Mechanistic Research Illuminating Connection Among Depression, Stress, and Survival

By Vicki Brower

In a recent large study, patients with non–small-cell lung cancer who added beta blockers to radiotherapy showed better overall survival, distant metastasis–free survival, and disease–free survival than those receiving radiation alone.

In this 12-year retrospective study of 722 patients, 155 who took beta blockers for hypertension and heart disease survived for a mean of 23.7 months, compared with 567 patients treated with radiotherapy alone, who lived for a mean of 18.6 months. This outcome represents a 22% survival benefit for those on beta blockers after adjustment for other factors, said author Daniel Gomez, MD, a radiation oncologist at the University of Texas M. D. Anderson Cancer Center in Houston (May 2013, *Annals of Oncology*).

“Our results suggest that the use of beta blockers during radiotherapy may help to prevent the formation of metastases in patients with non–small-cell lung cancer,” Gomez said.

Although the underlying mechanism of metastasis is complex, it probably involves chronic stress conditions and prolonged exposure to stress hormones, such as nor-epinephrine, which stimulates tumor cell migration, Gomez observed. Beta blockers block the release of these stress hormones.

“Our findings agree with results from previous studies suggesting that beta blockers have a specific effect on the cascade of events that lead to metastases,” said study author Zhongxing Liao, MD, professor of radiation oncology, also at M. D. Anderson. “The fact that their use did not affect locoregional progression–free survival suggests that they affect the metastatic cascade rather than the primary tumor,” she said.

This study mirrors other recent research, such as a large, population-based study of breast cancer patients in Scandinavia, in which patients took one of two beta-adrenergic blockers, propranolol or atenolol, 1 year before diagnosis. Those taking propranolol were statistically significantly less likely to present with local tumor invasion, and they had lower probability of disease–specific mortality than matched nonusers (June 2013, *Journal of Clinical Oncology*).

These studies are two of many recent clinical and epidemiological studies (January 2014, *JNCI*). Indeed, the National Cancer Institute is sponsoring several prospective trials in the US and Israel to test whether beta blockers can prevent recurrence and metastasis of colorectal, ovarian, and breast cancers after surgery, said Shangar Ben-Eliyahu, PhD, principal investigator of one such study and professor of psychology at Tel Aviv University in Israel. These studies are examining the blockade of the postsurgical stress response, which suppresses immune function and fuels the growth of micrometastases, Ben-Eliyahu said.

Although research to determine whether such interventions targeting stress and depression can increase survival is ongoing, the 3-year-old NCI initiative, the Network on Biobehavioral Pathways, led by Paige Green McDonald, PhD, MPH, focuses on understanding molecular mechanisms that underlie the association between stress and depression in cancer. The goal is to elucidate these physiological pathways by using preclinical models and cellular studies.

“We are not developing or testing interventions,” emphasized McDonald, chief of the Basic Biobehavioral and Psychological Sciences Branch’s Behavioral Research Program. Ultimately, building a mechanistic knowledge base may help determine whether modifying stress pathways makes a difference in cancer outcome, she said.

The effort to develop a biobehavioral research agenda at NCI began in earnest in 2002 when it convened a meeting with other branches of the National Institutes of Health to discuss research on neural, behavioral, endocrine, and immune interactions in disease and health, McDonald said.

It culled recent studies of neuroimmune mechanisms focusing on stress and pain, as well as biological processes such as circadian rhythmicity, sleep, apoptosis, and disease outcomes, and it published a supplement in *Brain, Behavior, and Immunity* the next year that would serve as a blueprint for studies in cancer. A second supplement in 2003 gathered discoveries and highlighted new approaches for studying the connection.

Early Focus on Immune Response

The initiative’s first research focused primarily on immune response evident in blood, such as natural killer (NK) cell activity, as well as on DNA repair and
statistical correlations between endocrine responses and stress. In 2000, David Spiegel, MD, professor of medicine at Stanford University, found that women with advanced breast cancer who had abnormal daytime levels of the stress hormone cortisol were statistically significantly more likely to succumb to their disease than patients with normal levels (June 2000, JNCI). Under normal conditions, cortisol levels are high in the morning and drop in the evening. More recently, he found that women with metastatic breast cancer who were more depressed displayed more cortisol rhythm dysfunction and suppressed cell-mediated immunity (November 2009, Brain, Behavior, and Immunity). Recently, Spiegel statistically correlated cortisol dysfunction with lung cancer mortality (March 2013, Brain, Behavior, and Immunity). He is working on a large NCI-sponsored study of the relationship among sleep disturbance, cortisol patterns, and breast cancer survival.

Lorenzo Cohen, PhD, professor of oncology at M. D. Anderson, is also studying cortisol and survival. He found that depressive symptoms and cortisol dysfunction predicted survival in patients with renal cell cancer (August 2012, PLOS One). Cohen found a link among depression, cortisol dysfunction, and inflammatory signaling: Depressed patients had higher expression of proinflammatory and pro-metastatic genes in circulating leukocytes.

**Brain as Master Regulator**

The brain may be the missing link among emotions, stress, and cancer.

“The brain not only participates in the regulation of complex signaling systems used by a range of cells and structures but also is a master regulator that may promote or inhibit tumorigenesis,” McDonald said.

Clinical, preclinical, and lab studies indicate that downstream activation of the sympathetic nervous system, part of the autonomic nervous system that responds to stress, can initiate molecular signaling pathways involved in inflammation, DNA repair, angiogenesis, cell survival, metastasis, and therapy resistance (March 2006, and October 2013, Brain, Behavior, and Immunity). The stress hormones epinephrine, norepinephrine, and dopamine, known as catecholamines, released by the autonomic nervous system bind to alpha- and beta-adrenergic receptors, which are found on tumor cells and in the tumor microenvironment's stroma.

“Stress's effects on host cells, such as macrophages, not just tumors, also appear to be important for many pathways involved in tumor progression,” said Anil Sood, MD, professor of gynecologic oncology at M. D. Anderson and a member of the Network on Biobehavioral Pathways.

Some stress effects are bidirectional. Although the brain can produce chemicals that cause inflammation and cell damage, tumor-related inflammation also affects the brain and central nervous system processes and contributes to the dysregulation of the hypothalamic–pituitary–adrenal axis, which can affect inflammatory control, Sood said. This axis is a major component of the neuroendocrine system that controls reactions to stress and regulates many body processes, including the immune system, mood and emotions, and digestion.

Working with a rat model of leukemia, Ben-Eliyahu showed that provoking a physiological stress response by forced swimming, or using physiologically relevant doses of epinephrine, prostaglandin E2, or corticosterone, promoted leukemia progression and halved life span (April 2011, PLoS One). Conversely, prolonged beta-adrenergic blockade of the cyclooxygenase (COX) inhibitor etodolac, a nonsteroidal anti-inflammatory drug, increased survival, possibly by blocking tumor-related or normal levels of catecholamines and prostaglandins. COX is a proinflammatory enzyme, whereas prostaglandins regulate inflammation. The mediating mechanism: transient suppression of NK cell activity.

“Overall, it seems that environmental stress, epinephrine, and prostaglandins promote leukemia progression in rats, potentially through suppressing cell-mediated immunity. Thus, patients with hematological malignancies, which often exhibit diminished NK cell activity, may benefit from extended beta-blockade and COX inhibition,” they wrote.

Sood is studying the effects of stress hormones on ovarian cancer growth and progression.

“In mouse models of mammary cancer, we saw beta-adrenergic stimulation of angiogenesis and metastasis,” he said.

Surprisingly, stress-induced neuroendocrine activation had little effect on primary tumor growth but induced a 30-fold increase in distant metastases to the lung and lymph nodes (July 2010, Cancer Research). Beta-adrenergic signaling, which increased infiltration of macrophages into the primary tumor, mediated this effect. Drug-induced signaling produced the same effects, and stressed animals treated with the beta-blocker propranolol showed reversed macrophage infiltration and inhibited tumor spread.

“This study identifies activation of the sympathetic nervous system as a neural regulator of breast cancer metastasis and suggests new strategies for antimetastatic therapies targeting the beta-adrenergic system,” Sood said.

Chronic behavioral stress results in higher levels of catecholamines, greater tumor burden, and more invasive ovarian cancer growth through increased angiogenesis, according to a 2006 study in Nature Medicine by Susan Lutgendorf, PhD, of the University of Iowa in Iowa City. Activation of a signaling pathway by the adrenergic receptor mediates this effect. Tumors in stressed animals had increased vascularization and greater expression of the proangiogenic factors vascular endothelial growth factor, matrix metalloproteinase 2 (MMP-2), and MMP-9.

Lutgendorf later discovered that human ovarian cancer cells were protected from self-destruction, or anoikis, by norepinephrine or epinephrine (May 2010, Journal of Clinical Investigation). And last year, Sood showed that high levels of noradrenaline in human ovarian tumor cells statistically correlate with high levels of Src, a proto-oncogene, and that beta-adrenoreceptors on cancer cells are a key switch for tumor metastasis (January 2013, Nature).
Effects of Social Support and Isolation

Lutgendorf is also examining links between depression and social support or isolation and survival in ovarian cancer patients. She studied the presence of MMPs, vascular endothelial growth factor, interleukin 6, tumor norepinephrine, and NK cells. She found associations between these protumor substances and social isolation. Patients with higher levels of perceived social support showed lower levels of these factors in the tumor microenvironment and higher levels of NK cell activity in blood and tumor-infiltrating lymphocytes. Low levels of support were connected to depressive symptoms, proinflammatory compounds, and more tumor norepinephrine. In a 2012 Journal of Clinical Oncology study she found that depression was not associated with survival time but that higher levels of continuous social attachment were.

More mechanistic research will be needed to further understand potential causal connections among stress, depression, social isolation, and cancer, McDonald said, noting that this research is still in the early stage.

“We need to take clinical observations and experience and go back to the lab to try to recapitulate what may be occurring on a cellular level.”

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Downgrading Cancer Definitions: Overdiagnosis Fuels the Discussion

By Susan Jenks

Public-health messages for early detection of cancer may take on a more nuanced tone, experts agree, as researchers grapple with how best to quantify screening’s risk of overdiagnosis.

Although not a new phenomenon, overdiagnosis of some cancers is gaining renewed attention in the cancer community. That’s partly because of better technologies that detect premalignant and cancerous lesions, which otherwise might lie dormant for years without causing either clinical symptoms or death and yet often lead to invasive and sometimes harmful treatments.

This increasing attention coincides with a recommendation by the US Preventive Services Task Force in mid-2013 that individuals at high risk for lung cancer undergo annual spiral computed tomography scanning. Evidence from a massive randomized clinical trial involving more than 53,000 smokers and former smokers found that such tests may reduce relative lung cancer mortality by 20%, but they also carry a high false-positive rate. Some 40% of nodules in the study proved noncancerous upon needle biopsy, and 16 patients died within days of undergoing the procedure.

“In the past, the public-health message was much easier: Get screened,” said Steven Woloshin, MD, professor of medicine and of community and family medicine at Dartmouth Medical School in Hanover, NH, the site last fall of the first international conference on preventing overdiagnosis in cancer and other diseases. “The only problem is, it’s turning out to be much more complex than that,” he added.

A warning signaling possible overdiagnosis, Woloshin and others said, occurs when there’s a rising cancer incidence but no proportional reduction in the death rate from a particular cancer. In at least five cancers—thyroid, prostate, kidney, breast cancer, and melanoma—data from the past 30 years suggest that may be the case, according to a review article in JNCI titled “Overdiagnosis in Cancer,” by researchers in the Department of Veterans Affairs and Dartmouth’s Hitchcock Medical Center (published online April 22, 2010).

More recently, investigators at Duke University Medical Center in Durham, NC, estimated the overdiagnosis risk of the new low-dose computed tomography scans at 18.5%, which they suggested be incorporated into guidelines for any future mass screening program (Patz EF, Pinsky P, Gatsonis C, et al.: JAMA Internal Medicine, published online Dec. 9, 2013).

Exact figures of overdiagnosis across cancers, however, are not yet available. Nor would a broad-brush figure be helpful, because no consensus on the extent of the problem exists, which varies widely by cancer site, according to Richard Wender, MD, newly appointed chief cancer control officer for the American Cancer Society. Although overdiagnosis of pancreatic cancer, for example, is rare—around 10%, he said—in prostate cancer, where the issue of overdiagnosis first arose nearly two decades ago, 50%–60% of tumors detected through prostate-specific antigen screening are considered slow growing, posing no risk during a patient’s lifetime.

Moreover, too much emphasis on overdiagnosis, Wender cautioned, may swing the pendulum too far the other way, hampering ongoing screening efforts to find cancers at their earliest stages when they may be most curable.

“We cannot stop searching for these asymptomatic cancers; that’s not a good strategy,” he said. “Finding asymptomatic cancers is still our best chance of curing those with a potentially deadly disease.”

Even in breast cancer, for which a working group of experts at the National Cancer Institute has recently pushed to eliminate the word carcinoma from ductal carcinoma in situ (DCIS), he said, doctors still don’t