RESEARCH ARTICLE

Smoking and Cannabis Cessation: An Essential Component of Lung Cancer Treatment

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ABSTRACT

Tobacco smoking is the cause of almost 90% of lung cancers, accounting for 18% of cancer deaths worldwide in 2020. Cannabis is the most widely smoked illicit substance worldwide in the form of herb (marijuana) or resin combined with tobacco (joint) doubles the risk of bronchial carcinogenesis. The incidence of this cancer is expected to rise by 47% from 2020 to 2040 in the world. Despite advances in the cancer treatment, tobacco and cannabis control is the most effective measure for curbing this epidemic. Smoking cessation, at all stages of the cancer process, is associated with benefits in terms of cure, increased life expectancy, improved quality of life for patients, reduced medical or surgical. It is an essential component of lung cancer treatment which must involved cancer care providers. This review describes tobacco and cannabis cessation strategies in patients suffering from this frequent cancer.
Keywords: Tobacco smoking, Cannabis use, Lung cancer, Smoking cessation

I - Introduction

In 2020, the International Agency for Research on Cancer (IARC)[1] recorded 19.3 million new cases of cancer and 10 million deaths. Tobacco smoking is the leading cause of cancer deaths (18% of all cancer deaths ; survival for all bronchial cancer stages combined at five years is 17%). The incidence continues to rise worldwide and is expected to increase 47% from 2020 to 2040 [1] ; nevertheless, tobacco smoking is preventable [2,3]. Cannabis is the most frequently used illicit psychoactive substance worldwide, with around 192 million users in 2018, corresponding to 3.9% of the global population aged 15-64 [4]. It is smoked in the form of resin mixed with tobacco or alone in the form of herb (marijuana). In addition to psychoactive effects, it seems to be implicated in the development of cancer of the upper aerodigestive tract and lung A global tobacco and cannabis control policy is more essential than ever [5,6]. The aim of this article is to clarify the risks of lung cancer in tobacco and/or cannabis smokers, the benefits of abstinence, to review the medical practice recommendations of tobacco treatment for patients suffering from this cancer, in order to encourage healthcare professionals to be involved in cessation management [5-8].

II – Methods.

This review combines a selective search of the Pubmed database and a manual search of current publications.The Medline search was carried out over the period 2005 - 2024 using the following keywords and search equations : Lung cancer AND Cannabis (or marijuana) , cannabis (or matijuana) AND cannabis (or marijuana) cessation, as well as Lung cancer AND tobacco smoking AND Smoking cessation with "Title/Abstract" limits. The languages used were English and French. Of the 357 articles identified, 135 were selected for abstract review (after elimination of off-topic articles and duplicates) and 82 were finally retained for this review. Data were extracted from the selected articles using a collection grid. All authors participated in the writing and re-reading of the article.

III - Results

III - 1. SMOKING TOBACCO LEADING RISK FACTOR FOR LUNG CANCER.

Nearly 90% of lung cancers are linked to smoking, while occupational exposure to carcinogenic substances is responsible for only 5-10% of these cancers [9-12]. Cigarette smoke contains thousands of compounds, including over 60 carcinogens [2,9,10]. Most of the carcinogens contained in cigarette require a metabolic activation process, generally catalyzed by cytochrome P-450 enzymes to form DNA adducts, which are essential to the process of carcinogenesis. Polymorphisms in CYP1A1 and deletion of the glutathione- s-transferase (GSTM1) gene are associated with high levels of DNA adducts, suggesting that variations in metabolic pathways condition the vlnerability to carcinogens [1,2]. Tobacco smoke is involved in cell proliferation and neoangiogenesis [2].

Nicotine is not a carcinogen, but it increases the lung cancer risk in smokers by inducing dependence and prolonged smoking habit. The presence of nicotinic acetylcholine receptors (nAChR) on the cell membranes of lung cancer cell lines has been identified [13,14]. Mutations in the q-25 region of chromosome 15 (SNP rs16969968) containing the CHRNA5-CHRNA3-CHRNB4 gene cluster encoding α5, α3, β4 nAChRs, increase nicotine dependence and vulnerability to lung cancer [14,15].

Active smokers have an higher lung cancer risk compared with never smokers : RR = 10.92 (95% CI : 8.28-14.40) [16] and duration of exposure to tobacco smoke is a greater determinant of cancer risk than the total number of cigarettes smoked [2,3]. Involuntary exposure to tobacco smoke increases this risk by 25%[17].

III - 2. SMOKING CANNABIS ; ADJUVANT RISK FACTOR FOR LUNG CANCER.

In addition to cannabinoids, cannabis smoke contains the same toxic substances as tobacco smoke, notably a high concentration of aryl hydrocarbon hydroxylase (AHH), which converts PAHs into metabolites with greater carcinogenic potential [5]. Cannabis users often consume smaller quantities of tobacco than exclusive cigarette smokers but puff volume is greater, inhalation faster, smoke retention longer, which increases the contact time of the inhaled smoke with the bronchial mucosa [18,19]. Studies give divergent results on the risk of lung cancer induced by cannabis use. However, case-control and cohort studies have shown that tobacco and cannabis co-use doubles bronchial cancer risk [5]. A study carried out in New Zealand [20] where cannabis is rarely mixed with tobacco, highlighted that long-term cannabis use was associated with an increased risk of this cancer : RR= 5.7 (95% CI : 1.5-21.6) after adjustment for tobacco consumption. Data from a cohort of patients aged 60 or under, undergoing surgery for bronchial cancer suggest that cannabis and tobacco smokers, compared with tobacco smokers or non-smokers, were more likely to present a cancer [19].

III - 3. ADVANCES IN LUNG CANCER TREATMENT.

Progress in lung cancer treatment are leading to improved 5-year survival [21]. Surgical video-assisted techniques give better quality of life and higher survival in non-small-cell-lung-cancer (NSCLC) compared with open lobectomy ; perioperative chemotherapy found a survival benefit [22]. The treatment for locally advanced non-small-cell lung cancer (NSCLC) and for small-cell-lung-cancer (SCLC) have changed over the past years ; in addition to chemoradiation, combining consolidative immunotherapy or targeted therapies shown durable responses [23-26]. However smoking cessation is an essential component of lung cancer treatment.

IV - Smoking cessation in lung cancer patients.

IV - 1. BENEFITS OF SMOKING CESSATION.

IV - 1 - 1. Short-term benefits.

To never start smoking tobacco and cannabis or quit as soon as possible is the best way to avoid lung cancer risk. Smoking cessation rapidly improves cognitive performance, tissue oxygenation, appetite, reducing tiredness, breathless and cough [27].

IV - 1 - 2. Long-term Benefits.

Continued smoking in the early stages of NSCLC, is associated with increased risks of mortality and

recurrence. Continuing smoking in cases of limited-stage of SCLC, is associated with increased mortality [28]. Smoking cessation at the time of diagnosis of early-stage lung cancer improves prognosis : for NSCLC, 5-year survival is 33% for smokers versus 70% of abstainers, for non-disseminated NSCLC, 29% of smokers survive versus 63% of abstainers [28]. A prospective study [29] recruited current smokers with NSCLC (stages IA to IIIA) highlighted a reduced risk of all-cause mortality and disease progression, with 5-year overall survival (60.6% vs. 48.6% ; p = 0.001) and progression-free survival (54.4% vs. 43.8% ; p = 0.004) higher in abstainers than in continued smokers. Smoking cessation improves chemotherapy efficacy. Continued smoking may induce accelerated metabolism of irinotecan or erlotinib and increased adverse events with cysplatin-based chemotherapy ; quitting corrects these disorders [3,30]. All perioperative complications are more frequent (OR = 1.62; 95% CI : 1.25-2.11), one-year mortality is higher (OR = 1.50; 95% CI : 1.17-1.92), length of hospitalization is longer (9.0% p < 0.001) in smokers compared with non-smokers [7,31]. Smoking cessation as soon as possible, at best 4 weeks before surgery, reduces these risks (20% less per week) [8,31]. Smokers have a poorer response to radiotherapy, a higher risk of radiation pneumonia, lung infection, shorter life expectancy [3,7]. Finally, smoking cessation improves patients' quality of life (QoL), irrespective of the lung cancer treatment [27,28].

Prospective studies [32] have shown that current cannabis use was associated with the presence of cough (RR=2.04; 95% CI: 1.02 - 4.06) and sputum (RR=3.84; 95% CI: 1.62 - 9.07) or increased chest wheezing (RR=2.83; 95% CI: 1.89 - 4.23) and dyspnoea (RR=1.56; 95% CI: 1.33 - 1.83) [27]. Tashkin et al.[33] showed that bronchial symptoms improved after cessation of cannabis use.

IV - 2. SMOKING CESSATION MANAGEMENT.
IV - 2 - 1. Non-pharmacological treatment
The announcement of diagnosis is a teachable moment to quit smoking [3,34,35]. Assessing smokers' tobacco dependence, motivation to quit and information of the benefits of cessation, and of evidence-based treatment methods that increase smoking cessation outcomes compared with unassisted cessation [3,8,34,35].

Smokers with lung cancer have a higher level of motivation to quit than other patients (p < 0.003), the 6-month abstinence rate is higher (22% vs. 14% ; p < 0.024). However, around 20% of patients are still smoking 12 months after diagnosis. Factors predictive of continued smoking are high nicotine dependence, depressive disorders, social precariousness, drug use, smoking by spouse, (OR = 9.57; 95% CI : 2.50-36.44) [3,8,35]. Practitioners must provide empathy, avoide stigmatizing smokers, increase the patient's sense of self-efficacy. The "5 R's" method using open-ended questions can help patients to implement quit smoking : (1) Relevance (encouraging smoke rs to give their reasons for quitting), (2) Risks (helping them to identify the negative effects of smoking), (3) Rewards (asking them about benefits when quitting smoking), (4) Roadblocks (patient pecify the obstacles to quit), (5) Repetitions (repeating the motivational interview) [34,35].

Behavioral and cognitive therapies (BCT) are useful at each step of follow-up, increase the smoking cessation medications efficacy, reinforce the patient's sense self-efficacy, therapeutic compliance, control of craving [34-36]. Long-distance support (telephone counselling) and smokefree home reinforce patients abstinence [37]. Combining behavioral therapies with pharmacotherapies is the most effective strategy for smoking cessation [3,8,34,35]. Reducing consumption does not decrease all-cause of mortality, using pharmacotherapiesbut can prepare for cessation [9,35].

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IV - 2 - 2. Pharmacological treatment.
- Primary option.
Nicotine replacement therapy (NRT) in particular the combination of short-acting NRT (gum, lozenge, spray) and long-acting NRT (patch) represents the primary option increases the chances of success compared with placebo (OR = 2.73; 95% CI : 2.07-3.65), no carcinogenic effects of NRT have been reported [3,25,26], high doses are well tolerated [3,34,35,38,39].

Varenicline, an α4β2-AChR partial agonist, is an effective treatment, with a higher chance of success compared with placebo (OR = 2.88; 95% CI : 2.40-3.47). It has no drug interactions. Adverse events (nausea, vomiting, insomnia,

abnormal dreams) may affect patients undergoing chemotherapy, requiring dose adjustment [3,34,35,38]. The withdrawal of varenicline from the market represents a loss of opportunity to quit.

- Alternative option.
Bupropion is a dopamine and norepinephrine reuptake inhibitor, effective in smoking cessation compared with placebo (OR = 2.07; 95% CI : 1.75-2.45). It may require dosage adjustments in patients with hepatic or renal insufficiency, and reduces the convulsive threshold contraindicates its use in patients with epilepsy or brain metastases [3,34,35,38].

Cytisine (cytisinicline) is an alkaloid of plant origin that binds selectively to the α4β2AChR, increasing the chances of success compared with placebo (OR 2.21; 95% CI : 1.66- 2.97) [38]. Cytisine appears to tolerate smoking cessation well, with adverse events (nausea, abnormal dreams, insomnia) occurring in less than 10% [40,41]. Its lower cost could make it an affordable smoking cessation medication in low-income countries.

Nortriptyline is associated with higher quit rates compared with placebo (OR= 1.35; 95% CI : 1.02 -1.81) [38].

Drug therapy combinations (NRT and bupropion, varenicline and NRT or bupropion, NRT and e-cigarettes) may increase quite rates in hard-core smokers [34,42,43].

- Electronic cigarette and heated tobacco products?
Electronic cigarettes (e-cig.). Vaping is less toxic than smoking at short-term, although there is a lack of knowledge about long-term safety [38,44-46] and about their effectiveness in smoking cessation in smokers with lung cancer. E-cig. with exclusive use could be another way of facilitating smoking cessation [44,45]. Patients with cancer currently users of e-cigarettes were surveyed in a cross-sectional study about their patterns and reasons for use, beliefs and perceptions of risk for e-cigarettes and combustible cigarettes. Most participants identified smoking cessation as the reason for initiating (81%) e-cigarette use. However, 51% of patients reported current dual use of combustible cigarettes and e-cigarettes. Patients characterized e-cigarettes as less addictive, less expensive, less stigmatizing, and less likely to impact cancer treatment than combustible cigarettes (Ps <0.05)[47]. A study recruited smokers with cancer [48] (lung cancer n=19.8%) ; e-cig users compared with non-users were more dependent on nicotine, had made more quit attempts and were twice as often smokers during follow-up (OR = 2.0; 95% CI : 1.2-3.3). Studies are needed to verify the value of e-cig to quit smoking among lung cancer smokers.

Heated tobacco products. The tobacco industry reports that heated tobacco products (HTPs) can replace combustible cigarettes ; however, HTPs produce aerosols containing tobacco components [49]. There is a need to explore the risks of lung cancer posed by HTPs, via clinical trials and epidemiological studies using appropriate biomarkers [50].

IV - 2 - 4. How improving smoking cessation.
- Patient conditions
Precarious smokers, are at greater risk of not completing preoperative home rehabilitation before resection for

NSCLC [51], combination of NRT forms and longer follow-up help them quit smoking [52].

Transgender people frequently suffer from social precariousness, substance abuse disorders, psychiatric disorders and barriers to accessing healthcare; management of smoking cessation should include social support and relapse prevention planning [53].

Smokers infected with HIV often have a high nicotine dependence, psychiatric or substance use disorders [54], Varenicline is an efficacy stop smoking medication [55].
Patients with chronic obstructive pulmonary disease (COPD), often have a high level of nicotine dependence, depressive disorders [3,8,56]. Combinations of BCT and NRT, or pharmacological treatment and pulmonary rehabilitation are effective to quit smoking [57,58].

Psychiatric disorders often are associated with smoking and substance use disorders that make stopping smoking difficult [59-61]. A study comparing the relative risk of neuropsychiatric disorders and effectiveness of varenicline, bupropion, nicotine patch 21 mg and placebo in smokers with and without psychiatric disorders did not demonstrate a significant increase in neuropsychiatric adverse effects between the different médications. Varenicline was the most effective to stop smoking, nicotine patch or bupropion were more effective than placebo [62].

Tobacco and cannabis co-use. Simultaneous cessation of tobacco and cannabis is a coherent proposition in the event of co-use. A systematic review [63] and clinical practice showed that cannabis and tobacco users found it more difficult to quit cannabis than exclusive cannabis users and preferred to quit tobacco before cannabis. Cannabis use reflects an inappropriate strategy of adaptation to the environment and after quitting, abstinence is more stable when it is part of a global change of habitus [64]. Behavioral and cognitive therapies increase the patient's motivation to quit and strengthen adherence to treatment, facilitating the prevention of relapses after stopping [64,65]. Remote support methods provide additional assistance [66]. Pharmacological treatment contributes to cannabis cessation [67] : NRT limits withdrawal syndrome, craving and improves adherence to therapeutic monitoring [64-68], varenicline is at an experimental stage in this indication [69], cannabinoid agonists (dronabinol) appear promising [64]. The role of e-cig. to help people quit cannabis is poorly understood [70] severe toxic pneumonias following use containing THC has been described [71] ; these findings raise doubts about their use for harm-reduction. A specific inhibitor of cannabinoid receptor 1 signaling (CB1-SSi) [72], inhibits a subset of intracellular effects resulting from delta 9-tetrahydrocannabinol (THC) binding. A phase 2a, placebo-controlled crossover trial was carried out in volunteers suffering from cannabis use disorders. In the treated group, the positive subjective effects of cannabis and cannabis self-administration were reduced (p< 0.05) with good tolerability, suggesting that it is a potentially effective treatment for cannabisuse disorders.

- Medical procedures and interventions.
Non-invasive brain stimulation.
The Non-invasive brain stimulation (NIBs) may improve smoking abstinence rates after quitting smoking,

compared with usual treatment. RR=2.39 (95% CI = 1.26-4.55) [73].

Lung cancer screening and smoking cessation?
Several studies concluded that lung cancer screening using low-dose CTscans, aimed at patients who have smoked could reduce more than 20% lung cancer mortality [74,75]. Lung cancer screening can help to raise smokers' awareness of the need to stop smoking and to implement smoking cessation in a cost-effective manner [76,77]. However, in 2015, a survey conducted in US screening centers highlighted that only 36.6% of these sites provided optimal tobacco cessation services [78].

Improving smoking cessation management in cancer centers?
A cross-sectional study, has involved 28 cancer centers to clarify factors that improve smoking cessation [79], evidence-based smoking cessation assistance was provided in 15.4%, and median 7-day abstinence at month 6 was 18.4%. The best results were achieved by centers with a smoking treatment protocol and the best resources, including expert professionals to support smokers [79]. The organization of care for smokers and training for professionals in smoking cessation must be improved [80].

It is never too late to quit smoking!
Stopping smoking around the time of diagnosis (within 12 months) is associated with improved survival [7]. The benefits of quitting one year before diagnosis are shown, increasing with longer durations of abstinence [81]. Stopping smoking is beneficial at any time. Thus health-care providers should initiate, evidence-based, stopping smoking interventions for smokers ; they are an essential component of lung cancer treatment [82].

V - Discussion.
Tobbacco smoking is the leading risk factor for lung cancer [1,2]. The role of cannabis smoke is controversial since it is difficult to isolate the effects of cannabis which is in the majority of cases smoked with tobacco [5,18]. However, cannabis exposure doubles the risk of developing lung cancer and recent studies are in favor of an independent role of cannabis in the development of lung cancers [20]. Continued smoking is associated with an increase in the risk of all-cause mortality and tumor recurrence in patients suffering from this cancer [8,28]. The benefits of incorporating stopping tobacco smoking and cannabis use within all lung cancer treatment protocols is highlighted [27-31]. Smoking cessation pharmacotherapies are safe, vaping is less toxic than smoking at short-term although there is a lack of knowledge about long-term safety and efficacy in quitting [46].

Stopping tobacco smoking and cannabis use is feasible in patients with lung cancer, it is an integral part of lung cancer treatment [34,35]. Medical recommendations for smoking cessation are similar to those for the general smoking population and abstinence rate is comparable [3,8,34,35]. However, few data concerning the methods of helping to stop cannabis for lung cancer patients have been found in the literature [64], which is one of the limitations of this review The offer of smoking cessation assistance should be made to all smokers and more particularly at the time of screening [76-78] or diagnosis of lung cancer. Thus training in smoking cessation management must be improved for professionals who care for patients with lung cancer [80].

VI - Conclusion
Smoking is the cause of almost 90% of lung cancers, accounting for 18% of cancer deaths worldwide in 2020 and cannabis use is a risk factor for this cancer. Tobacco and cannabis control is the most effective measure for curbing the lung cancer epidemic. Smoking and cannabis cessation brings benefits to patients at all stages of the cancer process. The management of smoking cessation can be better integrated into the lung cancer screening. Professionals caring for patients with lung cancer must advise smokers to quit and support them during. They must be better trained to smoking cessation management which is an essential components of cancer treatment.

Conflict of Interest: The authors have no conflict of interest to declare.

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