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Breast Cancer

Lack of Survival Gain for Elderly Women with Breast Cancer

ESTHER BASTIAANNET,[a,b] JOHANNEKE E.A. PORTIELJE,[d] CORNELIS J.H. VAN DE VELDE,[a] ANTON J.M. DE CRAEN,[b] SUSANNE VAN DER VELDE,[a] PETER J.K. KUPPEN,[a] LYDIA G.M. VAN DER GEEST,[e] MARYSKA L.G. JANSSEN-HEIJNEN,[f] OLAF M. DEKKERS,[c] RUDI G.J. WESTENDORP,[b] GERRIT-JAN LIEFERS[a]

Departments of [a]Surgery, [b]Gerontology & Geriatrics, and [c]Clinical Epidemiology, Leiden University Medical Centre, Leiden, The Netherlands; [d]HAGA Hospital, Den Haag, The Netherlands; [e]Comprehensive Cancer Centre West Leiden, Leiden, The Netherlands, [f]Research, Eindhoven Cancer Registry, Comprehensive Cancer Centre South Eindhoven, Eindhoven, The Netherlands

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ABSTRACT

Background. **The number of elderly women with breast cancer is increasing and will become a major health concern. However, little is known about the optimal treatment for this age group. The aim of this study was to describe time trends for the overall Dutch breast cancer cohort with an emphasis on differences between young and elderly patients.**

Methods. **All adult female patients diagnosed in 1995–2005 were selected from the Netherlands Cancer Registry. Relative excess risks for death (adjusted for stage, histology, treatment, and grade) were estimated using a multivariate generalized linear model with a Poisson distribution, based on collapsed relative survival data, using exact survival times.**

Results. **Overall, 127,805 patients were included. Treatment of patients aged ≥75 years changed significantly over time: they received less surgery, more adjuvant hormonal treatment and chemotherapy, and more hormonal treatment without surgery. In contrast to younger patients, the relative survival did not improve significantly over time for elderly patients. With increasing age, the observed–expected death ratio decreased to almost 1.0.**

Conclusion. **Survival for elderly patients with breast cancer did not improve significantly. Observed–expected death ratios in the elderly are close to 1, indicating that excess mortality is low. Elderly patients with breast cancer have a higher risk for overtreatment and undertreatment, with a delicate therapeutic balance between breast cancer survival gain and potential toxicities. To improve breast cancer survival in the elderly, a critical reappraisal is needed of costs and benefits of hormonal as well as other treatments, and better selection of patients who can benefit from available therapies is warranted.** ***The Oncologist*** 2011; 16:415–423

Correspondence: Gerrit-Jan Liefers, M.D., Ph.D., Department of Surgery, Leiden University Medical Centre, P.O. Box 9600, 2300 RC Leiden, The Netherlands. Telephone: 0031-71-526-2309; Fax: 0031-71-526-6750; e-mail: g.j.liefers@lumc.nl Received July 16, 2010; accepted for publication February 11, 2011; first published online in ***The Oncologist*** *Express* on March 15, 2011. 1083-7159/2011/$30.00/0 doi: 10.1634/theoncologist.2010-0234

INTRODUCTION

In the western world, breast cancer survival has increased considerably over the last decades. The improved outcome for breast cancer patients has generally been attributed to better treatment options and the introduction of large-scale screening programs. Despite growing interest in elderly patients with breast cancer, little is known about the optimal treatment for this age group, and internationally agreed upon evidence-based recommendations do not exist [1]. Several publications have shown that improved survival has not been seen for elderly patients with breast cancer [2, 3]. On a similar note, a recent European study showed a significant improvement in survival from 1988 to 1999 for a variety of cancers, but at a slower rate for elderly patients [4].

The lack of survival improvement for elderly patients might be caused by undertreatment of this age group, with fewer patients receiving adequate local therapy and adjuvant therapy [5–8]. Elderly patients may, on the other hand, be at risk for overtreatment. Because of competing causes of death, elderly patients who suffer from breast cancer may die more often *with* cancer instead of *from* cancer than younger patients. Therefore, adequate cancer treatments may have a limited effect on survival in elderly patients. Because of the balance between treatment effects and side effects in terms of morbidity and mortality in elderly patients, especially in those with multiple diseases, aggressive treatment may not result in benefit.

We hypothesized that, in line with developments in younger patients, treatment of elderly patients with breast cancer has intensified in the past two decades. In order to evaluate the impact of treatment trends on survival, we studied a cohort of elderly female patients diagnosed with breast cancer in the Netherlands in 1995–2005 and compared their death rates with those of the age-matched general female population.

METHODS

Study Population

Patients were selected from the database of the Netherlands Cancer Registry. This nationwide Dutch network and registry of histo- and cytopathology regularly submits reports of all diagnosed malignancies to regional cancer registries. The national hospital discharge databank, which receives discharge diagnoses of admitted patients from all Dutch hospitals, completes case ascertainment. After notification, trained registry personnel collect data on diagnosis, staging, and treatment using the registration and coding manual of the Dutch Association of Comprehensive Cancer Centers. From this database, adult female patients with their first primary breast cancer diagnosed in 1995–2005 were selected. Patients with a previous history of other malignancies were excluded. The mass mammographic screening program in the Netherlands started in 1990–1991 for women aged 50–70 years; in 1997, the upper age limit of the screening program was increased to 75 years. In the Netherlands, the indication for adjuvant tamoxifen, in addition to node-positive disease, came to include women with hormone receptor–positive disease and node-negative high-risk breast cancer in 1992. Additionally, the adjuvant treatment duration was extended to 5 years instead of 2 years around 1996–1997.

Statistical Analysis

Breast cancer incidence was calculated per 100,000 women according to age category (15–64, 65–69, 70–74, 75–79, 80–84, 85–89, and ≥90 years) for the period 1995–2005. Trends in incidence rates were estimated based on linear regression of the log-transformed incidence rates with year of diagnosis as the regressor variable. The regression coefficient for year of diagnosis was used to calculate the estimated annual percentage change (EAPC). Stage was divided according to the tumor–node–metastasis (TNM) classification in the year of diagnosis. Pathological T, N, and M stage was used; if pathology was missing, clinical stage was used. Surgical treatment was divided into breast-conserving surgery (BCS), mastectomy, no surgery, and no treatment at all. Adjuvant chemotherapy or hormonal treatment was registered in patients who received surgery. Hormonal therapy as monotherapy was defined as the treatment for patients who only received (any kind of) hormonal treatment without surgery, chemotherapy, or radiotherapy. Adjuvant radiotherapy was registered for patients who received BCS, because this should be part of the treatment according to guidelines. Changes over time for treatment were tested using a linear model with separate years in the model.

Vital status and date of last follow-up were established either directly from the patient's medical record or through linkage of cancer registry data with municipal population registries (follow-up until January 1st, 2008), which record information on vital status. Relative survival is the preferred way to describe the prognosis of elderly patients with breast cancer, because it takes into account the risk for dying from causes other than the breast cancer [8]. Relative survival was calculated by the Hakulinen method as the ratio of the survival observed among the cancer patients and the survival that would have been expected based on the corresponding (age, sex, and year) general population. National life tables were used to estimate expected survival (Ederer II method). The relative excess risk (RER) for death by year of diagnosis was estimated using a multivariate

generalized linear model with a Poisson distribution, based on collapsed relative survival data, using exact survival times. The RER per year was adjusted for stage, histology, treatment, and grade. Relative mortality was calculated as the number of observed deaths during a 5-year interval divided by the number of expected deaths based on the corresponding general population.

Results

Overall, 127,805 patients were included in the study. Table 1 shows their characteristics; 38.6% of patients were aged ≥65 years at the time of diagnosis. Figure 1 shows the incidence according to age for invasive and in situ breast cancer. There was a small increase in the incidence of invasive breast cancer for patients aged 15–64 years, with an EAPC of 1.2% ($p < .001$), and for patients aged 65–74 years (EAPC, 1.9%; $p = .02$). For patients aged 75–84 years, the incidence of invasive breast cancer decreased over time, with an EAPC of −1.6% ($p = .02$). In contrast, the breast cancer incidence increased strongly in patients aged ≥85 years (EAPC, 3.2%; $p = .001$). For in situ breast cancer, the incidence increased for patients aged 15–64 years (EAPC, 1.8%; $p = .01$). For patients aged 65–74 years, the incidence of in situ breast cancer strongly increased, with an EAPC of 6.2% ($p = .001$), probably as a result of the increased upper age limit for screening. For patients aged 75–84 years, the EAPC was 2.4% ($p = .01$). For the oldest elderly, the incidence of in situ breast cancer showed a decreasing trend over time (EAPC, −3.1%; $p = .07$).

Supplemental online Figure 1 shows stage at diagnosis over time for the period 1995–2005 according to age. Patients aged <70 years usually presented with stage I disease; the stage distribution did not change over time. The number of patients who presented with stage I disease at ages 70–74 years increased significantly ($p < .001$). There were no large changes in the stage distribution for patients aged 75–79 years and 80–84 years. Over time, the number of patients with an unknown stage of disease decreased for patients aged ≥85 years.

Table 1. Characteristics of a Dutch cohort of 127,805 patients diagnosed with breast cancer

Characteristic	*n*	Percentage
Age (yrs)		
15–64	78,449	61.4
65–69	13,029	10.2
70–74	12,550	9.8
75–79	9,682	7.6
80–84	7,883	6.2
85–89	4,509	3.5
90+	1,703	1.3
Year		
1995	10,183	8.0
1996	10,475	8.2
1997	10,610	8.3
1998	10,944	8.6
1999	11,762	9.2
2000	11,923	9.3
2001	12,314	9.6
2002	12,100	9.5
2003	12,299	9.6
2004	12,652	9.9
2005	12,543	9.8
Morphology		
Ductal	89,471	70.0
Lobular	13,648	10.7
Other/combined/unknown	24,686	19.3
Invasive/in situ		
In situ (ductal/lobular)	10,518	8.2
Invasive	117,287	91.8
Grade		
1	15,748	12.3
2	37,524	29.4
3	34,904	27.3
Unknown	39,629	31.0
Overall	127,805	100

Treatment

Table 2 shows the treatment of breast cancer patients in The Netherlands over time, according to age. Table 2A shows the percentage of patients who received surgery; there was a slight but significant increase for the youngest patients ($p < .001$). There was no significant change over time for patients aged 65–74 years. However, for women aged ≥75 years, the percentage of patients who were operated upon significantly decreased over time.

Table 2B and 2C show the percentage of patients who received adjuvant chemotherapy or hormonal therapy in the cohort of patients who received surgery. For adjuvant hormonal treatment (during the study period, primarily tamoxifen), there was a significant increase in patients aged <70 years. For patients aged 70–74 years, there was no significant change after adjusting for stage. There was a significant increase for patients aged 75–84 years. For the oldest elderly, aged ≥85 years, there were no significant changes over time. For adjuvant chemotherapy, there was an increase over the years for all ages, although the percentage of the oldest elderly who received adjuvant chemotherapy remained low.

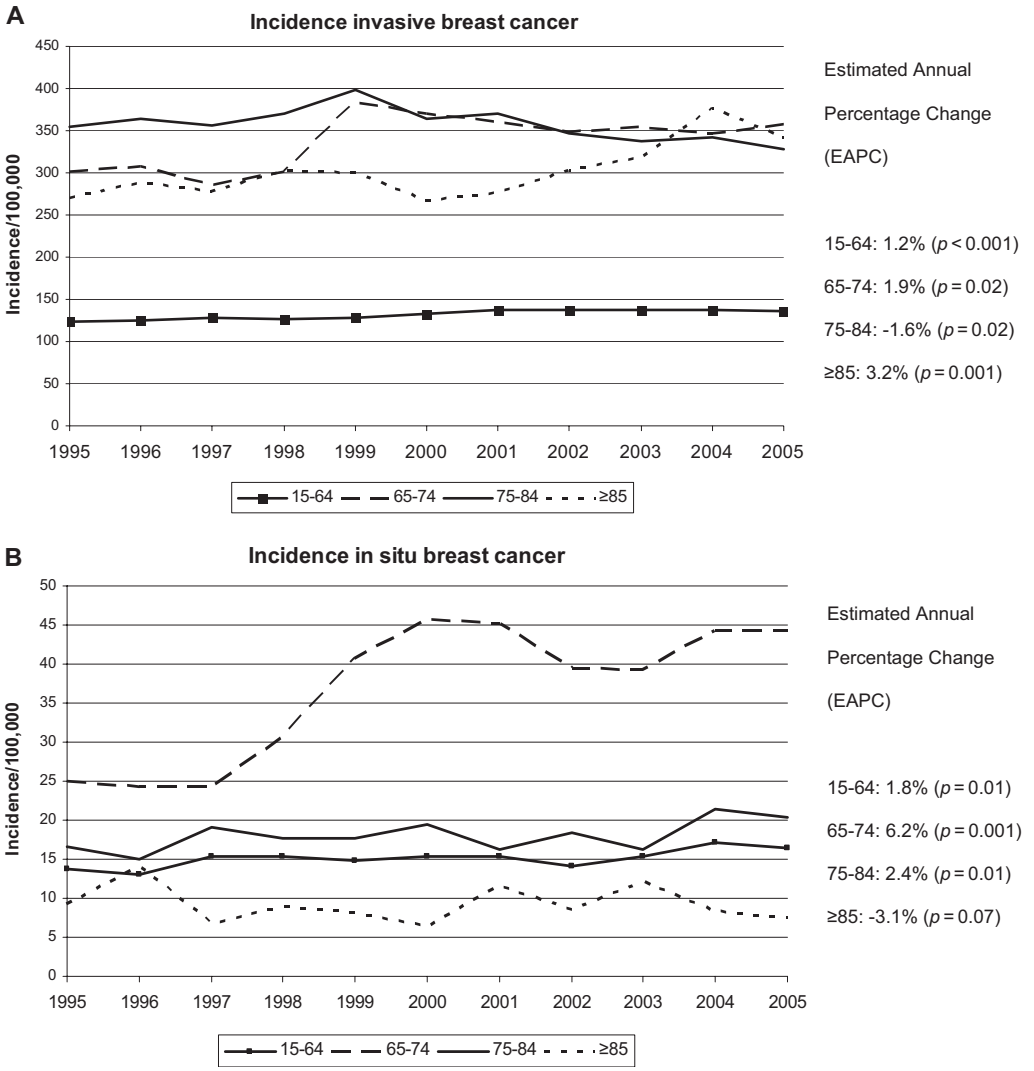

Figure 1. Incidence of invasive breast cancer **(A)** and in situ breast cancer **(B)** in The Netherlands in 1995–2005 according to age.

Table 2D shows the percentage of patients who received only hormonal therapy. For patients aged <75 years, there were no significant changes over time; however, for patients aged ≥75 year, the percentage of patients who received hormonal treatment as their only therapy increased significantly.

Table 2E shows the percentage of patients who received radiotherapy after BCS over time; for patients in all age groups, there was a significant increase, although the absolute number of patients aged ≥85 years receiving radiotherapy remained low.

Survival

Table 3 shows the 5-year relative survival over time according to age. The relative survival improved significantly over time for all patients up to age 79 years. For patients aged ≥80 years, the relative survival did not increase significantly over time. The RER for year of diagnosis remained significant after adjustment for stage, grade, histology, and treatment for patients aged <79 years, with RERs of 0.93–0.98 per year. The RER for year of diagnosis for patients aged ≥80 years was 0.99 per year and not significant. Figure 2 shows the observed–expected death ratios over time according to age. For all stages of disease, the observed–expected death ratio decreased with increasing age. Over time, the ratio decreased for most stages of disease for all patients up to age 74 years. For patients aged 75–84 years, the ratio decreased for stage II and stage IV patients, but remained stable for stage III patients. For the lower stages (in situ and stage I), the ratio decreased. For patients aged ≥85 years, the ratio did not change over time. Supplemental online Table 1 shows the actual proportions and Figure 2 represents the numbers on a log scale for clarity.

Table 2. Changes in treatment over time for breast cancer patients in The Netherlands (percentage of patients who received the treatment)

n		1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	Coefficient/ yr	*p*-value	Adjusted for stage
A. Surgery															
78,449	15–64	95	96	96	96	96	96	96	97	97	97	97	**0.3**	**<.001**	**<.001**
13,029	65–69	95	94	95	95	95	96	96	95	96	96	95	0.3	.05	.4
12,550	70–74	87	89	88	91	94	95	94	94	94	95	94	0.9	<.001	.2
9,682	75–79	87	87	86	85	86	84	85	82	86	86	86	−0.1	.2	**<.001**
7,883	80–84	75	77	79	78	74	76	79	76	75	73	71	**−0.2**	**.004**	**<.001**
4,509	85–89	63	64	63	60	63	62	59	60	58	58	53	**−0.3**	**<.001**	**<.001**
1,703	90+	41	44	46	40	49	42	41	41	34	34	37	**−0.4**	**.01**	**<.001**
B. Adjuvant hormonal treatment															
75,591	15–64	18	17	18	21	27	32	35	36	35	36	40	**1.2**	**<.001**	**<.001**
12,432	65–69	28	28	28	30	33	34	33	32	31	31	34	**0.2**	**<.001**	**<.001**
11,633	70–74	36	39	39	37	33	32	33	31	32	31	31	**−0.3**	**<.001**	0.9
8,283	75–79	37	41	40	44	46	47	43	46	43	40	45	**0.2**	**.02**	**<.001**
5,963	80–84	39	40	40	51	52	50	51	48	47	49	52	**0.5**	**<.001**	**<.001**
2,699	85–89	43	48	48	53	60	53	49	48	53	51	53	0.2	.1	.1
690	90+	53	42	56	38	60	51	51	55	42	48	48	−0.1	.7	.7
C. Adjuvant chemotherapy															
75,591	15–64	20	21	23	30	39	42	43	45	47	47	49	**1.3**	**<.001**	**<.001**
12,432	65–69	1	1	2	4	8	11	11	12	13	13	13	**1.9**	**<.001**	**<.001**
11,633	70–74	1	1	2	3	2	2	4	3	3	4	3	**0.9**	**<.001**	**<.001**
8,283	75–79	1	1	1	1	2	1	1	2	2	2	1	**0.8**	**.004**	**.001**
5,963	80–84	0	0	0	0	1	0	1	1	1	0	1	**1.5**	**.02**	**.02**
2,699	85–89	0	0	0	0	0	0	0	0	0	0	1	**3.5**	**.01**	**.01**
690	90+	0	0	0	0	0	0	0	0	0	0	0	**–**	**–**	**–**
D. Hormonal treatment monotherapy															
78,449	15–64	1	1	1	1	1	1	1	1	1	1	1	−0.01	.9	.7
13,029	65–69	2	3	2	2	2	1	1	3	2	2	2	−0.2	.2	.7
12,550	70–74	7	5	7	5	3	2	3	3	4	2	3	**−0.9**	**<.001**	.4
9,682	75–79	8	9	9	10	9	11	9	11	9	10	10	0.1	.08	**<.001**
7,883	80–84	18	17	15	17	19	17	16	16	18	21	24	**0.4**	**<.001**	**<.001**
4,509	85–89	26	28	26	29	30	29	31	32	33	36	38	**0.5**	**<.001**	**<.001**
1,703	90+	46	43	45	48	41	45	46	45	48	56	52	**0.4**	**.01**	**.001**
E. Radiotherapy after breast-conserving surgery															
44,731	15–64	84	82	81	77	76	80	80	83	85	85	83	**0.3**	**<.001**	**<.001**
7,165	65–69	80	75	78	77	76	80	83	83	87	87	88	**0.8**	**<.001**	**<.001**
5,667	70–74	81	83	84	74	73	77	79	83	86	85	85	**0.5**	**<.001**	**<.001**
2,683	75–79	75	79	72	79	69	77	74	80	77	81	82	**0.4**	**.01**	**.01**
1,298	80–84	61	62	58	59	53	53	60	69	71	78	68	**0.7**	**<.001**	**<.001**
488	85–89	16	32	29	26	32	20	35	36	42	46	40	**0.9**	**.001**	**.001**
141	90+	0	22	27	13	12	0	15	13	0	21	18	0.2	.8	.9

(A) shows the change in the percentage of patients who underwent surgery over time; **(B)** and **(C)** show the percentage of patients who received adjuvant treatment after surgery; **(D)** shows the percentage of patients who received only hormonal treatment; and **(E)** shows the percentage of patients who received radiotherapy after breast-conserving surgery.

Table 3. Five-year relative survival over time for a Dutch cohort of female breast cancer patients

Age (yrs)	1995	1996	1997	1998	1999	2000	2001	2002	2003	RER/yr	Adjusted RER/yr
15–65	84.3	85.0	85.9	86.2	86.5	88.2	88.5	89.1	89.9	**0.94 ($p < .001$)**	**0.93 ($p < .001$)**
65–69	87.2	85.2	87.0	87.0	89.5	90.0	91.1	89.5	94.2	**0.93 ($p < .001$)**	**0.93 ($p < .001$)**
70–74	74.9	76.0	74.2	82.0	89.8	90.7	87.1	89.3	92.4	**0.86 ($p < .001$)**	**0.97 ($p = .005$)**
75–79	76.2	74.5	70.4	74.1	77.6	76.9	78.8	76.7	82.1	**0.96 ($p < .001$)**	**0.98 ($p = .03$)**
80–84	72.7	71.4	73.2	72.5	65.2	73.4	76.8	78.4	75.3	0.98 ($p = .10$)	0.99 ($p = .33$)
85–89	63.4	71.0	67.3	70.4	64.4	66.1	72.1	68.4	73.7	0.99 ($p = .55$)	0.99 ($p = .50$)
≥90	54.9	86.7	58.9	61.4	62.9	69.3	76.5	74.9	69.2	0.95 ($p = .07$)	0.99 ($p = .94$)
Overall	81.7	82.3	82.4	83.5	84.7	86.3	86.7	87.0	88.5	**0.94 ($p < .001$)**	**0.95 ($p < .001$)**

RER indicates the relative excess risk for year of diagnosis with 1995 as a reference (adjusted for stage, histology, treatment, and grade).
Median follow-up, 5.4 years (range, 0–13); follow-up until January 2008.

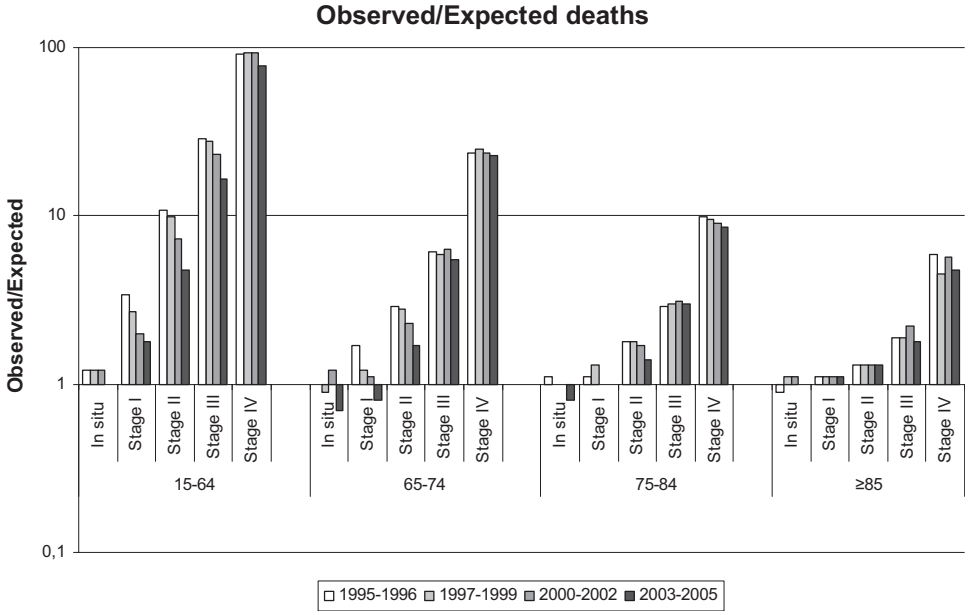

Figure 2. Observed deaths divided by the number of expected deaths at 5 years based on the general population according to age and time period.

Discussion

This study is one of the largest population-based studies in breast cancer patients. It shows that, in the Netherlands, in contrast to younger women, the relative survival for elderly women with breast cancer did not improve significantly over the study period, despite intensified systemic treatment. Because women aged >80 years make up almost 15% of the breast cancer population, it is worrisome that these women apparently do not profit from the advances made. A number of authors have argued that older breast cancer patients may not get appropriate treatment [5–7, 9]. In a Swiss population-based study of breast cancer patients diagnosed in 1989–1999, it was shown that the treatment of older women differed from that of the younger age groups. In that study, only 54% of elderly women received surgery and one third of them were subsequently treated with adjuvant therapy. Overall, 32% of all women received tamoxifen only. Survival was shown to be best in patients who were treated with both surgery and adjuvant therapy and worst in women who were not treated at all [6]. In our study population, at the start of observation (1995), surgery was part of breast cancer treatment for 81% of women aged 75–84 years and for 52% of women aged ≥85 years. Over time, these percentages decreased to 78% and 45%, respectively. The reduction in surgical treatment was accompanied by increased numbers of patients for whom therapy consisted of hormonal therapy only (mostly tamoxifen). Both overtreatment and undertreatment of the elderly could

influence the survival of this heterogeneous group of patients.

Overtreatment

Primary hormonal therapy is nowadays often used in preference to surgery in frail elderly patients with breast cancer, reasoning that these patients are often poor candidates for surgery and might die from other causes while controlling their breast cancer with hormonal therapy. This therapeutic strategy is supported by a number of studies showing that the omission of surgery from the treatment of older women with breast cancer does not jeopardize survival. For example, the Group for Research on Endocrine Therapy in the Elderly trial compared tamoxifen-only treatment with surgical treatment plus tamoxifen in healthy older patients. Although a significant difference in breast cancer survival was observed in that trial, there was no significant difference in overall survival [10]. Furthermore, a Cochrane analysis of all published trials with a similar design confirmed these findings [11]. The elderly patients in our cohort not only received more hormonal monotherapy, but adjuvant hormonal therapies also increased considerably over time. Unfortunately, we had no information concerning the hormone receptor status of the women in the present cohort or the use of tamoxifen versus an aromatase inhibitor, but the increasing use of adjuvant hormonal therapy is in line with national and international treatment guidelines for early breast cancer. Around 1992, adjuvant indications were extended to women with hormone receptor–positive disease and node-negative high-risk breast cancer, and in 1998 the adjuvant treatment duration was extended to 5 years instead of 2 years [12]. Therefore, in the course of the observation period, the amount of tamoxifen therapy increased significantly.

Why then did this greater use of effective anti–breast cancer treatment not result in a survival gain for elderly patients with breast cancer? The role of adjuvant therapy in geriatric oncology remains a highly debated question [13]. Elderly women have rarely been included in clinical trials because oncologists have been shown to be reluctant to offer participation because of advanced age and comorbidities. It may be inappropriate to prescribe systemic treatment to patients with a poor short-term prognosis who are unlikely to experience any benefit, but it could also be inappropriate to not prescribe systemic treatment to fit elderly who would benefit from the treatment. Whereas the oncological community has been very cautious to introduce chemotherapy in the adjuvant treatment of older women, hormonal therapies have been embraced eagerly for this age group, disregarding the lack of representation of women aged >75 years in trials of hormonal therapies. In the adjuvant studies of tamoxifen, which demonstrated fewer breast cancer relapses and longer overall survival in estrogen receptor–positive patients, the mean age was 62 years, and older women were hardly represented [14]. Most studies did not permit the inclusion of patients with active cardiovascular disease or hematologic, renal, or hepatic abnormalities and required participants to be fully ambulatory and able to independently perform activities of daily living, disregarding the fact that, above the age of 75, only 22% of women newly diagnosed with cancer are without serious comorbidity [9, 15].

Side effects associated with the use of tamoxifen that might put older patients at a higher risk for death are primarily a result of its procoagulant effects. In clinical studies, with a mean patient age of 65 years, deep vein thrombosis or pulmonary emboli were observed in 5%–10% of patients [14]. In a population-based study in Denmark, women treated with tamoxifen were at a 3.5-fold higher risk for deep vein thrombosis or pulmonary emboli and the risk increased with increasing age [16]. Hence, frail elderly patients have a significant risk for thrombotic fatalities.

Undertreatment

The standard primary therapy for early breast cancer is surgical resection, either by mastectomy or BCS. Both procedures are usually tolerated regardless of age; the main factor affecting surgical morbidity is not age, but rather the presence of comorbidity [13, 17–19]. As shown in other studies, in the present study the percentage of women who were not operated upon increased with advancing age. Moreover, the percentage of elderly patients who were operated upon decreased over time. Whether this is a result of increasing comorbidities over the years is not clear and should be studied.

Undertreatment of fit elderly may occur because they do not receive adjuvant chemotherapy. Better systemic adjuvant treatment options are thought to have made an important contribution to the better outcome of younger breast cancer patients [20]. For younger patients, a strong increase in adjuvant chemotherapy was seen, but very few elderly patients received adjuvant chemotherapy. However, recent trials suggest that, in fit elderly patients, standard chemotherapy is both effective and tolerated [5].

In order to improve the future outcome of elderly patients with breast cancer, it is important to not only prevent overtreatment of frail elderly patients but also to identify fit elderly patients who can profit from tailored treatments with chemotherapy or biologicals [4, 21]. We showed survival trends in our cohort by means of observed versus expected death rates and by means of relative survival figures.

The observed versus expected death rates demonstrate that breast cancer is the leading cause of death in younger breast cancer patients; however, a large majority of elderly patients die from causes unrelated to this disease. The relative survival figures show a decreasing relative survival risk for elderly women with breast cancer. These data indicate that the small group of elderly women with breast cancer who do not die from unrelated causes have a worse survival than younger patients. Compared with younger women, these fit elderly women apparently have a greater chance of dying as a result of breast cancer or breast cancer treatment. The survival gap between younger and older women may hence be caused by undertreatment of fit elderly women, or overtreatment, because they may suffer from unforeseen toxicities of treatment and the introduction of unexpected fatalities (supplemental online Fig. 2).

A critical reappraisal of treatment strategies and better selection of patients who can benefit from available therapies depend on future studies that facilitate the inclusion of a valid representation of older women and specifically address the heterogeneity of this age group with careful registration of comorbidities and geriatric parameters in order to correlate outcome. Meanwhile, careful evaluation of biological prognostic factors, performance status, and geriatric parameters, together with determination of life expectancy and patient preferences, provides relevant information for the oncologist and geriatrician to support treatment decisions and to distinguish the frail elderly from those with a good health status who may benefit most from more intensive treatment [4, 13, 22].

In conclusion, from 1995 to 2005, survival for elderly patients with breast cancer did not improve in The Netherlands, despite the increased use of systemic (primarily hormonal) therapies. Relative death risks in the elderly are close to 1, suggesting that excess mortality resulting from breast cancer is low and competing causes of death are high. Elderly patients with breast cancer have a higher risk for overtreatment as well as undertreatment, with a delicate therapeutic balance between breast cancer survival gain and potential toxicities that may increase the non–breast cancer death risk. To improve breast cancer survival in the elderly, a critical reappraisal is needed, as is better selection of patients who can benefit from available therapies. For elderly women, treatment should be better tailored, with surgery, radiotherapy, and systemic therapy for fit women and with more limited treatment or best supportive care for frail elderly women when survival is not expected to improve as a result of breast cancer treatment.

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AUTHOR CONTRIBUTIONS

Conception/Design: Esther Bastiaannet, Rudi G.J. Westendorp, Gerrit-Jan Liefers, Johanneke E.A. Portielje, Cornelis J.H. van de Velde, Anton J.M. de Craen, Peter J.K. Kuppen
Provision of study material or patients: Maryska L.G. Janssen-Heijnen, Cornelis J.H. van de Velde, Lydia G.M. van der Geest
Collection and/or assembly of data: Esther Bastiaannet
Data analysis and interpretation: Esther Bastiaannet, Olaf M. Dekkers, Gerrit-Jan Liefers, Johanneke E.A. Portielje, Anton J.M. de Craen, Peter J.K. Kuppen, Lydia G.M. van der Geest
Manuscript writing: Esther Bastiaannet, Maryska L.G. Janssen-Heijnen, Olaf M. Dekkers, Rudi G.J. Westendorp, Gerrit-Jan Liefers, Johanneke E.A. Portielje, Cornelis J.H. van de Velde, Anton J.M. de Craen, Susanne van der Velde, Peter J.K. Kuppen, Lydia G.M. van der Geest
Final approval of manuscript: Esther Bastiaannet, Maryska L.G. Janssen-Heijnen, Olaf M. Dekkers, Rudi G.J. Westendorp, Gerrit-Jan Liefers, Johanneke E.A. Portielje, Cornelis J.H. van de Velde, Anton J.M. de Craen, Susanne van der Velde, Peter J.K. Kuppen, Lydia G.M. van der Geest

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