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**Title:** Inducible nitric oxide synthase as a predictor for progression to lung cancer in patients with bronchial squamous dysplasia, a per patient analysis

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**Body:** Background: This study addressed the immunohistochemical (IHC) expression of iNOS, as a predictor for progression of bronchial Squamous Dysplasia (SD) to lung cancer(LC). Methods: A total of 114 patients (111 men and 3 women) with at least 1 bronchial SD, at least 1 follow-up evaluation and normal baseline chest computed tomography (CT) were evaluated. Median age was 68 years (range,44–84 yr) and median follow-up duration was 21 months (range,4-98 months). Follow-up included periodic white light and autofluorescence bronchoscopy and chest CT. Expression of iNOS (inducible nitric oxide synthase) in bronchial epithelium biopsy specimens was evaluated by immunohistochemistry (IHC).Diagnosis of carcinoma in situ (CIS) and/or LC were follow-up endpoints. Results: On follow-up CIS or LC were detected in 16% of patients. Progression to CIS or LC occurred more frequently in patients with, positive iNOS ( $p<0.001$ ) IHC expression, COPD ( $p=0.012$ ), positive and baseline high grade SD ( $p=0.035$ ). Multivariate analysis showed that risk for progression was closely related to iNOS expression (RR=10.521; 95% CI=2.75-40.3;  $p=0.001$ ) and airflow obstruction (RR=0.959;95% CI=0.923-0.997;  $p=0.044$ ).The positive and negative predictive values iNOS were 48% and 95%,respectively. Conclusion: In patients with bronchial SD, iNOS IHC expression and airflow limitation are independent risk factor for progression to CIS or LC. This study supports the hypothesis that inflammation and oxidative stress promote lung carcinogenesis.