Tokyo, Japan, found that methylation and mutations independently occur in adult gliomas (some tumors have both methylation and mutation) but that only mutations increased TERT expression (*Acta Neuropathol.* 2013;126:939–41). The second, from Newcastle University in Newcastle-upon-Tyne, UK, analyzed medulloblastoma and observed that mutations and hypermethylation were mutually exclusive and that both increased TERT expression (*Acta Neuropathol.* 2014;127:307–9). Hypermethylation occurred in various degrees in all subgroups, whereas only noninfant SHH featured mutations.

“I’m not surprised by these discrepancies,” Diede said, “because adult glioma is a totally different brain tumor from medulloblastoma and the pediatric cancers that Tabori’s group had studied.”

Agreeing in an e-mail, Ichimura added, “These studies collectively consolidate the significance of TERT alterations in diverse types of brain tumors, and I expect to see something similar in other types of human cancers too. Our task now is to translate these findings in the clinic to find a way to utilize TERT alterations as a biomarker or therapeutic target.”

But what about that infant SHH, with neither TERT promoter mutation nor methylation, as well as the scarcity of promoter mutations in pediatric gliomas? Perhaps, several researchers speculated, young brain cells already still have active telomerase and do not need any of the aberrations apparently so common among many other brain tumors.

**What Else Is Out There?**

Just the past year’s cascade of studies, one reacting to another, found an unexpected prevalence of two possibly mutually exclusive TERT promoter aberrations—hypermethylation and point mutations—in multiple cancers. Collectively, these studies validate efforts to move beyond the gene-centric approach to disease research that focuses on protein-coding genes and to embrace noncoding regulatory elements that can initiate and promote cancer.

“We completely missed the TERT promoter in all these years of whole-exome sequencing,” Killela said. “It’s the first promoter we identified, yet it has such significance. How many others are out there?”

---

**Why Is Breast Cancer Chemoprevention Such a Hard Sell?**

*By Judy Peres*

Antiestrogen agents can dramatically reduce breast cancer incidence. The U.S. Food and Drug Administration has already approved two such drugs, tamoxifen and raloxifene, for primary prevention in high-risk women. Two others, exemestane and anastrozole, appear even more effective at risk reduction.

But despite the recommendation of medical authorities, including the U.S. Preventive Services Task Force, the American Society of Clinical Oncology, and the National Institute for Health and Care Excellence in the UK, only about 1% of eligible women take a chemopreventive agent, according to Jack Cusick, Ph.D., head of the Centre for Cancer Prevention at Cancer Research UK.

Breast cancer chemoprevention remains “an enormously underutilized tool,” said Paul Goss, M.D., Ph.D., director of the Dana–Farber/Harvard breast cancer program. “Compared with statins or antihypertensive agents, the use of breast cancer chemopreventive drugs is very low, and yet the safety is as good if not better.”

According to breast experts, chemoprevention is a hard sell for several reasons:

- No simple but accurate way exists to assess breast cancer risk.
- A woman taking a risk-reduction drug has no way to know whether it’s working.
- Medical oncologists, who are best placed to have those discussions, often don’t think in terms of prevention and don’t see most at-risk women.
- Women fear side effects, and some doctors hesitate to prescribe potentially toxic drugs to healthy people.
- Manufacturers don’t promote the drugs for primary prevention, especially if the drugs are off-patent.
- No simple but accurate way exists to assess breast cancer risk.
- A woman taking a risk-reduction drug has no way to know whether it’s working.

Larry Wickerham, M.D., deputy chair of NRG Oncology (formerly NSABP, the National Surgical Adjuvant Breast and Bowel Project), said he believes that the National Cancer Institute could do more to educate the public about breast cancer chemoprevention.

**Promoting Prevention**

“Preventive cardiology didn’t exist 30 years ago,” Wickerham said, “but now every cardiologist treats cholesterol and blood pressure. The National Heart, Lung, and Blood Institute did a good job promoting preventive agents, first to the medical profession and then, in a sustained way, to the general public. Most people now know their levels and know the importance of controlling...
them.” By contrast, “NCI has not done a spectacular job of promoting the benefits of breast cancer chemoprevention.”

Wickerham and Sandra Swain, M.D., professor of medicine at Georgetown University in Washington, D.C., suggest that clinicians interested in getting into the practice of chemoprevention begin with patients who have biopsy-proven atypical hyperplasia or lobular carcinoma in situ.

“I pitch pretty hard to these women,” Wickerham said. “These high-risk women are easy to identify. You have to talk about the benefits and the side effects, and it takes time. But once you become knowledgeable and skilled at presenting the option of chemoprevention to this population that clearly stands to benefit, you can expand to additional populations at high risk.”

Wickerham stressed that nurses, physician assistants, and other medical personnel can start these conversations—not just physicians.

Potential toxic effects of risk-reducing medications are always an issue. Fran Visco, J.D., president of the National Breast Cancer Coalition, warns that “for a healthy population, we have to be certain that the risks are exceedingly small.”

But many advocates of prevention believe that the adverse events, including a slightly increased risk of uterine cancer for tamoxifen and bone thinning for anastrozole, have been exaggerated.

“Patients have unbelievably been oversold on the side effects,” said Marc Lippman, M.D., professor of medicine at the University of Miami. “There is a simple retort: Most women in the randomized trials of chemoprevention drugs could not correctly identify whether they were on the drug or a placebo. In the most recent anastrozole trial, 51% of women on the drug and 46% on placebo reported arthralgia [pain in the joints]. But even if you had the toxicity, these side effects go away as soon as you stop. So what’s the problem?”

**Risk-Benefit Analysis**

Patient advocates such as Visco would argue that the increased risk of endometrial cancer doesn’t go away, and many prevention proponents would agree.

“The Holy Grail is efficacy with no toxicity,” said Nancy Davidson, M.D., director of the University of Pittsburgh Cancer Institute and UPMC CancerCenter, “but we don’t have too many drugs that achieve that goal. Statins have their own side effects, but we’ve been able to articulate the benefit.

“On the whole,” continued Davidson, “breast cancer [risk reduction] drugs have pretty limited toxicity. For SERMs [selective estrogen receptor modulators, such as tamoxifen], the big side effects are postmenopausal symptoms—hot flashes—and a slightly increased risk of blood clots. Millions of women have taken hormone replacement therapy. The blood clot risk is not too different from that of tamoxifen. But patients didn’t hear about it.”

As for hot flashes, Davidson said, “They don’t happen to many women. It’s not unreasonable to give it a go and, if you have terrible symptoms, reconsider.”

“Compared with statins or antihypertensive agents, the use of breast cancer chemopreventive drugs is very low, and yet the safety is as good if not better.”

Since the side effects of SERMs and aromatase inhibitors, such as anastrozole, are somewhat different, switching to another agent is also an option.

Lippman pointed out that millions of people take medications to reduce risk of heart disease even though taking a statin or a baby aspirin carries considerable risk.

“The correct question is, ‘Is the benefit outweighed by the harm?’ I don’t think people appreciate that 125,000 cases of breast cancer in the U.S. could be prevented every year. Think of the health savings and the misery prevention.” Tamoxifen and raloxifene have also shown dramatic ability to prevent osteoporosis, “and as many women will die of osteoporosis as of breast cancer,” Lippman added.

Laura Esserman, M.D., director of the Breast Care Center at the University of California, San Francisco, said she believes that surrogates are a big reason for cardiac prevention’s success.

“What we’re trying to prevent is heart attacks or deaths from heart disease,” she said. “We’ve successfully established surrogates—blood pressure, cholesterol, weight—and shown that control of these affects eventual outcome. So surrogates become the endpoints for trials. We can identify who is at risk and monitor the early indicators. We don’t quite have those elements in place in breast cancer.”

Esserman said it would help if women had a way to know whether their treatment was working. Telling women to “take this pill for 5 years and hope for the best” is very difficult. We need to develop markers of impact. We need a way for me to say, ‘Let’s look and see how well this is working.’”

Breast density may be such a marker. Some evidence from adjuvant trials of tamoxifen indicates that the greatest reduction in risk of breast cancer recurrence occurred in women who showed a decrease in mammographic breast density early on. A drop in density thus could be a way of showing therapeutic effect.

**Signs of Progress**

Despite all the hurdles, things may be changing. Wickerham said that Cusick’s 1% figure may be outdated. NRG has been evaluating the decision-making process of women thinking about chemoprevention.

“We’re finding that 20%–25% accept SERM therapy,” he said.

Lippman, too, has had some success getting high-risk women to try chemoprevention.

“I explain everything,” he said, “and the women are smart. They understand they’re not doing it for life—only as long as it’s not bothering them.”
Esserman said that her Athena Breast Health Network, which sees more than 50,000 women at the University of California medical centers, now includes a routine risk assessment in its screening process.

“People in the top 5%–10% [for breast cancer risk] are identified, contacted by breast health specialists, and counseled about their options,” she said.

To the extent that cost is a disincentive, the Affordable Care Act will, starting next year, require new health insurance plans to cover chemoprevention with no copayment or deductible in high-risk women. That typically means a 5-year breast cancer risk of 1.67% or higher, which includes nearly all American women older than 55 years.

Meaning, European researchers are investigating reduced doses of tamoxifen to alleviate some side effects.

Per Hall, M.D., Ph.D., of the Karolinska Institute in Stockholm, was among the researchers who showed that a change in breast density might be a useful surrogate for therapeutic effect. Now his group is about to launch another trial to learn whether women who take lower doses of tamoxifen can achieve the same benefit with fewer side effects. The group plans to randomize 1,000 Swedish women to receive placebo or one of four daily doses of tamoxifen: 20, 10, 5, or 2.5 mg.

“We want to look at density decrease and compliance,” Hall said. “Are women taking the drug, and do they experience side effects? If 5 mg decreases density to the same extent as 20 mg, do the side effects decrease?”

In a later study, the group will test whether a lower dose also reduces breast cancer risk.

“In the 1980s we changed the daily dose from 40 to 20 mg, which is now the standard adjuvant dose,” said Hall. “No one ever tested whether lower doses were effective.”

© Oxford University Press 2014. DOI:10.1093/jnci/dju139

Treating Multiple Myeloma: The Cause for Optimism

By Marilyn P. Fenichel

Tev journalist Tom Brokaw’s multiple myeloma diagnosis came at a tipping point in understanding and treating this complex disease. Although still considered incurable, multiple myeloma can now be treated with new drugs, resulting in a median life expectancy of 5–7 years and a higher quality of life for many patients.

Multiple myeloma is a disease of plasma cells, a kind of white blood cell. Found in the bone marrow, plasma cells produce antibodies. With multiple myeloma, however, genetic changes in plasma cells cause oncogenes, such as cyclin D, FGFR3, or MAF, to become linked to the plasma cell program, causing cell proliferation. Other genetic changes, such as BRAF, KRAS, or NRAS mutations, can occur independently and promote cell growth. As the disease progresses, it can result in high levels of calcium, renal failure, anemia, and bone lesions—a constellation of problems referred to as CRAB.

Moreover, this cancer almost always comes back, often fiercely, and intervals between relapses tend to get shorter.

Information from the genomic sequencing of 200 patients, published in the January 2014 Cancer Cell, reveals multiple myeloma’s complexity.

“Every cancer cell within each patient looks different,” said Jens Lohr, M.D., Ph.D., instructor in medicine at the Dana–Farber Cancer Institute and first author of the study. “This makes therapy difficult because part of the myeloma may respond, while another part may not. It is increasingly clear that we are treating more than one disease in each patient.”

Nonetheless, many researchers and clinicians are optimistic about the prognosis of patients with multiple myeloma. Better up-front treatments combining immunomodulators, such as thalidomide and lenalidomide, and proteasome inhibitors, such as bortezomib, as well as steroids, are available. Most patients respond to these treatments, keeping the disease at bay longer.

Changes in the Field

Many factors are involved in the improved outcomes of multiple myeloma patients. Diagnostic techniques and disease awareness have improved, so patients are diagnosed earlier. A growing trend in the field is to treat these patients before major organ dysfunctions develop. A study in Spain and published in the New England Journal of Medicine found that for some patients, early treatment yielded a survival advantage at 3 years of follow-up. Further studies are needed to determine whether early treatment reduces genetic evolution and the heterogeneity of the involved tumors.

In the 1990s, before the new drugs became available, stem cell transplant was introduced for younger, fitter patients. An effective way to consolidate responses, the procedure involves harvesting the patient’s own stem cells and killing off disease-ridden marrow with chemotherapy. The healthy cells are then put back into the patient’s bone marrow. Although stem cell transplant does not cure multiple myeloma, remissions after transplant can last 10 years in 20%–25% of patients.

Combining immunomodulators and proteasome inhibitors has also proven to be a formidable weapon against the disease.