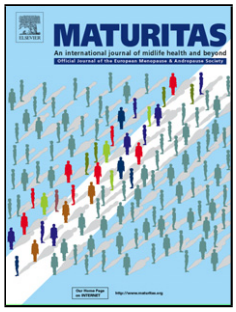

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Overeating, caloric restriction and mammographic density in Spanish women. DDM-Spain study

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Highlights

- Caloric intake above predicted levels seems to increase mammographic density.
- For every 20% increase in relative energy intake, mammographic density increased by 5%.
- Caloric restriction does not appear to affect breast density.

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 (≥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 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.

Keywords

Breast density; calories; energy intake; caloric intake; basal metabolic rate.

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

1. Introduction

Breast cancer is one of the major public health problems. Spain, with almost 28000 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 3,584 women, aged 45 to 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.

3. Results

Sixty-seven participants were excluded from the analyses: 36 did not have MD assessment; in another 11 women we could not calculate the relative caloric intake (due to missing data in the variables weight, height, age or physical activity) and, finally, 20 women were also excluded due to the lack of information of key covariates. Therefore, analyses included data from 3,517 women with complete information for all the variables of interest.

Table 1 shows the main characteristics of the study population, both globally and stratifying by menopausal status. The mean age was 56 years and 29% had university graduate. Most women (79%) were postmenopausal and 71% were overweight or obese. Almost half had 2 children (48%). Twelve percent had previous breast biopsies and 7% had family history of breast cancer. Most were never smokers (58%) and 41% were abstainers. When stratified by menopausal status it was observed that postmenopausal women had significantly lower educational level and higher BMI values than premenopausal women. They had more children and suffered from diabetes in greater proportion. The proportion of never-smokers, abstainers and sedentary women was also higher among postmenopausal women, group that also presented lower caloric intake and lower adherence to the Western dietary pattern. Finally, 18% of postmenopausal women had a MD higher than 50%, being this figure 41% for the premenopausal group.

Table 2 shows the OR and 95% confidence intervals (95%CI) between relative caloric intake and MD. We observed moderate evidence of an association between excessive caloric intake and MD. Women who consumed more calories than predicted (up to 40% more) presented

higher MD (OR=1.10, 95% CI=0.93-1.30), being this increase higher when caloric consumption exceeded 40% the predicted value (OR=1.41, 95% CI=0.97-2.03; p=0.07). On the contrary, breast density was not affected by the consumption of calories below the required. For every 20% increase in relative energy consumption MD increased by 5% (P = 0.178).

The effect on MD associated with every 20% increase in relative caloric consumption per category of the explanatory variables is depicted in Figure 1. Although there were no differences between the categories, the positive trend associated with the relative energy consumption was more pronounced in nulliparous women (OR=1.19, 95% CI=0.95-1.48), in women with family history of breast cancer (OR=1.19, 95% CI=0.92-1.55) and among women with high adherence to the Western dietary pattern (OR=1.12, 95% CI=0.98-1.27).

4. Discussion

The present study analyzes the association between MD and women's relative caloric intake taking into account the physical activity performed by women and their basal metabolic rate. While caloric restriction does not appear to affect breast density, a caloric intake above predicted levels could increase this phenotype.

One of the main advantages of our study is the large sample size and the population nature of the study. As far as we know, this is the first study analyzing the effect of relative caloric consumption on MD. In addition, because the physiological pathways and metabolic effects of calories differ according to the source from which they originate (calories from fats, proteins, carbohydrates, etc.) [16], we adjusted the models by the Western dietary pattern, previously identified in these women and associated with breast density [13]. In addition, this is a multicenter study conducted in 7 Spanish cities located throughout the Spanish territory, which allows us to collect the diversity of dietary patterns in our country. On the other hand, participation rates in breast cancer screening programs in Spain are high [17], and our participants have very similar characteristics to those of the national population of the same age range collected in the National Health Survey in terms of age, socioeconomic status, prevalence of smoking and physical activity [18], which supports the external validity of our results. Finally, the ordinal nature of the dependent variable was taken into account when using ordinal logistic regression models instead of the traditional logistic regression models.

Our study also has a number of limitations. Firstly, it is a cross-sectional study, so it is not possible to establish causal relationships between relative caloric intake and MD. Second, the

explanatory variables were self-reported and collected retrospectively, and therefore might be affected by recall bias. However, this bias would probably be non-differential, since MD assessment was blind and anonymous, thus resulting in an underestimate of the association studied. Third, MD density was visually assessed by a single radiologist, which may imply a degree of subjectivity. However, our experienced radiologist presented a high intraobserver concordance [14]. MD was measured using the Boyd's semi-quantitative scale instead of a computer-based quantitative method. However, these quantitative methods are not totally exempt from subjectivity, and we have confirmed that this visual scale is a risk predictor of subsequent breast cancer development [19]. On the other hand, our sample corresponds to the target population of the screening program (women aged 45 to 68 years), so the number of premenopausal women may have been insufficient to detect significant differences in some associations, especially for the most extreme categories of relative caloric intake. Finally, it should be noted that the use of different mammographic devices and different interviewers could have introduced some degree of heterogeneity. However, we have adjusted for these possible sources of error by including the screening program as a random effects term in the regression models.

Our results point to a higher MD in women with excessive caloric intake, though the association was marginally significant. High energy intake has not been consistently associated with an increased risk of breast cancer in human studies. Although most of them showed a positive association, there are also studies reporting no association [20]. However, it is difficult to evaluate the independent effect of energy intake on breast cancer risk, since it depends largely on body size and physical activity. To date, few epidemiological studies have explored the three components of the energy balance jointly, and all of them have shown an increased risk of breast cancer associated with the most unfavorable energy balance: high energy consumption, high body mass index and low physical activity [21]. This positive balance over an extended period of time results in weight gain and increased adiposity and, consequently, contributes to an increased risk of breast cancer in postmenopausal women [5].

Regarding its association with MD, there are previous studies that have detected a positive association between this phenotype and caloric intake [22-24], one of them based on the same participants of our study [22]. With respect to weight gain in adulthood, although previous studies have observed a positive relationship with MD, both in this same sample [6] and in others [7], other studies have described an inverse association [8]. Studies with transgenic mice have shown that weight gain stimulates the expression of the enzyme aromatase in the breast,

thereby increasing the local amount of estrogens [25]. This mechanism could be responsible for the higher MD associated with excessive caloric intake, since estrogens have been shown to be the major mitogens of epithelial cells in non-pregnant adult women [26].

Although there is sufficient evidence in experimental animals that limiting weight gain by caloric restriction prevents mammary tumors [9], we did not detect an association with MD in our study, possibly due to the lower amount of fatty tissue in the breast of thin women. Although this result should be confirmed in subsequent studies, it leads us to think that the possible relationship between caloric restriction and breast cancer risk in humans would not be mediated by MD.

In summary, our results show that, although caloric restriction does not affect MD, the consumption of calories well above the required, according to physical activity and body size, seems to be associated with an increase in MD. Therefore, this phenotype could play an intermediate role in the still not fully known relationship between excessive energy consumption and breast cancer risk. More powerful future studies would be desirable to confirm this finding and, therefore, make women aware of the importance of an adequate caloric intake.

Contributors

This research has been conducted by a multicenter group (DDM-Spain group).

María del Pilar del Pozo participated in the study concept and design, database depuration, analysis, interpretation of the data and drafting.

Adela Castelló participated in the study concept and design, analysis and interpretation of the data and critical revision of the manuscript.

Carmen Vidal participated in the study concept and design, acquisition of data and critical revision of the manuscript.

Dolores Salas-Trejo participated in the study concept and design, acquisition of data and critical revision of the manuscript.

Carmen Sánchez-Contador participated in the study concept and design, acquisition of data and critical revision of the manuscript.

Carmen Pedraz-Pingarrón participated in the study concept and design, acquisition of data and critical revision of the manuscript.

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Rafael Llobet participated in the acquisition of data and critical revision of the manuscript.
Jesús Vioque participated in the acquisition of data and critical revision of the manuscript.
Beatriz Pérez-Gómez participated in the study concept and design, analysis and interpretation of the data and critical revision of the manuscript
Marina Pollán participated in the study concept and design, analysis and interpretation of the data, drafting and critical revision of the manuscript.
Virginia Lope participated in the study concept and design, analysis and interpretation of the data, drafting and critical revision of the manuscript.
All authors saw and approved the final version of the submitted work.

Conflict of interest

The authors declare that they have no conflict of interest.

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This article presents independent research. The views expressed are those of the authors and not necessarily those of the Carlos III Institute of Health.

Ethical approval

The DDM-Spain study was conducted in compliance with the Helsinki Declaration. The study protocol was formally approved by the Bioethics and Animal Welfare Committee at the Carlos III Institute of Health. All participants signed a consent form, including permission to publish results from the current research.

Provenance and peer review

This article has undergone peer review.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. The datasets generated are not publicly available due to restrictions imposed by the Carlos III Ethic Committee, but are available from the principal investigator on reasonable request.

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Table 1. Participant characteristics according to menopausal status.

	TOTAL (n=3517)		PREMENOPAUSAL (n=751)		POSTMENOPAUSAL (n=2766)		*P* value
	n	%	n	%	n	%	
City, n(%)							
Corunna	523	14.9%	70	9.3%	453	16.4%	<0.001
Barcelona	486	13.8%	68	9.1%	418	15.1%	
Burgos	501	14.3%	198	26.4%	303	11.0%	
Palma	534	15.2%	51	6.8%	483	17.5%	
Pamplona	494	14.1%	171	22.8%	323	11.7%	
Zaragoza	486	13.8%	59	7.9%	427	15.4%	
Valencia	493	14.0%	134	17.8%	359	13.0%	
Age, mean (SD)	56.19	5.5	49.8	2.9	57.9	4.6	<0.001
Educational level, n(%)							
Primary school or less	1191	33.9%	122	16.3%	1069	38.7%	<0.001
Secondary or vocational training	1299	37.0%	273	36.4%	1026	37.2%	
University graduate	1021	29.1%	355	47.3%	666	24.1%	
Body mass index (kg/m^2), n(%)							
<20	64	1.8%	19	2.5%	45	1.6%	<0.001
20-24	941	26.8%	291	38.7%	650	23.5%	
25-29	1473	41.9%	253	33.7%	1220	44.1%	
>29	1039	29.5%	188	25.0%	851	30.8%	
Menarche, n(%)							
<12 years	799	22.7%	171	22.8%	628	22.7%	0.811
12 years	739	21.0%	155	20.6%	584	21.1%	
13 years	813	23.1%	183	24.4%	630	22.8%	
>13 years	1166	33.2%	242	32.2%	924	33.4%	
Number of children, n(%)							
Nulliparous	316	9.0%	78	10.4%	238	8.6%	<0.001
1	535	15.2%	153	20.4%	382	13.8%	
2	1686	47.9%	386	51.4%	1300	47.0%	
>2	980	27.9%	134	17.8%	846	30.6%	
Breast biopsy, n(%)							
No	3099	88.1%	664	88.4%	2435	88.0%	0.774
Yes	418	11.9%	87	11.6%	331	12.0%	
Family history of breast cancer, n(%)							
No	3262	92.8%	695	92.5%	2567	92.8%	0.806
Yes	255	7.3%	56	7.5%	199	7.2%	
Diabetes, n(%)							
No	3317	94.5%	738	98.3%	2579	93.4%	<0.001
Yes	194	5.5%	13	1.7%	181	6.6%	
Hormone replacement therapy use, n(%)							
No	3192	90.8%	751	100.0%	2441	88.3%	<0.001
Yes	325	9.2%	0	0.0%	325	11.7%	
Smoking status, n(%)							
Never smoker	2034	57.8%	320	42.6%	1714	62.0%	<0.001
Smoker or ex-smoker	1483	42.2%	431	57.4%	1052	38.0%	
Alcohol, n(%)							
Abstainer	1457	41.4%	281	37.4%	1176	42.5%	0.001
<10g/day	1450	41.2%	356	47.4%	1094	39.6%	
≥10 g/day	610	17.3%	114	15.2%	496	17.9%	

Physical activity, n(%)							
Sedentary/slightly active	834	23.7%	141	18.8%	693	25.1%	0.001
Moderately active	1829	52.0%	422	56.2%	1407	50.9%	
Active/very active	854	24.3%	188	25.0%	666	24.1%	
Caloric intake (Kcal/day), mean(SD)	2053.8	479.5	2135.5	486.3	2031.6	475.3	<0.001
Basal metabolic rate (Kcal/day), mean(SD)	1313.2	131.1	1323.8	131.1	1310.3	130.9	0.013
Predicted calories (Kcal/day), mean(SD)	2054.8	135.7	2070.7	128.7	2050.5	137.3	<0.001
Relative caloric intake, n(%)							
More than 20% below predicted calories	477	13.6%	83	11.1%	394	14.2%	0.001
Up to 20% below predicted calories	956	27.2%	183	24.4%	773	27.9%	
Within predicted calories	830	23.6%	170	22.6%	660	23.9%	
Up to 40% above predicted calories	1143	32.5%	290	38.6%	853	30.8%	
More than 40% above predicted calories	111	3.2%	25	3.3%	86	3.1%	
Western dietary pattern, n(%)							
Low adherence	881	25.1%	120	16.0%	761	27.5%	<0.001
Medium adherence	875	24.9%	166	22.1%	709	25.6%	
Moderate adherence	882	25.1%	212	28.2%	670	24.2%	
High adherence	879	25.0%	253	33.7%	626	22.6%	
Prudent dietary pattern, n(%)							
Low adherence	877	24.9%	181	24.1%	696	25.2%	0.816
Medium adherence	877	24.9%	188	25.0%	689	24.9%	
Moderate adherence	884	25.1%	198	26.4%	686	24.8%	
High adherence	879	25.0%	184	24.5%	695	25.1%	
Mediterranean dietary pattern, n(%)							
Low adherence	877	24.9%	199	26.5%	678	24.5%	0.623
Medium adherence	877	24.9%	189	25.2%	688	24.9%	
Moderate adherence	883	25.1%	178	23.7%	705	25.5%	
High adherence	880	25.0%	185	24.6%	695	25.1%	
Mammographic density (Boyd Scale), n(%)							
A: 0%	149	4.2%	8	1.1%	141	5.1%	<0.001
B: <10%	715	20.3%	85	11.3%	630	22.8%	
C: 10-25%	726	20.6%	95	12.6%	631	22.8%	
D: 25-50%	1124	32.0%	253	33.7%	871	31.5%	
E: 50-75%	616	17.5%	235	31.3%	381	13.8%	
F: >75%	187	5.3%	75	10.0%	112	4.0%	

The values of Western, Prudent and Mediterranean dietary patterns show the adherence of the study women to the different dietary patterns. The western pattern is characterized by a high intake of high-fat dairy products, processed meats, refined grains, sweets and high calorie drinks, the Mediterranean pattern characterized by high consumption of fruits and vegetables and the prudent pattern taking on characteristics of both.

Table 2. Association between relative caloric intake and mammographic density.

	n	OR[a]	**(95% CI)**	*P* value
Relative caloric intake				
More than 20% below predicted calories	477	0.97	(0.78 - 1.21)	0.796
Up to 20% below predicted calories	956	1.00	(0.84 - 1.19)	0.993
Within predicted calories	830	1.00		
Up to 40% above predicted calories	1143	1.10	(0.93 - 1.30)	0.272
More than 40% above predicted calories	111	1.41	(0.97 - 2.03)	0.070
Trend per 20% increase over the predicted range		1.05	(0.98 - 1.14)	0.178

Abbreviations: OR, Odds ratio; CI, confidence interval.

[a] Adjusted for age, menopausal status, body mass index, age at menarche, parity, smoking status, family history of breast cancer, previous biopsies and adherence to a Western dietary pattern. Screening center was included as a random effects term.

Titles and legends to figures

Figure 1. Mammographic density increase for every 20% increase in relative caloric consumption according to women characteristics.

*Adjusted for age, menopausal status, body mass index, age at menarche, parity, smoking status, family history of breast cancer, previous biopsies and adherence to a Western dietary pattern. Screening center was included as a random effects term.