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.

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).

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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Not Always Lethal

In screening, in general, “it’s always a matter, if you diagnose cancer, of whether it’s destined to kill someone, or he or she will die of something else,” said Barnett Kramer, MD, director of the National Cancer Institute’s division of cancer prevention.

Although the idea that cancer is not always lethal is difficult to grasp, he said, the public has become more aware that overdiagnosis and overtreatment may occur.

“Whether it has been incorporated into their belief system is another matter,” Kramer said. “The message of early detection is a strong sound bite,” and in several cancers, borne out by research.

Cervical cancer screening, for one, has had a huge impact on death from this cancer. In the United States, Kramer said, whereas in colon cancer, colorectal screening for occult disease through stool sampling and sigmoidoscopy have reduced cancer deaths, according to randomized clinical trials. Colonoscopy also appears beneficial, Kramer said, even though questions remain about its effectiveness on the colon’s right side, which is more difficult to access and where more aggressive flat lesions may lie.

But whether altering cancer terminology can alter public perceptions about the benefits and risks in cancer screening is unknown. That strategy seems to work in cervical cancer; noninvasive lesions are now called cervical intraepithelial neoplasm.

“When women hear this, they don’t have as emotional a reaction as if we called it cancer,” which reduces the risk of unnecessary treatments, Kramer said.

Similarly, with ovarian tumors, researchers have begun to distinguish aggressive tumors from those of low malignant potential by using molecular genetics—a research strategy also being used across many other cancers. Eventually, “it may be that we don’t need to chase down every abnormality,” Kramer said.

Laura Esserman, MD, director of the Carol Franc Buck Breast Care Center at the University of California, San Francisco, agrees. A vocal proponent of reassessing what happens when you screen, Esserman served as co-chair of the National Cancer Institute working group on overdiagnosis and helped coin the term IDLE for “indolent lesions of epithelial origin.”

Although looking at a lesion through a microscope may look like cancer, its behavior may be more important to progression, she said, citing neuroblastoma as one cancer that might trigger intervention but can spontaneously regress.

“It’s always a matter, if you diagnose cancer, of whether it’s destined to kill someone, or he or she will die of something else.”

“The problem for us [right now] is that everyone is so polarized about the benefits of screening,” Esserman said. “We may be saving lives, yes, but screening is not all good or all bad. We need to learn how to maximize the benefits while minimizing the harm” through interdisciplinary efforts and a willingness to change. Molecular information and a better understanding of mutations may help, she added, as researchers identify higher-risk groups, targeting them in screening—the model today for lung cancer screening. Then it’s more justified, she said.

“Wait and Watch” Registries

One initiative under way in California involves wait-and-watch registries for women diagnosed with DCIS, according to Esserman. Five universities in the state are collaborating to gather data for assessing the true risk of developing a metastatic cancer.

“We don’t know now what percentage of women go on to cancer,” she said. “But we do know well over 50% never will.”

With DCIS, most women in the US subsequently undergo biopsy, “even though 75% of what we biopsy is benign,” she said. “And if you look around the world, the threshold for biopsy differs dramatically. We biopsy more than anyone else.”

The American Cancer Society’s Barnett Kramer calls establishing such registries a wonderful idea for better determining actual risk.

“We need this type of research to answer questions, as long as women are well informed,” he said. “But I hope we don’t blame women for aggressively treating their DCIS. The goal of avoiding a cancer death is highly valued in our society.”

Wender said he also supports nomenclature changes for some cancers, including DCIS, as long as it provides greater clarity—a goal Esserman shares.

“We want to offer people a choice” in screening, she said. “Some people are risk averse; others are intervention averse. But we need data to know—is this [cancer] reasonable to watch? If there’s a 95% chance you’ll be okay at 5 years, we think it’s a reasonable thing to do.”

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