Perinatal and childhood factors and risk of breast cancer subtypes in adulthood

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Abstract

Background

Accumulated exposure to hormones and growth factors during early life may influence the future risk of breast cancer (BC). This study examines the influence of childhood-related, socio-demographic and anthropometric variables on BC risk, overall and by specific pathologic subtypes.

Methods

This is a case-control study where 1539 histologically-confirmed BC cases (23-85 years) and 1621 population controls, frequency matched by age, were recruited in 10 Spanish provinces. Perinatal and childhood-related characteristics were directly surveyed by trained staff. The association with BC risk, globally and according to menopausal status and pathologic subtypes, was evaluated using logistic and multinomial regression models, adjusting for tumor specific risk factors.

Results

Birth characteristics were not related with BC risk. However, women with high socioeconomic level at birth presented a decreased BC risk (OR=0.45; 95%CI=0.29-0.70), while those whose mothers were aged over 39 years at their birth showed an almost significant excess risk of hormone receptor positive tumors (HR+) (OR=1.35; 95%CI=0.99-1.84). Women who were taller than their girl mates before puberty showed increased postmenopausal BC risk (OR=1.26; 95%CI=1.03-1.54) and increased HR+ BC risk (OR=1.26; 95%CI=1.04-1.52). Regarding prepubertal weight, while those women who were thinner than average showed higher postmenopausal BC risk (OR=1.46; 95%CI=1.20-1.78), associated with HR+ tumors (OR=1.34; 95%CI=1.12-1.61) and with triple negative tumors (OR=1.56; 95%CI=1.03-2.35), those who were heavier than average presented lower premenopausal BC risk (OR=0.64; 95%CI=0.46-0.90) and lower risk of epidermal growth factor receptor positive tumors (OR=0.61; 95%CI=0.40-0.93).

Conclusion

These data reflect the importance of hormones and growth factors in the early stages of life, when the mammary gland is in development and therefore more vulnerable to proliferative stimuli.

Keywords: breast cancer subtypes, childhood factors, perinatal factors, early life factors, case-control study, Spain, hormone receptor, maternal age, childhood height, childhood weight.

1. Introduction

Breast cancer (BC) is the most frequent cause of cancer in Spanish women, with more than 25,200 new cases diagnosed per year [1]. During the last decades of the 20th century, it showed a steady increase in incidence, even among women younger than 45 years, though trends seem to level off in 2001 [2] . It is also the tumor with the highest mortality rate in Spanish women, accounting for 15.6% of all female cancer-related deaths in 2013 [3].

The intrauterine environment may influence the subsequent risk of BC in female offspring. Endogenous pregnancy hormones can act as growth factors increasing the stem cell population (and thereby the size of the organ and the number of susceptible stem cells later in life) or inducing cell proliferation. In so doing, these hormones increase the risk for genetic errors (oncogenic mutations or spontaneous somatic mutations), as well as the expansion of initiated clones. Additionally, estrogens and their metabolites can also act as genotoxic agents [4, 5]. Epidemiologic studies have shown moderate positive associations of BC risk with birthweight, birth length, maternal age and twin pregnancies; in contrast, pre-eclampsia or eclampsia seem to be inversely associated with the risk of this tumor [6-9].

Puberty is also a critical period for mammary gland development. Just before puberty, an exponential growth of the mammary gland, characterized by formation of terminal end buds, begins. These structures are considered the most vulnerable targets for carcinogens, and are still abundant during adolescence [10, 11]. There are studies that have described a positive relationship between BC risk and childhood height or height velocity as well as an inverse association with childhood obesity or body mass index (BMI) velocity [12-16].

BC represents a heterogeneous disease, and its risk factors vary by molecular-based BC subtypes [17, 18]. This study sought to investigate whether perinatal and childhood sociodemographic and anthropometric factors influence the risk of BC in adulthood, using a large population-based case control study in Spain. In addition, we also assessed whether these associations differed by specific BC subtypes.

2. Materials and Methods

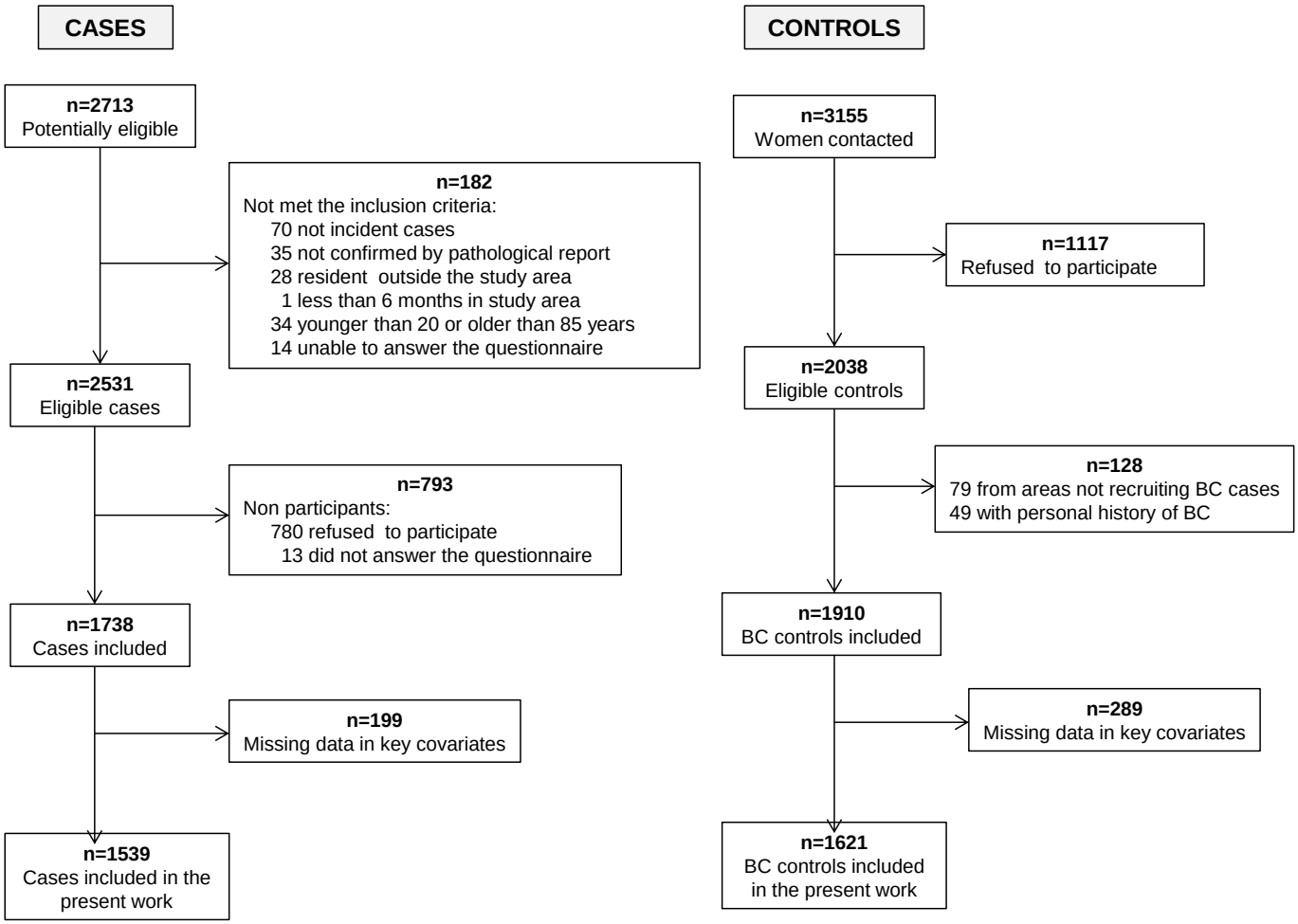
2.1 Study population

Multicase Control Spain (MCC-Spain) is a case-control study with population controls and incident cases treated in the oncologic units of 23 hospitals located in 12 Spanish provinces (Barcelona, Madrid, Navarra, Gipuzkoa, León,

Asturias, Murcia, Huelva, Cantabria, Valencia, Granada and Girona). It was carried out with the purpose to evaluate environmental and genetic factors associated with the risk of colorectal, breast, prostate, gastric tumors and chronic lymphocytic leukemia. Inclusion criteria required that participants had lived for at least 6 months in the study areas, were between 20-85 years old and were able to answer the epidemiological questionnaire. Given the hospitals and the resources available to us, the initial intention was to collect at least 1500 breast, 1500 colorectal cancer cases, 1000 prostate cancer cases, 500 gastric cancer cases and 500 chronic lymphocytic leukemias. Cases were identified as soon as possible after their diagnosis, through active search that included hospital admission registries and periodical visits to the collaborating hospital departments (i.e. gynecology, oncology, general surgery, radiotherapy and pathology departments, and breast cancer multidisciplinary units). Between September 2008 and December 2013 we recruited a total of 1738 histologically-confirmed BC cases (ICD-10: C50, D05.1, D05.7) with complete interviews and informed consent in 10 of these provinces (all except Murcia and Granada).

Population controls were randomly selected from the general practitioner lists of the hospital catchment area and were frequency matched to cases by age, sex and region, ensuring that in each region there was at least one control of the same sex and 5-year interval for each case. Participants were contacted by telephone, and those who agreed to participate signed an informed consent. We recruited a total of 1910 female controls. The study was approved by the Ethics Committee of all hospitals and participant primary care centers. Fig.1 show a flow chart displaying the selection process of breast cancer cases and controls. More details regarding the design of the study are provided elsewhere [19].

Fig.1: Flow chart displaying the selection process of breast cancer cases and controls. MCC-Spain study 2008-2013.



2.2 Data collection

Trained interviewers administered a structured computerized epidemiological questionnaire in a face-to-face interview. This questionnaire recorded sociodemographic and anthropometric data, family and personal history, gynecological, obstetric, medical, residential and occupational history, smoking and physical activity. Finally cases and controls completed a validated food frequency questionnaire. With respect to perinatal factors, the questionnaire collected information on socioeconomic level at birth (income of their parents when the women were born), maternal and paternal age at birth, birthweight, birth order and premature birth. With respect to childhood factors, the questionnaire collected information about how women were before having their first menstruation in comparison with their girl mates (heavier than average; average; thinner than average or taller than average; average; shorter than average) and age at menarche.

2.3 Breast cancer subtypes

Trained personnel reviewed all pathology records and registered information regarding estrogen receptor (ER), progesterone receptor (PR) and the human epidermal growth factor receptor (HER2) in BC cases. So, BC cases were sub classified by the following subtypes: hormone receptor positive tumors (HR+) (ER+ or PR+ with HER2-), HER2+ tumors (independent of ER or PR) and triple negative (TN) tumors (ER-, PR- and HER2-).

2.4 Statistical analyses

Descriptive analyses of participants' characteristics were performed for cases and controls. Categorical variables were described using absolute figures and percentages, and continuous variables using means and standard deviations. Significant differences between cases and controls were tested using Pearson chi-square for categorical variables and Student's t-test for continuous variables assuming equal variances.

The association of perinatal and childhood variables with BC risk was evaluated using logistic mixed regression models, including the province as a random effect term, as implemented in Stata´s *gllamm* command [20]. Models were adjusted for age, educational level, BMI one year before the interview, age at first birth, age at menarche, previous biopsies, family history of BC and menopausal status. We also conducted stratified analyses by menopausal status. Heterogeneity of effects among pre and postmenopausal women were assessed, including an interaction term between menopausal status and the corresponding variable of interest.

Finally, multinomial logistic regression models were used to evaluate the association of perinatal and childhood factors with each of the above-mentioned BC subtypes. These models were adjusted by the same set of variables described above, including the province as a random effect term. Heterogeneity of effects was tested using a Wald test comparing the coefficients obtained for the different cancer subtypes. All analyses were performed in STATA/MP 13.1 software.

3. Results

Response rates were 53.8% for healthy female controls and 68.7% for BC cases. Results presented in this manuscript are based on participants with no missing values in any of the selected confounders: 1539 BC cases (89%) and 1621 controls (85%). Table 1 shows the main characteristics of this population. In general, cases were slightly younger and had fewer children than controls. A sensitivity analysis testing the distribution of these variables in cases and controls excluded due to lack of information on any of the selected confounders showed similar results to those obtained here (data not shown).

Table 1: Socio-demographic characteristics of breast cancer cases and controls

	BC cases (N=1539)	Controls (N=1621)	p-val
Age, mean(SD)	56.0(12.1)	58.2(12.7)	<0.001
Educational level, N(%)			
less than primary school	215(14%)	235(14%)	
primary school completed	504(33%)	489(30%)	
secondary school	512(33%)	521(32%)	
university graduate	308(20%)	376(23%)	0.120
BMI, N(%)			
<20 Kg/m^2	88(6%)	114(7%)	
20-24 Kg/m^2	636(41%)	710(44%)	
25-29 Kg/m^2	528(34%)	509(31%)	
>29 Kg/m^2	287(19%)	288(18%)	0.130
Menopausal status, N(%)			
premenopausal	540(35%)	485(30%)	
peri-postmenopausal	999(65%)	1136(70%)	0.002
Number of children, N(%)			
none	311(20%)	308(19%)	
1-2	904(59%)	907(56%)	
3-4	284(18%)	341(21%)	
>4	40(3%)	65(4%)	0.029
Age at first birth, mean(SD)	26.7(4.9)	26.7(4.8)	0.939
Age at menarche, mean(SD)	12.8(1.6)	12.8(1.6)	0.139
Previous biopsies, N(%)			
none	1420(92%)	1585(98%)	
yes	119(8%)	36(2%)	<0.001
Family history of breast cancer, N(%)			
none	1152(75%)	1386(86%)	
second degree only	161(10%)	91(6%)	
1 first degree	197(13%)	134(8%)	
>1 first degree	29(2%)	10(1%)	<0.001

Table 2 shows the association between BC and perinatal and childhood factors, both globally and stratified by menopausal status. Although the number of cases was low, pre and postmenopausal women with high socioeconomic level at birth showed a decreased risk of BC (OR=0.45; 95%CI=0.29-0.70). Those women whose mother was aged over 39 years at their birth displayed greater BC risk (OR:1.30; 95%CI=0.98-1.73), although this result failed to attain statistical significance. Participants who reported being thinner than average during their prepubertal period showed an increased risk of BC (OR=1.34; 95%CI=1.14-1.57), and this association was stronger among postmenopausal women (OR=1.46; 95%CI=1.20-1.78). By contrast, those who reported being heavier than average during childhood showed decreased premenopausal BC risk (OR=0.64; 95%CI=0.46-0.90). Higher prepubertal height was also associated with greater risk of postmenopausal BC (OR=1.26; 95%CI=1.03-1.54).

Table 3 summarizes these results by BC tumor subtypes. In general, 66% of BC cases were HR+, 17% were HER2+ and 8% were TN tumors (similar to percentages described by another Spanish population-based study [21]. We could not classify 137 (9%) BC cases. The inverse association with socioeconomic level at birth was mainly confirmed for HR+ tumors, although, again, the number of cases in the high socioeconomic level was very low. The increased risk associated with advanced maternal age was almost significant for HR+ tumors (OR >39 years=1.35; 95%CI=0.99-1.84). Women who were taller than average in their prepubertal period also showed an increased risk of HR+ tumors (OR=1.26; 95%CI=1.04-1.52). Finally, with regard to prepubertal weight, those women who were thinner than average showed increased risk of HR+ (OR=1.34; 95%CI=1.12-1.61) and TN tumors (OR=1.56; 95%CI=1.03-2.35) while those who were heavier presented lower HER2+ BC risk (OR=0.61; 95%CI=0.40-0.93).

We didn't find any significant association with other perinatal or childhood variables, such as paternal age at birth, firstborn baby, premature birth, birth weight or age at menarche.

Table 2: Association between birth and childhood characteristics and breast cancer risk, both overall and broken down by menopausal status

	All women (N=3160)					Pre-menopausal women (N=1025)					Post-menopausal women (N=2135)					
	Cases	**controls**	**OR[a]**	**95% CI**	**P**	**Cases**	**controls**	**OR[a]**	**95% CI**	**P**	**Cases**	**controls**	**OR[a]**	**95% CI**	**P**	**P-int.[b]**
Socio-economic level at birth																
low	489	533	0.94	0.80 - 1.11	0.477	131	117	0.97	0.72 - 1.30	0.818	358	416	0.93	0.77 - 1.13	0.481	
middle	1017	1007	1.00			398	343	1.00			619	664	1.00			
high	30	78	0.45	0.29 - 0.70	<0.001	10	23	0.42	0.19 - 0.91	0.027	20	55	0.46	0.27 - 0.80	0.005	0.956
Maternal age at birth																
<30 years	708	793	1.00			258	252	1.00			450	541	1.00			
30–34 years	388	369	1.13	0.94 - 1.35	0.184	157	116	1.27	0.93 - 1.72	0.129	231	253	1.06	0.85 - 1.33	0.603	
35–39 years	194	208	1.01	0.80 - 1.26	0.949	71	65	1.07	0.73 - 1.58	0.723	123	143	0.97	0.74 - 1.29	0.858	
>39 years	136	110	1.30	0.98 - 1.73	0.066	40	29	1.28	0.76 - 2.15	0.358	96	81	1.31	0.94 - 1.82	0.116	
five-year trend			*1.04*	*0.98 - 1.11*	*0.174*			*1.06*	*0.95 - 1.17*	*0.310*			*1.04*	*0.96 - 1.11*	*0.339*	0.819
Paternal age at birth[c]																
<30 years	451	516	1.00			165	170	1.00			286	346	1.00			
30–34 years	410	408	1.07	0.87 - 1.32	0.509	152	124	1.19	0.85 - 1.67	0.321	258	284	1.02	0.79 - 1.31	0.871	
35–39 years	268	240	1.18	0.90 - 1.55	0.238	116	79	1.43	0.96 - 2.13	0.078	152	161	1.06	0.76 - 1.46	0.736	
>39 years	266	280	0.98	0.70 - 1.37	0.905	84	82	0.96	0.61 - 1.52	0.871	182	198	0.99	0.69 - 1.42	0.948	
five-year trend			*1.00*	*0.91 - 1.09*	*0.936*			*1.02*	*0.90 - 1.14*	*0.788*			*0.99*	*0.90 - 1.09*	*0.793*	0.534
Firstborn baby																
no	1111	1153	1.00			392	348	1.00			719	805	1.00			
yes	413	449	1.00	0.85 - 1.17	0.971	145	133	1.02	0.77 - 1.35	0.906	268	316	1.00	0.81 - 1.20	0.899	0.865
Premature baby																
no	1423	1522	1.00			502	456	1.00			921	1066	1.00			
yes	72	65	1.14	0.80 - 1.63	0.456	24	26	0.75	0.42 - 1.35	0.339	48	39	1.45	0.93 - 2.26	0.098	0.078
Birth weight																
<2.5 Kg	74	61	1.27	0.89 - 1.83	0.189	28	22	1.06	0.59 - 1.92	0.848	46	39	1.42	0.90 - 2.23	0.132	
2.5-3.9 Kg	987	1074	1.00			381	346	1.00			606	728	1.00			
>3.9 Kg	157	164	1.05	0.82 - 1.33	0.721	56	53	0.95	0.63 - 1.43	0.793	101	111	1.10	0.82 - 1.49	0.522	
not known	320	320	1.16	0.96 - 1.41	0.129	75	64	1.07	0.74 - 1.56	0.723	245	256	1.20	0.96 - 1.50	0.108	
trend			*0.95*	*0.78 - 1.16*	*0.616*			*0.94*	*0.68 - 1.31*	*0.726*			*0.96*	*0.75 - 1.22*	*0.715*	0.806
Prepubertal height																
shorter than average	237	258	1.00	0.82 - 1.23	0.971	83	87	0.83	0.58 - 1.18	0.295	154	171	1.11	0.86 - 1.43	0.436	
average	834	912	1.00			296	252	1.00			538	660	1.00			
taller than average	460	442	1.15	0.98 - 1.36	0.094	160	145	0.97	0.72 - 1.29	0.811	300	297	1.26	1.03 - 1.54	0.027	0.218
Prepubertal weight																
thinner than average	693	614	1.34	1.14 - 1.57	<0.001	215	169	1.11	0.83 - 1.48	0.475	478	445	1.46	1.20 - 1.78	<0.001	
average	583	670	1.00			222	188	1.00			361	482	1.00			
heavier than average	255	328	0.84	0.69 - 1.04	0.106	101	124	0.64	0.46 - 0.90	0.010	154	204	0.99	0.76 - 1.28	0.922	0.095
Age at menarche																
<13 years	678	688	1.00			251	215	1.00			427	473	1.00			
13 years	392	393	1.07	0.87 - 1.32	0.535	148	132	1.02	0.75 - 1.38	0.919	244	261	1.07	0.86 - 1.35	0.539	
>13 years	469	540	0.97	0.80 - 1.19	0.785	141	138	0.94	0.69 - 1.27	0.685	328	402	0.97	0.79 - 1.19	0.762	
trend per year			*1.00*	*0.90 - 1.11*	*0.967*			*1.00*	*0.92 - 1.10*	*0.948*			*0.98*	*0.93 - 1.04*	*0.489*	0.959

[a] OR and 95% CI adjusted for age, study level, BMI 1-year before the interview, age at first birth, previous biopsies, family history of breast cancer, age at menarche and menopausal status

[b] P-int.: P value of the interaction term between menopausal status and the corresponding variable

[c] Additionally adjusted by maternal age at birth

In italics: ORs, 95% CI and P values obtained with the corresponding variable as a continuous term

Table 3: Association between birth and childhood characteristics and breast cancer risk by tumor subtype

	Controls	HR+ (N=1016)				HER2+ (N=265)				TN (N=121)				
	(N=1621)	Cases	OR[a]	95% CI	P	Cases	OR[a]	95% CI	P	Cases	OR[a]	95% CI	P	P-het.[b]
Socio-economic level at birth														
low	533	339	1.02	0.85 - 1.23	0.818	76	0.81	0.59 - 1.10	0.173	39	0.94	0.62 - 1.42	0.758	
middle	1007	653	1.00			181	1.00			81	1.00			
high	78	21	0.49	0.30 - 0.82	0.007	8	0.69	0.32 - 1.49	0.347	1	-			0.244
Maternal age at birth														
<30 years	793	457	1.00			125	1.00			63	1.00			
30–34 years	369	262	1.17	0.95 - 1.43	0.130	63	1.06	0.76 - 1.48	0.725	30	0.98	0.62 - 1.54	0.918	
35–39 years	208	130	1.03	0.80 - 1.33	0.796	36	1.08	0.72 - 1.62	0.720	11	0.65	0.33 - 1.26	0.200	
>39 years	110	92	1.35	0.99 - 1.84	0.059	23	1.31	0.79 - 2.15	0.293	7	0.81	0.36 - 1.82	0.605	
five-year trend			*1.05*	*0.98 - 1.13*	*0.132*		*1.05*	*0.94 - 1.17*	*0.376*		*0.90*	*0.77 - 1.06*	*0.203*	0.169
Paternal age at birth[c]														
<30 years	516	291	1.00			75	1.00			45	1.00			
30–34 years	408	270	1.06	0.84 - 1.34	0.626	72	1.23	0.84 - 1.82	0.291	30	0.98	0.57 - 1.68	0.940	
35–39 years	240	184	1.18	0.87 - 1.61	0.283	47	1.46	0.88 - 2.41	0.139	17	1.06	0.51 - 2.19	0.873	
>39 years	280	176	0.93	0.64 - 1.36	0.709	46	1.26	0.68 - 2.32	0.462	15	0.93	0.38 - 2.28	0.880	
five-year trend			*0.97*	*0.88 - 1.07*	*0.590*		*1.11*	*0.95 - 1.30*	*0.184*		*0.96*	*0.76 - 1.22*	*0.759*	0.258
Firstborn baby														
no	1153	734	1.00			202	1.00			88	1.00			
yes	449	270	1.00	0.83 - 1.20	0.978	62	0.81	0.59 - 1.11	0.184	32	0.98	0.64 - 1.50	0.922	0.427
Premature baby														
no	1522	939	1.00			244	1.00			110	1.00			
yes	65	48	1.16	0.78 - 1.72	0.457	14	1.26	0.69 - 2.31	0.445	6	1.18	0.50 - 2.81	0.702	0.964
Birth weight														
<2.5 Kg	61	43	1.11	0.73 - 1.67	0.639	17	1.62	0.91 - 2.86	0.098	6	1.26	0.52 - 3.02	0.608	
2.5-3.9 Kg	1074	648	1.00			171	1.00			79	1.00			
>3.9 Kg	164	110	1.13	0.86 - 1.48	0.381	26	0.98	0.62 - 1.54	0.934	14	1.15	0.63 - 2.09	0.655	
not known	320	215	1.17	0.94 - 1.45	0.160	51	1.04	0.73 - 1.48	0.822	22	1.00	0.60 - 1.65	0.994	
trend			*1.05*	*0.85 - 1.31*	*0.631*		*0.82*	*0.58 - 1.17*	*0.281*		*1.03*	*0.63 - 1.67*	*0.904*	0.410
Prepubertal height														
shorter than average	258	153	1.00	0.79 - 1.27	0.993	42	0.97	0.67 - 1.41	0.863	23	1.26	0.76 - 2.07	0.371	
average	912	538	1.00			153	1.00			66	1.00			
taller than average	442	319	1.26	1.04 - 1.52	0.016	68	0.93	0.68 - 1.27	0.642	32	1.06	0.68 - 1.65	0.810	0.161
Prepubertal weight														
thinner than average	614	452	1.34	1.12 - 1.61	0.002	122	1.28	0.96 - 1.71	0.091	60	1.56	1.03 - 2.35	0.035	
average	670	377	1.00			107	1.00			43	1.00			
heavier than average	328	182	0.94	0.75 - 1.18	0.598	34	0.61	0.40 - 0.93	0.020	18	0.81	0.46 - 1.44	0.478	0.260
Age at menarche														
<13 years	688	449	1.00			117	1.00			46	1.00			
13 years	393	260	1.06	0.86 - 1.29	0.605	62	1.00	0.71 - 1.40	0.992	37	1.45	0.92 - 2.29	0.107	
>13 years	540	307	0.94	0.77 - 1.14	0.500	86	1.08	0.79 - 1.48	0.615	38	1.11	0.71 - 1.75	0.648	
trend per year			*0.98*	*0.93 - 1.03*	*0.450*		*1.01*	*0.93 - 1.10*	*0.782*		*1.06*	*0.94 - 1.19*	*0.330*	0.383

[a] OR and 95% CI adjusted for age, study level, BMI 1-year before the interview, age at first birth, previous biopsies, family history of breast cancer, age at menarche and menopausal status

[b] P-het.: P value of heterogeneity of effect between pathologic subtypes

[c] Additionally adjusted by maternal age at birth

In italics: ORs, 95 % CI and P values obtained with the corresponding variable as a continuous term

4. Discussion

This paper examines the association between recalled perinatal and childhood factors and BC in the adult stage, and evaluates whether these effects differ by menopausal status and tumor subtype. As main results we can highlight the increased risk of HR+ tumors associated with advanced maternal age at birth and the inverse association with prepubertal weight among all tumor subtypes.

One of the main strengths of this study is the use of histologically confirmed incident cases, as well as its substantial sample size, since it is the largest epidemiological study to date that analyses the association between BC risk and perinatal and childhood factors in the Spanish population. This is a multicenter study carried out in 10 Spanish provinces located throughout the Spanish geography covering rural and urban areas and accounting for 42% of the Spanish women according to the 2011 census [22]. Furthermore, it has been possible to evaluate potential interactions by menopausal status and explore possible differences by tumor subtypes. On the other hand, the statistical models used in this study included a random province-specific intercept term, which accounted for unexplained heterogeneity across different regions.

Several limitations should also be addressed. First, the explanatory variables of interest are self-reported and so they are subject to possible recall bias. However, if recall bias exists, it would probably be non-differential, thus implying an underestimation of the effects studied. To minimize recall error, the questionnaire included comparative measures, which are easier to recall than absolute measures. Furthermore, to recall prepubertal height and weight we also used visual body silhouettes, which have been validated as a reliable self-reported measure of adolescent body size [23], and we have found a high correlation between these two questions (Spearman's coefficient of 0.596; p-value<0.0001). On the other hand, these same questions were used in a previous published study [24] where we analyzed the influence of certain childhood-related variables on mammographic density in adult women, and we also detected an inverse association with prepubertal weight and a positive association with prepubertal height and with advanced maternal age at birth. Regarding a potential selection bias, we intended to recruit all cases with a first diagnosis of BC in the selected health areas, ensuring that very few incident cases were missed in the study. We could not use population cancer registries since in most of these regions there was not any such registry. Third, even though most established risk factors were taken into account in the present study, other unmeasured confounders may influence these associations. For example, alcohol consumption and diabetes were not considered here and according to the Spanish National Health Survey [25] , they are not equally distributed in the areas of the study. However, these and other unmeasured characteristics with a geographical distribution have

been at least partly accounted for through the random province term. Finally, we were limited by the small size when evaluating certain subgroup associations. This limitation hampered the analysis by BC subtypes, given the low frequency of TN tumors in our context.

Our results show an almost significant increased risk of HR+ BC among women born to older mothers (>39 years). Several previous systematic reviews have described a positive association with maternal age at birth, although there is heterogeneity among studies [8, 9, 14, 26]. Similarly to the prospective cohort study published by Xue et al [27], we have detected a stronger association among postmenopausal women and among women with HR+ tumors. Mother's age at birth has also been associated with higher mammorgraphic density [24], the most reliable phenotype risk marker for BC. These results would support the hypothesis that increased concentrations of endogenous hormones during pregnancy can alter BC risk in daughters [28]. However, the association between maternal age at birth and serum estrogen levels is not consistent; while some studies have reported no association [29, 30], others have found higher serum estrogen concentrations [31], higher bioavailability for estradiol [32] or higher levels of estrogen metabolites [33] among younger mothers. Finally, Panagiotopoulou et al. detected higher estradiol concentrations among mothers belonging to an intermediate age group [34].

Other hormones that seem to play a role in the intrauterine origin of BC are *s*ex hormone-binding globulin (SHBG), insulin-like growth factor I (IGF-1), insulin-like growth factor II (IGF-2) [35] and androgens [36]. However, there are few studies linking these hormones with age at pregnancy. Chen et al [37] detected higher serum IGF-1 and IGF-2 levels in younger mothers during their first trimester, whereas Troisi et al [31] found higher androgen concentrations in these women. So, with the available data there is uncertainty about to what extent maternal age at pregnancy is a marker of hormonal exposure in utero. An alternative, non-intrauterine hypothesis is based on maternal mitochondrial oocyte inheritance [38]. Van Noord proposed that maternal age at birth reflects the quality of the mitochondria, with which an individual begins his or her life. From the meiosis-I time onwards, the mtDNA would start to accumulate mutations even in the resting nondividing oocyte, since circular mtDNA lacks protection by histones or the DNA repair system [38].

Most studies analyzing the association between childhood fatness and BC have found an inverse relationship that seems to be stronger among premenopausal women [7, 39-43], although it has also been observed in the postmenopausal group [7, 40, 41, 44-46]. There are several hypotheses that have been postulated to explain this association. Childhood obesity has been associated with menstrual irregularities, anovulation and higher basal levels of insulin [47, 48]. Insulin acts on various organs to increase sex steroid bioavailability, and this

overexposure to estrogens in obese prepubertal children could trigger early pubertal development [49-51], increase the expression of tumor suppressor genes (such as BRCA1) and induce early differentiation of mammary epithelial cells, reducing the probability of malignant transformations [15, 52]. However, no differences were detected in steroid hormone levels by BMI or childhood body shape in some studies [53, 54]. Conversely, an inverse association has been detected between childhood body fatness and adult IGF-1 levels [55, 56], protein which has been associate with an increased risk of BC among premenopausal women [57, 58]. Finally, reduced progesterone levels have been proposed as a possible explanation for the inverse association between BMI and BC before menopause [59], mainly because this reduction exerts a negative feedback on the hypothalamic pituitary release of gonadotropins.

Although the inverse association between childhood body size and subsequent risk of BC is quite consistent, results by pathologic subtype are not homogenous. Faguerazzi et al only detected an inverse association with ER+ PR+ tumors [60], while Bardia et al described a stronger association with ER+/PR- tumors [44]. On the contrary, Li and Baer found a stronger effect for ER– subtypes [40, 45], and for HER2+ tumors [40]. Finally, Sangaramorthy et al showed no differences by estrogen receptor status [42]. Our results, in consonance with those of Baer and Li [40, 45], show an inverse association more pronounced among HER2+ and TN tumors, supporting an alternative pathway not mediated by sex hormones.

Previous studies have reported a positive association between BC and childhood height or height velocity [12, 13, 61-63]. One possible pathway links height to the number of cells in the body. Larger bodies contain more cells susceptible to undergo malignant transformation [61]. Another explanation is the positive relationship between height and IGF1 levels [61, 64, 65]. In our analyses, the association with prepubertal height was mainly observed among HR+ tumors. This result is in consonance with the second hypothesis, given that the positive association of IGF1 with BC risk seems to be confined to estrogen receptor positive malignancies [66].

Regarding socioeconomic level at birth, while some studies have found no association between BC and paternal occupational level [67] or maternal socioeconomic status [68], others have detected a positive relation with either paternal [69] or maternal education [70]. In the latter study, the effect was mediated by women's adult socioeconomic status and reproductive behaviors, factors that have been taken into account in our analysis. In our case, results are based on a subjective rating made by our participants comparing their families with others around them. Here, the small group of women who reported being born in a high social class had lower risk of BC. Lower socioeconomic status at birth could be a proxy of early-life conditions that could not be controlled for. For example,

lower parental socioeconomic status is associated with a "western" dietary pattern [71], which has also been linked to BC risk [72]. On the other hand, women with lower parental education presented higher circulating levels of the inflammation marker C-reactive protein [73] and, therefore higher risk of BC [74].

Previous studies have reported an increased BC risk with heavier birth weight [8, 75]. However we have not detected an association with this variable, although it should be noted that 21% of cases and 20% of controls were unable to answer. On the other hand, earlier age at menarche is consistently linked with an increased risk of premenopausal and postmenopausal BC [76]. However, we found no association, even though Spain is one of the European countries where age at menarche has decreased at a higher rate and since the 50s is one of the countries with a lower mean age [77].

In brief, our results suggest an increased HR+ BC risk associated with advanced maternal age at birth. Furthemore, those women who were taller or thinner than their mates in their prepubertal stage showed higher postmenopausal BC risk, mainly associated with HR+ tumors, while those who were heavier presented lower premenopausal BC risk associated with HER2+ tumors. Some of these perinatal and childhood factors are not easily modifiable. The economic and social changes in recent decades have led to a significant change in the lifestyle of women, such as a considerable delay in the age at first birth. In fact, Spain is the European country with the highest mean age of women at childbirth [78], reaching 32.3 years in 2014 [79]. On the other hand, the inverse association between BC and childhood weight detected in our study should be interpreted with caution in terms of prevention, especially when it is known that obesity is a stablished risk factor for postmenopausal BC [80] and that there is a strong positive association between high childhood BMI and adult obesity [81]. In this sense, Spain is one of the countries with higher risk of adult obesity-related morbidity, since it is the second country in Europe with the highest prevalence of childhood overweight and obesity [82], with 15.5% of obese girls aged 7-8 years in 2013 [83]. Moreover, according to one study carried out in screening attendants, Spanish women gained an average of 400 g per year since the age of 18 years [84]. Our results corroborate that early life exposures affect a woman's long-term risk of BC, and hence, prevention efforts should begin earlier in life, targeting potentially modifiable risk factors.

Conflict of interest

The authors declare no conflict of interest.

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