Evidence Accumulating That Depression May Hinder Survival

By Vicki Brower

Cancer survivors who are depressed are twice as likely to die prematurely as those who are not depressed, according to a new prospective population-based study by Dutch researchers. Lead author Floorje Mols, PhD, assistant professor of medical psychology and neuropsychology at Tilburg University in the Netherlands, found that 38% of depressed patients with lymphoma, multiple myeloma, endometrial, or colorectal cancer died over a 10-year period, compared with 19% without depression, after adjusting for major clinical predictors (May 2013, *Journal of Cancer Survivorship*).

“Depression is the most commonly studied psychological variable with respect to cancer mortality,” Mols said.

This study is one of a growing number that report a statistical correlation among mortality, depression, or stress in cancer patients and survivors. According to David Spiegel, MD, professor of medicine at Stanford University in Palo Alto, Calif., just as many oncologists now view pain as a symptom to be treated, they should also consider depression (which is two to three times higher in cancer patients than in the general population) a symptom to be treated to improve quality of—and possibly extend—life. In 1989, Spiegel found that women with metastatic breast cancer who participated in a year of supportive-expressive therapy not only had an improved quality of life but also lived 18 months longer than control subjects (37 vs. 19 months; October 1989, *The Lancet*).

Since that landmark report, many studies have explored an association between depression and survival, some of which found a statistical correlation, whereas others did not. Overall, Spiegel counts 15 randomized controlled studies in the field to date, eight of which do show a statistical correlation. These and many nonrandomized studies have provoked controversy and criticism.

“There was a degree of pessimism among everyone: patients, the advocacy community, and even the research community, who questioned whether it was worth continuing to pursue the class altogether,” Robson added.

With iniparib now a relic of PARP history, however, other true PARP inhibitors are charging ahead. Trials with patients carrying BRCA mutations suggest high response rates, even in patients who have grown resistant to all other forms of therapy.

“They look like they may be effective as single agents in BRCA mutation carriers,” Carey said, “which still makes them an exciting class of drugs.”
Some, such as Richard Sloan, PhD, Nathaniel Wharton Professor of Behavioral Medicine at Columbia University in New York, agree.

“Unlike the field of cardiology, definitive data linking depression, stress, and survival are lacking,” Sloan observed. “This being said, there is every reason that oncologists should be trained to attend to patients’ depression for quality of life.”

**Mixed Findings**

Spiegel’s own ongoing research has not produced consistent results. In 2007, he found that women with metastatic breast cancer who had supportive-expressive therapy had a better quality of life, though they did not live longer. However, a subgroup analysis indicated that the therapy benefited those with estrogen receptor-negative cancers, which are the most difficult to treat (July 2007, *Cancer*). Consisting of 20% of the group, women in the subgroup had a median survival time of almost 30 months, 21 months longer than those who received educational literature alone.

More recently, a secondary analysis of a randomized trial of supportive-expressive therapy with 125 women showed that decreasing symptoms of depression in the first year statistically correlated with longer survival (February 2011, *Journal of Clinical Oncology*). Median survival time was 53.6 months for women with decreasing depression over 1 year, and 25.1 months for women with increasing depression scores. One possible explanation, said Spiegel, is suppressed cell-mediated immunity in women with metastatic breast cancer who report more depressive symptoms as indicated by cortisol levels (2009, *Brain, Behavior, and Immunity*).

In another study in patients with newly diagnosed metastatic non–small-cell lung cancer, Jennifer Temel, MD, clinical director of thoracic oncology at Massachusetts General Hospital in Boston, wanted to determine how early palliative care affected mood, depressive symptoms, and quality of life. Patients were randomized to receive either early palliative care and standard care, or standard care alone (August 2010, *New England Journal of Medicine*). Of 151 participants, those who received palliative care were screened for anxiety and depression, were seen individually once per week, received less aggressive end-of-life care, and had rates of depression measured at baseline and at 12 weeks.

“At 3 months, levels of depression were lower for those receiving palliative care,” Temel said. Palliative care plus treatment resulted in meaningful improvements in quality of life, mood, and longer survival, by 2 months. “Depression may be a target to improve quality of life and survival,” Temel added.

In advanced renal cell cancer, Lorenzo Cohen, PhD, professor of general oncology and director of the Integrative Medicine Program at the University of Texas M. D. Anderson Cancer Center in Houston, conducted a prospective study with 217 patients to explore the interaction among psychological state, cancer progression, and the role of inflammatory gene expression and its regulation by glucocorticoid hormones. Depression was associated with higher risk of death: Specifically, dysregulated, higher levels of daytime cortisol levels statistically correlated with greater risk of death. Functional genetic profiles of patients linked depressive symptoms to increased expression of proinflammatory and prometastatic genes in circulating leukocytes.

“Depression is the most commonly studied psychological variable with respect to cancer mortality.

Several epidemiological studies and meta-analyses also indicate a statistical correlation among depression, progression and survival. In a 2009 meta-analysis of 26 studies with 9,714 patients, Jillian Satin, MA, of the University of British Columbia in Vancouver, found that when other factors were controlled for, depression (either self-reported or diagnosed), was a predictor of mortality but not disease progression.

Mortality was up to 25% higher in those with depressive symptoms and 39% higher in those diagnosed with major or minor depression (November 2009, *Cancer*).

But in a critique of a 2008 study, titled “Finding What Is Not There,” Coyne and coauthors describe how a randomized trial of risk of recurrence and improved survival in women with early-stage breast cancer who had psychosocial intervention in relation to an assessment group contains methodological and statistical problems that obscure null results (December 2008 and December 2009 *Cancer*).

“Studies like these give patients false hope,” Coyne said.

Nevertheless, Mol, Spiegel, and others maintain that not only must oncologists pay attention to patients’ depressive symptoms, but conducting additional, more rigorous clinical studies and further investigating the basic biology behind mechanisms that might explain the premature death–depression association are also important. Recent studies indicate (1) that metformin may increase survival in ovarian cancer patients who have type 2 diabetes, as well as reduce the risk of depression and dementia in those patients, and (2) that patients with bladder cancer who had high levels of depressive symptoms and short telomeres had a sixfold-reduced survival. Taken together, these findings provide reasons for more follow-up to elucidate what might drive these phenomena.

**Mechanistic Research**

Efforts to explain biological mechanisms that might account for the association began at the National Cancer Institute in 1998 when Michael Stefanek, PhD, came on board as chief of the basic biological research division, now the Basic Biobehavioral and Psychological Sciences Branch, was established.
The idea at the time was to study the impact of stress and emotions in cancer progression,” said Stefanek, who cowrote the 2009 Cancer critique with Coyne. “So much work still needs to be done in basic and translational research; we’ve jumped too far ahead to applications,” Stefanek said. In 2011 Paige McDonald, PhD, MPH, branch chief since 2006, founded the Network on Biobehavioral Pathways in Cancer to fund basic, mechanistic research of stress and depression in the context of cancer.

Describing herself as a healthy skeptic, McDonald agrees with Coyne that a lack of rigorous, randomized studies has hampered the field. She also agrees with Stefanek that developing new interventions before the basic science has been more fully elucidated is premature.

“One of the stumbling blocks to developing effective interventions is not understanding the mechanisms by which stress and depression may affect cancer,” McDonald said. “Without that mechanistic knowledge, we are shooting in the dark [developing and testing interventions],” McDonald added. Until recently, the tools to study this have been unavailable, she said. Ongoing studies sponsored by the network include biobehavioral influences and the ovarian cancer tumor microenvironment, and mechanisms of neuroendocrine regulation in ovarian cancer.

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Anxiety Fuels Growing Trends in Double Mastectomy

By Charlie Schmidt

Researchers have documented a growing trend in breast cancer treatment in recent years: Women diagnosed with cancer in one breast are increasingly having both breasts removed, even without genetic risks that warrant the procedure, which is called contralateral prophylactic mastectomy (CPM). These women face very low risks for contralateral breast cancer, and the original tumor is much more likely to recur in the bones or elsewhere in the body. So why these women choose CPM, along with the potential for surgical complications, has been a source of speculation.

A study in the September Annals of Internal Medicine reveals that many newly diagnosed women overestimate their risk of contralateral breast cancer and choose CPM out of a desire to extend life, despite paradoxically being aware that the procedure doesn’t increase survival.

“They understand objectively that CPM doesn’t extend life,” said lead author Shoshana Rosenberg, ScD, MPH, an epidemiologist at the Dana–Farber Cancer Center in Boston. “Yet on an emotional level they don’t think that conclusion applies to them.”

The paper raises some challenging issues. Nancy Davidson, MD, oncologist and professor at the University of Pittsburgh School of Medicine, said the findings show how clinicians sometimes fail to adequately counsel women during their decision-making process.

“If we did a better job describing the risks and benefits of CPM, then fewer women would be inclined to have it,” she said.

Still, the paper also shows how fear and anxiety can complicate the choices women make even when key information is available. That women choose CPM on the basis of survival—even when they know the evidence doesn’t support a survival benefit—reflects cognitive dissonance in the patient’s decision making, the authors claimed. According to Rosenberg, that’s especially true among patients younger than 40 years, who otherwise have low risk of breast cancer.

“These patients are saying, ‘I wasn’t supposed to get breast cancer in the first place.’ And so now they’re asking, ‘Why should I believe that my risk of contralateral cancer is low?’”

Tracking CPM Trends

In 2007, Todd Tuttle, MD, surgical oncologist at the University of Minnesota Medical School in Minneapolis, published the first national study documenting a rise in CPM. Tuttle and colleagues reviewed data from the SEER (Surveillance, Epidemiology, and End Results) program at the National Cancer Institute. Their results, published in the Journal of Clinical Oncology, showed that CPM rates had increased 150% from 1998 to 2003. Katherine Yao, MD, breast cancer surgeon at Northshore University Health System in Chicago, followed up a 2010 publication in Annals of Surgical Oncology, reporting that CPM rates had increased 10-fold from 1998 to 2007. Based on 1.2 million patients recorded in the American College of Surgeons National Cancer Database, this is the most recent national study available. It also showed that CPM rates were highest among white women younger than 40 years, living in high-income areas with access to quality insurance.

Because these national databases don’t record BRCA mutation status, investigators have relied on single-institution studies to assess CPM trends by inherited risk. At the Memorial Sloan–Kettering Cancer Center (MSKCC), for instance, just 13% of 407 patients given a CPM from 1997 to 2005 had either a BRCA mutation or a history of ovarian cancer.