COPD – A COMMON COMORBIDITY IN LUNG CANCER
COPD - LUNG CANCER

Two of the greatest challenges in pulmonary medicine
COPD is independently and closely related to Lung Cancer


COPD - LUNG CANCER

- **Lung cancer** is the **number one cause of death from cancer worldwide**

- Approximately **85% of lung cancer** occurs in current or former smokers

- Lung cancers **frequently occur** in patients with COPD

COPD - LUNG CANCER

- The risk of lung cancer increases with age and amount of smoke exposure

- Cigarette smoke is the common aetiological factor for both lung cancer and COPD

- Smoking accounts for an estimated 80–90% of the risk of developing COPD

Several studies have shown that airway obstruction is associated with increased risk of lung cancer independent of smoking!

Risk of lung cancer among COPD patients

- Previously: 2-fold increased risk associated with COPD

COPD - LUNG CANCER
Both diseases result from shared pathogenic mechanisms
Both diseases result from shared pathogenic mechanisms

- Smoking-related diseases
- Genetically-determined diseases
- Cluster in families
- Worsen with age
Mortality studies of patients with COPD suggest 20–30% die from lung cancer.

The most important underlying 
*Risk factor* 
for 
Lung Cancer 
is 
*COPD* 
greater 
than that attributed to 
smoking dose or age !
SUMMARY

- Pathogenic mechanisms
- Genetics
- Smoking
- Airflow obstruction
- Endoscopy-COPD-lung cancer
- Conclusions
1. Pathogenic mechanisms
COPD and Risk of Lung Cancer in Population

- Every year, over 1 million people die from lung cancer worldwide

- Cigarette smoking is the primary etiologic agent in 85–90% of all lung cancers

COPD and Risk of Lung Cancer in Population

- Only 10–15% of active smokers develop lung cancer !!

- Lung cancer is the 7th most common cause of cancer death worldwide in never smokers !!

Pathogenic mechanisms

COPD

Exacerbations-Pulmonary infections

Inflammation

Lung carcinogenesis

Carcinogenesis in general

Lung carcinogenesis
Carcinogenesis in general

- reactive **oxygen or nitrogen species**

- increase **cellular proliferation**

- upregulating **antiapoptotic pathways**

- stimulating **angiogenesis**

- Infections -**airway remodelling**-enhance **carcinogenesis**

Shared pathogenic mechanisms

- Occupational toxins
- Community air pollution

→ Accumulated and damaging mutations
→ Inflame and destroy airways alveoli
→ Dysplastic and ultimately neoplastic changes

**Shared pathogenic mechanisms**

- **Chronic inflammation** → role in the pathogenesis of lung cancer as a **tumour promoter**.


- Some **cytokines** (IL-6, IL-8, IL-10): can inhibit apoptosis, interfere with cellular repair and promote angiogenesis.

O’Byrne KJ, Dalgleish AG. Chronic immune activation and inflammation as the cause of malignancy. Br J Cancer 2001;85: 473–483
Shared pathogenic mechanisms

- These **cytokines** have also been implicated in **COPD progression**.

- Activation of nuclear (NF)-kB **transcription factor** may have **major relevance for cancer and COPD**.

Shared pathogenic mechanisms

- **COPD** patients have **impaired mucociliary clearance**.


- **Reduced mucociliary clearance from the lungs** may **increase risk cancer**?

2. Genetics
Genetically-determined diseases

- **A shared genetic susceptibility** to *chronic smoking-induced inflammation*.


- **Genetic variant** in the \( \alpha_5 \) subunit of the nicotinic acetylcholine receptor gene.


Genetically-determined diseases

- **Functional significance and susceptibility** to COPD and to lung cancer.


- **Susceptibility through overlapping pathogenic pathways**, such as those underlying smoking-induced inflammation

3. Smoking
Smoking-related diseases

- Smoking exposure is found in **85–90%** of those diagnosed with either **COPD** or **lung cancer**
Smoking - Lung Cancer

- Only 10–15% of chronic smokers get lung cancer!
  

- **Host susceptibility factors** have been implicated

- **Key risk factors:** age, smoking history, family history and impaired lung function
  
COPD – LUNG CANCER
MORE THAN A SHARED SMOKING HISTORY?
COPD – LUNG CANCER

MORE THAN A SHARED SMOKING HISTORY?

Yes!
Risk of lung cancer among COPD patients

- Six-fold higher

R.P. Young, R.J. Hopkins, T. Christmas, P.N. Black, P. Metcalf, G.D. Gamble, COPD prevalence is increased in lung cancer, independent of age, sex and smoking history, Eur Respir J 2009; 34: 380-386

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unmatched cohorts</th>
<th>Matched cohorts</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects n</td>
<td>control smokers</td>
<td>lung cancer</td>
<td>control smokers</td>
</tr>
<tr>
<td>654</td>
<td>445</td>
<td>301</td>
<td>301</td>
</tr>
<tr>
<td>Males %</td>
<td>57</td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td>Age yrs</td>
<td>66±9</td>
<td>65±10</td>
<td>66±9</td>
</tr>
<tr>
<td>Height cm</td>
<td>168±0.08</td>
<td>168±0.08</td>
<td>168±0.08</td>
</tr>
<tr>
<td>Weight kg</td>
<td>80±16</td>
<td>80±15</td>
<td>78±15</td>
</tr>
<tr>
<td>Smoking History</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age started smoking yrs</td>
<td>17±4</td>
<td>17±4</td>
<td>16±4</td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>20±7</td>
<td>20±7</td>
<td>19±7</td>
</tr>
<tr>
<td>Current smokers %</td>
<td>34</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td>Pack-ys</td>
<td>39±18</td>
<td>38±18</td>
<td>38±18</td>
</tr>
<tr>
<td>Lung Function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁: L</td>
<td>1.86±0.62</td>
<td>1.86±0.60</td>
<td>1.86±0.62</td>
</tr>
<tr>
<td>FEV₁: FVC %</td>
<td>87±16</td>
<td>78±23</td>
<td>96±23</td>
</tr>
<tr>
<td>History of comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>5</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Asthma</td>
<td>12</td>
<td>12</td>
<td>11</td>
</tr>
</tbody>
</table>

Data are presented as mean±s.e., unless otherwise stated. FEV₁: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease. *p-value for matched cohorts only.
COPD – LUNG CANCER

- Smoking-induced airway inflammation typically persists in those smokers with COPD for many years after quitting smoking.
  

- 50% of lung cancer cases are found in ex-smokers


COPD and squamous cell carcinoma

- Squamous cell carcinoma has a stronger association with **tobacco smoking** than other non-small cell lung cancers (NSCLC).

- **COPD** is a risk factor for the **squamous cell carcinoma** histological subtype in **smokers with surgically resectable** NSCLC.

- **Chronic bronchitis** is a risk factor for the **adenocarcinoma** histological subtype.

Bronchoscopies - “Marius Nasta” Institute
1999-2000-2001
8856 cases - lung cancer

1417 non-smokers

7439 smokers

16%

smokers ≥ 10 p/years

R Ulmeanu, CT- bronchoscopy corel. in lung cancer, 2006
7792 cases - lung cancer
"MARIUS NASTA“ Institute

R Ulmeanu, CT- bronchoscopy corel. in lung cancer, 2006
Lung Cancer - 7792 patients

SMOKERS ≥ 10 pack/ yrs

AGE OVER 45 YEARS

PRESENCE OF RESPIRATORY SIMPTOMATOLOGY

R Ulmeanu, CT - bronchoscopy corel. in lung cancer, 2006
7792 patients

MAJOR RISK - LUNG CANCER

INOPERABLE STAGE - MOMENT OF DIAGNOSIS

“BIG” SMOKERS $\geq 40$ pack/ yrs
4. Airflow obstruction
> 50% of lung cancer cases have coexisting moderate-to-severe COPD

A disproportionate number of lung cancer cases occur in smokers with pre-existing COPD compared with those with normal (or near normal) lung function!

An inverse correlation between the degree of airflow obstruction and lung cancer risk

Lung function and COPD prevalence according to stage and histology

- No relationship-stage

- Prevalence slightly higher in squamous cell lung cancers and small cell

The airflow obstruction

- Moderate or severe airflow obstruction: **significant predictor** of incident lung cancer.


- Lung cancer may itself cause an obstructive effect on spirometry.
The airflow obstruction

- Impaired lung function is more important than age or smoking exposure (pack-yrs)!

- Even in nonsmokers, impaired lung function is associated with an increased risk of lung cancer!


Emphysema - Lung cancer

- Emphysema (30–40% of long-term smokers) related to lung cancer independently of sex, age, smoking habits and airflow obstruction.


Emphysema - Lung cancer

- Asymptomatic lung cancers in 2–5% of patients with severe emphysema evaluated CT for lung volume reduction surgery.


- Lung cancer patients are significantly more likely to carry the mutated a1-antitrypsin allele than the general population.

Emphysema - Lung cancer

- Bronchoalveolar stem cells (BASC) proliferate to replace damaged alveolar cells

A. Bourdin, P.-R. Burgel, P. Chanez, G. Garcia, T. Perez, N. Rochee, Recent advances in COPD: pathophysiology, respiratory physiology and clinical aspects, including comorbidities, Eur Respir Rev 2009; 18: 114, 198–212

- Abnormal BASC proliferation due to carcinogens present in cigarette smoke may result in lung cancer.

5. Endoscopy-COPD-lung cancer
Endoscopy-COPD-lung cancer

a. Detection of precancerous bronchial lesions

b. Palliate inoperable lung cancer
Advances in endoscopic technology

-improved the detection of precancerous bronchial lesions

-associated with the occurrence of proximal squamous cell lung cancer (SCC) in high-risk individuals

Distribution and Outcome of Preneoplastic Lesions in Bronchial Epithelium

Various risk factors such as:

- smoking history
- past history of cancer
- chronic obstructive pulmonary disease.

5. Kunst P, With blue light into the depth, Annual Congress of ERS, Vienna 2009,
Early proximal lung cancer
Algorithm – Diagnosis and treatment

Fluorescence bronchoscopy (FUB)

Mild dysplasia

Moderate dysplasia

Severe dysplasia

Carcinoma in situ

FU 1 Year

FU 6 months

FU 3 months

treatment

No dysplasia

Mild dysplasia

FU 1 year

Moderate dysplasia

FU 6 months

Severe dysplasia:
Stabilisation/
progression

Endoscopy-COPD-lung cancer

a. Detection of precancerous bronchial lesions

b. Palliate inoperable lung cancer
LUNG CANCER

INITIAL DIAGNOSIS

75% INOPERABLE

LUNG CANCER

75% CASES

SIGNIFICANT NEED

TREATMENT OPTIONS

TO PALLIATE THIS SYMPTOMS

Lung cancer

OBSTRUCTION > 50% OF NORMAL LUMEN

compulsory association

ENDOSCOPY

CHIMIOThERAPY

RADIOThERAPY
COPD

Exacerbations-Pulmonary infections

Inflammation

Lung carcinogenesis

Carcinogenesis in general
6. CONCLUSIONS
COPD (or airflow limitation) closely associated with lung cancer, independent of smoking exposure dose and age

The magnitude of the association is much greater than generally appreciated
40–70% of lung cancer cases have coexisting COPD.

The risk of lung cancer among those with COPD may be closer to six-fold higher, much greater than the estimated two-fold increased risk previously associated with COPD.

The routine use of spirometry in smokers.

Identify those with COPD.


● Identify those with potential clinical benefits in smoking cessation


● Early diagnostic work-up for lung cancer, targeted bronchoscopy, CT screening

Future challenges

- Explaining the similarities between COPD and lung cancer, possibly at a genetic and molecular level.

- Design and conduct of clinical trials to improve the outcome of both diseases.

- The chromosome 15q25 locus: an important role in COPD

*Thomas L. Petty, Are COPD and Lung Cancer Two Manifestations of the Same Disease? Chest 2005;128;1895-1897*

A disproportionate number of lung cancer cases - from patients with pre-existing COPD

1 in 16 smokers with “normal” lung function get lung cancer

1 in 4 patients with COPD get lung cancer

Future challenges

- A new target for novel treatments