – 12-24 months 4 – 2-3 years 5 – 3-5 years 6 – >5 years 9 – Don't know	1=In the last 2 years 2=Between 2 and 5 years ago 3=More than 5 years ago 4=Never screened 5=DK if ever screened 999=DK (had screening but do not know when)	Years (continuous)	1=In the last 2 years 2=Between 2 and 5 years ago 3=More than 5 years ago 4=Never screened 9=DK if ever screened or had screening but do not know when
Physical activity during leisure activities	0. Inactive 1. A little active 2. Moderately active 3. Very active	1=Not very active 2=Moderately active 3=Very active 999=Don't Know	0. Inactive - <10 METs hr/week 1. Moderately active - 10 to 25 METs hr/week 2. Very active - >25 METs hr/week	1 = Not very active 2 = Moderately active 3 = Very active 9 = Don't know
Ever drinking alcohol at least once a month for at least one year	0 = No 1 = Yes . = Don't know	0 = No 1 = Yes . = Don't know	0 = No 1 = Yes . = Don't know	0 = No 1 = Yes . = Don't know
Night Shift Work	1 = Day 2 = Night 3 = Rotating 9 = Don't know . = Subject did not respond to this question	0 = Never shift or night work 1 = Permanent night work 2 = Rotating night work 3 = Permanent and Rotating night work 999: don't know or incomplete records	0 = Never shiftwork 1 = Ever shiftwork	0 = Never shiftwork 1 = Ever shiftwork 9 = Don't know

Appendix 2: Exposure prevalence of other common occupational exposures using a P-threshold of 25% & a P-threshold of 5%

P=25%	**Controls**	**Cases**
	N (%)	**N (%)**
Never cadmium	3455 (100.0)	3069 (100.0)
Ever cadmium	0 (0.0)	0 (0.0)
Never lead	3176 (99.9)	2790 (99.9)
Ever lead	3 (0.1)	2 (0.1)
Never polycyclic hydrocarbon	3031 (92.3)	2747 (93.6)
Ever polycyclic hydrocarbon	254 (7.7)	187 (6.4)
Never detergent	2009 (66.1)	1792 (66.8)
Ever detergent	1030 (33.9)	889 (33.2)
P=5%		
Never cadmium	3878 (97.4)	3479 (97.3)
Ever cadmium	105 (2.6)	97 (2.7)
Never lead	3517 (88.3)	3141 (87.9)
Ever lead	464 (11.7)	433 (12.1)
Never polycyclic hydrocarbon	3305 (83.0)	3036 (85.0)
Ever polycyclic hydrocarbon	676 (17.0)	535 (15.0)
Never detergent	2148 (54.1)	1930 (54.0)
Ever detergent	1821 (45.9)	1642 (46.0)

Appendix 3: Distribution of participant characteristics among prostate cancer controls ever exposed to heat and prostate cancer controls never exposed to heat

	MCC-Spain		PROtEuS		EPICAP		*p-values*[a]
	Never heat N(%)	**Ever heat N(%)**	**Never heat N(%)**	**Ever heat N(%)**	**Never heat N(%)**	**Ever heat N(%)**	
Total participants	764 (62.8)	453 (37.2)	1076 (68.6)	493 (31.4)	477 (65.7)	249 (34.3)	
Age; mean (SD)	65.3 (8.6)	67.8 (7.9)	64.3 (6.8)	65.6 (6.6)	65.8 (5.7)	63.9 (6.5)	<0.001
Education							
Less than primary	71 (9.3)	132 (29.1)	16 (1.5)	32 (6.5)	24 (5.0)	29 (11.7)	
Primary (6-16 years old)	198 (25.9)	191 (42.2)	363 (33.7)	317 (64.3)	192 (40.3)	158 (63.5)	
Secondary (16-18 years old)	250 (32.7)	98 (21.6)	220 (20.5)	82 (16.6)	71 (14.9)	25 (10.0)	
University	245 (32.1)	32 (7.1)	477 (44.3)	62 (12.6)	190 (39.8)	37 (14.9)	<0.001
Smoking							
Never smoker	211 (27.6)	121 (26.7)	323 (30.0)	125 (25.4)	155 (32.5)	60 (24.1)	
Ex-smoker	387 (50.7)	250 (55.2)	574 (53.4)	259 (52.5)	252 (52.8)	146 (58.6)	
Current smoker	166 (21.7)	82 (18.1)	179 (16.6)	109 (22.1)	70 (14.7)	43 (17.3)	0.13
Family history of prostate cancer							
No	681 (89.1)	398 (87.9)	940 (87.4)	436 (88.4)	400 (83.9)	202 (81.1)	
Yes	45 (5.9)	31 (6.8)	113 (10.5)	46 (9.3)	40 (8.4)	24 (9.6)	
Missing	38 (5.0)	24 (5.3)	23 (2.1)	11 (2.2)	37 (7.8)	23 (9.2)	<0.001
Body Mass Index (kg/cm^2)							
Underweight (<18.5)	4 (0.5)	2 (0.4)	6 (0.6)	6 (1.2)	2 (0.4)	3 (1.2)	
Normal weight (18.5-24.9)	205 (26.8)	92 (20.3)	323 (30.0)	140 (28.4)	139 (29.1)	56 (22.5)	
Pre-obesity (25.0-29.9)	382 (50.0)	246 (54.3)	530 (49.3)	216 (43.8)	229 (48.0)	123 (49.4)	
Obesity (≥30)	173 (22.6)	113 (24.9)	217 (20.2)	131 (26.6)	107 (22.4)	67 (26.9)	0.10
Race/Ethnicity							
White/Caucasian	760 (99.5)	450 (99.3)	927 (86.2)	416 (84.4)	415 (87.0)	231 (92.8)	
Other	4 (0.5)	3 (0.7)	149 (13.9)	77 (15.6)	62 (13.0)	18 (7.2)	<0.001

One-way ANOVA for continuous and chi-square for categorical

SD: standard deviation

[a]p-values for all studies combined

Appendix 4. The five most common jobs, the five most heat exposed jobs, and the five most common heat exposed jobs in each study

MCC-Spain	Job Code	Level (%)	Proportion (%)	Proportion of all jobs (%)
Five most common jobs				
Technical and commercial sales representatives	3415	0	0	4.84
Secretaries	4115	0	0	4.71
Car, taxi and van drivers	8322	0	0	3.21
Stall and market salespersons	5230	0	0	2.68
Machine-tool operators	8211	0.45	39	2.56
Five most heat exposed jobs				
Ore and metal furnace operators	8121	20	100	0.35
Fire-fighters	5161	10	100	0.04
Architects, engineers and related professionals not elsewhere classified	2149	10	47	0.32
Metal-heat-treating-plant operators	8123	5.7	100	0.05
Glass and ceramics kiln and related machine operators	8131	5.3	81	0.30
Five most common heat exposed jobs				
Machine-tool operators	8211	0.45	39	2.56
Field crop and vegetable growers	6111	2.4	96	2.27
Dairy and livestock producers	6121	2.4	100	1.63
Sheet metal workers	7213	0.7	100	1.58
Welders and flamecutters	7212	2.1	100	1.54
PROtEus				
Five most common jobs				
Finance and administration department managers	1231	0	0	3.01
Technical and commercial sales representatives	3415	0	0	2.85
Secondary education teaching professionals	2320	0	0	2.39
Heavy truck and lorry drivers	8324	0	0	2.27
Shop salespersons and demonstrators	5220	0	0	2.16
Five most heat exposed jobs				
Ore and metal furnace operators	8121	20	100	0.04
Fire-fighters	5161	10	100	0.29
Architects, engineers and related professionals not elsewhere classified	2149	10	47	0.72
Metal-heat-treating-plant operators	8123	5.7	100	0.01
Glass and ceramics kiln and related machine operators	8131	5.3	81	0.07
Five most common heat exposed jobs				
Machine-tool operators	8211	0.45	39	1.50
Cooks	5122	0.94	100	1.06
Plumbers and pipe fitters	7136	0.52	95	0.97
Welders and flamecutters	7212	2.1	100	0.94
Sheet metal workers	7213	0.7	100	0.74
EPICAP				
Five most common jobs				
Technical and commercial sales representatives	3415	0	0	2.95
Secondary education teaching professionals	2320	0	0	2.88
Heavy truck and lorry drivers	8324	0	0	2.10
Tree and shrub crop growers	6112	2.4	96	1.92
Building and related electricians	7137	0	0	1.83
Five most heat exposed jobs				
Fire-fighters	5161	10	100	0.12
Architects, engineers and related professionals not elsewhere classified	2149	10	47	0.46
Metal-heat-treating-plant operators	8123	5.7	100	0.02
Glass and ceramics kiln and related machine operators	8131	5.3	81	0.08
Glass-makers, cutters, grinders and finishers	7322	5.3	53	0.02
Five most common heat exposed jobs				
Tree and shrub crop growers	6112	2.4	96	1.92
Machine-tool operators	8211	0.45	39	1.08
Cooks	5122	0.94	100	1.04
Police officers	5162	1.2	100	0.91
Plumbers and pipe fitters	7136	0.52	95	0.88

Appendix 5: Associations between occupational heat exposure and prostate cancer risk stratified by time since last heat exposure (OR: Odds Ratio; 95% CI: 95% Confidence Interval)

	Last heat exposure ≥5 & <10 years ago		**Last heat exposure ≥10 & <20 years ago**		**Last heat exposure ≥20 years ago**	
	Control/Cases *(N)*	**OR (95% CI)[1]**	**Control/Cases *(N)***	**OR (95% CI)[1]**	**Control/Cases *(N)***	**OR (95% CI)[1]**
Never heat exposure	2317/2057	1 (ref)	2317/2056	1 (ref)	2317/2056	1 (ref)
Ever heat exposure	327/345	1.05 (0.88, 1.25)	230/196	0.97 (0.79, 1.20)	638/543	0.92 (0.80, 1.06)
Lifetime Cumulative Exposure[a]						
Low	39/39	1.07 (0.67, 1.69)	51/27	0.59 (0.36, 0.95)	312/273	0.92 (0.77, 1.10)
Medium	105/116	1.07 (0.81, 1.42)	60/64	1.21 (0.84, 1.75)	231/181	0.86 (0.69, 1.07)
High	183/190	1.03 (0.83, 1.29)	119/105	1.03 (0.78, 1.37)	95/89	1.09 (0.79, 1.49)
P-trend		0.64		0.77		0.45
Duration (Years)[b]						
> 0 - < 10	27/29	1.06 (0.61, 1.83)	26/18	0.74 (0.40, 1.38)	414/363	0.92 (0.79, 1.09)
≥ 10 - < 25	54/66	1.19 (0.81, 1.73)	69/54	0.88 (0.61, 1.28)	190/156	0.90 (0.71, 1.13)
≥ 25	246/250	1.02 (0.84, 1.24)	135/124	1.07 (0.82, 1.40)	34/24	1.01 (0.58, 1.75)
P-trend		0.68		0.91		0.30

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).

[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

Appendix 6: Associations between occupational heat exposure and prostate cancer for participants never/ever exposed to detergents (OR: Odds Ratio; 95% CI: 95% Confidence Interval)

	Never detergent		Ever detergent		P-values for interaction
	Control/Cases *(N)*	**OR (95% CI)**	**Control/Cases *(N)***	**OR (95% CI)**	
Never heat exposure	1648/1441	1 (ref)	672/610	1 (ref)	
Ever heat exposure	500/489	1.04 (0.89, 1.22)	1128/1032	1.00 (0.86, 1.16)	0.53
Lifetime Cumulative Exposure[a]					
Low	218/203	0.98 (0.79, 1.22)	467/440	1.03 (0.86, 1.23)	
Medium	138/157	1.22 (0.94, 1.57)	354/282	0.86 (0.71, 1.06)	
High	144/129	0.97 (0.75, 1.26)	307/310	1.10 (0.90, 1.36)	
P-trend		0.62		0.82	0.20
Duration (Years)[b]					
> 0 - < 10	183/182	1.05 (0.84, 1.32)	448/400	0.95 (0.79, 1.14)	
≥ 10 - < 25	127/114	0.97 (0.74, 1.28)	317/292	1.01 (0.82, 1.24)	
≥ 25	190/193	1.08 (0.86, 1.35)	363/340	1.06 (0.87, 1.29)	
P-trend		0.59		0.56	0.92

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).

[a]P*L*duration in years, cut points based on those of the controls overall

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

Prevalence of 5% for heat exposure and detergent exposure

Appendix 7: Associations between occupational heat exposure and prostate cancer for participants never/ever exposed to cadmium (OR: Odds Ratio; 95% CI: 95% Confidence Interval)

	Never cadmium		Ever cadmium		P-values for interaction
	Control/Cases *(N)*	**OR (95% CI)**	**Control/Cases *(N)***	**OR (95% CI)**	
Never heat exposure	2308/2024	1 (ref)	28/33	1 (ref)	
Ever heat exposure	1570/1455	1.00 (0.90, 1.10)	72/63	0.78 (0.40, 1.55)	0.45
Lifetime Cumulative Exposure[a]					
Low	669/625	0.99 (0.87, 1.13)	23/17	0.86 (0.35, 2.11)	
Medium	476/419	0.96 (0.82, 1.12)	21/20	0.71 (0.29, 1.72)	
High	425/411	1.05 (0.89, 1.23)	28/26	0.79 (0.34, 1.84)	
P-trend		0.86		0.51	0.88
Duration (Years)[b]					
>0 - <10	602/562	0.98 (0.86, 1.13)	34/18	0.54 (0.23, 1.25)	
>= 10 - <25	435/379	0.94 (0.80, 1.10)	14/26	2.02 (0.77, 5.29)	
>=25	533/514	1.05 (0.91, 1.22)	24/19	0.51 (0.19, 1.35)	
P-trend		0.76		0.75	0.09

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).

[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

Prevalence of 5% for heat exposure and metal exposure

Appendix 8: Associations between occupational heat exposure and prostate cancer for participants never/ever exposed to lead (OR: Odds Ratio; 95% CI: 95% Confidence Interval)

	Never lead		Ever lead		P-values for interaction
	Control/Cases *(N)*	**OR (95% CI)**	**Control/Cases *(N)***	**OR (95% CI)**	
Never heat exposure	2252/1981	1 (ref)	84/74	1 (ref)	
Ever heat exposure	1265/1160	0.98 (0.88, 1.09)	377/355	1.06 (0.73, 1.55)	0.95
Lifetime Cumulative Exposure[a]					
Low	589/554	1.00 (0.87, 1.15)	105/88	0.97 (0.62, 1.50)	
Medium	363/319	0.94 (0.79, 1.12)	132/118	1.00 (0.65, 1.54)	
High	313/287	0.98 (0.81, 1.18)	140/149	1.23 (0.80, 1.87)	
P-trend		0.63		0.25	0.72
Duration (Years)[b]					
>0 - <10	521/495	1.00 (0.86, 1.15)	116/84	0.83 (0.53, 1.29)	
>= 10 - <25	353/305	0.93 (0.78, 1.11)	95/98	1.13 (0.72, 1.78)	
>=25	391/360	1.00 (0.85, 1.18)	166/173	1.23 (0.82, 1.86)	
P-trend		0.74		0.10	0.34

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).

[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

Prevalence of 5% for heat exposure and metal exposure

Appendix 9: Associations between occupational heat exposure and prostate cancer for participants never/ever exposed to polycylic hydrocarbons (OR: Odds Ratio; 95% CI: 95% Confidence Interval)

	Never polycyclic aromatic hydrocarbons		Ever polycyclic aromatic hydrocarbons		P-values for interaction
	Control/Cases *(N)*	**OR (95% CI)**	**Control/Cases *(N)***	**OR (95% CI)**	
Never heat exposure	2203/1976	1 (ref)	129/78	1 (ref)	
Ever heat exposure	1102/1060	1.00 (0.89, 1.12)	536/457	1.37 (0.99, 1.88)	0.04
Lifetime Cumulative Exposure[a]					
Low	446/457	1.05 (0.90, 1.22)	242/186	1.25 (0.88, 1.78)	
Medium	355/316	0.93 (0.78, 1.10)	142/121	1.33 (0.90, 1.96)	
High	301/287	0.99 (0.82, 1.19)	152/150	1.62 (1.11, 2.37)	
P-trend		0.67		0.02	0.09
Duration (Years)[b]					
> 0 - < 10	447/440	1.00 (0.86, 1.17)	187/140	1.19 (0.82, 1.73)	
≥ 10 - < 25	290/284	1.02 (0.85, 1.23)	158/122	1.21 (0.82, 1.78)	
≥ 25	365/336	0.96 (0.81, 1.14)	191/195	1.69 (1.18, 2.43)	
P-trend		0.79		0.003	0.06

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).

[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

Prevalence of 5% for heat exposure and polycyclic aromatic hydrocarbon exposure

Appendix 10: Association between occupational heat exposure and prostate cancer risk using different combinations of lag years, durations and proportion thresholds

	P-threshold 5 & duration at least 1 year & lag 1 year	**P-threshold 5 & duration at least 5 years & lag 1 year**	**P-threshold 25 & duration at least 1 year & lag 1 year**	**P-threshold 25 & duration at least 5 years & lag 1 year**	**P-threshold 50 & duration at least 1 year & lag 1 year**	**P-threshold 50 & duration at least 5 years & lag 1 year**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Controls/cases (N)	3990/3581	3583/3241	3509/3130	3240/2890	3270/2949	3049/2739
Never heat exposure	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Ever heat exposure	1.00 (0.90, 1.10)	1.01 (0.90, 1.13)	0.97 (0.87, 1.09)	0.99 (0.87, 1.11)	1.00 (0.89, 1.13)	1.01 (0.88, 1.15)
Lifetime Cumulative Exposure[a]						
Low	0.99 (0.87, 1.13)	1.07 (0.90, 1.26)	0.90 (0.77, 1.07)	0.90 (0.71, 1.15)	1.01 (0.83, 1.21)	1.05 (0.74, 1.48)
Medium	0.97 (0.84, 1.13)	0.95 (0.81, 1.11)	0.99 (0.84, 1.17)	0.97 (0.82, 1.15)	0.99 (0.83, 1.18)	0.98 (0.82, 1.17)
High	1.03 (0.89, 1.20)	1.02 (0.87, 1.19)	1.03 (0.87, 1.21)	1.04 (0.88, 1.22)	1.02 (0.85, 1.21)	1.02 (0.86, 1.22)
P-trend	0.87	0.98	0.90	0.87	0.93	0.90
Duration (Years)[b]						
> 0 - < 10	0.97 (0.85, 1.11)	1.00 (0.83, 1.22)	0.93 (0.80, 1.08)	0.93 (0.74, 1.16)	0.97 (0.82, 1.14)	0.93 (0.73, 1.20)
≥ 10 - < 25	0.96 (0.82, 1.13)	0.96 (0.82, 1.13)	0.93 (0.77, 1.12)	0.93 (0.78, 1.12)	1.00 (0.82, 1.23)	1.01 (0.82, 1.23)
≥ 25	1.07 (0.93, 1.23)	1.05 (0.91, 1.21)	1.05 (0.90, 1.24)	1.05 (0.90, 1.24)	1.04 (0.87, 1.24)	1.04 (0.87, 1.24)
P-trend	0.57	0.69	0.85	0.82	0.72	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).

[a]P*L*duration in years, cut points based on those of the controls overall

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

Appendix 11: Association between occupational heat exposure and prostate cancer risk using different combinations of lag years, durations and proportion thresholds

	P-threshold 5 & duration at least 1 year & lag 5 years	**P-threshold 5 & duration at least 5 years & lag 5 years**	**P-threshold 25 & duration at least 5 years & lag 5 years**	**P-threshold 50 & duration at least 1 year & lag 5 years**	**P-threshold 50 & duration at least 5 years & lag 5 years**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Controls/cases (N)	3985/3580	3575/3237	3241/2899	3275/2962	3053/2749
Never heat exposure	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Ever heat exposure	0.99 (0.90, 1.10)	1.01 (0.90, 1.12)	0.99 (0.87, 1.11)	1.00 (0.89, 1.13)	1.01 (0.88, 1.15)
Lifetime Cumulative Exposure[a]					
Low	0.99 (0.87, 1.12)	1.06 (0.90, 1.26)	0.90 (0.71, 1.15)	1.00 (0.83, 1.21)	1.03 (0.73, 1.44)
Medium	0.95 (0.82, 1.10)	0.92 (0.79, 1.08)	0.96 (0.81, 1.14)	0.98 (0.82, 1.17)	0.97 (0.81, 1.16)
High	1.05 (0.90, 1.23)	1.04 (0.89, 1.22)	1.05 (0.89, 1.24)	1.03 (0.86, 1.22)	1.03 (0.86, 1.23)
P-trend	0.84	0.96	0.82	0.90	0.88
Duration (Years)[b]					
> 0 - < 10	0.96 (0.84, 1.10)	1.00 (0.83, 1.22)	0.93 (0.75, 1.17)	0.97 (0.82, 1.14)	0.92 (0.72, 1.18)
≥ 10 - < 25	0.97 (0.83, 1.14)	0.97 (0.83, 1.14)	0.96 (0.80, 1.15)	1.05 (0.86, 1.28)	1.05 (0.86, 1.29)
≥ 25	1.05 (0.91, 1.21)	1.04 (0.90, 1.20)	1.03 (0.88, 1.22)	1.01 (0.85, 1.21)	1.01 (0.85, 1.21)
P-trend	0.68	0.80	0.90	0.81	0.80

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).

[a]P*L*duration in years, cut points based on those of the controls overall

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

Appendix 12: Association between occupational heat exposure and prostate cancer risk using different combinations of lag years, durations and proportion thresholds

	P-threshold 5 & duration at least 1 year & lag 10 years	P-threshold 5 & duration at least 5 years & lag 10 years	P-threshold 25 & duration at least 1 year & lag 10 years	P-threshold 25 & duration at least 5 years & lag 10 years	P-threshold 50 & duration at least 1 year & lag 10 years	P-threshold 50 & duration at least 5 years & lag 10 years
	OR (95% CI)[1]	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**
Controls/cases (N)	3983/3577	3575/3227	3530/3153	3255/2905	3294/2975	3070/2758
Never heat exposure	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Ever heat exposure	1.00 (0.90, 1.10)	1.00 (0.90, 1.12)	0.97 (0.87, 1.08)	0.98 (0.87, 1.11)	1.00 (0.89, 1.13)	1.00 (0.88, 1.15)
Lifetime Cumulative Exposure[a]						
Low	0.99 (0.87, 1.12)	1.04 (0.88, 1.23)	0.91 (0.77, 1.07)	0.92 (0.73, 1.18)	1.01 (0.84, 1.21)	1.06 (0.75, 1.46)
Medium	0.96 (0.82, 1.11)	0.93 (0.80, 1.09)	1.00 (0.85, 1.17)	0.97 (0.82, 1.16)	0.98 (0.83, 1.17)	0.98 (0.82, 1.17)
High	1.05 (0.90, 1.24)	1.05 (0.89, 1.23)	1.01 (0.86, 1.20)	1.02 (0.86, 1.21)	1.01 (0.85, 1.21)	1.02 (0.85, 1.22)
P-trend	0.80	0.93	0.99	0.97	0.99	0.95
Duration (Years)[b]						
> 0 - < 10	0.98 (0.86, 1.11)	1.01 (0.83, 1.22)	0.94 (0.81, 1.09)	0.95 (0.76, 1.19)	0.97 (0.83, 1.15)	0.94 (0.74, 1.21)
≥ 10 - < 25	0.99 (0.85, 1.16)	0.99 (0.85, 1.15)	0.97 (0.81, 1.16)	0.97 (0.81, 1.16)	1.04 (0.86, 1.27)	1.05 (0.86, 1.27)
≥ 25	1.03 (0.88, 1.19)	1.01 (0.87, 1.18)	1.01 (0.86, 1.19)	1.01 (0.86, 1.20)	1.00 (0.83, 1.20)	1.00 (0.83, 1.20)
P-trend	0.84	0.95	0.91	0.97	0.92	0.9

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).

[a]P*L*duration in years, cut points based on those of the controls overall

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

Appendix 13: Associations between occupational heat exposure and prostate cancer in MCC-Spain using a Spanish JEM, stratified by categories of education (OR: Odds Ratio; 95% CI: 95% Confidence Interval)

	Less than primary or primary		Secondary or University		P-values for interaction
	Control/Cases *(N)*	**OR (95% CI)**	**Control/Cases *(N)***	**OR (95% CI)**	
Never heat exposure	96/89	1 (ref)	396/232	1 (ref)	
Ever heat exposure	336/349	1.07 (0.75, 1.53)	166/115	1.28 (0.94, 1.74)	0.94
Lifetime Cumulative Exposure[a]					
Low	68/68	0.94 (0.58, 1.52)	96/60	1.06 (0.72, 1.57)	
Medium	121/127	1.16 (0.77, 1.76)	46/37	1.59 (0.96, 2.62)	
High	147/154	1.06 (0.72, 1.58)	24/18	1.66 (0.85, 3.24)	
P-trend		0.60		0.04	0.98
Duration (Years)[b]					
> 0 - < 10	56/41	0.68 (0.40, 1.16)	66/42	1.11 (0.71, 1.74)	
≥ 10 - < 25	58/76	1.44 (0.89, 2.33)	43/26	1.02 (0.58, 1.77)	
≥ 25	222/232	1.08 (0.74, 1.57)	57/47	1.70 (1.09, 2.65)	
P-trend		0.33		0.04	0.69

Fully-adjusted ORs (conditional logistic regression models stratified by age group (5-year) and region and adjusted for 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

5.3. Paper III

Occupational heat exposure and colorectal cancer risk in the MCC-Spain study

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Occupational Heat Exposure and Colorectal Cancer Risk in the MCC-Spain Study

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What's new in the paper?
Heat exposures are common in many occupations, and the number of exposed workers is rising due to climate change. Occupational heat exposure may be relevant for cancer risk, but current knowledge is limited. Our study is among the first to explore associations between occupational heat exposure and colorectal cancer risk and provides some evidence for a positive association among females.

Abstract

Background: Heat stress is a growing concern for many workers. There is increasing interest in potential associations of occupational heat exposure and cancer risk. Here we examined occupational heat exposure and colorectal cancer (CRC) risk in a large Spanish case-control study.

Methods: We analysed 1,198 histologically confirmed CRC cases and 2,690 controls, frequency matched by age, sex, and region. The Spanish Job-Exposure Matrix, MatEmEsp, was used to assign heat exposure estimates to the lifetime occupations of participants. Three exposure indices were assessed: ever vs. never exposed, cumulative exposure and duration (years). We estimated odds ratios (ORs) and

95% confidence intervals (CIs), applying a lag-period of 5 years, adjusting for potential confounders.

Results: Overall, we found no association between occupational heat exposure and CRC risk (OR 1.09; 95% CI 0.92, 1.29). Among females (422 cases, 1366 controls), although results were based on small numbers, a moderate and positive association was observed for ever occupational heat exposure (OR 1.28; 95% CI 0.97, 1.70), and in the medium and high categories of lifetime cumulative exposure (ORs 1.42; 95% CI 0.94, 2.14 and 1.81; 95% CI 1.09, 3.03, respectively; *p-trend* = 0.01) and duration (ORs 1.29; 95% CI 0.74, 2.23 and 2.89; 95% CI 1.50, 5.58), respectively; *p-trend* = 0.005). Some evidence for an interaction between occupational heat exposure and sex was also found. No clear associations were observed for males.

Conclusions: This study provides evidence for a potential positive association between occupational heat exposure and CRC risk among females.

Key Terms: heat stress; workers; carcinogenesis; occupational health; high temperatures; health effects

1. INTRODUCTION

In many occupations, heat exposures are common (1). When temperatures intensify, the body's thermoregulatory system becomes overwhelmed, causing the core temperature to rise and leading to the development of heat stress (2). Heat stress exhibits some of the key

characteristics of human carcinogenesis[1]: genotoxicity, DNA repair alterations, genomic instability, oxidative stress, chronic inflammation, and altering of cell proliferation and cell death (3, 4, 5).

Colorectal cancer (CRC) is the third most common cancer, accounting for approximately 10% of all cancer cases, and the second most fatal cancer, responsible for 9.4% of all cancer deaths worldwide (6). In Spain, CRC was the most commonly diagnosed cancer in 2020, with an estimated 40,441 new cases, accounting for 14% of all newly diagnosed cancers (6). Established risk factors for CRC include older age, ethnicity, family history, obesity, lack of physical activity, smoking, alcohol intake, and consumption of red and processed meat (7). The International Agency for Research on Cancer (IARC) has also classified some occupational agents as possible colorectal carcinogens, including asbestos, night shift work, and occupational exposure as a firefighter although the evidence remains limited (8).

In previous work on occupational heat exposure and female breast (9) and prostate (10) cancer, results were mixed. Those ever occupationally exposed to heat had an increased risk of female breast cancer (OR 1.22; 95% CI 1.01, 1.46) in an analysis of 1389 breast cancer cases and 1434 controls in the MCC-Spain study. In contrast, there was no evidence for an association between occupational heat exposure and prostate cancer risk in a pooled analysis of data from 3 international case-control studies, including MCC-Spain.

To the best of our knowledge, only one previous study has evaluated occupational heat exposure and CRC risk. A cohort study of women (11) (n=413,877) in Finland undertaken between 1971 and 1995, reported no association between occupational heat exposure and various gastrointestinal cancers, including colon and rectal cancer. Some other studies investigating occupational heat exposure and different gastrointestinal cancers have had mixed results. A case-control study undertaken in Spain (12) between 1995 and 1999 (399 cases, 455 controls) observed no association between occupational heat exposure and stomach cancer risk. Two Spanish case-control studies, one undertaken between 1992 and 1995 (185 cases, 264 controls) (13) and another undertaken between 1995 and 1999 (161 cases, 455 controls) (14) observed no association between occupational heat exposure and pancreatic cancer. In contrast, another case-control study conducted in Finland (15) (595 cases, 1622 controls) between 1984 and 1987 found positive associations with pancreatic cancer. In a Spanish case-control study (16) (185 cases, 285 controls) investigating occupational heat exposure and oesophageal cancer risk in males between 1995 and 1999, no associations were observed. Other studies on occupational heat exposure and several other cancers have also had mixed results (17, 18, 19, 20, 21). Possible explanations for the inconsistent findings include insufficient power due to a limited number of cases, and varying methodologies, such as cross-sectional job assessment and only considering the longest worked occupation. Further studies are needed to untangle potential associations between occupational heat exposure and cancer risk.

Here we analysed occupational heat exposure and CRC risk in a population-based multicase-control study, expanding on the limited current knowledge and building on previous work on other cancer types.

2. STUDY POPULATION & METHODS

2.1 Study Data

The MCC-Spain study (22) (*www.mccspain.org*) is a population-based multicase-control study carried out between 2008 and 2013 including cases of five tumour types (colorectal, breast, prostate and stomach cancers and chronic lymphocytic leukaemia) and population controls from the catchment area of 23 hospitals in 12 Spanish regions. The study included 2,140 newly diagnosed CRC cases and 3,950 population controls. Inclusion criteria were age 20-85 years, residence in the catchment area for at least 6 months prior to recruitment, having no prior history of CRC and ability to answer the epidemiological questionnaire. Controls, frequency-matched to cases by age (in 5-year age groups), sex and region, were randomly selected from the administrative records of selected primary care health centres located within the hospitals' catchment areas and were invited to participate through the telephone. Response rates varied by centre and on average were 68% among cases and 54% among controls. Detailed occupational information for all jobs held for at least one year, along with a thorough personal and family medical history and information on lifestyle factors was obtained through face-to-face interviews performed by trained personnel.

The MCC-Spain Study followed the 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 gave written informed consent before participating in the study. The protocol of MCC-Spain was approved by the Ethics committees of all participating institutions.

2.2 Occupational heat exposure assessment

Job titles were coded according to the Spanish National Classification of Occupations (CNO-94) by two industrial hygienists blinded to the case-control status of participants. Estimates of the proportion of workers exposed to heat (P) and the level of exposure (L), considered as the proportion of working time with heat stress, were subsequently assigned using a Spanish Job Exposure Matrix (JEM), MatEmEsp (23), covering the period 1996-2005. In MatEmEsp, occupational heat exposure is defined as continual exposure to natural or artificial heat above the specific wet bulb globe temperature (WBGT) indices determined in ISO 7243, an international standard for the assessment of thermal environments (24). MatEmEsp provides heat exposure estimates for occupations in which at least 5% of workers are exposed to temperatures exceeding these WBGT indices. Heat exposure estimates in MatEmEsp are based on those in the Finnish JEM, FINJEM, and were extensively adapted to Spanish working conditions by local experts.

2.3 Statistical Analysis

Distributions of potential risk factors between CRC cases and controls, and between controls ever and never occupationally exposed to heat, were compared using Wilcoxon rank sum and chi-squared tests. Multivariate unconditional logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for the association between CRC risk and three different occupational heat exposure indices: ever, and lifetime cumulative exposure and duration of exposure. Colon and rectal cancer cases were also analysed separately.

Ever occupational heat exposure was defined a priori as having held at least one job with a P ≥25% and with an exposure duration of at least one year. We deemed participants 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 (355 controls, 233 cases). To allow for a possible cancer latency period, an a priori lag of 5 years was applied to all analyses. 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.

Lifetime cumulative exposure was calculated as the sum of the product of P, L, and duration of occupational heat exposure for all jobs with a P≥25% according to the above definition and was

categorised into tertiles according to the distribution among exposed controls.

Duration of occupational heat exposure was defined as the sum of the duration of occupational heat exposure for all jobs with a P≥25% according to the above definition. Overlapping jobs held during the same time period were considered part-time, so duration of these jobs was split equally between them. Duration was categorised into >0-<15 years, ≥15-<30 years and ≥30 years, based on approximate tertiles according to the distribution among exposed controls. The reference group for all analyses was never occupational heat exposure.

We excluded a subset of 176 controls and 271 cases here as their occupational history was collected using a different protocol. We additionally excluded participants who were exclusively housewives, as housework was not included in the JEM (244 controls, 138 cases). Participants with a previous personal history of cancer were excluded (283 controls, 157 cases). We also excluded participants who had missing occupational information, including missing occupational codes, or missing start/finish years (148 controls, 127 cases). For the present study, a subset including 1,198 CRC cases and 2,690 controls was analysed.

Basic models adjusted for age (as a continuous variable), region, sex, and education (less than primary, primary (6-16 years old), secondary (16-18 years old), university). A directed acyclic graph and *a priori* knowledge were used to identify other potential confounders. All models were also adjusted for cigarette smoking (never smoker, ex-

smoker, and current smoker), family history of CRC in a first degree relative (yes/no/missing), body mass index (BMI (kg/m^2)) within one year before diagnosis/interview date, and self-reported physical activity at work (sedentary, low active, moderately active, vigorously active, extremely active). We created a missing indicator as a third category for family history of CRC to include participants with missing information. We excluded participants with missing information on any of the other variables (54 controls, 16 cases). Ordinal variables were taken as continuous to test for linear trends, using unexposed participants as the reference category.

We assessed the impact of adjusting models for other potential confounders, including leisure time physical activity (inactive, a little active, moderately active, and very active) (both instead of physical activity at work, and in addition to physical activity at work), diet and alcohol consumption (constructed of scores assigned according to adherence to the World Cancer Research Fund recommendations for cancer prevention), available for a subset of participants (2,401 controls, 1,060 cases), and night shift work (ever vs. never). Night shift work was defined as a working schedule that involved working partly or entirely between 00:00 and 06:00 hr, at least three times per month. Further analyses were also conducted according to different strata of sex, cigarette smoking and education. We also conducted time window analyses 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 performed stratified analyses in those never and ever exposed to any metals (lead, cadmium, chromium, nickel, iron), any solvents (aliphatic and alicyclic hydrocarbons, aromatic hydrocarbons, chlorinated hydrocarbons, and other organic solvents), any pesticides (2,4-D, atrazine, captan, chlorpyrifos, dicuat, diuron, endosulfan, methomyl, pyrethrin, tiram), polycyclic aromatic hydrocarbons (PAHs) and detergents, and investigated possible interactions with occupational heat exposure. Some studies have previously linked some metals, solvents, and pesticides to an increased CRC risk (25, 26, 27, 28). In previous work on female breast cancer (9) and prostate cancer (10) in the MCC-Spain study, positive associations with occupational detergent and PAH exposure were found, although there is a lack of evidence in the literature for an association with colorectal cancer. We also assessed the confounding effects of these other occupational exposures by including the variables for the other occupational exposures in the model and assessing the magnitude in change of the OR for heat. All exposures estimates were assigned using the Spanish JEM, MatEmEsp. For this specific analysis, ever exposure was defined as having ever held at least one job with a $P \geq 5\%$ for a duration of at least one year, as exposure prevalence was low. For metals, solvents, and pesticides, individual occupational agents in the JEM were grouped together to increase exposure prevalence. We assessed only occupational exposures which were contained in MatEmEsp, and for which there were sufficient participants exposed to heat and the other occupational exposure to perform the analysis.

Finally, we explored the effect of a priori decisions on the results. In addition to the default P of ≥25%, exposure duration of at least 1 year and lag period of 5 years, we analysed alternative threshold combinations. We investigated P thresholds of ≥5% and ≥50%, an exposure duration of at least 5 years and lag periods of 1 and 10 years.

All analyses were conducted using Stata 17 (29).

3. RESULTS

Table 1 shows distributions of characteristics of the 1,198 cases and 2,690 controls. Cases were somewhat older than controls (65.6 years; SD 11.2 vs. 61.5 years; SD 11.8), less well educated, less likely to be current smokers, more likely to have a family history of CRC in a first degree relative, had a higher level of physical activity at work and more likely to be male. Characteristics of controls ever (n = 984) and never (n = 1,706) having occupational heat exposure are presented in *Appendix 1*. Controls ever having occupational heat exposure were somewhat older (63.8 years; SD 11.1 vs. 60.2 years; SD 11.9), more likely to have ever smoked cigarettes, less well educated, had a higher level of physical activity at work and were more likely to be male. Overall, 51% of cases and 37% of controls were classified as being ever occupationally exposed to heat. Occupations with the highest heat exposure (Level (%)) included operators of stationary industrial installations, blacksmiths and smiths, and boiler and steam engine operators. The most common heat exposed jobs included waiters, waitresses and bartenders, agricultural workers, cooks, bricklayers, and labourers in manufacturing industries *(Appendix 2*). Amongst those exposed, the

average duration of exposure was 23 years (SD: 16.6) and the average lifetime cumulative exposure was 587 (P*L*duration in years) (SD: 651).

In minimally-adjusted models, somewhat raised ORs were found for ever occupational heat exposure (OR 1.18; 95% CI 1.00, 1.38) and across categories of lifetime cumulative exposure and duration, although no trends across categories were observed (*Table 2*). In fully-adjusted models, there was no evidence for an association between ever occupational heat exposure and CRC risk (OR 1.09; 95% CI 0.92, 1.29). No discernible trends were observed across categories of lifetime cumulative exposure and duration, and there was no evidence for an exposure-response trend. In an analysis of colon cancer cases separately, ORs were lower. When analysing rectal cancer cases separately, slightly higher ORs were observed for ever occupational heat exposure (OR 1.23; 95% CI 0.97, 1.56) and in some categories of lifetime cumulative exposure and duration, although there were no discernible trends. When further adjusting models for leisure time physical activity, diet, alcohol consumption, and night shift work, findings were generally unchanged (not shown).

Table 3 shows the associations between occupational heat exposure and CRC risk stratified by sex. Among females, higher ORs were observed for ever occupational heat exposure (OR 1.28; 95% CI 0.97, 1.70), and in the medium and high categories of lifetime cumulative exposure (ORs 1.42; 95% CI 0.94, 2.14 and 1.81; 95% CI 1.09, 3.03, respectively; *p-trend = 0.01*) and duration (ORs 1.29; 95% CI 0.74, 2.23 and 2.89; 95% CI 1.50, 5.58), respectively; *p-trend = 0.005*),

with evidence of exposure-response trends along with some evidence of an interaction between occupational heat exposure and sex.

In an analysis stratified by cigarette smoking, somewhat higher ORs were observed among never smokers for ever occupational heat exposure (OR 1.26; 95% CI 0.97, 1.64) and in some categories of lifetime cumulative exposure and duration, although there was no evidence for an interaction between occupational heat exposure and cigarette smoking (*Table 4*).

In an analysis stratified by education a slightly higher OR was found for ever occupational heat exposure among more highly educated participants (OR 1.16; 95% CI 0.89, 1.50), although no obvious trends were observed across categories of lifetime cumulative exposure and duration for either lower or more highly educated participants, and there was no evidence for an interaction between occupational heat exposure and education (*Table 5*).

Findings were generally unchanged when adjusting models for other common occupational exposures: metals, solvents, pesticides, detergents, and PAHs (not shown). We further analysed associations stratified by these other common occupational exposures. Among participants never exposed to metals, we observed higher ORs for ever occupational heat exposure (OR 1.21; 95% CI 0.98, 1.49), and in the low and high categories of lifetime cumulative exposure and duration, although no interaction was found (*Appendix 3*). ORs were elevated among participants ever occupationally exposed to solvents for ever occupational heat exposure (OR 1.22; 95% CI 0.79, 1.87), and in some categories of lifetime cumulative exposure and duration.

However, there was no evidence for an interaction (*Appendix 4*). Among participants ever occupationally exposed to pesticides, higher ORs were found for ever heat exposure (OR 1.27; 95% CI 0.78, 2.09) and in the highest categories of lifetime cumulative exposure and duration (ORs 1.60; 95% CI 0.90, 2.84 and 1.45; 95% CI 0.81, 2.59, respectively) (*Appendix 5*). However, the majority of participants exposed to pesticides were also exposed to heat (771 participants (86%)), and there was no evidence for an interaction between occupational heat and pesticide exposure. We observed no associations among participants ever or never exposed to PAHs (*Appendix 6*). Among participants ever occupationally exposed to detergents higher ORs were observed for ever occupational heat exposure (OR 1.24; 95% CI 0.97, 1.58), and in some categories of lifetime cumulative exposure and duration, although no evidence was found for an interaction (*Appendix 7*).

In time window analyses, findings were generally unchanged when stratified by time at last heat exposure (*Appendix 8*). When using different P-thresholds, exposure durations and lag periods, as part of sensitivity analyses, results were generally unchanged (*Appendix 9-11*).

4. DISCUSSION

In this population-based case-control study we found no evidence overall for an association between occupational heat exposure and CRC risk and found no discernible trend across categories of lifetime cumulative exposure and duration. Some slightly higher ORs were observed when analysing rectal cancer separately. Among females,

ORs were somewhat higher, and there was some evidence for an interaction between occupational heat exposure and sex, although results were based on small numbers of females in some categories.

In previous work on occupational heat exposure and female breast (9) and prostate cancer (10) risk, positive associations were observed for female breast cancer, but not for prostate cancer. These findings reflect our results here, with positive associations found among females but not among males. There are a few possible explanations for the different associations between males and females. The average lifetime cumulative exposure and duration for males was twice that of females among participants occupationally exposed to heat, which could imply males were more acclimatised to working in hot environments. Adding to this, studies have shown males have a shorter heat acclimatisation period than females (30, 31). There were also some differences in the most common heat exposed jobs between males and females. The most common heat exposed jobs among males included bricklayers, carpenters, agricultural workers, and construction workers, while among females they included cooks, labourers in manufacturing industries, helpers and cleaners and launderers and ironers. This could indicate males were more commonly exposed to outdoor heat, while female heat exposure was mostly indoors, which may have caused discrepancies in the types and patterns of heat exposure. There could also be differences in other occupational co-exposures between the male and female occupations. Additionally, among those heat exposed, 24% of males self-reported being in the extremely active occupational physical activity category compared to only 18% of females. People with a

higher physical fitness are typically less vulnerable to heat stress. Evidence also shows women performing work at the same level as men experience greater core temperature rises due to their lower body mass, higher fat content and lower sweat output (32). The thermoregulatory responses of women may also vary over the menstrual cycle and at menopause due to the influences of reproductive hormones (33).

This study has several strengths. We were able to examine associations using a large number of histologically confirmed CRC cases and controls frequency matched by age, sex and region. The collection of comprehensive information on potential confounding factors allowed us to adjust our results appropriately. Participants were from multiple regions of Spain and provided detailed lifetime occupational histories, including a wide range of occupations, making results more generalisable. The availability of lifetime occupational history allowed us to examine the exposure of participants over the entire working life. Using a JEM allowed us to apply standardised heat exposures to all participants, limiting the chance of recall bias. This study contributes to the current limited evidence on occupational heat exposure and cancer risk, in particular CRC.

The study also has some limitations. The development of various exposure indices and definition of ever occupational heat exposure could have caused some non-differential misclassification bias, although the effect was likely minimal as results were generally unchanged in sensitivity analyses with a range of categories.

Additionally, due to the exploratory nature of this analysis, multiple comparisons were made without adjustment, so some of the results could have occurred by chance. Heat exposure estimates were assigned to job titles rather than to individual participants, so exposure variability between workers in the same job is not considered. This can cause Berkson errors (34), which may lead to reduced precision. In MatEmEsp, heat estimates only cover the period 1996 to 2005. Exposures outside this period could be misclassified. However, working conditions and heat exposures in most jobs are unlikely to have changed across more recent years. Also, some of the job titles were unspecific, which could have caused further misclassification errors.

The use of a JEM allowed us to explore additional chemical and physical exposures that can occur in conjunction with heat exposure in many occupations. However, the prevalence of other occupational exposures was low. In our analyses stratified by pesticide exposure, somewhat stronger associations were observed among participants ever occupationally exposed to pesticides, although no interaction between occupational heat and pesticide exposure was observed. Most workers exposed to pesticides were also exposed to heat, making it difficult to fully explore these findings in this study. There is some evidence in the literature linking pesticide exposure to an increased CRC risk (28), so future research may be useful.

5. CONCLUSIONS

This study provides little evidence overall for an association between occupational heat exposure and CRC risk, although there is evidence

for potential positive associations among females. Further research to investigate these findings in more depth is needed.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Table 1: Distributions of risk factors among colorectal cancer cases and controls

	Cases (N=1198) N(%)	**Controls (N=2690) N(%)**	***p-values***
Age; mean (SD)	65.6 (11.2)	61.5 (11.8)	<0.001
Sex			
Males	776 (64.8)	1324 (49.2)	
Females	422 (35.2)	1366 (50.8)	<0.001
Region			
Madrid	152 (12.7)	568 (21.1)	
Barcelona	275 (23.0)	565 (21.0)	
Navarra	87 (7.3)	201 (7.5)	
Guipuzcoa	79 (6.6)	275 (10.2)	
Leon	234 (19.5)	277 (10.3)	
Asturias	52 (4.3)	145 (5.4)	
Murcia	19 (1.6)	29 (1.1)	
Huelva	40 (3.3)	115 (4.3)	
Cantabria	91 (7.6)	271 (10.1)	
Valencia	60 (5.0)	106 (3.9)	
Granada	109 (9.1)	138 (5.1)	<0.001
Education			
Less than primary school	319 (26.6)	410 (15.2)	
Primary school	427 (35.6)	773 (28.7)	
Secondary school	281 (23.5)	837 (31.1)	
University	171 (14.3)	670 (24.9)	<0.001
Smoking			
Never smoker	469 (39.2)	1133 (42.1)	
Ex-smoker	560 (46.7)	982 (36.5)	
Current smoker	169 (14.1)	575 (21.4)	<0.001
Family history of colorectal cancer			
No	943 (78.7)	2341 (87.0)	
Yes	204 (17.0)	233 (8.7)	
Missing	51 (4.3)	116 (4.3)	<0.001
BMI (kg/cm^2); mean (SD)	27.4 (4.5)	26.5 (4.5)	<0.001
Physical activity at work			
Sedentary	126 (10.5)	521 (19.4)	
Low active	134 (11.2)	391 (14.5)	
Moderately active	388 (32.4)	855 (31.8)	
Vigorously active	341 (28.5)	586 (21.8)	
Extremely active	209 (17.5)	337 (12.5)	<0.001

Wilcoxon rank-sum for continuous and chi-square for categorical
Numbers may differ due to missing values; SD: standard deviation

Table 2: Associations between occupational heat exposure and colorectal cancer risk (OR: odds ratio, 95% CI: 95% confidence interval)

	Colorectal cancer Cases/Controls (N)	OR (95% CI)[a]	OR (95% CI)[b]	Colon cancer Cases/Controls (N)	OR (95% CI)[b]	Rectal cancer Cases/Controls (N)	OR (95% CI)[b]
Never heat exposure	585/1706	1 (ref)	1 (ref)	362/1706	1 (ref)	220/1706	1 (ref)
Ever heat exposure	613/984	1.18 (1.00, 1.38)	1.09 (0.92, 1.29)	341/984	1.00 (0.81, 1.22)	263/984	1.23 (0.97, 1.56)
Lifetime Cumulative Exposure[c]							
Low	153/328	1.21 (0.97, 1.52)	1.15 (0.92, 1.45)	82/328	1.02 (0.77, 1.35)	68/328	1.37 (1.00, 1.88)
Medium	198/328	1.14 (0.91, 1.42)	1.06 (0.85, 1.34)	117/328	1.04 (0.79, 1.36)	78/328	1.07 (0.77, 1.48)
High	262/328	1.17 (0.94, 1.47)	1.03 (0.82, 1.30)	142/328	0.93 (0.71, 1.24)	117/328	1.23 (0.90, 1.70)
P-trend		0.12	0.70		0.76		0.23
Duration (Years)[d]							
>0 - <15	223/451	1.19 (0.97, 1.45)	1.13 (0.92, 1.38)	130/451	1.06 (0.83, 1.35)	88/451	1.21 (0.91, 1.62)
≥15 - <30	119/185	1.24 (0.95, 1.62)	1.11 (0.84, 1.47)	61/185	0.96 (0.68, 1.35)	58/185	1.39 (0.97, 2.01)
≥30	271/348	1.13 (0.90, 1.41)	1.00 (0.80, 1.27)	150/348	0.93 (0.70, 1.23)	117/348	1.15 (0.83, 1.58)
P-trend		0.18	0.82		0.60		0.26

[a]Minimally adjusted models adjusted for age, sex, region, and education
[b]Fully adjusted models adjusted for age, sex, region, education, cigarette smoking, family history of colorectal cancer, BMI, and occupational physical activity
[c]P*L*duration in years, cut points for all analyses: low (>0 - <157), medium (>=157 - <588), and high (>=588)
[d]Based on the tertiles according to the distribution amongst exposed controls
The numbers of colon and rectal cancers may not equal the total number of colorectal cancers as tumour site was unknown in some cases

Table 3: Associations between occupational heat exposure and colorectal cancer risk stratified by sex (OR: Odds Ratio; 95% CI: 95% Confidence Interval)

	Males		**Females**		**P-values for interaction**
	Cases/ Controls (N)	**OR (95% CI)**	**Cases/ Controls (N)**	**OR (95% CI)**	
Never heat exposure	295/643	1 (ref)	290/1063	1 (ref)	
Ever heat exposure	481/681	1.02 (0.82, 1.27)	132/303	1.28 (0.97, 1.70)	0.37
Lifetime Cumulative Exposure[a]					
Low	106/166	1.22 (0.91, 1.65)	47/162	1.01 (0.69, 1.48)	
Medium	149/230	0.91 (0.68, 1.22)	49/98	1.42 (0.94, 2.14)	
High	226/285	0.93 (0.70, 1.24)	36/43	1.81 (1.09, 3.03)	
P-trend		0.54		0.01	0.03
Duration (Years)[b]					
>0 - <15	143/219	1.14 (0.87, 1.51)	80/232	1.12 (0.81, 1.54)	
>= 15 - <30	94/134	1.01 (0.72, 1.41)	25/51	1.29 (0.74, 2.23)	
>=30	244/328	0.91 (0.69, 1.19)	27/20	2.89 (1.50, 5.58)	
P-trend		0.43		0.005	0.02

All models are adjusted for age, region, education, cigarette smoking, family history of colorectal cancer, BMI, and occupational physical activity

[a]P*L*duration in years, cut points based on those of the overall population

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

Table 4: Associations between occupational heat exposure and colorectal cancer risk stratified by cigarette smoking (OR: Odds Ratio; 95% CI: 95% Confidence Interval)

	Never smokers		**Ever smokers**		**P-values for interaction**
	Cases/ Controls (N)	**OR (95% CI)**	**Cases/ Controls (N)**	**OR (95% CI)**	
Never heat exposure	246/767	1 (ref)	339/939	1 (ref)	
Ever heat exposure	223/366	1.26 (0.97, 1.64)	390/618	1.01 (0.81, 1.27)	0.47
Lifetime Cumulative Exposure[a]					
Low	57/123	1.24 (0.86, 1.80)	96/205	1.07 (0.80, 1.43)	
Medium	77/119	1.37 (0.96, 1.96)	121/209	0.94 (0.70, 1.27)	
High	89/124	1.17 (0.80, 1.70)	173/204	1.02 (0.75, 1.38)	
P-trend		0.18		0.99	0.67
Duration (Years)[b]					
>0 - <15	95/180	1.28 (0.94, 1.75)	128/271	1.03 (0.79, 1.35)	
>= 15 - <30	46/62	1.49 (0.95, 2.33)	73/123	0.91 (0.64, 1.30)	
>=30	82/124	1.08 (0.73, 1.60)	189/224	1.05 (0.78, 1.41)	
P-trend		0.35		0.87	0.69

All models are adjusted for age, sex, region, education, family history of colorectal cancer, BMI and occupational physical activity

[a]P*L*duration in years, cut points based on those of the overall population

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

Table 5: Associations between occupational heat exposure and colorectal cancer risk stratified by education (OR: Odds Ratio; 95% CI: 95% Confidence Interval)

	Primary school or less		**Secondary school or more**		**P-values for interaction**
	Cases/ Controls (N)	**OR (95% CI)**	**Cases/ Controls (N)**	**OR (95% CI)**	
Never heat exposure	273/532	1 (ref)	312/1174	1 (ref)	
Ever heat exposure	473/651	1.11 (0.89, 1.38)	140/333	1.16 (0.89, 1.50)	0.58
Lifetime Cumulative Exposure[a]					
Low	80/154	1.02 (0.74, 1.42)	73/174	1.29 (0.94, 1.78)	
Medium	155/220	1.12 (0.84, 1.48)	43/108	1.10 (0.74, 1.66)	
High	238/277	1.16 (0.88, 1.53)	24/51	0.89 (0.52, 1.52)	
P-trend		0.26		0.75	0.40
Duration (Years)[b]					
>0 - <15	143/248	1.07 (0.82, 1.40)	80/203	1.23 (0.90, 1.67)	
>= 15 - <30	87/118	1.17 (0.83, 1.65)	32/67	1.20 (0.74, 1.93)	
>=30	243/285	1.12 (0.85, 1.48)	28/63	0.94 (0.57, 1.55)	
P-trend		0.39		0.65	0.31

All models are adjusted for age, sex, region, cigarette smoking, family history of colorectal cancer, BMI and occupational physical activity

[a]P*L*duration in years, cut points based on those of the overall population

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

Supplementary Material Paper III

Appendix 1: Distributions of risk factors among controls ever and never occupationally exposed to heat

	Ever heat (N=984)	**Never heat (N=1706)**	***p*- values**
	N(%)	**N(%)**	
Age; mean (SD)	63.8 (11.1)	60.2 (11.9)	<0.001
Sex			
Males	681 (69.2)	643 (37.7)	
Females	303 (30.8)	1063 (62.3)	<0.001
Region			
Madrid	139 (14.1)	429 (25.2)	
Barcelona	262 (26.6)	303 (17.8)	
Navarra	57 (5.8)	144 (8.4)	
Guipuzcoa	69 (7.0)	206 (12.1)	
Leon	126 (12.8)	151 (8.9)	
Asturias	57 (5.8)	88 (5.2)	
Murcia	15 (1.5)	14 (0.8)	
Huelva	56 (5.7)	59 (3.5)	
Cantabria	111 (11.3)	160 (9.4)	
Valencia	29 (3.0)	77 (4.5)	
Granada	63 (6.4)	75 (4.4)	<0.001
Education			
Less than primary school	251 (25.5)	159 (9.3)	
Primary school	400 (40.7)	373 (21.9)	
Secondary school	221 (22.5)	616 (36.1)	
University	112 (11.4)	558 (32.7)	<0.001
Smoking			
Never smoker	366 (37.2)	767 (45.0)	
Ex-smoker	402 (40.9)	580 (34.0)	
Current smoker	216 (22.0)	359 (21.0)	<0.001
Family history of colorectal cancer			
No	864 (87.8)	1477 (86.6)	
Yes	76 (7.7)	157 (9.2)	
Missing	44 (4.5)	72 (4.2)	0.41
BMI (kg/cm2); mean (SD)	27.4 (4.4)	25.9 (4.4)	<0.001
Physical activity at work			
Sedentary	78 (7.9)	443 (26.0)	
Low active	99 (10.1)	292 (17.1)	
Moderately active	320 (32.5)	535 (31.4)	
Vigorously active	291 (29.6)	295 (17.3)	
Extremely active	196 (19.9)	141 (8.3)	<0.001

Wilcoxon rank-sum for continuous and chi-square for categorical

Numbers may differ due to missing values; SD: standard deviation

Appendix 2. The five most common jobs, the five most heat exposed jobs and the five most common heat exposed jobs

	Job Code	Level (%)	Proportion (%)	Proportion of all jobs (%)
Five most common jobs				
Administrative assistants without front-office duties not classified above	4300	0	0	6.87
Shop assistants and display clerks in shops, stores, kiosks and markets	5330	0	0	6.31
Sales representatives and sales technicians	3320	0	0	3.55
Domestic workers	9110	0	0	2.91
Waiters, waitresses, bartenders and the like	5020	25	25	2.56
Five most heat exposed jobs				
Operators in ore furnaces and primary metal melting furnaces	8121	100	100	0.27
Operators in secondary melting furnaces, metal casting and moulding machines; rolling mill operators	8122	100	100	0.23
Operators of glassmaking and ceramics kilns and similar machinery	8131	100	100	0.14
Blacksmiths and smiths	7521	100	100	0.13
Boiler and steam engine operators	8162	100	100	0.10
Five most common heat exposed jobs				
Waiters, waitresses, bartenders and the like	5020	25	25	2.56
Skilled own-account workers in agricultural activities, except in orchards, nurseries and gardens	6011	35	100	2.22
Cooks and other food preparers	5010	60	70	1.78
Bricklayers and masons	7110	25	100	1.68
Labourers in manufacturing industries	9700	25	30	1.40

Appendix 3: Associations between colorectal cancer and occupational heat exposure for participants never/ever exposed to metals (OR: Odds Ratio; 95% CI: 95% Confidence Interval)

	Never metals		**Ever metals**		**P-values for interaction**
	Cases/Controls (*N*)	**OR (95% CI)**	**Cases/Controls (*N*)**	**OR (95% CI)**	
Never heat exposure	521/1591	1 (ref)	64/113	1 (ref)	
Ever heat exposure	276/465	1.21 (0.98, 1.49)	567/861	0.96 (0.68, 1.36)	0.22
Lifetime Cumulative Exposure[a]					
Low	104/217	1.24 (0.94, 1.63)	159/260	1.07 (0.72, 1.57)	
Medium	92/155	1.12 (0.82, 1.53)	195/320	0.92 (0.63, 1.35)	
High	80/93	1.27 (0.88, 1.82)	213/281	0.88 (0.60, 1.31)	
P-trend		0.13		0.29	0.13
Duration (Years)[b]					
>0 - <15	121/256	1.23 (0.96, 1.60)	156/276	0.96 (0.65, 1.41)	
>= 15 - <30	50/91	1.07 (0.73, 1.58)	121/172	1.05 (0.70, 1.58)	
>=30	105/118	1.25 (0.90, 1.75)	290/413	0.91 (0.63, 1.33)	
P-trend		0.14		0.63	0.16

Adjusted for age, sex, region, education, cigarette smoking, family history of colorectal cancer, BMI and occupational physical activity

[a]P*L*duration in years, cut points based on those of the overall population

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

P-value of 5 for heat and metal exposure

*lead, cadmium, chromium, nickel, iron

Appendix 4: Associations between colorectal cancer and occupational heat exposure for participants never/ever exposed to solvents (OR: Odds Ratio; 95% CI: 95% Confidence Interval)

	Never solvents		Ever solvents		P-values for interaction
	Cases/Controls (*N*)	**OR (95% CI)**	**Cases/Controls (*N*)**	**OR (95% CI)**	
Never heat exposure	533/1595	1 (ref)	52/110	1 (ref)	
Ever heat exposure	691/1062	1.10 (0.92, 1.30)	154/262	1.22 (0.79, 1.87)	0.93
Lifetime Cumulative Exposure[a]					
Low	203/391	1.17 (0.95, 1.45)	60/87	1.64 (0.99, 2.72)	
Medium	234/352	1.08 (0.86, 1.35)	55/122	0.88 (0.53, 1.46)	
High	254/319	0.99 (0.77, 1.26)	39/53	1.29 (0.71, 2.33)	
P-trend		0.94		1.00	0.09
Duration (Years)[b]					
>0 - <15	214/424	1.15 (0.93, 1.42)	63/109	1.31 (0.80, 2.16)	
>= 15 - <30	130/193	1.15 (0.87, 1.51)	42/69	1.30 (0.75, 2.28)	
>=30	347/445	1.00 (0.80, 1.25)	49/84	1.02 (0.59, 1.76)	
P-trend		0.92		0.94	0.35

Adjusted for age, sex, region, education, cigarette smoking, family history of colorectal cancer, BMI and occupational physical activity

[a]P*L*duration in years, cut points based on those of the overall population

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

P-value of 5 for heat and solvent exposure

*aliphatic and alicyclic hydrocarbons, aromatic hydrocarbons, chlorinated hydrocarbons, and other organic solvents

Appendix 5: Associations between colorectal cancer and occupational heat exposure for participants never/ever exposed to pesticides (OR: Odds Ratio; 95% CI: 95% Confidence Interval)

	Never Pesticides		Ever Pesticides		P-values for interaction
	Cases/Controls (N)	**OR (95% CI)**	**Cases/Controls (N)**	**OR (95% CI)**	
Never heat exposure	543/1617	1 (ref)	41/86	1 (ref)	
Ever heat exposure	533/862	1.12 (0.94, 1.33)	307/464	1.27 (0.78, 2.09)	0.46
Lifetime Cumulative Exposure[a]					
Low	198/340	1.28 (1.03, 1.59)	64/138	1.19 (0.69, 2.06)	
Medium	184/294	1.08 (0.85, 1.37)	103/180	1.20 (0.69, 2.08)	
High	151/228	0.89 (0.68, 1.17)	140/146	1.60 (0.90, 2.84)	
P-trend		0.74		0.09	0.09
Duration (Years)[b]					
>0 - <15	182/351	1.21 (0.97, 1.50)	94/182	1.24 (0.74, 2.06)	
>= 15 - <30	119/179	1.21 (0.91, 1.60)	52/84	1.25 (0.67, 2.32)	
>=30	232/332	0.96 (0.76, 1.22)	161/198	1.45 (0.81, 2.59)	
P-trend		0.97		0.24	0.40

Adjusted for age, sex, region, education, cigarette smoking, family history of colorectal cancer, BMI and occupational physical activity

[a]P*L*duration in years, cut points based on those of the overall population

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

P-value of 5 for heat and pesticide exposure

*2,4-D, atrazine, captan, chlorpyrifos, dicuat, diuron, endosulfan, methomyl, pyrethrin, tiram

Appendix 6: Associations between colorectal cancer and occupational heat exposure for participants never/ever exposed to polycyclic aromatic hydrocarbons (PAHs) (OR: Odds Ratio; 95% CI: 95% Confidence Interval)

	Never PAHs		Ever PAHs		P-values for interaction
	Cases/Controls (N)	**OR (95% CI)**	**Cases/Controls (N)**	**OR (95% CI)**	
Never heat exposure	551/1646	1 (ref)	34/60	1 (ref)	
Ever heat exposure	637/1009	1.14 (0.96, 1.35)	204/317	1.00 (0.61, 1.65)	0.58
Lifetime Cumulative Exposure[a]					
Low	205/402	1.18 (0.95, 1.46)	56/76	1.40 (0.77, 2.54)	
Medium	224/352	1.10 (0.88, 1.38)	63/122	0.84 (0.48, 1.48)	
High	208/255	1.11 (0.86, 1.43)	85/119	0.91 (0.52, 1.60)	
P-trend		0.35		0.34	0.10
Duration (Years)[b]					
>0 - <15	215/447	1.14 (0.93, 1.40)	59/86	1.23 (0.68, 2.21)	
>= 15 - <30	115/184	1.18 (0.89, 1.56)	56/79	1.13 (0.63, 2.04)	
>=30	307/378	1.11 (0.88, 1.40)	89/152	0.81 (0.47, 1.40)	
P-trend		0.30		0.21	0.18

Adjusted for age, sex, region, education, cigarette smoking, family history of colorectal cancer, BMI and occupational physical activity

[a]P*L*duration in years, cut points based on those of the overall population

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

P-value of 5 for heat and PAH exposure

Appendix 7: Associations between colorectal cancer and occupational heat exposure for participants never/ever exposed to detergents (OR: Odds Ratio; 95% CI: 95% Confidence Interval)

	Never detergents		Ever detergents		P-values for interaction
	Cases/Controls (N)	**OR (95% CI)**	**Cases/Controls (N)**	**OR (95% CI)**	
Never heat exposure	414/1244	1 (ref)	171/456	1 (ref)	
Ever heat exposure	336/462	1.09 (0.87, 1.38)	504/865	1.24 (0.97, 1.58)	0.54
Lifetime Cumulative Exposure[a]					
Low	116/192	1.18 (0.89, 1.57)	144/286	1.36 (1.02, 1.82)	
Medium	117/153	1.09 (0.80, 1.50)	170/322	1.10 (0.82, 1.49)	
High	103/117	0.92 (0.65, 1.32)	190/257	1.23 (0.90, 1.68)	
P-trend		0.96		0.34	0.21
Duration (Years)[b]					
>0 - <15	91/163	1.15 (0.85, 1.57)	182/370	1.27 (0.97, 1.67)	
>= 15 - <30	59/90	1.08 (0.73, 1.60)	113/173	1.36 (0.98, 1.90)	
>=30	209/186	1.05 (0.78, 1.40)	209/322	1.08 (0.79, 1.48)	
P-trend		0.71		0.68	0.2

Adjusted for age, sex, region, education, cigarette smoking, family history of colorectal cancer, BMI and occupational physical activity

[a]P*L*duration in years, cut points based on those of the overall population

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

P-value of 5 for heat and detergent exposure

Appendix 8: Associations between occupational heat exposure and colorectal cancer risk stratified by time since last heat exposure (OR: Odds Ratio; 95% CI: 95% Confidence Interval)

	Last heat exposure ≥5 & <10 years ago		**Last heat exposure ≥10 & <20 years ago**		**Last heat exposure ≥20 years ago**	
	Cases/Controls (*N*)	**OR (95% CI)**	**Cases/Controls (*N*)**	**OR (95% CI)**	**Cases/Controls (*N*)**	**OR (95% CI)**
Never heat exposure	585/1706	1 (ref)	585/1706	1 (ref)	585/1706	1 (ref)
Ever heat exposure	224/403	1.10 (0.87, 1.39)	153/197	1.11 (0.84, 1.47)	236/384	1.06 (0.85, 1.32)
Lifetime Cumulative Exposure[a]						
Low	37/86	1.53 (0.99, 2.34)	24/51	1.47 (0.87, 2.47)	92/191	1.02 (0.77, 1.35)
Medium	74/139	1.07 (0.76, 1.51)	35/50	1.09 (0.68, 1.76)	89/139	1.07 (0.78, 1.46)
High	113/178	0.96 (0.71, 1.30)	94/96	0.99 (0.69, 1.42)	55/54	1.18 (0.76, 1.81)
P-trend		0.97		0.80		0.47
Duration (Years)[b]						
>0 - <15	39/103	1.29 (0.85, 1.94)	27/56	1.50 (0.90, 2.48)	157/292	1.07 (0.84, 1.35)
>= 15 - <30	50/85	1.34 (0.90, 1.99)	29/37	1.28 (0.75, 2.18)	40/63	0.86 (0.55, 1.34)
>=30	135/215	0.95 (0.71, 1.27)	97/104	0.92 (0.64, 1.31)	39/29	1.41 (0.82, 2.42)
P-trend		0.92		0.96		0.49

All models are adjusted for age, sex, region, education, cigarette smoking, family history of colorectal cancer, BMI and occupational physical activity

[a]P*L*duration in years, cut points based on those of the controls overall

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

Appendix 9: Association between occupational heat exposure and colorectal cancer risk using different combinations of lag years, durations and proportion thresholds

	P-threshold 5 & duration at least 1 year & lag 1 year	P-threshold 5 & duration at least 5 years & lag 1 year	P-threshold 25 & duration at least 1 year & lag 1 year	P-threshold 25 & duration at least 5 years & lag 1 year	P-threshold 50 & duration at least 1 year & lag 1 year	P-threshold 50 & duration at least 5 years & lag 1 year
	OR (95% CI)	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**
Controls/cases (N)	3045/1434	2837/1335	2697/1200	2518/1121	2366/1032	2260/980
Never heat exposure	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Ever heat exposure	1.12 (0.96, 1.31)	1.11 (0.94, 1.32)	1.09 (0.92, 1.29)	1.09 (0.91, 1.31)	1.07 (0.88, 1.29)	1.06 (0.87, 1.30)
Lifetime Cumulative Exposure[a]						
Low	1.21 (1.00, 1.48)	1.24 (0.98, 1.57)	1.15 (0.91, 1.44)	1.21 (0.89, 1.63)	1.11 (0.81, 1.51)	1.09 (0.68, 1.74)
Medium	1.06 (0.86, 1.30)	1.07 (0.87, 1.32)	1.07 (0.85, 1.35)	1.08 (0.85, 1.36)	1.06 (0.82, 1.38)	1.08 (0.83, 1.41)
High	1.05 (0.84, 1.31)	1.05 (0.84, 1.31)	1.04 (0.83, 1.31)	1.04 (0.82, 1.31)	1.05 (0.82, 1.34)	1.04 (0.81, 1.34)
P-trend	0.67	0.68	0.63	0.65	0.65	0.66
Duration (Years)[b]						
>0 - <15	1.18 (0.98, 1.43)	1.20 (0.96, 1.51)	1.14 (0.93, 1.40)	1.19 (0.93, 1.52)	1.06 (0.83, 1.35)	1.05 (0.77, 1.42)
>= 15 - <30	1.10 (0.86, 1.41)	1.10 (0.86, 1.41)	1.09 (0.83, 1.45)	1.09 (0.83, 1.45)	1.15 (0.83, 1.59)	1.15 (0.83, 1.59)
>=30	1.05 (0.86, 1.29)	1.05 (0.85, 1.29)	1.01 (0.80, 1.27)	1.00 (0.80, 1.27)	1.04 (0.81, 1.33)	1.03 (0.80, 1.33)
P-trend	0.66	0.67	0.84	0.88	0.64	0.69

All models are adjusted for age, sex, region, education, cigarette smoking, family history of colorectal cancer, BMI and occupational physical activity

[a]P*L*duration in years, cut points based on those of the controls overall

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

Appendix 10: Association between occupational heat exposure and colorectal cancer risk using different combinations of lag years, durations and proportion thresholds

	P-threshold 5 & duration at least 1 year & lag 5 years	**P-threshold 5 & duration at least 5 years & lag 5 years**	**P-threshold 25 & duration at least 5 years & lag 5 years**	**P-threshold 50 & duration at least 1 year & lag 5 years**	**P-threshold 50 & duration at least 5 years & lag 5 years**
	OR (95% CI)[1]	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**
Controls/cases (N)	3033/1430	2819/1328	2501/1117	2365/1033	2250/980
Never heat exposure	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Ever heat exposure	1.12 (0.96, 1.31)	1.12 (0.95, 1.33)	1.10 (0.92, 1.33)	1.06 (0.88, 1.29)	1.08 (0.88, 1.32)
Lifetime Cumulative Exposure[a]					
Low	1.24 (1.03, 1.51)	1.29 (1.02, 1.63)	1.26 (0.93, 1.70)	1.11 (0.82, 1.51)	1.17 (0.73, 1.87)
Medium	1.03 (0.84, 1.26)	1.05 (0.85, 1.30)	1.08 (0.86, 1.37)	1.08 (0.83, 1.40)	1.11 (0.85, 1.45)
High	1.03 (0.83, 1.29)	1.04 (0.83, 1.30)	1.04 (0.82, 1.31)	1.02 (0.79, 1.31)	1.02 (0.79, 1.32)
P-trend	0.83	0.77	0.64	0.74	0.70
Duration (Years)[b]					
>0 - <15	1.18 (0.97, 1.42)	1.20 (0.95, 1.50)	1.20 (0.94, 1.53)	1.05 (0.82, 1.33)	1.07 (0.79, 1.44)
>= 15 - <30	1.16 (0.92, 1.48)	1.17 (0.92, 1.50)	1.12 (0.85, 1.48)	1.18 (0.86, 1.63)	1.18 (0.85, 1.63)
>=30	1.02 (0.83, 1.25)	1.02 (0.83, 1.26)	1.01 (0.80, 1.28)	1.03 (0.79, 1.33)	1.03 (0.79, 1.33)
P-trend	0.78	0.73	0.81	0.66	0.67

All models are adjusted for age, sex, region, education, cigarette smoking, family history of colorectal cancer, BMI and occupational physical activity

[a]P*L*duration in years, cut points based on those of the controls overall

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

Appendix 11: Association between occupational heat exposure and colorectal cancer risk using different combinations of lag years, durations and proportion thresholds

	P-threshold 5 & duration at least 1 year & lag 10 years	P-threshold 5 & duration at least 5 years & lag 10 years	P-threshold 25 & duration at least 1 year & lag 10 years	P-threshold 25 & duration at least 5 years & lag 10 years	P-threshold 50 & duration at least 1 year & lag 10 years	P-threshold 50 & duration at least 5 years & lag 10 years
	OR (95% CI)[1]	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**	**OR (95% CI)[1]**
Controls/cases (N)	2990/1418	2776/1311	2653/1193	2467/1105	2342/1033	2228/976
Never heat exposure	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Ever heat exposure	1.13 (0.96, 1.32)	1.10 (0.93, 1.31)	1.11 (0.93, 1.31)	1.09 (0.90, 1.31)	1.10 (0.91, 1.33)	1.08 (0.88, 1.33)
Lifetime Cumulative Exposure[a]						
Low	1.22 (1.01, 1.48)	1.23 (0.97, 1.55)	1.14 (0.90, 1.43)	1.12 (0.82, 1.52)	1.11 (0.82, 1.51)	1.08 (0.67, 1.72)
Medium	1.07 (0.87, 1.31)	1.07 (0.86, 1.32)	1.15 (0.91, 1.44)	1.15 (0.91, 1.45)	1.19 (0.92, 1.54)	1.19 (0.91, 1.55)
High	1.03 (0.82, 1.30)	1.02 (0.81, 1.29)	1.02 (0.81, 1.30)	1.01 (0.79, 1.29)	1.02 (0.79, 1.31)	1.00 (0.77, 1.29)
P-trend	0.74	0.83	0.56	0.67	0.57	0.70
Duration (Years)[b]						
>0 - <15	1.18 (0.98, 1.43)	1.16 (0.93, 1.46)	1.14 (0.93, 1.40)	1.13 (0.88, 1.44)	1.12 (0.88, 1.43)	1.12 (0.83, 1.50)
>= 15 - <30	1.21 (0.96, 1.53)	1.22 (0.96, 1.54)	1.23 (0.94, 1.61)	1.23 (0.94, 1.61)	1.18 (0.87, 1.61)	1.18 (0.86, 1.61)
>=30	0.98 (0.79, 1.22)	0.97 (0.78, 1.21)	0.96 (0.76, 1.23)	0.95 (0.74, 1.21)	1.02 (0.78, 1.33)	1.00 (0.76, 1.31)
P-trend	0.91	0.98	0.85	0.98	0.63	0.77

All models are adjusted for age, sex, region, education, cigarette smoking, family history of colorectal cancer, BMI and occupational physical activity

[a]P*L*duration in years, cut points based on those of the controls overall

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

6. DISCUSSION

The current knowledge on occupational heat exposure and cancer risk is limited. We have examined potential associations between occupational heat exposure and various cancer types in large datasets with a relatively high heat exposure prevalence, overcoming some of the limitations of existing studies. The main results of our studies have been already described and discussed in the results section. An overall summary of the findings will be presented here, together with a discussion of the strengths and limitations, and suggestions for future research.

6.1. Main findings and contribution to current knowledge

In paper I, we observed increased risks of breast cancer for females ever occupationally exposed to heat, and for those with higher lifetime cumulative exposures and longer durations of exposure. Associations were stronger for hormone receptor positive tumours. HSPs have been shown to interact with oestrogen receptors, and hormone receptors are sensitive to alterations in HSP functions, which could explain these stronger associations[146]. Higher ORs were also observed among pre-menopausal women and among women first exposed before 30 years of age. This could be due to heat exposures occurring at a younger age, or before first full-term pregnancy, when the breast tissue is undifferentiated and has a heightened susceptibility to environmental exposures[147,148]. Only one previous study, to our knowledge, has evaluated associations

between occupational heat exposure and female breast cancer risk[117]. Our findings contrast with those of the previous study, which found no association for those ever occupationally exposed to heat and observed an inverse association between occupational heat exposure and breast cancer among pre-menopausal women. This could partly be explained by differences in the information on occupational history between the studies. The previous study only used occupations taken from a cross-section in time, which could have caused some misclassification errors. There are also likely to be differences in the patterns and types of occupational heat exposure experienced in Spain compared to in Finland, which could have affected the results.

In the second paper there was no evidence for an association between occupational heat exposure and prostate cancer risk overall. When applying a Spanish JEM to the Spanish MCC-Spain study data, ORs were elevated, although no significant trends were observed. Our study is the first to our knowledge to evaluate occupational heat exposure and prostate cancer risk. Some existing studies have evaluated other male androgen-related cancers. In one study, there were no associations between occupational heat exposure and male breast cancer risk[118]. Other studies on male breast cancer and testicular cancer observed positive associations[119,120]. However, in these studies, heat exposure prevalence was low, and the evaluation of occupational heat exposure was not well developed.

In paper III, the results overall provided no evidence for an association between occupational heat exposure and colorectal

cancer risk. Among females, higher ORs were observed, and there was some evidence for an interaction between occupational heat exposure and sex. This finding is discussed further in continuation. Overall results of paper III are consistent with the findings of most existing studies on occupational heat exposure and gastrointestinal cancer risks. One study found no associations between occupational heat exposure and various gastrointestinal cancer types, including colon and rectal cancer[124]. Other studies on stomach, oesophageal and pancreatic cancer also had null findings[121,122,123,126]. One previous study on occupational heat exposure and pancreatic cancer did observe a positive association, although it was not significant[125]. This inconsistency may be due to differences in occupational exposure assessment and study design.

Although the overall results of paper II and III do not support our hypothesis for an association between occupational heat exposure and cancer risk, positive associations were observed for female breast cancer risk in Paper I and for colorectal cancer risk among females in Paper III. We found increased risks for females ever occupationally exposed to heat, and for those with higher lifetime cumulative exposures and longer durations of exposure. We also found evidence for an interaction between occupational heat exposure and sex in paper III. There are several theories that could explain our different findings for males and females.

In both paper I and III there were differences in the types of heat exposed occupations undertaken by men and women. The most common heat exposed jobs among males included bricklayers,

carpenters, construction workers and welders and flame cutters. Among females, the most common heat exposed jobs included helpers and cleaners, waiters and bartenders, bakers and confectioners, and launderers and ironers. There were some heat exposed occupations that men and women did have in common across all studies, including manufacturing workers, cooks, and agricultural workers. However, men and women in the same occupations can often have different assigned tasks, work activities and conditions, usually as a result of perceived differences in physical capabilities or socialised gender roles[149]. Studies have shown men and women commonly experience different occupational exposure patterns, both between and within occupations[150,151]. It is therefore likely that the types and patterns of occupational heat exposure experienced by men and women in our studies were different. There are also likely to have been variations in other concomitant occupational exposures. Additionally, ill-fitting personal protective equipment, designed to fit the male body, can increase a woman's risk of exposure to other occupational agents[149]. There were also some differences between certain characteristics of male and female participants which could have affected the results. Males ever occupationally exposed to heat were generally older, more likely to have ever been cigarette smokers, and were more physically active at work compared to females ever occupationally exposed to heat.

The contrasting findings for males and females could also be explained by differences in thermoregulatory response caused by differences in certain physical traits and physiology between men and women. Women generally have a higher body fat content, lower body

mass and a higher surface-area-to-volume ratio compared to men, which impacts on their heat stress vulnerability[84]. Some studies have also shown women have a reduced sweating capability during heat exposure compared to men, due to a lower sweat gland output[152], resulting in reduced heat dissipation. Additionally, temperature regulation in women is affected by the menstrual cycle[153]. Reproductive hormones fluctuate across the menstrual cycle, with oestrogen peaking just before ovulation during the follicular phase and progesterone peaking later, in the luteal phase[154]. At elevated oestrogen levels, the core temperature threshold at which heat dissipation mechanisms are initiated is lower compared with during periods of elevated progesterone[155]. Oestrogen appears to promote heat dissipation and reduce body temperatures, while progesterone tends to have the opposite effect, instead favouring heat conservation[153,156]. Menopause and the use of hormone therapies such as hormonal contraceptive pills and hormone replacement therapy can cause further fluctuations in reproductive hormones which impact thermoregulation in women[156].

Another important consideration when interpreting differing results between males and females is the possibility of residual confounding. Males ever occupationally exposed to heat were generally more likely to have ever been cigarette smokers, were more physically active at work and were more likely to have ever performed night shift work compared to females ever occupationally exposed to heat. Although we were able to control for multiple confounders in each of the studies, it is possible that some confounding effect remained, due to imperfect measurement of the confounding variables or

inaccurate adjustment. The cigarette smoking variable used here did not take into consideration pack-years or the possibility of passive smoking, which could have resulted in inadequate control of confounding by cigarette smoking. Physical activity at work was self-reported, which could have introduced some errors and caused residual confounding to occur. Night shift work can also be challenging to characterise in epidemiological studies.

Results here among females contrast with the findings of two previous cohort studies that focussed on associations between occupational heat exposure and breast[117] and gastrointestinal[124] cancers among women as part of the Women's Occupational Cancer Study in Finland. The breast cancer study reported a significant inverse association between occupational heat exposure and female breast cancer risk among pre-menopausal women and reported no clear associations among post-menopausal women. In the gastrointestinal study, no associations were observed between occupational heat exposure and multiple gastrointestinal cancers, including colon and rectal cancer. These different findings may be in part due to different study designs. The previous studies were also limited by the use of cross-sectional occupations and the lack of availability of individual-level information on confounding factors. One previous study[122] on occupational heat exposure and oesophageal risk restricted participants to only men as there were a limited number of females. Other existing studies on various gastrointestinal cancers[121,123,125,126] do not appear to have considered associations between occupational heat exposure and cancer in men and women separately.

Other occupational exposures are likely to occur concomitantly with heat exposures in many workplaces, so it is important to understand potential interactions. In all papers here we evaluated some other occupational exposures in combination with occupational heat exposure. We first assessed potential confounding by other occupational exposures. In Paper I, the association between occupational heat exposure and breast cancer risk attenuated when adjusting for ever occupational detergent exposure. Results were generally unchanged when adjusting for a range of other common occupational exposures. In Paper II, findings remained largely the same when adjusting for various other occupational agents including cadmium, lead, detergents (cleaning or washing agents containing surfactants), and polycyclic aromatic hydrocarbons (PAHs). In Paper III, associations were generally unaltered when adjusting for metals, solvents, pesticides, detergents, and PAHs. We subsequently explored effect modification by other occupational exposures. In Paper I we found higher ORs for the association between occupational heat exposure and breast cancer among participants never occupationally exposed to detergents, and in the highest categories of lifetime cumulative exposure and duration, although there was no evidence for an interaction. In Paper II, when stratifying by polycyclic aromatic hydrocarbon (PAH) exposure, higher ORs were observed among participants ever occupationally exposed to PAHs and in the highest categories of lifetime cumulative exposure and duration, with evidence of exposure-response trends and some evidence of an interaction between occupational heat and PAH exposure. In Paper III higher ORs were observed among participants

ever occupationally exposed to pesticides and in the highest categories of lifetime cumulative exposure and duration. However, there was no evidence for an interaction between occupational heat and pesticide exposure. To the best of our knowledge, no previous studies have investigated potential interactions of occupational heat and other occupational agents, making this analysis and our findings novel. However, our analysis here was limited by the low number of participants exposed to both heat and the other occupational exposures, giving limited power. Furthermore, we were only able to analyse the occupational exposures which were available in the JEMs. In some instances, we also grouped other occupational exposures together to increase exposure prevalence. Our investigations surrounding potential interactions of occupational exposures here highlight the complexities of disentangling associations between multiple occupational exposures and potential health effects. Further studies examining concomitant heat and other occupational exposures in more depth would be valuable, given the potential mechanisms and the general lack of literature surrounding this topic.

6.2. Strengths and Limitations

In all papers a JEM was used to assign estimates of occupational heat exposures to the lifetime occupations of participants. JEMs are particularly useful for large-scale general population studies as they allow standardised occupational exposure estimates to be applied to participants in a systematic and unbiased way[158]. JEMs also enable the estimation of retrospective occupational exposures of participants

in a way which is generally more reliable than self-report methods, which can suffer from recall bias[159]. However, it is important to acknowledge the limitations of using a JEM to assign occupational exposure estimates. JEMs assign the same exposure estimates to all workers within the same job title and do not account for any exposure heterogeneity between workers in the same or similar occupations[160]. Inter-individual variations in heat exposures are probable. Heat exposures depend in part on various personal factors such as age, sex, physical fitness, acclimatisation, and the type of clothing worn. This may create non-differential misclassification of exposures which can attenuate ORs towards the null[158,161]. Additionally, JEM estimates do not incorporate temporal variations in occupational exposures. Heat exposures are likely to vary over the course of the day, day-to-day, or even throughout the year with the change in seasons. This additional dimension to occupational heat exposure is not captured in JEM exposure estimates. Occupational coding presents another challenge when using a JEM. Errors could occur when manually coding jobs from the self-reported occupational history which could lead to misclassification errors.

Paper II posed a few additional challenges. The job codes of two of the datasets required translation to ISCO88 codes before exposure estimates could be applied with the FINJEM. Translation of occupational codes is often complex, and there were multiple-to-one and one-to-multiple matches for some occupations which required evaluation and adaptation by an industrial hygiene expert. This might have introduced errors in some of the job codes, which could have caused misclassification of occupational exposures. In paper II we

pooled datasets from multiple countries and applied FINJEM heat estimates. FINJEM has previously been used successfully in epidemiological studies across different countries examining multiple occupational exposures[162]. Nevertheless, potential differences between occupational heat exposures need to be considered. In Finland, heat exposures may be lower in some occupations when compared to those in Spain or France, as Finland has a milder climate, with colder average temperatures and longer winters. Furthermore, there may have been economical differences between countries over the participants' lifetimes, which could have affected occupational heat exposures. A further difficulty with paper II was the harmonisation of individual datasets. During harmonisation, some information for certain variables was lost, as categories were collapsed to align the different scales used in the studies. Additionally, some variables, such as education, did not capture the exact same construct, which complicated the harmonisation process. Nonetheless, the data in individual studies was collected in a similar way, with face-to-face interviews conducted by trained personnel, and many of the variables were coherent. Through the pooling of datasets, we achieved a greater sample size than could be obtained with individual studies, which increased the power.

A strength of this work is the substantial number of participants in the datasets. The MCC-Spain study is large, and due to the availability of additional prostate cancer datasets we were able to conduct a pooled analysis in paper II, substantially increasing the number of participants in our study, resulting in greater power. The

prevalence of occupational heat exposure across all studies was also relatively high, which is something that many of the existing studies were limited by. However, although the overall number of participants was large across all papers, numbers in some stratified analyses in paper I and paper III were small. This limited our ability to examine associations with certain important factors such as menopausal status and breast cancer subtypes in paper I and sex in paper III.

We used a case-control study design in all papers here. It is important to consider some inherent limitations of case-control studies. In a case-control study, selection bias can arise if selection is related to occupational heat exposure or occupations in general[163]. Control subjects were a random sample of people recruited from the general population residing in the same district as the cases, which minimises the chance of selection bias. In MCC-Spain, selection of participants was related to socioeconomic status, with controls being more highly educated than cases. We tried to account for this as much as possible by adjusting for education or socioeconomic status and conducting stratified analyses by education or socioeconomic status. Recall bias is another limitation in case-control studies that use participant interviews to collect retrospective exposure information. Recall bias can cause misclassification of exposures. This bias occurs when individuals cannot recall all occupations/exposures accurately[164]. There may also be differential recollection of occupational history and exposures based on the participants disease status[165], although this is usually more of a concern in studies where the disease of interest can impair memory, such as brain tumours. Nonetheless, to

minimise recall bias, in all studies occupational histories and exposure information were collected in face-to-face interviews undertaken by trained personnel. Standardised questionnaires were also used to limit interviewer bias.

6.3. Future research

This is still a relatively new and developing area of research. With climate change causing increases in the global average temperature and the frequency and intensity of extreme weather events such as heat waves, the number of workers exposed to heat is projected to rise[136]. Occupational heat exposure is therefore becoming increasingly important. There is a need for further studies to build on the limited evidence currently available.

We need more studies that evaluate heat exposure in more depth, including different types, such as indoor and outdoor, and patterns of heat exposure, in order to fully understand the potential associations with cancer risk. Other studies on different cancer types would also be valuable to build on the current knowledge. Additionally, it would be useful for subsequent studies to focus on the most highly exposed workers, to disentangle possible associations. Understanding mechanisms of action could also help develop better prevention measures.

Instead of using JEM exposure estimates, future studies could attempt to measure individual level heat exposures among workers from multiple occupations. This would enable the assessment of variations in heat exposures between workers within the same

occupation and would minimise exposure misclassification. Furthermore, individual measurements would make it possible to evaluate a range of personal characteristics that can have an impact on a worker's heat exposure.

The possible effect modification by gender observed here needs to be explored further. Future research could seek to identify possible differential exposures between male and female workers. Further studies to evaluate potential mechanisms behind the gender-specific differences observed here would also be useful.

There is a need for more research on interactions of occupational heat and other occupational co-exposures. The main limitation for this specific analysis here was low power due to low numbers of participants being ever occupationally exposed to heat and other exposures concomitantly. To overcome this, larger studies are needed with a particular focus on occupations where workers are identified as being significantly exposed to both heat and other occupational exposures[110].

Previous studies have suffered from low numbers of participants and low heat exposure prevalence. The pooling and harmonisation of existing occupational cohorts would be extremely beneficial for future research on this topic and on other occupational health risks. Data pooling would allow for larger studies and an increased statistical power.

7. CONCLUSIONS

- Occupational heat exposure was associated with an increased risk of female breast cancer, especially for hormone receptor positive tumours.

- There was no evidence for an association between occupational heat exposure and prostate cancer risk.

- Overall, occupational heat exposure was not associated with an increased risk of colorectal cancer.

- Sex was an effect modifier of the association between occupational heat exposure and cancer risk. Females had a higher risk of cancer, including breast and colorectal, compared to males.

- There was some evidence for potential interactions between occupational heat exposure and other occupational exposures.

8. APPENDIX

Paper in preparation

The following paper has been part of the work undertaken by the candidate during the last few years. Although it is not presented as part of the thesis, a short description of this paper is provided below.

Occupational heat exposure and stomach cancer risk in the Stomach Cancer Pooling (StoP) Project

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Stomach cancer is one of the leading contributors to the global burden of cancer. Despite major declines in stomach cancer incidence and mortality over recent decades, it is still the fifth most diagnosed cancer worldwide, and the third leading cause of cancer death[1]. In 2020 there were more than 1 million new cases of stomach cancer diagnosed worldwide, and over 3 quarters of a million-stomach cancer deaths[2]. There are many well-known risk factors for stomach cancer including cigarette smoking, infection with *H. Pylori,* race, sex, genetics, and diet[3]. The International Agency for Research on Cancer has classified a number of occupational agents as stomach carcinogens, including work in the rubber manufacturing industry and exposure to x-radiation and gamma-radiation[4]. Several other occupational agents, including lead compounds, asbestos and nitrate, have been classified as possible stomach carcinogens, but there is limited evidence in humans[4].

Few studies have investigated the association between occupational heat exposure and stomach cancer. This study will expand on the limited current knowledge. Here we conducted a pooled analysis of associations between occupational heat exposure and stomach cancer risk using data from the stomach cancer pooling project (StoP). The StoP project and the datasets included in this study are discussed in more depth in continuation.

This study is based on the third release of the StoP Project; a consortium of 33 epidemiological studies, including a total of 12,753 gastric cancer cases and 30,682 controls (*www.stop-project.org*). Studies were identified through searches in electronic databases, backward citation tracking and contact with experts. Principal investigators were contacted and invited to participate. Investigators who agreed to participate provided the complete original dataset or a set of core variables from the study. Data harmonisation was conducted at a centralised single institution and a uniform rule was defined to recode each variable. Recruitment of studies and harmonisation of variables in the StoP project is described in detail elsewhere. In the StoP consortium, a total of 13 studies from Brazil, Canada, China, Italy, Japan, Russia, Spain and the USA contained some occupational information, such as questionnaire-based exposure information, or job titles and job durations. The present analysis is based on 3 included case-control studies with necessary information on occupational history and coded job titles, including two studies from Spain, MCC-Spain and PANESOES, and one study from Nebraska, USA. The remaining studies were excluded here as there was either no official job code available with which to estimate

history of occupational heat exposure or the job coding used was insufficiently detailed to allow for necessary translation.

Detailed information on each of these studies can be found elsewhere[5,6,7]. In brief, the MCC-Spain study is a multicentre, population-based, case-control study of five cancer types undertaken between 2008 and 2013 (www.mccspain.org). Histologically confirmed incident stomach cancer cases between the ages of 20 and 85 years old were recruited from 18 hospitals across 10 regions of Spain. Controls, frequency matched by age and sex, were identified from primary care centres located in the same area as hospitals from which cases were recruited. A computerised questionnaire was administered by trained personnel in face-to-face interviews. Response rates were 55% among stomach cancer cases and 53% among controls. The PANESOES study is a hospital-based case-control study undertaken between 1995 and 1999. Newly diagnosed, histologically confirmed, stomach cancer cases aged 30-80 years old were recruited from 9 hospitals in the Spanish provinces of Alicante and Valencia. Controls, frequency matched by age, sex and province were selected from the same hospitals as case subjects. Face-to-face interviews were conducted in hospital for all participants by trained interviewers, using a structured questionnaire. Overall, 91.9% of cases and 99.6% of controls, for all cancers in the PANESOES study, agreed to participate in the study. The Nebraska study is a population-based case-control study undertaken between 1988 and 1993. Incident stomach cancer cases aged 21 years or older were identified from the Nebraska Cancer Registry or through reviewing discharge diagnoses and pathology records of 14 hospitals across three regions.

All controls were frequency matched by age and sex. Controls under the age of 65 years were selected from the general population by random digit dialling, while controls aged 65 years and over were identified from Health Care Financing Administration Medicare files. Controls for deceased cases were selected from Nebraska mortality records with the additional matching factor of year of death. Cases and controls or their next-of-kin were interviewed by telephone. Response rates were 79% among stomach cancer cases and 72% among controls.

Analysis is ongoing and we are aiming to publish findings from this large-scale multi-country population-based study in early 2023.

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10. GLOSSARY

Barometric pressure – the pressure exerted by the weight of the air in the atmosphere

Black globe temperature – a measure of temperature that takes into account the interaction between convection and radiation of heat, resembling the thermal conditions felt by humans.

Natural wet-bulb temperature – a measure of temperature that considers the humidity of the surrounding environment.