from the German Breast Group (GBG44) randomly assigned 1,948 patients to receive neoadjuvant epirubicin and cyclophosphamide followed by docetaxel with or without Avastin. In the Avastin group, PCR was 18.4%, compared with 14.9% in the non-Avatin arm.

The other study, dubbed NSABP B-40, randomly assigned 1,206 patients to receive neoadjuvant docetaxel-based chemotherapy with or without Avastin. Adding Avastin statistically significantly increased the rate of PCR (34.5% with Avastin vs. 28.2% without). In both studies, Avastin was associated with more side effects. PCR still needs to be validated as a surrogate endpoint for clinical outcomes. Harry D. Bear, M.D., professor of surgical oncology at Virginia Commonwealth University and lead author of the NSABP B-40 trial, said, "At this time, the results of B-40 should not warrant any change in practice for the treatment of breast cancer. However, it does suggest that the issue of Avastin's potential to improve outcome is not settled."

Gunter Von Mincwitz, M.D., managing director of the German Breast Group Research Institute—the largest cooperative group in Germany working in breast cancer—and lead author of the GBG44 trial, said, "These trials highlight the fact that the benefit is relatively marginal given the drug's toxic effects. That being said, if a subgroup that gains substantial benefit can be identified (similar to trastuzumab for those with HER2-amplified tumor), the drug may indeed be resurrected in the metastatic setting as well."

These studies have renewed interest in Avastin, and trials continue to probe its efficacy in various disease settings. An exploratory subgroup analysis of a randomized phase III RIBBON-2 trial that enrolled metastatic breast cancer patients who had progressed on first-line chemotherapy without Avastin showed that triple-negative metastatic breast cancer had longer PFS. The study also found a non-statistically significant trend toward improved OS (published in Breast Cancer Research and Treatment, Feb. 22, 2012). The final data on OS are anticipated this spring. Other trials are evaluating Avastin in the adjuvant setting for breast cancer. BETH (NSABP B-44), an adjuvant phase III trial, is comparing chemotherapy plus trastuzumab with or without bevacizumab in HER2-positive early-stage breast cancer. Another phase III trial, ECOG 5103, is evaluating anthracycline and taxane-based adjuvant chemotherapy with or without Avastin for high-risk HER2-negative breast cancer. BEATRICE is another adjuvant phase III trial looking at the efficacy of adding Avastin in triple-negative breast cancer treated with docetaxel and carboplatin or docetaxel and FEC (5-fluorouracil, epirubicin, and cyclophosphamide). The BEVERLY-2 trial, published in The Lancet (Feb. 12, 2012), looked at the role of Avastin plus trastuzumab and chemotherapy in the neoadjuvant setting in histologically confirmed HER2-positive nonmetastatic inflammatory breast cancer. More than 60% of patients achieved PCR without an increase in adverse side effects. However, the researchers warn that survival data and long-term follow-up of this open-label, single-arm phase II study are warranted before drawing conclusions.

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Mirth and Medicine: Hope or Hype?

By Norra MacReady

Queenie Glenn first attended the Strength through Laughter program at the Montefiore Einstein Center for Cancer Care in the Bronx last December, and she came away a fan. “You can just laugh and feel good about yourself when you’re there,” explained Glenn, 59, who was diagnosed with chordoma in 2001 and experienced a recurrence 8 years later. “It gives me comfort when I go—it gives me something to look forward to.”

Strength through Laughter is one of several programs nationwide that marshal the power of humor to inspire and support to people with cancer and other serious illnesses. Proponents of laughter-based therapies cite research demonstrating the medical value of mirth, although more sober-minded investigators warn that such claims may be exaggerated. Still, these programs confer benefits that, though less tangible, may be just as real.

Laughing Together

It is a glorious March afternoon in Santa Monica, the kind of weather that turns visitors to Southern California into residents. At the Santa Monica Bay Women’s Club, the atmosphere is similarly lighthearted, as people gather for Humor, Heart, and Hope, a program for cancer patients and their loved ones that is being presented through the Humor Project Inc. and the Cancer Support Community—Benjamin Center.
Several speakers deliver jokes, funny stories, and inspirational messages. The audience is jovial even before the program begins, as though just anticipating the fun has put them in a good mood.

First up is Joel Goodman, Ed.D., founder of the Humor Project and a self-described full-time humor educator. Goodman started the Humor Project 34 years ago to help people “get more smileage out of their lives,” according to his background information. Inspiration for the project came in 1977 from an unlikely event: his father’s surgery for an aortic aneurysm. Goodman traveled from his home in Saratoga Springs, N.Y., to Houston, where his father’s operation was to take place. “If you wanted a ‘before’ picture of stress and anxiety, all you had to do was look at our family: We were uptight with tension and terror,” he recalled. He and his mother were staying at a hotel that provided shuttle service to the Methodist Hospital, where Michael DeBakey was scheduled to perform Goodman’s father’s surgery. Driving the shuttle was Alvin, whom Goodman described as “an angel in human disguise. He had this wonderful, spontaneous, childlike, playful, kid-ding, gentle sense of humor. And in the 4 minutes it took to get to the hospital, he magically transformed uptight, terrorized, stressed-out people like us into people who were able to laugh and chuckle and let go of some of their angst.” The surgery succeeded, and several weeks later, after he had returned home, Goodman wondered, “if humor has such good effects, why do we have to wait for the Alvins of the world to come into our lives? So that painful situation led me to start the Humor Project.”

In Santa Monica, Goodman’s message is that a more playful, even childlike, approach can help one tackle the challenges, or what he calls the “pop quizzes,” that life throws people. He chooses chuckles over guffaws, mixing puns and amusing anecdotes with self-help homilies. The remaining three speakers offered similarly uplifting and gently humorous fare, and the audience applauded at the end.

**Laughing Strong**

Strength through Laughter is the brainchild of Gloria Nelson, L.M.S.W., an oncology social worker at Montefiore. She started the program in 2008, after noticing that patients at the cancer center spent a surprising amount of time laughing and joking. She wondered whether they would be interested in a group devoted to socializing and support, as well as sharing some laughs. “Ethnic jokes and really dirty jokes are not allowed, but spicy jokes are fine,” she said in an interview. Some of the best fodder comes from the patients themselves or from people who hear about the program. “I get clean-cut jokes, I get dirty jokes, I get philosophical sayings sent to me. After one magazine ran an article about the project, a little old lady in Texas sent me more than 100 jokes, asking me to share them with the group. They were funny, clean-cut ones, too. And one of the doctors here gave me a book of racy jokes, although he warned me not to let the patients know where it came from.”

So far, the response has been enthusiastic, with 35–60 people attending the monthly gatherings, which include an outdoor barbeque in the summer and a holiday get-together in December. Nelson emphasized that the group is about more than just jokes. “We might have a doctor come and talk about insomnia; one time some Spanish dancers came and taught dancing. It’s become like a family environment. We have a lot of wonderful role models who make the most of life even when the prognosis is challenging.”

As with the Humor Project, Strength through Laughter uses levity to help patients connect on a deeper level. “I want people to share when they’re feeling fearful,” Nelson explained. “The group is for people who are focusing on living and being positive and who don’t want to feel alone. We have an ethnic and socioeconomic mix, but what everyone has in common is the challenge of living with cancer.”

**The Best Medicine?**

Research on the physical benefits of laughter is surprisingly scarce. “Some of the studies have shown that the ability to tolerate pain is better after exposure to humorous movies,” said Beth Lown, M.D., medical director of the Schwartz Center for Compassionate Healthcare at Massachusetts General Hospital in Boston. In one study, “after watching comedies and funny movies, the need for minor postoperative painkillers in orthopedic patients was reduced—not on the first day post-op, but after that.”

Other evidence suggests that laughter has a salutary effect on immune and cardiorespiratory function, but here again, the data are sketchy. “What we lack is a large, randomized, clinical trial to show that laughter has a clinically meaningful impact,” said Michael Miller, M.D., director of the Center for Preventive Cardiology at the University of Maryland Medical Center in Baltimore. His own research has shown that laughter elicited by humor—what he and his coauthors call mirthful laughter—is associated with an increased release of cellular nitric oxide and a corresponding improvement in vascular endothelial activity. Other investigators have come up with similar findings. But, he warned, “by and large these are small-scale studies. Some of the data are certainly engaging and support our hypothesis [of a beneficial effect of laughter], but we don’t have any large, outcome-based trials—and that’s what we sorely need.”

Not all investigators have been able to document a special benefit of laughter therapy. In a multicenter study of 178 children
undergoing stem cell transplantation, laughter therapy was one of several complementary stress-reduction techniques tested (the others were massage therapy and parental massage and relaxation/imagery). The authors found no differences between any of the interventions, compared with standard care, on measures of health-related quality of life. They concluded that “the current trial does not provide support for the benefits of massage and humor therapy in reducing distress in the pediatric [stem cell transplant] setting, and suggests some caution in the widespread application of these therapies.”

Know Your Audience

Even the biggest boosters of laughter therapy warn that it must be used judiciously. “I don’t think humor is always appropriate,” said Goodman. “There are occasions when the timing is just not right. We need to be sensitive to our audience, whether it’s someone who is facing a health crisis or a group of people who are under stress because, for example, they’ve just lost their jobs.”

Humor is highly subjective, said Lown. “One person’s funny story may be another person’s pain. It’s tricky to use humor if you’re not sure how it’s going to be interpreted by someone else. You have to know your patients, who they are, where they come from, and what their context is.”

“The more you know a person, the better your intuition will be,” added Goodman. “Look for nonverbal cues, for what makes them laugh or brings a smile to their face.” He suggested that clinicians interested in lightening their visits assemble a collection of amusing but inoffensive sayings and quotes. He offered one of his favorites, from Robert Frost: “The brain is a wonderful organ. It starts when you wake up in the morning and does not stop until you get to work.” When all else fails, Goodman uses the AT&T test: “Is it appropriate, timely, and tasteful? If you can answer yes to all three, chances are that humor will work for you rather than backfire against you.”

Clinicians should also become adept at identifying people who may not be receptive to laughter. “If [some people are] angry or extremely depressed, they’re not ready for the workshop,” Nelson pointed out.

Still, giving patients a place to laugh together and find support has real benefits, even if they cannot be precisely quantified. “It’s like taking a dose of medication,” Glenn said of the Strength through Laughter gatherings, “just laughing and smiling and not thinking about your sickness while you’re there.”

“I wish there were more data about this,” added Lown. “Unfortunately, sometimes the important things just can’t be measured. But it doesn’t mean they’re not important.”

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At Loose Ends: Telomere Theories of Aging and Cancer Begin To Converge

By Ken Garber

A ge is the single greatest risk factor for cancer. About 60% of cancer diagnoses occur in the 13% of the population aged 65 years or older. Why does aging lead to increased incidence of cancer?

One view holds that it’s not aging but time that produces cancer. Only over time, typically decades, can cells accumulate the DNA mutations and other alterations that cause the common epithelial cancers of the lung, breast, prostate, and colon. From this perspective, cancer coincides with aging but is not caused by it. But over the last 15 years our concept of aging has evolved, from an accumulation of damage that “just happens” to a consensus that aging is a regulated process that’s at least partially genetic. And cancer is now commonly viewed as mechanistically linked to this aging process.

But no universally accepted view of how aging causes cancer exists. One theory posits that a progressive loss of telomeres—the caps of noncoding DNA that protect the ends of chromosomes—helps propel aging and that genomic instability caused by such telomere dysfunction drives malignancy. According to another theory, an age-dependent deterioration of mitochondria, organelles that produce energy for the cell, causes both aging and cancer by generating reactive oxygen species (ROS) that damage DNA and proteins. Recent mouse studies from the laboratory of Ron DePinho, M.D., formerly at the Dana–Farber Cancer Institute in Boston and now president of the University of Texas M. D. Anderson Cancer Center in Houston, raise the possibility that the two processes are linked in aging—and perhaps in cancer. “We provided a ‘unified field theory’ for aging,” said DePinho, “by providing a direct molecular link.” Broad acceptance of DePinho’s theory hinges on definitive validation in humans, including the success of interventions designed to forestall aging and prevent cancer.

Linking Short Telomeres to Cancer

The field has room for a new theory, because no consensus exists on what causes aging and what links it to cancer. And much about telomeres remains mysterious. Telomeres have been observed since the 1930s, but only in recent decades have researchers worked out telomere biology in any detail. In 1978, Elizabeth Blackburn, Ph.D., then at Yale University in New York, won the Nobel Prize in Physiology or Medicine with Carol W. Greider and Elizabeth H. Blackburn for their discovery of telomerase, the enzyme that replenishes telomeres. But it was not until the late 1990s that telomere biology began to attract a broader audience within the aging and cancer research communities. Since then, a large number of studies have accumulated, providing considerable support for the idea that telomere dysfunction causes aging and cancer.

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