Stress, Immunity, and Cervical Cancer: Biobehavioral Outcomes of a Randomized Clinical Trail

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Abstract

Purpose: Cancer diagnosis and treatment imparts chronic stressors affecting quality of life (QOL) and basic physiology. However, the capacity to increase survival by improving QOL is controversial. Patients with cervical cancer, in particular, have severely compromised QOL, providing a population well-suited for the evaluation of novel psychosocial interventions and the exploration of mechanisms by which modulation of the psychoneuroimmune axis might result in improved clinical outcomes.

Experimental Design: A randomized clinical trial was conducted in cervical cancer survivors that were enrolled at ≥13 and ≤22 months after diagnosis (n = 50), comparing a unique psychosocial telephone counseling (PTC) intervention to usual care. QOL and biological specimens (saliva and blood) were collected at baseline and 4 months post-enrollment.

Results: The PTC intervention yielded significantly improved QOL (P = 0.011). Changes in QOL were significantly associated with a shift of immune system T helper type 1 and 2 (Th1/Th2) bias, as measured by IFN-γ/interleukin-5 ELISPOT lymphocyte precursor frequency; improved QOL being associated with increased Th1 bias (P = 0.012). Serum interleukin-10 and the neuroendocrine variables of cortisol and dehydroepiandrosterone revealed trends supporting this shift in immunologic stance and suggested a PTC-mediated decrease of the subject’s chronic stress response.

Conclusions: This study documents the utility of a unique PTC intervention and an association between changes in QOL and adaptive immunity (T helper class). These data support the integration of the chronic stress response into biobehavioral models of cancer survivorship and suggests a novel mechanistic hypotheses by which interventions leading to enhanced QOL could result in improved clinical outcome including survival.

The association between cancer patient survival and performance status at diagnosis, i.e., baseline quality of life (QOL), is well documented. Patient-reported outcomes, broadly addressed as QOL variables, are now integral components of cancer clinical trials (1) and highlight opportunities for psychosocial interventions to improve these outcomes for patients with cancer. Whether effective psychosocial interventions improve both patient QOL and survival remains controversial (2–10). Nevertheless, any potential cancer-specific survival benefit implies improved control of occult micrometastatic disease (11) and the immune system is a prime candidate effector for this biological antitumor activity. The recognition of cross-talk between neurologic, neuroendocrine, and immune systems has given rise to the concept of psychoneuroimmunology, the psychoneuroimmune axis, and the so-called “mind-body” connection (5, 12–15). This conceptual framework provides a foundation for biobehavioral paradigms (16–18) and for the postulation of potential mechanisms by which a psychosocial intervention might influence cancer patient survival (2, 5, 11, 17, 18).

Various studies evaluating if psychosocial interventions could affect cancer patient survival have been critically reviewed and revisited in recent meta-analyses that come to somewhat divergent conclusions (6–8). Roughly equal numbers of published trials show longer survival associated with psychosocial interventions or an absence of any associated survival benefit (6). Several factors have been identified that may contribute to this ambiguous body of data (3, 5). Study populations, in some cases, have been exceptionally heterogeneous,
have had different prognoses, or report only mild QOL disruptions. Furthermore, some interventions have shown only marginal improvement in (2) or poorly documented changes in QOL variables and thus may not be sufficiently efficacious to modulate the psychoneuroimmune axis. It is imperative that a psychosocial intervention be effective at improving QOL in a population with significant QOL disruption if it is to provide meaningful data on modulations of the psychoneuroimmune axis and insights into mechanisms for any potential survival benefit.

The diagnosis and treatment of cancer results in acute stressors; however, the persistent disruption of QOL in many survivors speaks to the chronic stress associated with this disease. Previous biobehavioral paradigms for generating hypotheses pertaining to biological mechanisms for the potential association between improved QOL and cancer patient survival have not focused on the concept of cancer survivorship as a chronic stressor. Chronic stress, in contrast to acute stressors, perturbs the psychoneuroimmune axis with the net effect of a more profound T helper type 2 (Th2) immunologic stance (17–20). T helper class is typically characterized by T lymphocyte cytokine secretion. IFN-γ is widely acknowledged as a prototypical Th1 cytokine (21) and interleukin (IL)-5 is indicative of highly polarized Th2 cells (22–24) providing respective measures of T helper class. It is widely held that a T helper type 1 (Th1) immune response is most desirable for effective antitumor immunity (21) and has been recently reported to be associated with improved disease-free and overall survival (25). The integration of the chronic stress response and its physiologic consequences into the existing biobehavioral model provides a paradigm that yields new mechanistic hypotheses for any potential mind-body interaction affecting cancer clinical outcomes (Fig. 1). Amelioration of chronic stress (18–20) is predicted to result in a shift of immune profile, via the psychoneuroimmune axis, to a more prominent Th1 stance with the potential to improve antitumor immunity (Fig. 1B). Thus, the mechanism by which a psychosocial intervention might affect clinical outcome may be related to the modulation of the antitumor immune response via modulation of the “stress response.”

The level of disruption of QOL seen in cervical cancer survivors is among the largest reported for any cancer population (26–29). In contrast to other cancer populations with less profound QOL disruption, this patient population has the opportunity for significant improvement in QOL and thus a greater likelihood of demonstrating associated psychoneuroimmune modulations. Thus, patients with cervical cancer provide a study population particularly well suited to examination of associations between psychosocial intervention–induced longitudinal improvement in QOL, biomarkers, and clinical outcomes. However, attempts to improve QOL for this underserved cancer survivor population have been hampered by multiple constraints, including socioeconomic barriers, resistance to traditional psychosocial interventions, as well as prominent sexual and reproductive concerns (26–28). Thus, we conducted a small, randomized feasibility trial of an innovative psychosocial telephone counseling (PTC) intervention designed for patients with cervical cancer. It was hypothesized that QOL would improve for patients receiving counseling, and that longitudinal analysis of select neuroendocrine and immune biomarkers could be conducted to permit early exploration of hypotheses for mind-body mechanisms by which interventions to improve QOL might ultimately improve clinical and biological outcomes.

### Patients and Methods

**Trial objectives and design.** A randomized study of PTC or “usual care” was conducted, enrolling 50 patients with cervical cancer, identified and recruited through the Cancer Surveillance Program of Orange, Imperial, and San Diego Counties and the Los Angeles Cancer Surveillance Program. The purpose of this study was to examine the methodologic feasibility of delivery of a PTC intervention, the determination of its potential benefits, and the investigation of potential associations between intervention-induced longitudinal modulations in QOL measures with longitudinal modulations in neuroendocrine and immune variables. This NIH-funded study was reviewed, approved, and monitored by the Institutional Review Board and Clinical Trials Protocol Review and Monitoring Committee and, was conducted in full concordance with the principles embodied in the Helsinki Declaration.
Table 1. Demographics

<table>
<thead>
<tr>
<th></th>
<th>Enrollees</th>
<th>Final study group</th>
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<tbody>
<tr>
<td></td>
<td>Usual care (n = 23)</td>
<td>PTC (n = 27)</td>
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<tr>
<td>Mean age (y)</td>
<td>49.0 (2.9)</td>
<td>49.3 (2.6)</td>
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<tr>
<td>Mean time (mo) from diagnosis to enrollment</td>
<td>17.2 (0.6)</td>
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<tr>
<td>White</td>
<td>34.8 (8)</td>
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<tr>
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<td>52.2 (12)</td>
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<tr>
<td>I</td>
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<td>II</td>
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<tr>
<td>Surgery only</td>
<td>26.1 (6)</td>
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<td>40.8 (11)</td>
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<td>63.0 (17)</td>
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<td>Employment</td>
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<td>Employed</td>
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</tr>
<tr>
<td>Not employed</td>
<td>34.8 (8)</td>
<td>37.0 (10)</td>
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</table>

NOTE: None of the differences between the usual care and “PTC” cohorts reached statistical significance (P > 0.05), either in the enrolled populations (enrollees) or those completing the study (final study group). Mean age and mean time from diagnosis to enrollment were evaluated by Student’s t test. All other variables, noted as a percentage of the designated population with absolute number in parentheses, were evaluated by the χ² test.

Patients. The study population included patients ascertained from the regional cancer registries with documented histologic diagnoses of squamous cell carcinoma of the uterine cervix, pathologic stage I, II, or III, who had undergone definitive treatment, who were fluent in English or Spanish as their primary language, who had access to a telephone, and who were able to understand and sign an informed consent form. The time from diagnosis variable for ascertainment from the registry was ≥9 and <24 months prior to enrollment. This time window was established to provide a target of 6 months of separation from primary treatment to minimize physiologic disruptions, whereas still permitting a reasonable likelihood of establishing contact in this mobile patient population. Patients were excluded if they had stage IV cervical carcinoma, used investigational drugs within 30 days of execution of the informed consent form, or were engaged in ongoing cancer treatment. Additionally, given our focus on the immune system, potential participants were excluded if they had undergone previous treatment with a biological response modifier (IFNs, interleukins) or prior immunotherapy within 4 weeks of study enrollment, required corticosteroids, or were under immunosuppression for any reason including organ allograft or HIV infection, in order to limit influence on T helper status of the immune system. Demographic variables are summarized in Table 1.

A bilingual female research associate contacted patients by telephone 1 to 2 weeks after posting of an initial introductory letter. Subjects desiring to participate in the study and who provided informed consent were scheduled for a baseline field visit for collection of QOL data and biological specimens. Subjects randomized to usual care were contacted in an identical time frame to subjects receiving PTC for scheduling of time 2 data collection.

Trial procedures. Biological specimens were collected in a standardized fashion. Saliva collection devices ("Salivette", Sarstedt) packaged with the MEMS IV Track Cap (AARDEX, Ltd.) covered pharmacy bottle accompanied by an Actiwacth (Mini Mitter, Co.) were sent to the subject’s address with instructions for use on the day of the field phlebotomist visit in collecting a morning saliva sample upon first awakening. The use of these two date, time, and activity-monitoring devices validated self-report and documented compliance with the early morning salivary collection procedure and instructions. Blood was collected at the subject’s residence in the afternoon and early evening; generally between 2:00 p.m. and 6:00 p.m. Plasma was collected on site and immediately placed on dry ice. Frozen plasma, collected Salivettes, and the remaining blood were transported to the laboratory for processing and cryopreservation. Aliquots of saliva and plasma were stored at -80°C until analysis. Peripheral blood mononuclear cells
(PBMC) were isolated by density centrifugation and cryopreserved in the vapor phase of liquid nitrogen until analyzed. The PTC intervention was specifically designed to help women cope with the stressful events and feelings of distress associated with cervical cancer. Subjects randomized to the PTC arm of the study received six counseling sessions, ~45 to 50 min in length, in their preferred language, consisting of five consecutive weekly sessions and a 1-month booster session, delivered by a psychologist. The organization and topics of the PTC intervention are noted in Table 2. A review letter, generated by the counselor after each session, recapitulated the session’s contents and reinforced adaptive coping strategies. All phone sessions were audiotaped for quality control with ~25% of all sessions reviewed (L. Wenzel).

QOL instruments were administered in the subject’s preferred language at baseline and 4 months after enrollment, ~2 weeks after the last counseling session (i.e., booster session) for those in the PTC arm. The Functional Assessment of Cancer Therapy-Cervical (FACT-Cx) was used as the primary QOL outcome as it is a multidimensional, combined generic and disease-specific QOL questionnaire for patients with cervical cancer (30, 31).

**End points.** Longitudinal evaluation of QOL and biomarkers were done for time 1 (T1) and time 2 (T2) as noted above. Salivary cortisol (lower limit of detection = 150 pg/mL) and dehydroepiandrosterone (DHEA; lower limit of detection = 150 pg/mL) concentrations were determined by chemiluminescent immunoassay (IBL, Inc.). Serum levels of IL-10 (lower limit of detection = 0.5 pg/mL) were determined in triplicate by standard ELISA (R&D Systems) according to the instructions of the manufacturer. IFN-γ and IL-5 ELISPOT analyses were done according to the instructions of the manufacturer (Mabtech, Inc.) using equimolar anti-CD3 (clone OKT3) and anti-CD28 (clone CD28.2; eBiosciences) saturated anti-mouseFc conjugated paramagnetic beads (Bang Laboratories Inc.) to provide primary and costimulatory signals exclusively to T lymphocytes. In contrast to other stimuli such as lipopolysaccharides, lectins, phorbol esters, or ionophores, this stimulus minimized the activation of other PBMC populations and the potential complicating secondary effects therein. T1 and T2 PBMCs from individual subjects were assayed simultaneously in triplicate over a range of input cell numbers/well (10⁴ to 10⁵/well) of freshly thawed, previously cryopreserved PBMC to determine IFN-γ and IL-5 precursor frequencies. All plates included PBMCs from a single cryopreserved normal donor as a positive internal assay control. The ratio of IFN-γ/IL-5 precursor frequencies provided a measure of Th1/Th2 immunologic stance. Standard flow cytometry was done on identical sample aliquots to enumerate the number of lymphocytes (CD3, CD4, CD8; including CD4+, CD25 high+ putative T₅₀), natural killer cells (CD16, CD56), natural killer T cells (CD3, CD56), and monococytes (CD14). All end points were evaluated in a blinded fashion with respect to randomization to treatment or usual care and biomarker analyses were done without knowledge of QOL outcomes.

**Statistical analysis.** We employed matched pair t tests and repeated measures ANOVA methods to examine differences between the PTC and usual care groups at two time points. To adjust for the possibility that improvement in QOL and changes in the immune system might be related to QOL at baseline, we also investigated changes over time in QOL, immune response and neuroendocrine variables after adjusting for the covariable QOL at T1 and other covariates using repeated measures ANCOVA methods. Correlations between psychosocial measures and immunologic stance were estimated using Spearman’s correlation coefficient (r).

### Table 2. PTC Structure

<table>
<thead>
<tr>
<th>Session 1</th>
<th>QOL and psychosocial interview</th>
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<tbody>
<tr>
<td>Session 2</td>
<td>Managing emotions and stress</td>
</tr>
<tr>
<td>Session 3</td>
<td>Enhancing health and wellness</td>
</tr>
<tr>
<td>Session 4</td>
<td>Addressing relational and sexual concerns</td>
</tr>
<tr>
<td>Session 5</td>
<td>Integration and summary</td>
</tr>
<tr>
<td>Session 6</td>
<td>Booster session</td>
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</table>

**Results**

This study was conducted between August 2004 and December 2005, with 36 subjects completing the entire study (Fig. 2, consort diagram), with a disproportionate dropout among younger and Latina subjects (Table 1). The diagnosis of cervical cancer was established at ≥13 and <22 months in the enrolled study population, easily meeting our target of 6 months of separation between completion of primary treatment and enrollment. No enrolled subjects developed recurrent disease during the course of their trial participation. There was no relationship between baseline FACT-Cx score and participant dropout with a mean score of 80.98 (SD, 13.68) for the subjects completing the study and 83 (SD, 14.21) for those that dropped out (P = 0.652). A total of six subjects had inadequate biological specimen collections, e.g., from one or more blood collections, inadequate recovered saliva, and insufficient PBMC isolated to perform all analyses. These six subjects and the inadequate biospecimens were randomly distributed between cohorts and were not significantly different from the remaining subjects in terms of QOL variables (P = 0.600) or demographic characteristics. Thus, 34 subjects were available for evaluation of PTC modulation of psychoneuroimmunological variables except for IFN-γ and IL-5 ELISPOT analyses that were performed on 30 subjects.

We showed a significant and sizable longitudinal PTC benefit, from T1 to T2, for the counseled participants on overall QOL as measured by a 6.7-point improvement in FACT-Cx with no improvement observed in the control population (P = 0.011; Fig. 3A). Subjects with high QOL at T1 may be less likely to improve simply because there is less room for improvement; hence, we adjusted for QOL at T1 in our comparisons between PTC and usual care. Adjusted means show an even larger difference in QOL over time (improvement in QOL = 7.0 for PTC versus -3.0 for usual care; P = 0.004 for adjusted difference based on ANCOVA). This difference persisted after adjusting for covariates including time from diagnosis to first visit (P = 0.018) and treatment with chemotherapy (P = 0.012) using multivariate ANOVA. The application of the FACT instrument to patients with a range of tumor types indicates that this level of change in the FACT-Cx represents a clinically meaningful improvement in QOL (32).

The improvement in QOL seen with the PTC cohort was associated with a larger decrease in morning first awakening salivary cortisol levels, a larger decrease in the molar cortisol/DHEA ratio, and an inverse association between modulation of QOL and serum levels of the counterregulatory or immunosuppressive cytokine IL-10, as depicted by the mean and SE for cohort of individual measurements (Fig. 3B). The longitudinal modulation of salivary cortisol/DHEA ratio approached, but did not reach, statistical significance (Supplementary Table S1). Nevertheless, the consistent pattern of longitudinal changes in
the selected biomarkers supports the effect of QOL improvement on the psychoneuroimmunology axis. Flow cytometric analyses showed no significant cohort differences in longitudinal modulation of natural killer cells, natural killer T cells, or CD4+ CD25 high+ populations within PBMC samples. However, a positive association between longitudinal changes in IL-10 and CD4+CD25 high+ putative T regulatory (Treg) cells was observed across the entire study population \( (P = 0.024) \), supporting the immunosuppressive role of IL-10 and a potential role of Treg cells. Improvement in FACT-Cx was significantly associated with an increase in Th1 bias, and conversely, a decline in FACT-Cx with a more pronounced Th2 immune system bias as measured by IFN-\( \gamma \)/IL-5 ELISpot PBMC precursor frequency \( (\text{Spearman correlation coefficient, } \tau = 0.6368; P = 0.0002, \text{two-tailed}) \). This significant association remained when longitudinal QOL and Th1/Th2 shifts in immune stance were evaluated as dichotomous variables \( (\text{Fig. 4B}; P = 0.012, \text{two-sided Fisher’s exact test}) \). QOL at T1 did not influence the change in immune or neuroendocrine variables; thus, no adjustment for baseline QOL was made for the comparisons. Additionally, biomarker differences between PTC and usual care were not explained by the covariates including time from diagnosis to enrollment or delivered treatment in multivariate ANOVA.

**Discussion**

We conducted a pilot feasibility study of a PTC intervention to show its potential efficacy and to explore associated physiologic consequences of longitudinal changes in QOL. We showed that PTC can be delivered to and significantly attenuate the profound disruption of QOL observed in patients with cervical cancer. This is particularly relevant in populations that, due to geographic or socioeconomic constraints, do not readily participate in organized psychosocial support group activities. Our exploration of the associated physiologic consequences of changes in cancer patient QOL was directed by a biobehavioral model incorporating the recognition of the chronic stress intrinsic to cancer survivorship. The documented effects of chronic stress on the neuroendocrine and immune systems include a Th2 immune system bias, increased immunosuppression, elevated cortisol, and increased cortisol/DHEA ratios \( (11, 17–19, 33) \), which guided our selection of biological variables for evaluation. Surprisingly, even in this small study population, we showed a significant increase in Th1 immune system bias in subjects with improved QOL. This observation was further supported by observed trends in neuroendocrine variables and a decrease in the counter-regulatory cytokine IL-10 \( (34, 35) \). These data suggest that future exploration of physiologic effects of chronic stress in the context of the biobehavioral model for cancer survivorship is warranted and provide support for possible immunologic mechanisms by which psychosocial interventions might yield improved clinical outcomes, potentially including cancer patient survival.

The fact that patients with cervical cancer, as a population, have among the most profound disruption of QOL and chronic stress \( (27–29) \) seen in cancer patients; both merit interventions to improve QOL and reduce this stress, thereby providing a study population well suited to mechanistic studies of psychoneuroimmunology \( (12–14) \). It is worthwhile to note that this population of cervical cancer survivors had a mean starting FACT-Cx score of \( \sim 80 \) (on a scale of 0-120), which is a score reflective of substantial disruption in multiple QOL domains and is consistent with the extensive published experience in this population. Cervical cancer survivors are also among the least likely to participate in traditional group, clinic-based psychosocial support interventions, due in part to prevalent socioeconomic and cultural factors \( (28, 29, 36–39) \). This suggests that a convenient psychosocial counseling intervention that did not require participant travel to a clinical center might be effective in this cancer survivorship population. Telephone-based psychosocial counseling interventions have these characteristics. Although such strategies have not been used in patients with cervical cancer, they have been successful as tested in breast cancer survivors \( (40–42) \) and are being investigated in other settings. Our demonstration that a PTC intervention could be successfully delivered and lead to a statistically significant, clinically meaningful improvement in QOL in this compromised cancer survivor population \( (32) \) supports the investigation of broader application of this therapeutic modality.
Numerous biological pathways involving the psychoneuroimmune axis have been advanced as potential mechanisms affecting the biological behavior of cancer (11, 17, 18, 43) and for psychosocial intervention-associated cancer patient survival benefits (44). These include endocrine and neuroendocrine shifts (14) that could lead to changes in the hormonal milieu with potential effects on cancer-specific survival of hormone responsive tumors. However, if psychosocial interventions can have an effect on survival in a wide range of tumor types, it seems unlikely that modulation of the neuroendocrine milieu alone will increase cancer-specific survival. Effects on tumor angiogenesis, growth, and metastasis by stress-associated modulation of soluble factors, such as vascular endothelial growth factor have been described (11). It is worthwhile to note that some of these factors, i.e., vascular endothelial growth factors, also play a role in suppressing antitumor immunity (45) perhaps through its affect on Treg cells (46). Similarly, the counterregulatory cytokine, IL-10, is increased in the setting of chronic stress (19), has an angiogenesis regulatory capacity (47), and also plays a role in Treg biology. Elevated cortisol levels seen with either acute or chronic stress have well-documented effects on the immune system (19). Similarly, stress levels of DHEA or DHEA sulfate are more variable, but the ratio of cortisol/DHEA is elevated in stressed populations and has been reported to be associated with Th1/Th2 immunologic profiles, with lower ratios associated with more prominent Th1 immune stance (48–50).

Several variations on the biobehavioral model have been proposed (11, 15, 16, 44) to provide a conceptual framework for potential mind-body connections in patients with cancer. The long-term disruption in QOL seen in many cancer patient populations can be considered to be indicative of chronic stressors. Thus, we incorporated physiologic consequences of chronic stress, as established in other disease states, into the biobehavioral model to guide the selection of biomarkers and generation of mechanistic psychoneuroimmune hypotheses. A dominant biological consequence of chronic stress is the shift in immune stance to a more pronounced Th2 profile (17, 51, 52). Chronic stress has also been associated with the expression of immunosuppressive elements, potentially mediated by or associated with changes in neuroendocrine factors (18–20, 33, 53, 54). This perturbation of the psychoneuroimmune axis, by chronic stress, including effects on the adaptive arm of the immune system, may play a role in the biological behavior of cancer and host defense (17, 18, 43, 52). Although longitudinal changes in nonspecific lymphoproliferative responses to anti-CD3 antibody stimulation and shifts in various cellular compartments of the innate and adaptive immune arms of the immune system have been documented in the setting of psychosocial interventions (11, 55), we are not aware of studies evaluating longitudinal associations between changes in cancer patient QOL and T helper profile. As it is now widely held that a Th1 dominant immune response is most desirable for sustained effective antitumor immunity, the evaluation of T helper status, specifically in the setting of the chronic stress associated with cancer survivorship, may lead to important mechanistic insights.

Fig. 3. QOL outcome and systemic biomarkers. Cohort-specific longitudinal change in QOL as measured by FACT-Cx total (A). Minimum to maximum scores: 0-108; higher scores, better QOL. –– PTC cohort; -----, usual care control cohort. Lines, changes in the mean of each cohort over time. PTC group: T1, mean ± SE (81.3 ± 3.88); T2, mean ± SE (88.51 ± 3.03). Control group: T1, mean ± SE (79.63 ± 2.96); T2, mean ± SE (76.94 ± 3.44). B, mean longitudinal changes (T2-T1) for individual determinations in each cohort for the designated variables. Filled columns, the control, usual care cohort; open columns, the PTC-receiving cohort; bars, SE. First graph, longitudinal change in cohort-specific FACT-Cx score, as above. Second and third graphs, mean changes in morning salivary cortisol and DHEA concentrations (nmol/L), respectively. Fourth graph, longitudinal change in the molar ratio of salivary cortisol/DHEA by cohort. None of the intercohort differences in these neuroendocrine variables reached statistical significance. Final graph, longitudinal change in serum IL-10 concentration (µg/mL). Evaluation of covariance is reported in the text.
These results were obtained in a relatively small study of a population of cervical cancer survivors. Although there were no statistically significant demographic differences between the PTC and usual care control groups, it is possible that the limited sample size masked the detection of interactions between clinical subgroups and evaluated outcomes. The potential effects of differences in disease stage and treatment on both psychological and biological variables were minimized by the designed enrollment of individuals well removed from their primary treatment. Multivariate analysis showed, even with this small sample set, that statistical significance of the PTC induced improvement in QOL along with the relationship between longitudinal changes in QOL and Th1/Th2 immunologic stance remained after accounting for differences from time of diagnosis to enrollment, stage, and therapy. Our observation that PTC resulted in a significant improvement in QOL within the study population argues for the ability to generalize this intervention to larger study populations in which such interactions, if present, are more likely to be detected. Importantly, the fact that longitudinal change in QOL was independently associated, regardless of cohort, with a shift in immunologic Th1/Th2 stance suggests that these disparities do not significantly contribute to the major findings of this study. As with many biomarker analyses that obtain specimens at discrete time points, it is important to recognize the limitations imposed by limited sampling. However, highly frequent, interval sampling is not practical for field collections of clinical study participants in studies such as this. Given these limitations, along with others, we were nevertheless impressed at the degree of association between longitudinal changes in QOL and T helper stance. The disparity in ethnicity of subjects dropping out of the study in the two cohorts is a matter of investigation and ongoing development of recruitment and retention methods.

These pilot data support further exploration into the efficacy of the PTC intervention for ameliorating the disrupted QOL of patients with cervical cancer in a larger sample size, and over a longer period of time. The cross-talk and integrated nature of the psychoneuroimmune axis is likely to be much greater than is currently appreciated. However, the incorporation of the chronic stress response into the biobehavioral model provides a basis for the generation and testing of new hypotheses for potential, psychoneuroimmune-based mechanisms by which a psychosocial intervention could improve cancer-specific clinical outcomes. Therefore, future evaluations of psychosocial intervention strategies and cancer-specific survival should include evaluation of the T helper status of the adaptive arm of the immune system and the biomarkers of chronic stress as psychoneuroimmune variables.

Acknowledgments

We acknowledge the support and contributions of Dr. Paige McDonald, the assistance of Robin Cowan and Odette Chida in the conduct of the study, and Drs. David L. Felten, Lee S. Berk, and Pathik D. Wadhwa for invaluable discussions. Finally, we thank Dr. Al Marcus for his pioneering efforts and support in the development of PTC, and Dr. David Cella for continued guidance in interpretation of patient-reported outcomes.
References

Correction: Article on Stress, Immunity, and Cervical Cancer

In the article by Nelson and coworkers about stress, immunity, and cervical cancer, beginning on page 2111 of the April 1, 2008, issue of Clinical Cancer Research, a word in the title was misspelled. The correct title of the article is “Stress, Immunity, and Cervical Cancer: Biobehavioral Outcomes of a Randomized Clinical Trial.”
Stress, Immunity, and Cervical Cancer: Biobehavioral Outcomes of a Randomized Clinical Trail


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