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Original article

Thyroid disorders and mammographic density in Spanish women: Var-DDM study

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ABSTRACT

Objectives: The association between breast cancer (BC) and thyroid disorders has been widely explored with unclear results. Mammographic density (MD) is one of the strongest risk factor for BC. This study explores the relationship between thyroid diseases and MD in Spanish women.
Materials & methods: This cross-sectional study covered 2883 women aged 47–71 years participating in 7 BC screening programs in 2010. They allowed access to their mammograms, had anthropometrical-measures taken, and answered a telephonic epidemiological interview which included specific questions on thyroid diseases. Percentage of MD was assessed with a semiautomatic-computer tool (DM-scan) by two trained radiologists. We calculated the geometric mean of MD percentages (mean MD). Multivariable mixed linear regression models with random screening-center-specific intercepts were fitted, using log-transformed percentage of MD as dependent variable and adjusting for age, body mass index, menopausal status and other confounders. e^{β} represents the relative increase of mean MD.
Results: 13.9% of the participants reported personal history of thyroid disease. MD was not associated to hyperthyroidism (e^{β}:1.05, 95%CI: 0.82–1.36), hypothyroidism (e^{β}:1.02, 95%CI: 0.75–1.38), thyroid nodules (e^{β}:1.01, 95%CI: 0.85–1.19) or thyroid cancer (e^{β}:1.03, 95%CI: 0.56–1.92). However, women with goiter had lower MD (mean $MD_{no\text{-}goiter}$: 13.4% vs mean MD_{goiter}: 10.6%; e^{β}:0.79, 95%CI: 0.64–0.98) and those with Hashimoto thyroiditis had higher MD (mean $MD_{no\text{-}thyroiditis}$: 13.3% vs mean $MD_{thyroidits}$: 25.8%; e^{β}:1.94, 95%CI: 1.00–3.77).
Conclusion: Functional thyroid disorders were not related to MD. However, MD was lower in women with goiter and higher in those reporting Hashimoto's thyroiditis. These relationships should be confirmed in future studies.

1. Introduction

Breast and thyroid glands have a close interrelationship;

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mammary cells express thyroid hormones receptors [1], and thyroid hormones are involved in the development and differentiation of normal breast tissue [2]. In addition, thyroid hormones have estrogen-like effects [3,4], modulate estrogen metabolism [5] and can increase the effects of estrogens in breast cancer (BC) cells [6]. On the other hand, estrogens are also involved in thyroid balance [7].

Up to date, there is not a complete understanding of the relationship between BC and thyroid disorders. Experimental data seem to point to an increased risk of breast tumors in hypothyroidism patients, due to hyper sensitization of the mammary glandular epithelium to prolactin and estrogen, which could promote BC growth [3,8], or due to the inhibition of oxidative stress-induced apoptosis [9]. In spite of that, two meta-analysis haven't found evidence of association between hypothyroidism and BC [10,11], although a more recent large cohort study, reported a slight decreased risk of BC in women with hypothyroidism and increased risk in women with hyperthyroidism [12]. Regarding autoimmune thyroiditis, some studies have found increased risk of BC in women with this disease [11], but evidence is also inconclusive [13]. Finally, higher prevalence of nontoxic goiter has been described in women with BC in comparison with healthy women [11], both in areas with sufficient iodine nutrition as well as in those with borderline or mild iodine deficiency [14].

Mammographic breast density (MD) is one of the strongest risk factors for BC [15], with a 4- to 6-fold gradient in risk between women with very dense breast compared with those with low MD [16]. The association between several BC risk factors and MD run in the same direction as those existing between them and BC. Family history of BC and hormone replacement therapy (HRT) are positively associated with both outcomes, whereas age and body mass index (BMI) are inversely associated with MD and positively associated with BC risk in postmenopausal women [17,18]. Moreover, MD, which has been proposed as an intermediate phenotype for BC [15] and may be on the causal pathway between BC and some or all of these risk factors, has also been related to response to tamoxifen [19] and to pathological response to neoadjuvant chemotherapy [20]. Thus, a possible BC risk factor, such as thyroid disorders, might influence BC risk through effects on an intermediate marker, such as MD. However, to our knowledge, there are not previous studies assessing a possible association between thyroid problems and this phenotype. Our aim is to explore the relationship between thyroid diseases and MD in Spanish pre and postmenopausal women attending BC screening programs.

2. Materials and methods

Participants' selection flowchart is summarized in Fig. 1. In 2007–2008 we launched DDM-Spain study, which was aimed to identify determinants of MD. In this project we recruited 3568 Spanish women in 7 public population based screening centers of several regions (Aragon, Balearic Isles, Castile-Leon, Catalonia, Galicia, Navarre and Valencia) and collected detailed epidemiological information. All women aged 50–69 (45–69 in some regions), regardless of nationality or legal status, are screened under these government-sponsored programs every 2 years. The average participation rate was 74.5% (range 64.7–84.0% across centers). Ten women who developed breast cancer within 6 months of the mammogram were excluded. All participants signed an informed consent form.

In 2010, we invited 3467 of these women to collaborate in Var-DDM Spain project, a second phase of the study, which did not include deceased participants (n: 4), new breast cancer cases (n: 7) and untraceable women (n: 80). A total of 3119 women agreed to participate (participation rate: 90%; age range: 47–71 years old; 99.2% caucasian), answering a new telephonic epidemiological questionnaire administered by trained interviewers, and allowing access to their mammographic history; we could locate the mammogram of this screening round in 2890 participants (92% of the participants). The average time between mammogram date and telephone interview was 8 months. In addition, anthropometric measurements were taken again at the screening centers for 2576 women. For the rest of them, self-reported weight was used to compute BMI (n: 307); 7 women did not provide this information and were excluded.

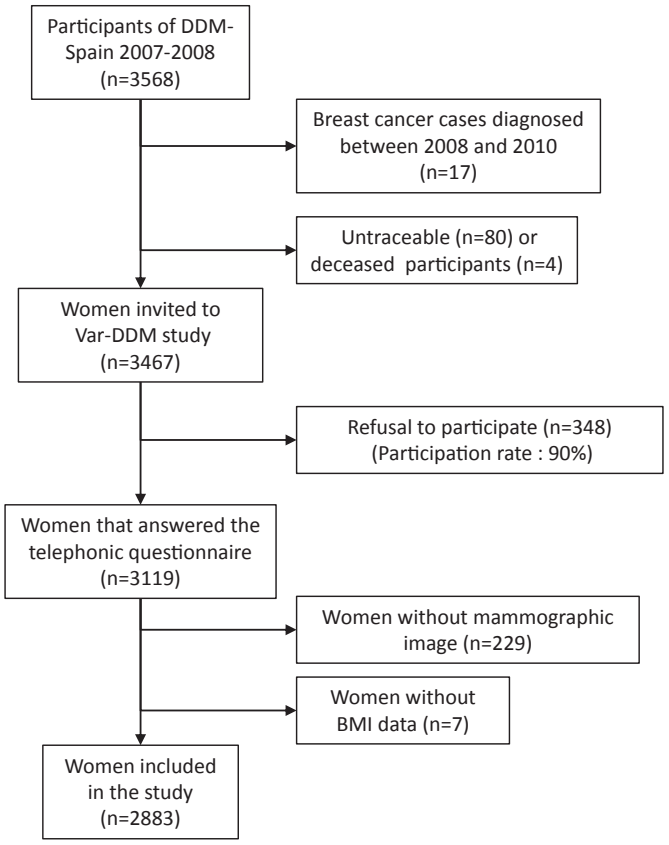

Fig. 1. Participation flowchart in Var-DDM study.

The questionnaire updated lifestyle information and diet using a validated food frequency questionnaire [21,22], and included several specific questions on the prevalence of thyroid diseases: a) Have you ever been diagnosed by a doctor of thyroid disease?; b) Do you know if the diagnosis of the thyroid disease was one of the following: hyperthyroidism, hypothyroidism, thyroiditis (Hashimoto's disease), thyroid nodule, goitre or thyroid cancer?; c) Have you ever taken any treatment for the thyroid disease? (Which treatment?, For how long?).

The percentage of MD in the cranio-caudal left mammograms was estimated in a continuous scale by two trained experienced radiologists, assisted by DM-Scan, a semi-automated computer tool designed by the Polytechnic University of Valencia (http://dmscan.iti.upv.es). DM-Scan has demonstrated high reproducibility and validity, with a substantial discriminative power to predict subsequent BC development [23,24]. Mammograms types varied across the screening centers: a) Mammograms from Galicia center were analogical images digitalized with scanner Totalook MammoAdvantage (max. optical-density 4.2); b) Fully digital images were provided by Catalonia (Siemens MAMMOMAT Novation^{DR}), Navarre (HOLOGIC LORAD SELENIA) and Valencia (Senographe 2000D Full