Cancer Prevention: Perspectives and Implications

"He is a better physician that keeps diseases off us, than he that cures them being on us; prevention is so much better than healing because it saves the labour of being sick."

Thomas Adams, 1618

Cancer prevention is commonly divided into three categories of prevention: primary, secondary, and tertiary. Primary prevention involves the avoidance of cancer causing exposures and behaviors. While the identification of tobacco as a principal carcinogen in cancers of the lung, head and neck, and bladder has enabled preventive efforts to be targeted at the prevention of individuals from initiating smoking, most malignancies do not have a clearly identified etiologic agent. Secondary prevention involves efforts directed at the cessation of exposure to carcinogenic agents as well as to screening individuals to detect malignancy at an earlier stage. This area includes efforts directed at smoking cessation as well as screening programs designed to detect cancer at an earlier stage when treatment may be more likely to result in cure. Screening programs have been very successful in certain areas and were reviewed in the November/December 1995 issue of Cancer Control. Tertiary prevention includes chemoprevention — the administration of agents intended to prevent the development of cancer. This issue of Cancer Control describes some of the recent progress that has been made in chemoprevention in several key areas.

Dr Eva Szabo and I review the status of biomarkers, particularly as identified in lung carcinogenesis. Numerous molecular markers may be able to serve as targets to interrupt the process of carcinogenesis. If these targets can be validated and rational interventions can be defined to interfere specifically with these steps in the carcinogenic process, then there is hope for real prevention of lung cancer development. The challenge remains to identify molecular targets associated with eventual cancer development in order to substitute such intermediate markers for the final endpoint of cancer development in clinical studies.

Drs Peter Greenwald and Sharon McDonald discuss the roles of diet and chemoprevention in cancer development. Many dietary agents have been investigated as possible chemopreventive agents. While most of the data regarding diet and cancer are based on epidemiologic studies, the intervention trials have used either supplements or synthetic analogues of dietary agents. As demonstrated with the betacarotene studies, such interventions are not always beneficial and may induce harm. Further integration of understanding of the mechanisms of carcinogenesis and the actions of nutritional substances on this process is needed before real progress can be made in this area.

Dr Scott Lippman reviews recent advances in head and neck chemoprevention. He describes multistep carcinogenesis and the biology of retinoids that have demonstrated activity in head and neck cancers, and he also reviews the oral premalignancy trials that demonstrated regression of leukoplakia in individuals treated with 13cisretinoic acid. In addition, Dr Lippman describes the exciting finding of reduction in the risk of developing second primary tumors following definitive treatment of early stage head and neck squamous cell cancers in individuals treated with 13cisretinoic acid. Exposure of the aerodigestive tract to tobacco carcinogens subjects head and neck cancers, lung cancers, and other aerodigestive cancers to this field cancerization process. In addition, a similar process may be involved in exposing the bladder urothelium to carcinogens (eg, tobacco-related carcinogens). The success in preventing second primary tumors in survivors of a first head and neck malignancy will determine the direction for future work in head and neck cancer prevention and hopefully will translate to prevention of first malignancies.

Drs Jean Joseph and Edward Messing provide an overview of the progress of chemoprevention in genitourinary cancers with specific attention to bladder and prostate cancer. Bladder cancer is an excellent model for chemoprevention, not only because superficial bladder cancer has a high rate of local recurrence, but also because it is a disease that is easily visualized by cystoscopy, is easily resected transurethrally, and should shed cells containing relevant intermediate markers in the urine. While prostate cancer is somewhat more difficult to study for chemoprevention, its high incidence makes it an important disease to target. The large Prostate Cancer Prevention Trial initiated in 1993 should provide important information regarding the ability of finasteride to prevent prostate cancer.

Finally, Drs Victor Vogel and Lisa Parker discuss the ethics of chemoprevention clinical trials. Complex issues are raised because, generally, the participants do not have cancer or may have only specified risk factors for cancer. The definition of risk, confidentiality and recruitment, randomization, informed consent, and trial monitoring are all critical issues associated with these trials. The use of placebos in these studies creates conflict for some investigators as well as for potential participants. Some studies required to monitor these treatments may be invasive and thus raise further issues on the ethics of conducting these studies in "healthy" individuals. Nevertheless, the success of identifying effective chemopreventive agents will rely on clinical chemoprevention trials. It is only through the education of investigators and potential study participants that these trials will be able to be conducted in a timely fashion with meaningful results.

In the previous issue of Cancer Control, Drs Bernard Fisher and Joseph Costantino reported the history of the National Surgical Adjuvant Breast and Bowel Program Breast Cancer Prevention Trial. They described the initial scientific basis for the hypothesis that tamoxifen could prevent or interfere with the progression of breast cancer in women, as well as the initial steps to conduct the breast cancer prevention trial, the justification, the objectives and major aspects of the trial, some of the difficulties that have arisen during the conduct of the trial, and some final comments regarding the anticipated completion of the trial with preliminary descriptions of the enrolled population. This trial represents a sentinel trial in the United States in administering an agent such as tamoxifen to women who have never had breast cancer but who meet criteria that identify them as being at high risk for its development. The final results of this trial will determine the risk/benefit ratio of such a chemopreventive agent in a very high risk population. With the rising incidence of breast cancer — largely related to increased screening efforts — more information about the prevention of this malignancy would be important progress.

As more molecular markers are validated to the gold standard endpoint of cancer incidence, chemoprevention trials may be able to be shortened and conducted with smaller sample sizes. The booming knowledge gained from the expanding field of molecular biology has opened real possibilities for this progress. Another direction for chemoprevention lies along local delivery systems for chemopreventive agents in order to minimize potential toxicities. The development of such locally directed...
interventions should enable the broader application of chemopreventive agents with less toxicity for the population at risk.

Chemoprevention should not be viewed as subjecting "healthy" individuals to potentially toxic treatments. We all have cells that, with the process of aging, will develop multiple molecular genetic defects that have the potential to transform and become neoplastic. In the same way that antihypertensive agents are directed at lowering blood pressure to prevent the subsequent development of stroke, heart failure, or myocardial infarction, chemopreventive agents may arrest the progression of genetic defects in cells undergoing transformation to prevent invasive cancer. This concept is key to the development of successful chemoprevention strategies.

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