cancer pathogenesis and clinicopathological differences between SqCC and AC using whole genome tiling path array comparative genomic hybridization (array-CGH). Identifying and characterizing these novel genetic changes will allow development of novel therapeutic strategies for clinical application.

**Methods:** A whole genome tiling path array-CGH was used to analyze gene expression profiles of 103 AC and 58 SqCC tumors. This method allows the detection of small segmental alterations such as micro-amplifications and focal deletions which may have been undetected by conventional cytogenetic methods. Array data was visualized using SeeGH software and subjected to a smoothing computational algorithm to determine chromosomal areas of gain and loss. The resulting frequencies of alteration for each locus were compared between AC and SqCC cancers using Fisher’s Exact Test and regions with difference of p<0.001 were considered statistically significant. This genomic data was then integrated with genome-wide expression data to identify genes deregulated as a result of copy number alterations specific to each NSCLC subtype.

**Results:** Subtype-specific copy number changes were identified. Regions of alteration disparity were mapped to chromosomes arms 2p, 3q, 4p, 4q, 8p, 12p, 19p, 19q, 20p, and 22q. Analysis of expression data for the genes in these regions identified 183 unique genes differentially expressed between the subtypes as a result of copy number changes. Clustering and principle component analysis confirmed that these gene signatures were able to accurately delineate the disease subtypes. Grouping of these genes by biological function showed that many important pathways are differentially altered in AC and SqCC in disease specific ways.

**Conclusions:** Whole genome array CGH comparison between AC and SqCC tumor genomes identified tumor subtype-specific genetic alterations. Integration of gene expression data delineated genes and pathways that could be important in phenotype differentiation. Characterization of these genes is now underway with the aim of defining new molecular targets for early diagnosis and treatment.
hybridised against female human genomic DNA to a high resolution array-Comparative Genomic Hybridisation (aCGH) platform containing ~43,000 probes (Agilent 44K Human Whole-Genome 44B arrays). Genomic regions with significant copy-number variation (CNV) (DNA gain/loss) were identified using an aberration detection algorithm (CGH Analytics V3.4).

**Results:** The most frequent CNVs in current smokers were gain of 1q21.1-q24.2 and 5p15.33-p12 (>60% of tumours) and loss of 8p23.3-p12 and 13q12.11-q34 (>20% of tumours). The most frequent CNVs in former smokers were gain at 1q25.2-q44 and 17q11.2-q25.3 (>50% of tumours) and loss at 13q12.11-q21.2 and 21q11.2-q22.3 (>20% of tumours). The most frequent CNVs in never smokers were gain at 7p22.1-p11.2 (50% of tumours) and loss at 8p23.3-p11.22 and 13q13.3-q14.3 (>50% of tumours). CNVs present in both current and former smokers were compared to identify recurrent (occurring in >30% of tumours, both smokers and former smokers) genomic aberrations. Frequent copy-number gain was observed at 1q21.1-q31.3, 1q31.1-q44, 3q26.1-q29, 5p15.33-p12, 7p22.1-p11.2, 7p11.1-q36.2, and 17q12.2-q25.3. Gain at 1q25.2-q31.3 occurred in more than 50% of current and former smokers, yet was rarely gained in never-smokers (8%).

**Conclusions:** In the chaos that occurs in lung cancer cells that develop in current and former smokers (with continued carcinogenic exposure and therefore high lung cancer risk), those aberrations in common with lung cancer cells that develop in former smokers (with no further carcinogenic exposure and therefore lower but persistent lung cancer risk) may represent irreversible causative genetic damage. Genes located in these aberrations represent strong chemoprevention targets. Our analysis has identified several loci frequently aberrant in both current and former smokers. These loci are now being further studied to identify the potential gene targets of aberration.

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**Session A7: Prevention & Early Detection**

**Monday, September 3**

A7-01

**Prevention & Early Detection, Mon, 13:45 - 15:30**

**The Danish randomized lung cancer CT screening trial. Results at baseline**

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**Objective:** The Danish lung cancer screening trial is a randomized trial comparing CT screening with no screening. The trial is done with the NELSON trial in the Netherlands, Europe. The final end point is lung cancer mortality.

**Methods:** From 2004 to 2006 4104 Danish smokers and previous smokers were randomized to either screening with annual low dose CT scans for 5 years or no screening. A history of cigarette smoking of at least 20 pack years was required. All had lung function tests, and questionnaires regarding psychosocial consequences of screening, smoking and smoking cessation at randomization and planned annually. All scans are performed with a 16 detector row CT scanner at low dose levels, and viewed independently by two board certified radiologists. Nodules identified in the baseline year were considered prevalence nodules.

Nodules were classified according to size and other characteristic:

- Nodules smaller than 5 mm and calcified nodules with a maximal diameter up to 20 mm were just tabulated.
- Uncalcified nodules with a diameter between 5 and 15 mm were re-scanned after 3 months; 1) if the size was stable or reduced no further action was taken. 2) If the nodule grew it was referred for invasive workup, as were uncalcified nodules larger than 15 mm.
- CT with contrast and PET CT was performed before any invasive procedures.

**Results:** At baseline 177 persons had nodules larger than 5 mm on the first scan, and almost all were rescanned after 3 months.

- Seventeen individuals (0.8%) with a suspicious lung nodule were referred to surgical exploration and all turned out to have cancer. One stage IA patient had segmental resection (adenocarcinoma (ACL) dominated by BAC features), ten patients (6 stage IA, 3 stage IB and 1 stage IIIB) had lobectomy (9 ACL and 1 squamous cell carcinoma (SQC), one stage IIIA had pneumonectomy (ACL)). The remaining five patients were in stage IIIB after diagnostic evaluation and received chemotherapy (3 non small cell lung cancer (NSCLC), probably ACL, 1 ACL, 1 SQC).
- Seventy one percent had ACL, 12% SQC and 17% NSCLC. No SCLC was diagnosed.
- Twelve of 17 lung cancers at base line were treated surgically, 8 of these were treated by VATS resection.
- One participant had a benign hamartoma (4 cm) removed by VATS local resection and one had a diagnostic VATS on suspicion of mesothelioma which turned out to be pleural tuberculosis.
- Rate of false positive diagnoses was 8.6 %.
- In the control group so far one patient had a lobectomy (ACL) stage 1, one had a pneumonectomy for a stage IIIA lung cancer, two had oncological treatment for stage 4 disease (ACL) and one patient died with lung cancer stage IIIB (ACL).

**Conclusion:** Screening facilitates minimal invasive treatment and can be performed with a low rate of false positive diagnoses.

A7-02

**Prevention & Early Detection, Mon, 13:45 - 15:30**

**Identification of polymorphisms in the Caspase-3 gene and their association with lung cancer risk**

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