

ORIGINAL ARTICLE

The influence of socioeconomic status and ethnicity on adjuvant systemic treatment guideline adherence for early-stage breast cancer in the Netherlands

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Background: We aimed to assess whether socioeconomic status (SES) and ethnicity affect adjuvant systemic therapy (AST) guideline adherence in early breast cancer patients in a health care setting with assumed equal access to care.

Methods: Data from all female patients surgically treated for primary unifocal early breast cancer between January 2005 and December 2014 were retrieved from the Netherlands Cancer Registry. We assessed the association between SES, ethnicity and non-adherence to adjuvant chemotherapy (CT) or endocrine therapy (ET) guideline indications with Poisson regression models, adjusting for clinicopathological variables.

Results: A total of 104 201 patients were included in the current analysis. Of patients without an indication, 4% and 13% received adjuvant CT or ET (overtreatment), whereas 39% and 14% of patients with an indication did not receive CT or ET (undertreatment). Medium and low SES patients were 1.01 (95% CI 1.00–1.01) and 1.01 (95% CI 1.00–1.01) times more likely to be undertreated and 0.85 (95% CI 0.76–0.94) and 0.67 (95% CI 0.60–0.75) times more likely to be overtreated with CT compared with high SES patients [resulting in an overall relative risk of CT use of 0.94 (95% CI 0.92–0.96) and 0.85 (95% CI 0.83–0.87), respectively]. No association between SES and ET guideline adherence or ethnicity and CT/ET guideline adherence was observed.

Conclusion: In the Netherlands, minimal SES disparities in CT guideline adherence were observed: low SES patients are less likely to be overtreated and marginally more likely to be undertreated with CT resulting in an overall decreased risk of receiving CT. No ethnic disparities in AST guideline adherence were observed.

Key words: breast cancer, guideline adherence, chemotherapy, endocrine therapy, socioeconomic status, ethnicity

Introduction

Adjuvant systemic treatment (AST) is an important pillar in the management of early-stage breast cancer. Since 1990 several (inter)national guidelines recommend AST in patients at higher risk of distant recurrence in order to improve clinical outcome [1, 2]. Appropriate use of AST decreases breast cancer mortality [3], and patients with a poor clinicopathological profile may clearly benefit of AST. On the other hand, in patients with a good prognostic profile AST benefits do not always outweigh its negative effects, such as associated (long-term) side-effects. Therefore, both

under- and overtreatment with AST should ideally be avoided to optimize breast cancer treatment while maintaining optimal quality of life.

Several studies from the U.S. report that actual AST prescription varies by insurance status [4–8], income [6, 8], socioeconomic status (SES) [9, 10] and ethnicity [8, 11–13]. These observed disparities could be explained by educated and/or more affluent women being more likely to seek medical care proactively whereas less affluent patients may not communicate as well with physicians and are less informed about treatment options [14–16]. Furthermore,

minority and low SES patients may receive care from different providers due to financial inequalities, geography, or insurance status, and between-provider variation in quality of care may cause socioeconomic or racial disparities in the availability of appropriate systemic therapies [10, 17].

In the Netherlands, healthcare insurance is mandatory and AST is fully reimbursed by all health insurers. Hence, in contrast to other healthcare systems, AST is available for all Dutch breast cancer patients irrespective of their background. The aim of the current population-based study is to assess whether socioeconomic and ethnical disparities in AST guideline adherence in early-stage breast cancer are also present in the Dutch equal access healthcare system. While financial incentives in the Netherlands are less likely to underlie AST decision-making, other SES or ethnicity related factors such as views and beliefs might still be of influence. This study can thus provide important clues for the relative importance of financial and non-financial SES/ethnicity associated determinants of AST adherence and could thereby aid in reducing breast cancer treatment disparities and increasing appropriate AST use globally.

Patients and methods

Data collection

From the Netherlands Cancer Registry (NCR) we obtained patient-, tumor-, treatment and hospital-characteristics of all women surgically treated for primary, unilateral, invasive breast cancer in the period of 2005 through 2014.

We used a SES indicator, which ranks neighbourhoods defined by postal code based on the aggregated value of houses and household income (average of 17 households/code), which was categorized in low (1st to 3th decile), medium (4th to 7th decile) and high (8th to 10th decile) [18]. Country of birth is registered by the NCR and corrected or supplemented with information from municipal population registries. For patients born <1970 without known country of birth ($\approx 25\%$ patients) a name-based approach was used to assess country of birth. Non-Dutch names are specific for 90%–95% of immigrants from Turkey and Morocco (the largest immigrant countries) and for 50%–75% of immigrants from Surinam and the Netherlands Antilles (third and fourth immigrant countries). This approach was not used for patients born >1969 because of the large number of second generation immigrants following immigration in the 1960s. Patients were categorized into Native Dutch, Non-Western Immigrant or Western immigrant according to the classification of Statistics Netherlands [19].

AST guideline recommendation

Chemotherapy (CT)/endocrine therapy (ET) indication was based on Dutch AST guidelines at time of treatment (three guidelines were active during our study period: 2005–2008, 2008–2012 and 2012–2014; supplementary Figure S1, available at *Annals of Oncology* online). We assessed guideline non-adherence as follows: CT/ET administration without such guideline indication (CT or ET ‘overtreatment’) or refrain CT/ET despite a guideline indication to administer CT/ET (CT or ET ‘undertreatment’). Risk of ET under- or overtreatment was evaluated in hormone-receptor positive patients only.

Patients with multifocal disease were excluded from the analysis, since guidelines are unclear about AST recommendation in such patients. Patients treated with neo-adjuvant therapy were excluded from the primary analysis, since AST eligibility is based on clinical assessment of the tumor, but were included in sensitivity analyses.

Risk of guideline discordant treatment

To obtain appropriate estimates of the relative risk of CT/ET under- or overtreatment in relation to SES/ethnicity, we used Poisson regression models instead of logistic regression (the latter estimates odds ratios that are more extreme than relative risks if the outcome of interest is common). We first assessed the unadjusted association between SES/ethnicity and guideline discordant CT/ET (model 1). Subsequently, we adjusted for year of diagnosis, age, morphology, grade, tumor size, axillary lymph-node involvement, ER-, PR- and Her2-status (model 2). Hereafter, we also adjusted for hospital-characteristics, and included a random intercept per hospital resulting in a mixed-effect model that takes patient clustering at a hospital-level into account (model 3). Lastly, we corrected for all clinicopathological and hospital-characteristics and mutually adjusted for SES and ethnicity (model 4). Models were conducted in patients with and without an indication for CT/ET to assess the risk for ‘undertreatment’ and ‘overtreatment’. Model 4 was also used to assess the association between SES/ethnicity and CT/ET, regardless of guideline recommendation. All variables were included as categorical variables, except for age which was treated as a continuous variable after assessment of the assumed log-linear relation by model transformations and comparing Akaike’s information criteria. Furthermore, all models were well calibrated. To evaluate a possible interaction between SES and ethnicity, an interaction term was added to model 4 and a likelihood-ratio test was carried out to assess statistical significance. The same approach was used to assess a possible interaction between SES and year of birth, year of diagnosis or age. Robust standard errors and appropriate 95% CIs were calculated with the Sandwich method.

A two-sided P value of <0.05 was considered statistically significant. Analyses were carried out using R version 3.1.3. For the mixed-effect Poisson regression analysis we used STATA version 14.1 supplemented with GLLAMM for obtaining robust 95% CIs using the Sandwich estimator of the covariance matrix [20].

Results

Between 2005 through 2014, 137 175 early breast cancer patients were surgically treated in the Netherlands (supplementary Figure S2, available at *Annals of Oncology* online). A total of 32 992 (24%) patients were excluded from the analysis (due to multifocality and/or neo-adjuvant therapy).

Baseline differences by SES and ethnicity

High SES patients were younger at time of diagnosis (59 vs. 64 years) and more often of Dutch origin (95% vs. 89%) when compared with low SES patients. We observed no notable differences in tumor characteristics (Table 1). Native Dutch patients were older, of higher SES and had tumors with more favorable characteristics (ER⁺/Her2⁻, low malignancy grade without axillary lymph-node involvement) when compared with immigrant patients (Table 2).

Guideline discordant treatment

Overtreatment was rare, 1780 (4%) and 3958 (13%) patients received CT/ET without such recommendation. Undertreatment was more frequent: 19 794 (38%) and 6740 (12%) patients did not receive CT/ET despite a guideline recommendation (Tables 3 and 4, respectively).

Five percent ($n = 565$) of high SES patients and 3% ($n = 362$) of low SES patients received CT without a recommendation. Medium and low SES patients had a 0.85 (95% CI 0.76–0.94) and

Table 1. Patient-, tumor-, hospital- and treatment characteristics of all Dutch female patients surgically treated for primary breast cancer stages I–IIIc between 2005 and 2014 (n = 118 907) by socioeconomic status (SES)

	Low SES n = 31 134 (26%)	Medium SES n = 49 345 (41%)	High SES n = 38 428 (32%)
Patient characteristics			
Year of diagnosis			
2005–2007	8859 (28.5)	13 344 (27.0)	10 348 (26.9)
2008–2011	12 573 (40.4)	19 911 (40.4)	15 381 (40.0)
2012–2014	9702 (31.2)	16 090 (32.6)	12 699 (33.0)
Age in years, mean (SD)	63.8 (14.7)	59.8 (13.1)	59.4 (12.2)
Ethnicity			
Native Dutch	26 994 (88.5)	45 590 (93.6)	36 126 (95.0)
Non-Western immigrant	2623 (8.6)	2101 (4.3)	1106 (2.9)
Western immigrant	896 (2.9)	1020 (2.1)	776 (2.0)
Missing	621	634	420
Hospital characteristics			
Type of hospital			
District	13 360 (48.8)	23 733 (51.2)	17 894 (49.4)
Top clinical	12 381 (45.2)	19 897 (42.9)	15 815 (43.7)
Academic	1624 (5.9)	2722 (5.9)	2512 (6.9)
Missing	3769	2993	2207
Tumor characteristics			
Morphology			
Ductal	23 183 (74.5)	36 962 (74.9)	28 735 (74.8)
Lobular	3373 (10.8)	5595 (11.3)	4506 (11.7)
Ductoobular	842 (2.7)	1634 (3.3)	1344 (3.5)
Adenocarcinoma	1037 (3.3)	1227 (2.5)	856 (2.2)
Other types	2699 (8.7)	3927 (8.0)	2987 (7.8)
Invasive tumor grade			
Grade 1	6247 (23.7)	10 588 (24.5)	8538 (25.2)
Grade 2	12 107 (46.0)	19 730 (45.6)	15 528 (45.9)
Grade 3	7967 (30.3)	12 985 (30.0)	9797 (28.9)
Missing	4813	6042	4565
Tumor size in cm, mean (SD)			
1.9 (1.4)		1.8 (1.4)	1.8 (1.4)
Missing	2610	3060	2301
Hormone receptor status			
ER and PR negative	4854 (15.9)	7778 (16.0)	5883 (15.6)
ER or PR positive	25 692 (84.1)	40 814 (84.0)	31 937 (84.4)
Missing	588	753	608
HER2 status			
Negative	24 646 (86.6)	39 847 (86.2)	31 248 (86.6)
Positive	3803 (13.4)	6402 (13.8)	4840 (13.4)
Missing	2685	3096	2340
Axillary lymph-node involvement			
N0	17 641 (63.5)	29 965 (64.6)	23 494 (64.6)
N1	7302 (26.3)	11 935 (25.7)	9496 (26.1)
N2	1793 (6.5)	2909 (6.3)	2160 (5.9)
N3	1062 (3.8)	1609 (3.5)	1219 (3.4)
Missing	3336	2927	2059
Treatment characteristics			
Type of surgery			
Breast-conserving	16 115 (51.8)	28 856 (58.5)	23 411 (60.9)
Ablative	12 328 (39.6)	18 394 (37.3)	13 681 (35.6)
Type of surgery unknown	2691 (8.6)	2095 (4.2)	1336 (3.5)
Axillary surgery			
No axillary surgery	5386 (17.3)	5868 (11.9)	4610 (12.0)
ALND	8363 (26.9)	12 847 (26.0)	9607 (25.0)
SNP	17 385 (55.8)	30 630 (62.1)	24 211 (63.0)

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Table 1. Continued

	Low SES <i>n</i> = 31 134 (26%)	Medium SES <i>n</i> = 49 345 (41%)	High SES <i>n</i> = 38 428 (32%)
Gene-expression profile use ^a			
No GEP use	12 062 (95.4)	19 634 (93.8)	15 038 (92.2)
GEP use	580 (4.6)	1304 (6.2)	1275 (7.8)
Missing	18 492	28 407	22 115
Adjuvant chemotherapy	10 595 (34.0)	20 768 (42.1)	16 492 (42.9)
Adjuvant endocrine therapy	17 293 (55.5)	26 463 (53.6)	20 556 (53.5)
Neo-adjuvant chemotherapy	2091 (6.7)	3736 (7.6)	3151 (8.2)
Neo-adjuvant endocrine therapy	583 (1.9)	717 (1.5)	574 (1.5)

^aThe use of gene-expression profiles (GEP) was only registered since 2012, patients treated before 2012 were coded as missing.

SD, standard deviation; SES, socioeconomic status; ER, estrogen receptor; PR, progesterone receptor; ALND, axillary lymph-node dissection; SNP, sentinel node procedure; GEP, gene-expression profile.

0.67 (95% CI 0.60–0.75) times higher risk of CT overtreatment compared with high SES patients, respectively. When analyzing the relation between SES and CT overtreatment per SES deciles, this revealed a similar trend toward a decreasing risk for CT overtreatment with decreasing SES (supplementary Figure S3, available at *Annals of Oncology* online).

Low or medium SES patients were marginally more likely to be undertreated with CT when compared with high SES patients (RR 1.01, 95% CI 1.00–1.01 and RR 1.01, 95% CI 1.00–1.01, respectively). CT administration—regardless of indication—was 0.85 (95% CI 0.83–0.87) times more likely in low SES patients when compared with high SES patients (supplementary Table S2, available at *Annals of Oncology* online). No association between SES and ET guideline discordant treatment was observed (Table 4; supplementary Table S2, available at *Annals of Oncology* online).

We observed no association between ethnicity and the risk of guideline discordant treatment. Immigrant patients were as likely as Native Dutch patients to be overtreated with CT in the fully adjusted models (RR 0.91, 95% CI 0.67–1.22 and RR 0.75, 95% CI 0.49–1.13 for Non-Western and Western immigrants). The same holds for the risk of CT undertreatment (RR 1.00, 95% CI 1.00–1.02 and RR 1.00, 95% CI 0.99–1.03 for Non-Western and Western immigrants). We observed no association between ethnicity and ET guideline discordant treatment or overall CT/ET administration (Table 4; supplementary Table S2, available at *Annals of Oncology* online).

We observed no differences in the association between SES and CT/ET over- or undertreatment by ethnicity (*P* value for interaction: CT overtreatment, *P*=0.211; CT undertreatment, *P*=0.976; ET overtreatment, *P*=0.927; and ET undertreatment, *P*=0.067). In addition, there was no statistically significant interaction between SES and year of birth, year of diagnosis or age and the risk of CT overtreatment.

Sensitivity analysis

Similar percentages of patients were treated with neo-adjuvant CT across SES categories. A higher incidence of neo-adjuvant CT was observed in Non-Western immigrants (11.9%) when

compared with Native Dutch or Western immigrant patients (7.1% and 8.6%, respectively). Sensitivity analysis—in which both adjuvant and neo-adjuvant treated patients were included—yielded similar results for the association between SES and risk of CT under- or overtreatment (supplementary Table S1, available at *Annals of Oncology* online). In addition, no association between ethnicity and guideline discordant CT administration observed (data not shown).

Discussion

In this nation-wide study, we observed minimal socioeconomic variations in adjuvant CT use in Dutch early-stage breast cancer patients. While low SES was associated with a relative 15% lower risk of receiving CT, the observed differences merely resulted from the higher chance of high SES patients to receive CT without such indication combined with a marginally higher risk for CT undertreatment in low SES patients. No association between SES and ET guideline adherence was observed and we did not observe any ethnic disparities.

Although the observed disparities in guideline adherence between SES categories on a relative risk scale are small in absolute terms, AST undertreatment is associated with mortality and AST overtreatment leads to unnecessary side-effects therefore both should be avoided to optimize curation chances while maintaining optimal quality of life. Several studies, predominantly conducted in the USA, report a lower frequency of CT in low SES patients [10, 21], patients with Medicaid insurance [4, 6, 7] or patients with lower income levels [8]. In a large study, using data of the National Program of Cancer Registries, 34% and 1% of early-stage breast cancer patients were, respectively, under- or over-treated with adjuvant CT and patients with Medicaid insurance were less likely (OR 0.64, 95% CI 0.48–0.85) to receive guideline concordant CT care compared with privately insured patients [11]. Others did not observe a significant association between SES and CT [12, 22]. We did not observe any socioeconomic disparities in ET guideline adherence which is in line with most studies addressing this association [11, 13, 21–24]. Wu et al. did

Table 2. Patient-, tumor-, hospital- and treatment characteristics of all Dutch female patients surgically treated for primary breast cancer stages I–IIIc between 2005 and 2014 (n = 134 071) by ethnicity

	Native Dutch n=125 480 (94%)	Non-Western immigrant n=6569 (5%)	Western immigrant n=2022(2%)
Patient characteristics			
Year of diagnosis			
2005–2007	34 768 (27.7)	1745 (26.1)	803 (25.8)
2008–2011	50 238 (40.0)	2773 (41.5)	1302 (41.8)
2012–2014	40 465 (32.3)	2161 (32.4)	1013 (32.5)
Age, mean (SD)	61.7 (13.8)	56.6 (13.6)	59.5 (14.4)
Socioeconomic status			
Low SES	26 997 (24.8)	2591 (45.1)	653 (36.9)
Medium SES	45 593 (41.9)	2068 (36.0)	669 (37.8)
High SES	36 126 (33.2)	1083 (18.9)	448 (25.3)
Missing	16 764	827	252
Hospital characteristics			
Type of hospital			
District	57 447 (50.2)	2687 (44.7)	1356 (49.0)
Top clinical	49 968 (43.7)	2818 (46.9)	1189 (42.9)
Academic	7050 (6.2)	506 (8.4)	224 (8.1)
Missing	11 006	668	349
Tumor characteristics			
Morphology			
Ductal	93 152 (74.2)	5200 (77.9)	2375 (76.2)
Lobular	14 603 (11.6)	503 (7.5)	315 (10.1)
Ductal and Lobular	4022 (3.2)	174 (2.6)	93 (3.0)
Adenocarcinoma	3544 (2.8)	212 (3.2)	96 (3.1)
Other types	10 150 (8.1)	590 (8.8)	239 (7.7)
Invasive tumor grade			
Grade 1	26 733 (24.7)	1125 (20.0)	640 (24.3)
Grade 2	49 654 (46.0)	2366 (42.1)	1202 (45.7)
Grade 3	31 627 (29.3)	2131 (37.9)	787 (29.9)
Missing	17 457	1057	489
Tumor size in cm (SD)			
1.8 (1.4)		1.8 (1.5)	1.8 (1.4)
Missing	9340	541	288
Hormone receptor status			
ER and PR negative	19 108 (15.5)	1351 (20.7)	502 (16.5)
ER or PR positive	104 295 (84.5)	5174 (79.3)	2541 (83.5)
Missing	2068	154	75
HER2 status			
Negative	100 835 (86.8)	5119 (82.3)	2466 (85.9)
Positive	15 369 (13.2)	1102 (17.7)	406 (14.1)
Missing	9267	458	246
Axillary lymph-node involvement			
N0	74 048 (64.5)	3714 (60.1)	1768 (62.9)
N1	29 638 (25.8)	1725 (27.9)	737 (26.2)
N2	7024 (6.1)	483 (7.8)	198 (7.0)
N3	4022 (3.5)	258 (4.2)	106 (3.8)
Missing	10 739	499	309
Treatment characteristics			
Type of surgery			
Breast-conserving	70 158 (55.9)	3934 (58.9)	1719 (55.1)
Ablative	47 031 (37.5)	2374 (35.5)	1146 (36.8)
Type of surgery unknown	8282 (6.6)	371 (5.6)	253 (8.1)
Axillary surgery			
No axillary surgery	18 268 (14.6)	1100 (16.5)	577 (18.5)
ALND	31 893 (25.4)	2050 (30.7)	836 (26.8)
SNP	75 310 (60.0)	3529 (52.8)	1705 (54.7)

Continued

Table 2. *Continued*

	Native Dutch <i>n</i> =125 480 (94%)	Non-Western immigrant <i>n</i> =6569 (5%)	Western immigrant <i>n</i> =2022(2%)
Gene-expression profile use ^a			
No GEP use	49128 (93.6)	2734 (95.6)	1228 (94.4)
GEP use	3332 (6.4)	125 (4.4)	73 (5.6)
Missing	73011	3820	1817
Adjuvant chemotherapy	48133 (38.4)	3424 (51.3)	1274 (40.9)
Adjuvant endocrine therapy	68462 (54.6)	3566 (53.4)	1704 (54.7)
Neo-adjuvant chemotherapy	8911 (7.1)	794 (11.9)	267 (8.6)
Neo-adjuvant endocrine therapy	2008 (1.6)	106 (1.6)	53 (1.7)

^aThe use of gene-expression profiles was only registered since 2012, patients treated before 2012 were coded as missing.

SD, standard deviation; SES, socioeconomic status; ER, estrogen receptor; PR, progesterone receptor; ALND, axillary lymph-node dissection; SNP, sentinel node procedure; GEP, gene-expression profile.

observe a borderline significant increased risk for ET guideline discordance in patients living in high-poverty areas but found no association between insurance type or education level [11]. Others report a lower risk of ET in women without insurance [8] or with Medicaid insurance when compared with women who were privately insured [12].

The present study is conducted in an equal access healthcare-system mandating insurance for all with full reimbursement of AST. Therefore, it is unlikely that the observed SES-associated disparities in CT administration are attributable to financial incentives. Our results suggest that high SES patients are more inclined to undergo all therapeutic options, even if there is no certain benefit and these could be potentially harmful, to overcome disease. This reasoning is supported by a recent population based study from the Netherlands in which high SES breast cancer patients were more likely to undergo axillary dissection [25]. In other forms of cancer this tendency to more aggressive treatment in high SES patients is also observed, such as a higher likelihood of receiving surgery for pancreatic or esophageal cancer in Dutch high SES patients [26, 27]. Internationally, this trend is also observed, for example illustrated by a higher incidence of lymph-node dissection in high SES colon cancer patients from Louisiana [28]. Together with the fact that high SES patients play a more proactive role in decision-making [14], this trend might explain the observed higher incidence of CT overtreatment. In the United States financial disparities could also underlie these findings, whereas in the Dutch system this is less likely. In this line of reasoning, physicians should be more responsive toward this tendency to opt for more aggressive treatment in high SES patients. Another possible explanation is a difference in physician's contributions to CT decision-making between SES categories. However, as our study design precludes detailed analysis on this observation, this remains speculation.

Our results indicate that ethnical disparities in AST guideline adherence can be excluded on an aggregated level. Some authors report higher incidence of AST administration in black [12] or Hispanic [12, 24] patients whereas others observe a lower risk of AST administration in minority patient groups [19]. Our findings are in line with two large recent studies who also did not

observe ethnical disparities in AST administration [8, 11]. Based on our study size, we can conclude that even the presence of very small ethnical disparities in AST guideline non-adherence can be excluded.

Our population-based approach allows a comprehensive overview of socioeconomic and ethnic variation in AST guideline adherence. The association between SES or ethnicity and guideline discordant AST at a nation-wide level in a healthcare system that seeks to provide equal access to care has not been assessed before. Nevertheless, use of this comprehensive real-life data reflecting routine clinical care comes with the cost of limited availability of detailed information per patient. First, reasons to deviate from guidelines and information on co-morbidities were unknown. It is important to note that deviation from AST guideline recommendations does not equal poor medical care. In addition, we had to rely on postal code information for determination of SES. Although this method has been used before [23] and has shown to accurately reflect SES of individual patients [29], this is prone to misclassification and could have diluted the observed association. Regarding ethnicity, for 25% of patients' country of birth was estimated based on a name-based approach. Although in this method is very specific for the largest immigrant countries a certain error measure could be included which could also have led to a diluted observed association. Then again, sensitivity analysis, in which we only included patients for whom country of birth was actually registered, also revealed no association between ethnicity and CT or ET under- or overtreatment.

In this study, conducted in an equal access care system, SES was not a limiting factor in obtaining appropriate care, which suggests that without financial disparities in health care reimbursement, better equality in the administration of AST is achieved. This finding is of great importance given that breast cancer is the most common cancer type and leading cause of cancer death among females worldwide.

In conclusion, although there is a relation between guideline discordant CT administration and SES in early-stage breast cancer patients treated in an equal access health care setting, the observed associations were rather small. Low SES patients are only slightly more likely to be undertreated and less likely to be

Table 3. Relative risk (RR) for adjuvant chemotherapy (CT) over- or under treatment in Dutch surgically treated patients with stadium I–IIc unifocal breast cancer who did not receive neo-adjuvant systemic treatment

			Unadjusted RR (95% CI)	P value	Model 2 RR (95% CI)	P value	Model 3 RR (95% CI)	P value	Model 4 RR (95% CI)	P value
Chemotherapy overtreatment										
	Number of patients without an indication for adjuvant CT ^a	Number of patients overtreated (%)								
SES										
High SES	12298	565 (5%)	1 [ref]		1 [ref]		1 [ref]		1 [ref]	
Medium SES	16722	660 (4%)	0.86 [0.77–0.96]	0.007	0.90 [0.81–1.01]	0.060	0.89 [0.80–1.00]	0.046	0.85 [0.76–0.94]	<0.001
Low SES	12923	362 (3%)	0.61 [0.54–0.69]	<0.001	0.67 [0.59–0.77]	<0.001	0.65 [0.57–0.74]	<0.001	0.67 [0.60–0.75]	<0.001
Ethnicity										
Native Dutch	46335	1659 (4%)	1 [ref]		1 [ref]		1 [ref]		1 [ref]	
Non-Western immigrant	1719	65 (4%)	1.06 [0.83–1.35]	0.660	0.89 [0.69–1.13]	0.330	0.78 [0.59–1.04]	0.093	0.91 [0.67–1.22]	0.523
Western immigrant	971	33 (4%)	0.95 [0.68–1.33]	0.760	0.82 [0.57–1.19]	0.290	0.77 [0.53–1.12]	0.168	0.75 [0.49–1.13]	0.170
Chemotherapy undertreatment										
	Number of patients with an indication for adjuvant CT ^a	Number of patients undertreated (%)								
SES										
High SES	15799	6151 (39%)	1 [ref]		1 [ref]		1 [ref]		1 [ref]	
Medium SES	20108	7455 (37%)	0.99 [0.98–0.99]	<0.001	1.00 [1.00–1.01]	0.600	1.01 [1.00–1.01]	0.066	1.01 [1.00–1.01]	0.049
Low SES	10192	3874 (38%)	0.99 [0.98–1.00]	0.140	1.01 [1.01–1.02]	<0.001	1.02 [1.01–1.03]	<0.001	1.01 [1.00–1.01]	<0.001
Ethnicity										
Native Dutch	46899	18054 (39%)	1 [ref]		1 [ref]		1 [ref]		1 [ref]	
Non-Western immigrant	2898	924 (32%)	0.95 [0.94–0.96]	<0.001	1.01 [1.00–1.03]	<0.001	1.01 [1.00–1.02]	0.032	1.00 [1.00–1.02]	0.268
Western immigrant	1251	500 (40%)	1.01 [0.99–1.03]	0.290	1.02 [1.01–1.04]	0.007	1.02 [1.00–1.03]	0.053	1.00 [0.99–1.03]	0.227

Adjusted for:

Model 1: unadjusted Poisson regression analysis for SES or ethnicity.

Model 2: model 1 + adjusting for the following clinicopathological factors: incidence year, age, morphology, invasive tumor grade, tumor size in categories (≤ 1 cm/ $1-2$ cm/ ≥ 3 cm), ER, PR, Her2 and axillary lymph-node involvement. All variables, except for age, were handled as categorical variables in the categories as depicted in the baseline tables or as stated in the brackets.

Model 3: mixed effect Poisson regression analysis including all variables of model 2, a random intercept per hospital and correcting for type of hospital (district/teaching/academic/topclinical) and region of treatment (12 specific regions in the Netherlands).

Model 4: fully adjusted mixed effect Poisson regression analysis including all clinicopathological and hospital factors, a random intercept per hospital and mutually adjusting for SES and ethnicity.

^aCT indication based on applicable treatment guideline at time of treatment. Patients with an indication for CT: patients under the age of 70 with lymph-node positive disease or lymph-node negative disease and unfavourable clinicopathological features.

Table 4. Relative risk (RR) for adjuvant endocrine therapy (ET) over- or under treatment in hormone-receptor positive surgically treated Dutch early-stage breast cancer patients with stadium I–IIc unifocal disease who did not receive neo-adjuvant systemic treatment									
			Unadjusted RR (95% CI)	P value	Model 2 RR (95% CI)	P value	Model 3 RR (95% CI)	P value	Model 4 RR (95% CI)
Endocrine therapy overtreatment									
	Number of patients without an indication for adjuvant ET ^a	Number of patients overtreated (%)							
SES			1 (ref)		1 (ref)		1 (ref)		1 (ref)
High SES	8945	938 (11%)	1.04 [0.96–1.13]	0.360	0.97 [0.87–1.07]	0.600	1.04 [0.94–1.14]	0.484	1.03 [0.94–1.14]
Medium SES	11234	1223 (11%)							0.517
Low SES	6718	987 (15%)	1.40 [1.29–1.52]	<0.001	1.05 [0.94–1.17]	0.370	1.06 [0.95–1.18]	0.332	1.02 [0.96–1.21]
Ethnicity			1 (ref)		1 (ref)		1 (ref)		1 (ref)
Native Dutch	28615	3664 (13%)	0.95 [0.81–1.11]	0.530	0.92 [0.75–1.13]	0.420	0.86 [0.69–1.06]	0.160	0.87 [0.69–1.09]
Non-Western immigrant	1191	145 (13%)	1.14 [0.94–1.37]	0.170	1.04 [0.82–1.33]	0.750	0.94 [0.70–1.27]	0.699	0.86 [0.62–1.19]
Western immigrant	673	98 (15%)							0.357
Endocrine therapy undertreatment									
	Number of patients with an indication for adjuvant ET ^a	Number of patients undertreated (%)							
SES			1 (ref)		1 (ref)		1 (ref)		1 (ref)
High SES	14662	1783 (12%)	1.00 [0.99–1.00]	0.790	1.00 [0.99–1.00]	0.660	1.01 [1.00–1.02]	0.004	0.99 [0.98–1.00]
Medium SES	19623	2368 (12%)	1.01 [1.00–1.01]	0.090	1.01 [1.00–1.01]	0.160	1.00 [1.00–1.01]	0.539	1.00 [0.99–1.01]
Low SES	12605	1618 (13%)							0.973
Ethnicity			1 (ref)		1 (ref)		1 (ref)		1 (ref)
Native Dutch	49690	6186 (13%)	1.00 [0.99–1.01]	0.900	1.01 [1.00–1.02]	0.080	1.01 [0.99–1.02]	0.307	1.01 [0.99–1.02]
Non-Western immigrant	2425	304 (13%)	1.01 [0.99–1.02]	0.490	1.01 [0.99–1.03]	0.320	1.01 [0.99–1.03]	0.381	1.00 [0.99–1.02]
Western immigrant	1196	157 (13%)							0.625
Adjusted for:									
Model 1: unadjusted Poisson regression analysis for SES or ethnicity.									
Model 2: model 1 + adjusting for the following clinicopathological factors: incidence year, age, morphology, invasive tumor grade, tumor size categories (≤1 cm/1–2 cm/≥3 cm), PR, Her2 and axillary lymph-node involvement. All variables, except for age, were handled as categorical variables in the categories as depicted in the baseline tables or as stated in the brackets.									
Model 3: mixed effect Poisson regression analysis including all variables of model 2, a random intercept per hospital and correcting for hospital type (district/teaching/academic/topclinical) and region of treatment (12 specific regions in the Netherlands).									
Model 4: fully adjusted mixed effect Poisson regression analysis including all clinicopathological and hospital factors, a random intercept per hospital and mutually adjusting for SES and ethnicity.									
^a ET indication based on applicable treatment guideline at time of treatment. Patients with an indication for ET: hormone receptor positive patients with lymph-node positive disease or lymph-node negative disease and unfavourable clinicopathological features.									

overtreated. We observed no ethnical disparities in AST guideline adherence in the Netherlands.

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