S7. Cancer prevention: Scientific anticipations and clinical hopes

D. Sidransky*
Johns Hopkins University, Dept. of Otolaryngology, HNCR Division, David Koch Cancer Research Bldg, Baltimore, MD, USA

Tumors arise through a series of genetic changes which include activation of protoocogenes and inactivation of tumor suppressor genes. There are many new technologies to identify rare cells containing genetic mutations in an excess background of normal cells. Theoretically, the identification of a clonal population of cells sharing an early genetic or epigenetic marker for malignant transformation would lead to valuable intermediate endpoints and could diagnose premalignant lesions amenable to chemoprevention. Ideally, these alterations would occur early in the tumor cascade, prior to the development of a clinically significant tumor. High throughput genomic approaches are describing many possible markers that must be precisely placed in histopathologic tumor models and tested in appropriate populations to better define their value. As an epithelial tumour grows, cancer cells are sloughed off the organ epithelium into body fluids such as blood plasma, urine or saliva. This makes it possible to detect molecular markers such as DNA mutations, methylation patterns or microsatellite instability in these samples before they are symptomatic or during chemoprevention approaches. There are several different types of cancer marker that can be detected in serum, urine or saliva samples. DNA can be analyzed for changes in gene copy number, chromosome translocations, deletions or loss of heterozygosity (LOH), telomere extension, microsatellite instability, promoter hypermethylation or point mutations. Mitochondrial DNA can also be analyzed for mutations. RNA can be analyzed for expression levels or point mutations, and proteins can be analyzed for structural alterations, changes in enzymatic activity, localization or expression patterns. Newer discovery techniques are advancing our knowledge of these potential markers at an accelerated pace. Recently, high-throughput screening approaches that can simultaneously analyze expression patterns of several genes and proteins have been used to search for cancer-associated molecules. Microarray analysis is now one of the most common ways to detect gene mutations, epigenetic alterations, and changes in gene expression in cancer and normal cells. This type of approach allows for rapid surveillance of many alterations or changes in expression of tens of thousands of genes in one experiment, and can be used to identify patterns in normal and precancerous or cancerous cells. High-throughput mass spectroscopy can now be used to compare protein profiles between cancerous and normal tissue samples, and to also detect cancer in patient samples. Early candidate markers for early detection included common p53 mutations in squamous cell carcinomas of the aerodigestive tract and ras mutations in adenocarcinomas of the colon and lung. Mitochondrial mutations are ubiquitous in many primary tumors and may be used to monitor tissue for early cancerous changes. The use of a panel of methylation markers including GSTP1 as an adjunct to histologic review may substantially augment prostate cancer diagnosis from needle biopsies. Other methylation markers show promise in monitoring the colon, lung, and oral cavity for early recurrence. Several protein-based assays have also been developed to detect cancer cells. Most of these are single antibody-based assays, but algorithms to analyze patterns in serum protein-mass spectra are improving. The sensitivity and specificity of a molecular marker cannot be fully realized until careful testing is carried out in large numbers of tumor specimens and compared with normal controls – to identify markers that are truly over-represented or qualitatively different in the neoplastic cells compared with normal cells. Incorporation of molecular-marker analysis into clinical trials is therefore a crucial part of marker development. Future clinical trials should be designed to incorporate assays to both identify molecular markers and to correlate known markers with patient outcome. The procurement of patient samples and subsequent testing in preneoplastic lesions to identify the timing of their appearance in tumor progression is of great importance. Further development of molecular markers depends on cooperation between molecular biologists and clinical researchers. Molecular biologists must take advantage of the numerous biopsy samples and paired controls that are already preserved in tissue banks, and clinical researchers must incorporate marker analysis into their trials. It has been difficult to translate the large-scale use of molecular markers to the clinic, owing to the difficulty and expense that is involved in developing the necessary platforms and technology to use these assays on a large number of samples. New high-throughput techniques are necessary to identify new markers and will soon contribute to the analysis of known markers in a cost-effective fashion for testing their ultimate clinical utility.