Psychosocial Telephone Counseling for Survivors of Cervical Cancer: Results of a Randomized Biobehavioral Trial

Lari Wenzel, Kathryn Osann, Susie Hsieh, Jo A. Tucker, Bradley J. Monk, and Edward L. Nelson

ABSTRACT

Purpose

Survivors of cervical cancer experience quality-of-life (QOL) disruptions that persist years after treatment. This study examines the effect of a psychosocial telephone counseling (PTC) intervention on QOL domains and associations with biomarkers.

Patients and Methods

We conducted a randomized clinical trial in survivors of cervical cancer, who were ≥ 9 and less than 30 months from diagnosis ($n = 204$), to compare PTC to usual care (UC). PTC included five weekly sessions and a 1-month booster. Patient-reported outcomes (PROs) and biospecimens were collected at baseline and 4 and 9 months after enrollment. Changes in PROs over time and associations with longitudinal change in cytokines as categorical variables were analyzed using multivariable analysis of variance for repeated measures.

Results

Participant mean age was 43 years; 40% of women were Hispanic, and 51% were non-Hispanic white. Adjusting for age and baseline scores, participants receiving PTC had significantly improved depression and improved gynecologic and cancer-specific concerns at 4 months compared with UC participants (all $P < .05$); significant differences in gynecologic and cancer-specific concerns ($P < .05$) were sustained at 9 months. Longitudinal change in overall QOL and anxiety did not reach statistical significance. Participants with decreasing interleukin (IL) -4, IL-5, IL-10, and IL-13 had significantly greater improvement in QOL than those with increasing cytokine levels.

Conclusion

This trial confirms that PTC benefits mood and QOL cancer-specific and gynecologic concerns for a multiethnic underserved population of survivors of cancer. The improvement in PROs with decreases in T-helper type 2 and counter-regulatory cytokines supports a potential biobehavioral pathway relevant to cancer survivorship.

J Clin Oncol 33:1171-1179. © 2015 by American Society of Clinical Oncology

INTRODUCTION

Cervical cancer is the leading cause of female cancer mortality and second most common cancer in women worldwide.¹ Survivors, many of whom are young and underserved minorities, experience quality-of-life (QOL) disruptions²⁻⁸ that can persist long after cancer treatment has ended,^{2,8,9} resulting in unmet supportive care needs.¹⁰ In a recent analysis of QOL data among US survivors of cancer, the authors note that survivors of cervical cancer have worse physical and mental health-related QOL compared with survivors of other cancer and adults with no cancer history.¹¹ This further illustrates the need for interventions that can be implemented easily to assist high-risk cancer survivor populations.

Considerable evidence exists showing that psychosocial interventions have positive effects on the psychosocial functioning and QOL of patients with cancer.¹²⁻²⁰ Interventions may help by reducing emotional distress and improving adjustment to illness via cognitive behavioral stress management,^{21,22} improving coping skills and relaxation training,²³⁻²⁵ and reducing the impact of symptoms and adverse effects.²⁶⁻²⁸ Within the intervention literature, the benefits of psychosocial telephone counseling (PTC) to improve QOL in survivors of cancer have also been well documented.²⁹⁻³²

The psychoneuroimmune axis provides a biologic construct for examining the effects of psychosocial interventions on clinical outcomes.³³⁻³⁵ The biologic benefits of a decreased chronic stress

Lari Wenzel, Kathryn Osann, Susie Hsieh, Jo A. Tucker, and Edward L. Nelson, University of California Irvine, Irvine, CA; and Bradley J. Monk, Creighton University School of Medicine at St Joseph's Hospital and Medical Center, Phoenix, AZ.

Published online ahead of print at www.jco.org on February 23, 2015.

Supported by the National Cancer Institute of the National Institutes of Health under Grants No. R01 CA118136-01 and P30CA062203.

Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Clinical trial information: NCT00496106.

Corresponding author: Lari Wenzel, PhD, Professor of Medicine, Professor of Public Health, University of California, Irvine, 100 Theory Dr, Ste 110, Irvine, CA 92697; e-mail: lwenzel@uci.edu.

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0732-183X/15/3310w-1171w/\$20.00

DOI: 10.1200/JCO.2014.57.4079

response are well documented in various disease states.³⁶⁻⁴⁰ A mechanism by which psychosocial intervention might impact cancer clinical outcomes is the promotion of antitumor immunity via modulation of the stress response.^{33-35,41,42} A biobehavioral paradigm that includes the relationships between cancer as a chronic psychological and physiologic stressor, incorporating biologic effects of chronic stress on neuroendocrine and immune parameters that may influence clinical outcome, provides the context for this proposed mechanism.⁴³⁻⁴⁵ Our pilot trial indicated that PTC intervention yielded significantly improved QOL associated with a shift in the ratio of T-helper class 1 to T-helper class 2 (Th1:Th2).³⁴ The purpose of this larger, longitudinal study was to examine the effect of PTC in survivors of cervical cancer on patient-reported outcomes (PROs) of QOL, depression, anxiety, and gynecologic concerns, together with associations in stress-related biomarkers. We hypothesized that patients who received PTC, as compared with patients receiving usual care (UC), would report better QOL, better mood, and fewer gynecologic concerns, which could be associated with improved stress-related biomarkers.

PATIENTS AND METHODS

Research Design and Study Sample

Between 2009 and 2012, survivors of cervical cancer were identified through the California Cancer Registries (Orange, Los Angeles, Imperial, and San Diego Counties). Survivors were considered eligible if they had stage I to IVA (locally advanced but without disseminated metastasis) disease, had completed definitive treatment at least 2 months earlier, and were able to read and speak English or Spanish. After passive physician approval for contact, survivors were mailed invitation letters and contacted by telephone. They were enrolled ≥ 9 and less than 30 months from diagnosis, which approximates a time of survivorship re-entry including psychological and physical adjustment¹⁵ and sequelae associated with late effects of treatment. Enrolled survivors were randomly assigned with stratification by ethnicity. The protocol was amended in 2010 to allow for 2:1 random assignment (PTC: UC) to compensate for loss to PTC arm enrollment. Patients were excluded if they had undergone treatment with biologic response modifiers or prior immunotherapy within 4 weeks of study enrollment, used investigational drugs within 30 days, required corticosteroids, or were immunosuppressed. The institutional review boards of both the University of

Fig 1. CONSORT diagram of ascertainment and recruitment. PTC, psychosocial telephone counseling.

California Irvine and California Cancer Registries approved the protocol. All participants provided written informed consent.

Intervention

On PTC assignment, participants received a precall (5 minutes) to reintroduce the purpose of the intervention and schedule session I, a QOL/psychosocial interview (generally 60 minutes). Sessions II to IV (range, 20 to 60 minutes) included topics of managing stress and emotions, health and wellness, and managing relationship and sexuality concerns. In these sessions, based on the transactional model of stress and coping,^{31,46,47} problems or stressors and accompanying emotions were identified, and problem-solving, social support, thought-changing, or role-playing communication skills strategies were used. A tailored summary letter with homework suggestions was prepared and mailed to the participant after each session, reinforcing skills training. Session V was a summary and integration session; the 1-month booster reviewed progress. Protocol fidelity was assessed via weekly counselor supervision (L.W.) of audiotapes, session notes, and homework letters.

Study Measures

Surveys were mailed in advance, with follow-up phone calls as needed. The Patient-Reported Outcomes Measurement Information System (PROMIS) emotional distress depression short form includes eight items, scored from 1 to 5 points (where 1 = never and 5 = always), in which the patient indicates how true each statement has been during the last 7 days. Consistent with PROMIS scoring convention (<http://www.nihpromis.org>), the scale score was computed using prorating when more than 50% of items were answered. A high score connotes more depression. The PROMIS emotional distress anxiety short form includes seven items, similarly scored. Both PROMIS scales demonstrated internal consistency coefficients ≥ 0.95 . The Brief Symptom Inventory (BSI-18), a shortened version of the BSI developed to assess psychological distress, includes a global severity score and subscales measuring depression, anxiety, and somatization.^{48,49} Patients are asked to respond in terms of how they have been feeling during the last 7 days; items are rated on a 5-point Likert scale from 0 (not at all) to 4 (always/extremely). Both measures are considered a proxy for chronic stress in this setting.

The Gynecologic Problems Checklist (GPC)⁸ identifies the type and magnitude of gynecologic problems using the following two subscales: gynecologic problems (eg, pelvic pain, vaginal dryness; Cronbach's $\alpha = .72$) and sexual dysfunction (eg, pain with intercourse, loss of interest in sexual activities; Cronbach's $\alpha = .90$). The subscales are summed for a GPC total score.

The Functional Assessment of Cancer Therapy (FACT)–Cervical (FACT-Cx) is a multidimensional, combined generic and disease-specific QOL questionnaire including the FACT–General (FACT-G) questionnaire (version 4), consisting of four subscales (Physical, Social, Emotional, and Functional Well-Being),⁵⁰ and an Additional Concerns subscale representing cervical cancer–specific concerns. Patients indicate how true each statement has been during the last 7 days. The Additional Concerns subscale can be analyzed separately (Cronbach's $\alpha = .72$) and summed with other subscales to produce the FACT–Cx score (Cronbach's $\alpha = .92$). The FACT–Trial Outcome Index is a sum of the Physical Well-Being, Functional Well-Being, and Additional Concerns subscales.

Biomarker Measures

Biospecimens were collected at the participant's locale following verbal and written instructions. Standard phlebotomy was performed into EDTA Vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ). Blood was transported at ambient temperature from the collection site to the laboratory and processed typically within 60 to 180 minutes, with any variation from these conditions noted. Plasma was collected by centrifugation, aliquoted and stored at -80°C until batched analyses. Samples were tested in duplicate with Milliplex MAP High Sensitivity Human Cytokine Magnetic Bead Kit, HSCYTMA-60SK (EMD Millipore, Billerica, MA). Plasma samples were prepared in accordance with the manufacturer's instructions.⁵¹ Patient samples from all three time points were run on a single plate. Data were collected with MAGPIX xPONENT software (Luminex, Austin, TX) and analyzed with Milliplex Analyst 5.1 software (EMD Millipore).

Table 1. Descriptive Characteristics of Study Population

Characteristic	UC		PTC		P
	No. of Patients	%	No. of Patients	%	
Race/ethnicity					.69
White/non-Hispanic	44	49.4	61	53.0	
Hispanic	39	43.9	44	38.3	
Other*	6	6.7	10	8.7	
Education					.46
$\leq$ High school	34	38.2	49	43.4	
Some college/graduate	55	61.8	64	56.6	
Stage					.54
I	67	75.3	80	71.4	
II-IVA	22	24.7	32	28.6	
Treatment					.37
Surgery only	44	49.4	56	48.7	
Radiation only	9	10.1	6	5.2	
Chemotherapy $\pm$ radiation therapy	36	40.4	53	46.1	
Age at diagnosis, years	n = 89		n = 115		.85
Mean	44.9		44.6		
SD	9.5		9.7		
Time from diagnosis to baseline, months	n = 89		n = 115		.95
Mean	19.4		19.4		
SD	5.8		5.0		
Patient-reported outcomes, scores					
FACT-Cx	n = 88		n = 115		.69
Mean	124.0		125.3		
SD	23.5		24.9		
FACT-TOI	n = 88		n = 112		.71
Mean	87.4		86.4		
SD	16.2		18.3		
FACT Additional Concerns	n = 88		n = 115		.49
Mean	44.5		43.7		
SD	8.0		8.5		
FACT-G	n = 88		n = 112		.44
Mean	79.5		81.5		
SD	18.3		18.6		
ED Depression T-score	n = 89		n = 114		.50
Mean	52.8		53.7		
SD	9.6		9.9		
ED Anxiety T-score	n = 89		n = 114		.95
Mean	53.9		53.8		
SD	11.0		11.8		
BSI-GSI standard score	n = 89		n = 115		.89
Mean	51.8		51.6		
SD	11.1		12.3		
BSI Depression standard score	n = 89		n = 115		.99
Mean	54.6		54.7		
SD	11.4		11.6		
BSI Anxiety standard score	n = 89		n = 115		.80
Mean	46.3		46.7		
SD	9.3		10.5		
GPC-Total	n = 84		n = 110		.52
Mean	20.4		21.1		
SD	8.1		8.3		

Abbreviations: BSI, Brief Symptom Inventory; ED, Emotional Distress (Patient-Reported Outcomes Measurement Information System); FACT-Cx, Functional Assessment of Cancer Therapy–Cervical; FACT-G, Functional Assessment of Cancer Therapy–General; FACT-TOI, Functional Assessment of Cancer Therapy–Trial Outcome Index; GPC, Gynecologic Problems Checklist; GSI, Global Severity Index; PTC, psychosocial telephone counseling; SD, standard deviation; UC, usual care.

*Other includes African American, Asian, and Native American.

Statistical Analyses

The primary outcome was change in FACT-Cx score from baseline to 4 months. We estimated that with 100 patients per arm, the study would have 80% power to detect a significant between-group difference of 5.0 in overall QOL change, based on our pilot study.³⁴ Secondary outcomes include change in FACT-G, FACT-Trial Outcome Index, and Additional Concerns subscales; the PROMIS emotional distress depression and anxiety measures; the BSI Global Severity Index and subscales (depression, anxiety, and somatization); and the GPC total score.

Comparisons of baseline characteristics were performed using univariable analysis of variance and χ^2 analyses. Published scoring algorithms

were used for the PROMIS, BSI, and FACT measures. Changes over time in PROs were compared between study arms using multivariable analysis of variance for repeated measures. Effect sizes were calculated as the difference between arms divided by the pooled baseline standard deviation. Data were adjusted for patient age and baseline values. Trends over time were tested from baseline to 4-month follow-up and baseline to 9-month follow-up, with a significance level of $P < .05$. To examine differences in change over time related to treatment, an additional grouping factor was added. No adjustment for multiple comparisons was made. Because of the multiple outcomes and time points, significance values should be interpreted conservatively.

Fig 2. Longitudinal change in patient-reported outcomes. Data for psychosocial telephone counseling (PTC) patients (solid blue lines) and usual care (UC) patients (dashed gold lines) at baseline, at 4 months (time 2 [T2]), and at 9 months (time 3 [T3]) for individuals for whom data are present for all three time points. Error bars represent SEs. (A) Longitudinal change in the Functional Assessment of Cancer Therapy–Cervical (FACT-Cx) Additional Concerns subscale ($n = 145$). (B) Longitudinal change in the Gynecologic Problems Checklist (GPC; $n = 139$). (C) Longitudinal change in the Patient-Reported Outcomes Measurement Information Systems (PROMIS) Depression T-score ($n = 149$). (D) Longitudinal change in the FACT-Cx for patients whose treatment involved surgery alone (solid blue line represents patients who received PTC, $n = 42$; dashed gold line represents patients who received UC, $n = 37$). (E) Longitudinal change in the FACT-Cx for patients whose treatment included radiation therapy (solid blue line represents patients who received PTC, $n = 34$; dashed gold line represents patients who received UC, $n = 36$).

Patients with missing follow-up questionnaires were excluded from longitudinal analyses. Random missing items on returned questionnaires, totaling 1.5% of all possible items, were handled according to the administration/scoring procedures in the Functional Assessment of Chronic Illness Therapy manual, prorating scores under the constraints that more than 50% of items in any subscale and more than 80% of all items must be completed (www.facit.org).

Associations between longitudinal changes in PROs and cytokine levels were investigated across patients using an F test for trend. Change in cytokine levels was classified into quintiles because of non-normality, with the lowest two quintiles representing decreasing cytokines and the highest two quintiles representing increasing levels. Specimens with variance from ambient transportation and overtly lipemic samples were excluded. Associations after exclusions were similar to associations before exclusions, with slightly higher significance despite smaller numbers. This subgroup, excluding compromised biologic samples, was considered to better represent the true association and, therefore, is presented in the results.

RESULTS

Participant Recruitment and Baseline Characteristics

A total of 685 eligible patients were approached to participate, and 204 patients (30%) enrolled (Fig 1). Of those enrolled, 115 patients were randomly assigned to PTC and 89 were assigned to UC. The mean participant age was 43 years, with an average of 19 months from diagnosis. Table 1 lists the characteristics of the two arms. There were no significant baseline differences between study arms or ethnic groups.

Overall study retention rates were 82% at 4 months ($n = 168$) and 74% at 9 months ($n = 151$). At 4 months, 93% of UC patients ($n = 83$) and 74% of PTC patients ($n = 85$) were retained. Those with higher depression (T-score ≥ 60) who were randomly assigned to the PTC arm were significantly more likely to drop out of the study ($P < .05$), either before or after session I (the psychosocial interview). Other factors associated with attrition in the PTC arm included single marital status and high school education or less. Of those who completed the 4-month assessment, 90% of UC participants ($n = 75$) and 89% of PTC participants ($n = 76$) were retained at 9 months. Eighty-nine percent of participants assigned to PTC completed session I, and 80%

completed all six sessions. Participants received remuneration of \$50 subsequent to each assessment.

Changes in Psychosocial and QOL Status at 4 Months

After adjusting for age and baseline values, comparison of measures at 4 months after enrollment indicated that patients assigned to PTC demonstrated significantly better scores than patients assigned to UC (Fig 2) for depression and gynecologic and cancer-specific concerns (Table 2). Although there was no significant difference in overall QOL, PTC participants had a 2.4-point decrease in the FACT Additional Concerns subscale, compared with a 0.82-point decrease in the UC group ($P = .040$). Similarly, PTC patients demonstrated a 2.59-point decrease in gynecologic problems, compared with a 0.13-point decrease in the UC group ($P = .040$). Patients receiving PTC had a 3.13-point decrease in mean PROMIS depression T-scores compared with a 0.59-point decrease in the UC group ($P = .014$). This effect was also observed on the BSI Depression scale ($P = .041$). There were no significant differences in PROMIS anxiety T-scores. Effect sizes are listed in Table 2.

Changes in Psychosocial and QOL Status at 9 Months

A comparison of measures from baseline through 9 months after enrollment indicated that patients assigned to PTC demonstrated significantly better scores than those assigned to UC for gynecologic and cancer-specific concerns (Fig 2). Specifically, PTC participants improved by 2.99 points in cancer-specific concerns compared with 1.38 points in the UC group ($P = .025$). Similarly, PTC participants demonstrated a continued improvement in gynecologic problems of 2.88 points compared with 0.82 points for UC participants ($P = .045$; effect sizes listed in Table 2).

Changes in Psychosocial and QOL Status by Cancer Treatment Group

There were significant time $\times$ study arm $\times$ treatment (ie, surgery only ν chemoradiotherapy) interaction effects on overall QOL ($P = .046$), cancer-specific concerns ($P = .002$), depression as measured by the BSI ($P = .018$), and gynecologic problems ($P = .036$). As indicated

Table 2. Differences Over Time for PROs for PTC and UC

PRO	Absolute Difference at 4 Months (T2 – T1)*					Absolute Difference at 9 Months (T3 – T1)*				
	UC	PTC	PTC – UC	P	Effect Size†	UC	PTC	PTC – UC	P	Effect Size†
FACT-Cx	2.62	5.90	3.28	.258	0.14	4.37	7.19	2.82	.134	0.12
FACT-TOI	1.57	3.75	2.18	.212	0.13	3.00	4.68	1.68	.170	0.10
FACT Additional Concerns	0.82	2.40	1.58	.040	0.20	1.38	2.99	1.61	.025	0.20
FACT-G	1.72	3.54	1.82	.349	0.10	3.15	4.28	1.14	.450	0.06
ED Depression T-score	–0.59	–3.13	–2.54	.014	0.25	–1.47	–2.80	–1.32	.215	0.13
ED Anxiety T-score	–0.89	–2.97	–2.08	.068	0.21	–2.00	–3.16	–1.16	.464	0.12
BSI-GSI standard score	–0.76	–3.35	–2.59	.092	0.23	–0.90	–2.83	–1.93	.185	0.17
BSI Depression standard score	–0.84	–3.21	–2.37	.041	0.21	–1.39	–2.28	–0.89	.502	0.08
BSI Anxiety standard score	0.71	–1.49	–2.21	.103	0.22	0.44	–1.48	–1.92	.166	0.19
GPC-Total	–0.13	–2.59	–2.46	.043	0.31	–0.82	–2.88	–2.06	.045	0.26

Abbreviations: BSI, Brief Symptom Inventory; ED, Emotional Distress (Patient-Reported Outcomes Measurement Information System); FACT-Cx, Functional Assessment of Cancer Therapy–Cervical; FACT-G, Functional Assessment of Cancer Therapy–General; FACT-TOI, Functional Assessment of Cancer Therapy–Trial Outcome Index; GPC, Gynecologic Problems Checklist; GSI, Global Severity Index; PRO, patient-reported outcome; PTC, psychosocial telephone counseling; T1, baseline; T2, 4 months; T3, 9 months; UC, usual care.

*Differences adjusted for age and baseline value.

†Effect size = difference between arms/standard deviation.

Table 3. Effect Size for Differences Over Time by Treatment Group

Patient-Reported Outcome	Effect Size*				Group × Time × Treatment Interaction, <i>P</i>
	Surgery Only		Radiation Therapy ± Chemotherapy		
	T1 to T2	T1 to T3	T1 to T2	T1 to T3	
FACT-Cx	0.23	0.00	0.02	0.24	.046
FACT-TOI	0.21	0.04	0.03	0.25	.022
FACT Additional Concerns	0.23	0.07	0.14	0.49	.002
FACT-G	0.19	0.01	0.00	0.13	.302
ED Depression T-score	0.25	0.03	0.25	0.31	.298
ED Anxiety T-score	0.11	0.07	0.31	0.33	.379
BSI-GSI standard score	0.33	0.01	0.12	0.35	.140
BSI Depression standard score	0.39	0.10	0.01	0.28	.018
BSI Anxiety standard score	0.22	0.09	0.23	0.32	.674
GPC-Total	0.35	0.04	0.24	0.49	.036

Abbreviations: BSI, Brief Symptom Inventory; ED, Emotional Distress (Patient-Reported Outcomes Measurement Information System); FACT-Cx, Functional Assessment of Cancer Therapy–Cervical; FACT-G, Functional Assessment of Cancer Therapy–General; FACT-TOI, Functional Assessment of Cancer Therapy–Trial Outcome Index; GPC, Gynecologic Problems Checklist; GSI, Global Severity Index; T1, baseline; T2, 4 months; T3, 9 months.

*Effect size = difference between arms/standard deviation.

in Table 3, a significant three-way interaction effect for time × arm × treatment supports a difference in the response to counseling between patients treated with surgery only and patients receiving chemoradiotherapy (Figs 2D and 2E). Specifically, the PTC surgery-only group attained treatment benefits at 4 months in QOL, depression, and gynecologic problems, whereas the PTC patients treated with chemoradiotherapy demonstrated a slower, steady improvement with larger effect sizes at 9 months than at 4 months (Table 3).

Associations Between PROs and Cytokines

Because the chronic stress response is associated with a heightened Th2 cytokine response, we examined the plasma Th2 cytokines interleukin (IL) -4, IL-5, and IL-13. A significant inverse trend was observed between change in FACT-Cx and change in Th2 cytokines grouped into quintiles (Fig 3). Participants with a longitudinal decrease in Th2 cytokines had significantly greater improvements in FACT-Cx scores compared with patients with increasing cytokines after adjusting for age and baseline QOL ($P = .001$, $P = .016$, and $P = .005$ for IL-4, IL-5, and IL-13, respectively; Appendix Table A1, online only). Patients with a longitudinal decrease in plasma IL-10, a counter-regulatory cytokine associated with the chronic stress response, also showed an increase in QOL ($P = .001$; Fig 3). These significant relationships held for the FACT-G and the Additional Concerns subscale as well (data not shown). The association between decrease in IL-6 and improvement in depression was not statistically significant ($P = .083$; Appendix Table A1). There were no significant PTC versus UC differences in biomarkers.

DISCUSSION

We conducted a randomized clinical trial of a PTC intervention on an ethnically and racially diverse sample that yielded an improvement in PROs and identified longitudinal associations between improved QOL and improved cytokines. In the era of rapidly advancing therapeutics, the proportion of patients with cancer with extended survival is increasing, making attention to maximizing overall health imperative. Results of this trial indicate that this PTC intervention has a

positive effect on symptoms of depression, cervical cancer–specific concerns that affect QOL, and gynecologic problems. Our survivor population began the study reporting general QOL scores similar to those of other adult patients with cancer but reporting slightly more distress than a normative noncancer population. Notably, PTC participants' 4- and 9-month scores on both measures of distress improved to levels at or less than (better than) national norms. Although some may question the power of telephone counseling to address such sensitive topics, we assert that for vulnerable survivors of cancer, the opportunity to extend an intervention via telephone may be the optimal (and often only) way to reach this population.

For the cohort as a whole, treatment effects were larger closest in time to intervention delivery (ie, 1 to 4 weeks after the booster session).

Fig 3. Associations between longitudinal change (time 1 [T1; baseline] to time 2 [T2; 4 months]) in serum cytokine levels and Functional Assessment of Cancer Therapy–Cervical (FACT-Cx) scores. The mean change in FACT-Cx scores is depicted for all patients by quintiles (Qs) of longitudinal change in cytokines; the lowest two Qs represent decreasing changes in cytokines; the middle Q includes zero change; and the highest two Qs represent increasing changes in cytokines (interleukin [IL] -4, $n = 103$, $P = .001$; IL-5, $n = 114$, $P = .016$; IL-13, $n = 102$, $P = .005$) and in the counter-regulatory cytokine IL-10 ($n = 114$, $P = .001$).

However, both gynecologic and cancer-specific improvements were sustained at 9 months. We believe that a larger overall sustained effect across measures would have been observed if PTC had been continued beyond the six sessions (ie, maintenance therapy), providing a direction for future research. In fact, supportive interventions, such as PTC, may be particularly useful for survivors of cancer at greatest risk for QOL disruption and distress.^{52,53} In this sample, patients who had only surgery experienced their peak treatment effect at the 4-month interval, which roughly coincided with the end of PTC. Patients treated with chemoradiotherapy, however, seemed to benefit more slowly but steadily after PTC ended. This may argue for identifying diminished health status, based on initial cancer treatment or late-stage disease, as an important factor in the timing or continuation of a counseling intervention to improve QOL. In the scenario of vulnerable cancer survivor populations, it has been recommended that population-level interventions for high-risk groups such as this could be implemented with relatively modest resources,^{54,55} noting that

telephone and Internet platforms will increase “scalability and reach of effective interventions.” The positive effects on QOL, mood, and gynecologic concerns observed in this trial may be sustained through a cost-effective maintenance approach, designed to benefit geographically and ethnically diverse populations.

Despite promising results, there are several study limitations. The sample size was calculated to assess a primary intervention effect based on overall QOL.³⁴ Unfortunately, we did not reach our desired enrollment, primarily because of differential dropout of patients between study arms. Ironically, a primary predictor of likelihood of dropping out of counseling before or after session I was a heightened level of depression at baseline. If compliance levels of PTC matched the control arm, we might have seen greater effect sizes associated with depression change and perhaps a significant difference in overall QOL; alternatively, given the severity of depression among dropouts, those who dropped out may have been resistant to treatment as a result of the severity of their depression, thus reducing effect sizes. As is, effect

Fig 4. Cancer survivorship and a biobehavioral paradigm. (A) A depiction of the biobehavioral paradigm integrating the psychoneuroimmune axis as it pertains to cancer survivorship. The diagnosis and treatment of a tumor imparts chronic psychological and physiologic stress that leads to disruption of multiple domains, which are interconnected via the psychoneuroimmune axis and which lead to decreased psychological and biologic health, resulting in compromised survivorship. (B) The documented impact of the psychosocial telephone counseling (PTC) intervention on this construct. Domain elements were modulated in association with PTC; anxiety (black) did not show significant modulation, and blue text represents elements that were not evaluated. We documented a positive impact of the PTC intervention on three of the four domains supporting a similar positive impact on cancer survivorship. DHEA, dehydroepiandrosterone; IL, interleukin; QOL, quality of life; Th2, T-helper type 2.

sizes in the current study are in the small to modest range,⁵⁶⁻⁵⁸ influenced by the many survivors who began the study doing well. In addition, the UC group improved their QOL over time, which differs from our pilot study (ie, also decreasing the observed effect size), despite lack of a control condition. A future study could focus on patients with heightened baseline depression scores and/or lower QOL scores, further tailor the counseling, and include an attention control condition. Additional limitations include lack of adjustment for multiple outcome comparisons, necessitating future trial confirmation. The study population was composed of survivors of cervical cancer who resided entirely within southern California, limiting the generalizability of our findings for other geographic and survivor populations.

In this study, we opted to use plasma cytokine assays for evaluating immunologic stance because practical limitations prohibited use of enzyme-linked immunospot assays. Circulating cytokine levels are subject to myriad influences, resulting in levels that are highly variable. Therefore, we categorized change into quintiles to provide maximal information regarding associated magnitude of cytokine change relative to the magnitude of change in QOL. It is conceivable that if enzyme-linked immunospot analyses were used, as in our pilot, more robust differences would be detected. Nevertheless, our data provide

evidence of a shift in immune stance with decreasing Th2 and counter-regulatory cytokine levels. We believe that the association between decreasing Th2 cytokines and improved QOL holds promise for future inquiry and is consistent with a biobehavioral paradigm incorporating the psychoneuroimmune axis for cancer survivorship^{33,34,40,59} (Fig 4).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

Conception and design: Lari Wenzel, Kathryn Osann, Edward L. Nelson

Collection and assembly of data: Lari Wenzel, Kathryn Osann, Susie Hsieh, Jo A. Tucker, Edward L. Nelson

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

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GLOSSARY TERMS

cytokines: cell communication molecules that are secreted in response to external stimuli.

health-related quality of life (HRQoL): a broad multidimensional concept that usually includes self-reported measures of physical and mental health.

psychosocial: the psychological (emotional) and social aspects of a disease and its treatment. Some of the psychosocial aspects of cancer are its effects on patients' feelings, moods, beliefs, the way they cope, and relationships with family, friends, and coworkers.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Psychosocial Telephone Counseling for Survivors of Cervical Cancer: Results of a Randomized Biobehavioral Trial**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Lari Wenzel

No relationship to disclose

Kathryn Osann

No relationship to disclose

Susie Hsieh

No relationship to disclose

Jo A. Tucker

No relationship to disclose

Bradley J. Monk

No relationship to disclose

Edward L. Nelson

No relationship to disclose

Acknowledgment

We acknowledge Paige McDonald, PhD, Chief, Basic Biobehavioral and Psychological Sciences Branch, Division of Cancer Control and Population Sciences at the National Cancer Institute, and Al Marcus, David Cella, Kathy Garrett, and Kimlin Ashing-Giwa, consultants on RO1 CA118136-01. We are grateful to the many survivors of cervical cancer who participated in this study and to Nissa Chantana, PsyD, Rosa Marie Kolts, MFT, Melissa Campitelli-Smith, PsyD, and Sandra Sappington, BA.

Appendix**Table A1.** FACT-Cx Scores and Changes in Cytokines

Factor	Quintiles for Change in Cytokines				
	Q-1 (low)	Q-2	Q-3	Q-4	Q-5 (high)
IL-4 Δ					
No. of patients	21	19	21	21	21
Mean Δ cytokine	-31.18	-4.31	0.15	3.43	20.02
Mean Δ FACT-Cx	11.29	5.63	7.24	-0.10	-1.38
SE	2.85	2.99	2.85	2.87	2.86
<i>P</i> for trend	.001				
IL-5 Δ					
No. of patients	21	23	23	24	23
Mean Δ cytokine	-1.21	-0.15	0.02	0.18	1.55
Mean Δ FACT-Cx	11.54	6.62	0.91	3.17	2.63
SE	2.84	2.72	2.72	2.67	2.71
<i>P</i> for trend	.016				
IL-13 Δ					
No. of patients	18	20	22	21	21
Mean Δ cytokine	-6.11	-0.50	0.00	0.48	3.61
Mean Δ FACT-Cx	10.06	8.50	5.24	-1.23	1.31
SE	3.14	2.98	2.84	2.91	2.91
<i>P</i> for trend	.005				
IL-10 Δ					
No. of patients	23	22	23	23	23
Mean Δ cytokine	-23.80	-3.27	0.91	4.96	22.43
Mean Δ FACT-Cx	10.18	7.92	4.54	3.76	-2.04
SE	2.68	2.74	2.68	2.69	2.68
<i>P</i> for trend	.001				
IL-6 Δ					
No. of patients	22	23	23	24	22
Mean Δ cytokine	-5.53	-0.50	0.23	1.37	7.16
Mean Δ Depression T-score	-2.59	-6.27	-1.21	0.54	-1.24
SE	1.71	1.66	1.66	1.63	1.74
<i>P</i> for trend	.083				

Abbreviations: FACT-Cx, Functional Assessment of Cancer Therapy–Cervical; IL, interleukin.