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Author

Meyskens, F L, Jr

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Chemoprevention of Breast and Colon Cancer

Frank L. Meyskens Jr, MD

Address

Chao Family Comprehensive Cancer Center, College of Medicine,
University of California at Irvine, 101 The City Drive South, Route 81,
Building 23, Orange, CA 92868-3201, USA.
E-mail: flmeyske@msx.ndc.mc.uci.edu

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The field of chemoprevention of human cancer is relatively new, and unqualified positive results of successes have been few [1]. Two recent large randomized trials, one involving patients with prior polyps and the other with women at high risk for breast cancer, offer evidence that the approach will validate extensive experimental data and is fundamentally sound.

The smaller trial involved 930 patients who had a colorectal adenoma removed in the recent past [2]. Experimental data in animals suggested that dietary calcium bound secondary bile acids, which were carcinogenic in animal models. The results of epidemiologic studies have been mixed, however, with an association of colorectal cancer found in some cases and not in others. For some time it has been accepted that colorectal adenomas are precursors to colon cancer and that their eradication is tantamount to prevention of malignancy in this organ site.

In this multi-institutional trial led by investigators from the Norris Cotton Comprehensive Cancer Center and the Dartmouth-Hitchcock Medical Center, potential subjects were identified by monitoring colonoscopy and pathology records for individuals who had adenomas removed within 3 months before treatment. Eight hundred and sixty participants were randomized, and with a dropout rate of about 10% the study had an 80% power to detect a 25% reduction in the recurrence of adenomas. After a 3-month placebo run-in period to assess compliance with study medication, subjects were equally randomized to either 3 grams of calcium carbonate or identical placebo. The study was double blinded, with neither the subjects nor staff cognizant of the treatment assignment. Participants were scheduled to undergo colonoscopy 9 months after randomization and again 3 years later. Daily dietary nutrient intake and adherence were assessed, and imbalances were controlled for in the analysis.

After both the first (9 months) and second (45 months) study interval the relative risk (RR) for the treat-

ment group for one adenoma was about 0.75 to 0.80, depending on exactly how the analysis was done. The effect of calcium on recurrence of adenoma was similar regardless of the location of the recurrent adenoma. The side effects in the two arms were similar, as was adherence, about 90% after 1 year and 80% after 4 years.

This benchmark study is the first randomized clinical trial to demonstrate a lowering effect of a dietary compound on recurrent colorectal adenomas, and it supports the notion that calcium carbonate may have a real—but moderate—chemopreventive effect against colorectal neoplasm.

The second randomized trial that has yielded impressively positive results is the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-1 Study, in which the preventive activity of the anti-estrogen tamoxifen has been assessed in women at high risk for breast cancer [3]. Experimental data in animals has indicated that tamoxifen inhibits the growth of breast tumors. This agent has also been effective in prolonging survival when used as adjuvant therapy in early-stage disease and has reduced the incidence of contralateral breast cancer significantly. The metabolism, pharmacokinetics, and side effects of the drug are well known and, in general, tamoxifen has been well tolerated.

In this national multi-institutional trial led by investigators of the NSABP, potential participants were identified and subsequently underwent extensive evaluation of risk. This large trial involved 13,388 patients who were at increased risks for breast cancer for one of three reasons: 1) age over 60 years; 2) age between 35 and 59 years, with a 5-year predicted risk for breast cancer of at least 1.66%; or 3) history of lobular carcinoma *in situ*. The probability of occurrence over time was based on a multivariable logistic regression model using combinations of risk factors, known as Gail's algorithm [4].

Women were assigned equally to either tamoxifen (20 mg/d) or an identical placebo in a double-blinded fashion. Extensive statistical methods were developed to address the appropriate scheme for stratification, randomization, and analysis. Overall, the cumulative rate of invasive and noninvasive breast cancers was reduced nearly 50% in women taking tamoxifen for 5 years ($P < 0.00001$). The benefit occurred almost immediately and continued throughout the duration of the trial. The reduction in invasive breast cancers was significant in every year of follow-up, and decreased risk occurred in women of all

ages. Similar benefits were seen in women with a history of lobular carcinoma, and remarkably, a reduction in risk of over 86% was seen in women with a history of atypical hyperplasia. Interestingly, tamoxifen reduced the occurrence of estrogen-receptor-positive tumors by nearly 70%, but no difference in the occurrence of estrogen-receptor-negative tumors was seen.

Tamoxifen has complex effects on the bones, the cardiovascular system, and other estrogen-sensitive organs and tissue. A number of beneficial and adverse effects were demonstrated. Overall, no altered rate of several parameters of ischemic heart disease was demonstrated; however, the rates of stroke, pulmonary embolism, and deep-vein thrombosis were significantly elevated in the tamoxifen group, especially among older women. Also of concern was the significantly elevated rate ($RR=2.53$) of endometrial cancer in women taking tamoxifen. On the other hand, a reduction was seen in hip, radius, and spine fractures in women in the treatment group ($RR=0.55-0.74$).

In considering the risks and rewards of such a trial, assessment of overall health benefits is important. Women in the tamoxifen group had nearly a doubling of moderately bothersome hot flashes and vaginal discharge. Overall, fewer deaths occurred in the tamoxifen group (57 vs 71), with a relative risk of 0.81; however, the 95% confidence interval spanned from 0.56 to 1.16, and longer

follow-up will be necessary before definitive conclusions regarding the total health benefit of tamoxifen can be made. Based on the positive findings in the tamoxifen study, a new trial (P-2) comparing the effects of tamoxifen with those of another agent, raloxifene (which has a different estrogen tissue profile), has just been started.

The results of these trials, using two very different drugs and endocrine and non-endocrine organs, provide strong evidence that prevention of cancer in humans is possible. A major long-term goal of chemoprevention will be to enhance the effectiveness of these compounds while producing agents that have fewer side effects.

References and Recommended Reading

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