presence of transformed or preneoplastic cells in the patient's respiratory tract. In recent years some biomarkers have been proposed with potential diagnostic or prognostic value in lung cancer. Unfortunately, most of these biomarkers have not been validated in large populations and still lack an unambiguous demonstration of clinical usefulness. Along the same lines, the identification of biomarkers for the early detection and for premalignant lesions has had a relatively limited success. The study of carcinogenesis models to search for new biomarkers, the development of new highly sensitive molecular techniques, and the availability of large series of patients for which well protocolized and standardized sample collection is organized, may help to solve this urgent need for a robust and validated early detection molecular tool. In clinical settings, the lung cancer early detection biomarkers will be analyzed in non invasive specimens (blood, sputum, exhaled air) with automatized techniques.
Low dose spiral computerized axial tomography (spiral CT) is effective for the detection of small early lung cancers. Although published data seem promising, there has been a significant degree of discussion concerning the potential of overdiagnosis in the context of spiral CT-based screening. We and others have analyzed the phenotypic and genetic alterations in the small pulmonary malignancies resected within research spiral CT screening trials. Our aim was to determine whether their malignant molecular features are similar to those of resected lung tumors diagnosed conventionally. We analyzed 17 biomarkers of lung epithelial malignancy. The molecular alterations and the frequency of phenotypic or genetic aberrations were very similar when screen detected and non-screen detected lung cancers were compared, suggesting that the screen detected tumors are genuine neoplastic growing cells.

113 INVITED

Chemoprevention

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Incidence and mortality associated with lung cancer has not been significantly modified since more than 25 years, despite introduction of new cytotoxic drugs and development of multidisciplinary approaches combining surgery, chemotherapy and radiotherapy. This points out how much chemoprevention approaches are necessary. Complete characterization of molecular determinants of lung carcinogenesis is essential to allow rational and targeted development of chemopreventive agents. Molecularly targeted agents are currently being studied in all treatment settings including that of chemoprevention, which is defined as the use of natural or synthetic agents to interrupt the process of carcinogenesis and to prevent or delay tumour occurrence. Lung cancer chemoprevention trials have being highly disappointing notably when performed in current smokers. Interesting but preliminary results have being obtained in trials focusing at former or never smokers. Progress in chemoprevention is reliant on the collaborative efforts of researchers in basic science and clinical settings who study the biology of lung cancer with the goal of uncovering new mechanisms of carcinogenesis. Small molecules which target specific receptors or mutations such as inhibitors of epidermal growth factor receptor or RAS will have an increasingly significant role as they are associated with more tolerable side-effects and may prove more effective. Development of a risk model with intermediate endpoints is essential for future chemoprevention studies.

Scientific Symposium
Ovarian cancer – an update

114 INVITED

Ovarian cancer diagnostics: update on proteomics

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Proteomics is the study of proteins and protein signaling pathways and how they effect the process, diagnosis, and intervention for science. While many consider cancer a disease of genes, one must remember that it is the protein that is the work horse and the most readily detectable of the subcellular information sources. Key questions are how to harness the information resources of proteomics for optimal use. Multiple approaches of proteomics have evolved for application to ovarian cancer and other cancers. Measurements of proteins and their activated components in tissue and biological materials can provide an insight into the biology and behavior of the cancer. Another application is using proteins and protein patterns for descriptive purposes.
A good screening test is one that has high sensitivity, high specificity, is readily done, and for which there is an intervention that can make a difference. Proteomic pattern development from serum proteins fits the requirement for easy access to source material. Techniques using high throughput mass spectrometry platforms coupled with complex bioinformatics for detection of proteins and/or protein patterns are under development. Results to date show that the process of matrix-associated laser desorption and ionization mass spectrometry can yield datastreams from which protein diagnostics for ovarian and other cancers have been advanced. The general sensitivity and specificity of these experimental screening developments has been good, 85–95%, but inadequate for use as a diagnostic due to the translation to poor positive predictive value, necessitating too many invasive procedures yielding false positive designations. Work is ongoing by our group and others to optimize quality control, robotics, and reproducibility. It is important that any platform(s) selected is valid, reliable, and reproducible across users. Clinical studies are under development to build diagnostic patterns of early disease recurrence and for differentiation of benign disease and unaffected women from those harboring cancer.
A second and advancing approach of proteomics is applied to the classification of protein signals and pathways to assessment of clinical behavior in response to treatment. Many targeted agents are being applied to ovarian cancer other cancers. Their putative mechanisms of action, validated in the laboratory and xenograft or transgenic animal models, needs to be confirmed in patients. One approach to this is through surrogate biomarkers. However, there are very few biomarkers that have been validated as to the demonstration of their accuracy for what happens in the tumor. For example, it is clear that inhibition of epidermal growth factor receptor results in rash, commonly on the face and chest. However, it has not been globally confirmed that inhibition of EGFR in skin resulting in rash is concomitant with inhibition of EGFR in tumor. Hence, there was need to develop technologies that can be applied to small tumor samples, such as needle biopsies, for analysis of biochemical modificaiton within the tumor. Our group has applied laser capture microdissection and reverse phase tissue lysate microarrays and measured changes in biochemical protein profiles before and into therapy with molecular targeted agents. Examples of these will be presented.

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Molecular predictors of ovarian cancer response and progression

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Multiple gene alterations take place during tumor development and progression and could specifically contribute to the treatment response and eventually impact on disease outcome. A large survey of recent published data, integrated with our own data, indicate that loss of TP53 gene function may contribute to a platinum-based chemotherapy resistance and to taxane sensitivity, but in both early and advanced stage patients the impact of TP53 mutation status in overall survival is still debated. However a deeper characterization of mutational spectrum seems to indicate that distinct type of mutations might result in short-term survival benefit. Even in the case of BRCA family genes, the questions of whether epithelial ovarian cancer (EOC) carriers of BRCA mutations have specific prognostic patterns or BRCAness phenotype could account for platinum sensitivity have not yet been solved. Taken together these data suggest that even if these genetic molecular markers cannot be considered the single prognostic driving forces they may influence overall survival in selected populations. Recent technological developments, enabling simultaneous measurement of many parameters ("omic" approaches), hold the promise to more effectively address the multifactorial basis of drug resistance and to help in identifying new molecular predictive markers. The microarray analysis of the transcriptome in advanced stage EOC samples has provided a wealth of data on differential gene expression and has identified sets of dysregulated genes potentially associated to EOC pathogenesis, progression and worse prognosis. Validation of these genes needs to be done at protein level and the importance of their differential expression has to be related to the clinical impact. Tissue microarray (TMA) technology, allowing the simultaneous analysis of hundreds of specimens on a single paraffin block, could greatly improve the reproducibility of immunohistochemistry (IHC). IHC validation of the prognostic significance of two Ig-CAMs, initially identified through the transcriptome analysis, indicated that their differential expression was significantly associated in specific subgroups of patients with poor prognosis. Present data await validation in independent case materials but since now suggest that a deeper understanding of ovarian cancer cell biology may have multiple implications and potentially could allow identification of prognostic markers.