This issue of CA—A Cancer Journal for Clinicians contains two articles that discuss state-of-the-art cancer prevention for situations frequently encountered in primary care, namely, how to help cigarette smokers quit, and how to manage a woman at high risk for breast cancer.

Helping Smokers Quit

John Hughes, MD, emphasizes that all clinicians are obligated to determine whether their patients smoke and to advise current or recent smokers to quit and/or maintain the quit status. However, even the busiest clinician is expected to go beyond merely giving advice; given the broad selection of effective quit strategies (i.e., self-help literature, nicotine replacement therapy, non-nicotine medications like bupropion, and proven psychosocial interventions), the clinician should individualize therapy, set realistic quit targets, and establish a follow-up surveillance program.

Genetic Predisposition

Recent data from twin studies and research on nicotine effect suggest a role for genetic variation in the dopaminergic regulatory system as a determinant of the propensity to become a habitual smoker. The assumption underlying these studies is that individuals with genetic polymorphisms that cause a shortage of dopamine are more likely to become smokers—to facilitate the release and circulation of dopamine—than individuals with genetic polymorphisms that increase circulating dopamine. Specifically, individuals who have expression of the dopamine transporter gene variant SLC6A3-9 are less likely to smoke. Moreover, if such individuals smoke and subsequently quit, they are more likely to have long abstinence periods. In the near future, clinicians will be able to test smokers for nicotine metabolism status, which could lead to better pharmacogenetic therapy for recalcitrant smokers.

A continuing challenge to pediatricians and family practitioners, of course, is the epidemic of teenage smoking in the US. All health professionals must work with merchants, the media, and local government to keep cigarettes out of the hands of children and adolescents.

Breast Cancer Prevention

Victor Vogel, MD, MHS, presents an updated review of prevention options for women who have an increased risk of developing breast cancer based on family history, personal breast health factors, and age. In the recently completed National Breast Cancer Prevention Trial, five years of tamoxifen decreased the risk.

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of both non-invasive and invasive breast cancer by about 50%. Because stage 1 endometrial cancer, deep vein thrombophlebitis, and pulmonary embolism were increased in the treated patients, the practitioner must carefully weigh the patients’ risk for breast cancer versus the low risk of side effects before recommending tamoxifen therapy in asymptomatic high-risk women.

Practitioners should encourage eligible women with increased risk of breast cancer to participate in the second-generation Study of Tamoxifen and Raloxifene, or STAR trial, which compares the potentially less toxic selective estrogen receptor modifier raloxifene with tamoxifen. Because the risk of cancer is potentially greater in women who carry BRCA1/2 mutation and because the effectiveness of tamoxifen is unknown for this risk group, Dr. Vogel succinctly presents the pros and cons for bilateral prophylactic mastectomy. He also reviews the rationale for lifestyle modification that could potentially reduce breast cancer incidence in all women regardless of age and family history.

A Caveat About Cancer Prevention Strategies
The reader should be aware that several other strategies to prevent common adult cancers are being evaluated. In the Alpha-Tocopherol Beta Carotene Cancer Prevention Study, more adult Finnish smokers who were randomized to beta carotene died of lung cancer than did those in vitamin or placebo-treated groups, suggesting an unsuspected deleterious effect of beta carotene in current smokers. A similar adverse effect with beta carotene was documented in a group of asbestos-exposed male smokers in the Beta Carotene and Retinol Efficacy Trial. These trials present a strong warning to all practitioners and to the public: Seemingly innocuous micronutrients or complementary therapies may have unintended adverse effects, especially in subjects who continue to smoke. Carefully conducted clinical trials are necessary before a prevention regimen can be recommended in populations at high risk for cancer.

Ongoing Research in Chemoprevention of Cancer
Colon cancer has been a target for prevention because of its high incidence in the US and because adenomatous polyps are a suitable surrogate or intermediate marker of the disease. Although the epidemiology of colon and rectum cancer suggests that high fiber diet, calcium supplements, and multivitamins could lower the risk of the disease, there are no positive large-scale intervention studies using micronutrients in people with sporadic bowel polyps.

Recent epidemiologic studies and exciting preclinical studies suggest that nonsteroidal anti-inflammatory drugs have an effect on prostaglandin synthesis that can reduce polyp formation. In a limited clinical trial of patients with fa-
milial adenomatous polyposis (FAP). sulindac decreased existing polyps and prevented new polyp formation. In the past two years, carefully conducted pilot studies in FAP subjects verified that both a cyclooxygenase (COX)-2 inhibitor (Celebrex)\(^8\) and the apoptosis-promoting agent sulindac-sulfone (Exisulind) can prevent polyp formation.\(^9\) Placebo-controlled prospective trials of COX-2 inhibitors in adults who have adenomatous polyps or who are members of hereditary non-polyposis kindreds are actively accruing subjects.

The demonstration that high-dose 13-cis-retinoic acid achieved a 67% major response rate in oral pre-malignant dysplasia led to a series of translational cellular/molecular studies that are the basis for our current understanding of oral carcinogenesis and the action of differentiating agents like retinoic acid.\(^10\) Subsequent research has contributed to our knowledge of apoptosis, retinoic acid receptor-beta induction, and the molecular biology of oral carcinogenesis (i.e., loss of heterozygosity and the importance of P53 mutations).\(^11\) As the mechanism of retinoic acid binding and signal transduction between the cytoplasm and the nucleus is elucidated, investigators will be able to optimize dose and duration of therapy to obtain optimum clinical results. Cis-retinoic acid and its congener fenretinide are currently under study in the prevention of breast, ovarian, and lung cancers.

The study of markers of risk for cancer and surrogate endpoint biomarkers holds great promise for cancer chemoprevention.\(^12\) One of the most interesting markers is apoptosis, or programmed cell death, in dysplastic lesions or carcinoma in situ. If the induction of apoptosis occurs, then it should be possible to test the beneficial effect of chemotherapy agents such as COX-2 inhibitors and fenretinide, either in vitro or in vivo, through multiple-needle biopsies. It is very likely that within the next five years, researchers will utilize new technologies such as microarray techniques and combinatorial chemistry to identify novel molecular targets and natural or synthetic agents for chemoprevention.

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