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

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ABSTRACT

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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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	1.06 (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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