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Overeating, caloric restriction and mammographic density in Spanish women. DDM-Spain study

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ABSTRACT

Objectives: Mammographic density (MD) is a strong risk factor for breast cancer. The present study evaluates the association between relative caloric intake and MD in Spanish women.

Study design: We conducted a cross-sectional study in which 3517 women were recruited from seven breast cancer screening centers. MD was measured by an experienced radiologist using craniocaudal mammography and Boyd's semi-quantitative scale. Information was collected through an epidemiological survey. Predicted calories were calculated using linear regression models, including the basal metabolic rate and physical activity as explanatory variables. Overeating and caloric restriction were defined taking into account the 99% confidence interval of the predicted value. Odds ratios (OR) and 95% confidence intervals (95%CI) were estimated using center-specific mixed ordinal logistic regression models, adjusted for age, menopausal status, body mass index, parity, tobacco use, family history of breast cancer, previous biopsies, age at menarche and adherence to a Western diet.

Main outcome measure: Mammographic density.

Results: Those women with an excessive caloric intake ($\geq$ 40% above predicted) presented higher MD (OR = 1.41, 95%CI = 0.97–2.03; p = 0.070). For every 20% increase in relative caloric consumption the probability of having higher MD increased by 5% (OR = 1.05, 95%CI = 0.98–1.14; p = 0.178), not observing differences between the categories of explanatory variables. Caloric restriction was not associated with MD in our study.

Conclusions: This is the first study exploring the association between MD and the effect of caloric deficit or

Abbreviations: BMI, body mass index; BMR, basal metabolic rate; DDM-Spain, Determinants of Mammographic Density in Spain; MD, mammographic density; OR, odds ratio; 95%CI, 95% confidence interval

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excessive caloric consumption according to the energy requirements of each woman. Although caloric restriction does not seem to affect breast density, a caloric intake above predicted levels seems to increase this phenotype.

1. Introduction

Breast cancer is one of the major public health problems. Spain, with almost 28,000 cases diagnosed in 2015, occupies an intermediate position in the European ranking [1]. Early detection is one of the keys to success in the prognosis of this disease, reducing the mortality rate. Mammographic density (MD) represents the percentage of radiologically dense fibroglandular tissue on a mammogram, and is one of the strongest breast cancer risk factors [2]. The biological mechanisms linking MD and breast cancer are not entirely clear, although it appears that stromal cells, extra-cellular matrix proteins and their interaction with the epithelial component are involved [3]. Although MD has a strong genetic component, it is also influenced by other conditions. Thus, MD decreases with age, body mass index (BMI), number of pregnancies and menopause, whereas it seems to increase with hormone replacement therapy use [2].

Energy intake is essential for body function. However, the balance between total energy consumption and total energy expenditure is difficult to achieve for many people. In 2002, the Institute of Medicine Food and Nutrition Board published the Dietary Reference Intake, estimated according to energy needs, which is the energy intake necessary to maintain the energy balance of healthy adults by sex, age, weight, height and level of physical activity [4]. Obesity is the result of a positive imbalance between energy intake and energy expenditure, and there is strong evidence that overweight, obesity and weight gain in adulthood increase the risk of postmenopausal breast cancer [5]. Adult weight gain has also been positively associated with MD in some [6,7], but not all [8], previous studies.

According to the International Agency for Research on Cancer, there is sufficient evidence from experimental studies that limiting body weight gain by caloric restriction causes a protective effect on mammary gland cancer [9]. On the contrary, the evidence in epidemiological studies is less consistent [10]. Mechanisms underlying anticancer effects involve changes in growth factor signaling, inflammation, angiogenesis, autophagy and the sirtuin pathway [11].

The objective of this study is to evaluate the association between excessive or deficit caloric consumption, based on daily energy expenditure and body size, and MD in Spanish women attending breast cancer screening programs.

2. Methods

DDM-Spain (Determinants of Mammographic density in Spain) is a cross-sectional multicenter study based on 3584 women, aged 45–68 years, recruited between October 2007 and July 2008 from breast cancer screening programs in the following Autonomous Communities: Aragon, Balearic Isles, Castile-Leon, Catalonia, Galicia, Navarre, and Valencian Region. The average participation rate was 74.5%, ranging from 64.7% in Corunna to 84.0% in Zaragoza. Women previously diagnosed with breast or ovarian cancer were excluded, as well as women with mammoplasty or breast implants and those who were not able to answer the questionnaire. Participants signed an informed consent and were interviewed in their respective screening centers by trained interviewers. The questionnaire included detailed information on basic sociodemographic characteristics, family and personal history, gynecological, obstetric and occupational history, physical activity, alcohol, and tobacco consumption. Post-menopausal status was defined as absence of menstruation in the last 12 months. Dietary intake during the preceding year was also collected using a 117-item food frequency questionnaire previously validated [12]. From these data we also evaluated the level of adherence to a Western dietary pattern, already associated with MD in a previous study [13], and characterized by low intake of whole grains and low-fat dairy products and by a high intake of high-fat dairy products, refined grains, processed meat, sweets, high-calorie drinks, sauces and convenience foods. Height, weight, waist and hip were directly measured by the interviewer. The study was approved by the ethics committee of the Carlos III Institute of Health. More details can be found in a previous study [6].

To measure MD, we used Boyd´s semi-quantitative scale, which classifies density into six categories: A (0%), B (1–10%), C (10–25%), D (25–50%), E (50–75%), F (> 75%). The readings, anonymous and blind, were performed by a single experienced radiologist based on the left craniocaudal mammogram. To test the reliability of the radiologist, a subsample of 25 mammograms per center was reevaluated showing a high intraobserver concordance [14].

The basal metabolic rate (BMR), defined as the energy required to perform vital body functions at rest, was calculated from the study by Sabounchi et al. [15], which provides meta-predictive equations using 17 categories of regression models and 20 different subpopulations. These equations take into account age, gender, race, weight, and height. Once the BMR was calculated, we built a mixed linear regression model to predict the expected caloric intake. In this model, the dependent variable was the amount of calories consumed, the physical activity reported by women was the independent variable, the BMR was included as an offset, and the screening center was introduced as a random effects term. Therefore, observed versus expected energy consumption (relative caloric consumption) was the variable of interest in our analyses. Those women whose caloric intake was within the 99% confidence interval of the predicted intake (predicted calories +2.58 times the standard error) were considered as the reference group. Overeating was defined as caloric consumption exceeding the upper limit of that range, and the caloric deficit as a consumption below the lower limit of that range. Relative caloric intake was divided into 5 categories: very deficient caloric consumption (observed/expected consumption $\leq$ 0.80), slightly deficient caloric consumption (observed/expected consumption > 0.80 and < 1), normal caloric consumption (observed/expected consumption = 1), moderate overeating (observed/expected consumption > 1 and < 1.40) and considerable overeating (observed/expected consumption $\geq$ 1.40).

Characteristics of the participants were described using percentages or mean values, and were compared using Pearson's chi-square test or Student's t-test. The association between MD, expressed in the 6 ordinal categories described before, and relative caloric intake was assessed using ordinal logistic regression models with random center-specific intercepts, adjusted for age, menopausal status, body mass index, number of children, tobacco, family history of breast cancer, previous biopsies, age at menarche and level of adherence to a Western dietary pattern. The screening center was again introduced as a random effects term. These models assume that the odds ratios (ORs) remain constant, irrespective of the cut-off chosen to dichotomize the response variable, the so-called proportional odds assumption. The Brant test was used to verify this assumption. We also analyzed the increase in MD per every 20% rise in relative caloric intake by category of other explanatory variables. The potential effect modification was tested using the Likelihood Ratio Test to compare the final model with a model that also included an interaction term between relative caloric intake (continuous) and the corresponding explanatory variable. Analyses were performed using the statistical software package STATA / MP 14.0.