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Epidemiology, Etiology, and Prevention of Lung Cancer

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Abstract:
Bronchopulmonary cancers are common cancers with a poor prognosis. It is the leading cause of death by cancer in Algeria and in the world. Behind this unfavorable prognosis hides numerous disparities according to age, sex, and exposure to risk factors, ranking 4th among incident cancers and developing countries including Algeria, all sexes combined. It ranks 2nd cancers in men and 3rd among women. Whatever the age observed, the incidence of this cancer is higher in men than in women, however the gap is narrowing to the detriment of the latter. The results of scientific research agree to relate trends in incidence and mortality rates to tobacco consumption, including passive smoking. Furthermore, other risk factors are mentioned such as exposure to asbestos in the workplace or to radon for the general population, or even genetic predisposition. However, the weight of these etiological and/or predisposing factors is in no way comparable to that of tobacco in the genesis of lung cancer and the resulting mortality.
We provide a literature review in our article on the descriptive and analytical epidemiology of lung cancer.

Keywords: Lung Cancer, Incidence, Mortality, Risk Factors

1. Introduction

Before the 1920s, cases of lung cancer were rare. Over the next two decades, an increasing incidence was observed, although this was attributed to improved diagnosis and some related factors. Incidence and mortality increased rapidly. There was an age factor, as people aged 60 were 100 times more likely to be diagnosed with lung cancer than those aged 40, and a sex factor, as men were 7 times more likely that women receive this diagnosis. In the 1960s, the incidence among men peaked and then began to decline, while among women the rate continued to increase. By 1983, the male-to-female ratio had decreased to 2.8 **[1].**

In the 1950s, systematic records of tobacco use among patients with multiple illnesses began to be recorded. It was then recognized that non-smokers did not contract lung cancer. It was realized that the link between tobacco use and cancer could only be demonstrated by large-scale prospective studies which would make it possible to establish histories of tobacco use in apparently healthy people, for whom we could ensure the followed over several years. The weakness of these studies was the lack of reliability of self-assessments of smoking habits. The first study to establish a cause and effect link between cancer and tobacco use was therefore carried out among doctors, who were considered more reliable than the general

population in this regard. 40,000 British doctors, recruited for the study by Richard Doll and Austin Bradford Hill in the 1950s, were monitored for the next 25 years **[2].** Since these doctors were closely monitored, their smoking history was more reliable than certain other studies, and the effects of changes in smoking habits could therefore be studied.

2. Worldwide incidence of lung cancer:

Lung cancer has been the most common type of cancer worldwide since 1985 **[1].** In 2002, there were 1.35 million new cases, or 12.4% of new cases of cancer. It was also the leading cause of cancer deaths with 1.18 million deaths, or 17.6% of cancer deaths worldwide. Lung cancer is the leading cancer in men in terms of incidence and mortality, in women its incidence comes in 3rd place after breast cancer and colorectal cancer, it comes in second place after breast cancer in terms of mortality **[3].**

In 2012, the number of new cases was estimated at 1.82 million including 1.24 million men and 0.58 million women, mortality was 1.59 million people. Lung cancer represents 13% of all cancer cases that were diagnosed in 2012, and represents a percentage of 19.4% of cancer-related mortality.

In 2018, new cases worldwide were estimated at 46,363 (31,231 men and 15,132 women), the change in the incidence rate between 1990 and 2018 is -0.3% per year on average among men (2010-2018) and + 5.3% per year on average for women

Throughout the world, it is by far the most common cancer in men with the highest rates observed in North America and Europe (in Eastern Europe in particular). Moderately high rates are also observed in Australia/New Zealand and East Asia (China and Japan). The highest rates are found in North America and Europe. China also has a relatively high incidence **[2,3,4]** .

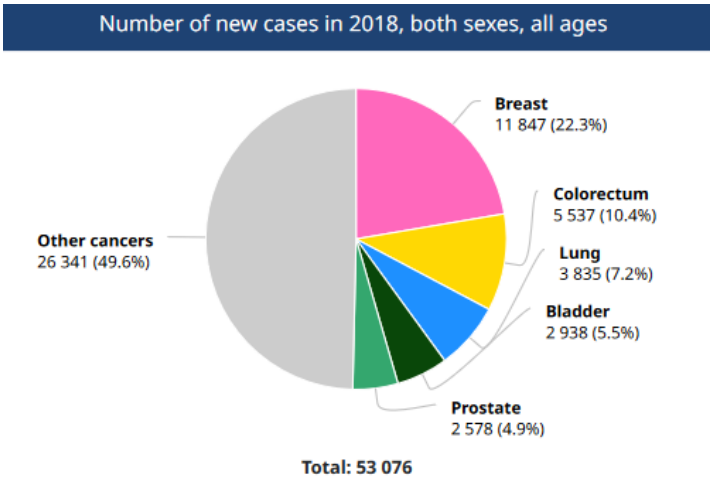

Figure 1: Global lung cancer incidence 2018 (Globocan 2018)

1. Lung cancer in women

Lung cancer ranks 4th among incident cancers, all sexes combined. It ranks 2nd among cancers in men and 3rd among women. Whatever the age observed, the incidence of this cancer is higher in men than in women, however the gap is narrowing to the detriment of the latter. The evolution of cases of this cancer in the female population raises questions. Indeed, while the incidence of lung cancer is generally stable, or even decreasing, in men (**Figure 2**) and mortality is decreasing, this is not the case in women. On the contrary: female incidence and mortality rates have increased sharply since 1990. **(Figure 3)[5]**

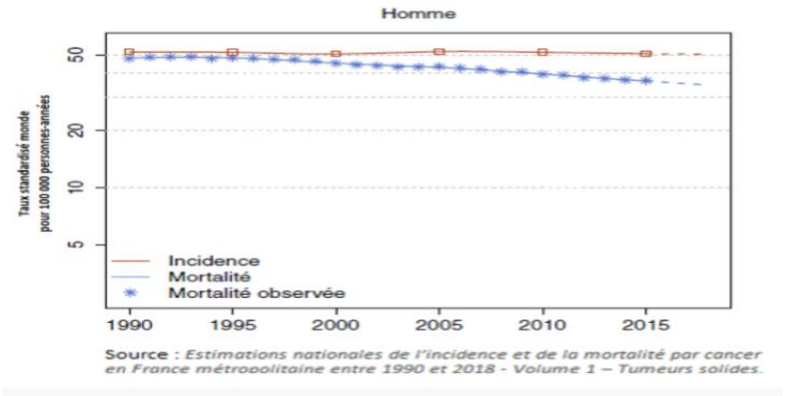

Figure 2: incidence curve of lung cancer in men (Europe 2015) (Inca 2015)

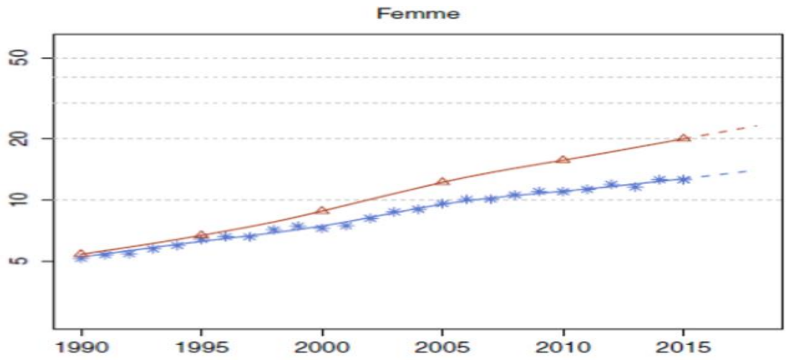

Figure 3: incidence curve of lung cancer in women (Europe, Inca 2015)

In the United States and Europe, mortality linked to lung cancer has been decreasing in men for almost ten years while it is constantly increasing in women.

Between 1990 and 2006, the mortality rate from lung cancer among men decreased by 25% while at the same time lung cancer mortality among women increased by almost 7%. At the same time, overall cancer-related mortality has decreased by nearly 12% in the female population.

These changes in the mortality rate are mainly linked to epidemiological characteristics and primarily tobacco consumption. There is a very good correlation between the reduction in smoking in men, the reduction in incidence and then mortality from lung cancer and also a correlation between the increase in tobacco consumption among women and the increase number of lung cancers and deaths. Improvements in lung cancer treatments have significantly prolonged progression-free survival (PFS) as well as overall survival (OS) at 12 or 24 months, but with a very modest impact on long-term survival. Indeed, American statistics show that five-year survival for lung cancer increased from 13% in 1975 to 16% in 2000 **. [6]**

2. Age distribution :

In Western countries, where the prevalence of bronchopulmonary cancer is high, age is a major determinant of the risk of developing this type of cancer. Its incidence is thus multiplied by 90 in men and by 30 in women when we compare the ages of 35 and 75 years. The aging of the population alone does not explain the increase in the incidence of lung cancer in Europe, since we also observe an increase in the number of premature deaths, occurring before the age of 65. The age of onset of bronchial cancers varies in Europe from one country to another, mainly resulting from the smoking habits of populations **(Table I**). The analysis of incidences in age groups under 45 years, between 45 and 65 years and over 70 years, shows that in the next 20 years, Greece, Spain, France and Belgium will have the highest incidence

of bronchial cancer in Europe. Conversely, as is already the case in the United States, the incidence should decrease in men in the countries of Northern Europe, and in the United Kingdom, but continue to increase in women. **[7].**

Table I: distribution of lung cancer by age in Europe (Inca 2015) [8]

< 44 ans		45-69 ans		> 70ans	
Pays	Taux	Pays	Taux	Pays	Taux
Hommes					
Grèce	4,1	Belgique	214	Pays-Bas	722
Espagne	4,0	Pays-Bas	201	Royaume-Uni	664
France	3,3	Italie	201	Belgique	645
Belgique	3,0	Luxembourg	198	Irlande	513
Luxembourg	2,7	Grèce	166	Luxembourg	513
Autriche	2,5	Royaume-Uni	161	Finlande	510
Italie	2,5	France	157	Danemark	450
Union européenne	*2,5*	*Union européenne*	*164*	*Union européenne*	*447*
Femmes					
Pays-Bas	1,4	Danemark	87	Royaume-Uni	182
Danemark	1,4	Royaume-Uni	70	Irlande	176
Autriche	1,3	Irlande	58	Danemark	129
Luxembourg	1,	Pays-Bas	44	Autriche	91
Royaume-Uni	1,0	Suède	34	*Union européenne*	*76*
Belgique	1,0	Autriche	31	Luxembourg	65
Grèce	1,0	*Union européenne*	*30*	Suède	63
Allemagne	0,9	Luxembourg	28	Finlande	63
Suède	0,9	Belgique	25	Italie	60
Union européenne	*0,9*	Allemagne	25	Allemagne	59

3. Geographic distribution:

Nearly 60% of incident cases of bronchopulmonary cancer occur in industrialized countries. It therefore occupies first place in terms of prevalence and mortality in humans in Europe, North America, the Caribbean, South America, Australia, New Zealand and South-East Asia. Worldwide, the highest incidence is found among the black male population of Louisiana (110/100,000 inhabitants). It is 62/100,000 among white Americans and on average 52/100,000 in Europe. Conversely, this incidence remains low in rural India (1.5/100,000 inhabitants), in East and West Africa (5/100,000 inhabitants)**. [9]** In men, the highest incidence is found in Belgium (75.2/100,000 inhabitants). These regional variations are essentially significant in men, suggesting the associated role of risk factors of occupational and industrial origin. , while the variations noted among women parallel the size of urban areas, probably linked to smoking **[10]**

In Algeria,

30,000 new cases of cancer are diagnosed each year, with a 50% increase in the number of people affected between 1986 and 2000 (ANDS, 2003). That is, 3,399 new cases of cancer were recorded during the year 2003 in the Center region (except the region of Bejaïa and Blida), with a sex ratio equal to 0.92 **(Hammouda et al, 2003**). [11] These latter figures are unfortunately increased each year with less and less support.

Lung cancer occupies first place in men, it represents 15% of male cancers followed by colorectal and bladder cancer. While in women, breast cancer ranks first, followed by colorectal, cervical and thyroid cancer (Hammouda **et al, 2003**). **[11]** Statistical data provided by the cancer registry concerning the Sétif region estimate that bronchopulmonary cancer represents 18% of cancers. It comes in first position with a standardized incidence rate (compared to the world population) of 15.5/100,000 inhabitants **(Hamdi Cherif et al, 1991).** More recent data **(2015)** provided in the cancer registry of the Wilaya of Oran, indicate that the standardized incidence of cancer is 105.4 **/100,000** in males and **111.5/100 000** among females. **[12]**

A rigorous classification of the cancers most frequently recorded in the population of Western Algeria made it possible to classify lung cancer in 2nd position, with an attack percentage of 10.9% in both sexes.

Lung cancer occupies the first position among males with a percentage equal to 23.4%, followed by bladder cancer and colorectal cancer. While it ranks 11th among females with a percentage of 1.1% and is well ahead of breast cancer. The latter is ranked first with a percentage of 55.5% (**Fouatih et al, 2015) [13]**

In 2018, lung cancer is placed in 2nd position after breast cancer according to Globocan estimates, with 3835 new cases of all sexes combined, a prevalence of 3645 cases treated during the same year, and an estimated mortality of 3826 deaths placing it ranked first in terms of mortality. **(Table 2).** It is more common in men with an incidence of 17.7/100,000 inhabitants and 2.9/100,000 inhabitants in women **(Figure 4,5) [14]**

Table 2: Incidence, prevalence, mortality of lung cancer Algeria 2018 (Globocan)

	New cases				Deaths				5-year prevalence (all ages)	
Cancer	Number	Rank	(%)	Cum.risk	Number	Rank	(%)	Cum.risk	Number	Prop.
Breast	11 847	1	22.3	5.62	3 367	2	11.4	1.73	33 915	163.11
Lung	3 835	2	7.2	1.31	3 826	1	13.0	1.24	3 645	8.68
Colon	3 201	3	6.0	0.94	1 752	4	5.9	0.47	7 455	17.75
Bladder	2 938	4	5.5	0.91	1 379	5	4.7	0.35	8 056	19.18
Prostate	2 578	5	4.9	1.40	1 033	10	3.5	0.17	5 788	27.28
Stomach	2 241	6	4.2	0.69	2 001	3	6.8	0.59	3 051	7.26
Rectum	2 229	7	4.2	0.65	1 232	7	4.2	0.33	5 548	13.21
Thyroid	2 103	8	4.0	0.51	261	21	0.89	0.06	7 116	16.94
Non-Hodgkin lymphoma	1 716	9	3.2	0.44	932	11	3.2	0.25	4 635	11.03
Brain, nervous system	1 686	10	3.2	0.41	1 326	6	4.5	0.34	4 507	10.73
Cervix uteri	1 594	11	3.0	0.94	1 066	9	3.6	0.69	4 389	21.11
Leukaemia	1 578	12	3.0	0.36	1 125	8	3.8	0.28	4 459	10.61
Nasopharynx	1 340	13	2.5	0.34	504	18	1.7	0.16	3 952	9.41
Gallbladder	1 263	14	2.4	0.40	735	14	2.5	0.21	1 422	3.39

Figure 4: Incidence of cancers by sex - Globocan estimates 2018 Algeria (Hamdicherif)

4. Distribution of lung cancer according to histological type and its prognosis

Lung cancers are classified into two broad categories: non-small cell lung cancer (NSCLC) which accounts for 85% of all lung cancers and small cell lung cancer (SCLC) which accounts for 15% (Herbst , Heymach , and Lippman 2008 **) [15].** NSCLC often appears in peripheral lung tissues (MacRedmond et al. 2006) **[16],** 25% of NSCLC cases affect non-smokers (Sun, Schiller, and Gazdar 2007) **[17].** NSCLC is characterized by a longer doubling time (Aberle et al. 2014) **[18],** is divided into 3 pathological subtypes adenocarcinoma, squamous cell carcinoma and large cell carcinoma

- Adenocarcinoma is the most common type of NSCLC, it represents 38.5% of all cases of lung cancer (Howlader et al, 2010; (Herbst , Heymach , and Lippman 2008 **)[15]** . It appears in the form of a

peripheral nodule (Kodama et al. 1984 **)[19],** it is linked to tobacco but is also very common in non-smokers and particularly in women (Saito et al. 2017 **)[20].**

- Epidermoid which represents 20% of all lung cancers (Herbst , Heymach , and Lippman 2008 **)[15],** it is strongly linked to smoking, squamous cell carcinoma usually occurs in the respiratory tract centrally (Tomashefski et al. 1990) **[21]** and it is characterized by squamous differentiation (Kumar V et al, 2013).) **[22].**
- large cell carcinoma which represents 2.9% of all lung cancers (Herbst , Heymach , and Lippman 2008) **[15]** , it is closely linked to smoking. Occurs as a large peripheral mass, is characterized by rapid growth and early metastasis (Ginsberg, Grewal , and Heelan 2007) **[23].**

Small cell lung cancer is the most aggressive form of lung cancer accounting for 14% of all lung cancers (American Cancer Society, 2014), it is associated with tobacco exposure (Herbst , Heymach , and Lippman 2008 **) [15].** Frequently appears as a central mass, and approximately 25% are present in the periphery (Colby T et al, 1995) **[24].**

Risk factors

Agents recognized as carcinogenic to the lung

The responsibility **of tobacco in** the occurrence of this disease is a clearly established fact. Thus, it is estimated that 80% to 90% of lung cancers are directly linked to
smoking **[25**]. It is the presence of carcinogenic substances in tobacco smoke which explains this phenomenon. This major risk factor presents certain variations depending on the mode of tobacco consumption and individual characteristics:

- The quantity of cigarettes smoked each day. The greater it is, the more the risk increases.
- The duration of smoking. The longer a person smokes, the greater their risk of lung cancer.
- The age of smoking initiation. Although this has not been formally demonstrated, the earlier tobacco consumption occurs, the higher the risk.
- The way of inhaling smoke. The more frequent and deeper the inhalation, the more the risk increases.
- Use of a filter. It could slightly reduce the risks.

Tobacco smoke contains more than 2,500 substances, nearly 60 of which have been identified as probable or possible carcinogens. The question of the association between bronchial cancer and passive exposure to tobacco smoke was raised in the early 1980s by two publications highlighting an excess risk among the wives of smokers. Since then, more than 50 epidemiological studies have been devoted to analyzing the effects of exposure to environmental tobacco smoke, whether at home (exposure by the smoking spouse) or in the workplace. These studies almost constantly note a significant increase in the risk of mortality from bronchial cancer in both exposure situations. **[26]**

Asbestos is undoubtedly the most common occupational exposure associated with bronchial cancer. All types of asbestos fibers are now recognized as a risk factor for lung cancer. The sectors most at risk are the textile industry (OR 2 to 10), the thermal insulation sector (OR 3 to 6), asbestos cement manufacturing (OR 1.5 to 5.5), and friction materials (OR from 1.5 to 3.5) **[27].**

Silica , the relative risk of lung cancer associated with occupational exposure to crystalline silica is generally between 1.2 and 1.4, this relative risk, in the presence of silicosis, being more generally between 2 and 2, 5, and about 1.6 after adjusting for smoking **.[28]**

It emerges from the analysis of the most recent cohorts concerning subjects exposed to cadmium in the workplace, that the risk of lung cancer is observed in the populations having had the oldest exposures, and levels of cumulative exposure probably the highest, with possible association with other carcinogenic agents, sometimes incompletely evaluated. The risk of lung cancer associated with environmental exposures to cadmium has been less documented **. [29]**

The existence of a risk of radiation-induced lung cancer is now well established, and several studies provide estimates of the dose-response relationship, particularly for external exposure or inhalation of radon. . Uncertainties remain regarding the estimation of doses and risks associated with internal exposures.

Among other epidemiological factors, the role of hormonal replacement is regularly evaluated in population analyses. While several cohort studies with 10,000 to 20,000 participants were negative, a slight increase in the risk of non-small cell lung cancer (NSCLC) was observed in the VITAL study **,[30]** a large epidemiological study of nearly 168,000 individuals in the United States. In this study, the relative risk of developing lung cancer was increased by a factor of 1.48 only for hormonal replacements combining estrogens and progestins but was not observed during replacement with estrogens alone (RR: 1. 04). Furthermore, the Swiss study by Bouchardy et al. showed that patients taking antiestrogens for breast cancer had a reduction in mortality when lung cancer occurred, thus supporting the hypothesis that hormonal replacement modifies the prognosis of lung cancer **. [31]**

Risk factors still debated

The data overall are unconvincing in the production industry for an association between lung cancer and exposure to artificial mineral fibers (mainly glass wool, rock wool, slag wool). It is currently too early to assess the risk of lung cancer linked to refractory ceramic fibers.

Concerning diesel fumes, the EPA (Environmental Protection Agency) states its conclusion as follows: “In conclusion, epidemiological studies on the risk of lung cancer associated with exposure to diesel fumes show evidence consistent with a causal link. . The observed association is unlikely the result of chance or bias. Many studies did not have information on tobacco, but it is unlikely that tobacco is the cause of these results, particularly because the populations compared in these studies have similar socio-economic characteristics. The strength of the association (between 1.2 and 2.6) is relatively modest by epidemiological standards, and a dose-response relationship has been observed in several studies. Finally, the fact that diesel fumes increase the risk of lung cancer in humans is very biologically plausible **” [32].**

Many learned societies consider that this conclusion is consistent with the data in the literature.

The association between pesticides and lung cancer risk is a difficult question to document given the numerous products used and their evolution depending on the period of use and the types of crops **[33].**

There are other carcinogenic substances of occupational origin, other than asbestos, promoting lung cancer, they are listed on the tables of occupational diseases: •ionizing radiation, •chromic acid and chromates, •tars coal, coal oils and coal combustion soot, • inhalation of arsenical dust or vapor, • inhalation of dust or vapor containing arsenic pyrites, • inhalation of asbestos dust , • nickel matte roasting operations, • work in iron mines, • inhalation of dust or smoke containing cadmium, • inhalation of cobalt dust associated with tungsten carbide, • bis (chlormethyl) ether Other substances can cause lung cancer such as beryllium, **[27]**

The atmospheric pollution :The collective expertise of Inserm (National Institute of Health and French Medical Research) and Afsset (French Agency for Environmental and Occupational Health Safety) made

public in October 2008, demonstrated that the atmospheric pollution, of automobile and industrial origin, is a factor, although minor compared to tobacco, but which could promote lung cancer. This pollution is due to gases, such as sulfur dioxide (SO2), nitrogen dioxide (NO2), ozone (O3) and diesel fumes (Trédaniel et al., 2009). However, these are preliminary data which must be verified. **[33].**

Personal and family history : Personal history of respiratory conditions is also a risk factor for lung cancer, particularly in people with chronic obstructive pulmonary disease (COPD), silicosis, berylliosis and tuberculosis. Likewise, people who have already had lung cancer are more likely to develop a second lung cancer than the general population. Furthermore, a case of familial lung cancer also increases the risk of occurrence of this cancer (Li et al., 2008) **[34]** . The existence of protective genetic factors is highly probable and could explain why a large number of smokers (more than 80%) do not develop lung cancer because they have the capacity to better metabolize the carcinogenic constituents contained in cigarette smoke. On the contrary, there are also genetic susceptibility factors favoring this cancer. Certain gene polymorphisms are known to be associated with increased risk of lung cancer. This is the case for the genes coding for the α3, α5 and β4 subunits of the nicotinic acetylcholine receptors, for which certain nucleotide polymorphisms are strongly linked to smoking dependence and lung cancer (Amos et al., 2008). **[35];** and for the TERT gene which codes for telomerase reverse transcriptase (McKay et al., 2008). However, the mechanisms by which these polymorphisms are associated with cancers are not known. Furthermore, Bell et al described the presence of a p.T790M germline mutation in the EGFR gene in a family with multiple cases of bronchiolo -alveolar type adenocarcinoma (Bell et al. 2005). This mutation was already known as a somatic mutation, that is to say only present in tumor cells. The presence of this mutation is associated with resistance to anti-EGFR treatment. More recently, a germline mutation in exon 21 of the EGFR gene (p.V843I) has also been described (Ikeda et al. 2008 **) [35,36].**

Conclusion

Lung cancer remains a major public health issue, with possible primary prevention (smoking) and desirable secondary prevention. Despite therapeutic advances, the prognosis remains poor, good knowledge of the risk factors for lung cancer is an effective means of reducing the incidence of bronchopulmonary cancer, according to numerous updated studies, tobacco constitutes the primary risk factor in the carcinogen of this type of cancer , it is important to highlight recent epidemiological data in terms of mortality and prevalence in our country to guide a preventive approach in planning strategies to combat lung cancer.

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