The prognostic and predictive effect of body mass index in hormone receptor-positive breast cancer

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Abstract

Background

Obesity has been associated with an adverse prognosis and reduced efficacy of endocrine therapy in patients with hormone receptor-positive (HR+) breast cancer (BC). This study determines the prognostic and predictive effect of body mass index (BMI) on the disease-free survival (DFS) of postmenopausal HR+ BC patients.

Methods

Patients were identified from the DATA study (NCT00301457), a randomised controlled trial evaluating the efficacy of six versus three years of anastrozole after two to three years of adjuvant tamoxifen in postmenopausal women with HR+ BC. Patients were classified as normal weight (BMI: 18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), or obese (≥30 kg/m²). The primary endpoint was DFS, evaluated from randomisation (prognostic analyses) or three years after randomisation onwards (predictive analyses; aDFS) using multivariable Cox regression analyses. P-values were two-sided.

Results

This study included 678 normal weight, 712 overweight, and 391 obese patients. After a median follow-up of 13.1 years, overweight and obesity were identified as negative prognostic factors for DFS (hazard ratio (HR)=1.16; 95% confidence interval (CI): 0.97-1.38 and HR=1.26; 95% CI 1.03-1.54, respectively). The adverse prognostic effect of BMI was observed in women aged <60 years, but not in women aged ≥60 years (p-interaction=0.009). The effect of extended anastrozole on aDFS was similar in normal weight (HR=1.00; 95% CI 0.74-1.35), overweight (HR=0.74; 95% CI 0.56-0.98), and obese patients (HR=0.97; 95% CI
0.69-1.36) (p-interaction=0.24).

**Conclusion**

In this study among 1,781 HR+ BC patients, overweight and obesity were adverse prognostic factors for DFS. BMI did not impact the efficacy of extended anastrozole.
Introduction

One in five women worldwide are estimated to be obese by 2025 [1]. Obese patients are more likely to develop comorbidities, such as diabetes mellitus, cardiovascular disease, and several types of cancer [2]. Obesity has also been associated with an increased risk of hormone receptor-positive (HR+) breast cancer (BC) in postmenopausal women and an adverse prognosis after BC diagnosis [3-8]. Potential mechanisms for this elevated risk and adverse prognosis include an increased peripheral conversion of androgens to oestrogens in adipose tissue, higher leptin concentrations, hyperinsulinemia, and obesity-mediated inflammation [6].

In the general population, however, the association between obesity and all-cause mortality tends to differ between younger and older adults [9]. The majority of studies observed no adverse association between obesity and all-cause mortality in adults aged ≥65 years [10-13]. In patients with BC, the association between obesity and outcomes may also differ by age or menopausal status [7, 14, 15]. In a large meta-analysis of 82 studies including 213,075 BC survivors, for example, numerically stronger associations between obesity and all-cause mortality and breast cancer-specific mortality (BCSM) were observed in premenopausal versus postmenopausal women [7]. In addition, two studies observed an inverse association between a higher body mass index (BMI) and all-cause mortality in older BC patients, though results were inconclusive for BCSM [14, 15].

Over the years, the impact of BMI on the efficacy of (extended) endocrine therapy has also been studied in postmenopausal women with HR+ BC. Tamoxifen seems to be equally effective across BMI classes [16]. However, conflicting results have been reported on the association between BMI and the efficacy of aromatase inhibitors [17-19]. The ATAC trial, for example, observed a trend towards a reduced benefit of five years of anastrozole...
versus five years of tamoxifen in patients with a higher BMI [17]. In addition, the ABCSG-6a trial only observed a benefit of three additional years of anastrozole following five years of tamoxifen in normal weight patients, while no benefit was observed in overweight or obese patients [19]. However, in the BIG 1-98 trial, BMI did not affect the efficacy of five years of letrozole versus tamoxifen [18].

The present post-hoc study was performed within the framework of the DATA study, a randomised controlled trial that evaluated the efficacy of six versus three years of anastrozole after two to three years of adjuvant tamoxifen in postmenopausal women with HR+ BC [20, 21]. The primary aim of this exploratory analysis was to explore the association between BMI and disease outcomes in the DATA study cohort as a whole and by age subgroups. The secondary aim was to explore the association between BMI and the efficacy of extended anastrozole therapy.

**Methods**

**Study design and participants**

The DATA study (NCT00301457) was an open-label, phase 3, randomised controlled trial in which postmenopausal women with HR+ BC received either six or three years of anastrozole (1 mg orally once a day) after completing two to three years of adjuvant treatment with tamoxifen without signs of disease recurrence [20]. From 2006 to 2009, 1912 patients were recruited from 79 hospitals in the Netherlands and screened for eligibility. The final study population consisted of 1860 patients, of whom 1660 were disease-free at three years after randomisation. The main efficacy results have been published elsewhere [20, 21].
For the current analysis, all patients with a baseline BMI measurement were selected. Underweight patients (BMI: <18.5 kg/m²) were excluded because of the small number of patients.

This study was approved by the medical ethics committee of the Radboud University Medical Centre (Nijmegen, the Netherlands). Written informed consent was obtained from all patients.

**Data collection and definitions**

Height and weight were measured by the treating physician or self-reported by the patient at randomisation, and used to calculate BMI. We categorised BMI according to the World Health Organization criteria: normal weight (BMI: 18.5-24.9 kg/m²), overweight (BMI: 25.0-29.9 kg/m²), or obese (BMI: ≥30.0 kg/m²). Follow-up was performed by the treating physician every six months during the first six years after randomisation and yearly thereafter. A mammogram was done once a year. Database lock: March 7, 2022.

**Endpoints**

The primary endpoint was disease-free survival (DFS). Secondary endpoints were overall survival (OS), BC-specific mortality (BCSM), and other-cause mortality (OCM). The following events ended a period of DFS: BC recurrence, second primary BC, second primary cancer (excluding basal cell or squamous cell carcinoma of the skin and carcinoma in situ of the cervix), or death from any cause. A period of OS ended as a result of death from any cause. All BC-related deaths were included in the analysis of BCSM, while all non-BC-related deaths were included in the analysis of OCM.
Statistical analysis

Baseline characteristics were compared by BMI class and assigned treatment. The Chi-squared test and the Mann-Whitney U test were used to assess differences in categorical or continuous variables. The presence of a trend was evaluated using the Cochran-Mantel-Haenszel test and the Jonckheere-Terpstra test.

The prognostic effect of BMI was evaluated irrespective of assigned treatment from date of randomisation onwards. The predictive effect of BMI on the efficacy of six versus three years of anastrozole was assessed from three years after randomisation onwards (i.e. ‘adapted’ endpoints). Patients with a DFS event or patients who were lost to follow-up within three years after randomisation were excluded from the adapted analyses. DFS and OS were examined using Kaplan-Meier survival analyses and Cox regression analyses, when adjusting for potential confounders. BCSM and OCM were determined with competing risk methodology, using the Fine and Gray model when adjusting for potential confounders. Differences between BMI classes and treatment groups were assessed with the log-rank test and the Gray’s test. In the absence of an event, patients were censored at the last follow-up visit in all analyses. Death not related to BC was considered a competing event in the analysis of BCSM. BC-related death was considered a competing event in the analysis of OCM. Missing data of confounders were imputed.

Prognostic analyses were stratified by age (<60 versus ≥60 years). The cut-off point of 60 years, i.e., 57 years at BC diagnosis, was chosen to distinguish younger postmenopausal women from older postmenopausal women, as some younger patients were premenopausal at BC diagnosis [22, 23]. The BMI-by-age and treatment-by-BMI interaction terms were calculated using likelihood-ratio tests.

P-values were two-sided and considered statistically significant at a value of ≤0.05.
All statistical analyses were performed with SPSS (version 25) and Stata (version 17).

Results

Patient characteristics

Overall, 1781 patients were included in the analysis on the prognostic effect of BMI (Figure 1). Of these, 678 (38.0%) were normal weight, 712 (40.0%) overweight, and 391 (22.0%) obese at randomisation. A higher BMI class was associated with higher age, presence of cardiovascular disease, and higher tumour stage (Table 1). In the total study population, the use of (neo)adjuvant chemotherapy decreased with increasing BMI. However, in the stratified analyses by age, the association between BMI and (neo)adjuvant chemotherapy disappeared (Supplementary Tables 1 and 2).

BMI as a prognostic factor

After a median follow-up period of 13.1 years (IQR: 12.5-13.9) beyond randomisation, 706 patients had developed a DFS event and 484 patients had died. Details about endpoint events per BMI class are presented in Table 2.

The 13-year DFS rates (95% confidence interval (CI)) were 66.2% (62.4%-69.7%) in normal weight, 59.5% (55.7%-63.1%) in overweight, and 52.4% (47.2%-57.4%) in obese patients (Figure 2A). Overweight and obese patients experienced a deterioration in DFS when compared with normal weight patients (adjusted hazard ratio (HR)=1.16; 95% CI 0.97-1.38; p=0.10 and adjusted HR=1.26; 95% CI 1.03-1.54; p=0.03, respectively) (Table 3, Supplementary Table 6).
The 13-year OS rates (95% CI) were 77.6% (74.1%-80.6%) in normal weight, 71.5% (68.0%-74.7%) in overweight, and 67.7% (62.5%-72.2%) in obese patients (Figure 2B). When compared with normal weight patients, this resulted in an adjusted HR of respectively 1.20 (95% CI 0.97-1.48; p=0.10) and 1.16 (95% CI 0.91-1.48; p=0.23) for overweight and obese patients (Table 3, Supplementary Table 7).

Overweight and obese patients also experienced numerically higher BCSM rates when compared with normal weight patients (Figure 2C). The 13-year cumulative incidence of BCSM (95% CI) was 11.2% (9.0%-13.8%) in normal weight, 14.4% (11.9%-17.1%) in overweight, and 16.5% (12.9%-20.5%) in obese patients. In multivariable analysis, this resulted in a HR of respectively 1.25 (95% CI 0.93-1.68; p=0.15) and 1.36 (95% CI 0.97-1.91; p=0.07) for overweight and obese patients (Table 3, Supplementary Table 8).

Furthermore, overweight and obese patients had numerically higher OCM rates when compared with normal weight patients (Figure 2D). However, in multivariable analysis, the cumulative incidence of OCM was similar in overweight and obese patients (HR=1.12; 95% CI 0.83-1.52; p=0.45 and HR=1.01; 95% CI 0.71-1.43; p=0.96, respectively) (Table 3, Supplementary Table 9).

Age showed to be a statistically significant effect modifier of the association between BMI and DFS (p-interaction=0.009) and was nearly statistically significant for the association between BMI and OS (p-interaction=0.07) (Table 3). Specifically, overweight and obese patients aged <60 years experienced a statistically significant deterioration in both DFS and OS when compared with normal weight patients of the same age, whereas no adverse prognostic effect of overweight and obesity was observed in patients aged ≥60 years. The association between BMI and OCM also differed by age (p-interaction=0.02), but the association between BMI and BCSM was similar in both age groups (p-interaction=0.56).
BMI as a predictive factor for benefit of extended endocrine therapy

Overall, 1589 patients were included in the analysis on the predictive effect of BMI: 613 (38.6%) normal weight, 628 (39.5%) overweight, and 348 (21.9%) obese patients (Figure 1). Supplementary Tables 3-5 present the baseline characteristics according to assigned treatment for every BMI class separately. Obese patients who received six years of anastrozole were more frequently diagnosed with a node-positive tumour when compared with those who received three years of anastrozole (72% versus 61%, \(p=0.04\)). All other baseline characteristics were equally distributed between treatment groups.

In the total DATA study cohort (\(N=1660\)), six versus three years of anastrozole resulted in a HR of 0.86 (95% CI 0.72-1.01; \(p=0.073\)) for adapted DFS (aDFS) and a HR of 0.93 (95% CI 0.75-1.16; \(p=0.53\)) for adapted OS (aOS), respectively [21].

The effect of six versus three years of anastrozole on aDFS was similar in normal weight (adjusted HR=1.00; 95% CI 0.74-1.35; \(p=1.00\)), overweight (adjusted HR=0.74; 95% CI 0.56-0.98; \(p=0.04\)), and obese patients (adjusted HR=0.97; 95% CI 0.69-1.36; \(p=0.85\)) (p-interaction=0.24) (Figure 3, Figure 4A-C).

In the analysis of aOS, the effect of six versus three years of anastrozole differed between normal weight (adjusted HR 1.48; 95% CI 0.98-2.23; \(p=0.06\)), overweight (adjusted HR 0.72; 95% CI 0.51-1.02; \(p=0.07\)), and obese patients (adjusted HR 0.92; 95% CI 0.60-1.41; \(p=0.72\)) (p-interaction=0.03) (Figure 3, Figure 4D-F). These results did not differ between patients aged <60 years and patients aged \(\geq60\) years (Supplementary Figure 1).

Results of both adapted BCSM (aBCSM) and adapted OCM (aOCM) were comparable to those of aOS in every BMI class (Figure 3, Figure 5A-F).
Discussion

In this study, we evaluated the prognostic and predictive effect of BMI in 1,781 postmenopausal women with non-metastatic HR+ BC from the phase III DATA study. We confirmed the results from previous studies, showing a negative association between obesity and DFS in the overall study population. Interestingly, however, subgroup analyses demonstrated that the association between obesity and DFS was statistically significant in patients aged <60 years, but not in patients aged ≥60 years. The effect modification by age is of potential interest.

We observed that obesity was associated with a decrease in DFS and OS in younger postmenopausal HR+ BC patients only. However, while obesity was also associated with an increase in OCM in younger patients only, it seemed to increase the risk of BCSM irrespective of age. These findings indicate that different mechanisms might apply to the association between obesity and OCM and the association between obesity and BCSM. Primarily, the increased risk of OCM in younger obese patients may be the result of developing cardiovascular or metabolic diseases at a younger age [2]. In our study, we collected causes of death, but numbers of events per subcategory, i.e., cardiovascular death, were too low to perform additional analyses. Secondarily, the lack of an adverse association between obesity and OCM in older patients may be attributed to the “obesity paradox”, which has earlier been described for patients with cancer [24]. Potential age-specific explanations for the obesity paradox include a reduced osteoporotic fracture risk due to a higher bone mineral density, reverse causation, and survival bias [10, 12, 25, 26]. Reverse causation occurs when previously overweight or obese patients are misclassified as normal weight as a result of disease-related unintentional weight loss right before the BMI measurement. This misclassification may result in an overestimation of the mortality risk in
normal weight patients, thereby minimizing the adverse prognostic effect of overweight and obesity in older patients. The obesity paradox does however not seem to apply to the association between BMI and BCSM, as we observed that obese patients experience an increased risk of BCSM irrespective of age in our study. This increased risk can be explained by several mechanisms, including higher oestrogen levels as a result of increased aromatization in adipose tissue, hyperinsulinemia, and obesity-mediated inflammation [6]. The results of our study suggest that these biological mechanisms equally impact the prognosis of younger and older postmenopausal HR+ BC patients with obesity. Nonetheless, the use of BMI has its limitations. BMI does not distinguish between fat and muscle mass, and is therefore an inadequate measure of body composition [26]. We did not have information about body composition, and in particular the presence of sarcopenia, in our cohort of patients. Several studies have however shown that sarcopenia adversely impacts the prognosis of patients with (metastatic) BC [27-30].

In our study, we did not observe a reduced efficacy of extended anastrozole therapy in overweight or obese postmenopausal women with HR+ BC. In the analysis of aOS, we did however observe a potential difference in treatment effects between BMI classes. In fact, six versus three years of anastrozole was associated with a non-statistically significantly increased risk of death in normal weight patients (HR=1.48; 95% CI: 0.98-2.23), whereas it was associated with a non-statistically significantly decreased risk of death in overweight patients (HR=0.72; 95% CI: 0.51-1.02). Obviously, as the number of patients and events per subgroup was low, this difference in treatment effects could simply be a chance finding. Alternatively, one might speculate that normal weight patients receiving extended aromatase inhibition are at an increased risk of developing endocrine resistance, as an increased risk of BCSM was also observed. We did however not observe a decrease in the
DFS of normal weight patients receiving extended aromatase inhibition, though this might also be the result of a decrease in the incidence of second primary cancers in the extended therapy group. In addition, one might speculate that normal weight patients receiving six years of anastrozole experience an increased risk of death due to adverse events, i.e., cardiovascular events or bone fractures. In a previous report of the DATA study, it was shown that the incidence of cardiovascular events and bone fractures during the first six years after randomisation did not differ between patients receiving six versus three years of anastrozole, but the incidence of osteopenia or osteoporosis was higher in the extended therapy group [20]. Considering the fact that normal weight patients do not experience an obesity-mediated increase in bone mineral density, it is possible that normal weight patients experience an increased risk of osteoporotic fractures when receiving extended aromatase inhibition. Unfortunately, we do not have data about the incidence of bone fractures after the first six years of randomisation. Apart from focussing on the increased risk of death in normal weight patients, one might question why overweight patients experienced a reduced risk of death when receiving extended aromatase inhibition in our study. This is an unexpected finding, as both the ATAC trial and the ABCSG-6a trial observed a reduced efficacy of (extended) anastrozole therapy in postmenopausal HR+ BC patients with a higher BMI [17, 19]. Furthermore, it is well described that oestrogen levels of postmenopausal women increase with a higher BMI, thereby increasing the risk of BC events [6]. Therefore, results of our study should be interpreted with caution until further research on this topic is available.

The major strength of our study is the use of data from patients who participated in a randomised controlled trial, in which endpoints were well-defined and consistently measured during follow-up. Another strength of our study is the long-term follow-up period
of more than 13 years after randomisation. Our study also has some limitations. Patients may experience changes in body weight after BC diagnosis [31-34]. We obtained information about BMI at randomisation, i.e. 2-3 years after diagnosis, and did not collect information about BMI at BC diagnosis. The impact on the study results is however expected to be small as a recent meta-analysis by Chan et al. showed that the adverse prognostic effect of obesity on OS remained present, regardless of the moment of BMI measurement [7]. Our study also lacked information about diet, physical activity, socio-economic status, and other factors that may be associated with BMI. The use of self-reported measurements of height and weight in some patients can be considered another limitation of this study. However, in the meta-analysis by Chan et al., the association between obesity and all-cause mortality was similar in studies which used measured versus self-reported values [7]. Furthermore, BMI was not a stratification factor in the DATA study [20]. The efficacy results of the subgroup analyses by BMI should therefore be considered as explorative.

In our study among 1,781 postmenopausal women with HR+ BC, we have shown that obese patients experienced an increased risk of BCSM irrespective of age. These findings highlight the need for maintaining a healthy BMI in all patients with HR+ BC. In addition, we did not observe a reduced efficacy of extended anastrozole therapy in overweight and obese patients. Therefore, we conclude that (extended) aromatase inhibitor therapy can also be considered in overweight and obese patients with HR+ BC.
Data availability

Study data underlying this manuscript will be made easily available to any request to the corresponding author.

Funding

This work was supported by AstraZeneca.

Conflicts of interest

SWML reports grants from AstraZeneca during the conduct of the study; grants from Eli Lilly outside the submitted work. SMEG reports grants from AstraZeneca during the conduct of the study; institutional grants from Roche, Pfizer, Novartis, Eli Lilly, Daiichi Sankyo, AstraZeneca and Gilead outside the submitted work; personal fees from AstraZeneca outside the submitted work. ACPS and ALTI report grants from AstraZeneca during the conduct of the study. CHS is chair of the Board of Dutch national breast cancer guidelines. JRK reports grants from AstraZeneca, MSD, Eisai, Eli Lilly, and GSK outside the submitted work. AHH reports grants from the Dutch Breast Cancer Research Group during the conduct of the study and outside the submitted work. AHH has been an Advisory Board member for Eli Lilly. AHH received support from Pfizer to attend the ESMO 2022 congress. SCL reports grants from AstraZeneca during the conduct of the study and outside the submitted work; grants from Eurocept Plaza, Roche, Genentech, Gilead Sciences, Tesaro, Novartis, and Agendia outside the submitted work; consulting fees from AstraZeneca; payment or honoraria from Daiichi Sankyo; other financial support for attending meetings from Daiichi Sankyo; non-financial support from Genentech (drug), Roche (drug), Gilead Sciences (drug), Novartis (drug), Agendia (gene expression tests), and AstraZeneca (drug). SCL has a patent (UN23A01/P-EP) pending on a method for assessing homologous recombination deficiency in ovarian cancer cells. MLS reports grants from the Dutch Cancer Society, Servier Pharma, Nutricia, Kankeronderzoekfonds Limburg, ZonMW, the Jules Coenegracht Foundation, Academische Alliantie, NWA-ORC, and TKI outside the submitted work. IJHV reports grants from AstraZeneca during the conduct of the study; grants from Pfizer and Eli Lilly outside the submitted work. VCGT-H reports grants and personal fees from AstraZeneca during the conduct of the study and outside the submitted work; grants and personal fees from Novartis and Eli Lilly; grants from Roche, Pfizer, Daiichi Sankyo, and Gilead outside the submitted work. VCGT-H has a consulting role for AstraZeneca, Eli Lilly, and Novartis. The other authors have...
declared no conflicts of interests.

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References


Table 1. Baseline characteristics of study participants according to BMI class (N (%))

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<th>Obese (N = 391)</th>
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</tr>
<tr>
<td>Breast-conserving surgery</td>
<td></td>
<td></td>
<td></td>
<td>0.63</td>
</tr>
<tr>
<td>Yes</td>
<td>331 (49)</td>
<td>351 (49)</td>
<td>197 (50)</td>
<td></td>
</tr>
<tr>
<td>Prior (neo)adjuvant chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Yes</td>
<td>485 (72)</td>
<td>478 (67)</td>
<td>245 (63)</td>
<td></td>
</tr>
<tr>
<td>Previous duration of tamoxifen</td>
<td></td>
<td></td>
<td></td>
<td>0.38</td>
</tr>
<tr>
<td>Median – years (IQR)</td>
<td>2.3 (2.1 – 2.5)</td>
<td>2.3 (2.1 – 2.5)</td>
<td>2.3 (2.1 – 2.5)</td>
<td></td>
</tr>
<tr>
<td>Recommended treatment duration of anastrozole</td>
<td></td>
<td></td>
<td></td>
<td>0.70</td>
</tr>
<tr>
<td>3 years</td>
<td>337 (50)</td>
<td>344 (48)</td>
<td>201 (51)</td>
<td></td>
</tr>
<tr>
<td>6 years</td>
<td>341 (50)</td>
<td>368 (52)</td>
<td>190 (49)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI = body mass index; ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; IQR = interquartile range; PR = progesterone receptor.

Percentages may exceed 100% because of rounding.

Missing values: smoking history (n = 38), tumour status (n = 2), histological grade (n = 54) and HER2 status (n = 135).
Table 2. Endpoint events in the total study population according to BMI class (N (%))

<table>
<thead>
<tr>
<th>Endpoint events in the total study population according to BMI class (N (%))</th>
<th>Normal weight (N = 678)</th>
<th>Overweight (N = 712)</th>
<th>Obese (N = 391)</th>
<th>Number of events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free survival event(^a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence of the primary tumour</td>
<td>231</td>
<td>287</td>
<td>188</td>
<td>112 (48) 133 (46) 97 (52)</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>20 (9)</td>
<td>16 (6)</td>
<td>13 (7)</td>
<td></td>
</tr>
<tr>
<td>Regional recurrence</td>
<td>25 (11)</td>
<td>24 (8)</td>
<td>16 (9)</td>
<td></td>
</tr>
<tr>
<td>Distant recurrence(^b)</td>
<td>83 (36)</td>
<td>114 (40)</td>
<td>83 (44)</td>
<td></td>
</tr>
<tr>
<td>Visceral</td>
<td>44 (19)</td>
<td>70 (24)</td>
<td>43 (23)</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>53 (23)</td>
<td>66 (23)</td>
<td>56 (30)</td>
<td></td>
</tr>
<tr>
<td>Soft tissue</td>
<td>10 (4)</td>
<td>21 (7)</td>
<td>15 (8)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (1)</td>
<td>1 (&lt;1)</td>
<td>5 (3)</td>
<td></td>
</tr>
<tr>
<td>Second, (non-)invasive breast cancer</td>
<td>20 (9)</td>
<td>30 (10)</td>
<td>21 (11)</td>
<td></td>
</tr>
<tr>
<td>Second, non-breast cancer</td>
<td>73 (32)</td>
<td>72 (25)</td>
<td>40 (21)</td>
<td></td>
</tr>
<tr>
<td>Death without prior breast cancer event</td>
<td>29 (13)</td>
<td>53 (18)</td>
<td>36 (19)</td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>153</td>
<td>204</td>
<td>127</td>
<td>79 (52) 103 (51) 65 (51)</td>
</tr>
<tr>
<td>Breast cancer related</td>
<td>62 (41)</td>
<td>74 (36)</td>
<td>49 (39)</td>
<td></td>
</tr>
<tr>
<td>Not breast cancer related</td>
<td>35 (23)</td>
<td>40 (20)</td>
<td>18 (14)</td>
<td></td>
</tr>
<tr>
<td>Second primary malignancy</td>
<td>9 (6)</td>
<td>13 (6)</td>
<td>15 (12)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>18 (12)</td>
<td>21 (10)</td>
<td>16 (13)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>12 (8)</td>
<td>27 (13)</td>
<td>13 (10)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>12 (8)</td>
<td>27 (13)</td>
<td>13 (10)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Patients may have had multiple disease-free survival events at the same moment.
\(^b\)In some patients multiple locations of recurrence were reported.
Table 3. Multivariable analyses of primary and secondary outcomes according to BMI class at randomisation, overall and stratified by age at randomisation

<table>
<thead>
<tr>
<th>BMI</th>
<th>Normal weight</th>
<th>Overweight</th>
<th>Obese</th>
<th>Reference</th>
<th>(s)HR(^a) (95% CI)</th>
<th>P-value</th>
<th>(s)HR(^a) (95% CI)</th>
<th>P-value</th>
<th>P interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease-free survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients (N = 1781 patients, 706 events)</td>
<td>1.00</td>
<td>1.16 (0.97-1.38)</td>
<td>0.10</td>
<td>1.26 (1.03-1.54)</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 years (N = 1023 patients, 323 events)</td>
<td>1.00</td>
<td>1.29 (1.00-1.67)</td>
<td>0.05</td>
<td>1.83 (1.36-2.46)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60 years (N = 758 patients, 383 events)</td>
<td>1.00</td>
<td>1.04 (0.82-1.33)</td>
<td>0.72</td>
<td>0.94 (0.72-1.23)</td>
<td>0.63</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients (N = 1781 patients, 484 events)</td>
<td>1.00</td>
<td>1.20 (0.97-1.48)</td>
<td>0.10</td>
<td>1.16 (0.91-1.48)</td>
<td>0.23</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 years (N = 1023 patients, 191 events)</td>
<td>1.00</td>
<td>1.46 (1.05-2.04)</td>
<td>0.03</td>
<td>1.62 (1.09-2.42)</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60 years (N = 758 patients, 293 events)</td>
<td>1.00</td>
<td>1.02 (0.77-1.34)</td>
<td>0.90</td>
<td>0.93 (0.68-1.26)</td>
<td>0.62</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Breast cancer-specific mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients (N = 1781 patients, 247 events)</td>
<td>1.00</td>
<td>1.25 (0.93-1.68)</td>
<td>0.15</td>
<td>1.36 (0.97-1.91)</td>
<td>0.07</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 years (N = 1023 patients, 119 events)</td>
<td>1.00</td>
<td>1.44 (0.96-2.18)</td>
<td>0.08</td>
<td>1.32 (0.78-2.25)</td>
<td>0.31</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60 years (N = 758 patients, 128 events)</td>
<td>1.00</td>
<td>1.04 (0.67-1.60)</td>
<td>0.88</td>
<td>1.28 (0.83-1.99)</td>
<td>0.27</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other-cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients (N = 1781 patients, 237 events)</td>
<td>1.00</td>
<td>1.12 (0.83-1.52)</td>
<td>0.45</td>
<td>1.01 (0.71-1.43)</td>
<td>0.96</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 years (N = 1023 patients, 72 events)</td>
<td>1.00</td>
<td>1.39 (0.79-2.45)</td>
<td>0.25</td>
<td>2.01 (1.11-3.33)</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60 years (N = 758 patients, 165 events)</td>
<td>1.00</td>
<td>1.00 (0.70-1.44)</td>
<td>0.99</td>
<td>0.75 (0.50-1.13)</td>
<td>0.17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI = body mass index; CI = confidence interval; (s)HR = (subdistribution)hazard ratio.

In the analyses of breast cancer-specific mortality and other-cause mortality, we reported sHR instead of HR.

\(^a\)The full multivariable models of the total study population are displayed in Supplementary Tables 6-9.

Analyses were adjusted for age (≥60 years versus <60 years), history of cardiovascular disease (yes versus no), smoking history (yes versus no), tumour status (≥pT2 versus pT1), nodal status (pN positive versus pN negative), histology (lobular versus other), histological grade (histological grade 3 versus histological grade 1 and 2), hormone receptor status (oestrogen receptor-positive or progesterone receptor-positive versus oestrogen receptor-positive and progesterone receptor-positive), and previous chemotherapy (yes versus no). Age was excluded as a confounding factor in the stratified analyses by age.
**Figure headings**

**Figure 1.** Flowchart of included patients

**Figure 2.** Disease-free survival (A), overall survival (B), breast cancer-specific mortality (C), and other-cause mortality (D), according to BMI class at randomisation

**Figure 3.** Multivariable analyses of primary and secondary endpoints evaluating the efficacy of 6 versus 3 years of anastrozole, stratified by BMI class at randomisation

**Figure 4.** Adapted disease-free survival according to assigned treatment in normal weight (A), overweight (B), and obese (C) patients, and adapted overall survival according to assigned treatment in normal weight (D), overweight (E), and obese (F) patients

**Figure 5.** Adapted breast cancer-specific mortality according to assigned treatment in normal weight (A), overweight (B), and obese (C) patients, and adapted other-cause mortality according to assigned treatment in normal weight (D), overweight (E), and obese (F) patients
Figure 1

1912 patients were screened for eligibility for inclusion in the phase III DATA study.

1860 eligible patients enrolled

1781 patients included in the analyses on the prognostic effect of BMI

678 normal weight patients
712 overweight patients
391 obese patients

192 excluded
- 176 disease-free survival event within 3 years
- 16 lost to follow-up

79 excluded
- 68 baseline BMI not documented
- 11 underweight

52 ineligible
- 3 no informed consent
- 3 no pathological breast cancer confirmation
- 18 not postmenopausal
- 3 metastasis
- 7 breast cancer recurrence
- 13 previous treatment with endocrine therapies other than tamoxifen
- 5 medical history of breast cancer within the previous 10 years
- 2 other malignancy within 5 years before randomisation
<table>
<thead>
<tr>
<th>BMI group (kg/m²)</th>
<th>Number of patients</th>
<th>Number of events</th>
<th>(s)HR* (95% CI)</th>
<th>P-value</th>
<th>10-year rate (95% CI)</th>
<th>P interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adapted disease-free survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.5-24.9 (normal weight)</td>
<td>306</td>
<td>87</td>
<td>1.00 (0.74-1.35)</td>
<td>1.00</td>
<td>71.5 (65.9-76.4)</td>
<td>0.24</td>
</tr>
<tr>
<td>25.0-29.9 (overweight)</td>
<td>324</td>
<td>94</td>
<td>0.74 (0.56-0.98)</td>
<td>0.04</td>
<td>71.0 (65.5-75.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>≥30 (obese)</td>
<td>167</td>
<td>69</td>
<td>0.97 (0.69-1.36)</td>
<td>0.85</td>
<td>58.8 (50.6-66.2)</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Adapted overall survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.5-24.9 (normal weight)</td>
<td>306</td>
<td>57</td>
<td>1.48 (0.98-2.23)</td>
<td>0.06</td>
<td>82.2 (77.2-86.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>25.0-29.9 (overweight)</td>
<td>324</td>
<td>23</td>
<td>0.72 (0.51-1.02)</td>
<td>0.07</td>
<td>81.4 (76.6-85.3)</td>
<td>0.11</td>
</tr>
<tr>
<td>≥30 (obese)</td>
<td>167</td>
<td>44</td>
<td>0.92 (0.60-1.41)</td>
<td>0.72</td>
<td>74.2 (66.4-80.4)</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Adapted breast cancer-specific mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.5-24.9 (normal weight)</td>
<td>306</td>
<td>28</td>
<td>1.50 (0.83-2.73)</td>
<td>0.18</td>
<td>8.0 (5.3-11.4)</td>
<td>0.19</td>
</tr>
<tr>
<td>25.0-29.9 (overweight)</td>
<td>324</td>
<td>23</td>
<td>0.80 (0.45-1.41)</td>
<td>0.43</td>
<td>7.0 (4.5-10.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>≥30 (obese)</td>
<td>167</td>
<td>18</td>
<td>0.83 (0.42-1.66)</td>
<td>0.61</td>
<td>10.5 (6.3-15.7)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Adapted other-cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.5-24.9 (normal weight)</td>
<td>306</td>
<td>29</td>
<td>1.38 (0.76-2.49)</td>
<td>0.29</td>
<td>9.9 (6.7-13.7)</td>
<td>0.11</td>
</tr>
<tr>
<td>25.0-29.9 (overweight)</td>
<td>324</td>
<td>38</td>
<td>0.70 (0.45-1.09)</td>
<td>0.11</td>
<td>11.6 (8.3-15.4)</td>
<td>0.11</td>
</tr>
<tr>
<td>≥30 (obese)</td>
<td>167</td>
<td>26</td>
<td>0.99 (0.56-1.74)</td>
<td>0.97</td>
<td>15.4 (10.1-21.6)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Abbreviations: BMI = body mass index; CI = confidence interval; (s)HR = (subdistribution)hazard ratio.

In the analyses of breast cancer-specific mortality and other-cause mortality, we reported SHR instead of HR.

*Analyses were adjusted for age (≥60 years versus <60 years), history of cardiovascular disease (yes versus no), smoking history (yes versus no), tumour status (pT2 versus pT1), nodal status (pN positive versus pN negative), histology (lobular versus other), histological grade (histological grade 3 versus histological grade 1 and 2), hormone receptor status (oestrogen receptor-positive or progesterone receptor-positive versus oestrogen receptor-positive and progesterone receptor-positive), and previous chemotherapy (yes versus no).
**Normal weight patients**

Adapted disease-free survival

Log-rank P-value = 0.62

3-year anastrozole: 10-yr aDFS: 73.9% (95% CI: 68.4%-79.6%)

6-year anastrozole: 10-yr aDFS: 71.6% (95% CI: 65.9%-77.6%)

**Overweight patients**

Adapted disease-free survival

Log-rank P-value = 0.08

3-year letrozole: 10-yr aDFS: 85.6% (95% CI: 79.3%-91.7%)

6-year letrozole: 10-yr aDFS: 71.5% (95% CI: 65.6%-77.6%)

**Obese patients**

Adapted disease-free survival

Log-rank P-value = 0.04

3-year fulvestrant: 10-yr aDFS: 58.5% (95% CI: 50.9%-66.2%)

6-year fulvestrant: 10-yr aDFS: 55.6% (95% CI: 45.8%-66.2%)

**Adapted overall survival**

Log-rank P-value = 0.05

3-year anastrozole: 10-yr aOS: 87.5% (95% CI: 83.1%-91.9%)

6-year anastrozole: 10-yr aOS: 82.2% (95% CI: 77.2%-86.2%)

Number at risk

3-year anastrozole 307 297 285 277 271 262 251 239 231 221 127

6-year anastrozole 306 296 289 280 272 262 250 242 227 212 114

Follow-up starting from 3 years after randomisation (years)

Follow-up starting from 3 years after randomisation (years)

Log-rank P-value = 0.05

3-year anastrozole: 10-yr aOS: 76.2% (95% CI: 70.5%-82.7%)

6-year anastrozole: 10-yr aOS: 61.4% (95% CI: 55.1%-67.7%)

Number at risk

3-year anastrozole 304 292 278 269 252 234 220 206 200 177 108

6-year anastrozole 324 309 298 292 281 272 257 246 249 223 127

Follow-up starting from 3 years after randomisation (years)

Follow-up starting from 3 years after randomisation (years)

Log-rank P-value = 0.10

3-year anastrozole: 10-yr aOS: 77.8% (95% CI: 72.8%-82.8%)

6-year anastrozole: 10-yr aOS: 67.8% (95% CI: 62.2%-73.4%)

Number at risk

3-year anastrozole 304 290 289 284 276 263 256 246 249 148

6-year anastrozole 324 317 311 303 297 290 281 272 264 145

Follow-up starting from 3 years after randomisation (years)

Follow-up starting from 3 years after randomisation (years)

Log-rank P-value = 0.63

3-year anastrozole: 10-yr aOS: 77.8% (95% CI: 72.8%-82.8%)

6-year anastrozole: 10-yr aOS: 74.2% (95% CI: 66.4%-81.4%)

Number at risk

3-year anastrozole 181 175 167 159 153 144 139 129 118 105 58

6-year anastrozole 167 150 148 143 134 125 117 113 96 46

Follow-up starting from 3 years after randomisation (years)
Figure 5

Adapted breast cancer-specific mortality

Normal weight patients

- 3-year anastrozole: 10-yr aBCSM: 8.9% (95% CI: 3.7-9.9%)
- 6-year anastrozole: 10-yr aBCSM: 8.9% (95% CI: 3.3-11.4%)

Gray's P-value = 0.12

Follow-up starting from 3 years after randomisation (years)

Number at risk
3-year anastrozole: 307
6-year anastrozole: 306

Overweight patients

- 3-year anastrozole: 10-yr aBCSM: 8.5% (95% CI: 5.9-12.4%)
- 6-year anastrozole: 10-yr aBCSM: 7.2% (95% CI: 4.8-10.2%)

Gray's P-value = 0.40

Follow-up starting from 3 years after randomisation (years)

Number at risk
3-year anastrozole: 301
6-year anastrozole: 300

Obese patients

- 3-year anastrozole: 10-yr aBCSM: 11.9% (95% CI: 7.5-17.5%)
- 6-year anastrozole: 10-yr aBCSM: 10.3% (95% CI: 8.1-15.7%)

Gray's P-value = 0.72

Follow-up starting from 3 years after randomisation (years)

Number at risk
3-year anastrozole: 181
6-year anastrozole: 167

Adapted other-cause mortality

D

Adapted breast cancer-specific mortality

Normal weight patients

- 3-year anastrozole: 10-yr aOM: 8.6% (95% CI: 4.1-12.9%)
- 6-year anastrozole: 10-yr aOM: 9.9% (95% CI: 6.7-13.7%)

Gray's P-value = 0.17

Follow-up starting from 3 years after randomisation (years)

Number at risk
3-year anastrozole: 307
6-year anastrozole: 306

Overweight patients

- 3-year anastrozole: 10-yr aOM: 15.0% (95% CI: 11.1-19.9%)
- 6-year anastrozole: 10-yr aOM: 8.3% (95% CI: 5.3-12.7%)

Gray's P-value = 0.26

Follow-up starting from 3 years after randomisation (years)

Number at risk
3-year anastrozole: 304
6-year anastrozole: 303

Obese patients

- 3-year anastrozole: 10-yr aOM: 16.5% (95% CI: 10.1-23.1%)
- 6-year anastrozole: 10-yr aOM: 15.4% (95% CI: 10.1-21.6%)

Gray's P-value = 0.85

Follow-up starting from 3 years after randomisation (years)

Number at risk
3-year anastrozole: 181
6-year anastrozole: 167