

An interview with Leslie Ford, MD, of the National Cancer Institute's Division of Cancer Prevention

## Are Americans ready for cancer prevention in a pill?

By Cori Vanchieri

**P**reventing cancer should be an easy sell. But for a variety of reasons, Americans have not yet embraced the concept, despite years of highly publicized exploration at the National Cancer Institute for ways to prevent breast, prostate, and colon cancers. Some drugs, like tamoxifen, have shown their worth, but not without side effects. As the associate director for clinical research in NCI's division of cancer prevention, Leslie Ford, MD, has overseen several of the big cancer prevention trials, including the Breast Cancer Prevention Trial (BCPT; tamoxifen vs placebo), STAR (Study of Tamoxifen and Raloxifene), and the Prostate Cancer Prevention Trial (finasteride vs placebo). She says we've still got some work to do before the American public is ready to think of cancer like heart disease.

### **Community Oncology: You've said Americans may not be ready for cancer prevention.**

*Dr. Ford:* People are very comfortable thinking about treating their hypertension or their high cholesterol with drugs that have side effects because they know that by reducing their cholesterol number, for example, they might avoid having a stroke or a heart attack. But they haven't made the leap in the cancer arena to the thought that if they took a drug, they might avoid getting cancer. A lot of it has to do with the fact that we don't have that intermediate step as we do in cardiology. By treating high blood pressure, you're reducing a risk fac-

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tor for a stroke. In oncology, we don't have that sort of handle to say 'We're treating this problem so you won't get cancer.'

**Tamoxifen was one of the first drugs shown to prevent cancer, reducing risk by half. Yet several studies indicate that most women at high risk for the disease are choosing not to take tamoxifen. What are the barriers?**

It's likely a combination of things. Tamoxifen is probably not being offered as aggressively as it should be. I think that's happening because of its side effects and because tamoxifen came out of the cancer arena. When we started the Breast Cancer Prevention Trial, the whole publicity around it was, "We're giving a cancer drug to healthy people." However, the cancer drug happened to be a hormonal intervention, not a chemotherapy drug. And the idea that these were healthy people gets back to our lack of an identifiable thing that puts them in a category that's not "healthy." Now, if they have atypical hyperplasia or lobular carcinoma in situ [LCIS], that gets us closer: They have a thing that needs to be treated. But if they just have a lot of family members with breast cancer and a lot of biopsies that never showed anything, you're stuck. The other issue is the concern over increasing the risk of endometrial cancer or pulmonary embolism or deep-vein thrombosis [DVT], although those risks haven't stopped many postmenopausal women from taking hormone replacement therapy.

### **Who should consider taking tamoxifen as a preventive?**

For premenopausal women, the risks are very small. There are very few endometrial cancers, if any, because women still continue to cycle, and all of the vascular effects of tamoxifen are much smaller. So I've always thought that for a woman in her 40s at an extremely high risk of breast cancer, it's



**Dr. Leslie Ford**

kind of a 'no brainer' that she would want to do this for 5 years and reduce her risk. For postmenopausal women, the risk issues are more real, unless they've had a hysterectomy, which puts them in a lower risk group.

**Results of the STAR trial are expected in summer 2006. If raloxifene [Evista] compares**

### **well with tamoxifen, will more women be willing to try this drug to prevent breast cancer?**

Raloxifene originally came to market as a way to prevent and treat osteoporosis. There's not a postmenopausal woman who isn't at risk of osteoporosis just by virtue of her age. Assuming the drugs are equivalent in preventing breast cancer, even if their risk profiles are the same, raloxifene already has a prevention indication for osteoporosis. So, I think the drug's maker [Eli Lilly] will position raloxifene as a drug that's approved for healthy women and now, not only will it prevent your bones from thinning, but it will also prevent you from getting breast cancer. I think it will catch on because it doesn't have that stigma of being a cancer drug.

### **What risks does raloxifene carry?**

The current label has language about DVT and pulmonary embolism and stroke risks similar to tamoxifen's, but the drug presumably doesn't have an endometrial cancer risk. However, it hasn't been studied as long or in as many women as tamoxifen. STAR would be the definitive trial on endometrial cancer risk.

**NCI has been a big supporter of COX-2 inhibitor studies. Last fall, NCI was sponsoring 23 prevention trials to test celecoxib (Celebrex) to prevent various cancers. But the COX-2 inhibitors face a different future than they did a year ago.**

One of the downsides of studying drugs for prevention in lots of people enrolled in randomized clinical trials for long periods is that you find out a lot about them that you might not otherwise have found out in postmarketing surveillance. Of course, Celebrex is the most topical example. We still have to sort out a lot of things about those data.

**Now that the FDA requires black box warnings on Celebrex, and Vioxx (rofecoxib) is off the market, what are NCI's plans?**

We're not going to abandon the COX pathway. The interaction between inflammation and carcinogenesis is where everything seems to be leading. Rather than dropping it because of some increased risk, we have to put it into context. Getting some efficacy data on Celebrex from the Adenoma Prevention with Celecoxib [APC] trial will help. That's due soon.

Each study was reviewed by the investigators and IRBs. We required that consent forms be updated and participants be reconsented. Many of the studies have been reopened.

One thing that's been lost in the whole argument is the potential gastrointestinal benefit of the COX-2 inhibitors. Aspirin and other NSAIDs are involved in 16,000 deaths and 100,000 hospitalizations a year from GI bleeds. Those are real numbers that people often dismiss.

**Since the heart attack risks of Vioxx and Celebrex were revealed in cancer prevention studies, will chemoprevention studies be more difficult to do?**

I think the opposite should happen. They shouldn't be putting the brakes on the prevention studies. The cardiovascular effects with Celebrex came out in a cancer prevention study rather than in an arthritis study because it's unethical to do placebo-controlled trials for more than a couple of weeks in an arthritis population. So all of the arthritis and pain trials subsequent to the initial ones are done with an NSAID as the comparator. If they both have an increased risk, you're not going to see any difference.

You have to move to another population in order to ethically do a placebo control. You could say that's what happened with the prostate drug finasteride [Proscar]. That's certainly what happened with Celebrex. It was the cancer prevention population that enabled us to use a placebo control. I view it as a good thing that you find

out what your parameters are—what your benefits and your risks might be. I wish there was a way we could make the public understand. Everything in life requires choices. But it takes a big effort to educate people about the side effects of the things that they take without even thinking, like statins. These drugs can have liver side effects. But people believe that the risk of high cholesterol leading to a heart attack is worse than that potential.

**You mentioned finasteride, another drug that turned up surprising risks when it was tested as a chemopreventive agent.**

Finasteride is another good example of a drug that had been approved by the FDA to treat benign prostatic hyperplasia based on a 3-year study. Then we put the drug in a 7-year study, the Prostate Cancer Prevention Trial [PCPT], looking for anything bad that could possibly happen. We found a 25% reduction in tumors—which is a huge deal—plus a small potential increased risk of the tumors diagnosed being high grade. How do you sort through that and how do you translate that into a recommendation for taking this or not? It becomes a major problem for a pharmaceutical company to interpret and to deal with the FDA and the public.

**Do you know yet why men who were taking finasteride in the PCPT and got prostate cancer had higher-grade tumors?**

There's been a lot of re-review of the slides. It doesn't appear that there is a hormonal effect causing high-grade tumors. There is definitely a documented decrease in the volume of the gland in men who are on finasteride. So if you shrink the volume and then do a random biopsy, you'd be more likely to pick up a tumor in a smaller gland than if you're fishing around in a big gland. There's some reason to expect that part of the high-grade finding could be an artifact

based on the volume.

There's also a large grant for the Molecular Biology of the PCPT. It's a major effort involving six of the leading universities in the country doing prostate cancer research. Most, if not all, of them have SPOREs [Specialized Program of Research Excellence grants] looking at different aspects of the etiology and genetics of prostate cancer. That project also has a large pathology core and is looking at diet and the antioxidants and oxidative stress hypotheses. It's a really exciting project that was funded this past spring for 5 years and will make extensive use of the stored specimens collected during the PCPT.

### **So are we not ready to make recommendations about men taking finasteride to reduce prostate cancer risk?**

Such a recommendation would be based on the FDA approving a label change for a new indication. That has not happened yet. What urologists have been saying is if a man has benign prostatic hyperplasia and is being treated or is considering being treated with finasteride, this is kind of a two-for-one. He may also get the benefit of reduced risk of developing prostate cancer. I would be happier if we had a full airing at the FDA for label indications, recognizing that there are benefits—a 25% reduction in risk versus some risk—increasing the possibility of a high-grade cancer.

### **Is there any kind of a risk score for prostate cancer like the Gail score for breast cancer?**

No. That's the other thing that people hope to get out of the PCPT. But it's still only 18,000 men, half of whom are on placebo. The Gail score used in the BCPT came from data in an earlier project, which included 250,000 women followed for many years. So, again, we're not quite there yet. Maybe a combination of

the PCPT and 12-year data from the PLCO [Prostate, Lung, Colorectal, Ovarian] Cancer Screening Trial will give us something like that. But, for now, these are age and family history, presence of prostatic intraepithelial neoplasia, and that's about it.

### **Where does the SELECT trial stand—testing vitamin E and selenium to prevent prostate cancer?**

Selenium and Vitamin E Cancer Prevention Trial (SELECT) has finished its accrual of more than 35,000 men. This trial is a major public health service, because vitamin E and selenium are supplements that people take routinely. They're sold in health food stores. But, as we know from the recent literature, they can have cardiovascular side effects. So it's critical to test these kinds of things that people already take simply because they read about their possible benefits in magazines.

### **What other compounds is NCI studying for cancer prevention?**

We have phase II studies of resveratrol, the compound from the skin of red grapes, and lycopene, which is the tomato paste hypothesis. We have a number of soy protocols, plus a study of epigallocatechin gallate, the active ingredient in green tea that's been formulated in a capsule. Then there are some drugs that come from other venues, such as PPARgamma, the oral diabetes drug we're testing for lung cancer prevention. Just in phase I is a nitric oxide-donating aspirin for colorectal cancer prevention. This formulation of aspirin is expected to avoid the gastrointestinal toxicity that can occur with aspirin and other NSAIDs.

### **Will we ever have markers, like a cholesterol number, for different cancers?**

Polyps are the closest we have so far. There's still the question of whether you're preventing the right polyps, the polyps that would go on

to cancer. In breast cancer, atypical hyperplasia and LCIS certainly seem to be keys to whether a woman is on the causal pathway that puts her at a higher risk for breast cancer. The Early Detection Research Network is trying to find those secretory proteins or serum biomarkers that might distinguish people's risk. I know there is one validation study in lung cancer looking at a polymorphism.

There certainly is a lot going on, like a new gene array that predicts who is more likely to have a recurrence in breast cancer. You could easily imagine backing that up 10 years to see who is most likely to develop breast cancer. If you think of cancer as a continuum—as the carcinogenesis process and not the event of cancer—there's absolutely no reason to think that you couldn't back way up. Instead of preventing metastases or blood vessels growth, ie, angiogenesis, why not prevent the first occurrence? That's really where we need to be focusing with agents that are acceptable, given the "health" of the person.

### **What role do you see community oncologists playing in chemoprevention?**

They are critical to its success—embracing the idea and talking to primary care physicians about it. All of our work is in clinical trials right now, and accrual is difficult. But these are not cancer patients. They're not seen by oncologists; they're seen by community doctors who find polyps and remove them or might see a patient with dyspepsia and order an endoscopic exam or tell a former smoker "we'll just have to watch you." It would help if prevention trials became more of a routine part of what community physicians think about when they counsel individuals. Community oncologists are the cancer authorities in the community, so they could help encourage community doctors to get involved.