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ORIGINAL REPORT

Obesity and Risk of Recurrence or Death After Adjuvant Endocrine Therapy With Letrozole or Tamoxifen in the Breast International Group 1-98 Trial

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ABSTRACT

Purpose
To examine the association of baseline body mass index (BMI) with the risk of recurrence or death in postmenopausal women with early-stage breast cancer receiving adjuvant tamoxifen or letrozole in the Breast International Group (BIG) 1-98 trial at 8.7 years of median follow-up.

Patients and Methods
This report analyzes 4,760 patients with breast cancer randomly assigned to 5 years of monotherapy with letrozole or tamoxifen in the BIG 1-98 trial with available information on BMI at randomization. Multivariable Cox modeling assessed the association of BMI with disease-free survival, overall survival (OS), breast cancer–free interval, and distant recurrence-free interval and tested for treatment-by-BMI interaction. Median follow-up was 8.7 years.

Results
Seventeen percent of patients have died. Obese patients (BMI $\geq$ 30 kg/m^2) had slightly poorer OS (hazard ratio [HR] = 1.19; 95% CI, 0.99 to 1.44) than patients with normal BMI ($<$ 25 kg/m^2), whereas no trend in OS was observed in overweight (BMI 25 to $<$ 30 kg/m^2) versus normal-weight patients (HR = 1.02; 95% CI, 0.86 to 1.20). Treatment-by-BMI interactions were not statistically significant. The HRs for OS comparing obese versus normal BMI were HR = 1.22 (95% CI, 0.93 to 1.60) and HR = 1.18 (95% CI, 0.91 to 1.52) in the letrozole and tamoxifen groups, respectively.

Conclusion
There was no evidence that the benefit of letrozole over tamoxifen differed according to patients' BMI.

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INTRODUCTION

Obesity is a well-documented adverse prognostic factor in early-stage breast cancer.[1-3] The causal mechanism by which obesity influences prognosis remains to be elucidated, but it has been suggested that it relates to the biology of the disease or to treatment being less effective in obese patients.[1,4] The mechanism whereby obesity might affect adjuvant cytotoxic therapy could differ from any such effect on adjuvant endocrine therapy. Thus some studies have shown that obese patients received reduced doses of adjuvant chemotherapy and that this was associated with a worse outcome.[5,6] However, in a retrospective multivariate analysis of 2,887 patients with node-positive breast cancer enrolled onto the Breast International Group (BIG) 02-98 trial, obesity remained an independent prognostic factor for disease-free survival as well as overall survival despite similar relative dose-intensities of chemotherapy with docetaxel and doxorubicin, or cyclophosphamide, methotrexate, and fluorouracil among obese and nonobese patients.[7] In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial involving 3,385 women with lymph node-negative, estrogen receptor–positive breast cancer, the benefit of tamoxifen did not vary across body mass index (BMI) groups.[8] Aromatase inhibitors depend on a reduction in peripheral formation of estrogen by aromatization, mainly in adipose tissue, in postmenopausal women. The investigators of the Arimidex, Tamoxifen Alone or in Combination (ATAC) Trial reported that although tamoxifen was equally effective across all BMI categories, anastrozole was

significantly less effective in postmenopausal women with a BMI exceeding 30 kg/m^2. They suggested that estrogen suppression with anastrozole may not be complete in obese women.[9]

The purpose of the present report is to examine the same questions in the context of the BIG 1-98 trial[10] comparing letrozole, an aromatase inhibitor that suppresses estrogen more effectively than anastrozole,[11,12] versus tamoxifen in postmenopausal women with early breast cancer.

PATIENTS AND METHODS

Patients

The BIG 1-98 study is a randomized, phase III, double-blind trial comparing 5 years of monotherapy with tamoxifen or with letrozole, or with sequences of 2 years of one followed by 3 years of the other for postmenopausal women with endocrine-responsive early invasive breast cancer.[10,13-15] From 1998 to 2003, BIG 1-98 enrolled 8,028 women into one of two randomization options (Fig 1).The letrozole (Femara; Novartis, Basel, Switzerland) dose was 2.5 mg daily, and the tamoxifen dose was 20 mg daily. The ethics committees and required health authorities of each participating institution approved the study protocol, and all patients gave written informed consent. Details of eligibility, design, and protocol requirements were published in the first report of the overall study results.[13] A total of 4,922 patients were randomly assigned to letrozole or tamoxifen monotherapy for 5 years. The results of the monotherapy comparison were first published in 2007[14] at 4.3 years of median follow-up and were most recently updated at 8.7 years of median follow-up (range, 0 to 12.4 years).[15] This report is based on the most recent update[15] and includes 4,760 patients after excluding 162 who did not have a height measurement recorded to allow the calculation of baseline BMI (Fig 1).

Height and weight were recorded at randomization, before the start of adjuvant endocrine treatment, and were used to calculate baseline BMI, which was classified according to defined groups: normal (< 25 kg/m^2), overweight (25 to < 30 kg/m^2), and obese (≥ 30 kg/m^2). The primary trial end point was disease-free survival (DFS), defined as the time from randomization to the first of the following events: invasive recurrence in local, regional, or distant sites; a new invasive cancer in the contralateral breast; any second (nonbreast) primary cancer; or death without a prior cancer event. In the absence of an event, DFS is censored at the last follow-up visit. Secondary end points included breast cancer–free interval, defined as the time from randomization to the first breast cancer event, and distant recurrence–free interval, defined as the time from randomization to the first invasive recurrence in a distant site: each ignored second (nonbreast) primary cancers and were censored at death without a prior cancer event or at last follow-up visit. Overall survival (OS) was defined as the time from randomization to death resulting from any cause or was censored at date last known alive. After the initial trial results were released in 2005, patients assigned to tamoxifen monotherapy were so informed and offered the chance to cross-over to letrozole for the remainder of their adjuvant therapy, and 619 (25.2%) did so; the follow-up of these patients is censored at the date of selective cross-over.[16]

Statistical Analysis

The associations between the BMI groups and other patient and disease characteristics were evaluated using the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables. The Kaplan-Meier method was used to estimate distributions of disease outcomes according to BMI groups.

Multivariable Cox proportional hazards models[17] were used to test heterogeneity of disease outcomes according to BMI categories (2-*df* likelihood

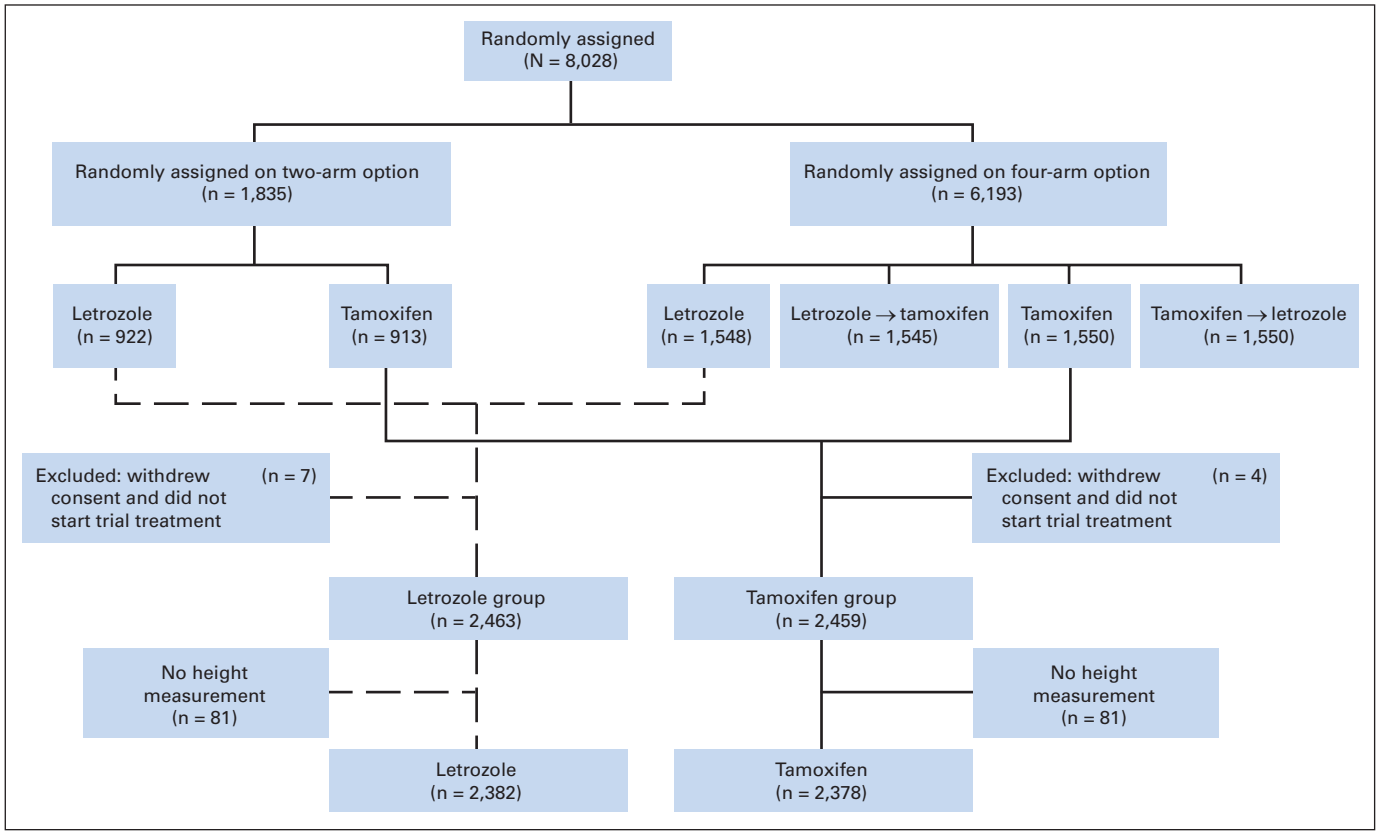

Fig 1. CONSORT diagram showing the analytic cohort of 4,760 patients enrolled in the BIG 1-98 clinical trial.

Table 1. Characteristics of 4,760 of 4,922 Patients Randomly Assigned in BIG 1-98 Trial Monotherapy Population Who Had Weight and Height Data Reported at Randomization, According to BMI at Randomization

	BMI (kg/m^2) at Randomization						
	< 25 (normal) (n = 1,929)		25 to < 30 (overweight) (n = 1,734)		≥ 30 (obese) (n = 1,097)		
Characteristic	No.	%	No.	%	No.	%	*P**
Randomized treatment assignment							
Letrozole	958	50	880	51	544	50	.760*
Tamoxifen	971	50	854	49	553	50	
Age, years							
Median	60		62		62		< .001†
Range	38-90		39-88		42-85		
< 56	655	34	414	24	258	24	
57-61	435	23	395	23	253	23	
62-67	413	21	470	27	291	27	
≥ 68	426	22	455	26	295	27	
Diagnosis to randomization, months							
Median	1.2		1.2		1.4		.179†
Quartile 1 to quartile 3	0.9-3.0		0.9-3.0		0.9-3.4		
Geographic regions‡							
AUS/NZ	161	8	161	9	158	14	< .001*
South America	59	3	63	4	43	4	
Eastern Europe	229	12	327	19	265	24	
Western Europe/other	1,480	77	1,183	68	631	58	
Prior chemotherapy							
Yes	465	24	433	25	317	29	.010*
No	1,464	76	1,301	75	780	71	
Local therapy							
BCS+RT	1,016	53	856	49	505	46	.013*
BCS without RT	61	3	65	4	49	4	
Mastectomy+RT	334	17	320	18	231	21	
Mastectomy without RT	513	27	492	28	308	28	
Other	5	0	1	0	4	0	
Nodal status							
Negative/Nx	1,161	60	1011	58	578	53	< .001*
Positive	767	40	722	42	516	47	
Unknown	1		1		3		
Tumor grade							
1	530	31	444	29	261	28	.701*
2	913	53	813	53	496	54	
3	290	17	274	18	165	18	
Unknown	196		203		175		
Tumor size, cm							
Median	1.7		1.9		2.0		< .001†
Quartile 1 to quartile 3	1.2-2.4		1.3-2.5		1.5-2.8		
≤ 2	1,299	68	1,037	60	584	54	
2-5	554	29	606	35	444	41	
≥ 5	63	3	76	4	54	5	
Unknown	13		15		15		
Peritumoral vascular invasion							
No	1,439	82	1,264	81	775	79	.322*
Yes	321	18	301	19	201	21	
Unknown	169		169		121		
Centrally assessed ER status							
Absent	21	1	28	2	12	2	.331*
Present	1,390	99	1,251	98	772	98	
Unknown	518		455		313		
Centrally assessed PgR status							
Absent	202	14	155	12	65	8	< .001*
Present	1,204	86	1,127	88	720	92	
Unknown	523		452		312		

(continued on following page)

Table 1. Characteristics of 4,760 of 4,922 Patients Randomly Assigned in BIG 1-98 Trial Monotherapy Population Who Had Weight and Height Data Reported at Randomization, According to BMI at Randomization (continued)

Characteristic	BMI (kg/m^2) at Randomization: < 25 (normal) (n = 1,929) No.	%	25 to < 30 (overweight) (n = 1,734) No.	%	≥ 30 (obese) (n = 1,097) No.	%	*P**
Centrally assessed HER2							
Negative	1,323	92	1,218	94	734	93	.155*
Positive	113	8	78	6	59	7	
Unknown	493		438		304		
Centrally assessed Ki67 LI							
Median	12		12		12		.903†
Quartile 1 to quartile 3	6-18		7-19		7-18		
< 14%	1,259	68	1,137	68	743	69	
≥ 14%	606	32	543	32	334	31	
Unknown	64		54		20		
History of diabetes							
Yes	47	2	87	5	125	11	< .001*
No	1,882	98	1,645	95	971	89	
Unknown	0		2		1		
Smoking history							
Yes	751	39	587	34	327	30	< .001*
No	1,178	61	1,147	66	770	70	
HRT before randomization							
No	1,074	56	1,156	67	826	75	< .001*
Within the last 3 months	437	23	269	16	118	11	
> 3 months ago	418	22	309	18	153	14	
History of hypercholesterolemia							
Yes	146	8	149	9	101	9	.256*
No	1,783	92	1,585	91	996	91	
History of hypertension							
Yes	396	21	576	33	531	48	< .001*
No	1,533	79	1,158	67	566	52	
History of CVA/TIA							
Yes	29	2	36	2	18	2	.399*
No	1,900	98	1,698	98	1,079	98	
History of any ischemia							
Yes	47	2	53	3	73	7	< .001*
No	1,882	98	1,681	97	1,024	93	
History of any cardiac morbidity							
Yes	146	8	136	8	135	12	< .001*
No	1,783	92	1,598	92	962	88	

Abbreviations: BCS, breast-conserving surgery; BMI, body mass index; ER, estrogen receptor; LI, labeling index; Nx, nodes not assessed; PgR, progesterone receptor; RT, radiotherapy.

*χ^2 test.

†Kruskal-Wallis test.

‡The geographic regions were defined as: AUS/NZ: Australia, New Zealand; South America: Brazil, Peru, Argentina, Chile; Eastern Europe: Czech Republic, Russia, Hungary, Poland, Slovenia, and Turkey; Western Europe/Other: the rest of countries in the BIG 1-98 trial (including Canada, South Africa).

ratio test) and to estimate hazard ratios (HR) and 95% CIs comparing obese or overweight versus normal weight. The proportional hazards assumption was assessed using Schoenfeld residuals. Because the hypothesis focuses on the obese versus normal BMI groups, the pairwise comparisons are reported regardless of the result of the global test. The multivariable models adjusted for age at randomization (continuous variable), geographic region, nodal status, tumor grade, tumor size, radiotherapy, mastectomy, centrally determined estrogen receptor/progesterone receptor status, centrally determined HER2 status, prior hormone replacement therapy, history of diabetes, smoking status, and history of hypertension and were stratified by randomization option (two- or four-arm option) and prior chemotherapy use (yes or no).

Treatment-by-BMI (pairwise) interaction was tested in Cox models using 1-*df* Wald tests. With our BMI and outcome event distributions and assuming exponential distribution, there was at least 71% power to detect an interaction ratio of 1.67 using large sample partial likelihood tests for treatment-by-BMI groups interaction in a Cox model (eg, treatment HR for BMI ≥ 30 kg/m^2 relative to treatment HR for BMI < 25 kg/m^2), which is similar magnitude to the interaction ratio for distant recurrence in ATAC.[9] Subpopulation treatment effects pattern plots were used to summarize the 8-year OS according to treatment group and the HRs comparing letrozole versus tamoxifen across the continuum of BMI values with tests for treatment-by-BMI interaction.[18,19]

Cumulative incidence functions for breast cancer recurrence (accounting for competing risks of second [nonbreast] malignancies and deaths without a prior cancer event) and for distant recurrence (accounting for competing risks of death without prior cancer event) were estimated and compared

among BMI groups using 2-*df* Gray's test[20] with adjustment of stratification factors of randomization option (two- or four-arm option) and prior chemotherapy use (yes or no).

All reported *P* values are two-sided. The analyses were carried out using SAS version 9.2 (SAS Institute, Cary, NC) and R 2.10.1 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients

The analytic cohort of 4,760 patients were randomly assigned to tamoxifen (n = 2,378) or letrozole (n = 2,382) for 5 years as monotherapy. Of these, 1,097 patients (23%) were obese (BMI ≥ 30 kg/m^2) and 1,734 (36%) were overweight (BMI 25 to < 30 kg/m^2) at randomization. The overall median BMI at randomization was 26.1 kg/m^2 (mean = 26.8 kg/m^2; standard deviation = 5.1 kg/m^2). Table 1 shows the characteristics of the study population according to BMI categories. The median time from diagnosis to randomization was 1.3 months, which did not differ between treatment groups. Obese patients had larger tumors ($P < .001$) and more positive lymph nodes ($P < .001$), and tumors were more often progesterone receptor positive ($P < .001$). Obese patients were older (age ≥ 62 years, $P < .001$) and had more comorbidities, such as diabetes, and history of hypertension and any cardiac morbidity. No significant differences were detected in tumor grade, estrogen receptor status, peritumoral vascular invasion, HER2 status, or Ki67 status. Prior treatment varied by BMI, with obese patients being more likely to have had a mastectomy and prior chemotherapy.

Outcomes

At 8.7 years median follow-up, DFS events were observed in 1,272 patients, and 829 died. The proportions of patients with DFS events were 24%, 27%, and 30% among normal, overweight, and obese patients, respectively, and the proportions who died were 15%, 17%, and 21%, respectively. Obese patients had more bone and visceral metastases as site of first DFS event and had more deaths without a prior cancer event (Table 2). Among all patients, there was evidence of heterogeneity in OS according to the three

Table 2. Disease Outcomes at 8.7 Years of Median Follow-Up in BIG 1-98 Trial Monotherapy Population, According to BMI at Randomization

	BMI (kg/m^2) at Randomization					
	< 25, Normal		25 to < 30, Overweight		≥ 30, Obese	
Disease Outcome	No.	%	No.	%	No.	%
Patients	1,929		1,734		1,097	
Death	293	15	303	17	233	21
Any distant recurrence	222	12	236	14	167	15
Any breast cancer recurrence	311	16	303	17	201	18
DFS event	471	24	471	27	330	30
Site of first of DFS event						
Local	38	8	34	7	15	5
Contralateral breast	46	10	35	7	12	4
Regional	22	5	11	2	9	3
Distant: soft tissue/nodes	12	3	19	4	10	3
Distant: bone	79	17	84	18	71	22
Distant: viscera	100	21	103	22	75	23
Other breast cancer	9	2	7	1	6	2
Second (nonbreast) primary	93	20	97	21	63	19
Death without prior cancer event	72	15	81	17	69	21

Abbreviations: BMI, body mass index; DFS, disease-free survival.

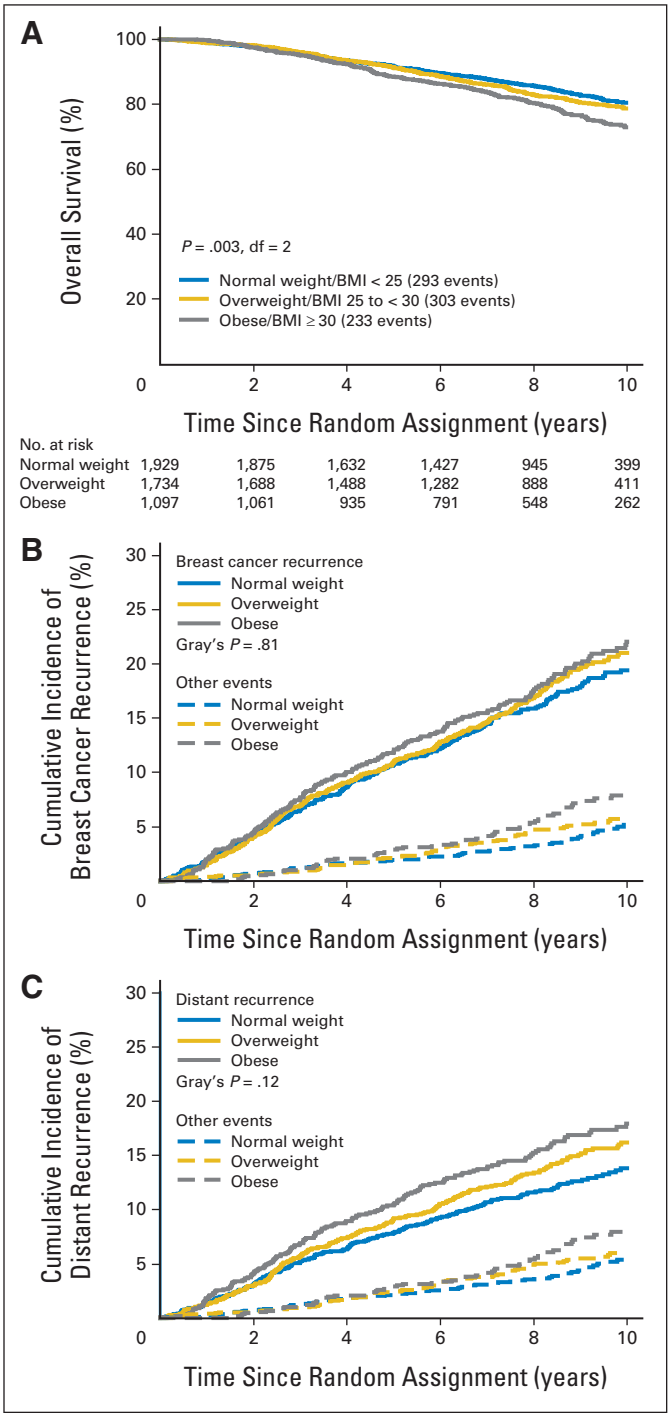

Fig 2. (A) Overall survival according the three body mass index (BMI) groups is shown in the Kaplan-Meier curve; *P* value tests for heterogeneity among the three groups with 2 *df*. (B) Cumulative incidence of breast cancer recurrence and (C) distant recurrence comparing normal, overweight, and obese BMI groups. Comparisons of BMI groups using Gray's test *P* value stratified by chemotherapy use and random assignment option.

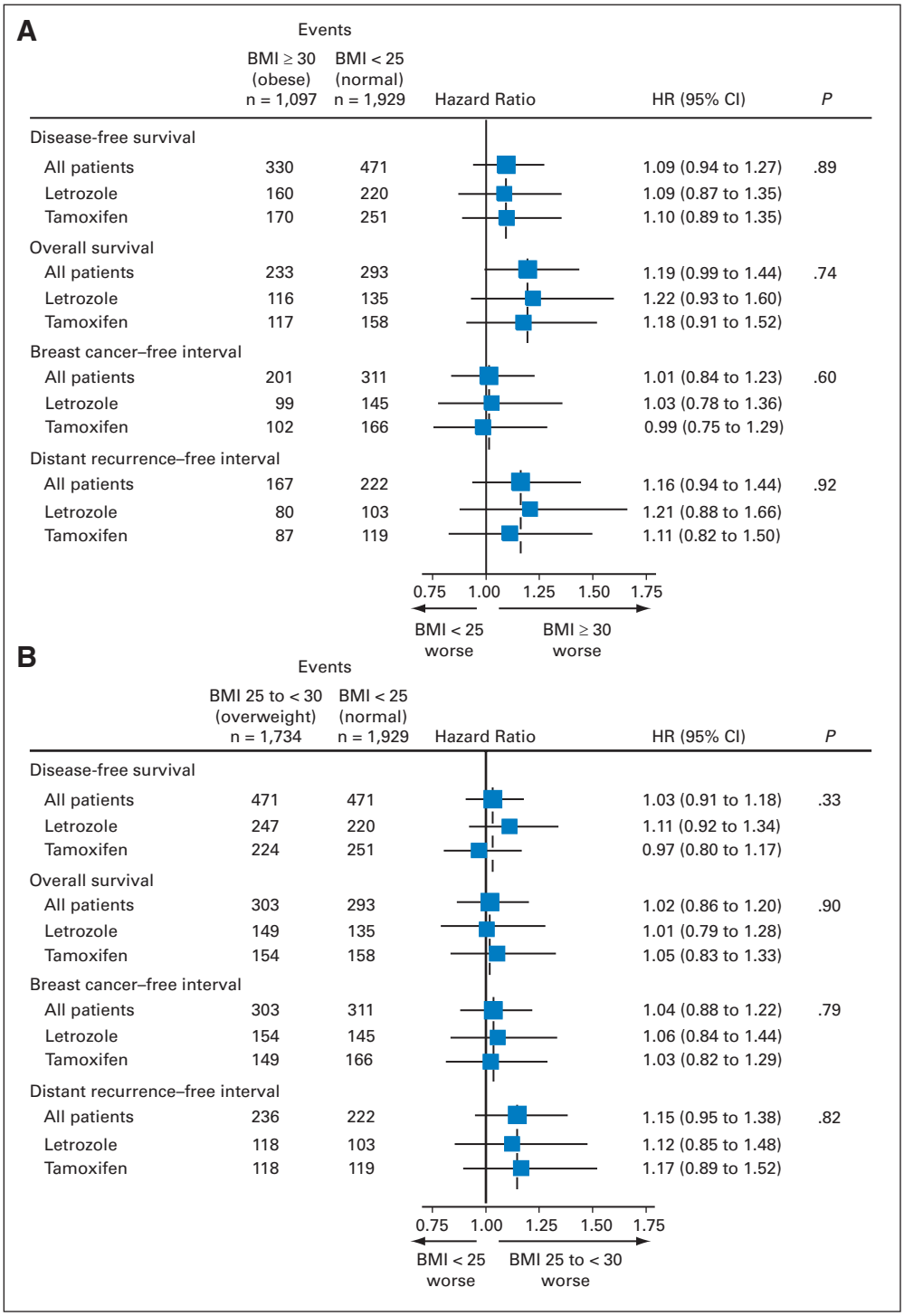

Fig 3. Hazard ratios (HRs), 95% CIs, and *P* values from multivariate Cox models comparing (A) obese, body mass index (BMI) ≥ 30 kg/m^2 and (B) overweight, BMI 25 to less than 30 kg/m^2, with normal-weight patients, BMI less than 25 kg/m^2, adjusted for patient/disease characteristics and stratified by chemotherapy use and randomization option. *P* values are for 1-*df* tests of treatment-by-BMI interaction from multivariate Cox model that adjusted for prognostic factors and stratified by chemotherapy use and random assignment option. The size of the boxes is inversely proportional to the SE of the HR.

BMI categories (likelihood ratio test $P = .003$, $df = 2$; Fig 2A), and some indication of heterogeneity in distant recurrence–free interval according to BMI categories ($P = .11$, $df = 2$, data not shown). Analyses of the cumulative incidence of distant recurrence and breast cancer recurrence accounting for the competing risks of second (nonbreast) primaries and deaths without a prior cancer event illustrate that the observed results for OS were not entirely due to breast cancer (Fig 2B,2C).

Obese patients tended to have a greater hazard of death (HR = 1.19; 95% CI, 0.99 to 1.44) compared with patients with normal weight (Fig 3A), although no difference in OS was observed among overweight (BMI 25 to < 30 kg/m^2) versus normal weight patients (HR = 1.02; 95% CI, 0.86 to 1.20; Fig 3B). These effects were not observed for breast cancer–free interval, distant disease–free interval, or DFS (Figs 3A and 3B).

There was no indication that the relative hazard of obesity versus normal weight on OS was different between treatment arms ($P = .74$

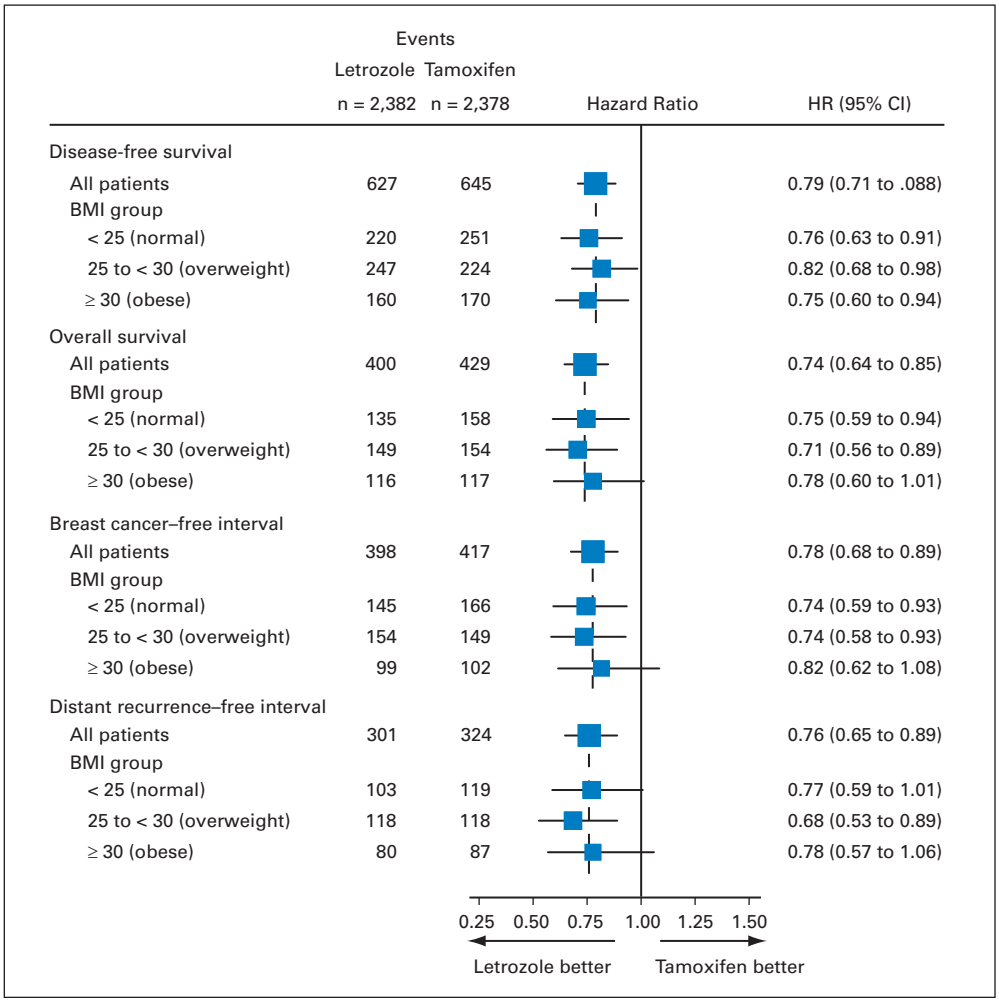

Fig 4. Hazard ratios (HRs) and 95% CIs from multivariate Cox models comparing letrozole versus tamoxifen according to body mass index (BMI) groups, adjusted for patient/disease characteristics and stratified by chemotherapy use and random assignment option. The size of the boxes is inversely proportional to the SE of the hazard ratio.

for interaction; Fig 3A). The estimated HR for OS was 1.22 (95% CI, 0.93 to 1.60) comparing obese versus normal weight patients in the letrozole arm and 1.18 (95% CI, 0.91 to 1.52) in the tamoxifen arm. For distant recurrence–free interval, similar estimates of HR comparing obese versus normal weight were observed for letrozole (HR = 1.21; 95% CI, 0.88 to 1.66) and for tamoxifen (HR = 1.11; 95% CI, 0.82 to 1.50; $P = .92$ for interaction; Fig 3A). Figure 4 summarizes treatment comparisons within BMI groups, showing that letrozole is superior to tamoxifen in all BMI groups for all end points.

The subpopulation treatment effects pattern plots analysis of 8-year OS according to treatment, looking at BMI as a continuum rather than categorically (Fig 5A), also showed no evidence of treatment-by-BMI interaction ($P = .76$). The similar benefits of letrozole over tamoxifen across the continuum of BMI levels is illustrated by relatively constant HRs over all BMI levels (Fig 5B).

DISCUSSION

On the basis of the patients enrolled in the BIG 1-98 trial, this report confirms the results of numerous other studies showing that obese (BMI $\geq$ 30 kg/m^2) patients with breast cancer are diagnosed with a generally poorer prognostic profile. However, after taking prognostic factors into account, obese patients in our study still have a trend to poorer OS than normal-weight patients (BMI $<$ 25 kg/m^2).[1,2] The results of this study with an HR of 1.19 (95% CI, 0.99 to 1.44) for OS are consistent with those of the Danish study reporting an HR of 1.09 (95% CI, 1.00 to 1.18) for OS for the first 10 years of follow-up.[2] The present results also show that poorer OS is mediated by more distant recurrences as well as deaths without a prior cancer event.

The investigators of the ATAC Trial sought to determine "if anastrozole is relatively more effective than tamoxifen in preventing recurrences in postmenopausal women with early-stage breast cancer and a high BMI" among 4,939 estrogen receptor–positive women randomly assigned in their trial.[9] Contrary to this hypothesis, they found that although tamoxifen was equally effective across all BMI categories, anastrozole was significantly less effective in postmenopausal women with a BMI exceeding 30 kg/m^2. They suggested that estrogen suppression with anastrozole may not be complete in obese women.[9] This possibility is supported by data from the Austrian Breast and Colorectal Cancer Study Group (ABCSG) 12 Trial reporting that overweight (BMI $>$ 25 kg/m^2) premenopausal patients treated with goserelin plus anastrozole had a poorer DFS and OS than normal-weight patients.[21] Several studies have reported that estrogen

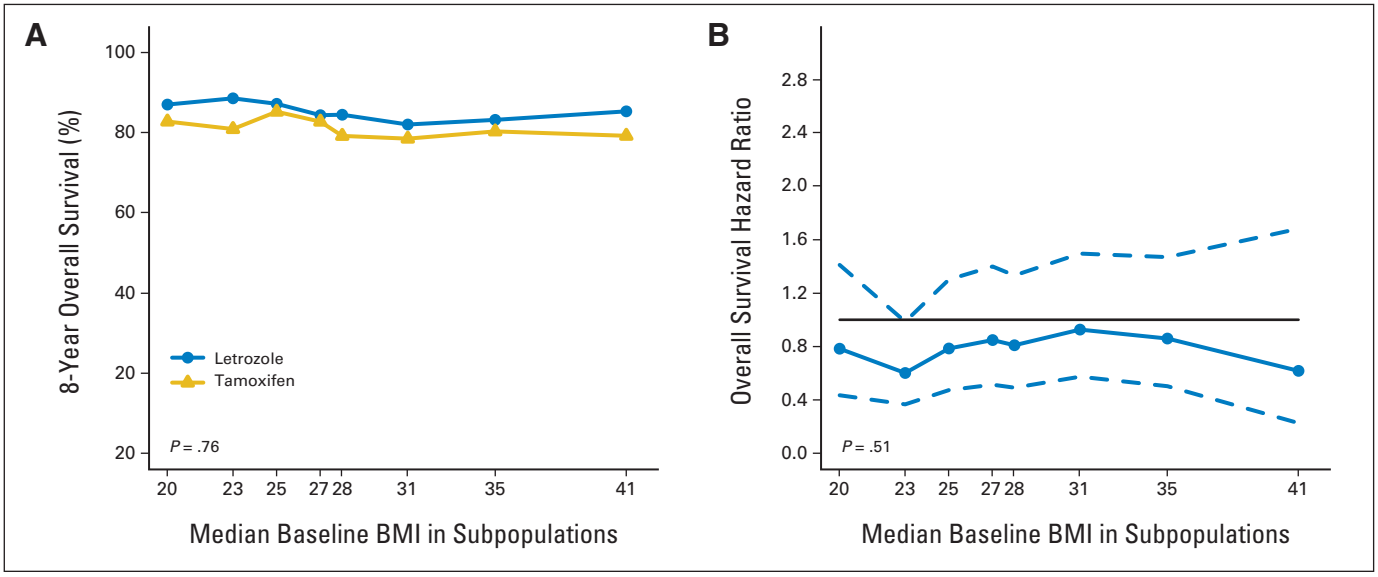

Fig 5. Subpopulation treatment effect pattern plots showing (A) 8-year overall survival according to randomly assigned treatment group across a continuum of baseline body mass index (BMI) subpopulations and (B) overall survival hazard ratio (solid line) with 95% confidence bands (dashed lines) comparing letrozole versus tamoxifen across a continuum of baseline BMI subpopulations.

suppression is more complete with letrozole than with anastrozole.[11,12] One possible inference from the contrast between the findings of ATAC and the present study may therefore be that letrozole is sufficiently active to overcome any incomplete suppression seen with anastrozole. This explanation is reassuring because it indicates that a dose of 2.5 mg of letrozole is sufficient to inhibit the larger amount of estrogens that obese women produce from peripheral aromatization of androstenedione.[21a]

Several models have been suggested to explain the biologic mechanisms underlying the poorer prognosis in obese patients with breast cancer. These involve complex relationships between estrogen synthesis, insulin resistance, and altered adipokine and cytokine production.[22,23] Obese patients have higher levels of estrone, estradiol, and free circulating estradiol and reduced levels of sex hormone binding globulin.[24] In addition, cytokines secreted by the adipocytes can upregulate the aromatase enzyme to further increase the estrogen production, which may stimulate tumor cell growth.[25] Obesity is a component of the metabolic syndrome that also includes hyperglycemia, hyperinsulinemia, and insulin resistance. Insulin has mitogenic, antiapoptotic, and proangiogenic properties, and breast cancer cells have been shown to express the insulin receptor.[26] Several studies have demonstrated that hyperinsulinemia is an independent adverse prognostic factor in breast cancer[27-30] and that adiponectin is also related to breast cancer prognosis.[31] Finally, obesity causes subclinical inflammation, increasing the levels of proinflammatory mediators, which may parallel increasing levels of aromatase.[32]

In summary, this report with a median of 8.7 years of follow-up is in broad agreement that obesity is an independent adverse prognostic factor for death after breast cancer, although the statistical significance is marginal after allowance for multiple other patient characteristics. Letrozole was more effective than tamoxifen in reducing disease-free survival events, overall deaths, breast cancer recurrences, and distant metastases across all BMI categories.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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