Occupation, occupational exposures and mammographic density in Spanish women

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ABSTRACT

***Introduction*:** Mammographic density (MD), the proportion of radiologically dense breast tissue, is a strong risk factor for breast cancer. Our objective is to investigate the influence of occupations and occupational exposure to physical, chemical, and microbiological agents on MD in Spanish premenopausal women.

***Methods*:** This is a cross-sectional study based on 1,362 premenopausal workers, aged 39-50, who attended a gynecological screening in a breast radiodiagnosis unit of Madrid City Council. The work history was compiled through a personal interview. Exposure to occupational agents was evaluated using the Spanish job-exposure matrix MatEmESp. MD percentage was assessed using the validated semi-automated computer tool DM-Scan. The association between occupation, occupational exposures, and MD was quantified using multiple linear regression models, adjusted for age, educational level, body mass index, parity, previous breast biopsies, family history of breast cancer, energy intake, use of oral contraceptives, smoking, and alcohol consumption.

***Results*:** Although no occupation was statistically significantly associated with MD, a borderline significant inverse association was mainly observed in orchard, greenhouse, nursery, and garden workers (β=-6.60; 95% confidence interval (95%CI)=-14.27; 1.07) and information and communication technology technicians (β=-7.27; 95%CI=-15.37; 0.84). On the contrary, a positive association was found among technicians in art galleries, museums, and libraries (β=8.47; 95%CI=-0.65; 17.60). Women occupationally exposed to fungicides, herbicides, and insecticides tended to have lower MD. The percentage of density decreased by almost 2% for every 5 years spent in occupations exposed to the mentioned agents.

***Conclusions*:** Although our findings point to a lack of association with the occupations and exposures analyzed, this study supports a deeper exploration of the role of certain occupational agents in MD, such as pesticides.

Key words: breast density; occupation; chemical agents; physical agents; job-exposure matrix, DDM-Madrid

Abbreviations

MD: mammographic density
BMI: body mass index
IARC: International Agency for Research on Cancer
95%CI: 95% confidence interval
CNO: National Classification of Occupations
MatEmESp: Spanish job-exposure matrix

1. INTRODUCTION

Mammographic density (MD), defined as the percentage of radiologically dense fibrous and glandular tissue seen on the mammographic image, represents an important breast cancer risk factor (Boyd et al., 2007, 2005). A key feature of MD, compared to other established risk factors for breast cancer, is its dynamic and modifiable nature. MD decreases progressively with age, transition to menopause, number of children, and body mass index (BMI). On the contrary, the use of combined hormonal therapy seems to increase this phenotype (Assi et al., 2012; Huo et al., 2014).

Breast cancer is the most frequent tumor and the second cause of cancer death in Spanish women (Ferlay et al., 2018) The origin of this tumor is multifactorial, and occupational factors have hardly been considered in the risk assessment (Fenga, 2016). The number of recognized occupational carcinogens has been increasing in recent decades. In 2017, 47 agents and 12 occupations or industries were recognized by the International Agency for Research on Cancer (IARC) with sufficient evidence of carcinogenicity in humans (Loomis et al., 2018). It has been estimated that around 5% of all cancers in Spain can be directly attributed to exposures that are considered occupational (Kogevinas, 2012). However, the true magnitude of the oncological workload could be greater, partly due to the new substances that are continuously introduced into the work environment without having been previously evaluated, and to the large number of possible carcinogens with still inconclusive evidence (IARC group 2B) (Kogevinas, 2012; Loomis et al., 2018). Some agents recognized by the IARC as carcinogens for breast cancer have been detected in occupational settings, such as X-radiation, gamma radiation, ethylene oxide, polychlorinated biphenyls, and night shift work involving circadian disruption (World Health Organization, 2020).

Previous studies detected an association between breast cancer risk and certain occupations, such as teachers, nurses, social workers, cashiers, women who work in the cosmetic, chemical, and pharmaceutical industry, hairdressers, and telephone operators (Goldberg and Labreche, 1996; Kourmousi and Alexopoulos, 2016; Lie et al., 2007; Pollán and Gustavsson, 1999). An association with night shift work has also been found (Megdal et al., 2005). However, there are only two previous studies that attempted to identify the occupations associated with higher MD, detecting higher risk among teachers and nurses (García-Pérez et al., 2017), and lower risk among managers and administrators in public sectors, agricultural workers and services and sales workers (Li et al., 2018). Regarding occupational exposures, as far as we know, there are hardly any studies that have evaluated their association with MD. While Lope et al. detected an increased MD among women occupationally exposed to perchloroethylene, ionizing radiation, mold spores, and aliphatic/alicyclic hydrocarbon solvents (Lope et al., 2018), other two studies associated this marker with self-reported history of night shift work (Pedraza-Flechas et al., 2017; Peplonska et al., 2012).

The identification of new occupational exposures that modulate MD is useful in two complementary aspects. On the one hand, it can provide a better understanding of the pathways by which certain agents exert their carcinogenic role on breast cancer and, on the other, its value as a marker of early biological effect and its modifiable nature allows the detection of workers with greater risk and establish prevention strategies. Given the limited information available, and the fact that published studies are based on predominantly postmenopausal women, in whom the breast tissue involution and the fall in hormone levels could have a significant influence, our objective is to identify the occupations associated with higher MD and to evaluate the influence of the occupational exposure to chemical, physical, and microbiological agents on MD in Spanish premenopausal working women.

2. MATERIALS AND METHODS

2.1 Study Population and data collection

DDM-Madrid is a cross-sectional study conducted between June 2013 and May 2015 (Lope et al., 2019). A sample of 1466 premenopausal workers, aged between 39 and 50, was recruited from the Madrid City Medical Diagnostic Center (*Madrid Salud*), where the women went for their routine gynecological examination. Women were invited to participate by phone prior to their screening visit. Those who accepted signed an informed consent document and answered an epidemiological survey previously used in the DDM-Spain study (DDM-Spain et al., 2012). This questionnaire was administered by three interviewers on the same day as the one scheduled for their medical examination. The participants also answered a 117-item food frequency questionnaire that included eating habits during the previous year, and which has been previously validated in the Spanish population (INMA-Valencia Cohort Study et al., 2013).

The craniocaudal and mediolateral oblique views of the 2D mammograms of both breasts were collected. The percentage of MD from the craniocaudal mammogram of the left breast was evaluated by an experienced radiologist using the DM-Scan computer tool, a free semi-automated software that quantifies MD in full-field digital images with high reproducibility and validity (Llobet et al., 2014; Pollán et al., 2013). The internal consistency of the radiologist was evaluated by conducting a pilot study with 100 women whose mammograms were duplicated and read again. An intra-class correlation coefficient of 0.87 was obtained between the first and second reading (95% confidence interval (95%CI)=0.82-0.92). Women whose MD could not be measured were excluded, as well as those who had analogical mammograms.

The epidemiological questionnaire included a section on occupational history, with information on the most recent occupation, the longest occupation, and time worked in each of them. Occupations were coded according to the 2011 National Classification of Occupations (CNO-11) (Instituto Nacional de Estadística (INE), 2020). The present study includes active women who had been working for at least one year, or women who stopped working during the previous year, but had worked for more than a year in their last occupation.

Occupational exposure to chemical, physical, and microbiological agents was assessed using the Spanish job-exposure matrix (García et al., 2013; MatEmEsp.org, 2020). This matrix has been developed specifically for Spanish workers, covering the period 1996-2005, and includes 52 chemical, 11 physical, and 2 microbiological agents, in alignment with those included in the Finnish job-exposure matrix (Kauppinen et al., 2009). The estimates to develop the matrix were made by a panel of hygienists and specialists with extensive experience in industrial hygiene in Spain. For each agent at each job title, the prevalence of exposure (proportion of exposed workers) and the intensity of exposure (1-year average concentration levels) were quantitatively assessed. The matrix considers as “exposed occupations” those in which at least 5% of the workers had a mean annual exposure level that exceeded the reference exposure level, which was obtained from the 2012 Spanish occupational Threshold Limit Values Document (Instituto Nacional de Seguridad e Higiene en el Trabajo (INSHT), 2012). In the case of ionizing radiation, those that exceeded 0.2 mSv were considered as “exposed occupations”. Since this matrix is based on the 1994 National Classification of Occupations (CNO-94), we had to recode the occupations found in our study from the CNO-11 to the CNO-94. This task was carried out by the same hygienists who developed the matrix.

2.2 Ethical approval

The DDM-Madrid study was conducted in accordance with the Declaration of Helsinki guidelines and was approved by the Ethics and Animal Welfare Committee of the Carlos III Institute of Health.

2.3 Statistical analysis

Characteristics of the participants were described with absolute values and percentages. Mean MD values and their corresponding 95%CIs were also calculated according to the women characteristics and compared using the Wald test.

Multiple linear regression models were used to analyze the association of MD with occupations and with the exposure to chemical, physical, and microbiological agents. An independent model for each occupation and each agent was performed. The response variable was the percentage of MD. Models were adjusted for age (continuous), educational level (primary school or less, secondary school, university graduate), BMI (continuous), parity (nulliparous, 1, 2, >2 children), previous breast biopsies (yes, no), family history of breast cancer (none, second degree only, first degree), daily caloric intake (continuous), use of oral contraceptives (never, past use, current use), smoking status (never, ex-smoker, current smoker), and alcohol consumption (never, <10 g/d, $\geq$10 g/d). We only considered those occupations with at least 10 workers and those agents to which at least 10 women were exposed. Given the low number of participants in some occupations, we have repeated these analyses adjusting only for age and BMI in the Supplementary material, Table S1 and Table S2. Furthermore, to take into account the problem of multiple comparisons or multiple testing (which occurs when a set of statistical inferences is considered simultaneously), *P*-values were also suitably adjusted by controlling the expected proportion of false positives (False Discovery Rate), as proposed by Benjamini & Hochberg (Benjamini and Hochberg, 1995).

Finally, the duration of exposure was also evaluated, both for each occupation and for each agent, using the number of months exposed as an explanatory variable and analyzing the increase or decrease in MD for every 5 years of exposure. All analyses were performed using STATA/MP 15.0 software.

3. RESULTS

Results presented in this manuscript are based on 1362 women (93%). The general characteristics of the study population, as well as the mean percentage of MD according to these characteristics, are presented in Table 1. The mean percentage (± standard deviation) of MD in the study population was 34.3 ± 17.4. The mean age was 44 ± 2.8 years. More than half attended university (61%), had a BMI between 18.5 and 24.9 kg/m^2 (66%), had two or more children (53%), ever used oral contraceptives (59%), and consumed less than 10 g/day of alcohol (66%). Furthermore, 38% of women never smoked, and the mean calorie intake was 1978 ± 677 kcal/d. MD was significantly higher in women with lower BMI, in nulliparous women, in those who had never used oral contraceptives, in women with high caloric intake, and in workers who had previous breast biopsies. The mean duration of the participants' last occupation was 16 years.

Table 2 shows the association between MD and occupations with at least 10 workers. Although no occupation was statistically significantly associated with MD, an inverse association was observed in the information and communication technology sector (β=-7.27; 95%CI=-15.37; 0.84), and among skilled workers in orchards, greenhouses, nurseries, and gardens (β=-6.60; 95%CI=-14.27; 1.07). In contrast, technicians in art galleries, museums, and libraries (β=8.47; 95%CI=-0.65; 17.60) presented higher MD. Regarding the analysis by duration of employment, we also did not observe an association. It is worth noting that MD of women who worked in art galleries, museums, and libraries increased by 3% for every 5 years worked in this occupation (β=2.98; 95%CI=-0.55; 6.51), while MD of information and communication technology technicians decreased 2% (β=-1.98; 95%CI=-4.06; 0.11).

With respect to the association between MD and occupational exposure to different chemical, physical, and microbiological agents (Table 3), workers exposed to fungicides, herbicides, and insecticides of the endosulfan type had lower MD (β=-6.19; 95%CI=-12.56; 0.19). The participants most exposed to these agents were workers in orchards, greenhouses, nurseries, and gardens, as well as the agricultural, forestry, and natural environment technicians (data not shown). In addition, exposure to other types of insecticides (chlorpyrifos, methomyl and pyrethrin) also showed an inverse association with MD (β=-5.73; 95%CI=-11.63; 0.17). Workers in the aforementioned sectors, as well as kitchen assistants and cleaning staff in offices, hotels, and other similar establishments were exposed to these insecticides (data not shown). Participants exposed to microbiological agents, specifically non-human bacteria and mold spores, as well as workers exposed to gasoline, volatile sulfur compounds, and animal dust also showed an inverse association with MD (β=-6.60; 95%CI=-14.27; 1.07). The workers in orchards, greenhouses, nurseries, and gardens were the occupations exposed to the mentioned agents. Finally, an inverse association was detected with exposure to wood dust (β=-5.44; 95%CI=-11.70; 0.82), an agent to which a greater diversity of occupations were exposed.

Regarding the exposure time (Table 3), we observed that MD decreased for every 5 years spent in occupations exposed to herbicides, fungicides, insecticides of endosulfan type (β=-1.53; 95%CI=-3.32; 0.26), other types of insecticides (β=-1.63; 95%CI=-3.35; 0.08), and wood dust (β=-1.61; 95%CI=-3.43; 0.22).

Supplementary Tables S1 and S2 show the association of MD with occupations (Table S1) and occupational exposures (Table S2) adjusting only for age and BMI. As can be seen, the estimators of the associations described go in the same direction as those observed in Tables 2 and 3. In some associations, the *P*-values are somewhat less significant, but in other exposures, as in the case of pesticides, the inverse association is reinforced.

4. DISCUSSION

This study analyzes the association between occupation, occupational exposure to physical, chemical, and microbiological agents and MD in a sample of more than 1300 workers in Madrid. Although, in general, none of the occupations or occupational exposures studied were consistently associated with MD, we found an inverse association among women employed in agricultural activities, and among workers exposed to pesticides, gasoline, volatile sulfur compounds, animal and wood dust, and microbiological agents.

Women who worked in orchards, greenhouses, nurseries, and gardens had lower MD. Li et al, in a study that included 4,867 Chinese women from the National Cancer Screening Program, also observed lower MD among agricultural workers (Li et al., 2018). However, in another study that tried to identify occupations associated with high MD, these professionals were not included (García-Pérez et al., 2017). However, this finding is consistent with recent epidemiological studies that have shown lower breast cancer risk in gardeners, farmers, carpenters or workers employed in the agricultural sector in general (Kaneko et al., 2019; Katuwal et al., 2018). Workers employed in these activities are exposed to pesticides and, to a lesser extent, to microbiological agents, gasoline (polycyclic aromatic hydrocarbons), volatile sulfur compounds, and animal dust (MatEmEsp.org, 2020), compounds that have been inversely associated with MD in our study. Lope et al (Lope et al., 2018) also found an inverse relationship between MD and exposure to gasoline. However, they found no association with exposure to pesticides, volatile sulfur compounds, and animal dust (Lope et al., 2018).

The 13 study participants included in occupational category 3733 (Technicians in art galleries, museums, and libraries) were all “library technicians” or “auxiliary library technicians”. The higher MD detected in these workers is difficult to explain. Several previous studies have detected an excess risk of breast cancer among these professionals (Pollán et al., 2001; Teitelbaum et al., 2003; Zheng et al., 2002). One of them detected this association in young and parous women (Teitelbaum et al., 2003). Pollán et al attributed the association observed among Swedish men to possible exposure to electromagnetic fields of frequencies above the ELF-range from electronic security systems, or to the sedentary behavior of these professionals (Pollán et al., 2001). The potential exposure to carcinogenic chemicals has not been characterized in these professionals (Snedeker, 2006). This occupation involves extensive handling of printed paper, yet little is known about transfer of dyes or inhalation of paper treatments. The solvent formaldehyde is used in paper finishing and in manufacturing carbonless paper (Snedeker, 2006) and, precisely, occupational exposure to this solvent was associated with higher MD in Spanish women (Lope et al., 2018).

Although some of the pesticides studied are probably or likely human carcinogens (captan, diuron), mammary carcinogens (diuron), xenoestrogens (2-4D, diuron, endosulfan, and methomyl), and cholinesterase inhibitors (chlorpyrifos), ecological studies have not found a general pattern of association between exposure to these pesticides and breast cancer risk (Brody et al., 2004; Reynolds et al., 2005). Regarding MD, while one study showed that women exposed to dichlorodiphenyltrichloroethane (DDT) in utero had higher MD in their adult stage (Krigbaum et al., 2020), two other studies showed lower breast density in women with high circulating levels of persistent organic compounds (Diorio et al., 2013; Rusiecki et al., 2020). Given that these and other lipophilic chemical compounds are mainly stored in adipose tissue, and that many of them induce an obesogenic effect (La Merrill et al., 2013), we could hypothesize that these pesticides, stored in the fatty tissue of the breast, could alter the structure of the breast tissue, increasing the fat (no dense) mass of the breast and, thereby, decreasing the relative proportion of dense tissue.

Regarding the limitations of the study, it should be noted that, due to the cross-sectional design, interpretations of causality between MD and occupational factors cannot be made, and possible variations in the MD of women over time cannot be taken into account. Second, it would have been very interesting to evaluate the association of occupational exposures with the absolute area of dense and non-dense breast tissue, to be able to confirm if the association detected with the agricultural sector is due to an increase in the fatty tissue of the breast. However, we could not obtain this information because the DICOM files did not contain the metadata that indicates the pixel size of the mammograms, necessary to do the conversion from pixel to cm^2. Third, although we had mammograms of both breasts, only the density of the cranio-caudal mammogram of the left breast was assessed. This fact does not imply a bias, since several studies have shown a high correlation between MD measurements in both breasts (Ciatto et al., 2005; Maskarinec et al., 2006). Furthermore, to our knowledge, MD has not been associated with breast cancer laterality (Hennessey et al., 2014). Fourth, despite having adjusted the models for the main established predictors, residual confounders, associated with specific occupations or with MD, may have interfered with the detected associations. Fifth, since women were recruited in a single center in Madrid, the external validity of the study is limited. It could also suffer from a selection bias, since certain characteristics of the workers (such as the presence of previous breast pathologies, having private insurance or having a high workload that prevents them from going to the center) could influence the participation rate. Another limitation to consider is the problem of multiple comparisons, the possibility of finding associations that are falsely positive or negative by chance. To address this problem, we have provided adjusted *P*-values by Benjamini & Hochberg method (Benjamini and Hochberg, 1995). However, from an epidemiological point of view, we have preferred to discuss the results based on the magnitude of the association, the consistency of the observed associations, and the biological plausibility. On the other hand, we have focused on the analysis of the last occupation and on expositions that took place the previous year. We decided to do so because MD is a dynamic trait, and certain environmental factors can modulate it (Nazari and Mukherjee, 2018). Thus, the influence of exogenous exposures on density could cease when exposure is interrupted. Anyway, a sensitivity analysis was fitted including women who reported being actively working in the same occupation during the last 5 years (93% of the total sample), and the results were very similar to those observed in Table 2 and Table 3 (data not shown). Another limitation is that the assessment of exposure using a job-exposure matrix implies a classification bias, generally non-differential, caused by the variability of exposure within and between occupational groups. This misclassification could imply an underestimation of the effects found. However, the use of these matrices provides greater statistical power, by allowing the grouping of workers from different occupations for which a similar range of exposure was estimated. Finally, we must be cautious with associations based on a low number of exposed workers.

One of the main strengths of the study is the high participation rate and its novelty. As far as we know, there are only two previous articles that have studied the association of MD with occupations (García-Pérez et al., 2017) or with occupational exposures other than night shift work (Lope et al., 2018), both with a lower number of premenopausal women than those included in this analysis. Furthermore, all mammograms were measured on a continuous scale using a validated computer-assisted method and by a single reader that showed high internal consistency. Since the participants underwent their routine gynecological examination at the Madrid medical diagnostic center, mammograms were obtained in the context of routine clinical practice, without the need for additional mammograms, and using the same equipment. Finally, we have used the first general population job-exposure matrix specifically designed for the Spanish working population (García et al., 2013). MatEmESp has allowed us to relate exposure to occupational agents to MD in an efficient and detailed way, without having to resort to matrices built in other countries for other working populations.

5. CONCLUSIONS

In general, our findings point to an absence of association with the occupations and exposures studied. Library technicians had a higher MD, while women involved in agricultural sector occupations had a lower MD, although both associations did not reach the statistical significance. Occupational exposure to pesticides, gasoline, volatile sulfur compounds, animal dust, wood dust, and bacteria of non-human origin was also inversely associated with breast density. Further research is needed to confirm whether these results reflect real associations.

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Table 1. Descriptive characteristics and mammographic density of the DDM-Madrid participants.

	n (%)	Mammographic density (%) mean (95%CI)	*P*-value	*P*-value[a]
Total	1362 (100)	34.3 (33.3; 35.2)		
Age, years			0.015	0.391
<45	727 (53.4)	35.4 (34.1; 36.6)		
>=45	635 (46.6)	33.0 (31.7; 34.4)		
Education			0.001	0.344
Primary school or less	60 (4.4)	31.0 (26.5; 35.4)		
Secondary school	475 (34.9)	32.6 (31.1; 34.1)		
University graduate	826 (60.7)	35.5 (34.3; 36.7)		
Age at menarche, years			0.007	0.512
< 12	311 (23.0)	32.0 (30.1; 34.0)		
12-13	731 (54.1)	34.6 (33.4; 35.9)		
>13	309 (22.9)	35.8 (33.8; 37.8)		
Body mass index, kg/m^2			<0.001	<0.001
<18.5	22 (1.6)	43.9 (35.8; 52.0)		
18.5-24.9	894(65.7)	38.9 (37.8; 40.0)		
25-29.9	309 (22.7)	26.9 (25.3; 28.6)		
≥30	136 (10.0)	19.0 (16.8; 21.3)		
Number of children			<0.001	0.001
None	323 (23.7)	37.1 (35.1; 39.1)		
1	321 (23.6)	34.8 (32.8; 36.8)		
2	642 (47.1)	32.8 (31.6; 34.1)		
>2	76 (5.6)	32.1 (28.4; 35.7)		
Age at first child, years			0.140	0.119
Nulliparous	323 (23.7)	37.1 (35.1; 39.1)		
<25	73 (5.4)	29.1 (25.2; 33.0)		
25-29	284 (20.9)	32.9 (31.1; 34.8)		
30-34	454(33.3)	33.3 (31.8; 34.9)		
>34	228 (16.7)	35.5 (33.1; 37.8)		
Breastfeeding, months			0.804	0.581
< 3	354 (34.1)	33.1 (31.2; 35.0)		
4-6	386 (37.2)	33.7 (32.1; 35.3)		
> 6	298 (28.7)	33.4 (31.5; 35.3)		
Use of oral contraceptives			0.002	0.011
Never	510 (37.7)	36.1 (34.5; 37.8)		
Past use	795 (58.8)	33.4 (32.2; 34.5)		
Current use	46 (3.4)	31.0 (26.5; 35.5)		
Energy intake, Kcal/day[b]			0.142	0.012
<1672.1	403 (33.4)	33.4 (31.7; 35.1)		
1672.1-2151.1	403 (33.4)	35.8 (34.1; 37.5)		
>2151.1	403 (33.4)	35.2 (33.5; 36.9)		
Physical activity (MET-h/week)				
No	567(41.8)	32.9 (31.5; 34.3)	0.002	0.911
≤12	340(25.1)	33.8 (31.9; 35.6)		
>12	449(33.1)	36.4 (34.7; 38.1)		
Tobacco consumption			0.037	0.151
Never	518 (38.0)	35.5 (34.0; 37.0)		
Former smoker	480 (35.2)	33.9 (32.3; 35.4)		
Current smoker	364 (26.7)	33.1 (31.3; 34.9)		
Alcohol consumption, g/day			0.476	0.812
Never	245 (20.3)	34.1 (31.8; 36.3)		
<10	793 (65.6)	35.0 (33.8; 36.2)		
≥10	170 (14.1)	35.2 (32.6; 37.8)		
Family history of breast cancer			0.877	0.858
None	1058 (77.7)	34.2 (33.2; 35.2)		
Second degree only	211 (15.5)	34.8 (32.3; 37.3)		
First degree	93 (6.8)	34.0 (30.4; 37.5)		
Previous breast biopsy			<0.001	<0.001

No	1222 (89.8)	33.5	(32.6; 34.5)		
Yes	139 (10.2)	41.0	(38.1; 43.9)		
Duration of employment, years				0.028	0.086
<12	489 (35.9)	35.3	(33.8; 36.9)		
12-20	465 (34.1)	34.5	(32.9; 36.1)		
>20	408 (30.0)	32.8	(31.1; 34.4)		

[a] Adjusted for age and body mass index.

[b] Variable in tertiles

Table 2. Association between mammographic density, occupation, and duration of employment.

		Exposed vs non-exposed					Time of exposure				
Code[a]	Occupation[b]	n	β[c]	(95%CI)	*P*-val	*P*-BH[d]	Mean[e]	β[f]	(95%CI)	*P*-val	*P*-BH[d]
1	Directors and managers	11	-1.89	(-11.50; 7.73)	0.701	0.901	137	-1.35	(-5.02; 2.32)	0.471	0.707
2	Technicians and intellectual and scientific professionals	271	-0.64	(-2.95; 1.68)	0.590	0.901	181	-0.28	(-0.97; 0.40)	0.417	0.707
21	Healthcare professionals	19	1.75	(-5.65; 9.16)	0.643	0.869	204	0.33	(-1.73; 2.39)	0.756	0.903
2121	Non-specialized nurses	11	5.85	(-3.79; 15.48)	0.234	0.721	216	1.46	(-1.16; 4.08)	0.275	0.721
232	Other teachers and teaching professionals	11	-4.18	(-13.79; 5.42)	0.393	0.668	201	-1.81	(-4.39; 0.77)	0.169	0.657
2329	Teachers and teaching professionals not classified under other headings	10	-2.68	(-12.79; 7.44)	0.604	0.963	197	-1.47	(-4.22; 1.28)	0.294	0.798
24	Professionals in the physical, chemical, mathematical, and engineering sciences	20	-1.47	(-8.86; 5.93)	0.697	0.869	205	-0.26	(-2.27; 1.75)	0.801	0.903
246	Technicians engineers (except agricultural, forestry, electrical electronic, and ICT)	10	-7.64	(-19.09; 3.81)	0.191	0.632	174	-2.26	(-5.89; 1.37)	0.222	0.657
26	Specialists in organization of public administration and companies, and in marketing	105	-2.15	(-5.45; 1.14)	0.201	0.692	161	-0.80	(-1.90; 0.30)	0.155	0.703
262	Specialists in organization and administration	102	-2.18	(-5.53; 1.17)	0.202	0.632	159	-0.88	(-2.02; 0.25)	0.126	0.657
2623	Specialists in public administration	97	-2.42	(-5.85; 1.00)	0.165	0.721	159	-0.96	(-2.13; 0.20)	0.103	0.798
282	Sociologists, historians, psychologists, and other professionals in social science	80	2.42	(-1.38; 6.23)	0.212	0.632	186	0.17	(-0.95; 1.29)	0.766	0.893
2824	Labor and social education professionals	70	2.92	(-1.11; 6.94)	0.156	0.721	182	0.30	(-0.89; 1.48)	0.626	0.813
29	Culture and entertainment professionals	20	-3.75	(-10.96; 3.46)	0.307	0.692	167	0.03	(-2.27; 2.33)	0.978	0.985
291	Archivists, librarians, conservatives, and related	19	-5.40	(-12.81; 2.01)	0.153	0.632	159	-0.85	(-3.37; 1.67)	0.509	0.751
2912	Librarians, documentalists, and related	18	-5.66	(-13.28; 1.96)	0.145	0.721	158	-0.88	(-3.48; 1.71)	0.503	0.813
3	Technicians, support professionals	181	-0.30	(-2.90; 2.29)	0.818	0.721	183	0.04	(-0.71; 0.79)	0.922	0.941
31	Science and engineering technicians	16	3.00	(-5.76; 11.81)	0.500	0.806	186	2.17	(-1.02; 5.35)	0.182	0.703
33	Health technicians and professionals in alternative therapies	16	3.20	(-5.26; 11.65)	0.458	0.806	175	1.29	(-1.59; 4.16)	0.379	0.779
331	Laboratory health, diagnostic tests, and prosthetics technicians	10	0.56	(-10.18; 11.29)	0.919	0.951	182	0.71	(-2.59; 4.01)	0.673	0.872
36	Support professionals for administration management; forces and security forces technicians	65	-1.39	(-5.45; 2.66)	0.501	0.806	151	-0.01	(-1.37; 1.35)	0.985	0.985
361	Administrative and specialized assistants	20	-4.32	(-11.30; 2.67)	0.226	0.632	186	-1.01	(-3.00; 0.99)	0.323	0.657
3613	Management and administrative assistants	17	-4.19	(-11.79; 3.41)	0.280	0.280	198	-0.87	(-2.94; 1.21)	0.415	0.798
362	Customs, tax, and related agents that work in tasks of the public administration	45	0.09	(-4.81; 4.99)	0.972	0.972	135	0.81	(-1.01; 2.63)	0.380	0.701
3622	Support professionals of the public administration of social services	24	-1.40	(-8.14; 5.33)	0.683	0.963	128	1.04	(-1.58; 3.67)	0.435	0.798
3629	Other support professionals of the public administration for inspection and control tasks and similar tasks	13	6.44	(-2.70; 15.58)	0.167	0.721	154	2.31	(-0.84; 5.45)	0.150	0.798
37	Professionals supporting legal, social, cultural, sports, and related services	68	0.75	(-3.25; 4.75)	0.713	0.869	208	0.13	(-0.90; 1.16)	0.805	0.903
372	Sports women, trainers, sports activity instructors; recreational activity monitors	47	-0.52	(-5.27; 4.24)	0.832	0.917	236	-0.12	(-1.24; 1.01)	0.840	0.901
3723	Sports activities instructors	46	-0.49	(-5.30; 4.32)	0.842	0.966	239	-0.11	(-1.24; 1.02)	0.844	0.976
3733	Technicians in art galleries, museums, and libraries	13	8.47	(-0.65; 17.60)	0.069	0.721	130	2.98	(-0.55; 6.51)	0.098	0.798
38	Information and communication technology technicians	15	-7.27	(-15.37; 0.84)	0.079	0.692	216	-1.98	(-4.06; 0.11)	0.064	0.703
4	Accounting, administrative, and other office employees	646	1.25	(-0.53; 3.04)	0.169	0.660	209	0.12	(-0.34; 0.57)	0.618	0.795
430	Other administrative employees without public service tasks	628	1.34	(-0.45; 3.12)	0.142	0.632	210	0.15	(-0.30; 0.61)	0.505	0.751
4309	Administrative employees without public service tasks not classified under other headings	624	1.33	(-0.45; 3.11)	0.144	0.721	210	0.16	(-0.30; 0.61)	0.500	0.813
5	Catering, personal protection, and sales service workers	76	0.92	(-3.04; 4.88)	0.649	0.901	159	0.53	(-0.78; 1.84)	0.430	0.707
56	Health care workers in health services	10	0.99	(-8.64; 10.62)	0.840	0.914	163	0.67	(-2.40; 3.75)	0.668	0.903

583	Building maintenance and cleaning supervisors, supers, and housekeepers	31	-1.82	(-8.09; 4.44)	0.568	0.793	128	-0.81	(-3.49; 1.88)	0.555	0.795
5831	Maintenance and cleaning supervisors in offices, hotels, and other establishments	12	2.20	(-7.98; 12.38)	0.672	0.963	164	0.12	(-3.36; 3.60)	0.945	0.976
5833	Building superintendents	19	-4.22	(-12.11; 3.67)	0.294	0.721	106	-2.14	(-6.32; 2.04)	0.316	0.798
59	Protection and security services workers	27	2.60	(-3.79; 8.99)	0.426	0.806	189	0.68	(-1.18; 2.54)	0.476	0.801
5923	Local policewomen	21	3.42	(-3.77; 10.61)	0.352	0.721	201	0.82	(-1.22; 2.86)	0.430	0.798
6120	Skilled workers in orchards, greenhouses, nurseries, and gardens	20	-6.60	(-14.27; 1.07)	0.092	0.721	225	-1.46	(-3.42; 0.51)	0.147	0.798
7	Craftswomen and skilled workers in manufacturing and construction industries (except facility and machinery operators)	70	-0.15	(-4.39; 4.08)	0.944	0.944	157	0.06	(-1.41; 1.52)	0.941	0.941
7899	Officers, operators, and craftswomen of other trades not classified under other headings	69	-0.76	(-5.03; 3.51)	0.728	0.966	154	-0.31	(-1.82; 1.19)	0.681	0.939
9	Elementary occupations	83	-2.26	(-5.88; 1.35)	0.220	0.660	132	-0.85	(-2.36; 0.65)	0.267	0.707
9431	Ordinances	76	-2.10	(-5.88; 1.68)	0.277	0.721	135	-0.66	(-2.22; 0.89)	0.404	0.798

[a] Coded according to the 2011 National Classification of Occupations.

[b] Occupations with at least 10 exposed workers.

[c] Adjusted for age, education, body mass index, parity, oral contraceptives use, previous breast biopsies, family history of breast cancer, smoking, energy intake, and alcohol consumption.

[d] P-value adjusted by Benjamini & Hochberg´s method.

[e] Mean of months spent in the corresponding occupation.

[f] Increase or decrease in the percentage of mammographic density for every 5 years spent in the corresponding occupation. Adjusted for age, education, body mass index, parity, oral contraceptives use, previous breast biopsies, family history of breast cancer, smoking, energy intake, and alcohol consumption.

Table3. Association between mammographic density, exposure to occupational agents and time of exposure.

		Exposed vs non-exposed				Time of exposure				
Occupational agent[a]	n	β[b]	(95%CI)	*P*-val	*P*-BH[c]	Mean[d]	β[e]	(95%CI)	*P*-val	*P*-BH[c]
Chemical agents										
Organic dust										
Animal dust	20	-6.60	(-14.27; 1.07)	0.092	0.269	225	-1.46	(-3.42; 0.51)	0.147	0.415
Plant dust	45	-2.59	(-7.78; -2.61)	0.329	0.658	197	-0.85	(-2.34; 0.65)	0.267	0.815
Pulp or paper dust	17	2.83	(-5.37; 11.04)	0.499	0.862	167	0.70	(-1.99; 3.39)	0.610	0.815
Wood dust	28	-5.44	(-11.70; 0.82)	0.088	0.269	193	-1.61	(-3.43; 0.22)	0.085	0.415
Inorganic mineral dust										
Quartz dust	92	-2.32	(-6.04; 1.40)	0.222	0.527	166	-0.80	(-2.01; 0.42)	0.198	0.502
Other mineral dusts	88	-0.68	(-4.51; 3.15)	0.728	0.892	152	-0.44	(-1.82; 0.94)	0.532	0.815
Metals										
Chromium	69	-0.76	(-5.03; 3.51)	0.728	0.892	154	-0.31	(-1.82; 1.19)	0.681	0.815
Lead	28	-5.21	(-11.60; 1.17)	0.110	0.299	189	-1.36	(-3.22; 0.50)	0.153	0.415
Nickel	69	-0.76	(-5.03; 3.51)	0.728	0.892	154	-0.31	(-1.82; 1.19)	0.681	0.815
Cadmium	69	-0.76	(-5.03; 3.51)	0.728	0.892	154	-0.31	(-1.82; 1.19)	0.681	0.815
Fungicides[f]	29	-6.19	(-12.56; 0.19)	0.057	0.269	211	-1.53	(-3.32; 0.26)	0.094	0.415
Herbicides[g]	29	-6.19	(-12.56; 0.19)	0.057	0.269	211	-1.53	(-3.32; 0.26)	0.094	0.415
Insecticides										
chlorpyrifos, methomyl, pyrethrin	33	-5.73	(-11.63; 0.17)	0.057	0.269	203	-1.63	(-3.35; 0.08)	0.062	0.415
Endosulfan	29	-6.19	(-12.56; 0.19)	0.057	0.269	211	-1.53	(-3.32; 0.26)	0.094	0.415
Engine exhaust										
Diesel engine exhaust	28	2.53	(-3.59; 8.64)	0.418	0.794	174	0.79	(-1.15; 2.73)	0.427	0.773
Gasoline engine exhaust	25	3.46	(-3.06; 9.97)	0.298	0.629	189	0.88	(-1.07; 2.83)	0.375	0.713
Gasoline	20	-6.60	(-14.27; 1.07)	0.092	0.269	225	-1.46	(-3.42; 0.51)	0.147	0.415
Volatile sulfur compounds	20	-6.60	(-14.27; 1.07)	0.092	0.269	225	-1.46	(-3.42; 0.51)	0.147	0.415
Detergents	160	0.65	(-2.10; 3.40)	0.645	0.892	180	-0.02	(-0.84; 0.81)	0.966	0.966
Oil mists	70	-0.41	(-4.66; 3.84)	0.850	0.941	154	-0.23	(-1.73; 1.27)	0.765	0.831
Physical agents										
Cold	213	-1.73	(-4.17; 0.70)	0.163	0.413	172	-0.39	(-1.14; 0.37)	0.313	0.646
Heat	192	-0.72	(-3.32; 1.88)	0.586	0.892	191	-0.19	(-0.93; 0.55)	0.609	0.815
Low-frequency magnetic fields	797	-0.02	(-1.81; 1.78)	0.986	0.986	199	-0.08	(-0.54; 0.38)	0.729	0.815
Low-frequency magnetic ultrasounds	12	-1.14	(-11.27; 9.00)	0.826	0.941	178	0.14	(-2.98; 3.26)	0.930	0.965
Ultraviolet radiation	95	-1.05	(-4.55; 2.45)	0.556	0.892	210	-0.18	(-1.12; 0.75)	0.701	0.815
Ionizing radiation	26	3.67	(-2.84; 10.18)	0.269	0.601	194	1.10	(-0.80; 3.00)	0.258	0.613
Microbiological agents										
Mold spores	20	-6.60	(-14.27; 1.07)	0.092	0.269	225	-1.46	(-3.42; 0.51)	0.147	0.415
Bacteria of non-human origin	20	-6.60	(-14.27; 1.07)	0.092	0.269	225	-1.46	(-3.42; 0.51)	0.147	0.415

[a] Agents with at least 10 exposed workers.

[b] Adjusted for age, education, body mass index, parity, oral contraceptives use, previous breast biopsies, family history of breast cancer, smoking, energy intake, and alcohol consumption.

[c] P-value adjusted by Benjamini & Hochberg´s method.

[d] Mean of months exposed to the corresponding agent.

[e] Increase or decrease in the percentage of mammographic density for every 5 years exposed to the corresponding agent. Adjusted for age, education, body mass index, parity, oral contraceptives use, previous breast biopsies, family history of breast cancer, smoking, energy intake, and alcohol consumption.

[f] Includes captan and thiram.

[g] Includes 2,4-D, atrazine, diquat, and diuron.