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TRABAJO FIN DE GRADO

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

La influencia del estado socioeconómico en el cumplimiento de las recomendaciones de Saint Gallen en el cáncer de mama en estadios precoces.

Autor: Mónica Mirones Peral

Director/es: Javier Llorca

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ÍNDICE

ABSTRACT

Background: Socio-economic status (SES) is related to breast cancer diagnosis and prognosis. We study if SES of the participants is related to the adequacy of the treatment according to Saint Gallen consensus in Spanish women.

Methods: Breast cancer cohort was assembled from incident cases from MCC-Spain and prospective followed-up afterwards. Participants were then classified according to the consensus. Association between SES and Saint Gallen fulfillment was analyzed using multinomial logistic regression, adjusting for clinicopathological variables.

Results: 1110 patients in stages I and II were included. Women with university studies were twice as likely to receive over Saint-Gallen therapies (RRR = 2.27, 95%CI 1.26 – 4.09). We observed a 14% increase in the chances of being over Saint-Gallen per point of the SES score (RRR per point 1.14, 95%CI 1.03 – 1.25). In the simplified SES score, women at higher SES were over Saint-Gallen twice as those at lower SES (RRR 2.12, 95%CI 1.29 – 3.48).

Conclusions: Women at higher SES more often received 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 influence of these differences on the overall survival as well as its potential unwanted side effects.

Key words: Breast cancer, MCC-Spain, Saint-Gallen consensus, socio-economic status.

RESUMEN

Introducción: El estado socioeconómico (ESE) está relacionado con el diagnóstico y el pronóstico del cáncer de mama. Nuestro objetivo es analizar si el SES de los participantes está relacionado con la adecuación del tratamiento según el consenso de Saint Gallen en mujeres españolas.

Métodos: La cohorte de cáncer de mama se formó a partir de casos incidentes de MCC-España y posteriormente se realizó un seguimiento prospectivo. Los participantes fueron clasificados de acuerdo con el consenso. La asociación entre SES y el cumplimiento de Saint Gallen se analizó mediante regresión logística multinomial, ajustando por variables clínico-patológicas.

Resultados: Se incluyeron 1110 pacientes en estadios I y II. Las mujeres con estudios universitarios tuvieron el doble de probabilidades de recibir terapias que excedían Saint-Gallen (RRR = 2.27, IC del 95%: 1.26 - 4.09). Observamos un aumento del 14% en las posibilidades de estar por encima de Saint-Gallen por punto del score (RRR por punto 1.14, IC 95% 1.03 - 1.25). En la escala ESE simplificada, las mujeres con un ESE más alto fueron tratadas sobre Saint-Gallen dos veces más que las del ESE más bajo (RRR 2,12; IC del 95%: 1,29 a 3,48).

Conclusiones: Las mujeres con un ESE más alto reciben son más frecuentemente tratadas con terapias por encima de Saint-Gallen. No se encontró asociación entre ESE bajo y ser tratada por debajo de Saint Gallen. Se necesitan análisis posteriores para conocer la relación entre este resultado y la supervivencia, así como sus posibles efectos secundarios.

Palabras clave: Cáncer de mama, consenso de Saint-Gallen, estado socioeconómico, MCC-Spain.

THE INFLUENCE OF SOCIO-ECONOMIC STATUS ON THE FULFILLMENT OF SAINT-GALLEN RECOMMENDATIONS FOR EARLY-STAGE BREAST CANCER

1. INTRODUCTION

Breast cancer is the leading cause of female cancer in Europe, America and Australia. (1–5) In Europe is estimated to affect 1 in 10 women, accounting for 28.8% of the total of female cancer. (6) Evidence so far indicates that we can classify breast carcinoma according to their different histopathological and biological features as they also exhibit different behaviors leading to distinct therapeutic strategies. Classical immunohistochemistry markers including ER, PR and HER2 together with TNM staging are commonly used to clarify patient's prognosis and future management. (7)

Saint Gallen International Expert Panel (2013) reviewed substantial new evidence on aspects of the local and regional therapies for early breast cancer supporting a less aggressive approach, especially for the luminal disease in absence of HER2. Therapies for HER2-positive and "triple negative" disease remained almost unchanged. Yet still, clinical consideration of extension of the disease, performance status of the patient as well as their personal preferences and socioeconomic constraints will play a part in the definitive decision of the treatment. (8) In those areas of the world where multi-gene molecular assays are available, many clinicians rely on the results to approach decisions about adjuvant chemotherapy in the protocols of patients with Luminal ER-positive, HER2-negative disease on early stages, without systemic invasion. (9)

Socio-economic status (SES) has constantly been related to breast cancer diagnosis and prognosis for the past years leading to a variety of researches. In general, higher SES has been associated with higher incidence of breast cancer. (1,4,5,10,11) Several explanations have been proposed such as parity circumstances (1), hormonal circumstances including oral contraceptives and hormone replacement (12), access to healthcare, cancer awareness, screening methods (5), lifestyle habits (13) and other issues that need to be disclosed in future investigations.

On the other hand, most studies have shown significantly lower case-fatality rate for women with higher SES, probably related to some of the reasons mentioned above, women of higher SES are more likely to be diagnosed with a lower stage tumor and also they would probably adopt healthier lifestyles after diagnosis, including also a better psychological background (1,2,5,10). Other studies have shown that conservative surgeries and consecutive follow-ups are more common among women with higher SES which could also partly explain their lower case-fatality rate. (14)

The greater risk of breast cancer mortality among women with a higher level of education being these also related to a higher SES was a persistent and extended phenomenon in Europe in the 1990s. (15) However, more recent literature about 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 rate 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. Low SES patients were diagnosed at a later stage, had different tumor characteristics and more often received suboptimal treatment.(5)

Socio-economic position remains a strong predictor of poor survival for 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) Over mortality linked to low SES is only partly explained by delayed diagnosis (related to screening methods), unfavorable tumor characteristics and suboptimal treatments, which creates the need to discover other possible explanations. Other reasons linked to the patient's health, like comorbidity, lifestyle, attitude, knowledge and convictions also could play a role. Low SES patients are more often in complex psychosocial difficulties which complicate treatments, as most effective ones are sometimes linked to certain adverse effects that require a particular performance status including psychological support. They are also more likely to have misperceptions about cancer and treatment benefits, to miss their medical visits and to be less participatory. (14)

MCC-Spain intends to explore and combine different approaches in order to identify new risk factors and provide new data that might help to prevent their occurrence in the future. (16) In this paper we will study if socio-economic status of the participants is related to the adequacy of the treatment according to Saint Gallen Consensus.

2. MATERIALS AND METHODS

MCC-Spain began as a case-control study focused in the most frequent tumors in Spain including colorectal, female breast, prostate and gastric cancers and chronic lymphocytic leukaemia. This study was developed by the Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP) and carried out in 12 Spanish provinces (Asturias, Barcelona, Cantabria, Girona, Gipuzkoa, Granada, Huelva, León, Madrid, Murcia, Navarra and Valencia). Recruitment began in September 2008 and finished in December 2013, calling up 10,183 cases and controls between 20 and 85 years old who had lived in the catchment area for at least 6 months before the diagnosis and who were able to answer an epidemiological questionnaire. The design of this study has been published elsewhere (16).

Later in 2016 the MCC-Spain decided to assemble three different cohorts (colorectal, breast and prostate) using incident cases, only if histologically confirmed. They were recruited rapidly after diagnosis and placed into their proper cohort; colorectal (2140 cases), breast (1738 cases) and prostate (1112 cases). Their prospective follow-up has been performed between 2017 and 2018 by reviewing medical records. For patients whose last contact with the hospital had occurred 3 or more months before our revision of her medical record, The National Death Index (Índice Nacional de Defunciones -IND-) (17) was consulted to realize their vital status.

Patients alive at the follow-up were contacted by phone and asked to complete questionnaires regarding their quality of life: SF-12 (18) for each cohort and FACT/NCCN Breast Symptom Index (19) for breast cancer cohort specifically. From here on, we will only be referring to the breast cancer cohort.

Initial tumor information

In order to collect information on pathology characteristics and tumour extension, medical records of each patient were reviewed by trained personnel. 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).

Socio-economic status information

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

Educational level of both the participants and their companions was divided into four groups including less than primary, primary, secondary and university studies. Socio-Economic status of participants' parents was assorted attending to whether it was low, medium or high. Information regarding participants' longest occupation was also gathered and classified (according to the Spanish Occupational Classification) (20) into three further groups; low (V), medium (IIIb, IIIc, Iva, IVb) and high (IIIa, II, I).

In order to build the individual SES score, participants' education, SES of the parents and SOC were combined. Each of the variables score 0 – 3 or 0 – 2 attending its 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 – 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 bigger groups including low SES (0, 1, 2); medium SES (3, 4, 5) and high SES (6, 7). For those participants 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.

The contextual socioeconomic status was measured by the Urban Vulnerability Index (UVI-SE) as published in the Spanish Ministry of Foment(21). It combines five indicators based on the proportion of: unemployed, unemployed aged 16 – 29 years old, non-fixed employed, employed without qualification and people without studies. The UVI-SE score ranges from 0 (lower vulnerability) to 1 (higher vulnerability). Each patient was allocated to the UVI-SE of her area of last residence.

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 (LAU) boundaries. Based on the share of local population living in urban clusters and in urban centers, it classifies them into three types of area: Cities (densely populated areas), Towns and suburbs (intermediate density areas), Rural areas (thinly populated areas). (22)

Classification of the patients according to Saint-Gallen fulfillment

In order to classify the participants according to Saint-Gallen fulfillment, information described above (type of tumour and first line treatment) was used and compared to the recommendations given.

Systematic treatment recommendations agreed by Saint-Gallen consensus were:

- Luminal A-like: Endocrine therapy is the most critical intervention and is often used alone. Cytotoxics 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): Cytotoxics + anti-HER2 + endocrine therapy
- HER2 positive (non-luminal): Cytotoxics + anti-HER2
- Triple negative (ductal): Cytotoxics

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). Surgery of the axilla 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 the women except for the elderly and those with substantial comorbidity. (8)

When classifying our patients, we payed special attention to systemic therapies as rest of the recommendations were somewhat diffuse. Criteria followed were:

- 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 futile therapy. *Example: Women with basal-like tumour (ER-, PR-, HER2-) who had breast conserving surgery, radiotherapy, cytotoxics 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 cytotoxics; lacking anti-HER2 therapy.*

Assorting the participants in 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 concordance. (Cohen's kappa index = 0.76).

Statistical analysis

Descriptive Data are described using absolute frequencies and means with standard deviation. SES indicators and Saint-Gallen fulfillment were analyzed using Pearson's chi2 (one test for each of 5 indicators) and Analysis of Variance for the remaining indicator (UVI).

After adjusting for stage at presentation and histologic grade, the association between SES indicators and Saint-Gallen Fulfillment was analyzed using multinomial logistic regression including as regressors all seven SES indicators (one logistic regression for each regressor). Results are displayed as relative risk ratios with 95% confidence intervals. All statistical analyses were performed using *Stata 14/SE.*

3. RESULTS

Description of the sample

Overall, 1110 women with stages I and II at diagnosis were included in the analysis and later classified into three groups (In Saint-Gallen, Over Saint-Gallen and Under Saint-Gallen) according to the fulfilment of Saint-Gallen. Table 1 displays the main characteristics of the sample. Most of the women were postmenopausal (65%). Compared with the others, over St Gallen women were younger (52.9) and also more likely to be premenopausal. Tumour size was predominantly T1 (66%) and it was considered in St Gallen twice as often as over St Gallen or under St Gallen respectively (57.8% vs 21.2% vs 31%). For T2 (25.5%), the distribution was similar (42.1% vs 27.2% vs 30.7%).

In this study we only consider earlier stages including: stage I (57.4%) which are tumours smaller than 2.5 cm across and stage II (42.6%) tumour less than 5 cm across which could have spread (N1 = 32.9%) or not (N0 = 66.6%) to the axillary lymph nodes. Stage I tumours considered in St Gallen accounted 49.8% versus 14.4% of over St Gallen and 35.8% of under St Gallen. For the stage II tumours the proportions were more homogeneous (37.2% vs 32.1% vs 30.7%).

Regarding the intrinsic subtype, Luminal A was by far the most common tumour (68.4%); with a proper fulfilment of Saint-Gallen of 45.4%. Luminal B (19.3%) and Her2 (4.6%) tumours were frequently under Saint-Gallen (60.3% and 54.9% respectively). Basal-like tumours represent 7.8% of our sample, and they were predominantly in Saint-Gallen (74.4% vs 4.7% vs 20.9%). According to grade of differentiation, well differentiated accounted for 23% of breast cancers; moderately differentiated accounted 30.3% and bad differentiated 19.1%. Grade could not be obtained from medical records in 307 patients (27.7%). Proportions for Saint-Gallen fulfilment are displayed with detail in table 1.

When considering the treatment specifically, conservative surgery was performed in 861 participants and mastectomy in the remaining 249 with 72% of negative surgical margins. Chemotherapy was administered to 577 patients, 41.9% of them were considered over Saint-Gallen while 22% were under Saint-Gallen. From the 747 patients that received endocrine therapy only in 55.4% received in Saint-Gallen therapies while 30.9% were over Saint-Gallen. The remaining 363 did not receive endocrine therapy and 271 were considered under Saint-Gallen. Finally, immunotherapy was given to 107 participants being 58.9% treated according to Saint-Gallen.

Factors associated with over Saint-Gallen participants

In the crude analysis, women of higher educational level had the highest over Saint-Gallen rate (Table 2). Women with less than primary education were less frequently over Saint-Gallen than women with University studies (15.5% vs. 28.2%). When adjusting for stage at presentation and histologic grade (Table 3) women, the higher the education, the higher the probability of being over Saint-Gallen reaching RRR = 2.27 when compared with those in the lower education level (95%CI 1.26 – 4.09). No association between Educational Level of the companion and overtreatment of the patients was found (Table 2).

Women of higher SES were more often over Saint-Gallen (Table 2). These differences remained in the simplified SES score, High SES 29.9%, Medium SES 21.8% and Low SES 18.3%. Results adjusted for stage and histology grade (Table 3) showed a 14% increase in the chances of being over Saint-Gallen per point of the score (RRR per point 1.14, 95%CI 1.03 – 1.25). In the simplified SES score (Table 3) the probability for women of higher SES of being over Saint-Gallen was twice as those from lower SES (RRR 2.12, 95%CI 1.29 – 3.48).

No significative association was found between Saint Gallen fulfillment and SES of the parents, Degree of Urbanization (DGUR) or Urban Vulnerability Index (UVI) (Table 3).

Factors associated with under Saint-Gallen participants

The crude analysis showed that women of lower education are more likely to be under Saint-Gallen compared to those of higher education (Table 2). Nevertheless, the differences were scarce (less than Primary 37.9% and University studies 30.1%) and after adjusted analysis by stage at presentation and histologic grade no significant results were found. Same happened with the SES (Table 4), women with lower SES were more often under Saint-Gallen than those of higher SES (32.9% vs 27.5%). When adjusting the results, (Table 3) these differences disappeared (RRR 0.98, 95% CI 0.62 – 1.54).

4. 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 of high SES were associated with higher possibilities of being over Saint-Gallen (RRR per point 1.14, 95%CI 1.03 – 1.25), and therefore, overcome unnecessary side effects. Those of lower SES showed a higher range of under Saint-Gallen therapies; however, such disparities disappeared after adjustment by stage at presentation and histologic 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 (23); they have been predominantly conducted in the United States where there is not an equal access health system. Patients from Medicaid insurance (24) and those of lower income were less likely to receive guideline concordant systemic therapies compared with privately insured women (25,26). Therefore, it is plausible that such inequalities could be explainable by financial incentives.

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 (27). Patients of low SES 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 (14). Population based studies, also from the Netherlands, have reported higher incidence of axillary dissection in patients of high SES (28). In general, there has been reported constant tendency to more aggressive therapies in the majority of cancers (esophagus, colon, breast, etc.) in patients of higher SES (29,30).

Back to our study, we observed a significant increase of over Saint-Gallen rate in women of high SES (RRR 2.12, 95% CI 1.29 – 3.48), and also in those with university studies (RRR 2.27, 95%CI 1.26 – 4.09). Association of over Saint-Gallen therapies with other SES indicators like parents' SES, DGUR or UVI was not proved significant in any of the analysis. These differences could be explained by a variety of factors.

Firstly, women of high SES and higher educational level usually play a more proactive role in decision making and also, as said before, they tend to prefer more aggressive treatments including chemotherapies, aggressive surgeries, etc. 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 a higher educational

level is supposed. On the other hand, patients of lower SES are also considered less educated, so clinicians would have a higher contribution in decision making thus they will be more likely to get and 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 -which have not been considered in this study-; and obviously personal preferences and personal situation of the patients, which are not always related to the SES itself. In those hospitals where multi-gene molecular assays as Mamaprint© were available, clinicians might rely on their results when it comes to adjuvant therapy. In any case, SES was not a limiting factor in the decision as all the therapies mentioned above are funded by National Health System.

Possible consequences of our main result would affect both women and the system. Under Saint-Gallen women could have been related to higher mortality, however, differences in undertreatment ranges were not found. Over Saint-Gallen women, on the other side, would not experiment a decrease in mortality rates but, indeed, they would suffer more side effects which would suppose direct and indirect costs for both the patient and the system. The main goal in breast cancer treatment, and in any treatment in general, is always to optimize healing and survival rates without affecting the quality of life of the patients.

Finally, apart from the fact that over Saint-Gallen rate is consistently related to higher SES, it is important to notice that such disparities were not found when checking women of lower SES. If found, these inequalities would have been devastating for the system, as it is presumed to be of equal access. SES indicator DGUR, which is related to the area of residence and which could introduce some personal prejudices did not show any significant differences. UVI index, which measures the SES level of the area the patient is living in, was not proved to have any influence. This partly means 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 12 Spanish provinces, and given the universal coverage of the Spanish National Health System, they could provide a representative sample of the population.

Some limitations of this study should also be considered. Firstly, part of the information regarding SES was self-reported and could be influenced by women's feelings or beliefs; some participants did not report all the data required and others could have misreported, which could lead to misclassification bias. 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. Secondly, 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.

Summarizing, in this paper we observed that in the Spanish universal health system women of higher SES more often received 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 influence of these differences on the overall survival as well as its potential unwanted side effects.

5. ETHICS

MCC-Spain protocol was firstly approved by the Ethics committees of the participating institutions (16). 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.

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8. TABLES

Table 1. Description of the sample (n = 1110)

Variable	Category	Total	Saint-Gallen Fulfillment			p
			In St Gallen	Over St Gallen	Under St Gallen	
Age	*Mean (SD)*	56.1 (12.1)	56.6 (12.6)	52.9 (10.6)	57.6 (11.9)	< 0.001
Post menopause	*No*	389 (35.0)	153 (39.3)	120 (30.9)	116 (29.8)	< 0.001
	Yes	721 (65.0)	340 (47.2)	124 (17.2)	257 (35.6)	
Tumour Size	*T0*	19 (1.7)	7 (36.8)	5 (26.3)	7 (36.8)	< 0.001
	T1	732 (65.9)	350 (47.8)	155 (21.2)	227 (31.0)	
	T2	283 (25.5)	119 (42.1)	77 (27.2)	87 (30.7)	
	T3	15 (1.4)	4 (26.7)	2 (13.3)	9 (60.0)	
	T4	4 (0.4)	1 (25.0)	1 (25.0)	2 (50.0)	
	Tis	44 (4.0)	8 (18.2)	1 (2.3)	35 (79.6)	
	Miss	13 (1.2)	4 (30.8)	3 (23.1)	6 (46.2)	
Node Infiltration	*N0*	739 (66.6)	368 (49.8)	106 (14.3)	265 (35.9)	< 0.001
	N1	365 (32.9)	122 (33.4)	136 (37.3)	107 (29.3)	
	Miss	6 (0.5)	3 (50.0)	2 (33.3)	1 (16.7)	
Metastasis	*M0*	1080 (97.3)	474 (43.9)	242 (22.4)	364 (33.7)	0.05
	Miss	30 (2.7)	19 (63.3)	2 (6.7)	9 (30.0)	
Qx stage	*I*	637 (57.4)	317 (49.8)	92 (14.4)	228 (35.8)	< 0.001
	II	473 (42.6)	176 (37.2)	152 (32.1)	145 (30.7)	
Oestrogen receptor	*Negative*	150 (13.5)	85 (56.7)	13 (8.7)	52 (34.7)	<0.001
	Positive	959 (86.4)	407 (42.4)	231 (24.1)	321 (33.5)	
	Miss	1 (0.1)	1 (100.0)	0 (0.0)	0 (0.0)	

Progesterone receptor	*Negative*	245 (22.1)	120 (48.9)	16 (6.5)	109 (44.5)	<0.001
	Positive	860 (77.5)	371 (43.1)	226 (26.3)	263 (30.6)	
	Miss	5 (0.5)	2 (40.0)	2 (40.0)	1 (20.0)	
ErbB2	*Negative*	927 (83.5)	433 (46.7)	227 (24.5)	267 (28.8)	< 0.001
	Positive	183 (16.5)	60 (32.8)	17 (9.3)	106 (57.9)	
Intrinsic subtype	*Luminal A*	759 (68.4)	339 (44.7)	222 (29.3)	198 (26.1)	< 0.001
	Luminal B	214 (19.3)	75 (35.1)	10 (4.7)	129 (60.3)	
	Her2	51 (4.6)	15 (29.4)	8 (15.7)	28 (54.9)	
	Basal-like	86 (7.8)	64 (74.4)	4 (4.7)	18 (20.9)	
Grade of differentiation	*I: well differentiated*	255 (23.0)	123 (48.2)	74 (29.0)	58 (22.8)	< 0.001
	II: moderately differentiated	336 (30.3)	138 (41.1)	109 (32.4)	89 (26.5)	
	III: bad differentiated	212 (19.1)	117 (55.2)	16 (7.6)	79 (37.3)	
	Miss	307 (27.7)	115 (37.5)	45 (14.7)	147 (47.9)	
Surgery	*Conservative surgery*	861 (77.6)	392 (45.5)	184 (21.4)	285 (33.1)	0.37
	Mastectomy	249 (22.4)	101 (40.6)	60 (24.1)	88 (35.3)	
Surgical Margins	*Negative*	799 (72.0)	367 (45.9)	178 (22.3)	254 (31.8)	0.19
	Positive	162 (14.6)	67 (41.4)	38 (23.5)	57 (35.2)	
	Miss	149 (13.4)	59 (39.6)	28 (18.8)	62 (41.6)	
Chemotherapy	*No*	533 (48.0)	285 (53.5)	2 (0.4)	246 (46.2)	< 0.001
	Yes	577 (52.0)	208 (36.1)	242 (41.9)	127 (22.0)	
Endocrine	*No*	363 (32.7)	79 (21.8)	13 (3.6)	271 (74.7)	< 0.001
	Yes	747 (67.3)	414 (55.4)	231 (30.9)	102 (13.7)	
Immunotherapy	*No*	1003 (90.4)	430 (42.9)	223 (22.2)	350 (34.9)	0.004
	Yes	107 (9.6)	63 (58.9)	21 (19.6)	23 (21.5)	

Table 2. Association between SES indicators and Saint-Gallen Fulfillment

			Saint-Gallen Fulfillment			
			In St Gallen	Over St Gallen	Under St Gallen	
SES indicator	**Category**	**Total**				**p**
Education	*Less than primary*	161 (14.5)	75 (46.6)	25 (15.5)	61 (37.9)	0.06
	Primary	344 (31.0)	166 (48.3)	70 (20.4)	108 (31.4)	
	Secondary	396(35.7)	165 (41.7)	90 (22.7)	141 (35.6)	
	University	209 (18.8)	87 (41.6)	59 (28.2)	63 (30.1)	
Companion Ed.	*Less than primary*	108 (11.6)	49 (45.4)	20 (18.5)	39 (36.1)	0.36
	Primary	307 (32.9)	150 (48.9)	63 (20.5)	94 (30.6)	
	Secondary	301 (32.3)	119 (39.5)	67 (22.3)	115 (38.2)	
	University	216 (23.2)	96 (44.4)	49 (22.7)	71 (32.9)	
SES	*0*	52 (4.7)	23 (44.2)	8 (15.4)	21 (40.4)	0.06
	1	142 (12.8)	71 (50.0)	21 (14.8)	50 (35.2)	
	2	168 (15.1)	82 (48.8)	37 (22.0)	49 (29.2)	
	3	202 (18.2)	83 (41.1)	51 (25.3)	68 (33.7)	
	4	203 (18.4)	85 (41.9)	40 (19.7)	78 (38.4)	
	5	186 (16.8)	82 (44.1)	37 (19.9)	67 (36.0)	
	6	148 (13.3)	62 (41.9)	48 (32.4)	38 (25.7)	
	7	9 (0.8)	5 (55.6)	2 (22.2)	2 (22.2)	
Summary SES	*Mean (SD)*	3.40 (1.76)	3.33 (1.79)	3.66 (1.74)	3.33 (1.73)	0.0001
SES score	*Low*	609 (54.9)	163 (48.8)	61 (18.3)	110 (32.9)	0.02
	Medium	334 (30.1)	259 (42.5)	133 (21.8)	217 (35.6)	
	High	167 (15.0)	71 (42.5)	50 (29.9)	46 (27.5)	
SES parents	*Low*	365 (32.9)	166 (45.5)	71 (19.5)	128 (35.1)	0.59
	Medium	714 (64.3)	312 (43.7)	168 (23.5)	234 (32.8)	
	High	29 (2.6)	14 (48.3)	5 (17.2)	10 (34.5)	
DGUR	*Dense*	625 (74.5)	284 (45.4)	138 (22.1)	203 (32.5)	0.75
	Intermediate	149 (17.8)	64 (43.0)	30 (20.1)	55 (36.9)	
	Thinly	65 (7.7)	33 (50.8)	12 (18.5)	20 (30.8)	
UVI	*Mean (SD)*	0.50 (0.14)	0.50 (0.14)	0.51 (0.15)	0.49 (0.13)	0.03

Table 3. Fulfillment of Saint Gallen and socio-economic status. Relative Risk Ratio Adjusted for stage at presentation and histology grade

		Saint Gallen-Fulfillment			
		Over St Gallen		Under St Gallen	
SES indicator	**Category**	**RRR (95% CI)**	**p**	**RRR (95% CI)**	**p**
Education	*Less than primary*	1 (ref.)	-	1 (ref.)	-
	Primary	1.30 (0.75 – 2.26)	0.35	0.80 (0.52 – 1.22)	0.30
	Secondary	1.54 (0.90 – 2.65)	0.12	1.01 (0.67 – 1.52)	0.97
	University	2.27 (1.26 – 4.09)	0.006	0.93 (0.58 – 1.50)	0.77
Companion Ed.	*Less than primary*	1 (ref.)	-	1 (ref.)	-
	Primary	1.04 (0.55 – 1.96)	0.90	0.80 (0.48 – 1.31)	0.48
	Secondary	1.44 (0.76 – 2.71)	0.26	1.18 (0.72 – 1.95)	0.51
	University	1.36 (0.70 – 2.62)	0.37	0.93 (0.55 – 1.58)	0.80
SES	*Per point*	1.14 (1.03 – 1.25)	0.008	1.00 (0.93 – 1.08)	0.99
SES score	*Low*	1 (ref.)	-	1 (ref.)	-
	Medium	1.47 (1.00 – 2.15)	0.05	1.16 (0.85 – 1.58)	0.35
	High	2.12 (1.29 – 3.48)	0.003	0.98 (0.62 – 1.54)	0.92
SES parents	*Low*	1 (ref.)	-	1 (ref.)	-
	Medium	1.24 (0.87 – 1.76)	0.24	0.95 (0.71 – 1.27)	0.73
	High	0.79 (0.27 – 2.38)	0.68	1.02 (0.43 – 2.40)	0.97
DGUR	*Dense*	1 (ref.)	-	1 (ref.)	-
	Intermediate	1.12 (0.66 – 1.90)	0.68	0.89 (0.58 – 1.38)	0.61
	Thinly	0.73 (0.35 – 1.49)	0.39	0.81 (0.44 – 1.47)	0.48
UVI	*Per point*	1.26 (0.33 – 4.77)	0.73	0.82 (0.26 – 2.56)	0.73

RRR: relative risk ratio
Education: educational level of the patients
Companion Ed.: educational level of the patients' companions.

SES: socio-economic status
SES score: simplified socio-economic status
DGUR: degree of urbanization
UVI: urban vulnerability index