postmenopausal women to prevent osteoporosis and coronary heart disease, with the added advantage of preventing breast cancer," he said.

A crop of what Jordan calls "me too" drugs, modeled on tamoxifen, are also under investigation. These include toremifene, which has been approved for treatment of advanced breast cancer; idoxifene, in phase I and II trials in England for advanced breast cancer and osteoporosis; and droloxifene, for which phase I trials are completed and phase II trials are planned, Jordan said.

"All of these things sound great in theory," said Leslie Ford, M.D., associate director of NCI's Early Detection and Community Oncology Program, but only large-scale, long-term studies will uncover a low-level risk such as endometrial cancer with tamoxifen use. Although tamoxifen has been available for 30 years, she cautioned, "it wasn't until the late 1980s that we found out about tamoxifen and the uterus."

**The Retinoids**

Other tamoxifen alternatives may be the vitamin A derivatives, which are known as retinoids and come to breast cancer research from other areas of cancer treatment. Treatment with 13-cis-retinoic acid has reversed oral leukoplakia, a premalignant lesion, and prevented the development of secondary carcinomas of the head and neck, and all-trans-retinoic acid is used in treatment of acute promyelocytic leukemia.

Retinoids studied so far appear to induce differentiation in target tissues; in breast cancer, they are anti-proliferative in estrogen receptor-positive cell lines. In culture, all-trans- and 9-cis-retinoic acids inhibit cell growth, block cell cycle progression, and stimulate apoptosis.

It’s still early in the game for retinoids in breast cancer, but a study in-

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**Endometrial Cancers From Tamoxifen Are Not More Aggressive**

Two years ago, when an advisory committee to the Food and Drug Administration performed a regularly scheduled review of the safety of the Breast Cancer Prevention Trial (BCPT), the popular misconception was that FDA had called the meeting because it wanted the trial stopped because evidence suggested the drug caused virulent endometrial cancers.

Fears about the type of uterine tumor that might develop from tamoxifen use were based on a small, retrospective study from Yale University, New Haven, Conn., which no one else has replicated, noted Jeff Abrams, M.D., of the National Cancer Institute's Clinical Investigations Branch, and V. Craig Jordan, Ph.D., D.Sc., Breast Cancer Program director, Robert H. Lurie Cancer Center of Northwestern University, Chicago.

One theory held that tamoxifen caused damage directly to DNA, which would give rise to a more serious grade of neoplasm. Since then, research has shown that it is the drug's action on estrogen receptors that influences the risk of endometrial cancers.

Different researchers are using different words — reassessment, clarification — to describe the shift in thought about tamoxifen. It has long been recognized that endometrial cancer linked to tamoxifen is relatively rare, but researchers now believe that these tumors are largely low grade and treatable.

"About 0.1% of all women who take the drug develop endometrial cancer for every year of use," said Abrams. "That's one to two women per 1,000 per year," which is still a concern, but not as large a number as some studies had originally suggested.

"We're telling women that the overwhelming risk-benefit ratio is in favor of tamoxifen," said Richard R. Barakat, M.D., a gynecologic surgeon at Memorial-Sloan Kettering Cancer Center in New York.

Jordan's view is that the apparent increase in endometrial cancer from tamoxifen use results at least in part to higher detection rates; that is, detection of pre-existing carcinomas and detection of tumors that might otherwise have gone undiagnosed for years.

Investigators in the BCPT hope to complete patient accrual within a year, said Leslie Ford, M.D., associate director of NCI's Early Detection and Community Oncology Program. Within 2 years after that, preliminary results may be available, Abrams said, adding that, "it's very possible the benefits of tamoxifen will outweigh the risks in that setting as well."

— Jan Ziegler