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**Occupational exposures and mammographic density in Spanish women**

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**ABSTRACT**

**Objectives:** The association between occupational exposures and mammographic density (MD), a marker of breast cancer risk, has not been previously explored. Our objective was to investigate the influence of occupational exposure to chemical, physical, and microbiological agents on MD in adult women.

**Methods**: This is a population-based cross-sectional study based on 1476 female workers, aged 45-65 years, from seven Spanish breast cancer screening programs. Occupational history was surveyed by trained staff. Exposure to occupational agents was assessed by using the Spanish job-exposure matrix MatEmESp. Percentage of MD was measured by two radiologists using a semiautomatic-computer tool. The association was estimated using mixed log-linear regression models, adjusting for age, education, body mass index, menopausal status, parity, smoking, alcohol intake, type of mammography, family history of breast cancer, and hormonal therapy use, and including screening center and professional reader as random effects terms.

**Results**: Although no association was found with most of the agents, women occupationally exposed to perchloroethylene ($e^{\beta}$=1.51; 95%CI=1.04 to 2.19), ionizing radiation ($e^{\beta}$=1.23; 95%CI=0.99 to 1.52) and mold spores ($e^{\beta}$=1.44; 95%CI=1.01 to 2.04) tended to have higher MD. The percentage of density increased 12% for every 5-years exposure to perchloroethylene or mold spores, 11% for every 5-years exposure to aliphatic/alicyclic hydrocarbon solvents and 3% for each 5-years exposure to ionizing radiation.

**Conclusions**: Exposure to perchloroethylene, ionizing radiation, mold spores or aliphatic/alicyclic hydrocarbon solvents in occupational settings could be associated with higher MD. Further studies are needed to clarify the accuracy and the reasons for these findings.

**What this paper adds?**

- This study investigates the influence of occupational exposure to chemical, physical, and microbiological agents on mammographic density in Spain, using MatEmESp, a Spanish job-exposure matrix. Up to date, this is the first study exploring such association.
- Our results suggest that exposure to perchloroethylene, aliphatic/alicyclic hydrocarbon solvents, ionizing radiation, and to mold spores could be linked to higher mammographic density.

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- Our results indicate that certain occupational exposures may influence mammographic density, results that need to be confirmed in future studies.

## BACKGROUND

Mammographic density (MD) refers to the percentage of radiologically dense fibroglandular tissue that appears as white areas on a mammogram. It is one of the strongest known risk factors for breast cancer,[1 2] and is the factor with the greatest attributable fraction.[3] Indeed, 26% of breast cancers in women aged under 56 years were attributable to breast densities >50%. [1] Besides the genetic component,[4] it has been shown that MD declines progressively with increasing age, with increasing body mass index, with each pregnancy, and with menopausal transition.[3] By contrast, hormone replacement therapy, particularly treatments combining estrogen and progestin, was found to increase MD.[3] Given that the stroma is the major tissue component of the breast, the biological mechanisms through which MD may exert tumorigenic risk are likely to involve the stromal cells, extra-cellular matrix proteins, and their interaction with the epithelial component.[5]

Occupational studies have played an important role in the identification of carcinogens and potential risk factors, since exposure to occupational factors tend to be longer, more intense, and better documented than in other contexts. It has been estimated that, in 2004, 25.4% of the Spanish working population was exposed to carcinogens in the workplace.[6] Based on the assessments of the International Agency for Research on Cancer (IARC), there are 12 carcinogenic agents with sufficient or limited evidence in humans for breast cancer.[7] Among them, ionizing radiation, ethylene oxide, polychlorinated biphenyls, and shift work that involves circadian disruption have been detected in occupational settings. In addition, more than 200 chemicals may induce mammary gland tumors in experimental animals.[8] Among others, the list includes 36 industrial chemicals, 6 chlorinated solvents, 18 products of combustion, 10 pesticides, 18 dyes, 47 pharmaceuticals, and radiation. It has been estimated that more than 5000 U.S women have been exposed to 25 of these chemicals at work.[8] Furthermore, many of these substances are known as endocrine-disrupting chemicals, compounds that may disrupt normal mammary gland development and lead to adverse lifelong consequences, such as breast cancer.[9]

Regarding MD, to our knowledge the association between occupational exposures and mammographic density has barely been studied. In non-occupational environmental settings, a positive

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association has been observed with high serum levels of bisphenol A and mono-ethyl phthalate,[10] and with exposure to cadmium.[11] In contrast, an inverse association with some polychlorinated biphenyls congeners has also been described.[12] In two previous studies, our group sought to identify occupations with high MD in Spanish female workers,[13] as well as to evaluate the possible association between MD and self-reported history of nightshift work,[14] association that had been previously explored.[15] The availability of a job-exposure matrix, purpose-made for the Spanish working population, that allows to evaluate occupational exposure to chemical, physical, and microbiological agents,[16] makes it possible to explore the effect of such substances in the workplace. The aim of this study is thus to investigate the possible association between MD and current occupational exposure to chemical, physical, and microbiological compounds among a group of Spanish women with paid employment attending breast cancer screening programs.

## METHODS

DDM-Spain (Determinants of Mammographic Density in Spain) and Var-DDM (Variability of the Mammographic Density in Spanish Women) are two linked research projects carried out in Spain with the purpose of identifying determinants of MD. DDM-Occup is the branch of these projects which intends to deepen into the study of the occupations, occupational exposures to toxic agents, and working conditions that are associated with MD.

Briefly, for this cross sectional multicenter study, women aged 45–68 years were recruited between October 2007 and September 2008 from seven public population-based breast cancer screening centers located in the following regions: Aragon, Balearic Isles, Castile-Leon, Catalonia, Galicia, Navarre, and Valencian Region. Each center had to enroll at least 500 participants. Thus, the total number of participants was 3584 with an average participation rate of 74.5% (range: 64.7-84.0%). Women were contacted by telephone and those who agreed to participate signed an informed consent and were interviewed at the screening center by trained interviewers. Those women that reported previous breast or ovarian cancer, breast surgery or implant were excluded. In a second step, we also excluded 10 women who developed breast cancer within 6 months of the mammogram. The DDM-Spain study protocol was evaluated and formally approved by the Bioethics and Animal Welfare Committee at the Carlos III Institute of Health. Further details of the study design can be found in previous publications.[17,18]

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Given the high correlation between images of the left and right breast and between the two standard views (cranio-caudal and medio-lateral oblique),[19] we decided to use the cranio-caudal mammogram of the left breast for 3309 women in different formats: 1781 were analogical images digitalized with a Totalook MammoAdvantage scanner; 1376 were digital images (Senographe 2000D Full Field Digital Mammography System; Hologic-Lorad M-IV; Siemmens MAMMOMAT Novation DR) and the remaining 152 mammograms were originally digital mammograms printed on film and digitalized with a Microtek Medi-700 scanner. Two purpose-trained radiologists estimated the percentage of MD in a continuous scale. One radiologist read the mammograms from Castile-Leon, Balearic Islands, and Navarre and the other one read those from Aragon, Catalonia, Galicia, and Valencian Region. To this purpose, they used a free semi-automated computer tool (DM-Scan) designed by the Polytechnic University of Valencia,[20] which has shown high validity and reproducibility, and a good discriminative power for breast cancer risk prediction.[21] To evaluate intra and inter-rater agreement, each radiologist repeated the estimation of MD in 60 mammograms, and 243 images were read by both of them. Intraclass correlation coefficient (ICC) between raters was 0.91 (95%CI=0.89 to 0.92), while intra-rater ICC was 0.98 (95%CI=0.97 to 0.99) for radiologist 1 and 0.99 (95%CI=0.98 to 0.99) for radiologist 2.

At recruitment, women answered a complete epidemiological questionnaire that collected information on sociodemographic data, information on reproductive history, personal and family background, lifestyles, and diet. It also contained specific items to explore the occupational history, namely, the current work status of the women, their latter occupation, the occupation hold for the longest period and the time worked on each of them. For the present study, which if focused on current occupational exposures, we excluded those participants that had never had paid jobs (housewives) (n=477). In addition, we excluded: 1340 women who stopped working at least one year ago, 2 women who did not provide occupational history information, and 14 participants with incomplete information in some of the main confounding variables. Therefore, our final sample was 1476 women, aged 45-65 years, who were working at the time of the mammography or had stopped working less than a year ago.

Occupational titles were coded by industrial hygienists according to the Spanish Classification of Occupations 1994 (CNO-94),[22] a national system adapted from the International Standard Classification of Occupations 1988 (ISCO88). CNO-94 is organized into 4 levels. The first digit refers to one of ten major

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occupational sectors (0-9), with higher numbers indicating manual occupations. A greater number of digits means a higher level of detail in the job description.

Exposure to chemical, physical, and microbiological agents was assessed by linking occupations (CNO-94) to a job-exposure matrix (MatEmEsp).[16] This matrix has been specifically developed for Spanish workers, covering the period 1996-2005. Besides safety hazards, ergonomic and psychosocial risk factors, employment conditions and socio-demographic characteristics, this matrix includes 52 chemical, 10 physical, and 2 microbiological agents, in alignment with those included in the Finnish job-exposure matrix (FINJEM).[23] Estimates were established by a panel of industrial hygienists with extensive experience in industrial hygiene exposure assessment in Spain. For each agent in each job title, the prevalence of exposure (proportion of exposed workers) and the level (intensity) of exposure (1-year average concentration levels) were quantitatively assessed. The estimates were made based primarily on expert judgments, on data from risk assessments in Spanish companies and consulting bibliographical sources. For this study, we only considered those jobs held for at least one year and those agents for which at least 10 female workers were exposed. We considered as “exposed occupations” those in which at least 5% of the workers had a mean annual exposure that exceeded the reference exposure level, different for each agent and obtained from the 2012 Spanish occupational Threshold Limit Values Document. In the case of ionizing radiation, the 5% prevalence criterion was not taken into account, and we considered as “exposed occupations” those that exceeded 0.2 mSv.

In order to evaluate the association of MD with the exposure to a specific chemical, physical or microbiological agent, we fitted multivariate mixed linear regression models. For each agent we performed an independent model. We used the log-transformed percentage of MD as the dependent variable. The estimated regression coefficients and the corresponding limits of their 95% confidence intervals were exponentiated to calculate the relative change of the adjusted geometric mean of MD ($e^{\beta}$) and its 95% confidence interval comparing exposed women to a given agent with unexposed women. The main explanatory variable of interest was the specific agent, categorized as exposed (if the woman has been exposed to that agent in her current occupation or had ceased to be exposed to it less than a year ago) versus non-exposed (women non-exposed to the specific agent that were working at the moment of the study or that have stopped working less than a year ago). All models were adjusted for age at mammogram (continuous), menopausal status (pre/perimenopausal and postmenopausal), body mass index (continuous), educational level (less than primary education, primary education, secondary education, vocational training, higher secondary education,

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bachelor or equivalent and university education), parity (continuous), hormonal replacement therapy (no use, previous use, current use), first-degree relative with breast cancer (yes/no), smoking (never smoker, ex-smoker ≥6 months, and current smoker or ex-smoker <6 months), alcohol consumption (never drinker, <10g/day and ≥ 10 g/day), and type of mammogram (analogical, digital or printed & scanned image). In addition, these models included two-level nested random effects: the screening center intercept term and the professional radiologist. A sensitivity analysis was also fitted comparing workers exposed to an intensity of exposure equal or over the 75$^{th}$ percentile of the distribution of a given substance with workers non-exposed to that agent. We repeated all these analyses including women who reported being actively working in the last 5 years (N=1667). The results obtained were very similar and are presented (see later) in a supplementary table.

In a second phase, we explored the association between MD and exposure to those agents with an $e^{\beta}>1.20$ and $p<0.10$ obtained in the previous analyses, fitting a new model for each of these substances that was additionally adjusted for the time exposed to the remaining agents. Finally, we also assessed the duration of exposure to these occupational agents, using the number of months exposed as explanatory variable and analyzing the increase or decrease in MD per 5-year increase in the time exposed to each agent also adjusting for the time exposed to the remaining ones.

All analyses were performed with STATA/MP 14.0 software.

## RESULTS

Table 1 shows a summary of the main characteristics of the women, the percentage of them occupationally exposed to chemical, physical and microbiological agents, and the percentage of mammographic density. The mean age of study participants was 54.3 years. Most women were postmenopausal, and 66% were overweight or obese (≥25 Kg/m$^2$). Most of them had 1 or 2 children, had never used hormone replacement therapy, and had never smoked. According to exposure to occupational agents, 35% of workers had an occupation for which no exposure to any chemical substance was contemplated, while 30% had an occupation with exposure to more than 3 chemicals. As many as 38% of the women belonged to occupations without exposure to any physical agent, and only 18 women had occupations with exposure to mold spores or bacteria. On the other hand, women with higher MD were more frequently premenopausal, university women, thin women, nulliparous, hormone therapy users, with family history of breast cancer, smokers or former smokers, and with high alcohol consumption.

Table 2 analyses the association between MD and occupational exposure to various chemical, physical, and microbiological substances. Firstly, we evaluated the association comparing women exposed to a given agent with the rest of workers not exposed to it, showing only those agents for which there were ten or more women exposed. In a second phase, we compared women highly exposed to one substance (i.e., those exposed to an intensity of exposure equal or over 75$^{th}$ percentile) with the rest of workers not exposed to such substance. The first analysis showed a statistically significant positive association with exposure to perchloroethylene ($e^{\beta}$=1.51; 95%CI=1.04 to 2.19) and mold spores ($e^{\beta}$=1.44; 95%CI=1.01 to 2.04), and a borderline significant association with ionizing radiation ($e^{\beta}$=1.23; 95%CI=0.99 to 1.52) and aliphatic/alicyclic hydrocarbon solvents ($e^{\beta}$=1.47; 95%CI=0.94 to 2.30). The second analysis confirmed these results, although some associations failed to achieve statistical significance due to the lower number of exposed workers. Finally, both analyses also detected a non-expected lower MD among those workers exposed to nickel. Table S1 (supplementary data) shows the same analyses including those women who were working or stopped working less than five years ago. As can be observed, these results are very similar to those previously described.

When we analyzed the association between MD and those occupational agents with $e^{\beta}>1.20$ and $p<0.10$ in any of the previous analyses, we observed that the associations hardly changed when we fitted new models for each agent additionally adjusted for the time exposed to the other agents (Table 3). Finally, MD increased for every five years spent in occupations exposed to aliphatic/alicyclic hydrocarbon solvents ($e^{\beta}$=1.11; 95%CI=1.00 to 1.23), perchloroethylene ($e^{\beta}$=1.12; 95%CI=1.02 to 1.23), ionizing radiation ($e^{\beta}$=1.03; 95%CI=0.99 to 1.08), and mold spores ($e^{\beta}$=1.12; 95%CI=1.03 to 1.22).

Table 4 shows the occupations exposed to aliphatic/alicyclic hydrocarbon solvents, perchloroethylene, ionizing radiation, and mold spores, as well as the level of exposure and the prevalence of Spanish workers exposed to each of them, according to MatEmEsp. It is worth noting that most workers exposed to perchloroethylene were “Launderers, pressers, and similar”, and that most workers exposed to ionizing

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radiation in our study were “Nurses” (38 women). The exposure to aliphatic/alicyclic hydrocarbon solvents and to mold spores was due to a greater variety of occupations.

**DISCUSSION**

This study sought to investigate the association between MD and occupational exposure to a number of occupational agents in a sample of Spanish women attending breast cancer screening. Although, in general, no association was found with most of the substances studied, our results suggest that exposure to perchloroethylene, to aliphatic/alicyclic hydrocarbon solvents, to ionizing radiation, and to mold spores could be linked to higher MD.

With regard to perchlotoethylene, the IARC concluded that this compound is probably carcinogenic to humans, based on limited evidence in humans and sufficient evidence in laboratory animals.[24] It has been the solvent most commonly used in the dry cleaning industry since the 1950s. In 2005, perchloroethylene was used by about 90% of dry-cleaners in Spain, with a consumption of 2382 tons.[25] Although there is no evidence of an association between this solvent and breast cancer risk,[24 26 27] Gallagher et al detected slightly elevated breast cancer risk for highly exposed women via drinking-water contaminated with perchloroethylene in Massachusetts (USA).[28] Moreover, in 2011, this chemical was included as a potential endocrine disruptor by The Endocrine Disruption Exchange.[29] We have also detected an association between MD and the group of other chlorinated hydrocarbon solvents, although it did not reach statistical significance. Some of them have been identified as mammary gland carcinogens,[8] and have been detected in breast milk, confirming their availability to breast tissue.[30] However, the results of the literature are still contradictory with regard to breast cancer risk. While some studies found no association with this group of chemicals,[26 31] others have reported an increased risk.[32 33] In the last two studies, as in ours, the authors reported higher risk in those workers exposed for a longer time. Finally, other organic solvents for which we detected an increased MD are aliphatic/alicyclic hydrocarbon solvents. With respect to the first group, Glass et al observed that women exposed to aliphatic solvents had a 20% increase of breast cancer risk in an Australian population-based case-control study.[26]

The association between mold spores and MD has not been previously described and is difficult to explain. This result could be a chance finding or could be related to the exposure to mycotoxins, secondary chemical metabolites of different types of fungi. Among these mycotoxins, it is worth mentioning the zearalenone, a non-steroidal estrogenic mycotoxin, produced by Fusarium species that can be found in a wide range of cereals.[34 35] It has been associated with breast enlargement in humans and it has been included in many bust-enhancing dietary supplements.[35] Although the epidemiological evidence with regard to breast cancer risk is inconclusive,[35] recent studies have shown its potential to induce proliferation in human breast tumor cells,[34] and a recent case control study found an increased breast cancer risk associated with the concentration of one zearalenone metabolite in urine.[36]

A number of studies have indicated that MD corresponds more to alterations in stromal composition rather than epithelial changes.[5] Indeed, it has been suggested that high MD is promoted by remodeling and stiffening the existing stromal collagen microarchitecture.[37] The increased MD detected in our workers exposed to ionizing radiation could be explained within this stromal context, since it has been described that low-dose ionizing radiation exposures can perturb the breast stromal environment through the accumulation of senescence-like human mammary fibroblasts.[38] In our study, the occupation with higher number of workers exposed to ionizing radiation were nurses, precisely one of the professions with the highest association with MD previously reported by our team.[13 14] Since night shift work is very common in this profession, and it is classified as a possible cause of breast cancer,[39] we performed a sensitivity analysis including this possible confounding factor, but the estimation of the effect of exposure to ionizing radiation did not change. Although current doses are generally low due to the recognition of the long-term effects and the introduction of preventive measures, several studies continue reporting an increase in breast cancer risk among medical radiation workers, mainly among those who began working in the first half of the 20th century.[40 41]

Our study has several limitations. The cross-sectional design limits the possibility to assess changes in MD patterns across time. On the other hand, occupational history was self-reported and collected retrospectively and, thus, it is subject to possible recall bias, particularly with regard to time worked. Nevertheless, density assessment was blind and anonymous, and any recall bias would probably be non-differential, thus implying an underestimation of the effects studied. Another limitation relates to the mass-significance phenomenon, which may produce spurious associations due to the large number of comparisons. However, chance would only explain one of the statistically significant associations observed between the occupational agents and MD. Corrections for multiple significance testing were not applied due to the exploratory nature and the hypothesis generating approach of this study.[42] On the other hand, assessment of

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exposure with the use of a job exposure matrix implies a classification bias -generally non-differential- caused by variability of exposure both within and among the occupational groups considered, as well as possible changes in exposure across time. This misclassification could entail an underestimation of the effects. However, the use of such a matrix provides increased statistical power resulting from pooling workers from different occupations for which a similar range of exposure was estimated. We have also used different type of mammograms (digital and digitized digital or analogical images). However, this possible source of error has been taken into account by including this variable into the model, and the inclusion of the screening center as a random effect term also allows controlling this possible source of error. In addition, it is possible that some of the associations detected could be due to other confounding factors not taken into account in the analyses, as well as to the effect of simultaneous exposures to various agents. On the other hand, we have focused on current exposures without considering the past exposures (those that took place more than a year ago). We decided to do so because mammographic density has dynamic characteristics. It decreases with age, with BMI, and can be modified by hormonal exposures and other breast cancer risk factors. However, the influence of exogenous exposures on MD may cease when exposure is interrupted, as it is the case in most women who used postmenopausal hormone therapy.[43] This justifies our focus on current and not past exposures. In any case, results were very similar when the exclusion criteria were less strict and we included women who were working in the last 5 years. Finally, the low number of exposed women could have been insufficient to detect significant differences in some exposures, and we should be cautious about those associations based on a low number of exposed workers.

Some strengths should also be considered. Although there are previous studies that have analyzed the association between MD and night shift work,[14 15] up-to-date this is the first epidemiological study exploring the association with agents used in the workplace. In addition, population based breast cancer screening programs are available in all Spanish regions, and participation rates are high,[44] which support the external validity of our results. On the other hand, a validated software was used to obtain a continuous measure of MD allowing to explore associations more accurately, as recommended by Santen et al.[45] With regard to the exposure assessment, it is worth noting that we used the first general-population job-exposure matrix specifically designed for the Spanish working population. The detailed supported documentation for the sources and processes underlying exposure estimates make this matrix the best available source of information on exposure to occupational agents among Spanish workers.

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In conclusion, our results support the hypothesis of an increased MD among women occupationally exposed to perchloroethylene, ionizing radiation, mold spores and aliphatic/alicyclic hydrocarbon solvents. Limited statistical power prevents drawing conclusions regarding other exposures. Since this is the first study analyzing occupational exposures and MD, special caution is required in the interpretation of our results. Further investigations are needed to confirm these associations in different and larger populations and in studies that include direct exposure measurements.

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**CONTRIBUTORS**

VL, MP and BP-G designed the DDM studies. CP-P, PMo, CS, ME, CV, DS-T and CS-C coordinated participant recruitment in their respective provinces and contributed to the data collection. RL was responsible for reading mammograms. JA, MCG-G, MAA, RVDH and RACB contributed to the acquisition of occupational exposure data and to analysis and interpretation of results. JG-P, AMP-F and VL contributed to statistical analyses, interpretation of data, and wrote the initial version of the manuscript. All authors contributed to critical revisions of the draft manuscript and approved the final version.

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**COMPETING INTEREST**

The authors declare that they have no competing interests

**PATIENT CONSENT**

Written informed consent was obtained for all participants.

**ETHICS APPROVAL**

The Spanish Organic Law for the Protection of Personal Data was respected at all times. The DDM-Spain study protocol was evaluated and formally approved by the Bioethics and Animal Welfare Committee at the Carlos III Institute of Health.

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**Table1** Sociodemographic characteristics, exposure to occupational agents, and mammographic density among DDM-occup participants

| Characteristic | Total (N=1476) | | Mammographic density (%) | |
|---|---|---|---|---|
| | N | (%) | mean* | 95% CI* |
| Age, mean(SD) | 54.3 | (5.0) | 19.0 | (18.1 to 19.9) |
| Educational level | | | | |
| No formal school education/ First grade | 376 | (26) | 14.4 | (13.1 to 15.8) |
| Second grade / Vocational training | 861 | (58) | 19.9 | (18.7 to 21.2) |
| University graduate | 239 | (16) | 24.6 | (22.3 to 27.2) |
| Body mass index | | | | |
| <20 Kg/m$^2$ | 29 | (2) | 41.1 | (31.7 to 53.2) |
| 20-24 Kg/m$^2$ | 470 | (32) | 28.8 | (27.0 to 30.8) |
| 25-29 Kg/m$^2$ | 600 | (41) | 18.2 | (17.0 to 19.5) |
| >29 Kg/m$^2$ | 377 | (25) | 11.4 | (10.3 to 12.5) |
| Number of children | | | | |
| None | 184 | (12) | 25.2 | (22.2 to 28.6) |
| 1-2 | 954 | (65) | 19.4 | (18.3 to 20.6) |
| 3-4 | 320 | (22) | 15.2 | (13.8 to 16.8) |
| >4 | 18 | (1) | 15.1 | (9.6 to 23.8) |
| Menopausal status | | | | |
| Premenopausal | 459 | (31) | 26.6 | (24.6 to 28.7) |
| Postmenopausal | 1017 | (69) | 16.0 | (13.9 to 18.7) |
| Hormone replacement therapy use | | | | |
| Never | 1341 | (91) | 19.2 | (18.2 to 20.1) |
| Current use | 40 | (3) | 23.1 | (17.7 to 30.1) |
| Past use | 95 | (6) | 15.2 | (12.5 to 18.4) |
| First-degree relative with breast cancer | | | | |
| No | 1373 | (93) | 18.7 | (17.8 to 19.6) |
| Yes | 103 | (7) | 23.4 | (19.6 to 28.0) |
| Smoking | | | | |
| Never smoker | 786 | (53) | 17.1 | (16.0 to 18.2) |
| Former $\geq$6 months ago | 302 | (21) | 21.1 | (19.0 to 23.6) |
| Smoker or former <6 months | 388 | (26) | 21.5 | (19.7 to 23.6) |
| Alcohol | | | | |
| Never drinker | 523 | (35) | 18.2 | (16.8 to 19.8) |
| < 10g/day | 694 | (47) | 18.9 | (17.7 to 20.2) |

| | | | | | | |
|---|---|---|---|---|---|---|
| ≥ 10g/day | 259 | (18) | 20.8 | (18.6 | to | 23.2) |
| Region | | | | | | |
| Aragon | 204 | (14) | 16.1 | (14.2 | to | 18.3) |
| Balearic Islands | 225 | (15) | 15.2 | (13.4 | to | 17.3) |
| Castile-Leon | 203 | (14) | 28.0 | (25.0 | to | 31.2) |
| Catalonia | 220 | (15) | 10.2 | (9.1 | to | 11.4) |
| Galicia | 186 | (13) | 21.7 | (19.1 | to | 24.6) |
| Navarre | 230 | (16) | 33.7 | (30.8 | to | 36.8) |
| Valencian Region | 208 | (14) | 17.7 | (15.9 | to | 19.7) |
| Type of mammography | | | | | | |
| Analogical | 771 | (52) | 24.9 | (23.4 | to | 26.4) |
| Digital | 644 | (44) | 13.8 | (12.9 | to | 14.8) |
| Printed and scanned | 61 | (4) | 17.7 | (10.3 | to | 16.6) |
| Duration of employment | | | | | | |
| < 6 years | 342 | (23) | 21.0 | (19.1 | to | 23.0) |
| 6-15 years | 389 | (26) | 20.7 | (19.0 | to | 22.6) |
| 16-27 years | 363 | (25) | 18.4 | (16.6 | to | 20.5) |
| >27 years | 376 | (26) | 16.3 | (14.9 | to | 17.9) |
| **Occupational agents** | | | | | | |
| *Chemical agents* | | | | | | |
| Non exposed | 509 | (35) | 21.6 | (20.0 | to | 23.3) |
| Exposed to 1 chemical | 281 | (19) | 20.4 | (18.4 | to | 22.6) |
| Exposed to 2-3 chemicals | 238 | (16) | 17.8 | (15.7 | to | 20.1) |
| Exposed to >3 chemicals | 448 | (30) | 16.2 | (14.8 | to | 17.7) |
| *Physical agents* | | | | | | |
| Non exposed | 566 | (38) | 17.9 | (16.6 | to | 19.3) |
| Only exposed to heat or cold | 270 | (18) | 20.0 | (17.8 | to | 22.4) |
| Only exposed to non-ionizing radiation | 444 | (30) | 19.0 | (17.5 | to | 20.7) |
| Only exposed to ionizing radiation | 45 | (3) | 27.6 | (23.0 | to | 33.1) |
| Exposed to a mixture of physical agents | 151 | (10) | 19.2 | (16.5 | to | 22.3) |
| *Microbiological agents* | | | | | | |
| Non exposed | 1458 | (99) | 18.9 | (18.0 | to | 19.8) |
| Only exposed to mold spores | 14 | (1) | 29.3 | (19.7 | to | 43.6) |
| Only exposed to Bacteria of non-human origin | 0 | (0) | - | | | |
| Exposed to both | 4 | (0) | 33.8 | (14.7 | to | 77.8) |

* Geometric mean and 95% confidence intervals.

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**Table 2** Association between exposure to occupational agents and mammographic density

| | Exposed vs. non-exposed | | | | Highly exposed vs. non-exposed* | | | |
|---|---|---|---|---|---|---|---|---|
| **Occupational exposure agents** | **N†** | **$e^{\beta}$ ‡** | **95% CI** | **P** | **N§** | **$e^{\beta}$ ‡** | **95% CI** | **P** |
| **Chemical agents** | | | | | | | | |
| Organic solvents | | | | | | | | |
| Aromatic hydrocarbon solvents | | | | | | | | |
| Benzene | 127 | 0.91 | (0.79 to 1.05) | 0.189 | 125 | 0.90 | (0.78 to 1.04) | 0.148 |
| Toluene | 141 | 0.92 | (0.81 to 1.05) | 0.219 | 141 | 0.92 | (0.81 to 1.05) | 0.219 |
| Aliphatic/alicyclic hydrocarbon solvents | 11 | 1.47 | (0.94 to 2.30) | 0.090 | 5 | 1.82 | (0.94 to 3.53) | 0.075 |
| Chlorinated hydrocarbon solvents | 25 | 1.23 | (0.91 to 1.66) | 0.170 | 16 | 1.46 | (1.01 to 2.12) | 0.046 |
| Methylene chloride | 15 | 1.08 | (0.74 to 1.59) | 0.679 | 9 | 0.90 | (0.55 to 1.48) | 0.692 |
| Perchloroethylene | 16 | 1.51 | (1.04 to 2.19) | 0.030 | 13 | 1.58 | (1.05 to 2.39) | 0.030 |
| Other organic solvents | 18 | 1.10 | (0.77 to 1.56) | 0.611 | 9 | 1.10 | (0.67 to 0.81) | 0.704 |
| Formaldehyde | 23 | 1.26 | (0.92 to 1.72) | 0.147 | 11 | 1.15 | (0.74 to 1.81) | 0.529 |
| Organic dust | | | | | | | | |
| Animal dust | 10 | 1.17 | (0.73 to 1.88) | 0.503 | 5 | 0.77 | (0.40 to 1.49) | 0.434 |
| Flour dust | 250 | 0.94 | (0.84 to 1.05) | 0.247 | 176 | 0.90 | (0.80 to 1.02) | 0.110 |
| Leather dust | 10 | 0.95 | (0.60 to 1.53) | 0.842 | 8 | 0.95 | (0.56 to 1.61) | 0.857 |
| Plant dust | 404 | 0.97 | (0.89 to 1.07) | 0.575 | 397 | 0.98 | (0.89 to 1.07) | 0.611 |
| Pulp or paper dust | 382 | 0.96 | (0.87 to 1.06) | 0.420 | 382 | 0.96 | (0.87 to 1.06) | 0.420 |
| Synthetic polymer dust | 25 | 1.05 | (0.78 to 1.41) | 0.761 | 5 | 1.27 | (0.65 to 2.46) | 0.486 |
| Textile dust | 66 | 1.12 | (0.93 to 1.36) | 0.228 | 4 | 1.14 | (0.54 to 2.39) | 0.733 |
| Wood dust | 211 | 1.06 | (0.95 to 1.19) | 0.308 | 206 | 1.05 | (0.94 to 1.18) | 0.398 |
| Inorganic mineral dust | | | | | | | | |
| Man-made mineral fibers | 10 | 0.92 | (0.58 to 1.48) | 0.732 | 7 | 0.85 | (0.49 to 1.50) | 0.578 |
| Quartz dust | 19 | 0.86 | (0.61 to 1.21) | 0.375 | 7 | 0.89 | (0.51 to 1.57) | 0.696 |
| Other mineral dusts | 399 | 0.94 | (0.86 to 1.04) | 0.242 | 389 | 0.95 | (0.86 to 1.04) | 0.261 |
| Metals | | | | | | | | |
| Chromium | 18 | 0.78 | (0.55 to 1.11) | 0.172 | 6 | 0.56 | (0.31 to 1.03) | 0.060 |
| Lead | 39 | 0.92 | (0.72 to 1.16) | 0.469 | 12 | 0.79 | (0.52 to 1.22) | 0.293 |
| Nickel | 13 | 0.68 | (0.45 to 1.02) | 0.064 | 4 | 0.48 | (0.23 to 1.01) | 0.055 |
| Fungicides¶ | 15 | 1.08 | (0.73 to 1.58) | 0.700 | 6 | 0.90 | (0.49 to 1.64) | 0.727 |
| Herbicides** | 15 | 1.08 | (0.73 to 1.58) | 0.700 | 6 | 0.90 | (0.49 to 1.64) | 0.727 |
| Insecticides | | | | | | | | |
| Chlorpyrifos | 217 | 1.06 | (0.94 to 1.18) | 0.337 | 214 | 1.05 | (0.93 to 1.17) | 0.429 |
| Endosulfan | 15 | 1.08 | (0.73 to 1.58) | 0.700 | 9 | 1.09 | (0.67 to 1.79) | 0.731 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Methomyl | 213 | 1.04 | (0.93 to 1.17) | 0.451 | 200 | 1.05 | (0.93 to 1.18) | 0.434 |
| Pyrethrins | 217 | 1.06 | (0.94 to 1.18) | 0.337 | 207 | 1.05 | (0.93 to 1.17) | 0.433 |
| Engine exhaust | | | | | | | | |
| Diesel engine exhaust | 16 | 0.92 | (0.64 to 1.34) | 0.672 | 8 | 0.76 | (0.45 to 1.28) | 0.305 |
| Gasoline engine exhaust | 12 | 1.17 | (0.76 to 1.80) | 0.470 | 4 | 0.78 | (0.37 to 1.62) | 0.500 |
| Gasoline | 127 | 0.89 | (0.77 to 1.02) | 0.094 | 124 | 0.89 | (0.78 to 1.03) | 0.118 |
| Carbon monoxide | 41 | 1.04 | (0.82 to 1.32) | 0.738 | 12 | 0.76 | (0.50 to 1.17) | 0.212 |
| Volatile sulfur compounds | 21 | 0.90 | (0.65 to 1.25) | 0.530 | 12 | 0.76 | (0.50 to 1.17) | 0.217 |
| Detergents | 704 | 0.98 | (0.91 to 1.07) | 0.707 | 175 | 0.90 | (0.79 to 1.03) | 0.122 |
| **Physical agents** | | | | | | | | |
| Cold | 330 | 0.99 | (0.90 to 1.08) | 0.759 | 145 | 1.04 | (0.91 to 1.19) | 0.532 |
| Heat | 196 | 1.06 | (0.94 to 1.19) | 0.346 | 83 | 1.09 | (0.92 to 1.30) | 0.302 |
| Low frequency magnetic fields | 537 | 1.05 | (0.97 to 1.14) | 0.197 | 537 | 1.05 | (0.97 to 1.14) | 0.197 |
| Low-frequency ultrasound | 25 | 0.98 | (0.72 to 1.31) | 0.868 | 13 | 1.14 | (0.75 to 1.72) | 0.540 |
| Ultraviolet radiation | 41 | 1.02 | (0.81 to 1.29) | 0.858 | 10 | 1.26 | (0.79 to 2.02) | 0.331 |
| Ionizing radiation | 54 | 1.23 | (0.99 to 1.52) | 0.058 | 14 | 1.22 | (0.82 to 1.81) | 0.337 |
| **Microbiological agents** | | | | | | | | |
| Mold spores | 18 | 1.44 | (1.01 to 2.04) | 0.041 | 4 | 1.92 | (0.92 to 4.02) | 0.084 |

* Comparing workers exposed to an intensity of exposure equal or over 75th percentile of the distribution with workers not exposed to the respective agent.

† Number of exposed workers. Only those agents with at least 10 exposed workers are shown.

‡ $e^{\beta}$ represents the relative increase of the geometric mean of the percentage of MD. Models adjusted for age, educational level, menopausal status, body mass index, parity, hormonal replacement therapy use, first-degree relative with breast cancer, smoking, alcohol intake, and type of mammogram.

§ Number of workers exposed to 75th percentile of the distribution or more.

¶ Include captan and thiram.

** Include 2,4-D, atrazine, diquat and diuron.

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**Table 3** Association between exposure to occupational agents, time of exposure and mammographic density

| | Exposed vs. non-exposed | | | | Time of exposure | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Five-year trend | | |
| **Occupational exposure agents*** | **N†** | **$e^{\beta}$ ‡** | **95% CI** | **P** | **P25§** | **P75¶** | **$e^{\beta}$ ****| **95% CI** | **P** |
| Aliphatic/alicyclic hydrocarbon solvents | 11 | 1.48 | (0.95 to 2.30) | 0.087 | 3 | 30 | 1.11 | (1.00 to 1.23) | 0.047 |
| Perchloroethylene | 16 | 1.52 | (1.05 to 2.20) | 0.027 | 7.3 | 24 | 1.12 | (1.02 to 1.23) | 0.021 |
| Ionizing radiation | 54 | 1.23 | (0.99 to 1.52) | 0.061 | 17 | 31 | 1.03 | (0.99 to 1.08) | 0.119 |
| Mold spores | 18 | 1.45 | (1.02 to 2.05) | 0.037 | 4 | 25 | 1.12 | (1.03 to 1.22) | 0.008 |

* Agents with $e^{\beta}>1.20$ and $P<0.10$ obtained in Table 2.

† Number of exposed workers.

‡ $e^{\beta}$ represents the relative increase of the geometric mean of the percentage of MD. Models adjusted for age, educational level, menopausal status, body mass index, parity, hormonal replacement therapy use, first-degree relative with breast cancer, smoking, alcohol intake, type of mammogram, and the time exposed to the remaining agents shown in the table.

§ 25th percentile of the distribution of the exposure time to the corresponding agent in years.

¶ 75th percentile of the distribution of the exposure time to the corresponding agent in years.

** $e^{\beta}$ represents the relative increase of the geometric mean of the percentage of MD. $e^{\beta}$ and 95% confidence intervals per 5 years spent in occupations exposed to the respective agent; adjusted for age, educational level, menopausal status, body mass index, parity, hormonal therapy use, first-degree relative with breast cancer, smoking, alcohol intake, type of mammogram, and the time exposed to the remaining agents shown in the table.

**Table 4** Occupations exposed to several occupational agents. Prevalence and levels of exposure in Spanish workers covering the period 1996-2005.

| Code (CNO-94) | Occupation | N* |
|---|---|---|
| **Aliphatic/alicyclic hydrocarbon solvents** | | |
| 7240 | Painters, varnishing, papermakers, and similar | 1 |
| 7723 | Print recorders and similar workers | 1 |
| 7726 | Silk screen printers and stampers in plate and in textiles | 1 |
| 7937 | Upholsterers, mattresses, and similar | 3 |
| 8220 | Responsible for operators of machinery for manufacturing chemicals | 1 |
| 8250 | Head of printing, binding, and manufacturing of paper products | 1 |
| 8260 | Responsible for operators of machinery for the production of textile and leather goods | 2 |
| 8331 | Machine operators for the production of rubber products | 1 |
| **Perchloroethylene** | | |
| 7622 | Electronic equipment adjusters and repairers | 1 |
| 8323 | Operators of polishing machines, galvanizing, and coating of metals | 2 |
| 9122 | Laundresses, pressers, and similar | 13 |
| **Ionizing radiation** | | |
| 2121 | Physicians | 7 |
| 2130 | Veterinarian | 1 |
| 2720 | Nurses | 38 |
| 3049 | Other operators of optical and electronic equipment | 2 |
| 3121 | Medical laboratory technicians | 2 |
| 7230 | Construction Electrician and similar | 2 |
| 7340 | Team leaders of equipment of mechanics and fitters of electrical and electronic equipment | 1 |
| 7622 | Fitters and repairers of electronic equipment | 1 |
| **Mold spores** | | |
| 1401 | Management of farms, hunting, fishing, and forestry with less than 10 employees | 2 |
| 6011 | Self-employed workers in agricultural activities, except in orchards, nurseries, and gardens | 2 |
| 7801 | Slaughterer and workers in the meat and fish industries | 2 |
| 7803 | Workers in milk processing and dairy processing; Ice cream maker | 2 |
| 8250 | Head of printing, binding and manufacturing of paper products | 1 |
| 8270 | Responsible for operators of machinery for the production of food, beverages, and tobacco | 1 |
| 8374 | Machine operators for the production of bakery products, confectionery, chocolate products, and cereal products | 1 |
| 9410 | Agricultural laborers | 3 |
| 9500 | Laborers in mining | 1 |

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| | | |
|---|---|---|
| 9700 | Laborers in manufacturing industries | 3 |

* Number of women exposed in our study.

† Prevalence (%) of workers exposed in Spain according to MatEmEsp.

‡ Annual dose of equivalent radiation in milligrams per cubic meter of air for aliphatic/alicyclic hydrocarbon solvents and perchloroethylene. In millisieverts per year for ionizing radiation, and in colony forming units per cubic meter of air sampled for mold spores. Source: MatEmEsp.