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The influence of socio-economic status on the fulfilment of Saint-Gallen recommendations for early-stage breast cancer

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Socio-economic status (SES) is related to breast cancer diagnosis and prognosis. We study if SES is related to the adequacy of the treatment according to Saint Gallen consensus in Spanish women with incident breast cancer. Breast cancer cohort was assembled from incident cases from MCC-Spain and prospective followed-up afterwards. Participants were then classified according to the Saint-Gallen consensus in three categories (In Saint-Gallen, who received therapy accorded by Saint Gallen; Over Saint-Gallen, who received some additional therapy; or Under Saint-Gallen, who did not receive the complete therapy). Association between SES and Saint-Gallen fulfilment was analyzed using multinomial logistic regression, adjusting for clinicopathological and patient-related variables. 1115 patients in stages I and II were included. Women with university education were 58% more likely to receive over Saint-Gallen therapies (RRR = 1.68; 95%CI 0.84–3.33). In the simplified SES score, women with higher SES were over Saint-Gallen 52% more than those with lower SES (RRR = 1.52; 95%CI 0.88–2.64). Women with higher SES more often received over Saint-Gallen therapies. Further analyses are needed to understand the influence of these differences on the overall survival as well as its potential unwanted side effects.

Keywords Breast cancer, MCC-Spain, Saint-Gallen consensus, Socio-economic status

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Breast cancer was the most common cancer among women in Europe, America, and Australia in 2021[1–8]. Similarly, recent data shows that breast cancer, along with cervical cancer, is the most frequently diagnosed cancer among women in regions like Sub-Saharan Africa[9]. Based on this information, it can be understood that cancer is the leading cause of death globally.

In Europe is estimated to affect 1 in 10 women, accounting for 27.8% of the total of female cancer[10]. Evidence suggests that we can classify breast cancer according to their different histopathological and biological features as they also exhibit different behaviours leading to distinct therapeutic strategies. Classical immunohistochemistry markers including oestrogen receptors (ER), progesterone receptors (PR) and HER2 overexpression, together with TNM staging are commonly used to clarify patient's prognosis and future management[11].

Socio-economic status (SES) has been related to breast cancer diagnosis and prognosis. In general, higher SES has been associated with higher incidence of breast cancer[1,4,5,12–15]. Several explanations have been proposed such as lower parity and having the first child at higher age[1], higher use of hormonal contraceptives and hormone replacement therapy, access to healthcare, cancer awareness, screening methods[5], and lifestyle habits[16].

On the other hand, the greater risk of breast cancer mortality among women with higher levels of education, which is also related to higher SES, was a persistent and widespread phenomenon in Europe during the 1990s[17]. However, more recent literature on the 2000s period provides ambiguous information referring to mortality rates. Some studies indicate a higher mortality for women with higher SES. Women with higher SES have lower parity rates and delay of first birth which increase their breast cancer risk and could also lead to worse prognosis[1]. Others demonstrate that breast cancer patients of low SES have a significantly increased risk of dying as a result of breast cancer compared to the risk in patients of high SES[18]. Low SES patients were diagnosed at a later stage, had different tumour characteristics and were more likely to receive suboptimal treatment[5].

Having said that, most studies have shown a significantly lower case-fatality rate in women with higher SES[18], probably related to some of the reasons mentioned above, women with a higher SES are more likely to be diagnosed with a lower stage tumour and, also, they would probably adopt healthier lifestyles after diagnosis, also including a better psychological background[1,2,5,12,15,18]. Other studies have shown that conservative surgery and consecutive follow-up are more common among women with higher SES, which could also partly explain their lower case-fatality rate[19]. Even waiting lists for breast cancer surgery are shorter for higher SES patients[20].

Socio-economic position remains a strong predictor of poor survival in deprived women compared with affluent women, even after adjustment for other known prognostic factors including age, ethnicity, access to care variables (extent and size) and tumour subtype adjusting for ER, PR and HER2 [4]. Higher rate of death from breast cancer linked to low SES is only partly explained by delayed diagnosis (related to screening methods), unfavourable tumour characteristics and suboptimal treatments, which creates the need to discover other possible explanations. Other reasons related to the patient health, such as comorbidity, lifestyle, attitude, knowledge and convictions may also play a role in prognosis. Low SES patients are more often in complex psychosocial difficulties, which complicate treatments, as the most effective ones are sometimes linked to adverse effects that require a particular performance status including psychological support. They are also more likely to have misperceptions about cancer and the treatment benefits, to miss their medical visits and to be less participatory[19].

The Saint Gallen International Expert Panel (2013) reviewed substantial new evidence on aspects of local and regional therapies for early breast cancer. The panel emphasized the need for less aggressive approaches, especially for luminal disease in the absence of HER2, while noting that treatments for HER2-positive and triple-negative disease remained largely unchanged. However, they highlighted the importance of considering disease extension, patient performance status, and personal preferences alongside socioeconomic constraints when determining the definitive treatment strategy[21]. In regions with access to multi-gene molecular assays, clinicians often rely on these results to guide decisions about adjuvant chemotherapy in early-stage Luminal ER-positive, HER2-negative cases without systemic invasion[22].

In this paper, we study if SES was related to the adequacy of the treatment according to Saint Gallen Consensus in a cohort of Spanish women with incident breast cancer diagnosed between 2008 and 2013.

Methods

MCC-Spain began in 2008 as a case-control study focused on the most frequent tumours in Spain including colorectal, female breast, prostate and gastric cancers and chronic lymphocytic leukaemia[23]. Later on, recruited cases of breast, prostate and colorectal cancer were followed-up[24]. From here on, we only refer to the breast cancer cohort. Our initial cohort consists of 1738 incident breast cancer cases recruited, of which 1685 were followed-up in 18 hospitals of 10 Spanish provinces (Asturias, Barcelona, Cantabria, Girona, Gipuzkoa, Huelva, León, Madrid, Navarra and Valencia) in the MCC-Spain project. Their prospective follow-up has been performed between 2017 and 2018 by reviewing medical records. Only Women with breast cancer in pathological stages I or II were included in this analysis (1115 patients).

Control selection

The selection of controls is described elsewhere[23]. Briefly, controls were selected from a general population base, with the aim of comparing individuals diagnosed with cancer (cases) with those without the disease (controls). Controls were selected by random sampling of individuals residing in the same geographic areas as the cases, with similar socio-demographic characteristics, ensuring that the controls adequately represent the general population at risk of developing cancer.

The procedure included identification of controls through population-based registries, and these were matched to cases by criteria such as age, sex and region of residence, to minimize potential biases in the comparison. In addition, controls were selected so that they had no history of cancer at the time of inclusion in the study, ensuring that any differences observed between cases and controls could be associated with the exposure of interest rather than with disease-related factors.

Inclusion/exclusion criteria

The recruitment process and exclusion/inclusion criteria are detailed in the elsewhere[23], which has now been referenced. For this manuscript, the inclusion criteria were as follows: women with tumor stage I or II and complete information available on TNM classification. Of the 1,738 women recruited between 2008 and 2013 as part of the MCC-Spain project, 496 were excluded due to being in stage III or IV, and 126 were excluded as they could not be classified as stage I. Additionally, one woman was excluded due to missing data on metastasis (Fig. 1).

Given that there are people whose information about tumor size, node infiltration or metastasis is not available, in order to validate our results, we decided to do the analysis considering ($n = 1115$) and without considering ($n = 1009$) these women. Since the results are so similar, here are exposed those obtained from the analysis of all subjects. You can consult the others in supplementary material (Tables 1, 2 and 3).

Socio-economic status information

Socio-Economic Status (SES) was measured by a compendium of variables including: Educational Level, Educational Level of the partner, Socio-Economic Position[25] of both the patient and their parents and finally Degree of Urbanization and Urban Vulnerability Index[26]. These variables were compared individually and also combined as scores (26).

In order to build the individual SES score, participants' education, SES of the parents and Spanish Occupational Classification (SOC), based on 1994 National Classification of Occupations, were combined[25]. Each of the variables has a score of 0–3 or 0–2 corresponding to the number of categories being 0 the lowest level. During the questionnaire, 70 patients did not report their occupation and their parents' economic position; 4 did not report parents' economic position and 298 did not report their occupation. Only those who reported the three variables were assembled into a score from 0 to 7 by combining the points received in the described categories. Once divided into these categories a simplified SES score was created, dividing the participants into three larger groups including low SES (0, 1, 2); medium SES (3, 4, 5) and high SES (6, 7). For those participants

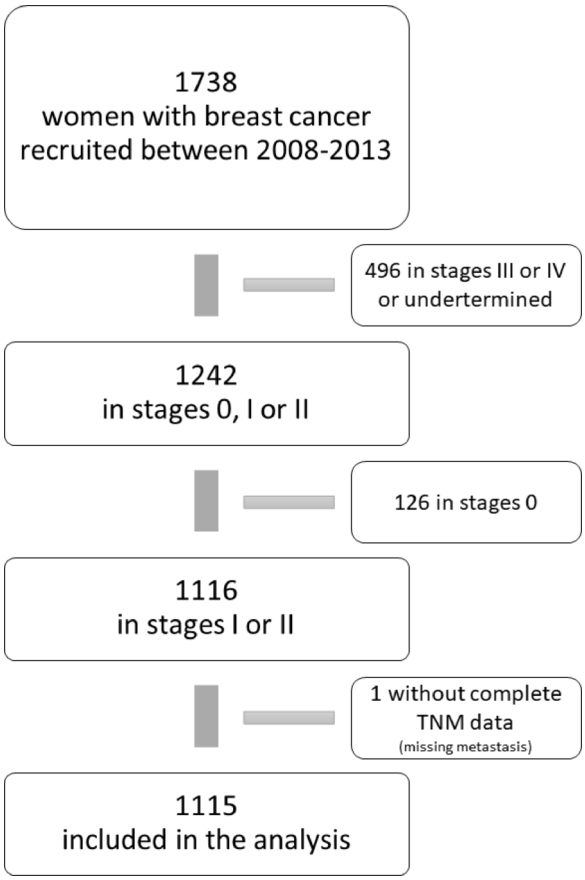

Fig. 1. Flowchart of inclusion and exclusion criteria.

Variable	Category	Total*	Saint-Gallen fulfilment**			p
			In Saint-Gallen N = 518 (46.5%)	Over Saint-Gallen N = 243 (21.8%)	Under Saint-Gallen N = 354 (31.7%)	
Age	Mean (SD)	56.1 (12.3)	56.8 (12.6)	52.1 (10.6)	57.9 (12.2)	< 0.001
Post-menopause	No	396 (35.5)	159 (40.2)	123 (31.0)	114 (28.8)	< 0.001
	Yes	719 (64.5)	359 (49.9)	120 (16.7)	240 (33.4)	
Tumour size	T0	14 (1.3)	4 (28.6)	4 (28.6)	6 (42.8)	0.105
	T1	748 (67.0)	367 (49.0)	148 (19.8)	233 (31.2)	
	T2	315 (28.3)	134 (42.5)	84 (26.7)	97 (30.8)	
	T3	19 (1.7)	5 (26.3)	4 (21.1)	10 (52.6)	
	T4	0 (0)	-	-	-	
	Tis	6 (0.5)	2 (33.3)	2 (33.3)	2 (33.3)	
	Miss	13 (1.2)	6 (46.2)	1 (7.6)	6 (46.2)	
Node infiltration	N0	725 (65.0)	386 (53.3)	101 (13.9)	238 (32.8)	< 0.001
	N1	377 (33.8)	124 (32.9)	140 (37.1)	113 (30.0)	
	N2	11 (1.0)	7 (63.6)	1 (9.1)	3 (27.3)	
	Miss	2 (0.2)	1 (50.0)	1 (50.0)	0 (0.0)	
Metastasis	M0	1023 (91.8)	470 (45.9)	226 (22.1)	327 (32.0)	0.498
	Miss	92 (8.2)	48 (52.2)	17 (18.5)	27 (29.3)	
TNM stage	I	519 (46.5)	291 (56.1)	56 (10.8)	172 (33.1)	< 0.001
	II	596 (53.5)	227 (38.1)	187 (31.4)	182 (30.5)	
Oestrogen receptor	Negative	151 (13.5)	91 (60.3)	12 (7.9)	48 (31.8)	< 0.001
	Positive	963 (86.4)	426 (44.2)	231 (24.0)	306 (31.8)	
	Miss	1 (0.1)	1 (100.0)	0 (0.0)	0 (0.0)	
Progesterone receptor	Negative	256 (23.0)	137 (53.5)	14 (5.5)	105 (41.0)	< 0.001
	Positive	856 (76.7)	379 (44.3)	229 (26.7)	248 (29.0)	
	Miss	3 (0.3)	2 (66.7)	0 (0.0)	1 (33.3)	
ErbB2	Negative	934 (83.8)	453 (48.5)	224 (24.0)	257 (27.5)	< 0.001
	Positive	181 (16.2)	65 (35.9)	19 (10.5)	97 (53.6)	
Intrinsic subtype	Luminal A	673 (60.4)	294 (43.7)	221 (32.8)	158 (23.5)	< 0.001
	Luminal B	305 (27.3)	139 (45.6)	12 (3.9)	154 (50.5)	
	Her2	48 (4.3)	16 (33.3)	7 (14.6)	25 (52.1)	
	Basal-like	86 (8.0)	69 (77.5)	3 (3.4)	17 (19.1)	
Grade of differentiation	I: Well differentiated	260 (23.3)	130 (50.0)	69 (26.5)	61 (23.5)	< 0.001
	II: Moderately differentiated	367 (32.9)	155 (42.2)	115 (31.4)	97 (26.4)	
	III: Bad differentiated	215 (19.3)	127 (59.1)	10 (4.6)	78 (36.3)	
	Miss	273 (24.5)	106 (38.8)	49 (18.0)	118 (43.2)	
Surgery	Conservative surgery	858 (76.9)	410 (47.8)	180 (21.0)	268 (31.2)	0.240
	Mastectomy	257 (23.1)	108 (42.0)	63 (24.5)	86 (33.5)	
Surgical margins	Negative	794 (71.2)	383 (48.2)	169 (21.3)	242 (30.5)	0.444
	Positive	153 (13.7)	65 (42.5)	36 (23.5)	52 (34.0)	
	Miss	168 (15.1)	70 (41.7)	38 (22.6)	60 (35.7)	
Chemotherapy	No	508 (45.6)	289 (56.9)	1 (0.2)	218 (42.9)	< 0.001
	Yes	607 (54.4)	229 (37.7)	242 (39.9)	136 (22.4)	
Endocrine	No	347 (31.1)	85 (24.5)	13 (3.7)	249 (71.8)	< 0.001
	Yes	768 (68.9)	433 (56.4)	230 (30.0)	105 (13.6)	
Immunotherapy /	No	1002 (89.9)	450 (44.9)	223 (22.3)	329 (32.8)	0.008
Anti-HER2 treatment***	Yes	113 (10.1)	68 (60.2)	20 (17.7)	25 (22.1)	

Table 1. Women with breast cancer in pathological state I or II by Saint-Gallen fulfilment. Description of the sample ($n = 1115$). *In total, percentages are presented by column. ** In the Saint-Gallen Fulfilment's categories, percentages are presented by rows. *** Of these, 100 (88.5%) had received anti-Her2 treatment.

who were missing only one of the variables a similar score was created, also classifying them into low SES (0,1); medium SES (2, 3) and high SES (4, 5). Participants missing two of them were excluded from this score[26].

The Degree of urbanization (DGUR) was also used in order to consider participants' residence as a SES indicator. It is a classification that indicates the character of an area. The latest update of the classification is based on 2011 population grid and the 2016 Local Administrative Units boundaries. Based on the share of local

SES indicator	Category	Total*	Saint-Gallen Fulfilment**			p
			In Saint-Gallen	Over Saint-Gallen	Under Saint-Gallen	
Education	Less than primary	167 (15.0)	84 (50.3)	21 (12.6)	62 (37.1)	0.001
	Primary	354 (31.7)	179 (50.6)	70 (19.8)	105 (29.6)	
	Secondary	394 (35.4)	167 (42.4)	92 (23.3)	135 (34.3)	
	University	200 (17.9)	88 (44.0)	60 (30.0)	52 (26.0)	
Partner education	Less than primary	112 (11.9)	56 (50.0)	17 (15.2)	39 (34.8)	0.162
	Primary	322 (34.3)	164 (50.9)	65 (20.2)	93 (28.9)	
	Secondary	299 (31.9)	125 (41.8)	65 (21.7)	109 (36.5)	
	University	206 (21.9)	96 (46.6)	49 (23.8)	61 (29.6)	
SES	0	53 (4.8)	25 (47.2)	8 (15.1)	20 (37.7)	0.003
	1	146 (13.1)	76 (52.0)	20 (13.7)	50 (34.2)	
	2	172 (15.4)	89 (51.7)	33 (19.2)	50 (29.1)	
	3	207 (18.6)	92 (44.4)	54 (26.1)	61 (29.5)	
	4	198 (17.7)	82 (41.4)	38 (19.1)	78 (39.4)	
	5	189 (17.0)	86 (45.5)	40 (21.2)	63 (33.3)	
	6	140 (12.5)	62 (44.3)	48 (34.3)	30 (21.4)	
	7	10 (0.9)	6 (60.0)	2 (20.0)	2 (20.0)	
Summary SES	Mean (SD)	3.37 (1.76)	3.29 (1.79)	3.71 (1.73)	3.26 (1.71)	0.003
SES score	Low	341 (30.6)	176 (51.6)	55 (16.1)	110 (32.3)	0.001
	Medium	614 (55.1)	269 (43.8)	138 (22.5)	207 (33.7)	
	High	160 (14.3)	73 (45.6)	50 (31.3)	37 (23.1)	
SES parents	Low	364 (32.7)	172 (45.3)	68 (18.7)	124 (34.1)	0.175
	Medium	713 (64.2)	325 (45.6)	171 (24.0)	217 (30.4)	
	High	34 (3.1)	18 (52.9)	4 (11.8)	12 (35.3)	
DGUR	Cities	612 (73.4)	293 (47.9)	132 (21.6)	187 (30.5)	0.652
	Town and suburbs	149 (17.9)	66 (44.3)	30 (20.1)	53 (35.6)	
	Rural areas	73 (8.7)	39 (53.4)	14 (19.2)	20 (27.4)	
UVI	Mean (SD)	0.50 (0.14)	0.50 (0.15)	0.51 (0.16)	0.50 (0.14)	0.030

Table 2. Socio-economic status indicators by Saint-Gallen fulfilment. *In total, percentages are presented by column. ** In the Saint-Gallen Fulfilment's categories, percentages are presented by rows. *Education* educational level of the patients, *Partner Education* educational level of the patients' partners, *SES* socio-economic status, *SES score* simplified socio-economic status, *DGUR* degree of urbanization, *UVI* urban vulnerability index.

population living in urban clusters and in urban centres, it classifies them into three types of area: Cities (densely populated areas), Towns and suburbs (intermediate density areas) and rural areas (thinly populated areas)[27].

Initial tumour information

Tumour location, differentiation's degree, immunohistochemical characteristics (hormonal receptors, Erb-B2) and TNM status were dug out from each of the patients' records. During the follow-up, information regarding histological grade at diagnosis, complete clinical/pathological remission, grade of response to treatment, relapse, second primary tumour and current patient's vital status was also gathered.

Initial first-line treatment information

For each patient, information about their first-line treatment was also collected from their medical records and classified into surgery (conservative /mastectomy), hormonotherapy, chemotherapy, immunotherapy and radiotherapy (all of them classified into neoadjuvant, adjuvant or palliative administrations).

Classification of the patients according to Saint-Gallen-2013 fulfilment

In order to classify the participants according to Saint-Gallen fulfilment, information described above (type of tumour and first line treatment) was used and compared to the recommendations given. It is necessary to highlight that, although the last Saint Gallen International Breast Cancer Consensus Conference was held in 2017 [12], we employ the Saint Gallen International Expert Panel of 2013 [21] given that our analysis was recruited about the time of this panel. In this way, it is important to note that this manuscript aims to assess whether medical practices between 2008 and 2013 aligned with the evolving scientific understanding reflected in the 2013 St. Gallen Consensus. In addition, the fact that employ the Saint Gallen International Expert Panel of 2013 is employed means that the results of this manuscript, replicated in a more recent sample of women with breast cancer and following the recommendations of the 2017 St. Gallen International Expert Panel, may be different.

Systematic treatment recommendations agreed by Saint-Gallen 2013 consensus were:

SES indicator	Category	Saint Gallen-Fulfilment			
		Over Saint-Gallen		Under Saint-Gallen	
		RRR (95% CI)	p	RRR (95% CI)	p
Education	Less than primary	1 (ref.)	-	1 (ref.)	-
	Primary	1.14 (0.63– 2.11)	0.654	0.88 (0.57 – 1.35)	0.551
	Secondary	1.14 (0.60 – 2.15)	0.684	1.28 (0.81 – 2.02)	0.283
	University	1.68 (0.84– 3.33)	0.844	1.03 (0.61 – 1.75)	0.905
Partner education	Less than primary	1 (ref.)	-	1 (ref.)	-
	Primary	0.91 (0.47 – 1.79)	0.791	0.91 (0.55 – 1.49)	0.704
	Secondary	1.09 (0.54 – 2.17)	0.814	1.45 (0.87 – 2.42)	0.155
	University	1.03 (0.50 – 2.13)	0.927	1.09 (0.63 – 1.89)	0.756
SES	Per point	1.04 (0.93 – 1.17)	0.421	1.02 (0.94 – 1.12)	0.579
SES score	Low	1 (ref.)	-	1 (ref.)	-
	Medium	1.16 (0.76 – 1.78)	0.479	1.32 (0.95 – 1.82)	0.100
	High	1.52 (0.88 – 2.64)	0.135	0.96 (0.59 – 1.57)	0.881
SES parents	*Low*	1 (ref.)	-	1 (ref.)	-
	Medium	0.99 (0.68 – 1.45)	0.977	0.94 (0.70 – 1.27)	0.679
	High	0.41 (0.12 – 1.39)	0.153	0.94 (0.43 – 2.05)	0.885
DGUR	Cities	1 (ref.)	-	1 (ref.)	-
	Town and suburbs	0.94 (0.55 – 1.61)	0.822	1.01 (0.66 – 1.56)	0.957
	Rural areas	0.64 (0.31 – 1.29)	0.212	0.76 (0.42 – 1.36)	0.357
UVI	Per point	0.86 (0.23 – 3.24)	0.822	0.99 (0.33 – 2.99)	0.987

Table 3. Fulfilment of saint Gallen and socio-economic status. Relative risk ratio adjusted. *RRR* relative risk ratio (Adjusted for stage at presentation, histological grade, and age), *Education* educational level of the patients, *Partner Education* educational level of the patients' partners, *SES* socio-economic status, *SES score* simplified socio-economic status, *DGUR* degree of urbanization, *UVI* urban vulnerability index.

- Luminal A-like: Endocrine therapy is the most critical intervention and is often used alone. Chemotherapy may be added in selected patients with high risk profiles.
- Luminal B-like (HER2 negative): Endocrine therapy for all patients and cytotoxic therapy for most.
- Luminal B-like (HER2 positive): Chemotherapy + anti-HER2 + endocrine therapy.
- HER2 positive (non-luminal): Chemotherapy + anti-HER2.
- Triple negative (ductal): Chemotherapy.

Regarding surgery and radiotherapy; the Panel agreed that, in general, conservative surgery – only if followed by radiotherapy of the whole breast - was as appropriate a mastectomy (except for high-risk profiles including young age, microcalcifications, *BRCA1* o *BRCA2* genes, etc.). Axillary surgery could be omitted only if radiotherapy was arranged, but it was required if three or more sentinel nodes were involved or if they were clinically involved before surgery and confirmed by biopsy. Radiotherapy was an option for almost all these women except for the elderly and those with substantial comorbidity[21].

When classifying our patients, we paid special attention to systemic therapies as rest of the recommendations were somewhat diffuse. We created three categories using the following criteria:

- In Saint-Gallen women: participants who received the therapy accorded by Saint Gallen. *Example: Women with luminal A-like tumour (ER+, PR+, HER2-) who had breast conserving surgery, radiotherapy and endocrine therapy.*
- Over Saint-Gallen women: participants that, even if they received everything they were supposed to, also received some additional therapy. *Example: Women with basal-like tumour (ER-, PR-, HER2-) who had breast conserving surgery, radiotherapy, chemotherapy and endocrine therapy.*
- Under Saint-Gallen women: participants that did not received the complete therapy that was recommend, even if they received something else. *Example: Women with HER2 tumour (ER-, PR-, HER2+) who had breast conserving surgery, radiotherapy, endocrine therapy and chemotherapy; lacking anti-HER2 therapy.*

The classification of participants into these three groups could be considered rather subjective, as the consensus provided recommendations and not protocols, and also because individual cases might be considered. In order to check our agreement while classifying them, two different observers classified a sample of 50 women reaching 76% inter-rater reliability. (Cohen's kappa index = 0.76). The same categories have been previously employed in Gomez-Acebo I. et al.[28].

SES indicator	Category	Saint Gallen-Fulfilment			
		Over Saint-Gallen		Under Saint-Gallen	
		RRR (95% CI)	p	RRR (95% CI)	p
Education	Less than primary	1 (ref.)	-	1 (ref.)	-
	Primary	1.56 (0.90– 2.72)	0.112	0.79 (0.53 – 1.19)	0.269
	Secondary	2.20 (1.28 – 3.79)	0.004	1.09 (0.73 – 1.63)	0.655
	University	2.73 (1.53– 4.87)	0.001	0.80 (0.49 – 1.29)	0.358
Partner education	Less than primary	1 (ref.)	-	1 (ref.)	-
	Primary	1.30 (0.71 – 2.41)	0.395	0.81 (0.50 – 1.32)	0.403
	Secondary	1.71 (0.92 – 3.18)	0.089	1.25 (0.77 – 2.03)	0.361
	University	1.68 (0.88 – 3.20)	0.113	0.91 (0.54 – 1.53)	0.730
SES	Per point	1.15 (1.05 – 1.26)	0.002	0.99 (0.92 – 1.07)	0.831
SES score	Low	1 (ref.)	-	1 (ref.)	-
	Medium	1.64 (1.14 – 2.37)	0.008	1.23 (0.91 – 1.66)	0.173
	High	2.19 (1.37 – 3.51)	0.001	0.81 (0.51 – 1.29)	0.374
SES parents	Low	1 (ref.)	-	1 (ref.)	-
	Medium	1.33 (0.95 – 1.86)	0.096	0.93 (0.69 – 1.23)	0.602
	High	0.56 (0.18 – 1.72)	0.313	0.92 (0.43 – 1.99)	0.841
DGUR	Cities	1 (ref.)	-	1 (ref.)	-
	Town and suburbs	1.01 (0.32 – 1.63)	0.971	1.26 (0.84 – 1.89)	0.267
	Rural areas	0.80 (0.42 – 1.52)	0.490	0.80 (0.45 – 1.42)	0.451
UVI	Per point	1.48 (0.43 – 5.03)	0.524	0.92 (0.31 – 2.69)	0.873

Table 4. Fulfilment of saint Gallen and socio-economic status. Relative risk ratio. Crude model ($n = 1115$). *RRR* relative risk ratio (Crude model), *Education* educational level of the patients, *Partner Education* educational level of the patients' partners, *SES* socio-economic status, SES score: simplified socio-economic status, *DGUR* degree of urbanization, *UVI* urban vulnerability index.

Statistical analysis

Data are described using absolute frequencies and means with standard deviation. SES indicators and Saint-Gallen fulfilment were analysed using Pearson's chi[2] (one test for each of 5 indicators) and Analysis of Variance for the remaining indicator.

Multinomial logistic regression used to investigate the association between all seven SES indicators and Saint-Gallen fulfilment while adjusting for stage at presentation, histological grade, and age. Results are displayed as relative risk ratios (RRR) with 95% confidence intervals since they allow direct comparison of relative risks across multiple outcome categories. The p-values provided are two-sided (Bilateral). Additionally, the crude model of the multinomial logistic regression was created.

The same analysis was carried out removing those women for whom we do not have information about tumour size, node infiltration or metastasis (supplementary material, Tables 4 and 1; $n = 1009$). All statistical analyses were performed using *Stata 16/SE software (Stata Co., College Station, Tx, US).*

Results

Description of the sample

Overall, 1115 women with stages I and II at diagnosis were included in the analysis and later classified into three groups (In Saint-Gallen: 46.5%, Over Saint-Gallen: 21.8% and Under Saint-Gallen: 31.7%) according to the fulfilment of Saint-Gallen. Table 4 displays the main characteristics of the sample. Most women were postmenopausal (64.5%; self-reported variable). Compared to the others, over Saint-Gallen women were younger (52.1 years). Tumour size was predominantly T1 (67%) and it was considered in Saint-Gallen twice (49%) as often as over Saint-Gallen (19.8%) or under Saint-Gallen respectively (31.2%). The distribution was similar for T2 (28.3%).

In this study we only consider earlier stages including: stage I (46.5%) which are tumours smaller than 2.5 cm across and stage II (53.5%) tumour less than 5 cm across which could have spread (N1 = 33.8%) or not (N0 = 65%) to the axillary lymph nodes. Stage I tumours considered in Saint-Gallen accounted 56.1% versus 10.8% of over Saint-Gallen and 33.1% of under Saint-Gallen. For the stage II tumours the proportions were more homogeneous.

Regarding the intrinsic subtype, Luminal A was by far the most common tumour (60.4%); 43.7% with a proper fulfilment of Saint-Gallen. Luminal B (27.3%) and Her2 (4.3%) tumours were frequently under Saint-Gallen (51% and 52% respectively). Basal-like tumours represent 8% of our sample, and they were predominantly in Saint-Gallen (77.5%). According to the grade of differentiation, 23.3% of our patients were well differentiated; 32.9% were moderately differentiated; and 19.3% were poorly differentiated. Grade could not be obtained from medical records in 273 patients (24.5%). The proportions for Saint-Gallen fulfilment are displayed with detail in Table 4.

When considering the treatment specifically, 858 participants (76.9%) underwent conservative surgery and the remaining 257 underwent mastectomy (23.1%), with 71.2% having negative surgical margins. Chemotherapy was administered to 607 patients, 39.9% of them were considered over Saint-Gallen while 22.4% were under Saint-Gallen. From the 768 patients that received endocrine therapy only in 56.4% received in Saint-Gallen therapies while 30% were over Saint-Gallen. The remaining 347 did not receive endocrine therapy and 249 (71.8%) were considered under Saint-Gallen. Finally, immunotherapy/anti-HER2 treatment was given to 113 participants being 60.2% treated according to Saint-Gallen.

It is important to note that, irrespective of the Saint-Gallen group classification, 7.95% of patients with estrogen receptor (ER)-negative tumors and 40.23% of patients with progesterone receptor (PR)-negative tumors received anti-hormone therapy. Notably, none of the HER2-negative patients received anti-HER2 therapy. Regarding the distribution of treatments, 45.56% of the sample underwent chemotherapy, while radiotherapy was more commonly utilized, with 76.71% of patients receiving this modality (data not shown).

Factors associated with over Saint-Gallen participants

In the crude analysis, women of higher educational level had the highest over Saint-Gallen rate (Table 1). Women with less than primary education were less frequently over Saint-Gallen (12.6%) than women with university studies (30%). When adjusting for stage at presentation, histological grade and age (Table 2), the higher the education, the higher the probability of being over Saint-Gallen reaching RRR = 1.68 (95%CI 0.84–3.33) when compared with those in the lower education level. This trend has not been seen between educational level of the partner and overtreatment of the patients was found.

Women with higher SES were more likely to be over Saint-Gallen (Table 1). These differences remained in the simplified SES score. Results adjusted for stage, histological grade and age (Table 2) showed a 4% increase in the chances of being over Saint-Gallen per point of the score (RRR per point 1.04; 95%CI 0.93–1.17). In the simplified SES score (Table 2) the probability of women with a higher SES being over Saint-Gallen was 52% higher compared to those with a lower SES (RRR 1.52; 95%CI 0.88–2.64).

No significative association was found between Saint-Gallen fulfilment and parenteral SES, Degree of Urbanization (DGUR) or Urban Vulnerability Index (UVI) (Table 2).

The supplementary material presents the results of the crude regression model (Table 3). In this crude model, the trend observed in the adjusted analysis becomes significant. This suggests that a higher socioeconomic level is associated with an increased likelihood of receiving additional therapies, although the association does not reach statistical significance.

Factors associated with under Saint-Gallen participants

The crude analysis showed that women with lower education were more likely to be under Saint-Gallen compared to those with higher education (Table 1). Nevertheless, the differences were scarce (less than Primary 37.1% and University education (26%) and after adjusted analysis by stage at presentation, histological grade and age no significant results were found. The same happened with the SES (Table 1), women with lower SES were more often under Saint-Gallen (32.3%) than those of higher SES (23.1%). When adjusting the results, (Table 2) these differences disappeared (RRR 0.96; 95% CI 0.59–1.57).

Discussion

In this study we observed socioeconomic variations in the treatment of early-stage breast cancer patients despite universal health insurance coverage in Spain. Women with high socio-economic status were 50% more likely to be over-treated (above Saint-Gallen) than those with lower socio-economic status (RRR 1.52; CI95% 0.88–2.64), and therefore, may be exposed to unnecessary side effects. Those with lower SES showed a higher percentage of women who are treated under Saint-Gallen recommendations, which disappeared after adjustment for stage at presentation and histological grade. This finding is of great importance given that breast cancer is the most common cancer type and the leading cause of cancer death among women worldwide.

Other studies relating SES with treatment have reported a higher frequency of undertreatment in low SES patients[29]; they have been predominantly conducted in the United States where there is not an equal access to the health system. Patients from Medicaid insurance[30] and those of lower income were less likely to receive guideline concordant systemic therapies compared with women with privately insurance[31,32]. Therefore, it is plausible that such inequalities could be explainable by financial counterincentives.

A different study carried on the Netherlands, where there is equal access care system, suggested that women of high SES were more prone to undergo aggressive therapeutic interventions, even if there was no evidence of benefit and could potentially be harmful[33]. Low SES patients were less likely to be overtreated and slightly more likely to be undertreated, but this difference was mostly explained by the tendency of higher SES women of choosing more aggressive therapies. Conservative surgery was more often performed in women of high SES as higher follow-up proportion was presumed[19]. Population-based studies, also from the Netherlands, have reported higher incidence of axillary dissection in patients with high SES[34]. In general, a tendency to more aggressive therapies in patients of higher SES has been reported in most cancers (esophagus, colon, breast, among others)[35,36].

Returning to our study, not only we observed an increase in the number of women receiving treatment according to the Saint Gallen recommendations among those with high socioeconomic status (RRR 1.52), but also in those with university education (RRR 1.68). These differences could be explained by a variety of factors.

Firstly, women with a high SES and higher educational level tend to play a more proactive role in decision making[37–39] and also they tend to prefer more aggressive treatments[33] including chemotherapy, aggressive surgery, etc. The physicians' contribution should also be noted; in general, not only do the patients play a more proactive role, but also the practitioners tend to count more on the patient's opinion if the patient has a higher

educational level. Secondly, patients of lower SES are also considered to be less educated[40], so clinicians would play a more significant role in decision making, increasing the likelihood of patients receiving 'In Saint-Gallen' therapy. Professionals should be aware of this tendency specially in a system that is seeking to provide equal access to health care. Other reasons that could explain these deviations from the recommendations could be patients' comorbidities[41,42] -which have not been considered in this study. In any case, SES was not a limiting factor in the decision as all the therapies mentioned above are funded by Spanish National Health System[43].

Finally, apart from the fact that being treated over Saint-Gallen recommendation rate is consistently related to higher SES, it is important to note that such disparities were not found when examining women of lower SES. If found, these inequalities would have been devastating for the system, as it is presumed to be of equal access. The SES indicator DGUR, which is related to the area of residence and which could introduce some personal bias, did not show any significant differences. The UVI index, which measures the SES level of the area the patient is living in, did not prove to have any influence. This suggest that only the individual characteristics of the patient have an impact in the final decision, as only her individual SES and educational level showed an association.

Strengths and limitations

Converting recruited cases in the case-control phase on the MCC-Spain into three prospective cohorts (colorectal, breast and prostate) is one of the main strengths of this study because of its efficiency. We took advantage of the recruitment itself and also information and samples collected during the first phase. This led us to the inception of the cohort at only the cost of the follow-up. Moreover, the study enrolled women aged 20–85 years from 10 Spanish provinces, and given the universal coverage of the Spanish National Health System, they could provide a representative sample of the population, tough the present work only includes women diagnosed in stages I and II.

Some limitations of this study should also be considered. Firstly, according to the Saint-Gallen 2013 consensus, the classification of breast cancer into intrinsic subgroups requires the consideration of estrogen receptor (ER) and progesterone receptor (PR) positivity, Ki67 expression levels, and genomic scores. Unfortunately, due to the unavailability of these data, we were unable to incorporate Ki67 and genomic scores into our analysis, which may have affected the precision of the subtype classification. Secondly, part of the information regarding SES data were self-reported, which may be subject to bias arising from the participants' perceptions or beliefs; some participants did not report all the data required and others could have misreported, which could lead to misclassification bias. In addition, given the retrospective aspect of the information, recall bias may also be present in the study. However, as women were not aware of the main hypotheses of the study, had we introduced some information bias we would expect it to be non-differential, which would make more robust the results obtained. Thirdly, both the Urban Vulnerability Index and the degree of urbanization are ecological in nature, which can lead to ecological bias. Finally, as in any cohort, some participants have been lost during the follow-up. We have tried to minimize it by collecting data from medical records. Nevertheless, due to the small number of patients without follow-up, we assume that bias -if exists- would be minimum.

Conclusion

Summarizing, in this paper we observed a trend that in the Spanish universal health care system women with higher SES were more likely to receive over Saint-Gallen therapies. Being at lower SES was not associated with over or under Saint-Gallen treatment. Further analyses are needed to understand the impact of these differences on the overall survival as well as its potential unwanted side effects.

Data availability

The data will be available upon request to the corresponding author given that data cannot be shared openly in order to protect study participant privacy.

Received: 18 July 2024; Accepted: 11 April 2025
Published online: 23 April 2025

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Acknowledgements

We thank all the subjects who participated in the study and all MCC-Spain collaborators.

Author contributions

TDS, IGA, and JAM have analysed, prepared, designed, written and revised the manuscript.BPG, MG, and PA have participated in the interpretation of the data. GCV, AMD, and MM have revised the manuscript.MOS, GFT, and AMB have contributed to draft the work.JB, AS, and MFO have revised the analysis of data. TFV, and AE have helped in the analysis of the data.AA, EA, and NA have helped in the conception of the manuscript. MK, MP, and JLL have substantively revised the work and approved the submitted version.All the authors have participated in the acquisition of the data at some point in the study.

Funding

The study was partially funded by the "Accion Transversal del Cancer", approved on the Spanish Ministry Council on the 11th October 2007, by the Instituto de Salud Carlos III-FEDER (PI08/1770, PI08/0533, PI08/1359,

PS09/00773-Cantabria, PS09/01286-León, PS09/01903-Valencia, PS09/02078-Huelva, PS09/01662-Granada, PI11/01403, PI11/01889-FEDER, PI11/00226, PI11/01810, PI11/02213, PI12/00488, PI12/00265, PI12/01270, PI12/00715, PI12/00150, PI14/01219, PI14/0613, PI15/00069, PI15/00914, PI15/01032, PI17CIII/00034, PI18/00181), by the Fundación Marqués de Valdecilla (API 10/09), by the ICGC International Cancer Genome Consortium CLL (The ICGC CLL-Genome Project is funded by Spanish Ministerio de Economía y Competitividad (MINECO) through the Instituto de Salud Carlos III (ISCIII) and Red Temática de Investigación del Cáncer (RTICC) del ISCIII (RD12/0036/0036)), by the Junta de Castilla y León (LE22A10-2), by the Consejería de Salud of the Junta de Andalucía (PI-0571-2009, PI-0306-2011, salud201200057018tra), by the Conselleria de Sanitat of the Generalitat Valenciana (AP_061/10), by the Recercaixa (2010ACUP 00310), by the Regional Government of the Basque Country, by the Consejería de Sanidad de la Región de Murcia, by the European Commission grants FOOD-CT-2006-036224-HIWATE, by the Spanish Association Against Cancer (AECC) Scientific Foundation, by the Catalan Government- Agency for Management of University and Research Grants (AGAUR) grants 2017SGR723 and 2014SGR850, by the Fundación Caja de Ahorros de Asturias and by the University of Oviedo. We acknowledge support from the grant CEX2018-000806-S funded by MCIN/AEI/ https://doi.org/10.13039/501100011033, and support from the Generalitat de Catalunya through the CERCA Program.

Declarations

Competing interests
The authors declare no competing interests.

Ethics
MCC-Spain protocol was approved by the Ethics committees of the participating institutions[23]. The study has been carried out following national and international directives (code of ethics, declaration of Helsinki), and the Spanish law on data confidentiality (Ley Orgánica 15/1999 of December 13 on the Protection of Personal Data [LOPD]). All the participants were informed at recruitment about the purpose of the study and signed and informed consent including the authorization for following-up the patient via medical records or phone calls. Patients included in the prospective cohorts were only those who agreed in being followed-up. To assure confidentiality, data is secured by removing personal information in the datasets. The database was registered in the Spanish Agency for Data Protection, number 2102672171. Permission to use the study database will be granted to researchers outside the study group after revision and approval of each request by the Steering Committee.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-98469-z.

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