Scientific Symposium

Screening and prevention of lung cancer

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New optical methods

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The gradual shift from central to peripheral lung cancers has left a sizeable minority of central, exfoliating lesions, whose cells can be found in sputum. Unfortunately, initial screening studies failed to show a decrease in mortality associated with chest radiographs and/or sputum cytology. Sputum cytology has however improved and additional techniques, including immuno-cytochemistry and computer-based optical imagery have been developed. Preneoplasias and early epithelial cancers are often not discernable during fiberoptic bronchoscopy because, at these early stages, changes of the mucosa are subtle. The performance of flexible bronchoscopes has continuously improved and videobronchoscopy is now widely used. The new videochip bronchoscopes may afford a better image quality allowing a more accurate evaluation of the mucosal surface, with computerized processing. The major recent progress is autofluorescence bronchoscopy (AFB) that was linked to the observation that tumorous tissue could be distinguished from normal by a loss of autofluorescence. For AFB examination, a monochromal light of 442 μm is directed at mucosa, sub-epithelial fluorophores are stimulated to emit light of longer wave lengths and these millions of emitted fluorescence signals are digitalized into a real-time video image of bronchial mucosa, through the AFB systems, allowing distinction between area showing normal and abnormal fluorescence. Biopsies of abnormal areas are performed at the end of the whole procedure. Several studies have reported that addition of AFB to conventional white-light bronchoscopy increases the detection rate of preneoplastic lesions and early cancers. These studies have also pointed out the low positive predictive value of autofluorescence bronchoscopy such that a large number of biopsies in fact show normal histological results and new systems try to solve this problem.
The cost of AFB, its invasiveness and the duration of examination prohibit its use for mass screening purposes. The best field for AFB remains exploration of patients identified on the basis of sputum. AFB technology may also be of clinical value in detecting synchronous occult cancers in patients at very high-risk including lung cancer patients with roentgenographically visible or occult lung cancers prior to their curative treatment or patients with head and neck cancers, as well as workers occupationally exposed to bronchial carcinogens. AFB may also be of use for surveillance.

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Spiral CT screening

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Based on the results of several completed and ongoing lung cancer screening trials in different parts of the world, several new position statements from professional organizations have been released in 2004 and 2005. The recommendations of the Como conference (2003) include an informed-decision making for – more specified now – high risk individuals aged above 45 or 50 years of age who are current or former smokers with at least 20 to 30 pack-years of cumulative exposure and without life-limiting co-morbidities, and not to screen for lung cancer outside clinical trials. The American Cancer Society continues to recommend that CT screening not be performed in asymptomatic at risk persons, but recognizing that many heavy smokers choose on their own to be screened, they recommend informed decision making, and performance of the CT screening test in experienced centers that are linked to multidisciplinary specialty groups for diagnosis and follow-up. In contrast, the US Preventive Services Task Force makes no recommendation for or against the use of CT screening in their latest updated recommendations, and also advice to discuss the pros and cons with the screenee. They also conclude that from the available data we can conclude that spiral CT screening can diagnose lung cancer at a significantly earlier stage than by current clinical practice. Currently, a large number of non-randomised cohort studies on lung cancer spiral CT screening trial have been completed, while several randomised trials are ongoing. In the cohort studies completed 55 to 85 percent of the cancers detected at baseline and 60–100 percent of the cancer detected at annual repeat are stage I tumors. This markedly better than the current state of practice where only 15–20% of all newly diagnosed lung cancer cases are in stage I. Since the introduction of spiral CT screening in the 1990s in Japan, the 5 year survival rate of all stages of lung cancer has improved from 48.8% to 80.4%. Although these data are very promising, they do not prove that lung cancer screening improves lung cancer survival, because it might be possible that by screening people only know their diagnosis earlier without living any longer (lead time bias). Of great interest is, however, the observation by Henschke *et al.* (2005), who found a clear relationship between tumor size and lymph node status in the ELCAP screening cohort. The percentages of cases with no lymph node metastases was 91%, 85%, 63% and 61% for tumor size categories of <15 mm, 16–25 mm, 26–35 mm, and >35 mm, respectively. These percentages are much higher than previously reported in the SEER registry, and confirms the usefulness of asymptomatic lung cancer at small sizes, and supports the hypothesis that the smaller the cancer detected, the better the prognosis is. Invasive procedure for benign lesions have been performed in 4–22% at baseline and 14–55% during incidence screening. Percentages of interval cancers vary between 0 and 33%.

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Molecular markers in lung cancer risk assessment

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A major obstacle in conducting lung cancer prevention studies is the inability to identify truly high-risk cohorts and the inability to predict the course of developing invasive lung cancer. For effective applying lung cancer prevention strategy, we have to select individuals at different risk levels and use different preventive measurements. For example, aggressive preventive strategies, including the use of agents with certain side effects, might be justified if the individuals with very high probability to develop invasive lung cancer within 3 years whereas only well tolerated agents such as natural products should be given to those at low and intermediate risk. Because most individuals at risk of developing lung cancer lack clinical symptoms or identifiable signs, molecular measurements (i.e., biomarkers), which accumulate from the beginning of tumorigenesis and are detectable with current technologies, may prove to be valuable clinical tools in assessing individuals' cancer risk. In applying molecular analysis for predicting lung cancer risk, two major factors should be taken into account, i.e. the level of exposure to tobacco carcinogens and the inherited genetic background. Inherited genetic variables, often in the form of single nucleotide polymorphism (SNP), can be used to determine individual's susceptibility to tobacco carcinogens. Although a number of SNP have been associated with lung cancer risk, the risk predicting value of these SNP are often insufficient for clinical applications. Because these genetic variables could not modulated by preventive agents, they cannot be used to assess treatment efficacy. Therefore, somatic changes contributing to lung tumorigenesis will be better predictors or markers for lung cancer risk assessment as well as intermediate endpoints of lung cancer prevention. Early genetic and epigenetic alterations, such as LOH in regions harboring critical tumor suppressor genes (e.g., 3p14, 9p21, and 17p13) and promoter hypermethylation (p16, DAP-kinase, and FHIT), have been frequently detected in bronchial epithelium of heavy smokers long before lung cancer development. The potential value of these alterations in predicting cancer development is under investigation. Other common abnormalities in tobacco-damaged airways include activation of telomerase, overexpression of tumor antigens, and expression of alternative spliced transcripts. With advances in technologies, we are in the process to develop a risk prediction model based on gene expression profiles obtained at different stages of tumorigenesis. Expression signatures may then allow us to predict lung cancer development and be used to assess efficacy of prevention.

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Early lung cancer detection biomarkers and the molecular profiling of CT screen detected lung nodules

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Decrease in lung cancer mortality will only be possible if reduction of tobacco consumption habits is achieved, and new molecular-targeted therapies and early detection techniques are developed. In my presentation I will review recent progress in the field of biomarkers for early detection of lung cancer and will summarize our work on the molecular profile of small pulmonary nodules resected from lung cancer spiral CT-based screening protocols.
A successful lung cancer screening program will require high levels of sensitivity and specificity. It is also very important to hit upon the subpopulation of individuals with higher risk to develop lung cancer in order to improve detection rates and lower cost/benefit ratios. To achieve these aims, a combination of imaging techniques with well characterized and validated molecular markers may prove very beneficial. Biomarkers may inform about genetic predisposition to lung cancer or suggest the