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Absolute Benefit of Adjuvant Endocrine Therapies for Premenopausal Women With Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Early Breast Cancer: TEXT and SOFT Trials

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ABSTRACT

Purpose
Risk of recurrence is the primary consideration in breast cancer adjuvant therapy recommendations. The TEXT (Tamoxifen and Exemestane Trial) and SOFT (Suppression of Ovarian Function Trial) trials investigated adjuvant endocrine therapies for premenopausal women with hormone receptor–positive breast cancer, testing exemestane plus ovarian function suppression (OFS), tamoxifen plus OFS, and tamoxifen alone. We examined absolute treatment effect across a continuum of recurrence risk to individualize endocrine therapy decision making for premenopausal women with human epidermal growth factor receptor 2 (HER2) –negative disease.

Patients and Methods
The TEXT and SOFT hormone receptor–positive, HER2-negative analysis population included 4,891 women. The end point was breast cancer–free interval (BCFI), defined as time from random assignment to first occurrence of invasive locoregional, distant, or contralateral breast cancer. A continuous, composite measure of recurrence risk for each patient was determined from a Cox model incorporating age, nodal status, tumor size and grade, and estrogen receptor, progesterone receptor, and Ki-67 expression levels. Subpopulation treatment effect pattern plot methodology revealed differential treatment effects on 5-year BCFI according to composite risk.

Results
SOFT patients who remained premenopausal after chemotherapy experienced absolute improvement of 5% or more in 5-year BCFI with exemestane plus OFS versus tamoxifen plus OFS or tamoxifen alone, reaching 10% to 15% at intermediate to high composite risk; the benefit of tamoxifen plus OFS versus tamoxifen alone was apparent at the highest composite risk. The SOFT no-chemotherapy cohort—for whom composite risk was lowest on average—did well with all endocrine therapies. For TEXT patients, the benefit of exemestane plus OFS versus tamoxifen plus OFS in 5-year BCFI ranged from 5% to 15%; patients not receiving chemotherapy and with lowest composite risk did well with both treatments.

Conclusion
Premenopausal women with hormone receptor–positive, HER2-negative disease and high recurrence risk, as defined by clinicopathologic characteristics, may experience improvement of 10% to 15% in 5-year BCFI with exemestane plus OFS versus tamoxifen alone. An improvement of at least 5% may be achieved for women at intermediate risk, and improvement is minimal for those at lowest risk.

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INTRODUCTION

For premenopausal women with hormone receptor–positive early breast cancer, adjuvant tamoxifen for at least 5 years[1,2] has been a standard treatment during the past 15 years. Adjuvant chemotherapy and/or ovarian function suppression (OFS) may be recommended in addition to tamoxifen. Two international randomized phase III trials—TEXT (Tamoxifen and Exemestane Trial) and SOFT (Suppression of Ovarian Function

Trial)[3]—recently demonstrated that 5 years of adjuvant treatment with the aromatase inhibitor (AI) exemestane, in combination with OFS, improves outcomes relative to tamoxifen plus OFS or tamoxifen alone.[4,5] SOFT further showed that tamoxifen plus OFS improves outcomes relative to tamoxifen alone in women who are at sufficient risk to warrant adjuvant chemotherapy and remain premenopausal afterward and that tamoxifen alone remains an appropriate option for some premenopausal women.[5]

The improvements in efficacy have tradeoffs, with adverse effects and events,[4-7] and follow-up is currently too short to assess impact on overall survival. The population relative treatment effects (ie, hazard ratios [HRs]) and 5-year estimates of breast cancer–free interval (BCFI) are imprecise for individualized treatment decisions. In subgroup analyses, the relative treatment effects seemed consistent across subgroups defined by conventional clinicopathologic factors.[4,5]

The TEXT and SOFT trial results were also considered separately according to chemotherapy use, which was determined by physician and patient choice and reflected an assessment of recurrence risk. For example, lymph node–positive disease was much more frequent in the TEXT and SOFT chemotherapy cohorts (66% and 57%, respectively) than in the no-chemotherapy cohorts (21% and 9%, respectively).[4] Although the treatment efficacy HRs were consistent regardless of chemotherapy use (eg, exemestane plus OFS *v* tamoxifen: BCFI HR, 0.65 [95% CI, 0.49 to 0.87] and 0.59 [95% CI, 0.32 to 1.14] in the SOFT chemotherapy and no-chemotherapy cohorts, respectively), the absolute treatment effect at 5 years was greater for patients who received chemotherapy than those who did not (7.7% and 1.3%, respectively).[4,5] With trials conducted at 510 institutions in 27 countries, patients' clinicopathologic characteristics were heterogeneous within the cohorts defined by chemotherapy use.[8] A standardized characterization of all patients' recurrence risk may provide further elucidation of the absolute treatment effect, beyond that estimated according to chemotherapy status alone.

To better inform selection among three adjuvant endocrine therapy options for premenopausal patients, we investigated the absolute magnitude of treatment benefit in TEXT and SOFT according to a quantitative composite measure of recurrence risk. The composite measure was a means to systematically characterize the spectrum of recurrence risk of all trial patients, as done previously for postmenopausal women.[9] The evaluation was conducted according to trial and chemotherapy use, which reflect uncontrolled physician choices, to isolate the randomized endocrine therapy comparisons. We focused here on patients with human epidermal growth factor receptor 2 (HER2)–negative disease because adjuvant trastuzumab with chemotherapy is now indicated for most patients with HER2-positive disease, a practice that changed during trial conduct; the HER2-positive population will be the subject of a separate investigation.

PATIENTS AND METHODS

Study Designs

The designs and conduct of the trials have been described previously.[3-5] In both trials, eligible premenopausal women had invasive early breast cancer assessed as 10% or more estrogen receptor (ER) or progesterone receptor (PgR)–expressing cells by local determination.

TEXT was designed to determine the role of adjuvant therapy with the AI exemestane versus tamoxifen in premenopausal women treated with OFS from the start of adjuvant therapy. Between November 2003 and March 2011, 2,672 eligible women were randomly assigned at a 1:1 ratio to 5 years of exemestane plus OFS or 5 years of tamoxifen plus OFS. OFS was performed through gonadotropin-releasing hormone agonist triptorelin administration, bilateral oophorectomy, or ovarian irradiation. Chemotherapy was optional and, if administered, was started concurrently with triptorelin. Random assignment was stratified according to intended use of adjuvant chemotherapy and lymph node status.

SOFT was designed to determine the value of adding OFS to tamoxifen and the role of exemestane plus OFS in two cohorts of premenopausal women: those who remained premenopausal after completion of (neo)adjuvant chemotherapy and those for whom adjuvant tamoxifen alone was considered suitable treatment. Between December 2003 and January 2011, 3,066 eligible women were randomly assigned at a 1:1:1 ratio to 5 years of exemestane plus OFS, tamoxifen plus OFS, or tamoxifen alone. Random assignment was stratified according to use of prior chemotherapy, lymph node status, and intended initial method of OFS (if randomly assigned to OFS).

The ethics committee at each participating center approved the study protocols, and all patients provided written informed consent for trial participation, including protocol-mandated central pathology review. Eighty-four percent of trial patients had tumor tissue prospectively collected for central review of histopathologic features and expression of ER, PgR, and HER2 and Ki-67 labeling index (hereafter, Ki-67) at the International Breast Cancer Study Group Central Pathology Office as previously described.[10]

End Point and Statistical Considerations

The analysis population included 4,891 patients with hormone receptor–positive, HER2-negative tumors. Excluded from the intention-to-treatment trial populations (n = 5,707) were: five ineligible patients (locally assessed as hormone receptor negative and no central assessment), 64 patients for whom central assessment of submitted material did not detect any ER or PgR, and 747 patients with tumors assessed centrally or locally as HER2 positive (Fig 1).

The end point for this analysis was BCFI, defined as time from random assignment to first appearance of invasive breast cancer recurrence (local, regional, or distant) or invasive contralateral breast cancer; in the absence of an event, patients were censored at date of last follow-up. BCFI, rather than disease-free survival, was chosen as the end point to disregard second (nonbreast) malignancies that occurred at similar frequencies across treatment groups and the few deaths that occurred without a prior cancer event.[4,5] The median follow-up was 6 years in TEXT and 5.6 years in SOFT.

To define the composite measure of recurrence risk (hereafter referred to as composite risk), a Cox proportional hazards model for BCFI, stratified by cohort (defined by trial and chemotherapy use) and treatment assignment, was estimated for the entire hormone receptor–positive, HER2-negative analytic population. This stratified model, rather than a model estimated in the control group patients only,[11,12] was necessary because the two trials did not have a common control group, and we preferred to examine the two trial populations using the same risk scale. Prognostic factors included in the model and their groupings were specified a priori on the basis of usual clinical cutpoints and prior St Gallen Consensus statements, and there was no intention to optimize the model on the basis of model selection procedures (Table 1). The exceptions were as follows: grouping those with ER levels lower than 50% together, instead of creating two groups of ER levels lower than 10% (n = 39) and ER levels between 11% and 49% (n = 157), because of small numbers with low ER expression in this hormone receptor–positive, HER2-negative population; adding a subgroup of Ki-67 ≥ 26% or higher, corresponding to the upper 20th percentile of the distribution; and omitting peritumoral lymphovascular invasion

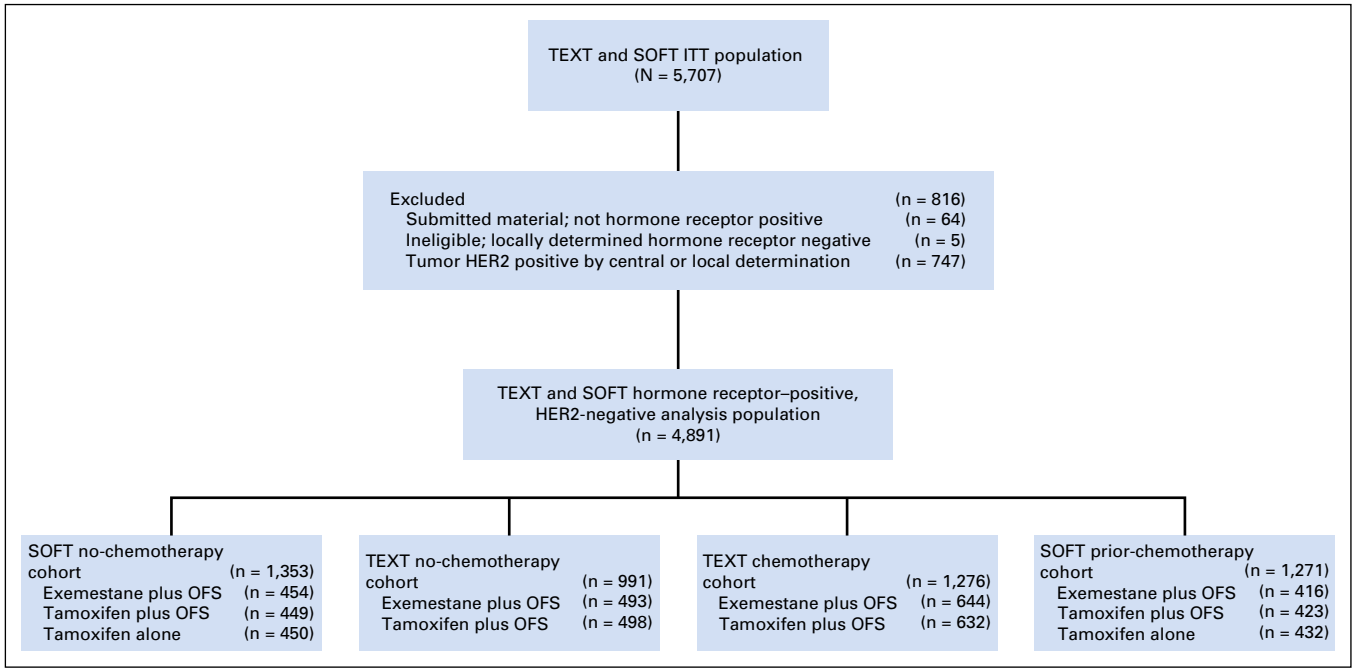

Fig 1. Flow diagram of the 4,891 patients included in the TEXT (Tamoxifen and Exemestane Trial) and SOFT (Suppression of Ovarian Function Trial) hormone receptor–positive, human epidermal growth factor receptor 2 (HER2) –negative analysis population. OFS, ovarian function suppression.

because it did not add to the model (parameter estimate ± standard error, 0.04 ± 0.10). Unknown categories were included because of unavailable data. For tumor grade and ER and PgR expression, the centrally determined values were used when available, and locally determined values were used otherwise; Ki-67 expression was available only from central assessment. For each trial patient, the value of composite risk was calculated by summing the model parameter estimates corresponding to her observed clinicopathologic factor values. The nonparametric sliding-window subpopulation treatment effect pattern plot (STEPP) methodology[13,14] was used to investigate patterns in absolute treatment effect, as measured by Kaplan-Meier estimates of 5-year BCFI (*y*-axis), across the continuum of the values of composite risk (*x*-axis).

RESULTS

Characteristics of the 4,891 patients in the hormone receptor–positive, HER2-negative analysis population according to cohort, as defined by trial and chemotherapy use, are summarized in Table 1. The relation of each factor with BCFI, without regard for cohort or treatment assignment, is summarized in Figure 2. The clinicopathologic characteristics with greatest contribution to the composite measure of recurrence risk relative to the complementary reference categories were young age (< 35 years), four or more positive lymph nodes, and grade 2 to 3 tumor (Table 2).

Overall, the 5-year BCFI was 90.8% (473 of 4,891 patients had invasive breast cancer events), ranging from 98.6% to 77.5% among patients with composite risk in the lowest and highest quartiles, respectively (Fig 3). The sliding-window STEPP similarly illustrates 5-year BCFI across the continuum of composite risk, ranging near 100% in STEPP subpopulations with the lowest composite risk to below 70% in the subpopulation with the highest composite risk. As expected from the distributions of the individual factors (Table 1) and their role in decision making about chemotherapy, the composite risk distributions were shifted lower in the cohorts that did not receive chemotherapy and higher in those that did (Fig 4). The STEPPs of 5-year BCFI according to composite risk showed distinct patterns of absolute treatment effect (Fig 4).

Patients for Whom Tamoxifen Alone Was Considered Appropriate Adjuvant Therapy: SOFT No-Chemotherapy Cohort

In the SOFT cohort of patients who did not receive chemotherapy, in which tamoxifen alone was considered an appropriate therapy for eligible patients, the composite risk was lowest, and 5-year BCFI was 96.1% overall (Figs 4A and 4B). Patients did well with all endocrine therapies. There was no apparent pattern across the spectrum of composite risk, suggesting no clinically relevant improvement in 5-year BCFI with exemestane plus OFS or tamoxifen plus OFS versus tamoxifen alone (standard of care) in this lower-risk patient cohort.

Patients for Whom OFS Was Planned As Part of Adjuvant Therapy: TEXT Cohorts

In the TEXT cohort of patients whose treatment included OFS but not chemotherapy, 5-year BCFI was 96.1% overall, and exemestane plus OFS on average improved 5-year BCFI by 3.6% versus tamoxifen plus OFS. The pattern of treatment effect according to composite risk distribution was striking (Figs 4C and 4D). Improvement in 5-year BCFI was minimal—approximately 1%—in subpopulations with lowest composite risk for whom 5-year BCFI was consistently 95% or more in both treatment

Table 1. Clinicopathologic Characteristics of the Hormone Receptor–Positive, HER2-Negative Analysis Population

Characteristic	Cohort: No Chemotherapy SOFT (n = 1,353) No.	%	No Chemotherapy TEXT (n = 991) No.	%	Chemotherapy TEXT (n = 1,276) No.	%	Prior Chemotherapy SOFT (n = 1,271) No.	%	All Patients (N = 4,891) No.	%
Age at random assignment, years										
< 35	20	1.5	37	3.7	141	11.1	232	18.3	430	8.8
35-39	103	7.6	113	11.4	221	17.3	375	29.5	812	16.6
40-44	370	27.3	341	34.4	442	34.6	407	32.0	1,560	31.9
45-49	625	46.2	385	38.8	403	31.6	213	16.8	1,626	33.2
≥ 50	235	17.4	115	11.6	69	5.4	44	3.5	463	9.5
No. of positive nodes										
0	1,235	91.3	776	78.3	401	31.4	527	41.5	2,939	60.1
1-3	117	8.6	213	21.5	561	44.0	510	40.1	1,401	28.6
≥ 4	1	0.1	2	0.2	314	24.6	234	18.4	551	11.3
Tumor size (pathologic), cm										
Unknown	9	0.7	3	0.3	21	1.6	50	3.9	83	1.7
≤ 2	1,162	85.9	791	79.8	593	46.5	630	49.6	3,176	64.9
> 2	182	13.5	197	19.9	662	51.9	591	46.5	1,632	33.4
ER expression, %										
Unknown	14	1.0	17	1.7	23	1.8	17	1.3	71	1.5
< 50	36	2.7	20	2.0	65	5.1	75	5.9	196	4.0
≥ 50	1,303	96.3	954	96.3	1,188	93.1	1,179	92.8	4,624	94.5
PgR expression, %										
Unknown	22	1.6	19	1.9	26	2.0	23	1.8	90	1.8
< 20	55	4.1	58	5.9	163	12.8	233	18.3	509	10.4
20-49	66	4.9	70	7.1	133	10.4	131	10.3	400	8.2
≥ 50	1,210	89.4	844	85.2	954	74.8	884	69.6	3,892	79.6
Tumor grade										
1	504	37.3	252	25.4	165	12.9	199	15.7	1,120	22.9
2	724	53.5	587	59.2	725	56.8	729	57.4	2,765	56.5
3	125	9.2	152	15.3	386	30.3	343	27.0	1,006	20.6
Ki-67 expression, %										
Unknown	270	20.0	189	19.1	240	18.8	266	20.9	965	19.7
< 14	506	37.4	269	27.1	199	15.6	248	19.5	1,222	25.0
14-19	324	23.9	262	26.4	293	23.0	303	23.8	1,182	24.2
20-25	152	11.2	135	13.6	234	18.3	216	17.0	737	15.1
≥ 26	101	7.5	136	13.7	310	24.3	238	18.7	785	16.0

NOTE. Values for grade and ER and PgR expression were centrally determined if available and locally determined otherwise; Ki-67 expression was available only by central determination.

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor; SOFT, Suppression of Ovarian Function Trial; TEXT, Tamoxifen and Exemestane Trial.

groups. In contrast, in the subpopulations with highest composite risk, the treatment effect for exemestane plus OFS versus tamoxifen plus OFS was on the order of 10% absolute improvement in 5-year BCFI, with exemestane plus OFS achieving 5-year BCFI of 95% or more, as in subpopulations with lower composite risk in this cohort who did not receive chemotherapy.

Among TEXT patients initiating adjuvant chemotherapy and gonadotropin-releasing hormone analog concurrently, overall 5-year BCFI was 89.3%, with an average 5.8% absolute improvement with exemestane plus OFS versus tamoxifen plus OFS. Consistent benefit was evident in this cohort across the entire continuum of composite risk (Figs 4E and 4F). The smallest absolute improvement in 5-year BCFI was approximately 3% among patients in the subpopulation with lowest composite risk and 5-year BCFI of 95% or more in both treatment groups. Improvement in 5-year BCFI ranged from 5% to 15% as composite risk increased in this cohort of patients who received chemotherapy.

Patients Remaining Premenopausal After (neo)Adjuvant Chemotherapy: SOFT Prior-Chemotherapy Cohort

In the SOFT cohort of patients who remained premenopausal after chemotherapy, overall 5-year BCFI was 82.5%. On average, exemestane plus OFS improved 5-year BCFI by 5.4% and 7.4% versus tamoxifen plus OFS and tamoxifen alone, respectively, with a 2.0% improvement for tamoxifen plus OFS versus tamoxifen alone. A consistent benefit with exemestane plus OFS was evident across the continuum of composite risk (Figs 4G and 4H). The absolute benefit was smallest—on the order of 3% absolute benefit—in the subpopulations with lowest composite risk, in which 5-year BCFI was more than 90% for all three treatment groups. Thereafter, with increasing composite risk, the absolute benefit with exemestane plus OFS ranged from approximately 5% to upward of 10% to 15% versus tamoxifen alone. Also apparent was the benefit, on the order of approximately 5%, of adding OFS to tamoxifen versus tamoxifen alone for subpopulations with higher composite risk; this benefit diminished in subpopulations with lower composite risk.

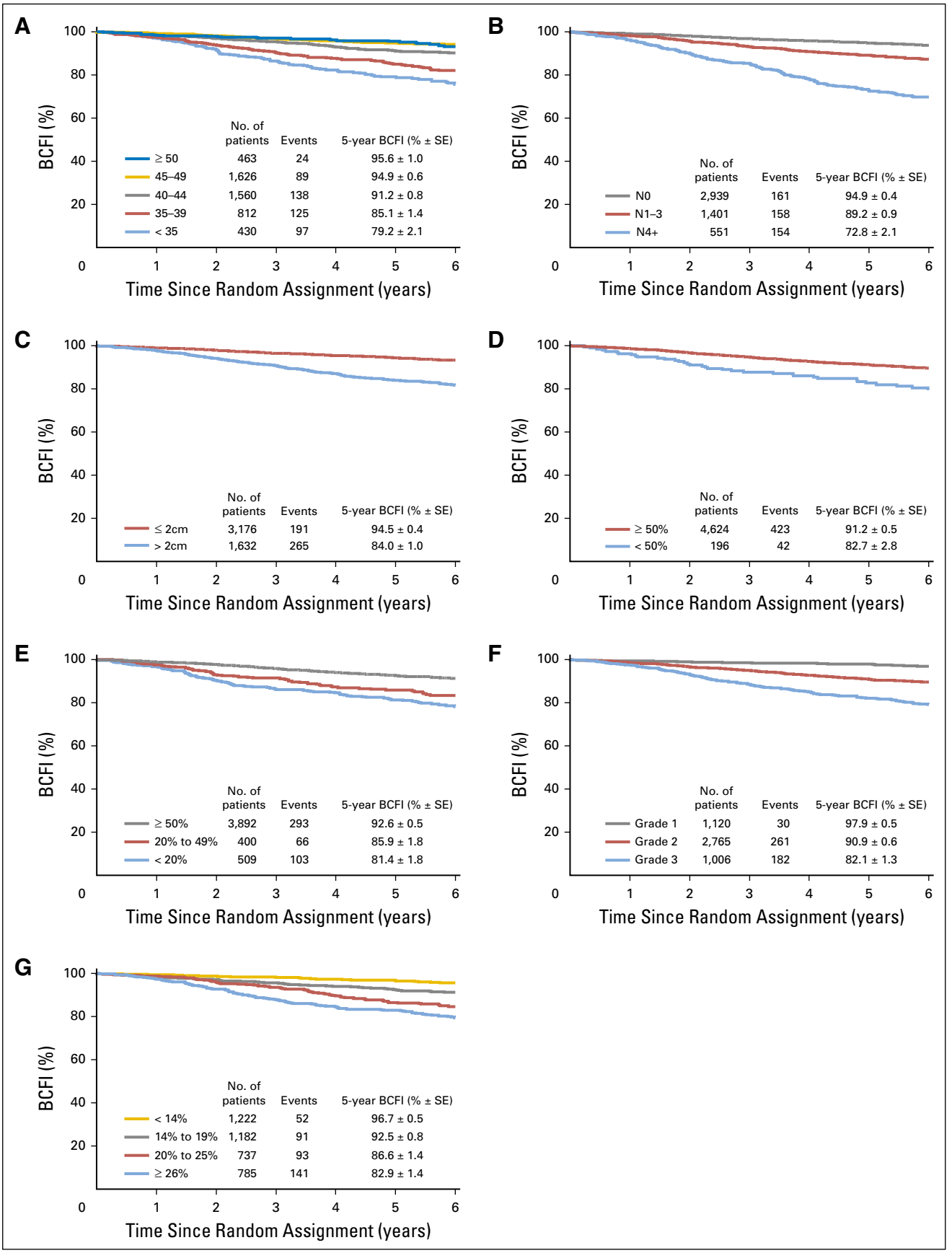

Table 2. Cox Proportional Hazards Model for Defining the Composite Measure of Recurrence Risk for the Hormone Receptor–Positive, HER2-Negative Analysis Population of TEXT and SOFT

Parameter	Parameter Estimate	SE	χ^2	*P*	HR	95% CL
Age at random assignment, years						
< 35	0.81	0.16	25.7	< .01	2.2	1.6 to 3.1
35-39	0.54	0.15	13.4	< .01	1.7	1.3 to 2.3
40-44	0.23	0.14	2.8	.10	1.3	1.0 to 1.7
45-49	0 (ref)					
≥ 50	0.16	0.23	0.5	.49	1.2	0.7 to 1.8
No. of positive nodes						
0	0 (ref)					
1-3	0.38	0.12	9.2	< .01	1.5	1.1 to 1.9
≥ 4	1.12	0.13	69.1	< .01	3.1	2.4 to 4.0
Tumor size, cm						
Unknown	0.61	0.26	5.4	.02	1.8	1.1 to 3.1
≤ 2	0 (ref)					
> 2	0.42	0.10	16.1	< .01	1.5	1.2 to 1.9
ER expression, %						
Unknown	−0.10	0.58	0.0	.86	0.9	0.3 to 2.8
< 50	0.23	0.17	1.8	.18	1.3	0.9 to 1.8
≥ 50	0 (ref)					
PgR expression, %						
Unknown	0.95	0.51	3.5	.06	2.6	1.0 to 7.0
< 20	0.45	0.12	13.7	< .01	1.6	1.2 to 2.0
20-49	0.27	0.14	3.6	.06	1.3	1.0 to 1.7
≥ 50	0 (ref)					
Tumor grade						
1	0 (ref)					
2	0.93	0.21	18.6	< .01	2.5	1.7 to 3.8
3	1.10	0.24	20.8	< .01	3.0	1.9 to 4.9
Ki-67 expression, %						
Unknown	0.08	0.19	0.2	.66	1.1	0.7 to 1.6
< 14	0 (ref)					
14-19	0.07	0.19	0.1	.72	1.1	0.7 to 1.6
20-25	0.29	0.19	2.2	.14	1.3	0.9 to 1.9
≥ 26	0.45	0.21	4.7	.03	1.6	1.0 to 2.3

Abbreviations: CL, confidence limit; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; PgR, progesterone receptor; ref, referent; SOFT, Suppression of Ovarian Function Trial; TEXT, Tamoxifen and Exemestane Trial.

DISCUSSION

The TEXT and SOFT trial results provide new adjuvant endocrine therapy options for premenopausal women that require individual decision making considering potential benefits and adverse effects. The complementary trials were designed to account for the differences worldwide in the use of chemotherapy and OFS as part of adjuvant therapy for premenopausal women with hormone receptor–positive disease. In our analysis, we emulated a clinician's synthesis of available information to estimate the individual patient's risk of recurrence by calculating a composite measure of recurrence risk from conventional clinicopathologic factors, including age, nodal status, tumor size, tumor grade, and ER, PgR, and Ki-67 expression. On average, the magnitude of absolute benefit with exemestane plus OFS versus tamoxifen with or without OFS was as great as the benefit with 5 years of AI versus tamoxifen for postmenopausal women—approximately 3% to 4% at 5 years.[15-17] However, it ranged widely from less than 1% to greater than 15% depending on risk of recurrence, as quantified by the composite measure of recurrence risk.

Among women at lowest risk of recurrence who had excellent outcomes with all endocrine therapies—exceeding 95% freedom from breast cancer at 5 years—minimal benefit with exemestane plus OFS was evident. For these women, any benefit of exemestane plus OFS over tamoxifen alone may be judged insufficient to outweigh the additional adverse effects. For women at higher risk of recurrence, initiation and continuation of exemestane plus OFS was of greater benefit, in the range of 10% to 15% at 5 years. Moreover, when the AI cannot be tolerated, the benefit of tamoxifen plus OFS versus tamoxifen alone was also apparent for these women. For women whose recurrence risk was intermediate, the benefit of exemestane plus OFS over tamoxifen with or without OFS was moderate, approximately 5% at 5 years, requiring a balanced discussion of benefits and adverse effects. OFS results in menopausal symptoms and sexual effects,[5,7] and the use of an AI versus tamoxifen requires consideration of adverse event tradeoffs,[4,6] as documented among postmenopausal women.[15,17] Consideration of preference, tolerance, and cost should also

Fig 2. Kaplan-Meier estimates of breast cancer–free interval (BCFI) in the overall hormone receptor–positive, human epidermal growth factor receptor 2–negative analysis population according to patient and tumor characteristics. (A) Age at random assignment, (B) nodal status, (C) tumor size, (D) estrogen receptor expression, (E) progesterone expression, (F) tumor grade, and (G) Ki-67 expression.

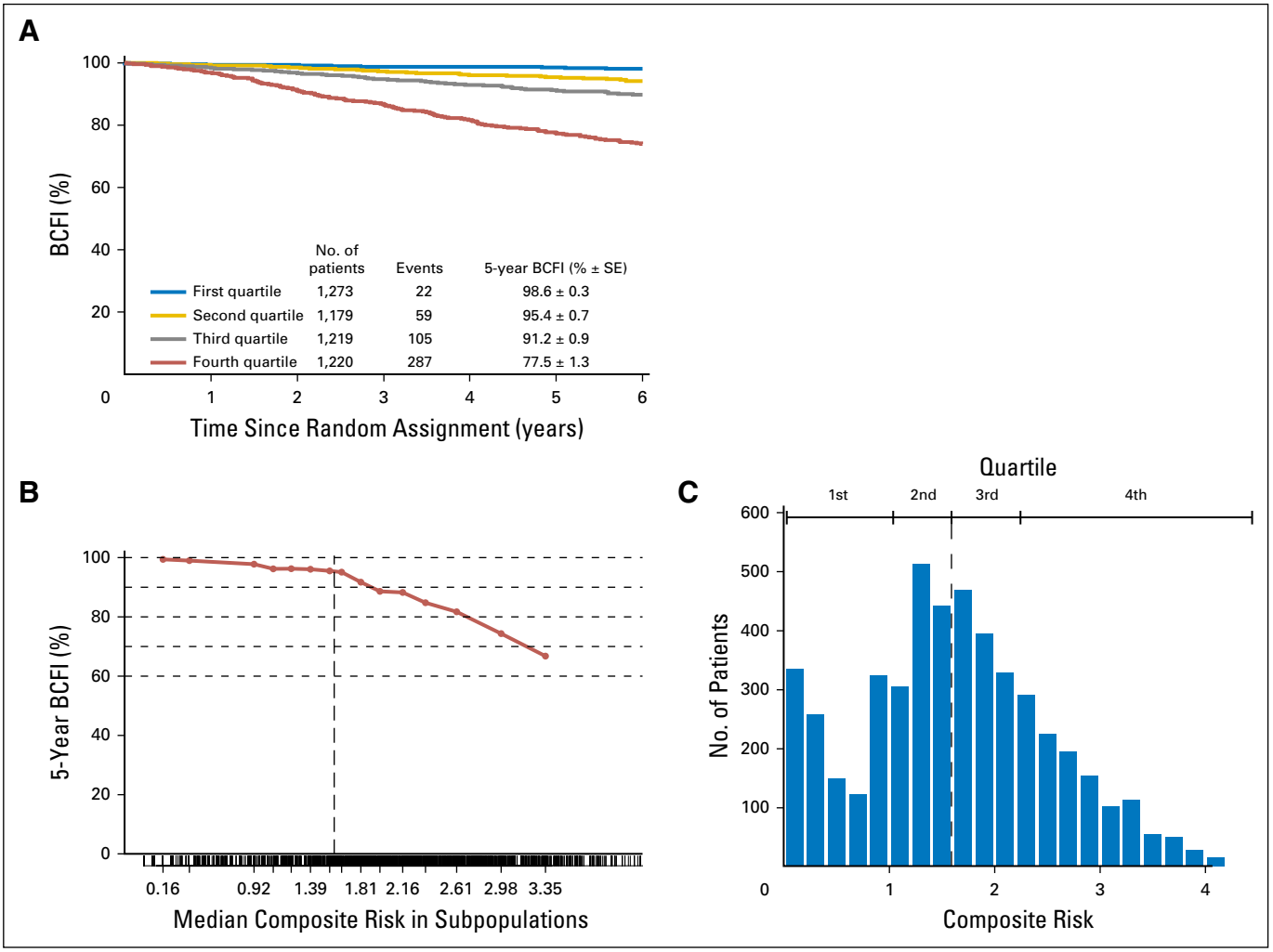

Fig 3. Breast cancer–free interval (BCFI) in the overall hormone receptor–positive, human epidermal growth factor receptor 2 (HER2) –negative population according to composite risk. (A) Kaplan-Meier estimate of BCFI according to quartile of composite risk distribution. (B) Subpopulation treatment effect pattern plot of 5-year BCFI (*y*-axis) according to composite risk subpopulation (*x*-axis). (C) distribution of composite risk scores with quartiles of the distribution marked by horizontal lines. The vertical dashed line indicates the median composite risk of 1.59 in the overall hormone receptor–positive, HER2-negative analysis population; the 25th and 75th percentiles are 1.01 and 2.21, respectively. The rug plot along the *x*-axis illustrates the distribution of composite risk values.

inform the decision-making process in this subset of patients at intermediate risk of recurrence.

One such scenario was represented by the patients with lower composite risk who were premenopausal after chemotherapy and enrolled in SOFT. These women had 5-year freedom from breast cancer exceeding 90% and an absolute benefit with exemestane plus OFS on the order of 3%.

A second intermediate clinical risk scenario were patients enrolled in TEXT with higher composite risk for whom OFS but not chemotherapy was planned. For patients enrolled in TEXT, the decision not to administer chemotherapy included knowledge that all patients would receive OFS, whereas in SOFT, OFS was administered by random assignment. Consequently, the TEXT no-chemotherapy cohort tended to have higher-risk characteristics than the SOFT no-chemotherapy cohort of patients, who were considered suitable for tamoxifen alone (Table 3). The magnitude of benefit with exemestane plus OFS versus tamoxifen plus OFS displayed a distinct pattern for patients in this scenario, with an absolute benefit of approximately 10% among subpopulations at the higher end of composite risk. The patients assigned to exemestane plus OFS from the start of adjuvant therapy had excellent outcomes using combined endocrine therapy without chemotherapy. The TEXT results suggest that in the intermediate-risk clinical scenario where the physician and patient decide to forego chemotherapy but use OFS, initiation of adjuvant OFS with the AI rather than with tamoxifen provides the greatest probability of remaining free from breast cancer at 5 years.

The composite measure of recurrence risk was derived within the TEXT and SOFT populations; it may not be directly applicable to other trial or patient cohorts and was not intended to be applied to future individual patients. The composite risk was an efficient means to systematically characterize a population of nearly 5,000 patients as a representation of algorithms and assays that may be used clinically worldwide. It is worth considering the distribution of patient characteristics relative to the overall median composite risk, because the treatment effect

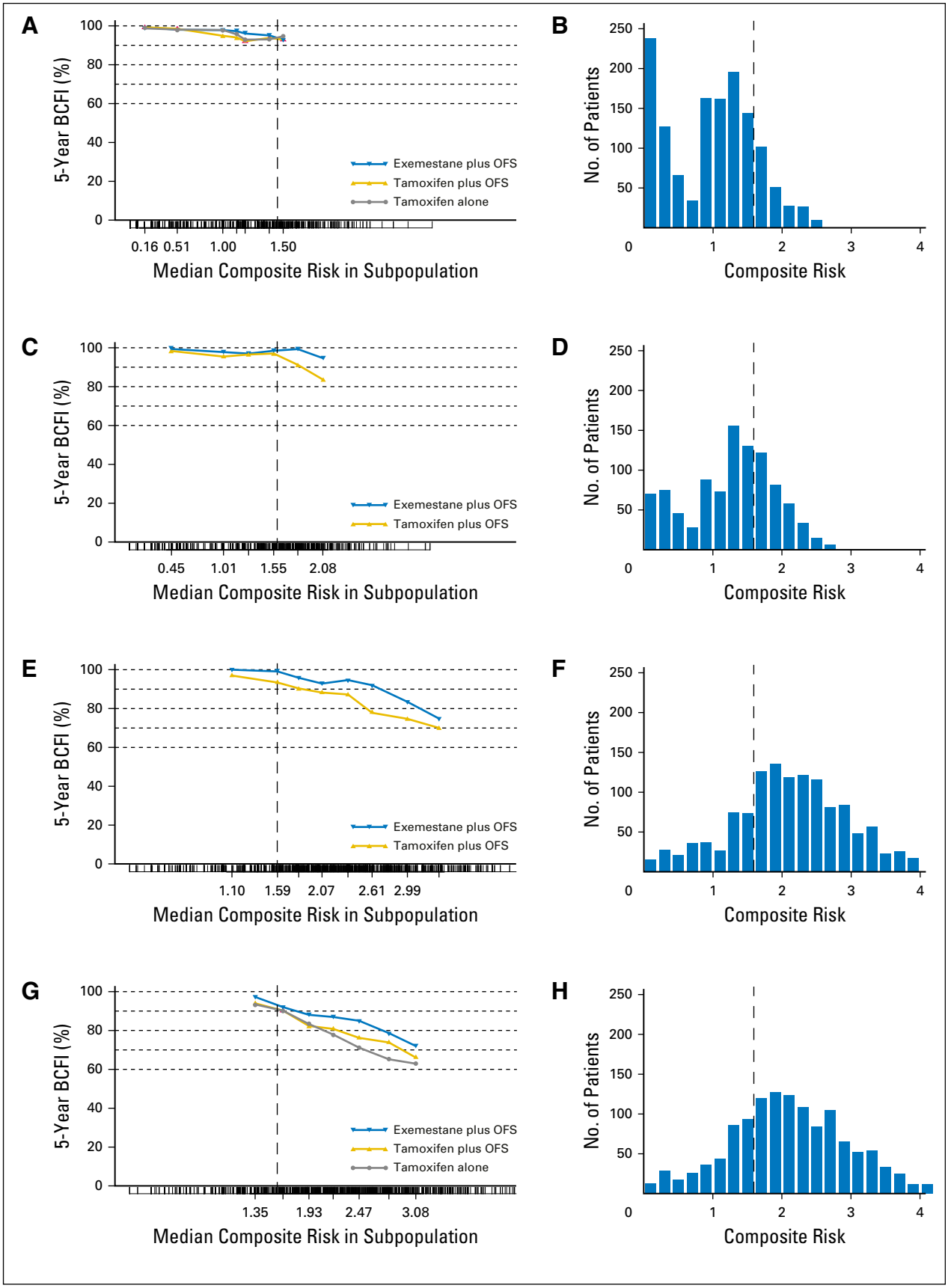

Table 3. Distribution of Composite Measure of Recurrence Risk According to Clinicopathologic Characteristics

Characteristic	No. of Patients	Composite Risk Quartile (%)*			
		1	2	3	4
Cohort					
SOFT no chemotherapy	1,353	50	34	14	3
TEXT no chemotherapy	991	33	34	26	6
TEXT chemotherapy	1,276	11	13	30	45
SOFT prior chemotherapy	1,271	10	17	30	43
Age at random assignment, years					
< 35	430	3	4	22	71
35-39	812	10	16	30	44
40-44	1,560	19	26	32	23
45-49	1,626	45	27	18	10
≥ 50	463	33	40	18	8
No. of positive nodes					
0	2,939	37	33	22	8
1-3	1,401	13	15	38	35
≥ 4	551	—	2	9	89
Tumor size (pathologic), cm					
Unknown	83	4	7	34	55
≤ 2	3,176	36	31	22	11
> 2	1,632	8	11	30	51
ER expression, %					
Unknown	71	13	17	28	42
< 50	196	12	12	18	58
≥ 50	4,624	27	25	25	23
PgR expression, %					
Unknown	90	9	17	26	49
< 20	509	3	8	22	67
20-49	400	13	13	26	48
≥ 50	3,892	31	28	25	16
Tumor grade					
1	1,120	85	10	4	1
2	2,765	12	35	31	22
3	1,006	—	10	31	59
Ki-67 expression, %					
Unknown	965	25	23	26	26
< 14	1,222	64	21	11	5
14-19	1,182	20	37	27	15
20-25	737	2	28	36	35
≥ 26	785	0	9	31	59

NOTE. Percentages sum across the rows.
Abbreviations: ER, estrogen receptor; PgR, progesterone receptor; SOFT, Suppression of Ovarian Function Trial; TEXT, Tamoxifen and Exemestane Trial.
*Quartiles defined by composite risk cutoffs of 1.01, 1.59, and 2.21.

patterns generally diverged around this point in the spectrum of composite risk. For example, the 2015 St Gallen Consensus Panel considered age younger than 35 years, four or more positive lymph nodes, persistent premenopausal estrogen level after adjuvant chemotherapy (ie, the SOFT chemotherapy cohort), and grade 3 tumor as factors warranting the use of OFS or an AI plus OFS.[18] Indeed, in the TEXT and SOFT hormone receptor–positive, HER2-negative population, age younger than 35 years, four or more positive lymph nodes, and grade 3 tumor were the most influential features contributing to a high composite risk relative to their referent categories (Data Supplement). When considered with coexisting factors, 93% (age < 35 years), 98% (≥ four positive nodes), and 90% (grade 3 tumor) of patients had composite risk greater than the overall median of the distribution (Table 3; Data Supplement). Chemotherapy was administered to 87%, 99%, and 72% of these patients, respectively (Table 1), and the benefit of exemestane plus OFS versus tamoxifen, with or without OFS, would have been at least 5% and could have been as much as 10% to 15% for most of these patients, depending on composite risk. Thus, in addition to younger patients, those patients considered—by clinicopathologic features or an assay—to be at high risk of recurrence have potential for large absolute benefit with the use of adjuvant exemestane plus OFS.

That our model for composite risk included Ki-67 measured in a central laboratory may be considered a limitation. The clinical utility of Ki-67 measured locally by immunohistochemistry remains uncertain.[19,20] However the inclusion of proliferation genes in multigene assays underscores the importance of including a measure of proliferation as part of a prognostic measure.[21,22] The STEPP method facilitated investigation of a continuous factor in relation to disease outcome, but some features may be considered shortcomings. Investigating absolute treatment effect required the specification of the 5-year time point. The method illustrates pattern rather than focusing on testing comparisons of 5-year BCFI or defining cutpoints for the continuous factor. In addition, TEXT and SOFT did not investigate sequential treatment strategies analogous to tamoxifen followed by AI for postmenopausal women, and we do not know if 5 years of exemestane plus OFS is more efficacious than a sequential strategy. At the median follow-up of fewer than 6 years, 4% of patients with hormone receptor–positive, HER2-negative disease had died, and follow-up was too short to estimate treatment effects on overall survival. Further follow-up of TEXT and SOFT patients is essential to guide patient care.

TEXT and SOFT demonstrated that premenopausal women with hormone receptor–positive disease benefit, on average, from exemestane plus OFS versus tamoxifen with or without OFS. However, individualized treatment decisions should weigh the benefits against the adverse effects and costs of these therapy options. In the absence of predictive biomarkers, consideration of a patient's prognosis, as illustrated by STEPP analysis of a composite measure of recurrence risk in the TEXT and SOFT populations, is integral to this decision making. The STEPP analysis further supports the option of adjuvant tamoxifen alone without chemotherapy for some premenopausal women with hormone receptor–positive, HER2-negative disease at low risk of recurrence. It also demonstrates that the absolute improvement in 5-year BCFI with exemestane plus OFS over tamoxifen—with or without OFS—is substantial in some women with hormone receptor–positive, HER2-negative disease, particularly those regarded as having high recurrence risk.

Fig 4. Subpopulation treatment effect pattern plot of 5-year breast cancer–free interval (BCFI) in the hormone receptor–positive, human epidermal growth factor receptor 2 (HER2) –negative population according to (A, C, E, G) composite risk subpopulations and (B, D, F, H) distribution of composite risk for each of the four cohorts defined by trial and chemotherapy use. (A, B) SOFT (Suppression of Ovarian Function Trial) no-chemotherapy cohort, (C, D) TEXT (Tamoxifen and Exemestane Trial) no-chemotherapy cohort, (E, F) TEXT chemotherapy cohort, and (G, H) SOFT prior-chemotherapy cohort. The vertical dashed lines indicate the median composite risk of 1.59 in the overall hormone receptor–positive, HER2-negative analysis population. OFS, ovarian function suppression.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Absolute Benefit of Adjuvant Endocrine Therapies for Premenopausal Women With Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Early Breast Cancer: TEXT and SOFT Trials

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