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Substantial increase in the use of adjuvant systemic treatment for early stage breast cancer reflects changes in guidelines in the period 1990–2006 in the southeastern Netherlands

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ABSTRACT

Background: This study evaluated trends in adjuvant systemic treatment among breast cancer patients and analyzed the factors on which treatment choice was based.
Patients and methods: Patients diagnosed with early stage breast cancer in 1990–2006 were selected from the registry of the Comprehensive Cancer Centre South (n = 8261). The probability of receiving therapy was determined per characteristic for the periods 1990–1997, 1998–2001 and 2002–2006, separately.
Results: The use of any adjuvant systemic treatment increased from 37% in 1990–1997 to 51% in 1998–2001 and 53% in 2002–2006 (p for trend < 0.0001). In the period 1990–1997, lymph node status (positive vs. negative: probability ratio (PR = 25.8; 95% CI, 16.5–40.4) and age ($\geqslant$ 60 vs. $\leqslant$ 35 years: PR = 0.01; 95% CI, 0.00–0.02) were the main determinants of the likelihood of receiving chemotherapy. From 1998 onwards, age remained the most important factor in decreasing the likelih
ood of receiving chemotherapy. During 1990–1997 the use of hormonal therapy was mainly determined by positive lymph node status (PR = 35; 95% CI, 25–49) and age ($\geqslant$ 70 vs. $\leqslant$ 35 years: PR = 9.3; 95% CI, 4.4–20), whereas positive hormone receptor status mainly affected hormonal therapy use (PR = 17; 95% CI, 10–28) in the period 2002–2006. Marked differences were observed between hospitals in the adoption of adjuvant systemic treatment for node–negative patients.
Conclusions: The impact of patient and tumour characteristics on treatment choice varied over time, reflecting major changes in the Dutch treatment guidelines. Patients older than 70 years received almost no chemotherapy.

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1. Introduction

As the majority of breast cancers are diagnosed at an early stage,[1] treatment is focused on cure and the prevention of relapse. Adjuvant chemotherapy and hormonal therapy have proven to be effective in preventing or delaying relapses and increasing survival in patients with early stage breast cancer.[2–4] Therefore, these therapies have become part of the treatment plan of many of these patients. Based on results from clinical trials and reviews, the guidelines for adjuvant systemic treatment have evolved over time and strategies have become more tumour and patient specific than ever before.[5,6]

Rising trends in the actual use of chemotherapy and hormonal therapy among breast cancer patients have been observed in the USA, regardless of lymph node and oestrogen receptor status.[7,8] Women with node-positive tumours and younger women were more likely to receive chemotherapy than women with node-negative tumours and older women.[7,8] Adjuvant systemic treatment for older women usually consisted of hormonal therapy alone and was given irrespective of the oestrogen receptor status of their tumours.[7]

Previous studies on factors influencing the choice of adjuvant systemic treatment in clinical practice found that increasing age decreased the likelihood of receiving chemotherapy,[8–10] that patients with a large tumour, positive lymph node status and negative hormone receptor status were more likely to receive chemotherapy[8,9,11] and that women with a positive hormone receptor status more often received hormonal therapy.[10,11]

This study was undertaken to assess the extent to which adjuvant systemic treatment patterns among women with early stage breast cancer have changed from 1990 to 2006 in the southeastern part of the Netherlands. Special attention was paid to the independent factors that played a role in the choice of treatment during three different time periods in which major changes in the guidelines occurred.

2. Patients and methods

The Comprehensive Cancer Centre South (Eindhoven Cancer Registry, CCCS) records data on all patients newly diagnosed with cancer in the southeastern part of the Netherlands, an area with 2.4 million inhabitants (about 15% of the Dutch population). This population-based registry is notified by six pathology departments, ten community hospitals and two radiotherapy institutes. Registration takes place around six months after diagnosis. Trained registry personnel actively collect data on diagnosis, staging and treatment from the medical records after notification by pathologists and medical registration offices. The infrastructure of, and good access to, Dutch health care facilities, together with the notification procedures used, have made it possible to establish cancer registries with a completeness exceeding 95%.[12]

All patients diagnosed with a breast tumour, defined as C50.0–C50.6 according to ICD-O-3, in the period 1990–2006 were selected from the database of the Comprehensive Cancer Centre South (CCCS). Only patients diagnosed with early stage breast cancer (stages I–IIIa) according to the International Union Against Cancer (UICC) TNM Classification of Malignant Tumours[13] were included in the study cohort.

Due to major changes in the Dutch guidelines for adjuvant systemic treatment in breast cancer in 1998 and 2002,[14,15] characteristics of the patients included in the study cohort were shown for the periods 1990–1997, 1998–2001 and 2002–2006, separately. Age at diagnosis was classified into five groups: $\leqslant$35, 36–49, 50–59, 60–69 and $\geqslant$70 years. The following tumour characteristics were recorded: tumour size ($\leqslant$1.0 cm, 1.1–2.0 cm, 2.1–5.0 cm and >5.0 cm), lymph node status (positive or negative), histologic tumour grade (well differentiated (low grade), moderately differentiated (intermediate grade) and poorly or undifferentiated (high grade)) and oestrogen receptor (ER) and progesterone receptor (PR) status (positive or negative). Moreover, the following treatments that patients received after diagnosis were defined: chemotherapy (yes/no), hormonal therapy (yes/no), radiation therapy (yes/no), breast surgery (breast-conserving surgery or mastectomy) and combinations of the aforementioned therapies. Serious comorbidity was recorded according to a slightly modified version of the Charlson classification[16] with classification based on the number of comorbidities at time of diagnosis (none, 1, $\geqslant$2). An indicator of socioeconomic status was provided at aggregated level for each postal code as described before.[17] Socioeconomic status was categorised as high, intermediate and low, and postal codes of care-providing institutions, such as nursing homes, were assigned to a separate category. Hospital of treatment was coded 1–7, including in this study only patients that were treated at the seven largest hospitals in the CCCS registry area.

2.1. *Analyses*

Patient and tumour characteristics are displayed according to the period of diagnosis. Trends in the distribution of the characteristics across the three periods (1990–1997, 1998–2001 and 2002–2006) were evaluated by *p*-value for linear trend computed by univariate logistic regression analyses, by categorising the diagnostic periods and characteristics as ordinal variables. Distribution of the adjuvant systemic treatment (chemotherapy only, hormonal therapy only, both chemotherapy and hormonal therapy or any adjuvant systemic treatment) is shown according to lymph node status, age and year of diagnosis. In these figures, age at diagnosis was classified into four groups: $\leqslant$35, 36–49, 50–69 and $\geqslant$70 years based on the Dutch breast cancer treatment guidelines.[14] The probability of receiving chemotherapy or hormonal therapy was determined per tumour and patient characteristic and presented by period of diagnosis. Since the parameter under study (receiving adjuvant systemic treatment) was not a rare event, odds ratios are not good approximations of probability ratios (risk ratios or prevalence ratios), as these overestimate the probability.[18] Probability ratios were therefore computed by SAS Proc Genmod using a modified Poisson regression approach. The following variables, which are considered to likely affect the use of adjuvant systemic treatment in breast cancer patients, were included in the model: age, tumour size, lymph node status, histologic tumour grade, hormone receptor status, non-systemic cancer therapies, number of comorbidities, socioeconomic status and hospital of treatment. Difference in the probability of receiving adjuvant systemic treatment within a characteristic was assessed by the chi-square test using Proc Genmod, whilst adjusting for the other characteristics.

Table 1 – Distribution of patient and tumour characteristics of women with early stage breast cancer, according to period of diagnosis

Characteristics	Period of diagnosis			
	1990–1997	1998–2001	2002–2006	*p*-Value for linear trend
	(*N* = 3281)%	(*N* = 2034)%	(*N* = 2946)%	
Age				0.960
⩽35 years	4	3	3	
36–49 years	25	24	26	
50–59 years	25	25	27	
60–69 years	25	23	22	
⩾70 years	21	26	22	
Tumour size				<.0001
⩽1.0 cm	15	21	19	
1.1–2.0 cm	42	43	44	
2.1–5.0 cm	40	33	34	
>5.0 cm	3	3	3	
Lymph node status				0.434
Positive	37	39	38	
Negative	59	58	58	
Unknown	4	3	4	
Histologic tumour grade				<.0001
Well	5	14	26	
Moderate	15	24	36	
Poor	15	20	20	
Unknown	65	42	18	
Hormone receptor status				<.0001
ER+ and/or PR+	60	67	80	
ER- and PR-	11	12	16	
Unknown	29	21	4	
Non-systemic cancer therapies				<.0001
BCS alone	2	4	3	
BCS and RT	51	57	62	
Mastectomy alone	29	26	22	
Mastectomy and RT	16	12	10	
Other/none/unknown	3	2	3	
Therapy				<.0001
S	23	16	10	
S + RT	40	33	36	
S + RT + ST	28	36	36	
S + ST	8	14	15	
ST	1	1	2	
Other/none/unknown	0	0	1	
Number of comorbidities				<.0001
None	48	61	56	
1	15	22	21	
⩾2	5	10	12	
Unknown	33	7	11	
Socioeconomic status				0.038
High	30	29	31	
Intermediate	38	40	41	
Low	28	26	23	
Institutionalised (nursing homes)	4	4	4	
Unknown	0	0	2	
Hospital of treatment				0.805
1	14	15	14	
2	12	11	11	
3	17	18	15	
4	6	5	7	
5	15	16	18	
6	13	13	13	
7	23	22	22	

ER: Oestrogen receptor; PR: Progesterone receptor; BCS: Breast-conserving surgery; RT: Radiation therapy; S: surgery; ST: systemic therapy.

Variation in administration of any adjuvant systemic treatment in the seven hospitals was determined over time. Results in the Tables are presented by period of diagnosis (1990–1997, 1998–2001 and 2002–2006) and in the Figures by year of diagnosis. For all analyses the SAS/STAT® statistical software (SAS system 8.2, SAS Institute, Cary, NC) was used.

3. Results

Table 1 lists the patient and tumour characteristics of the 8,261 women with early stage breast cancer included in the study, according to period of diagnosis. The use of adjuvant systemic treatment, irrespective of the type, increased from 37% in 1990–1997 to 51% in 1998–2001 and 53% in 2002–2006 (p for trend <0.0001). The mean age at diagnosis was similar for all three periods (58, 59 and 58 years, respectively). Size of the breast tumours at diagnosis decreased significantly over time (p for trend <0.0001). When not taking into account the large proportion of patients with an unknown histologic tumour grade or hormone receptor status, the proportion of patients with a well-differentiated tumour increased from 14% in 1990–1997 to 32% in 2002–2006, whilst the percentage

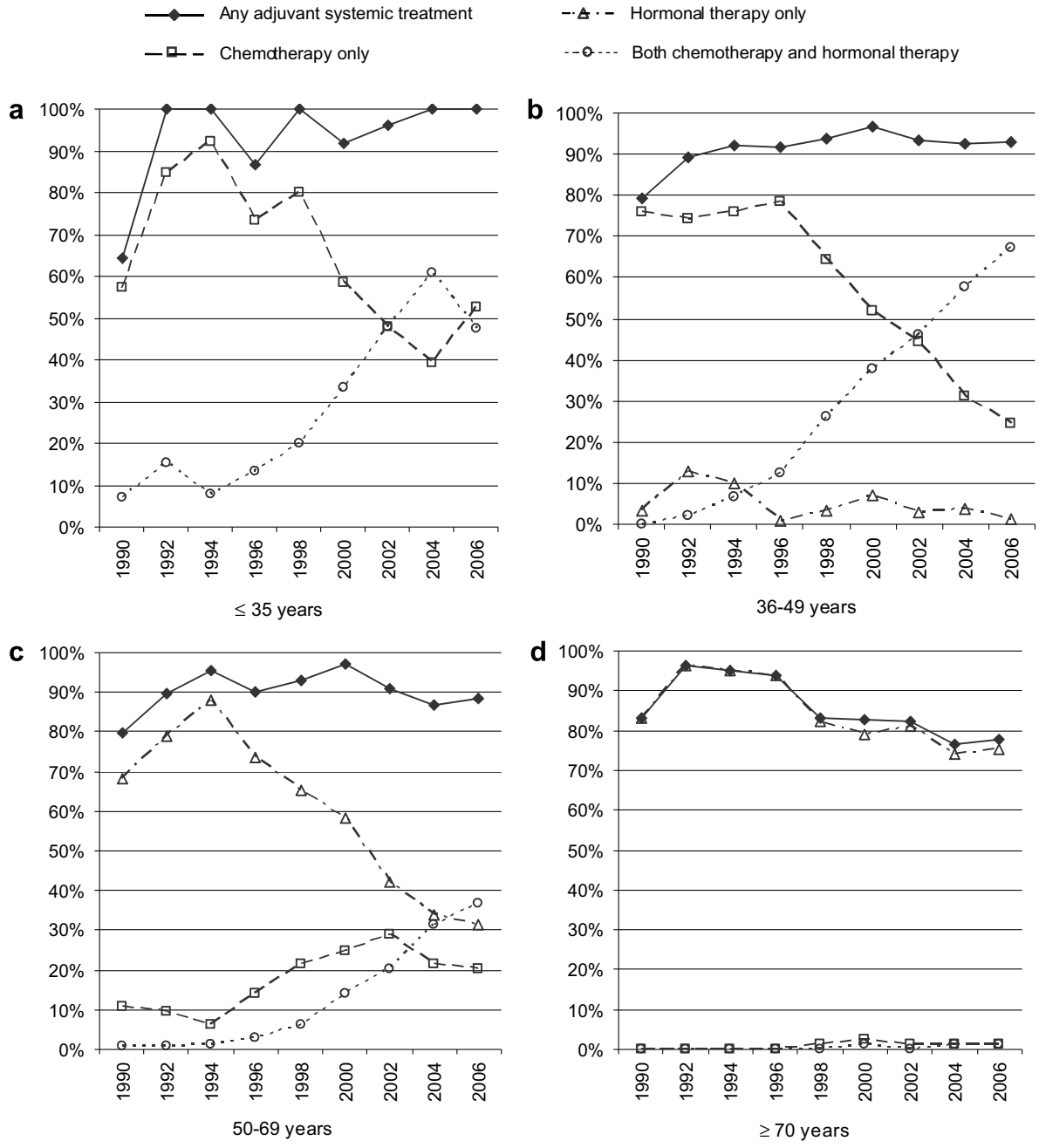

Fig. 1 – Proportion of women with early stage node-positive breast cancer receiving adjuvant systemic treatment, by age and year of diagnosis. Chemotherapy, hormonal therapy and both are mutually exclusive, any adjuvant systemic treatment is the sum of the three aforementioned. Age categories are based on the Dutch breast cancer treatment guidelines.[14]

of women with ER- and/or PR-positive tumours was stable over time, with 85% in 1990–1997 and 84% in 2002–2006. The percentage of women with breast-conserving surgery and radiation therapy increased, whilst the percentage of women with mastectomy, with or without radiation therapy, decreased (p for trend <0.0001). Breast cancer therapy combinations including systemic therapy increased significantly over time (p for trend <0.0001).

Figs. 1a–d and 2a–d present the time trends in adjuvant systemic treatment by age category and year of diagnosis for women with early stage breast cancer with positive nodes (Fig. 1) or negative nodes (Fig. 2), excluding 298 patients for whom information on lymph node status was not available. Amongst patients ⩽35, 36–49 and 50–69 years with node-positive breast cancer, the percentage receiving both hormonal therapy and chemotherapy increased over time, being 47%, 67% and 37%, respectively, in 2006. Of the patients of 70 years and older, less than 2% received chemotherapy. For node-negative patients, the percentage receiving any adjuvant systemic treatment increased for all age groups from 1996

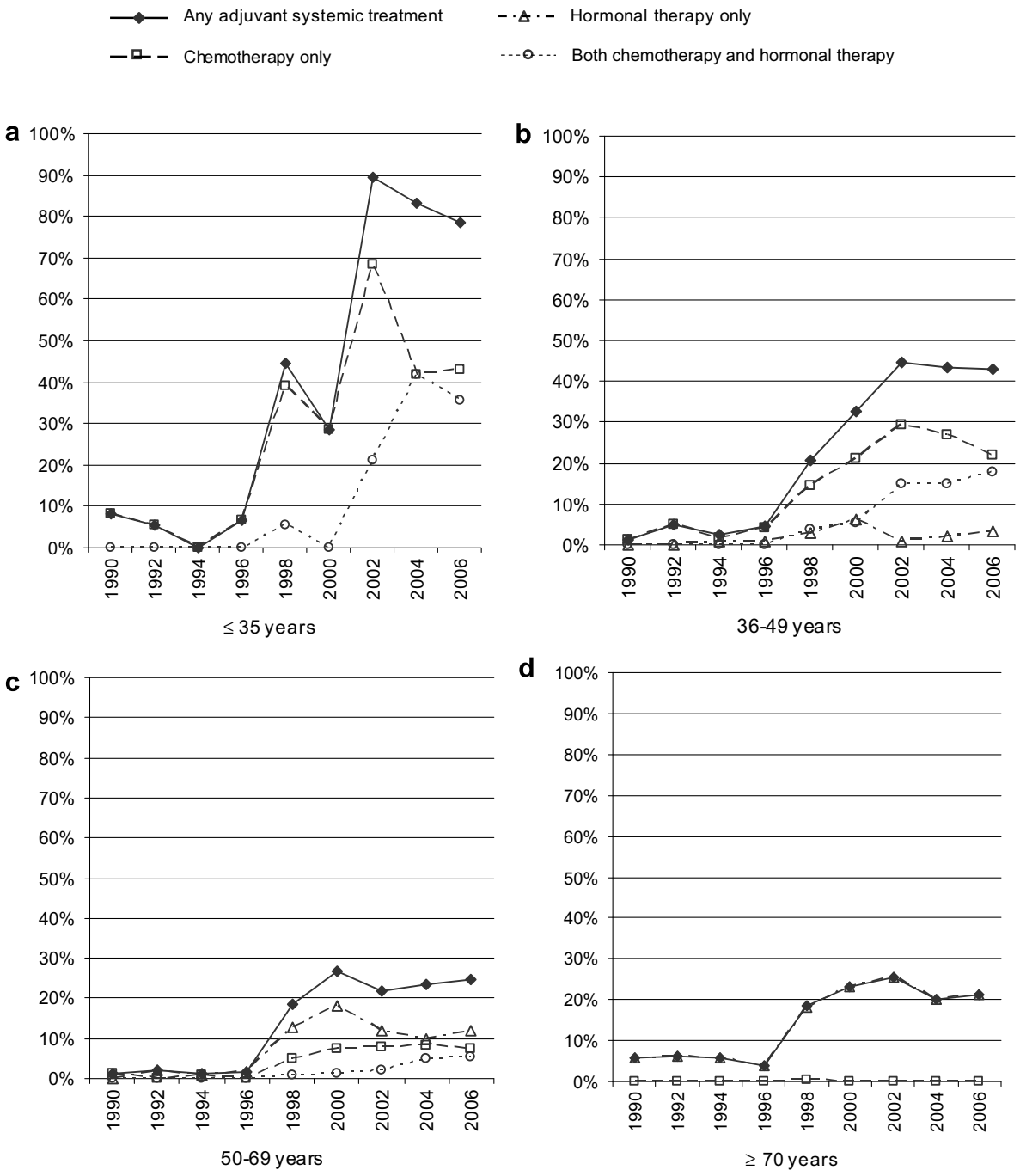

Fig. 2 – Proportion of women with early stage node-negative breast cancer receiving adjuvant systemic treatment, by age and year of diagnosis. Chemotherapy, hormonal therapy and both are mutually exclusive, any adjuvant systemic treatment is the sum of the three aforementioned. Age categories are based on the Dutch breast cancer treatment guidelines.[14]

onwards and seemed to stabilise around 2000 for patients 50 years and older with approximately 23% usage, and around 2002 for patients younger than 50 years with approximately 44% usage for patients 36–49 years and approximately 83% usage for patients ⩽35 years. None of the node-negative patients aged ⩾70 years received chemotherapy in the period 1990–2006.

The independent predictors of the probability of receiving chemotherapy changed over time, as presented in Table 2. Decrease in the use of chemotherapy with advancing age was seen in 1990–1997 as well as in 1998–2001 and 2002–2006. In the period 1990–1997, positive lymph node status and younger age were the only significant predictors for the use of chemotherapy. From 1998 onwards, increasing tumour size, poor tumour differentiation and negative hormone receptor status were additional factors that were positively associated with the probability of receiving chemotherapy, taking into account non-systemic cancer therapies (breast-conserving surgery, mastectomy and radiation therapy), number of comorbidities, socioeconomic status and hospital of treatment. Univariate analyses showed that in all three periods, patients with comorbidity compared to patients without comorbidity and patients with a low socioeconomic status, or who were institutionalised at the time of diagnosis, compared to patients with a high socioeconomic status were less likely to receive chemotherapy. Moreover, univariate analyses showed a difference in the administration of chemotherapy between the seven hospitals. However, these differences were no longer significant after adjustment for potential confounders in the multivariate analyses.

Results of the multivariate analyses of the characteristics that influence the probability to receive hormonal therapy are shown in Table 3. The use of hormonal therapy in the period 1990–1997 was determined by the presence of positive lymph nodes, increasing age and positive hormone receptor status. In the period 1998–2001, additional predictors of the probability to receive hormonal therapy were increasing tumour size and poor differentiation of the tumour. In 2002–2006 age had become a less important factor in the choice of hormonal therapy use compared to the other two periods, and a positive hormone receptor status became the most important factor determining hormonal therapy use. Non-systemic cancer therapies, the number of comorbidities, socioeconomic status and hospital of treatment were also included in the multivariate model but showed no significant relation with the use of hormonal therapy.

Table 2 – Probability of receiving adjuvant chemotherapy[a] for women diagnosed with early stage breast cancer by tumour and patient characteristics, according to period of diagnosis

Characteristics	1990–1997		1998–2001		2002–2006	
	PRadj	(95% CI)	PRadj	(95% CI)	PRadj	(95% CI)
Age						
⩽35 years	1	–*	1	–*	1	–*
36–49 years	0.92	(0.81–1.1)	1.2	(0.95–1.5)	0.94	(0.82–1.1)
50–59 years	0.24	(0.19–0.31)	0.68	(0.53–0.86)	0.66	(0.57–0.76)
⩾60 years[b]	0.01	(0.00–0.02)	0.13	(0.09–0.19)	0.14	(0.11–0.18)
Tumour size (cm)						
⩽1.0	1	–	1	–**	1	–*
1.1–2.0	1.2	(0.89–1.6)	1.5	(1.1–1.9)	1.8	(1.4–2.1)
2.1–5.0	1.2	(0.88–1.6)	1.7	(1.3–2.2)	2.2	(1.8–2.6)
>5.0	1.2	(0.86–1.7)	2.1	(1.5–2.9)	2.3	(1.8–3.0)
Lymph node status						
Negative	1	–*	1	–*	1	–*
Positive	26	(17–40)	3.6	(3.0–4.3)	2.3	(2.1–2.6)
Histologic tumour grade						
Well	1	–	1	–*	1	–*
Moderate	1.1	(0.76–1.6)	1.3	(0.97–1.7)	1.4	(1.2–1.7)
Poor	1.3	(0.98–2.0)	1.7	(1.3–2.3)	2.2	(1.8–2.5)
Unknown	1.2	(0.88–1.7)	1.3	(0.96–1.7)	1.6	(1.3–1.9)
Hormone receptor status						
ER+ and/or PR+	1	–	1	–*	1	–*
ER- and PR-	1.2	(0.99–1.4)	2.1	(1.8–2.4)	1.6	(1.4–1.7)
Unknown	1.1	(0.96–1.2)	0.61	(0.48–0.77)	0.82	(0.57–1.2)

PRadj: Probability Ratio, adjusted for age, tumour size, lymph node status, histologic tumour grade, hormone receptor status, non-systemic cancer therapies, number of comorbidities, socioeconomic status and hospital of treatment; 95% CI: 95% Confidence interval; ER: Oestrogen receptor; PR: Progesterone receptor. Due to low numbers, patients with tumour size 'unknown' and lymph node status 'unknown' were deleted from the analysis ($N = 3$).

*$p < 0.0001$; **$p = 0.0001$–0.001: Statistically significant difference in the probability of receiving chemotherapy within the categories of that specific characteristic.

a Chemotherapy alone, or in combination with hormonal therapy.

b Patients aged 60–69 years and ⩾70 years have been grouped together due to low number of patients older than 70 years receiving chemotherapy.

There were no large differences observed between the hospitals in the administration of any adjuvant systemic treatment for early stage node-positive breast cancer patients in the period 1990–2006. For node-negative breast cancer patients, marked differences were seen between the seven hospitals of treatment (see Fig. 3). Node-negative breast cancer patients treated in hospitals which were early adopters of the guidelines (hospitals 1, 3 and 6) were more likely to

Table 3 – Probability of receiving adjuvant hormonal therapy[a] for women diagnosed with early stage breast cancer by tumour and patient characteristics, according to period of diagnosis

Characteristics	1990–1997		1998–2001		2002–2006	
	PRadj	(95% CI)	PRadj	(95% CI)	PRadj	(95% CI)
Age						
⩽35 years	1	–*	1	–*	1	–**
36–49 years	1.2	(0.53–2.6)	1.5	(0.82–2.6)	0.90	(0.73–1.1)
60–69 years	6.7	(3.2–14)	2.7	(1.5–4.7)	0.92	(0.75–1.1)
50–59 years	8.1	(3.8–17)	3.3	(1.9–-5.8)	1.0	(0.83–1.3)
⩾ 70 years	9.3	(4.4–20)	3.3	(1.9–5.9)	1.1	(0.88–1.3)
Tumour size						
⩽1.0 cm	1	–	1	–*	1	–*
1.1–2.0 cm	1.2	(1.0–1.4)	1.5	(1.2–1.8)	1.7	(1.4–2.1)
2.1–5.0 cm	1.2	(0.99–1.4)	1.5	(1.3–1.9)	2.3	(1.9–2.7)
>5.0 cm	1.2	(0.99–1.5)	1.9	(1.4–2.4)	2.2	(1.7–2.7)
Lymph node status						
Negative	1	–*	1	–*	1	–*
Positive	35	(25–49)	3.7	(3.2–4.3)	2.9	(2.6–3.2)
Unknown	18	(12–27)	2.3	(1.7–-3.1)	2.5	(2.0–-3.2)
Histologic tumour grade						
Well	1	–	1	–*	1–	–*
Moderate	1.1	(0.94–1.3)	1.3	(1.1–1.5)	1.3	(1.1–1.4)
Poor	1.1	(0.95–1.3)	1.6	(1.3–1.9)	1.7	(1.5–1.9)
Unknown	1.1	(0.94–1.3)	1.2	(1.0–1.4)	1.2	(1.0–1.4)
Hormone receptor status						
ER+ and/or PR+	1	–**	1	–*	1	–*
ER- and PR-	0.84	(0.74–0.96)	0.2	(0.14–0.30)	0.06	(0.04–0.10)
Unknown	0.94	(0.86–1.0)	0.6	(0.47–0.63)	0.45	(0.33–0.61)

PRadj: Probability Ratio, adjusted for age, tumour size, lymph node status, histologic tumour grade, hormone receptor status, non-systemic cancer therapies, number of comorbidities, socioeconomic status and hospital of treatment; 95% CI: 95% Confidence interval; ER: Oestrogen receptor; PR: Progesterone receptor. Due to low numbers, patients with tumour size 'unknown' were deleted from the analysis ($N = 2$).

*$p < .0001$; **$p = 0.01$–0.05: Statistically significant difference in the probability of receiving hormonal therapy within the categories of that specific characteristic.

a Hormonal therapy alone, or in combination with chemotherapy.

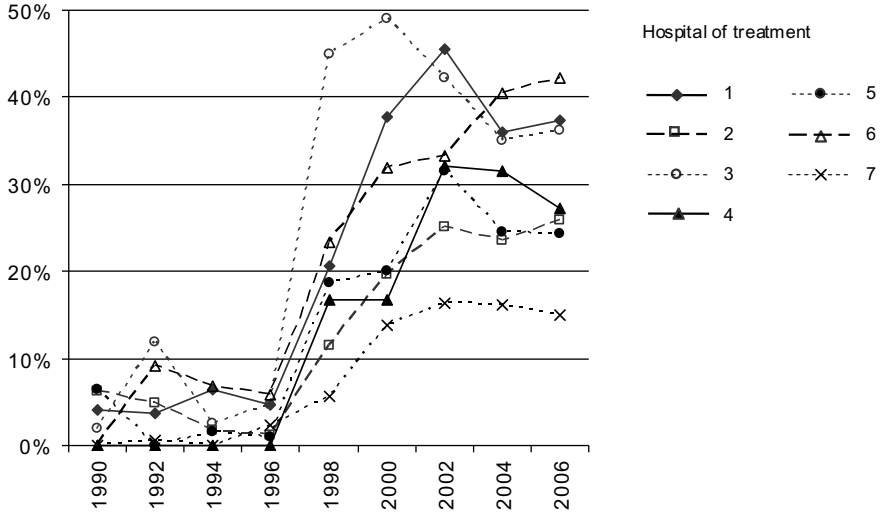

Fig. 3 – Proportion of women with early stage node-negative breast cancer receiving adjuvant systemic treatment (chemotherapy and/or hormonal therapy), by hospital of treatment and year of diagnosis.

receive any adjuvant systemic therapy compared with patients treated in hospital 7, which was a late adopter of the treatment guidelines. This was seen in the period 1998–2001 as well as in the period 2002–2006, after adjustment for potential confounders (PR 2.5; 95% CI 1.7–3.6 and PR 1.5; 95% CI 1.3–1.9, respectively).

4. Discussion

The use of adjuvant systemic treatment for patients with early stage breast cancer increased significantly over time, from 37% in the period 1990–1997, to 53% in 2002–2006. This increase differed according to patients' age and tumour characteristics. In the earlier years (1990–1997) age and lymph node status were the most important determinants in the choice of adjuvant systemic treatment, whilst from 1998 onwards the decision became increasingly dependant on the hormone receptor status, tumour size and histologic tumour grade, which is in accordance with the incorporation of these factors in the treatment guidelines.[14] Whilst several studies have demonstrated the impact of guidelines on the use of adjuvant systemic treatment in clinical practice,[7,8,19–22] this study is the first to quantify relative effect estimates by calculating adjusted probability ratios in three subsequent time periods, characterised by major changes in treatment guidelines.

During the whole study period, age remained the most important factor in the decision whether or not a patient should receive chemotherapy. Like in previous published studies, the use of chemotherapy, alone or in combination with hormonal therapy, decreased with increasing age.[3,7–9,20,21,23–26] The fact that older women are less likely to be treated with adjuvant chemotherapy may be explained by many factors, including comorbidities and lack of evidence for the benefit of chemotherapy for women aged 70 years and older.[3,7,8,10,20,21,23,27,28]

The use hormonal therapy, however, was much less dependant on age: in the period 2002–2006 age was no longer a significant predictor of the use of hormonal therapy, which is in accordance with the findings of other studies.[25,29] Over the years, the hormone receptor status became the most important factor to determine whether or not a patient should receive therapy. This is in line with the guidelines, recommending only hormonal therapy for patients with a breast tumour with a positive hormone receptor status from 1998 onwards.[14]

Next to the patient and tumour characteristics shown in Tables 2 and 3, which are incorporated in the current guidelines, several other factors that may influence the choice of adjuvant systemic treatment in clinical practice, such as comorbidity, socioeconomic status and hospital of treatment, have been taken into account in this study. In our study, comorbidity was no longer associated with the use of adjuvant systemic treatment after adjusting for potential confounders, whilst previous studies found a small, though significant, decrease in the likelihood of receiving chemotherapy when comorbidity was present.[3,8,9] For node-negative breast cancer patients, this study found marked differences in the use of adjuvant systemic treatment between the seven community hospitals in the southeastern part of the Netherlands. The observed pattern illustrates that there have been early and late adopters of the treatment guidelines, despite the coordinating role of the CCCS in the diffusion of the guidelines in this area. Whether this variation is due to the physicians based in these hospitals or other hospital characteristics could not be determined from the data used in this study.

HER2/neu is a tumour marker that plays a role in predicting the response to specific adjuvant systemic treatments for women with breast cancer.[30] No trend could be evaluated for this tumour characteristic as HER2/neu status was not available in the registry in all three time periods (1990–1997, 1998–2001 and 2002–2006). In the near future, HER2/neu overexpression should be included in studies analysing factors associated with the use of adjuvant systemic treatment for patients with early stage breast cancer, as more clinicians will be considering it when deciding which adjuvant systemic treatment options should be offered to their patients.

In conclusion, trends in adjuvant systemic treatment over a large period of time (1990–2006) showed that treatment with hormonal therapy and chemotherapy increased over time, especially for patients with node-negative breast cancer. In the earlier years (1990–1997) the probability of receiving adjuvant systemic treatment was mainly determined by age and lymph node status, whilst from 1998 onwards, hormone receptor status, tumour size and histologic tumour grade were also taken into account when deciding if and which systemic therapy options should be offered to a patient. Patient's age remained an important factor when deciding on the use of chemotherapy and, as is reflected by the marginal use in patients $\geqslant$70 years, most clinicians do not consider it to be an effective treatment option for their elderly patients. Moreover, hospital variation showed that there were early and late adopters of the treatment guidelines in clinical practice, despite the coordinating role of the CCCS in the diffusion of the guidelines in southeastern part of the Netherlands.

Conflict of interest statement

Ms. M.P.P. Sukel and Dr. RMC Herings are employees of the PHARMO Institute for Drug Outcomes Research. This research institute performs financially supported studies for several pharmaceutical companies. This study, however, was performed as part of the Ph.D programme of Ms. M.P.P. Sukel, initiated by Dr. L.V. van de Poll-Franse and Prof. Dr. J.W.W. Coebergh of the Comprehensive Cancer Centre South and was not financially supported by any pharmaceutical company.

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