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Occupation and mammographic density: a population-based study (DDM-Occup)

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Abbreviations

ICC: Intraclass correlation

Abstract

Introduction: High mammographic density is one of the main risk factors for breast cancer. Although several occupations have been associated with breast cancer, there are no previous occupational studies exploring the association with mammographic density. Our objective was to identify occupations associated with high mammographic density in Spanish female workers.

Methods: We conducted a population-based cross-sectional study of occupational determinants of high mammographic density in Spain, based on 1476 women, aged 45–68 years, recruited from seven screening centers within the Spanish Breast Cancer Screening Program network. Reproductive, family, personal, and occupational history data were collected. The latest occupation of each woman was collected and coded according to the 1994 National Classification of Occupations. Mammographic density was assessed from the cranio-caudal mammogram of the left breast using a semi-automated computer-assisted tool. Association between mammographic density and occupation was evaluated by using mixed linear regression models, using log-transformed percentage of mammographic density as dependent variable. Models were adjusted for age, body mass index, menopausal status, parity, smoking, alcohol intake, educational level, type of mammography, first-degree relative with breast cancer, and hormonal replacement therapy use. Screening center and professional reader were included as random effects terms.

Results: Mammographic density was higher, although non-statistically significant, among secondary school teachers (e^{β}=1.41; 95%CI=0.98-2.03) and nurses (e^{β}=1.23; 95%CI=0.96-1.59), whereas workers engaged in the care of people (e^{β}=0.81; 95%CI=0.66-1.00) and housewives (e^{β}=0.87; 95%CI=0.79-0.95) showed an inverse association with mammographic density. A positive trend for every 5 years working as secondary school teachers was also detected (*p*-value=0.035).

Conclusions: Nurses and secondary school teachers were the occupations with the highest mammographic density in our study, showing the latter a positive trend with duration of employment. Future studies are necessary to confirm if these results are due to chance or are the result of a true association whose causal hypothesis is, for the moment, unknown.

Key Words: mammographic density; occupation; breast cancer; school teachers; nurses; DDM-Occup

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1. Introduction

Mammographic density, i.e., the portion of the breast that is radiopaque and appears white on a mammogram, is one of the strongest known risk factors for breast cancer. This risk is four to five times greater among women with density in more than 75% of the breast compared to women with little or no dense tissue (Boyd et al., 2005; Boyd et al., 2007; McCormack and dos Santos Silva, 2006), and it is associated with all pathologic subgroups of breast cancer (Pollan et al., 2013a).

Insofar as the possible etiological hypotheses about the relationship between mammographic density and breast cancer are concerned, breast-tissue proliferation is associated with exposure both to mitogens (hormones and growth factors, which influence cell division in breast stroma and epithelium) and mutagens (proteins and lipids, which influence the likelihood of genetic damage to these cells) (Martin and Boyd, 2008).

In 2012, breast cancer was the leading tumor, in terms of new cases and deaths, in all European countries (Ferlay et al., 2013). In Spain, incidence and mortality rates accounted for 29% of all female cancer-related cases in 2012 (Ferlay et al., 2013) and 15.1% of cancer-related deaths in 2014 (Carlos III Institute of Health, 2017).

Early detection and therapeutic advances have improved survival and quality of life of breast cancer patients. However, the increasing access of women to the labor market, their incorporation into traditionally male-dominated occupations, and the emergence of new industries and technologies during the last decades have been reflected in an increased occupational exposure to physical, chemical, and biological agents, as well as to employment conditions that entail high breast cancer risk (Ekenga et al., 2015; Fenga, 2016; Glass et al., 2015; Golubnitschaja et al., 2016; Purdue et al., 2015). Some occupations associated with increased breast cancer risk include teachers, nurses, flight attendants, social workers, cashiers, and women working in cosmetics, chemical, and pharmaceutical industry (Hankinson et al., 2008; Pollan and Gustavsson, 1999). However, to our knowledge, no study has been conducted to evaluate the association between occupations and mammographic density. Accordingly, this study sought to identify occupations associated with high mammographic density in the context of an ongoing population-based cross-sectional study of occupational determinants of mammographic density in Spanish women (DDM-Occup).

2. Materials and methods

2.1 Study population

The DDM-Occup study (Occupational Determinants of Mammographic Density in Spain) is a cross-sectional multicenter study that aims to investigate the relationship between occupational determinants (occupations, occupational exposures to risk agents, and employment conditions) and mammographic density in Spanish women. This study is a continuation of the initial studies DDM-Spain/Var-DDM (Determinants of Mammographic Density in Spain), whose design and methodology have been previously described (Lope et al., 2011; Lope et al., 2012; Pollan et al., 2012). Briefly, 3584 women, aged 45–68 years, were recruited from specific screening centers within the Spanish Breast Cancer Screening Program network in the following Autonomous Regions: Galicia, Catalonia, Navarre, Aragon, Balearic Isles, Valencian Region, and Castile-Leon. Women were recruited from October 7, 2007 through July 14, 2008, and invited by telephone to participate in the study. Those who agreed to participate signed an informed consent and were given an appointment at the screening center on the same day as that scheduled for their mammogram. The average participation rate was 74.5% (range 64.7–84.0% across centers)

Women were interviewed by trained interviewers. The questionnaire collected demographic data, family and personal background information, and gynecologic, obstetric and occupational history. With respect to occupational history, for each woman, the last and the longest-held occupations were collected and coded according to the National Classification of Occupations of 1994, which is based on the European Union version of the International Standard Classification of Occupations, ISCO 88. The time worked in each occupation was also collected.

Three screening center used analogical mammography devices. Three centers used full-field digital machines and the other one used originally digital mammograms printed on film and afterwards digitalized. The percentage of mammographic density was assessed from the cranio-caudal mammogram of the left breast by two trained, experienced radiologist using the DM-Scan, a semi-automated computer-assisted tool previously validated by our group (Llobet et al., 2014; Pollan et al., 2013b), and freely available for non-commercial use (Institute of Computer Technology-Universitat de València (Spain), 2017). We obtained these mammograms for 3309 women, aged 45-68 years, with negative results in the screening. To evaluate intra- and inter-rater intraclass correlation (ICC), each radiologist repeated mammographic density estimation in 60 images, and 243 randomly selected mammograms (~35 per region) were read by both radiologists. Inter-rater ICC was 0.91 (95%CI=0.89-0.92), while intra-rater ICC was 0.98 (95%CI=0.97-0.99) for rater 1 and 0.99 (95%CI=0.98-0.99) for rater 2.

Of the 3309 women enrolled in the study, we excluded participants that had never had paid jobs (housewives (n=476)), who were analyzed in a separate analysis. In addition, we excluded 1340 women who stopped working at least one year ago, and 2 women who did not answer occupational history questions.

Finally, 1476 women (excluding 14 women with missing in covariates) were working at the moment of the mammography or had stopped working less than one year before. The average percentage of mammographic density was 26.5%.

2.2 Ethical approval

The DDM-Spain study protocol was formally approved by the bioethics and animal welfare committee at the Carlos III Institute of Health and all participants signed a consent form, including permission to publish the results from the current research.

2.3 Statistical analysis

The association between mammographic density and occupation was evaluated by using mixed linear regression models, an independent model for each occupation. The response variable was the logarithm of the percentage of dense breast tissue, and the main explanatory variable of interest was the specific occupation, categorized as: yes, if at the moment of the mammography the woman was working in that occupation or had left it less than a year ago; or no, in any other case (reference group, i.e., women who were working, or stopped working less than a year ago, in other occupations). We estimated the association with mammographic density for those occupations held for at least 1 year and for those with at least 10 working women. The estimated regression coefficients and standard errors of these models were exponentiated to calculate the ratio of geometric means comparing exposed and non-exposed women. All models were adjusted for the following fixed effects: age at mammography (continuous), body mass index (continuous), menopausal status (pre/perimenopausal and postmenopausal), parity (continuous), smoking status (never smoker, former smoker≥6 months, and smoker/former smoker<6 months), alcohol intake, educational level, type of mammography (analogical, digital or printed & scanned image), first-degree relative with breast cancer (yes/no) and hormonal replacement therapy use (current use, past use or no use). In addition to these fixed effects, the linear regression models included two random effects: a center-specific intercept term that accounted for unexplained variations of high mammographic density across screening centers (such as sociodemographic differences between regions, different lifestyles, different mammography devices used in the screening centers, etc.); and the professional reader of the mammography (radiologist).

Additional models were also fitted to compare each occupation only with others within the same occupational sector (i.e., those occupations having the same first digit) to assess the possible existence of a socioeconomic gradation of risk that could confound the results.

In a second phase, we explored the relationship between occupation and mammographic density according to the years that these women had worked in each occupation. For this purpose, the main explanatory variable of interest was the number of years working in a specific occupation, and we evaluated the increase or decrease in mammographic density per a 5-year increase in the time spent on the occupation of interest.

Additionally, we assessed the relationship between the group of housewives (women who have never worked) and mammographic density with the purpose of comparing their results with those of working women.

Finally, 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).

All analyses were performed in Stata14.0 (StataCorp LP, College Station, Texas, USA), and R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Table 1 shows the main characteristics and mammographic density of these participants. The women's mean age was 54 years; most of them were overweight or obese women (66.2%); most were postmenopausal (68.9%), with 1-2 children (64.6%) and never smokers (53.2%). 7.0% of participants reported having at least one first-degree relative with breast cancer and only 2.7% of women were taking hormonal replacement therapy. A summary of the main characteristics of the excluded women and the percentage of mammographic density is shown in Supplementary material, Table S1.

Table 2 shows the association between mammographic density and those occupations with 10 or more workers. A positive association, close to the statistical significance, was found for workers in 'Sector 2: Technicians and intellectual and scientific professionals' (e^{β}=1.16; 95%CI=1.00-1.34). Within this sector, a higher mammographic density was encountered among professionals associated with 2nd and 3rd cycle university in teaching, and more specifically among secondary school teachers (e^{β}=1.41; 95%CI=0.98-2.03), and among nurses (e^{β}=1.23; 95%CI=0.96-1.59). However, in intragroup comparisons that took as reference only job codes having the same first digit, attenuation of associations toward unity was observed in all occupations, including secondary school teachers and nurses (data not shown). On the other hand, 'Workers engaged in the care of people and similar (except nursing assistants)' registered an inverse relationship, very close to the statistically significance, with mammographic density (e^{β}=0.81; 95%CI=0.66-1.00). Finally, the group of 'Housewives' registered a statistically significant inverse association (e^{β}=0.87; 95%CI=0.79-0.95). Additionally, *p*-values adjusted by multiple comparisons are shown in Supplementary material, Table S2.

Finally, table 3 shows the associations between mammographic density and occupation by working time (5-year increase). This table displays only those occupations with 10 or more workers and $e^{\beta}\geq 1.10$ or $e^{\beta}<0.90$ in the previous analysis. Positive statistically significant association with working time was found among secondary school teachers (*p*-value for 5-year trend=0.035). On the other hand, salesclerks and display racks in shops, stores, kiosks and markets (*p*-value for 5-year trend=0.024), and housekeeping service workers (*p*-value for 5-year trend=0.047) showed a statistically significant decrease in mammographic density per 5-year increase in the time spent on the abovementioned occupations.

4. Discussion

To our knowledge, this is the first study that analyzes the association between occupations and mammographic density. In general, secondary school teachers and nurses were the occupations with the highest mammographic density. A positive trend with for 5 years working as secondary school teachers was also detected.

The occupation showing the strongest and positive association with mammographic density in our study corresponds to secondary school teachers. The association between teachers and risk of breast cancer is not consistent in the literature: whereas some authors have reported an increased risk of breast cancer (Goldberg and Labreche, 1996; Petralia et al., 1998; Pollan and Gustavsson, 1999; Welp et al., 1998), other studies suggest that teachers are not at an increased risk (Calle et al., 1998; Petralia et al., 1999). On the other hand, this occupation belongs to 'Professions associated with 2nd and 3rd cycle university in teaching', a sector that has also been associated positively with mammographic density in our study. This sector encompasses higher-status occupations (professional occupations that are at the top of the National Classification of Occupations of 1994, and are characterized by the highest levels of socioeconomic prestige indexes), and some authors have reported a higher breast cancer risk among these higher-status workers (Golubnitschaja et al., 2016; Pudrovska et al., 2013). In line with this finding, housewives in our study showed a statistically significant lower mammographic density.

Another occupation with a high mammographic density of our study was 'Nurses'. Some authors found positive associations (Goldberg and Labreche, 1996; MacArthur et al., 2007; Petralia et al., 1998; Rice et al., 2016) with breast cancer whereas others did not find any relationship (Calle et al., 1998; Koppes et al., 2014; Petralia et al., 1999). Nurses represent one of the main occupational populations investigated in studies of night-shift work (Fenga, 2016), classified as a possible cause of breast cancer (group 2A) by the International Agency for Research on Cancer (IARC, 2010). In fact, DDM-Spain participants with long-term exposure to night-shift work showed higher mammographic density in a previous study conducted by our group (Pedraza-Flechas et al., 2017). One possible biological mechanism is based on the reduced production of melatonin caused by exposure to light at night. Nevertheless, several other mechanisms have also been postulated, such as the alteration of the peripheral functions due to the desynchronization with sleep-wake cycle, sleep disruption, lifestyle factors (such as poor quality diets, less physical activity and higher body mass index), and lower vitamin D (Fritschi et al., 2011).

On the other hand, the higher mammographic density risk found in our teachers and nurses could also be owing to the fact that these two professions are related to a high level of stress, because these women are dealing with sensitive people (children and sick people), and their professions require a high degree of authority and responsibility at work. In this sense, Pudrovska et al. explored an estrogen-related pathway (reproductive history (later age at first birth and lower parity), health behaviors (regular alcohol use, sedentary lifestyle, and obesity for post-menopausal cancers), and life-course estrogen cycle (including early age at menarche, late age at menopause, and hormone replacement therapy)) as well as a social stress pathway (occupational experiences) as potential explanations for the effect of higher-status occupations on breast cancer incidence. The authors suggested that stressful interpersonal experiences could promote breast cancer development via prolonged dysregulation of the glucocorticoid system and exposure of the breast tissue to adverse effects of chronically elevated plasma cortisol levels (Pudrovska et al., 2013; Pudrovska, 2013). Moreover, in agreement with the finding detected in our teachers, Pudrovska et al. (Pudrovska et al., 2013) also observed that breast cancer risk was cumulative with the longer duration of holding the stressful occupation. On the other hand, some studies have shown that the effect of higher-status occupations decreases only modestly and remains large in magnitude and statistically significant after adjustment for reproductive histories and other estrogen-related variables (Dano et al., 2004; Larsen et al., 2011).

Our study has a series of limitations. Firstly, this is a cross-sectional study, meaning that the effect of changes in density patterns could not be investigated. Secondly, the explanatory variable of interest and adjustment variables were self-reported, and thus, susceptible to the possible influence of recall bias. Nevertheless, since density was assessed on a blind, anonymous basis, any recall bias would be non-differential, which would, in turn, imply underestimation of the associations studied. In addition, even though DM-Scan (the semi-automated tool used to assess the mammographic density) has a friendly interface and is relatively easy to use, the radiologist still has to remove unwanted characteristics in the mammogram and manipulate the software to establish what he/she believes represents the right amount of dense tissue. A fully-automated version based on machine learning techniques is currently under development and will be available in the short term. Another limitation is the availability of different types of mammographies (analogical, digital or printed & scanned image). However, we have adjusted for these possible sources of error by including this factor into the model.

Another aspect addressed in the analysis is the problem of multiple comparisons (the possibility to find associations that are falsely positive/negative by random chance). In the supplementary data, we have provided adjusted *p*-values by Benjamini & Hochberg method. However, from an epidemiologic standpoint, we have preferred to discuss the results in the light of a series of factors, namely, the magnitude of the e^{β} per se, the consistency of the associations observed, and biologic plausibility.

On the other hand, only left breast cranio-caudal mammogram was used in the analyses, which could introduce a potential bias in contrast to other authors that included views of each breast (Rice et al., 2016). However, some studies have shown a high correlation between mammographic density measurements in both breasts (Ciatto et al., 2005; Maskarinec et al., 2006). On the other hand, to the best of our knowledge, mammographic density has not been associated in relation to breast cancer laterality (Hennessey et al., 2014). Finally, some authors suggest that there is a slightly higher frequency of breast cancer in the left breast compared with the right, although not all studies show a left-sided predominance of breast cancer (Hennessey et al., 2014).

On the other hand, we analyzed the last occupation instead of the longest-held occupation because mammographic density has dynamic characteristics and it varies in time. Therefore, if a specific occupation is related to an increase or decrease in mammographic density, from a biological point of view it seems logical to think that it is due to the last occupation. Recent changes in mammographic density would be related to recent occupations or work-related exposures.

One of the main advantages of our study lies in the population-based nature of the study sample and the high average participation rate. Indeed, our participants display sociodemographic and lifestyle characteristics similar to those seen in the Spanish National Health Survey in the same age range

(Ministry of Health, Social Services and Equality, 2017). On the other hand, to our knowledge, this is the first study to date exploring the association between occupational determinants and mammographic density. Lastly, in order to minimize a possible healthy worker effect, only employed women were considered. Furthermore, we have analyzed a group of non-employed women, housewives, to compare their results with those of working women, and specifically with housekeeping service workers.

5. Conclusions

Nurses and secondary school teachers were the professionals with the highest association with mammographic density in our study, showing the latter a positive trend with duration of employment, whereas workers engaged in the care of people and housewives showed an inverse association with mammographic density.

These findings may reflect the influence of occupational conditions, such as night-shift work, estrogen-related pathways (reproductive history, health behaviors, and life-course estrogen cycle), and/or psychosocial workplace exposures. Further studies are necessary to confirm if they are due to chance, may be influenced by the small sample size or are the result of a true association whose causal hypothesis is unknown.

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