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ORIGINAL REPORT

Physical and Psychosocial Recovery in the Year After Primary Treatment of Breast Cancer

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ABSTRACT

Purpose
The 2000 National Institutes of Health Consensus Conference on Adjuvant Therapy of Breast Cancer recommended chemotherapy for all women with invasive cancer greater than 1 centimeter. Studies of long-term breast cancer survivors have found poorer quality of life (QOL) in women who received adjuvant chemotherapy. The aim of this article is to characterize physical and psychosocial recovery as a function of chemotherapy receipt in the year after medical treatment completion.

Patients and Methods
Prospective longitudinal survey data (RAND SF-36 and Breast Cancer Prevention Trial [BCPT] Symptom Scales) collected from 558 women with breast cancer enrolled on the Moving Beyond Cancer (MBC) psychoeducational intervention trial were compared according to receipt of chemotherapy. MBC study enrollment occurred within 4 weeks after the end of primary treatment (eg, surgery, chemotherapy, radiation). Self-report questionnaire data collected at enrollment and at 2, 6, and 12 months thereafter were examined, controlling for intervention and with propensity score adjustment for imbalance of covariates. Outcome analyses were carried out by fitting linear mixed models by using SAS PROC MIXED.

Results
Longitudinal SF-36 scale scores did not differ by chemotherapy treatment exposure, and both groups improved significantly ($P < .01$) in the year after primary treatment ended. However, adjuvant chemotherapy treatment was associated with significantly more severe physical symptoms, including musculoskeletal pain ($P = .01$), vaginal problems ($P < .01$), weight problems ($P = .01$), and nausea ($P = .03$).

Conclusion
Physical and psychosocial functioning improved significantly after breast cancer treatment, independent of receipt of adjuvant chemotherapy. Women who received chemotherapy experienced more severe and persistent physical symptoms that should be more effectively managed as part of survivorship care.

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INTRODUCTION

Primary breast cancer treatments are complex, including surgery, chemotherapy, biotherapy, radiation therapy, and reconstructive surgery, often extending more than a year after diagnosis. Research on treatment effects on quality of life (QOL) has focused on the time immediately post diagnosis, primarily describing the acute impact of surgery[1,2] and chemotherapy on women's lives.[3-8] Other studies have examined the effects of various treatments on breast cancer survivors many years after diagnosis and initial treatment.[9-15] Cross-sectional studies of long-term breast cancer survivors[10,13,16] have suggested that adjuvant chemotherapy is associated with poorer physical functioning and overall QOL and more severe symptoms,[15,17,18] in part because of the protracted course of treatment as well as the persistent residual symptoms (eg, fatigue, neuropathy, pain). However, few prospective studies have examined the impact of chemotherapy on the trajectory of women's recovery during the year immediately after treatment completion.[18,19]

Controlled research from our group tested a psychoeducational intervention designed to enhance recovery after primary treatment of breast cancer.[20-23] We reported in this journal that a role-modeling videotape, focused on promoting realistic expectations and approach-oriented coping, helped women recover their energy significantly more quickly in the 6 months after intervention.[22] Women in the Moving Beyond Cancer (MBC) trial

were evaluated at four time points in the year after the end of primary treatment, providing an opportunity for a detailed examination of their recovery.[22] On the basis of cross-sectional data from breast cancer survivors several years beyond this time period,[10,12,13] we hypothesized that patients with exposure to chemotherapy would experience worse physical functioning with slower recovery than women without chemotherapy and would have more severe symptoms in the year after primary treatment. By using propensity score adjustment in the analysis, this report describes the recovery of women in the MBC study cohort in the year after primary treatment and asks the following questions: What is the impact of chemotherapy on the recovery trajectory of physical and psychosocial functioning? Are there differences in the type, severity, and recovery pattern of symptoms according to chemotherapy treatment exposure? We conducted these analyses with the intent of being able to answer queries from our patients who frequently ask, "When will I recover from the effects of my breast cancer treatments?"

PATIENTS AND METHODS

Study Participants and Recruitment

Between July 1, 1999 and June 30, 2002, the MBC study enrolled 558 women with stage I or II breast cancer on a randomized trial evaluating the impact of three different interventions on recovery in the year after primary treatment.[20,22,24] Participants were recruited from three geographic areas of the United States (Los Angeles, Kansas City, Washington, DC), as described in earlier publications.[20,24] All participants were included in a registration telephone call that occurred within 6 weeks of surgical treatment, after which time they were tracked until the end of their primary breast cancer treatments (either surgery alone, surgery with radiation therapy, surgery and chemotherapy, or surgery followed by chemotherapy and radiation therapy) and then were approached about participation in the full study.[20,24] Enrollment on the randomized intervention study occurred within 4 weeks after the end of primary therapy, and all prospective data collection occurred in the post-treatment period in the subsequent 12 months.

Procedures and Instruments

At registration, just after definitive surgery, all patients completed a telephone-administered version of the RAND SF-36 10-item physical functioning and five-item mental health scales to allow comparison of women who subsequently enrolled or did not enroll on the MBC study.[20,24] At study enrollment, a questionnaire booklet was mailed to the patient, and additional surveys were mailed at three subsequent time points after random assignment and intervention (at 2 months, 6 months, and 12 months post enrollment). The booklet included a comprehensive battery of validated instruments, including those described in this section of the article, which are examined in these analyses.[20] Patients also reported the chemotherapy treatment regimen received; however, medical chart review was not done, so information on specific doses or number of cycles of therapy was not available.

The RAND SF-36 contains 36 items in eight individual scales (ie, physical functioning, role-function physical, pain, vitality/energy, mental health, role-function emotional, social functioning, general health perceptions) assessing health-related QOL in the past month.[25-27] It is scored from 0 to 100, and 100 is the most favorable score. General population norms are available.[26] The full SF-36 was administered at enrollment and follow-up surveys; only the physical function and mental health scales were used at registration.[24] The SF-36 can also be scored as the Physical Component Summary Scale (PCS) and the Mental Component Summary Scale (MCS),[28] for which standardized norm mean scores are 50; scores of 60 or 40 represent one standard deviation (SD) greater or less than the population mean.

The Breast Cancer Prevention Trial (BCPT) symptom checklist[29] assessed vasomotor symptoms, nausea, bladder problems, vaginal problems, musculoskeletal pain, cognitive problems, and weight problems; two additional items were about arm swelling and decreased range of motion ipsilateral to surgery, which were averaged into a measure of arm problems.[30] Women reported the severity of each problem by rating them from 0 (not at all) to 4 (extremely) for the extent to which they were bothered by the problem in the past 4 weeks.

Statistical Methods

Descriptive statistics were used to examine demographic and clinical characteristics for the overall sample and by chemotherapy status. Mean scores for the SF-36 scales, the SF-36 summary scales, and the BCPT symptom severity scores at enrollment and registration were similarly examined. To adjust for potential case-mix differences (ie, nonidentical distributions of background characteristics) according to receipt of chemotherapy, we considered several a priori covariates that were based on previous literature, and we conducted separate least-squares regression analyses to compare adjusted means between patients with and without chemotherapy on the SF-36 PCS and MCS summary scales as well as on the eight SF-36 scales at each assessment point. The differences in the patterns of characteristics among participants suggested a need to consider whether outcome differences between patients with and without chemotherapy might reflect not only distinctions in QOL outcomes but also distinctions in patient case-mix. Thus we proceeded to use propensity scores in our analysis on the basis of the theory that adjustment for propensity scores can be expected to yield balance in the distribution of background characteristics across treatment groups.[31]

To estimate propensity scores, we used logistic regression to model an indicator for chemotherapy status as a function of patient covariates. By using the method of Rosenbaum and Rubin,[32] we arrived at a suitable propensity-score model, which included main effects of eight characteristics, namely age, education level, race/ethnicity, marital status, employment status, household income, mastectomy status, having had radiation, and all two-way interaction terms among these eight factors. This model achieved satisfactory balance in the distribution of background characteristics after controlling for the propensity score, which motivated our use of this model to obtain an estimated propensity score for each individual.

Outcome analyses were carried out by fitting linear mixed models by using SAS PROC MIXED (SAS Institute, Cary, NC). Separately for each outcome, we started with a model that included fixed effects associated with an indicator for chemotherapy, time since enrollment (in months), an interaction between those two terms, and the estimated propensity score. The randomly assigned MBC intervention condition also was controlled. For the BCPT symptom models, we also included menopausal status at baseline. We fit each model with a random intercept; a random intercept and slope; and a random intercept, slope, and quadratic trajectory, incorporating fixed effects for quadratic patterns over time in the latter models. The random slope terms allowed different individuals to have different time trends, and the random quadratic terms allowed different individuals to have different curvature in the patterns of their outcomes over time. The presentations here were chosen by selecting one of these models on the basis of whether the improvements in model fit from random intercept to random intercept plus slope and, when appropriate, from random intercept plus slope to random intercept plus slope and quadratic trajectory were significant on the basis of likelihood-ratio tests. The resulting analyses can be interpreted as providing comparisons over time on QOL outcomes between patients with and without chemotherapy, adjusting for case-mix characteristics. We plotted the fitted values over time from the linear mixed models, with separate lines representing the patients with and without chemotherapy. All data presentations used MBC study enrollment time point as the baseline for the scores over the 12-month post-treatment period.

RESULTS

Participant Characteristics

At registration interview, women who subsequently had chemotherapy reported slightly poorer SF-36 mental health scores (69.0 *v* 72.2; $P = .03$) but no difference in SF-36 physical functioning scores.[20] Table 1 presents the demographic and medical characteristics of the study participants according to adjuvant chemotherapy status at enrollment. Women who had received chemotherapy

Table 1. Patient Demographics and Clinical Characteristics at Study Enrollment

Characteristic	Total (N = 558) No.	%	Chemotherapy (n = 279) No.	%	No Chemotherapy (n = 279) No.	%	P
Age, years							< .01*
Mean	56.9		52.4		61.4		
SD	11.3		10.0		10.8		
Months since surgery							< .01*
Mean	5.7		7.9		3.6		
SD	2.8		2.1		1.3		
Ethnicity							
White	480	86	240	86	240	86	.92
Nonwhite	77	14	39	14	38	14	
Marital status							
Married	441	79	244	87	197	71	< .01
Not married	117	21	35	13	82	29	
Education							
Post college	200	36	98	35	102	37	.97
College degree	153	27	79	28	74	27	
Some college/associate	135	24	67	24	68	24	
Less than college	70	13	35	13	35	13	
Income, $†							
> 100,000	368	68	171	63	197	74	< .01
≤ 100,000	172	32	101	37	71	26	
Site							
Los Angeles	279	50	140	50	139	50	.73
Washington, DC	160	29	83	30	77	28	
Kansas	119	21	56	20	63	23	
Lumpectomy							
Yes	435	78	204	73	231	83	< .01
No	123	22	75	27	48	17	
Mastectomy							
Yes	183	33	112	40	71	25	< .01
No	375	67	167	60	208	75	
Breast reconstruction‡							
Yes	85	15	56	20	29	10	< .01
No	471	85	223	80	248	90	
Radiation							
Yes	380	69	188	68	192	70	.71
No	172	31	88	32	84	30	
Tamoxifen							
Yes	304	54	129	46	175	67	< .01
No	255	46	150	54	104	37	
Menopausal at enrollment							
Yes	356	65	147	53	209	77	< .01
No	193	35	131	47	62	23	
Intervention arm							
A: control	187	34	94	34	93	33	.96
B: video intervention	187	34	92	33	95	34	
C: video + counseling	184	33	93	33	91	33	

Abbreviation: SD, standard deviation.
*By *t* test.
†n = 18 missing.
‡n = 2 missing.

were significantly younger (52.4 years *v* 61.4 years; $P < .01$) and were significantly different in income, marital status, type of surgery, breast reconstruction, use of endocrine therapy, and menopausal status. The mean time from definitive breast cancer surgery to enrollment was 5.7 months across the entire sample and was significantly shorter for the nonchemotherapy group (3.6 months *v* 7.9 months; $P < .01$). Patients reported receiving the following chemotherapy regimens: 48% received doxorubicin and cyclophosphamide (AC) or fluorouracil, doxorubicin, and cyclophosphamide (FAC); 17% received cyclophosphamide, methotrexate, and fluorouracil (CMF); 26% received AC followed by a taxane; 17% received some other regimen.[20]

Table 2. RAND SF-36 and BCPT Symptom Scales at Enrollment

Scale	Total (N = 558)		Chemotherapy (n = 279)		No Chemotherapy (n = 279)		
	Mean	SD	Mean	SD	Mean	SD	*P*
RAND SF-36							
PCS	45.1	9.9	45.0	9.6	45.3	10.24	.78
MCS	49.0	10.1	48.7	9.9	49.3	10.3	.43
Physical functioning	76.4	22.0	76.8	20.9	75.9	23.1	.62
Role, physical	50.0	41.8	49.3	41.4	50.7	42.1	.68
Mental health	75.8	16.1	75.3	16.0	76.3	16.3	.46
Role, emotional	69.5	38.9	70.5	38.2	68.5	39.7	.54
Energy	51.5	22.3	50.6	21.6	52.4	23.0	.34
Social functioning	77.7	23.2	76.0	23.1	79.3	23.2	.09
Bodily pain	72.4	21.8	73.0	21.1	71.8	22.5	.52
General health perceptions	70.9	18.5	69.3	17.8	72.6	19.1	.04
BCPT symptoms*							
Hot flashes	1.22	1.21	1.35	1.18	1.09	1.21	< .01
Nausea	0.17	0.45	0.23	0.53	0.11	0.34	< .01
Bladder problems	0.32	0.60	0.28	0.51	0.36	0.68	.14
Vaginal problems	0.48	0.89	0.68	1.04	0.30	0.66	< .01
Musculoskeletal pain	1.06	0.99	1.17	1.04	0.96	0.94	.01
Cognitive problems	0.64	0.92	0.78	0.99	0.51	0.83	< .01
Weight problems	0.98	0.98	1.15	1.04	0.81	0.89	< .01
Arm problems	0.34	0.64	0.31	0.59	0.38	0.68	.17

Abbreviations: RAND SF-36, RAND short-form 36; BCPT, Breast Cancer Prevention Trial; SD, standard deviation; PCS, physical component summary scale; MCS, mental component summary scale.
*Higher scores indicate greater severity of symptoms.

We compared enrollment characteristics between completers (n = 400) and noncompleters (n = 158) of the 12-month survey.[22] Those completing the 12-month survey were significantly older; more likely to use tamoxifen; have less pain, better general health, fewer weight problems, and fewer cognitive problems; and have fewer depressive symptoms[22] (data not shown). Roughly equal proportions of 12-month completers and noncompleters received chemotherapy. The MBC study random assignment was stratified for chemotherapy use as well as marital/partner status.

Table 2 presents data on the SF-36 and BCPT symptom scale scores at study enrollment by receipt of chemotherapy. There were statistically significant differences for general health perceptions (but no other SF-36 scales), with worse scores for chemotherapy recipients. For the BCPT symptom scores at enrollment, chemotherapy was associated with more severe hot flashes, nausea, vaginal problems, musculoskeletal pain, cognitive problems, and weight problems. Only bladder problems and arm problems did not differ significantly between the two groups.

Recovery in the Year After Treatment Ends

Figure 1 shows the trajectory of recovery of PCS and MCS during the year post treatment. For both treatment groups, the scores improve significantly over time ($P < .01$ for both PCS and MCS) but without significant differences related to chemotherapy exposure ($P = .50$ and $P = .10$, respectively). Scores for the MCS exceed the population mean of 50 by 1 year later, whereas the scores on the PCS are less than 50, which suggests a slower recovery of physical function for both groups of women. Figure 2 shows the scores for the eight scales of the SF-36. The pattern of recovery

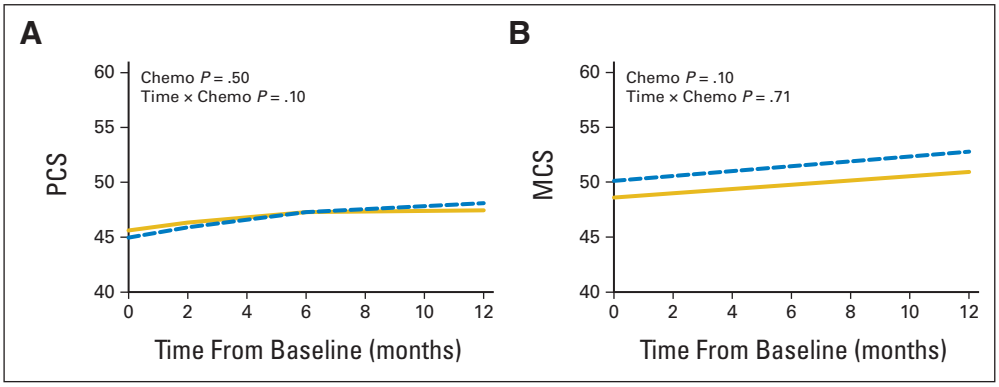

Fig 1. Propensity-adjusted mixed model results for trajectory of physical and mental component summary scales of the short-form 36 in the year after primary treatment. (A) Physical component summary (PCS; $P = .50$). (B) Mental component summary (MCS; $P = .10$). Solid gold line, no chemotherapy (chemo); dashed blue line, chemo.

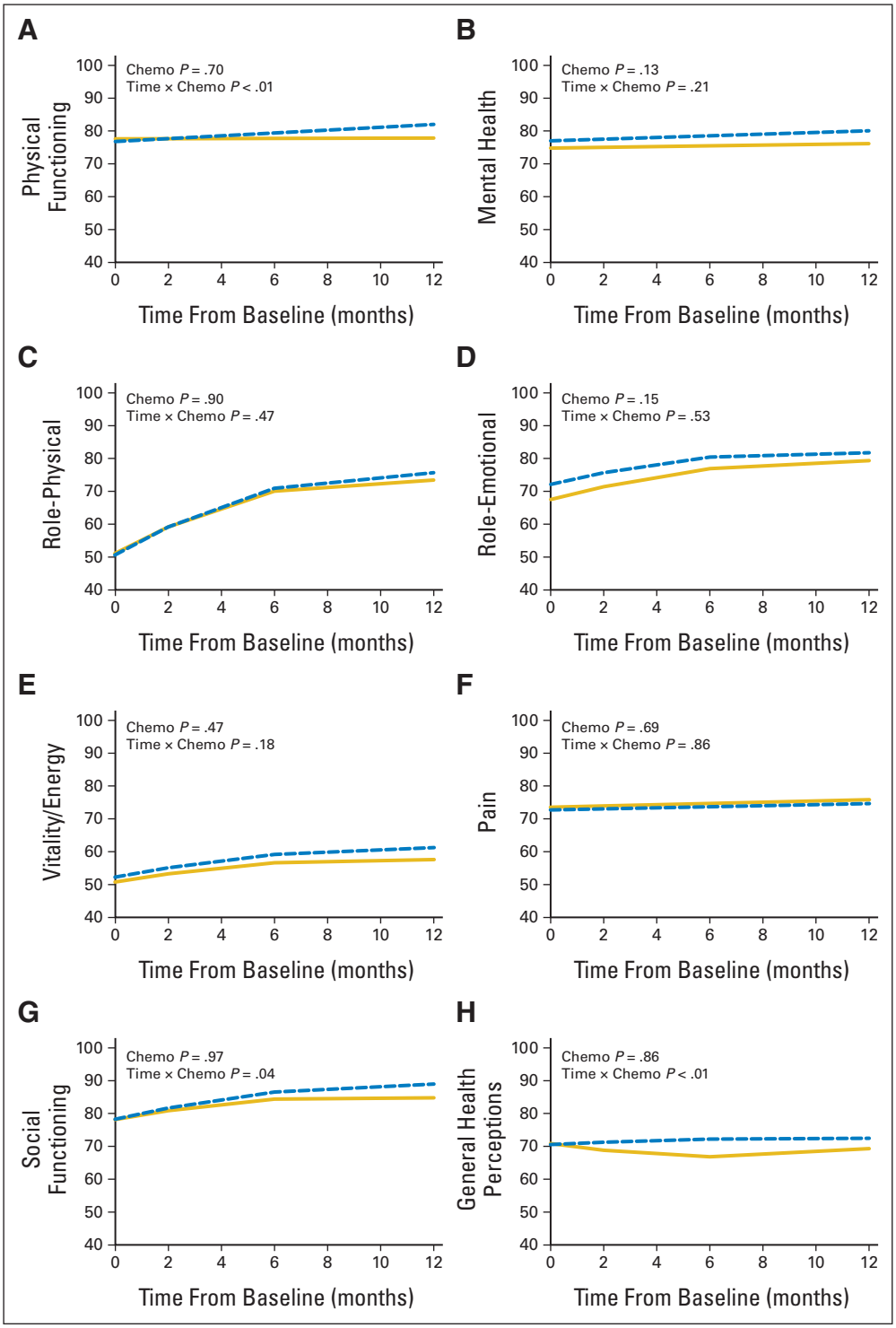

Fig 2. Propensity-adjusted mixed model results for trajectory of the eight short-form 36-item (SF-36) scales in the year after primary treatment. (A) SF-36 physical functioning (P = .70); (B) SF-36 mental health (P = .13); (C) SF-36 role-physical functioning (P = .90); (D) SF-36 role-emotional functioning (P = .15); (E) SF-36 vitality/energy (P = .47); (F) SF-36 pain (P = .69); (G) SF-36 social functioning (P = .97); (H) SF-36 general health perceptions (P = .86). Solid gold line, no chemotherapy (chemo); dashed blue line, chemo.

according to receipt of chemotherapy is similar, with both groups showing substantial improvements over time, especially in role-physical and role-emotional functioning (Figs 2C and 2D). The vitality/energy scores (Fig 2E) are lower than the population norms for both groups of patients and slowly improve over time. For physical functioning, social functioning, and general health perceptions scales (Figs 2A, 2G and 2H), there is a significant time-by-chemotherapy interaction term, which suggests that the chemotherapy patients and nonchemotherapy patients do not differ at baseline but that chemotherapy patients fare somewhat better over time, which could be related to the greater time that has elapsed since their initial breast cancer diagnosis compared with women who did not receive chemotherapy who are more proximate to their diagnosis.[20]

Impact of Chemotherapy on Symptoms

We next evaluated the eight BCPT symptom scale severity scores across the four assessment points (Figs 3A to 3H). Women who received chemotherapy had significantly more severe nausea ($P = .03$), vaginal problems (eg, vaginal dryness, pain with intercourse; $P < .001$), musculoskeletal problems ($P = .01$), and weight problems ($P = .01$) than those not receiving chemotherapy. For nausea and cognitive problems, women who received chemotherapy had higher severity scores than nonchemotherapy patients in the first 4 months after the end of treatment but had significantly lower scores thereafter ($P = .02$ for nausea and $P = .03$ for cognitive problems for interaction with time). Arm problems initially were slightly more severe for the nonchemotherapy patients, but they became more severe for the chemotherapy patients over time ($P < .01$ for the

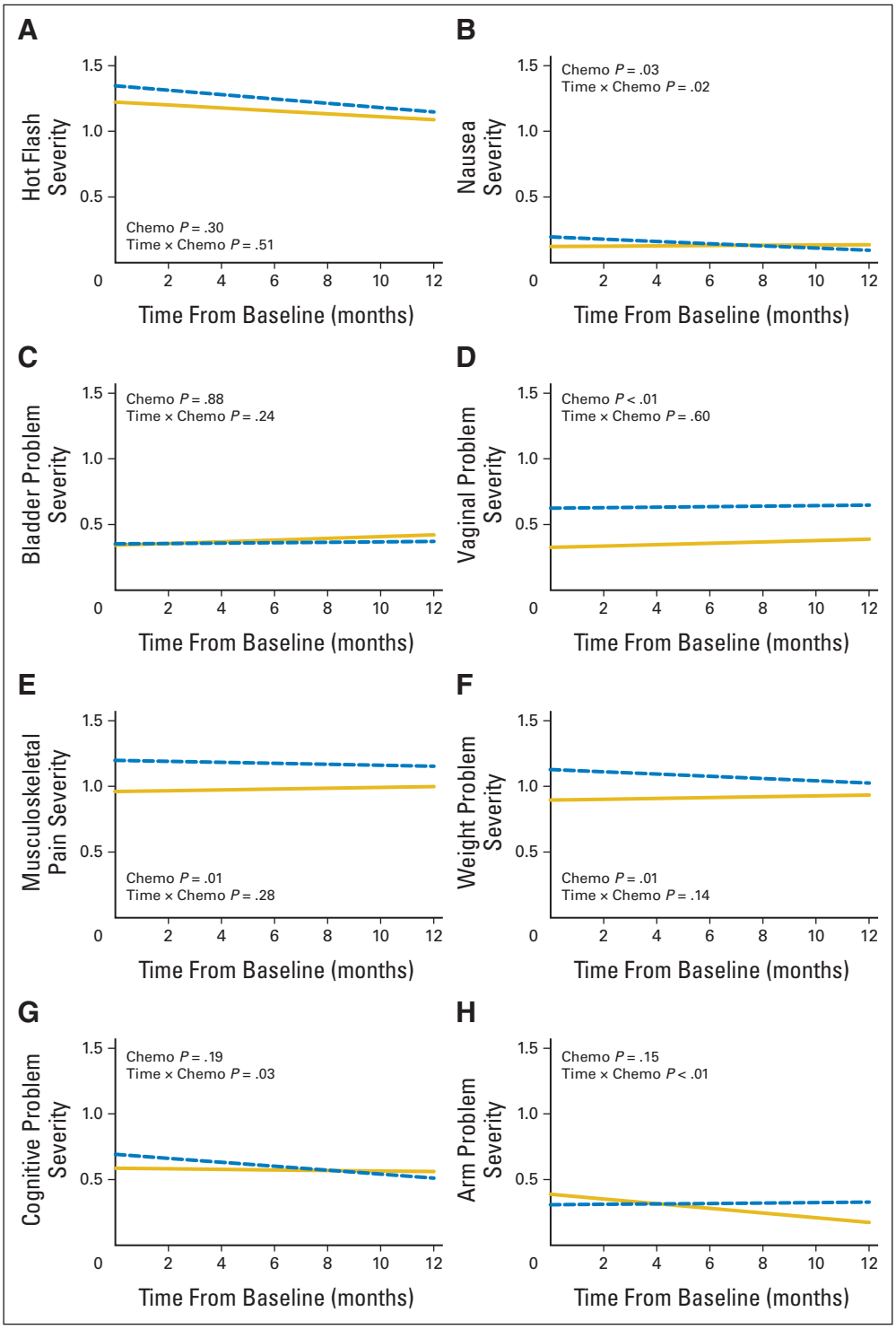

Fig 3. Propensity-adjusted mixed model results for Breast Cancer Prevention Trial symptom scales showing severity of symptoms after primary treatment. (A) Hot flashes ($P = .30$); (B) nausea ($P = .03$); (C) bladder problems ($P = .88$); (D) vaginal problems ($P < .01$); (E) musculoskeletal pain ($P = .01$); (F) weight problems ($P = .01$); (G) cognitive problems ($P = .19$); (H) arm problems ($P = .15$). Solid gold line, no chemotherapy (chemo); dashed blue line, chemo.

time-by-chemotherapy interaction). Bladder problems and hot flashes did not differ significantly between groups. For both groups, the most severe and persistent physical symptoms (predicted scores approaching or greater than 1, indicating slight to moderate perceived severity) were hot flashes, musculoskeletal pain problems, and weight problems.

DISCUSSION

At the time of the 2000 National Institutes of Health Consensus Conference on Adjuvant Therapy of Breast Cancer,[33] all women with a tumor greater than 1 centimeter were advised to receive adjuvant chemotherapy, even though it was known to have acute and potentially longer-term effects on QOL and symptoms.[12,34] A decade later, breast cancer treatments are being tailored according to tumor-specific gene expression profiles that can more successfully assess the risk for recurrence and need for chemotherapy.[35,36] Even with these tools, patient preferences may still influence decision making, and accurate information about the impact of chemotherapy treatment on physical and psychosocial functioning, as well as symptoms, may be helpful. There are limited comparative data from clinical trials on these patient-reported outcomes (PROs) from contemporary adjuvant chemotherapy trials[37,38] with absence of no treatment comparison groups. As a result, observational PRO data can provide valuable information that may be of help in decision making. The purpose of reporting the observational post-treatment data from the MBC trial was to examine differences in recovery after adjuvant chemotherapy by using a contemporaneous no-chemotherapy comparison group. On the basis of prior research with long-term survivors, we predicted that chemotherapy would have a negative impact on physical functioning and symptoms.[10,13] Here, we examined whether prospective longitudinal PRO data collected in the year after treatment could support a causal relationship between chemotherapy exposure and these long-term effects. The observational nature of the data collection in the MBC study required the use of propensity-score adjustment accounting for differences in who was likely to receive chemotherapy (eg, younger age, hormone receptor–negative tumors). Although the outcomes in this study were self-reported QOL and symptoms and not survival, some medical and demographic factors could affect subjective assessment of PROs. To our surprise, however, these propensity-adjusted analyses suggested few differences in PROs among women in the year post treatment, specifically in relationship to prior chemotherapy exposure (Figs 1 to 3).

Previous cross-sectional studies of breast cancer survivors have suggested negative effects of chemotherapy on QOL, and most specifically physical functioning and symptoms, but have not controlled for background characteristics associated with treatment exposure. Findings from a recent longitudinal study that utilized more sophisticated analytic techniques found no association between chemotherapy exposure and fatigue in the 6 months after breast cancer treatment, consistent with our results.[39] It is possible that the SF-36 was not sufficiently sensitive to detect nuanced differences in psychosocial parameters as a function of chemotherapy receipt. Although we did find some significantly different symptom outcomes among chemotherapy-treated patients, they are not so severe or disparate that such therapy should be avoided; however, patients can be informed that such symptoms may be a consequence of the treatment and that they may persist beyond the end of treatment.

Although we detected few outcome differences in the SF-36 scales trajectory by chemotherapy assignment, patients receiving chemotherapy may still experience more severe symptoms,[6,7,10,12,40] and these may be causing some of the lasting consequences of adjuvant therapy. We found greater severity of vaginal symptoms, musculoskeletal pain, and weight problems, which were all significantly worse in patients receiving chemotherapy and persisted throughout the 1 year of observation post treatment. Surprisingly, vasomotor symptoms were not significantly different ($P = .30$) by chemotherapy exposure even after controlling for menopausal status, but they were among the most severe symptoms in the two groups of patients. This observation no doubt relates to the greater tamoxifen use in women who did not receive chemotherapy, which continues in the year after primary treatment ends. The pattern of vaginal symptoms (ie, dryness, pain with intercourse) are consistent with our earlier research, and are more bothersome in women who received chemotherapy, with no improvement in severity over time.[9,10,12]

Potential limitations of this research include the representativeness of the study sample,[22] as well as lack of detailed information about chemotherapy regimens and stage of disease in the absence of medical chart review. The chemotherapy regimens reported by these women were representative of treatments in common use at the time. Contemporary treatments more often include taxanes, which may have a different toxicity profile.[41,42] Future research should more carefully assess information about specific chemotherapy regimens with the goal of determining their effects on QOL and symptom outcomes. This may be best accomplished within randomized, clinical trials. Although MBC study eligibility was limited to women with stages I and II disease, the findings are still relevant for women with more advanced disease (eg, stage III), who are often treated in a similar manner; however, a recent study by Bardwell et al[43] suggests that medical factors contribute little to the self-assessment of psychosocial outcomes in breast cancer survivors.[43,44] Questions also could be raised about whether trajectories for chemotherapy and nonchemotherapy patients can be explained by a modest number of covariates in a parametric model.

In conclusion, we have shown that the multiple aspects of health-related QOL improve in the year after primary breast cancer treatment, independent of use of chemotherapy; however, moderately severe symptoms persist, and many that are more severe occur in women who received chemotherapy. Prior work suggests that uncontrolled symptoms may contribute significantly to poorer physical and psychosocial health in breast cancer survivors.[20] With increasing attention to the needs of cancer survivors and the development of survivorship care plans,[45,46] future research should focus on the development and testing of symptom interventions to improve the health and well-being of these women.[47-49] Importantly, for patients in the immediate post-treatment phase of early breast cancer, we can now provide more specific information about the trajectory of physical and psychosocial recovery, and can estimate the differential impact of chemotherapy when it is indicated as a important component of adjuvant therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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