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Is there a relationship between the presence of lung mucosa preinvasive lesions and lung cancer incidence? Influence of tobacco consumption

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ABSTRACT

Although studied for years, the nature of the relationships between tobacco consumption, bronchial preinvasive lesions and lung cancer are still not completely elucidated. Objectives were to determine the relationship between tobacco consumption and lung mucosa preinvasive and invasive lesions and to describe patients' evolution according to baseline characteristics.

Methods: Bronchial biopsy specimens were taken at six predetermined sites in 156 males, current smokers, aged above 18 years. Relationships between smoking characteristics and preinvasive lesions indexes and between baseline characteristics and lung cancer occurrence during a prospective follow-up were examined.

Results: Maximum grade was hyperplasia for 16.7% of patients, metaplasia 33.3%, dysplasia 25.0%, and carcinoma in situ 1.3%. For 23.7% of patients, all biopsies were considered normal. Preinvasive lesion indexes were related to smoking intensity (cigarettes/day). Lung cancer incidence during the follow-up was 19.9%. No association between severity of mucosa lesions at baseline and incidence of cancer during the follow-up period was observed.

Conclusion: The majority of smokers had mucosa lesions, but a relatively small number of them would have a cancer, and there was a poor correlation between severity of mucosalesions and incidence of cancer. Even if an evolution from preinvasive lesions to an invasive cancer is plausible and coherent with current concepts, this link does not appear strong enough to recommend the use of systematic classic endoscopy for targeting of a sub-group of higher risk smokers who would require a closer follow up.

1. Introduction

Tobacco smoking is the main risk factor of lung cancer: almost 90% of lung cancer incidence and mortality are attributable to cigarette smoking [1]. Smokers develop progressive histological changes of their bronchial epithelium, described for more than 30 years [2,3]. These morphologic and genetic alterations of the bronchial epithelium may follow a sequential progression from a normal epithelium, to hyperplasia, metaplasia, mild, moderate and severe dysplasia, carcinoma in situ (CIS), and eventually invasive cancer [3]. In fact, the natural evolution of epithelium alterations seems to be more complex: based on the *field cancerization* concept, the entire bronchial mucosa would be damaged in patients exposed to tobacco, with the coexistence of multiple lesions at various stages [4,5]. Experimental and clinical studies showed that most of these lesions are able to spontaneously regress, and only a small number of them will progress to an invasive cancer, even in case of CIS [6–10]. Moreover, a cancer does not occur only in a preexistent known high grade lesion, but could occur randomly in the damaged mucosa [11].

Although studied for years, the nature of relationships between tobacco consumption and preinvasive and invasive lesions with clinical cancer are not still completely elucidated. Do smoking

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duration and intensity have the same impact on the genesis of both types of lesions? In fact, few have prospectively studied the influence of tobacco smoking on both preinvasive mucosa alterations and cancerization (clinical cancer) in the same patients [9].

We hypothesized that a clinical study, including high risk patients without lung cancer diagnosis at inclusion, with systematic biopsies at predetermined sites on the bronchial tree, and a long-term follow-up, would help clarifying these concepts. This study had two objectives: to determine the nature of the relationship between tobacco consumption and both types of lesions (preinvasive vs. lung cancer) and to describe the evolution of these patients according to baseline mucosa characteristics.

2. Methods

2.1. Patients

One hundred fifty six patients were prospectively entered into this study from 1996 to 2001. Inclusion criteria were: male aged above 18 years, current cigarette smoker, with an endoscopy indication (i.e. patient with history of laryngeal or esophageal cancer, or a minimum smoking history of 10 packs-year). Exclusion criteria were: endoscopy contraindication (e.g. clotting disorders contraindicating biopsies), professional cancer factor exposition, known lung cancer. All patients gave their consent to the study. The study protocol was approved by the local ethic committee (CCPPRB de Lorraine).

2.2. Endoscopy

All patients underwent bronchofiberscopy under local anesthesia (hydroxyzine 50 mg, one hour before investigation, and local application of lidocaine solution) according to ERS recommendations [12].

Biopsy specimens were taken at six predetermined sites in the bronchial tree: carina of the trachea, bifurcation of right upper lobe/right main bronchi, bifurcation of middle lobe/right lower lobe bronchi, bifurcation of right lower lobe/segments bronchi, bifurcation of left upper lobe/lingular lobe bronchi, bifurcation of left upper lobe/left lower lobe bronchi.

Usual biopsy mean size was 3 mm^2 with 1.5 mm thickness. All biopsies were paraffin-embedded and stained with hematoxylin and eosin.

2.3. Histological evaluation

Bronchial biopsy specimens were reviewed conjointly by two trained pathologists according to 2004 WHO criteria for preinvasive bronchial lesions [13]. Biopsies were classified according to microscopical characterisrics, as follow: 1 = normal or inflammatory, 2 = hyperplasia, 3 = metaplasia, 4 = dysplasia (mild, moderate, and severe), 5 = carcinoma in situ. Basal cell hyperplasia is the most common type of hyperplasia. It diagnosis requires, at least, a three layer thickness. The D index was calculated as the proportion of biopsies exhibiting "normal or inflammatory", "hyperplasia", "metaplasia", "mild dysplasia" among the total number of biopsies examined for one given patient, and MD index was calculated as the proportion of biopsies exhibiting, "moderate, and severe dysplasia" and "CIS" among the total number of biopsies examined for one given patient. Inflammation, a very common finding in smokers' mucosa, was present in almost all biopsies, including "normal" ones.

Table 1
Tobacco consumption characteristics of the 156 included men.

Variable	Mean	Standard-deviation	Minimum	Maximum
Pack-years*	45.7	24.3	9	150
Age of initiation (years)	17.0	4.1	7	36
Duration of smoking (years)	37.9	11.6	9	61
Smoking intensity (pack/day)	1.2	0.5	0.22	3

* Twenty cigarettes/pack.
One patient had smoked for 9 years and 11 months.

2.4. Data collection

The following data concerning tobacco use were recorded or calculated by the physician before endoscopy: age at initiation, duration of smoking (years), mean number of cigarettes smoked per day the year preceding endoscopy (defined as "smoking intensity"), and number of pack-year.

Patients were followed-up from the date of the biopsy to the date of an event or the end of the observation period on 31 December 2010. Mean follow-up duration was 5 years. During follow-up, deaths, causes of death, cancer occurrence, were recorded from hospital and practitioners.

2.5. Statistical analysis

Analysis consisted of (1) a description of population baseline characteristics (values was expressed as mean ± sd or percentage), (2) a study of relationship between smoking characteristics and grades indexes using nonparametric methods (i.e. Kruskal–Wallis test, and Spearman correlation coefficients), (3) a study of relationship between baseline characteristics (i.e. grades indexes and smoking characteristics) and lung cancer occurrence (using univariate Wilcoxon test, age adjusted non parametric ANOVA, and Chi-square test).

3. Results

3.1. Baselines characteristics

One hundred and fifty-six men, mean age 53 ± 11 years, were included. All were current smokers at inclusion, with a mean pack-year of 45.7 (Table 1). Reasons why they underwent endoscopy were: head or neck cancer 18%, lung cancer suspicion 21%, high-risk patients 42%, other and non specified reasons 19%.

Globally, 767 biopsies (5.5/patient) were evaluated (range: 4 to 6). For less than a quarter of patients (23.7%), all biopsies were considered normal; the maximum grade was hyperplasia for 16.7% of patients, metaplasia 33.3%, dysplasia 25.0%, and CIS 1.3% (2 patients). Globally, as emphasized by D and MD indexes, 7.6% biopsies revealed a dysplasia and/or a CIS, and 22.2% a metaplasia, a dysplasia and/or a CIS (Table 2).

In reason of sub-group sizes, and in accordance with pathophysiological concepts, we defined 3 groups for following analyses: "normal and hyperplasia", "metaplasia", and "dysplasia and CIS".

3.2. Relationship between smoking characteristics and grade indexes

There was no significant relationship between baseline grade indexes and lung cancer occurrence: 19 cases (16.5%) occurred among normal/hyperplasia/metaplasia group and 8 cases (19.5%) among dysplasia and CIS group ($p = 0.66$) (Table 3).