Overview: NCI Workshop on Investigational Strategies for Detection and Intervention in Early Lung Cancer¹

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The reason why the NCI Workshop on Investigational Strategies for Detection and Intervention in Early Lung Cancer was convened in Annapolis, Maryland, relates to the growing excitement over reports of clinical trials suggesting benefit with the retinoid chemointervention approach in the upper airway, tamoxifen intervention with breast cancer, and the perceived potential of the growing body of information elucidating the nature of the early steps of epithelial cancer.

Annapolis, by virtue of its proximity to Bethesda and the National Institutes of Health, ensures a healthy representation of the National Institutes of Health program staff. In the course of the Workshop, the opportunity existed for scientists, clinicians, and NIH program staff to learn more about the exciting opportunities provided in the approaches to early lung cancer. Because this is a new area which requires the close collaboration of a broad range of professionals, a corresponding evolution will be required in the trial methodology for these new directions. An intention of the Organ System Program staff and the organizing committee was to foster a full exploration of the scientific issues related to applications of emerging knowledge of early cancers and to identify mechanisms to potentially catalyze progress in this area of work. In considering the possibility of developing effective secondary prevention tools, i.e., tools for early cancer detection or biochemical intervention, there are several classes of issues.

First, there are questions regarding the science of understanding early cancer. What are the sequences of critical genetic events or critical levels of genetic events leading to the emergence of a malignant clone of cells? What are the critical promotion factors in the process of carcinogenesis? What are the relevant markers which map the field carcinogenesis process in a fashion which lends them to application as early detection or intermediate end point discriminants? These are significant scientific questions and with the powerful molecular tools which have been recently developed basic scientists can become totally immersed by the opportunities provided in studying this area.

A second level of questions arises if one attempts to apply the fruit of the recently elucidated tumor biology. How does one scale up a molecular probe for lung cancer screening applications? The long experience with cervical cancer screening, as well as the more recent experience with human immunodeficiency virus screening, demonstrates the complexity of the process of screening. An assay must be validated with great precision to permit responsible population-based application. Standardization of methodology for specimen acquisition, processing, analysis, and assay interpretation are all aspects of cytological screening of the cervix which are still controversial events after 50 years of experience with that screening tool. Can a prior consideration of this issue permit more efficient resolution of these issues for the next generation of bimolecular probes used for population-based screening?

The technical issues with screening approaches may be ameliorated if automated procedures are developed for specimen preparation and analysis. The interpretation of the reproducibility which plague conventional histological or cytological analysis may be reduced with the incorporation of quantifiable end points. Trade offs between access to screening population and use of expensive instrumentation will need to be resolved. For the potential number of subjects at risk for lung cancer, the large number mandates the requirement for an economical screening assay. Using innovative screening strategies with more than one assay, the possibility exists to develop a screening algorithm with stratifications of biomarker analysis. For example, a simple but sensitive initial assay might identify subjects for further study, potentially using a more extensive battery of probes for the second tier analysis. Such strategies may greatly decrease the cost bases of cancer screening efforts.

Another critical issue for implementing screening approaches to lung cancer is the large issue of subject compliance. Many women do not get mammography due to such factors as fear, economics, or indifference. A major challenge for the cancer prevention community is to develop a greater understanding on the part of the average person about public health strategies for cancer control. As with many preventive health measures, success with compliance may be the greatest when participation with such strategies begins even before birth, but today's challenge is to educate adults to the benefits of availing themselves to preventive measures.

In light of the recent positive pilot trial experience with tamoxifen intervention in suppressing new primary breast cancer, there is enthusiasm to broaden strategies to other organ systems. On the basis of a growing body of information, we propose that the lung autocrine growth factor, gastrin-releasing peptide, may play a role in lung carcinogenesis similar to that of estrogen in breast carcinogenesis. Using existing biotechnology tools the possibility exists to study the result of neutralizing individual tumor growth factors to determine their benefit. As we identify the central promotion factors in the preclinical phase of cancer, intervention approaches which target such factors may be more successful.

An important issue with intervention research since it will generally involve healthy individuals is that closer attention must be paid to pharmacology to minimize toxicity in order to obtain optimal subject compliance.

Finally, the new early detection and intervention trials will have to evolve new clinical trial strategies to allow these studies to proceed over a practical time frame and include a manageable number of subjects. These objectives can be addressed by the appropriate application of biomarkers. For example, biomarkers that stratify subject risk may be useful to define subject populations at enhanced risk for cancer. Biomarkers for early cancer detection may track events that occur later in the process.

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of carcinogenesis than markers of risk, but they may also be applied to define “higher risk” study populations. As previously mentioned, biomarkers can be validated for application as surrogate or intermediate end point markers. These markers could indicate beneficial effects on carcinogenesis with new intervention agents in advance of traditional clinical trial end points (such as frequency of death due to cancer). Careful application of biomarkers can accelerate the pace of intervention research progress.

The challenges of serious prevention research for lung cancer are complex, multi-dimensional, and numerous. This workshop is an initial step in defining the magnitude of the challenge. The evident enthusiasm of the participants in this forum suggests that the promise of this prevention-oriented approach is becoming rapidly more evident. An ongoing dialogue including at least epidemiologists, public health workers, basic scientists, statisticians, oncologists, primary care providers, pathologists, thoracic surgeons, and pulmonologists is critical and it is the sincere hope of the Workshop Organizers that the Annapolis Conference will provide a boost to this effort.
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