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Differential benefit of adjuvant docetaxel-based chemotherapy in patients with early breast cancer according to baseline body mass index

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Abstract

Purpose

Lipophilic drugs, such as taxanes, have a high affinity for adipose tissue and a resulting higher volume of distribution. Here, we reanalyzed clinical trial data to investigate whether the efficacy of docetaxel-based chemotherapy differs from non-docetaxel–based chemotherapy in patients with breast cancer according to their baseline body mass index (BMI).

Patients and Methods

We retrospectively analyzed data from all of the patients in the adjuvant BIG 2-98 trial (ClinicalTrials.gov identifier: NCT00174655; N = 2,887) comparing non-docetaxel– to docetaxel-containing chemotherapy. BMI (kg/m2) was categorized as follows: 18.5 to < 25, lean; 25 to < 30, overweight; and ≥ 30, obese. Disease-free survival (DFS) was the primary endpoint, and overall survival (OS) was the secondary endpoint. A second-order interaction was assessed among treatment, BMI, and estrogen receptor (ER) status.

Results

There was no difference in DFS or OS according to BMI in the non-docetaxel group, while reduced DFS and OS were observed with increasing BMI category in the docetaxel group. Adjusted hazard ratios for DFS and OS were, respectively, 1.12 (95% CI, 0.98 to 1.50; *P* = .21) and 1.27 (95% CI, 1.01 to 1.60; *P* = .04) for overweight versus lean groups and were 1.32 (95% CI, 1.08 to 1.62; *P* = .007) and 1.63 (95% CI, 1.27 to 2.09; *P* < .001), respectively, for obese versus lean groups. Similar results were obtained when considering ER-negative and ER-positive tumors separately and when considering only patients who received a relative dose intensity ≥ 85% for docetaxel. A joint modifying role of BMI and ER status on treatment effect was evident for DFS (adjusted *P* = .06) and OS (adjusted *P* = .04).

Conclusion

This retrospective analysis of a large adjuvant trial highlights a differential response to docetaxel according to BMI, which calls for a body composition–based re-evaluation of the risk-benefit ratio of the use of taxanes in breast cancer. These results now must be confirmed in additional series.

Introduction

The proportion of women with increased adiposity, reflected by an elevated body mass index (BMI), has been increasing in most parts of the world during the past decades, with 64% of women in the United States being either overweight or obese according to the latest estimates.[1] The global health effects of high BMI have been described and include the well-known elevated risk for developing cardiovascular disease and diabetes mellitus.[2] The obesity–breast cancer (BC) connection also has been extensively described; high BMI has been associated in postmenopausal women with a higher risk of developing BC and worse prognosis in patients with BC.[3,4] Recently, it has also been shown that even postmenopausal women with normal BMI but increased body fat have an increased risk of developing BC.[5]

It is known that differences in the pharmacokinetic/pharmacodynamic activities of drugs, and especially lipophilic drugs, can exist between lean and obese patients. [6] Nevertheless, and despite the high frequency of overweight and obese patients with cancer, the efficacy of most of the anticancer drugs has not yet been thoroughly and systematically evaluated according to patient adiposity. Therefore, it remains questionable whether the main results from randomized clinical trials for cancer treatment are applicable to the different BMI subgroups.

Two examples of lipophilic drugs commonly used for treating BC are docetaxel and paclitaxel, both belonging to the taxane family. Their bulky polycyclic nature makes it difficult to make hydrogen bonds with water. Therefore, they usually are solubilized using high doses of surfactants or cosolvents to enable intravenous infusion, resulting in notable, additional toxicity.[7]

Here, according to the different lipophilic properties of the involved drugs, we aimed to investigate whether the efficacy of docetaxel-based chemotherapy differs from non-docetaxel–based chemotherapy in patients with BC according to their BMI by carrying out a retrospective analysis of an adjuvant trial of patients with early BC.

Patients and methods

Patients

We considered the patients from the adjuvant BIG 2-98 phase III trial (ClinicalTrials.gov identifier: NCT00174655).[8,9]
In brief, 2,887 patients were enrolled between June 1998 and June 2001 and randomly assigned to 1 of 4 treatment arms in a 1:1:2:2 ratio, as follows: (1) sequential control (4 cycles of doxorubicin at 75 mg/m2 and 3 cycles of cyclophosphamide, methotrexate, and fluorouracil [CMF]); (2) concurrent control (4 cycles of doxorubicin at 60 mg/m^2 plus cyclophosphamide at 600 mg/m^2 and 3 cycles of CMF); (3) sequential docetaxel (3 cycles of doxorubicin at 75 mg/m^2 , and 3 cycles of docetaxel at 100 mg/ m^2, followed by 3 cycles of CMF); or (4) concurrent docetaxel (4 cycles of doxorubicin at 50 mg/ m^2 plus docetaxel at 75 mg/ m^2, and 3 cycles of CMF). Women younger than 71 years with operable, clinical stage T1-3 invasive adenocarcinoma with > 1 positive lymph node were enrolled, and patients with metastatic BC were excluded. Although the initial 5-year analysis reported an improvement in disease-free survival (DFS) of borderline statistical significance for the

docetaxel arms compared with the control arms,[8] no significant difference was observed at the final 10-year analysis.[9] Patients from the control arms were grouped, as were those from the docetaxel arms, regardless of treatment schedule, as was done for the primary analysis of the initial study. The latest version of the database (June 2012) was used.

BMI was calculated from the height and weight measurements at the time of enrollment and categorized according the WHO definitions: underweight (< 18.5 kg/m^2), lean (≥ 18.5 and < 25 kg/m^2), overweight (≥ 25 and < 30 kg/m^2), and obese (≥ 30 kg/m^2). The actual body weight was used for the calculation of the body surface area (BSA). However, a protocol amendment reduced the chemotherapy dose to a maximum BSA of 2.0 m^2 after an obese patient died of a toxicity-related adverse effect. At that time, > 75% of the patients were already enrolled. Underweight patients (n = 48; Data Supplement) were excluded from this study, given their low frequency and their potentially adverse prognosis.[10]

Statistical analysis

The associations between the BMI categories and the clinicopathologic variables were assessed using Fisher's exact test. The categorized relative dose intensity (RDI) of the different chemotherapy agents[11] was compared between the BMI categories in each treatment arm using Fisher's exact test. The mean total dose per cycle is defined as the sum of the total dose of the treatment considered for each cycle divided by the number of cycles. RDI is the ratio of the received mean total dose to the planned dose (computed using the actual body weight) of the treatment considered. RDI is expressed as a percentage of the planned dose. The median follow-up time, as estimated by the reverse Kaplan-Meier method, was 10.1 years. The follow-up was curtailed at 10 years, because this was the minimal potential follow-up for all patients as per protocol. DFS and overall survival (OS) were considered as primary and secondary endpoints, respectively, as in the initial trial.[8] DFS was calculated from the date of random assignment to the first date of a local, regional, or distant relapse; of the diagnosis of a second primary cancer, including contralateral invasive BC; or of death from any cause. OS was defined as the time from study entry until death of any cause. Both DFS and OS were studied by Kaplan-Meier curves and Cox regression models. To explore whether the difference in sample size between docetaxel and non-docetaxel arms could affect the results, we randomly sampled as many patients from the former as from the latter. The treatment by BMI by estrogen receptor (ER) status second-order interaction was investigated, adjusting for standard prognostic variables. The reasons supporting the inclusion of the ER status in the interaction are based on well-known differences between ER-negative and ER-positive BC in terms of biology and treatment. Competing risk analysis of distant recurrences according to BMI categories was explored using crude cumulative incidence curves. These can be interpreted as the cumulative probability of distant metastases as first event[12] and are assessed by Fine and Gray semiparametric models on subdistribution hazards. [13] Exploratory analyses also considered BMI on a continuous scale. The analyses were adjusted for standard clinicopathologic variables: age (< 50 or ≥ 50 years), tumor size (< 2 or ≥ 2 cm), nodal status (< 4 or ≥ 4 positive nodes) and ER status (negative or positive). We considered the locally assessed ER status, because it was used for determining the administration of adjuvant endocrine treatment and was available for nearly all patients. In contrast, HER2 status was not considered as an adjusting variable in the main analyses, because it was only available for < 2,000 patients, thus considerably reducing the statistical power of the adjusted analyses.
However, we also conducted explorative analyses, in which the molecular subtypes were added as covariables (n = 1,122 patients). All *P* values were 2 sided at a significance level of .05, as a

reference indication, because no explicit sample size calculation was performed in this post hoc analysis of trial data. Because of this rationale and the prespecified hypothesis, a multiplicity correction for the type I error rate was not explicitly adopted. All analyses were performed with the use of R, version 3.6.1.

Results

Baseline BMI and patient characteristics

Baseline BMI was available for all patients in the BIG 2-98 trial. After excluding the underweight patients (Data Supplement), 47.4% of the patients were lean, 33.5% were overweight, and 19.1% were obese. In agreement with the literature, [14-16] older age at diagnosis and larger tumors were significantly associated with the increased BMI categories (Table 1). Of note, in this trial, all patients presented with axillary lymph node involvement; however, increased axillary lymph node involvement was showing evidence of association with BMI only in the docetaxel group, which was not expected given the randomized setting. Similar results were obtained when considering BMI as a continuous variable (data not shown).

Comparison of the dosing patterns of non-docetaxel– and docetaxel-based treatment according to BMI

We compared the proportion of patients having an RDI < 85%, a cutoff often used in the literature to define reduced dose intensity, [11] between the different BMI groups for each drug in the different arms (Data Supplement). Although there was no evidence of difference for any of the drugs in the non-docetaxel arms, there was a statistically significant increase in the proportion of patients with an RDI < 85% for docetaxel in the sequential docetaxel arm (lean, 4%; overweight, 2%; obese, 8%; *P* = .003) as well as in the concurrent docetaxel arm (lean, 8%; overweight, 13%; obese, 16%; *P* = .009).

Comparison of the efficacy of non-docetaxel– and docetaxel-based treatment according to BMI

We first investigated DFS in the non-docetaxel– and docetaxel-treated patients from the BIG 2-98 trial according to the BMI categories (Fig 1). Though no major or statistically significant difference was observed in the non-docetaxel arm (Fig 1A), a significant decrease in DFS was observed in overweight and obese patients compared with lean patients in the docetaxel-treated group (Fig 1D). The impact of BMI on DFS also remained statistically significant after adjusting for standard variables (Table 2). Considering BMI as a continuous variable, we then observed a significant increase in the hazard ratios (HRs) in the docetaxel-treated group (Data Supplement). Given the important differences in tumor biology and treatment regarding hormone receptor status (patients with ER-positive tumors having received adjuvant endocrine therapy), we also assessed the role of BMI on treatment benefit according to the ER status. In the non-docetaxel group, no significant difference was observed between the three BMI categories in patients who had ER-negative and ER-positive statuses (Figs 1B-1C). In the docetaxel group, the curves from both overweight and obese patients presented a lower DFS in those with ER-negative status, whereas, in the ER-positive group, only obese women presented with a lower DFS when compared with the overweight and lean ones (Figs 1E-1F). These observations remained statistically significant in the adjusted analyses (Data Supplement). We also observed higher HRs for DFS with increasing BMI in the docetaxel group only when considering BMI as a continuous variable, and only in patients with ER-negative tumors (Data Supplement). Considering OS, we observed consistent results compared with DFS when considering the categoric or continuous BMI in the global population of patients treated in the 2 treatment groups (Figs 2A, 2D), in the unadjusted as well as adjusted analysis (Table 3), and in the subgroups defined by ER status (Figs 2B-2C, 2E-2F; Data Supplement). Of note, results also were consistent when considering distant metastasis as an endpoint (Data Supplement). To allow a comparison between overweight and obese patients, we performed an additional analysis with parametrization for ordinal covariables (overweight v lean, and obese v overweight). In summary, there is no evidence of differences between overweight and obese patients in the non-docetaxel group, but we observed significant differences in the docetaxel-based group—mainly in the patients with ER-positive BC for DFS (adjusted HR, 1.37; 95% CI, 1.06 to 1.78; *P* = .02), OS (adjusted HR, 1.59; 95% CI, 1.14 to 2.22; P = .006), and distant metastases (adjusted HR, 1.43; 95% CI, 1.06 to 1.93; *P* = .02). It was also evident in the global population for OS (adjusted HR, 1.28; 95% CI, 1.00 to 1.64; *P* = .05).

The analyses also showed evidence for a second-order interaction for DFS (Wald *P* value for analysis, unadjusted for the covariables, = .05; *P* value for adjusted analysis = .06) and for OS (unadjusted *P* = .04; adjusted *P* = .04), thus supporting a joint modifying role of BMI and ER status on the treatment effect. Several observations, which should be interpreted with caution given the multiplicity of the comparisons, could be done when looking at the treatment effect according the different BMI/ER status combinations (Data Supplement). In summary, a benefit for docetaxel-based versus non-docetaxel–based treatment seems to be observed only with regard to OS for lean and overweight patients with ER-positive tumors, whereas docetaxel-based treatment appears to be detrimental for overweight patients with ER-negative tumors.

To explore whether the decreased DFS and OS, and the increased rate of distant recurrences, in heavier patients treated with docetaxel-based chemotherapy could be related to the increased proportion of patients who received less than the RDI of 85% for docetaxel, we repeated the analyses considering only patients within the docetaxel-based arms who had an RDI for docetaxel ≥ 85% and observed similar results with regard to DFS and OS (Data Supplement).

To explore whether the observed differences between docetaxel-based and non- docetaxel–based arms could be due to the different sample sizes, we randomly sampled as many patients from the former as from the latter. The results provided evidence with regard to the effect size that was similar to the ones presented in Table 2 and 3, with an expected decrease in significance caused by a halving of the sample size (Data Supplement).

To explore the contribution of the different molecular subtypes, we conducted adjusted DFS and OS analyses in the subgroup of patients for which centrally assessed ER, PR, HER2 and Ki67 results were available (n = 1,656), with the molecular subtypes as covariables. We observed consistent results for DFS and OS, with a decrease in statistical significance, which also was expected because of the decrease in sample size (Data Supplement).

Finally, an exploratory analysis revealed that the observed impact of BMI in the docetaxel-treated patients was present in patients treated in both the sequential and the concurrent docetaxel-based arms (Data Supplement).

Discussion

In this study, we demonstrated that overweight and obese patients treated with a docetaxel-based adjuvant chemotherapy regimen in the BIG 2-98 trial presented with worse DFS and OS as well as an increased risk of developing distant metastases compared with lean patients treated with the same chemotherapy regimen. Conversely, there was no difference according to the BMI categories in the patients treated without docetaxel. Importantly, the results were preserved when restricting the analysis to the patients who received ≥ 85% of the RDI for docetaxel. A previous study already investigated the effect of BMI on survival in this trial and reported obesity as an independent predictor of DFS and OS. [17] However, overweight patients were then analyzed together with lean patients, and all treatment arms were pooled together. Importantly, our results showed evidence for a second-order interaction for DFS and OS, here supporting a joint modifying role of BMI and ER status on the treatment effect. We consider these results to be relevant, because the trial was not conceived to be powered for these analyses. In addition, when exploring the groups of patients made by the different BMI and ER status categories, it appears that the benefit for docetaxel-based versus non-docetaxel–based treatment could be limited to lean and overweight patients with ER-positive tumors and, possibly, to lean patients with ER-negative tumors but that docetaxel-based treatment could even be detrimental for overweight patients with ER-negative tumors. These results, however, should be taken with caution, given the multiplicity of the tests.

The present observations could be explained by the lipophilic nature of docetaxel, which results in a higher volume of distribution [18] and a decreased efficacy at the distant level in patients with increased BMI. To the best of our knowledge, this is the first time that DFS, OS, and distant recurrences were compared between docetaxel-based and non-docetaxel–based chemotherapy regimens of a trial according to BMI. Pajares et al [19] investigated retrospectively the impact of BMI on survival among 5,863 patients with BC treated with or without taxanes in 4 adjuvant randomized clinical trials. They did not find a different outcome between lean and obese patients in terms of recurrence, overall survival, or BC-specific survival. In the same line, Ladoire et al [20] did not find a significant impact of obesity on DSF or OS among 4,996 patients with node-positive early BC treated with or without taxanes in 2 adjuvant clinical trials. Importantly, these 2 studies did not distinguish taxane-based versus non-taxane–based chemotherapy regimens in their analysis, as performed in this study.

Important limitations of our study are mainly related to its retrospective nature, with BMI being the only available surrogate for patient adiposity and not being collected longitudinally during follow-up; the lack of centralized information for all tumors regarding ER, PR, HER2 and Ki67 statuses; the lack of information regarding the type of endocrine therapy; and the lack of pharmacokinetic data. In addition, because follow-up data were not systematically collected after the administrative end of the trial after 10 years of follow-up, late effects could not be effectively investigated. However, the considered trial is unique, because, to the best of our knowledge, no other trial has compared the efficacy of taxane-based versus non-taxane-based regimens in the adjuvant setting without an upfront capping of the BSA in heavier patients to calculate the chemotherapeutic doses to be administered.

If our results are confirmed in other series, they could have several implications. First, they would question the actual benefit of treating heavier patients with adjuvant docetaxel-based regimens. Second, if the pharmacologic properties of docetaxel are indeed causing the observed differences in treatment efficacy according to patient adiposity, we could expect similar results for paclitaxel, another lipophilic drug from the taxane family widely used for the treatment of BC. Third, our findings question the validity and may explain the heterogeneity of the results reported in the various meta-analyses or pooled analyses that investigated the prognostic effect of BMI without acknowledging the heterogeneity of the administered treatments. Finally, according to study rationale, in a much broader context, this study emphasizes the gap in knowledge we have on the efficacy of the various anticancer treatments according to patient adiposity, especially for lipophilic drugs. Alternative, more complex hypotheses related to the different cancer biology according to adiposity and treatment pharmacology cannot be disentangled presently but should not be excluded. For instance, recent in vitro studies have demonstrated that adipocytes can upregulate the expression of the transport-associated major vault protein in epithelial cells, decreasing the nuclear accumulation of chemotherapy and leading to chemoresistance.[21] It remains to be demonstrated whether this adiposity-associated mechanism of chemoresistance differs according to the chemotherapeutic agent. As a next step, we are developing a prospective pharmacokinetics study and will be performing similar analyses in other adjuvant trials evaluating taxanes for treating BC.

To conclude, this retrospective analysis of a large adjuvant clinical trial highlights a differential response of taxanes, and more specifically docetaxel, according to BMI. These results now must be confirmed in additional series. If they are confirmed, then a body composition–based re-valuation of the risk-benefit ratio of the use of taxanes in BC should be considered.

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Table 1. Clinical and Pathologic Characteristics by Treatment and BMI Category in the Adjuvant BIG 2-98 Trial

	N (%) of patients							
	Docetaxel-Free Arm (n 5 959)				Docetaxel-Based Arm (n 5 1,880)			
Characteristics	**Lean (n=459)**	**Overweight (n=319)**	**Obese (n=181)**	***P***	**Lean (n=887)**	**Overweight (n=632)**	**Obese (n=361)**	***P***
Age, years								
< 50	285 (62)	162 (51)	65 (36)	< .0001	583 (66)	278 (44)	133 (37)	< .0001
≥ 50	174 (38)	157 (49)	116 (64)		304 (34)	354 (56)	228 (63)	
Tumor size, cm								
< 2	166 (36)	88 (28)	49 (27)	.01	315 (36)	181 (29)	106 (29)	.009
≥ 2	290 (64)	229 (72)	131 (73)		568 (64)	447 (71)	255 (71)	
Unknown	3	2	1		4	4	-	
N. of positive nodes								
1-3	259 (56)	165 (52)	96 (53)	.41	516 (58)	328 (52)	172 (48)	.001
≥ 4	200 (44)	154 (48)	85 (47)		371 (42)	304 (48)	189 (52)	
Grade								
1	30 (8)	17 (7)	12 (8)	.83	42 (6)	37 (7)	22 (8)	.33
2	175 (47)	112 (45)	74 (50)		371 (51)	237 (46)	144 (50)	
3	166 (45)	118 (48)	62 (42)		315 (43)	245 (47)	124 (43)	
Unknown	88	72	33		159	113	71	
ER status								
Negative	32 (29)	96 (30)	57 (31)	.78	247 (28)	172 (27)	110 (31)	.51
Positive	326 (71)	223 (70)	124 (69)		640 (72)	459 (73)	250 (69)	
Unknown	1	-	-		-	1	1	
PgR status								
Negative	168 (40)	117 (41)	66 (40)	.93	315 (39)	223 (39)	137 (42)	.57
Positive	257 (60)	169 (59)	97 (60)		492 (61)	354 (61)	189 (58)	
Unknown	34	33	18		80	55	35	
HER2 status								
Negative	250 (84)	175 (83)	115 (82)	.85	488 (82)	375 (81)	215 (86)	.24
Positive	47 (16)	35 (17)	25 (18)		110 (18)	86 (19)	35 (14)	
Unknown	162	109	41		289	171	111	

The *P* value is based on the Fisher's exact test.
Abbreviations: BMI, body mass index; ER, estrogen receptor; PgR, progesterone receptor.

Table 2. Results from univariable and multivariable Cox regression models for disease-free survival, with estimated HRs of the different BMI categories within the docetaxel-free and docetaxel-based chemotherapy arms

	Univariable			Multivariable		
Variable by arm	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Docetaxel-free arm						
BMI (n = 959)			.29*			.74*
Overweight *v.* lean	1.15	0.91 to 1.46	.25	1.07	0.85 to 1.36	.56
Obese *v.* lean	1.23	0.93 to 1.62	.15	1.11	0.83 to 1.47	.49
Age, years (n = 959): ≥ 50 *v.* < 50	1.19	0.797 to 1.47	.10	1.21	0.98 to 1.50	.08
Size, cm (n = 953): ≥ 2 *v.* < 2	1.94	1.50 to 2.51	<.0001	1.73	1.33 to 2.24	<.0001
N. of nodes (n = 959): ≥ 4 *v.* < 4	2.31	1.86 to 2.86	<.0001	2.15	1.73 to 2.69	<.0001
Local ER status (n = 958): positive v. negative	0.66	0.53 to 0.82	.0002	0.65	0.52 to 0.81	.0002
Docetaxel-based arm						
BMI (n = 1,880)			.003*			.03*
Overweight *v.* lean	1.16	0.98 to 1.38	.09	1.12	0.98 to 1.50	.21
Obese *v.* lean	1.46	1.16 to 1.72	.0006	1.32	1.08 to 1.62	.007
Age, years (n = 1880): ≥ 50 *v.* < 50	1.02	0.77 to 1.11	.84	0.95	0.81 to 1.11	.51
Size, cm (n = 1872): ≥ 2 *v.* < 2	1.66	1.51 to 2.35	<.0001	1.46	1.22 to 1.75	<.0001
N. of nodes (n = 1880): ≥ 4 *v.* < 4	2.06	1.88 to 2.73	<.0001	1.99	1.70 to 2.33	<.0001
Local ER status (n= 1878): positive *v.* negative	0.63	0.58 to 0.87	.0007	0.63	0.54 to 0.74	<.0001

No. of patients for multivariable analysis in docetaxel-free arm was 952 and in docetaxel-based arm was 1,870. No. of patients for univariable analyses are listed in leftmost column by variable. The reported BMI was based on a baseline measurement.
Abbreviations: BMI, body mass index; ER, estrogen receptor; HR, hazard ratio.
*Two-sided global Wald test from Cox regression model.

Table 3. Results from univariable and multivariable Cox regression models for overall survival, with estimated HRs of the different BMI categories within the docetaxel-free and docetaxel-based chemotherapy arms

	Univariable			**Multivariable**		
Variable by arm	**HR**	95% CI	***P***	**HR**	**95% CI**	***P***
Docetaxel-free arm						
BMI (n = 959)			.44*			.76*
Overweight *v.* lean	1.04	0.77 to 1.39	.80	0.96	0.71 to 1.29	
Obese *v*. lean	1.24	0.89 to 1.72	.21	1.10	0.78 to 1.54	
Age, years (n = 959): ≥ 50 *v*. < 50	1.21	0.94 to 1.57	.14	1.22	0.94 to 1.59	
Size, cm (n = 953): ≥ 2 *v*. < 2	2.11	1.53 to 2.92	<.0001	1.82	1.31 to 2.52	
N. of nodes (n = 959): ≥ 4 *v*. < 4	2.80	2.14 to 3.67	<.0001	2.55	1.94 to 3.35	
Local ER status (n = 958): positive v. negative	0.62	0.47 to 0.80	.0003	0.62	0.48 to 0.81	
1Docetaxel-based arm						
BMI (n = 1,880)			<.0001*			.0006*
Overweight *v.* lean	1.31	1.05 to 1.64	.02	1.27	1.01 to 1.60	.04
Obese *v*. lean	1.79	1.40 to 2.28	<.0001	1.63	1.27 to 2.09	.0001
Age, years (n = 1880): ≥ 50 *v*. < 50	1.06	0.87 to 1.28	.55	0.95	0.78 to 1.16	.63
Size, cm (n = 1872): ≥ 2 *v*. < 2	1.95	1.54 to 2.47	<.0001	1.64	1.29 to 2.08	<.0001
N. of nodes (n = 1880): ≥ 4 *v*. < 4	2.30	1.89 to 2.81	<.0001	2.20	1.80 to 2.68	<.0001
Local ER status (n= 1878): positive *v*. negative	0.45	0.37 to 0.54	<.0001	0.45	0.37 to 055	<.0001

No. of patients for multivariable analysis in docetaxel-free arm was 952 and in docetaxel-based arm was 1,870. No. of patients for univariable analyses are listed in leftmost column by variable. The reported BMI was based on a baseline measurement.
Abbreviations: BMI, body mass index; ER, estrogen receptor; HR, hazard ratio.
*Two-sided global Wald test from Cox regression model.

Figure 1. Kaplan-Meier curves for disease-free survival according to the body mass index categories in patients from (A-C) the docetaxel-free arms and (D-F) the docetaxel-based arms in (A, D) all patients and in patients with (B, E) estrogen receptor–negative and (C, F) estrogen receptor–positive tumors.

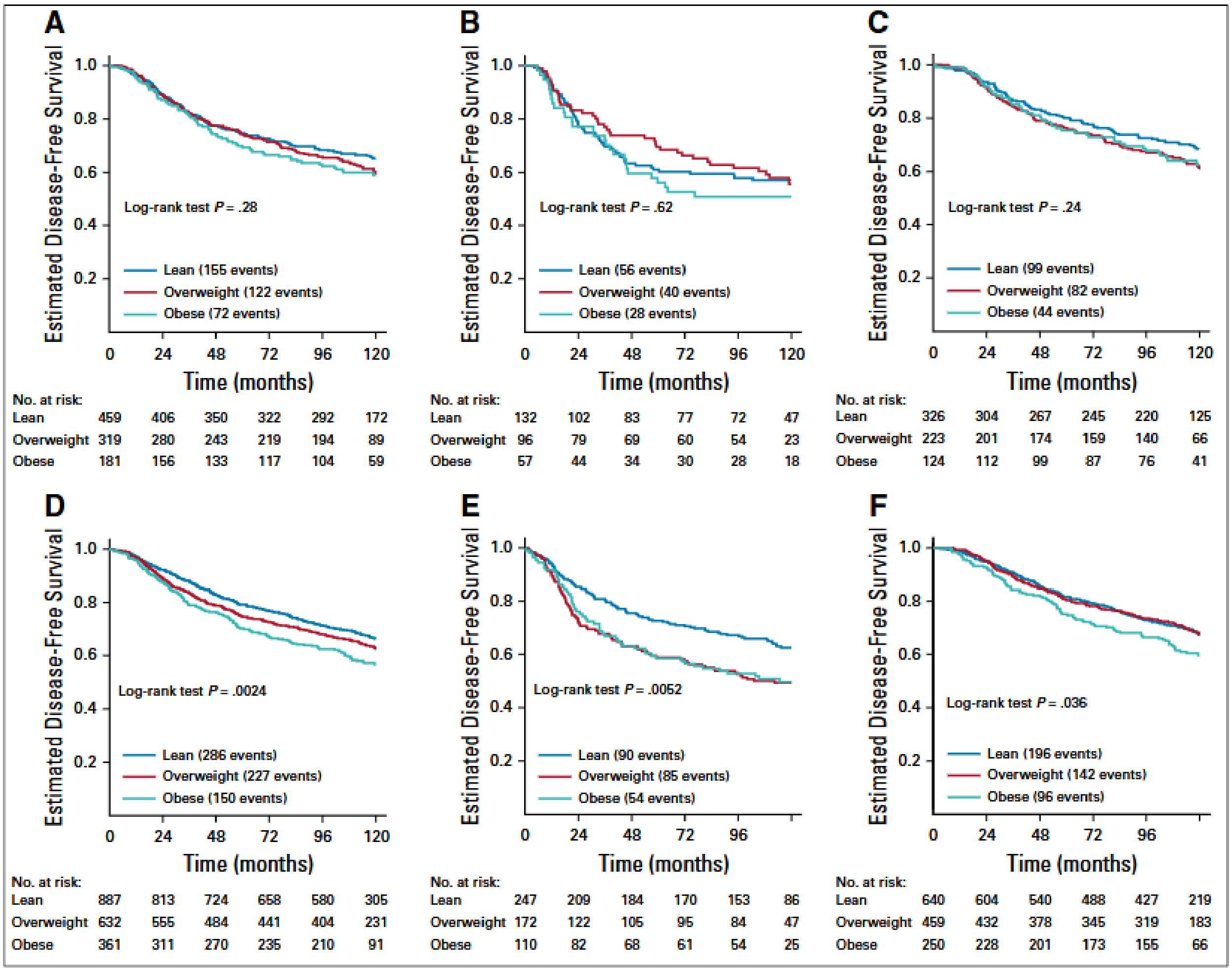

Figure 2. Kaplan-Meier curves for overall survival according to the body mass index categories in patients from (A-C) the docetaxel-free arms and (D-F) the docetaxel-based arms in (A, D) all patients and in patients with (B, E) estrogen receptor–negative and (C, F) estrogen receptor–positive tumors.