ISSN: 2536-7153 SJMLS

Sokoto Journal of Medical Laboratory Science 2023; 8(3): 61 - 72

SJMLS - 8(3) - 007

Cytological Changes in Respiratory Epithelium in Association with Marijuana Smoking

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Abstract

Marijuana is one of the commonly used illicit drugs in Nigeria. This study evaluated the cytological changes in the respiratory epithelium associated with marijuana smoking in Calabar Municipality, Cross River State, Nigeria. This study was a cross-sectional study involving 100 marijuana smokers and 50 marijuana non-smokers, aged 15 years and above. Sputum samples were aseptically collected, and smears prepared. The smears were fixed in 95% ethyl alcohol and were stained using Giemsa and Papanicolaou staining techniques. The stained smears were examined using x10 and x40 objectives of light microscope. Photomicrographs of stained smears were obtained. Data were represented in percentages in tables. Chi-square was used to determine statistical difference between two categorical variables. P-values $\leq$ 0.05 were considered significant. Marital status, level of education and age of subjects significantly influenced the smoking of marijuana (p=0.001). There was a significant increase in the number of marijuana smokers between the age of 15 – 24 (p=0.001) when compared with other age groups. There were also significant abnormalities (p=0.001) observed in the respiratory epithelium of marijuana smokers when compared with non-marijuana smokers. Respiratory cytology smears from marijuana smokers who have smoked for at least 10 years showed mild to moderate metaplasia, numerous acute and chronic inflammatory infiltrates while those who have smoked for more than 10 years showed giant epithelial cells, multinucleated cells and clumps of dysplastic cells. Data from this study showed that marijuana smoking causes inflammatory and dysplastic changes in the respiratory epithelium.

Key words: Marijuana, smokers, Respiratory epithelium, Cytology

Introduction

Cannabis sativa is a species of the Cannabaceae family that includes both marijuana and hemp varieties. Sativa strains grow favourably in warmer weather, with most strains originating from countries such as Mexico, Southeast Asia, Colombia and Thailand (Andre et al., 2016). Cannabis is Cultivated throughout the season and is harvested for its fiber, seeds, and oil. These products from cannabis plant are used for several purposes such as for industrial, nutritional, and medicinal purposes. Currently, cannabis strains grow wildly throughout many humid and tropical areas of the globe. Sativa strain – marijuana is known for being extremely pungent due to a distinct content that produces aromas that can range from fruity, citrus, and sweet to earthy, piney, and peppery (Adams *et al*., 2021). Cannabis sativa is the commonest used illicit drug globally (UNODC, 2018). It has been reported as the second most smoked substance after tobacco (Ribeiro *et al*., 2016). While cannabis consumption in legalized in some countries[5] (Hancox & Sears 2019), it is prohibited in several other countries (UNODC, 2018) such as Nigeria. In 2013, Uruguay became the first country to legalize recreational use of cannabis. Other countries to do so are Canada, Georgia, and South Africa, plus 18 states, two territories, and the District of Columbia in the United States, although the drug remains federally illegal in the U.S.A (Lemon, 2018).

Cannabis is the commonest abused drug reported across the different study populations in Nigeria. The burden of marijuana use is rising here in

Nigeria. The trend has been associated with certain age and lifestyle (Okpataku *et al*., 2014; Adamson *et al,* 2015). The prevalence of cannabis abuse among members of the general public was 10.8% and 22.7% among adolescents of 25 years and younger adults (UNODC, 2018). The frequency of abuse among secondary school students was between 0.6 and 34%, with a pooled prevalence of 12.5% (Famuyiwa, *et. al.*, 2011; Erah & Omatseye 2017). The abuse of cannabis among undergraduate students was also common, with a prevalence of 8–11% (Essien, 2010). The main psychoactive component of cannabis has been reported to be Tetrahydrocannabinol (THC), which is one of the 483 known compounds in the plan (Russo *et al*, 2013), together with at least 65 other cannabinoids (Newton, 2013), including cannabidiol (D'Souza *et al.,* 2009). Cannabis smoke is known to contains thousands of organic and inorganic chemical compounds such as tar. Tar is chemically similar to the tar found in tobacco smoke (Hashibe *et al.*, 2005). Known carcinogens such as nitrosamines, reactive aldehydes, and polycylic hydrocarbons have been identified in cannabis smoke (Hashibe *et al*., 2006; Ghasemiesfe *et al*., 2019).

Cannabis has been associated with both mental and physical effects, which include euphoria, altered states of mind and sense of time, difficulty concentrating, impaired short-term memory and body movement, relaxation and an increase in appetite (Riviello, 2010). Acute effects of prolonged smoking of marijuana include anxiety and panic, impaired attention and memory, an increased risk of psychotic symptoms and the inability to think clearly (Hall and Solowij, 2012; Oltmanns and Emery, 2015). Acute Marijuana smoking impairs a person's driving ability as it has been implicated in many road traffic accidents, especially in fatal cases (Karila *et a*l, 2014). Short-term use of cannabis is associated with bronchodilation, increase in blood pressure and heart rate (Gates *et al*., 2014). Heavy and prolonged smoking of marijuana may have biologically based physical, mental, behavioral and social health consequences (Gordon, 2013). It may be associated with diseases of the liver, lungs, heart, and vasculature (Tetrault *et al*., 2007). A limited number of studies have examined the effects of cannabis smoking on the respiratory system (Tashkin, 2013; Owen *et al*., 2014) Research has shown that prolonged and heavy marijuana smoking is associated with coughing, production of sputum, wheezing, and other symptoms of chronic bronchitis (Howden and Naughton, 2011). This current study evaluated the cytological changes in respiratory epithelium associated with marijuana smoking in Calabar Municipal, Cross River State, Nigeria, since limited numbers of studies have examined the effects of cannabis smoking on the respiratory system.

Materials and method

Study area

This study was carried out in Calabar Municipal Local Government Area, Cross River State between June and September, 2021. Calabar Municipal has its headquarters in Calabar city and covers an area of 55square metres (142km^2) with a population of 179,392 according to 2006 census (NIPOST, 2012). Calabar Municipal lies between the latitude 04^{o}15' and 5^{o}N and longitude 8^{o}25' E. It is bounded by Odukpani Local Government Area in the North, and in the East by the great Kwa River. The Southern areas are bounded by the Calabar River 5 miles and Calabar South Local Government.

Study subjects and population

A total of 150 subjects were enrolled in this study. The subjects comprised of 100 male and female marijuana smokers and 50 non marijuana smokers, aged between 15 years and above resident in Calabar Municipal.

Study design

In this study cluster sampling technique was used to recruit participants. Questionnaires which were distributed to the subjects were used to obtain demographic data. The subjects were grouped according to their responses to the questionnaire. The consent of the subjects to participate in the research was obtained using a consent form before the research commenced.

Ethical approval

Ethical approval was obtained from the National Drug Law Enforcement Agency, Calabar Cross River State before the commencement of this study.

Inclusion criteria
Marijuana smokers of different genders and aged 15 and above were included in this study.

Exclusion criteria
i. Non marijuana smokers with underlying respiratory disease and cigarette smokers.
ii. Individuals living in air polluted environment.

Sample collection
Well labelled wide mouth universal containers were given to selected subjects to collect their sputum samples. They were instructed to collect samples first thing in the morning before taking any food. There were to take a deep breath before producing the sputum into the sample container and placed into plastic bags. The sputum samples were retrieved on sample on the day for analysis.

Sputum smear preparation
The sputum samples were homogenized, and smears were prepared on clean grease free glass slides already well labelled. The smears were prepared in pairs and fixed immediately in 95% ethyl alcohol.

Staining and microscopy of sputum smear
The sputum smears were stained using Papanicolaou and Giemsa staining techniques. The sputum smears were dehydrated in ascending grades of alcohol, cleared and mounted using DPX. The smears were viewed using x10 and x40 magnification of light microscope.

Data analysis
Photomicrographs of smears were presented. Data was analyzed using Microsoft SPSS version 21.0. Chi square was used to compare difference between variables. Significant statistical difference was considered at $p \leq 0.05$.

Results and Discussion
This present study evaluated sputum samples obtained from 150 participants with 100 being marijuana smokers and 50 being non-smokers. From the cytology assessment of the sputum samples collected, only 4% of non-marijuana smokers had any form of cellular atypia. Conversely, 90% of marijuana smokers showed varying degrees of cellular atypia as shown in Table 1.

The age of participants in this study ranged from 15 to above 55years with majority within the 15 – 24 years age bracket (64%) and the lowest percentage of smokers recorded within the 55 years and above age bracket (4%). As seen in Table 2, from the respondents included in this study, a higher percentage of males engaged in marijuana smoking (56%) compared to females (44%). Also, marijuana smoking is more common among single individuals (78%) in comparison to their married counterparts (22%).
Table 3 shows a comparison of the respiratory epithelium of marijuana smokers according to duration of smoking. From the cytology photomicrographs we obtained, marijuana smokers with a duration of smoking between 1 to 10 years exhibited the greatest degree of atypical cellular transformations. These include the following: increased nuclear/cytoplasmic ratio, nuclear enlargement and pleomorphism, chromatin clumping and uneven chromatin distribution within the nucleus, nuclear condensation at the peripheral regions of the cell, peri-nuclear vacuolation, multinucleation, irregular nuclear membrane, hyperchromasia, squamous metaplasia, dysplasia keratinization and eosinophilia. Mild metaplasia was mostly seen in 1 to 5 years smoking duration representing 27% of the participants; moderate metaplasia was seen predominantly among the 6 to 10 years smoking duration (12%) while 22% of the participants exhibited dysplastic cellular changes, predominantly among the 11 years and above smoking duration group.

In addition to these cellular atypical changes, also seen were acute and chronic inflammation. Acute inflammation was indicated by aggregation of polymorphonuclear neutrophils and marked eosinophilia (Plate A) mostly seen in smoking group duration of 1 to 5 years. Chronic inflammation was mostly seen in smoking duration group of above 5 years. It presented as infiltration of lymphocytes and presence of giant cells (Plate F).

Table 1. Comparison of respiratory epithelium of marijuana smokers in Calabar Municipal with non-marijuana smoker

Variables	Marijuana smokers n=100	Non marijuana smokers n=50	p-Value
Normal cytology (%)	10 (10%)	48 (96%)	0.001
Abnormal cytology (%)	90 (90%)	2 (4%)	0.001
Total	**100 (100%)**	**50(100%)**	

Table 2. Demographic data of marijuana smoker in Calabar Municipal, Cross River State

Variable	No of smokers n(%)
Gender	
Male	56(56%)
Female	44(44%)
Marital status	
Married	22 (22%)
Single	78 (78%)
Level of education	
Primary	21(21%)
Secondary	34(34%)
Tertiary	45(41%)
Age range	
15-24	64 (64%)
25-34	22 (22%)
35-44	6(6%)
45-54	4(4%)
55 and above	4(4%)
Duration of smoking (yrs)	
1-5	51 (51%)
6-10	20 (20%)
11-15	28 (28%)
16-20	1 (1%)

Table 3. Comparison of respiratory epithelium of marijuana smokers according duration of smoking

Duration of smoking (yrs)	Normal epithelium n(%)	Metaplasia n(%)		Dysplasia n(%)	Total
		Mild	Moderate		
1 – 5	4(7.84)	27(52.94)	20(39.22)	0(0)	51(100.00)
6 – 10	4(20,00)	4(20,00)	12(60.00)	0(0)	20(100.00)
11 – 15	2(7.14)	3(10.71)	2(7,14)	21(75,00)	28(100.00)
16 – 20	0(0.00)	0(0.00)	0(0.00)	1(100.00)	1(100.00)
Total n (%)	**10(10%)**	**34(34%)**	**34 (34%)**	**22 (22%)**	**100(100.00)**

p=0.001

Cytology smear of marijuana smoker stained with Papanicolaou technique.

The smear showed normal superficial epithelial cells and numerous morphonuclear neutrophils as show in fig. 1. In fig. 2, the smear showed metaplastic epithelial cells with increased nuclear-cytoplasmic ratio and perinuclear vacuolation. Cytology smear of marijuana smokers in fig.3 showed mild dysplastic cells, multinucleated cell with peri-nuclear vacuolation. In fig 4, the cytology smear showed epithelial cells exhibiting metaplastic changes with Perinuclear vacoulation. Cytology smear of marijuana smokers in fig. 5 showed dysplastic cells with irregular chromatin and nuclei that condensed at the periphery of the cells. In fig. 6, the cytology smear of marijuana smokers showed dysplastic cells with keratinization and abnormal chromatin. The cells also showed increased nuclear-cytoplasmic ratio. Fig. 7 showed cytology smear dysplastic cells exhibiting Keratinization, with the presence of some mononuclear Lymphocytes. The cells also showed hyperchromasia. Fig. 8 showed cytology smear of marijuana smokers, showing budding hyphe of fungus.

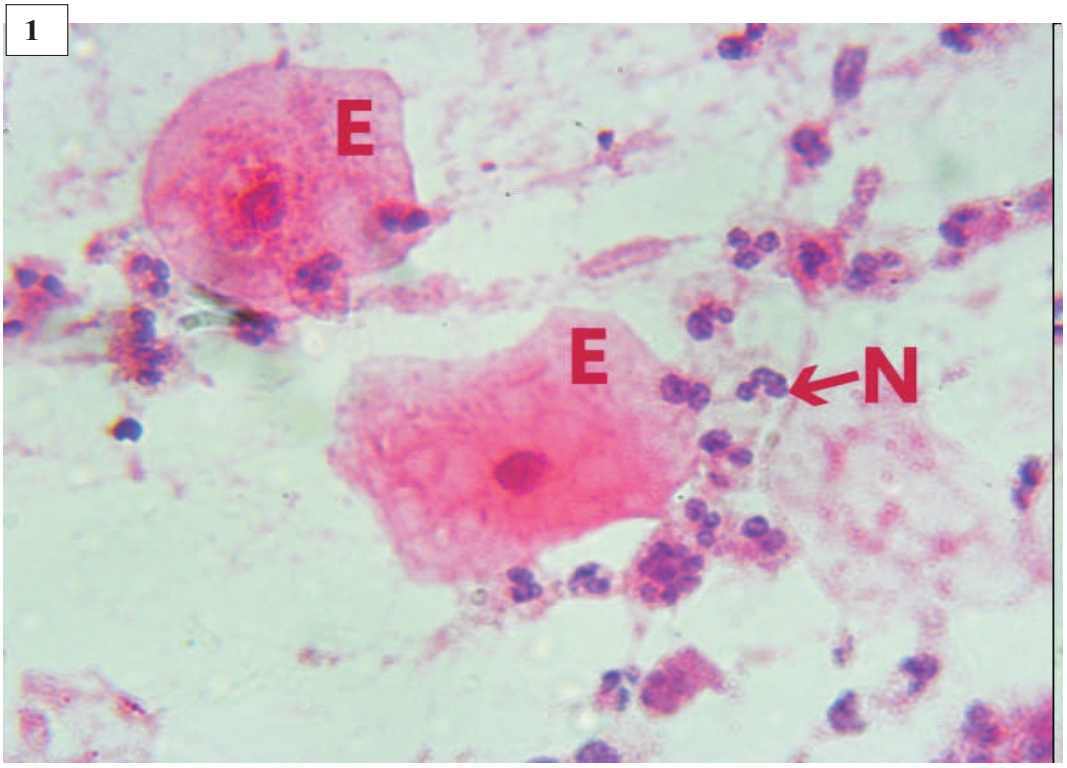

Fig. 1: Cytology smear of marijuana smoker stained with Papanicolaou stain. Papanicolaou stain x400.
E= Epithelia cell; N= Neutrophils

Fig. 2: Cytology smear of marijuana smoker stained with Papanicolaou stain. X 400.
M= metaplastic cells with perinuclear vacuolation.

Fig. 3: Cytology smear of marijuana smoker stained with Papanicolaou stain. X400.
M= metaplastic cells; N= multinucleated cell with peri-nuclear vacuolation.

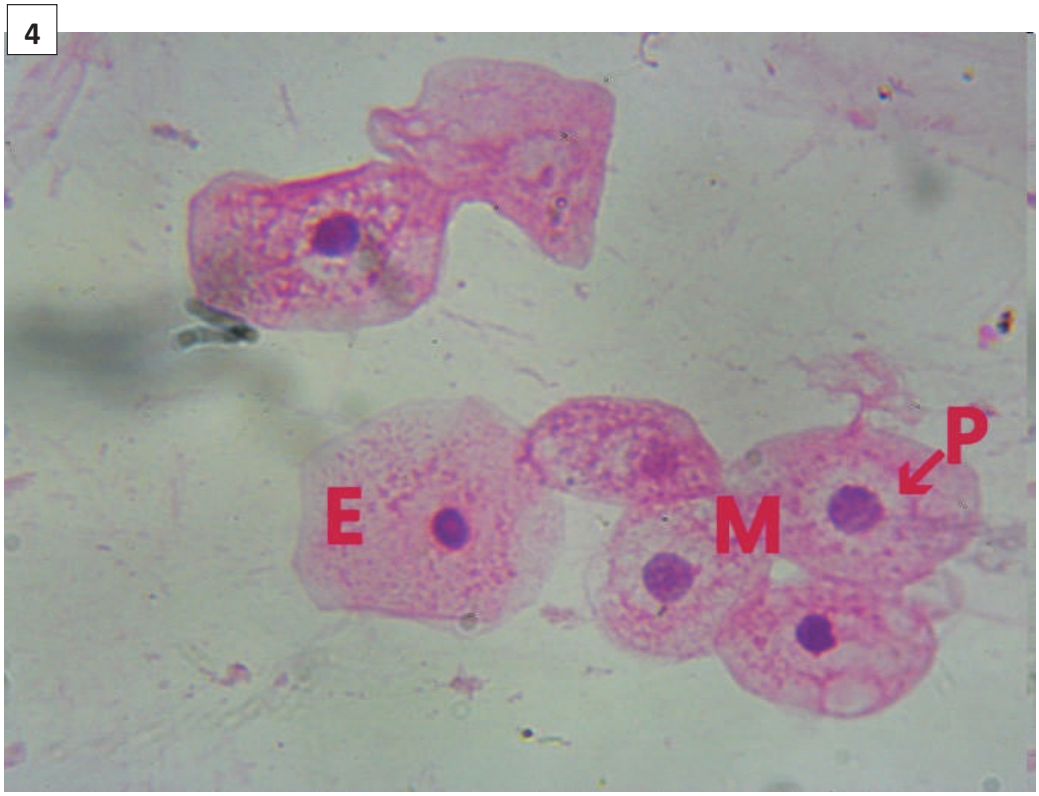

Fig. 4: Cytology smear of marijuana smoker stained with Papanicolaou stain. X400.
E= Epithelial cells; M= Metaplastic cells; P= Perinuclear vacuolation

Fig. 5: Cytology smear of marijuana smoker stained with Papanicolaou stain. X400.
D= Dysplastic cell.

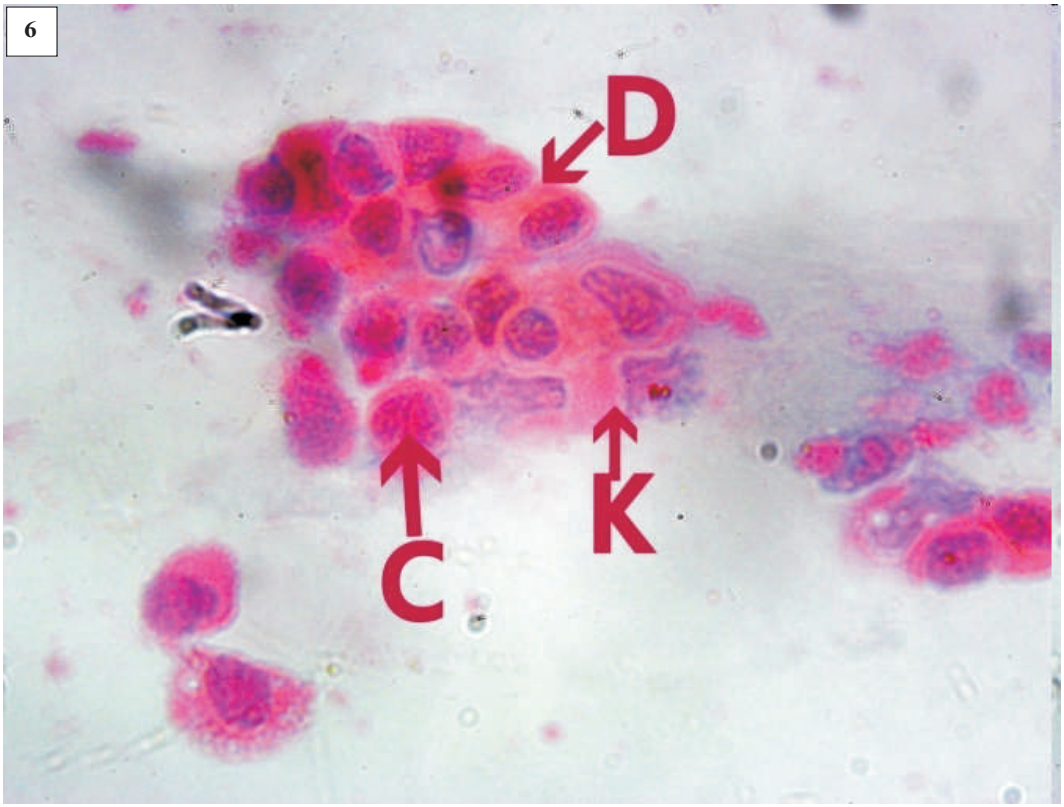

Fig. 6: Cytology smear of marijuana smoker stained with Papanicolaou staining. X 400.
K= Keratinization; D= dysplasia; C= chromatin.

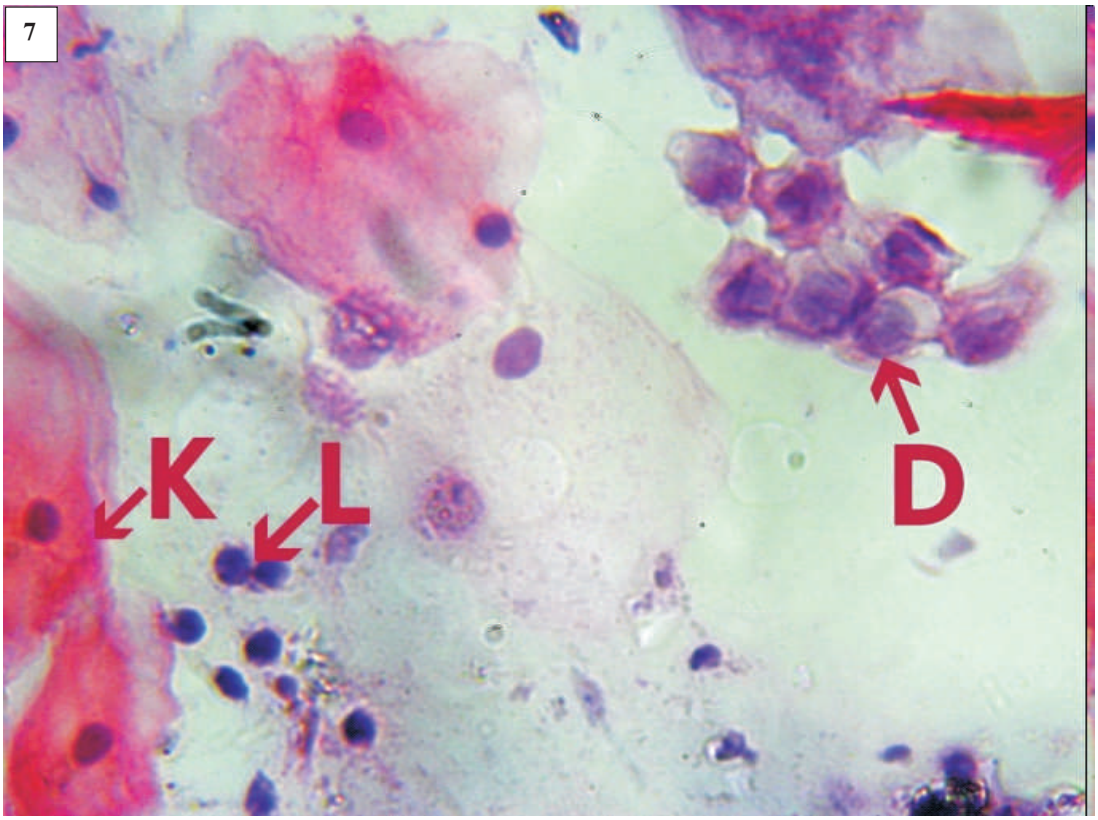

Figure 7: Cytology smear of marijuana smoker stained with Papanicolaou staining. X 400.
K= Keratin; L= Lympocytes; D= Dysplasia

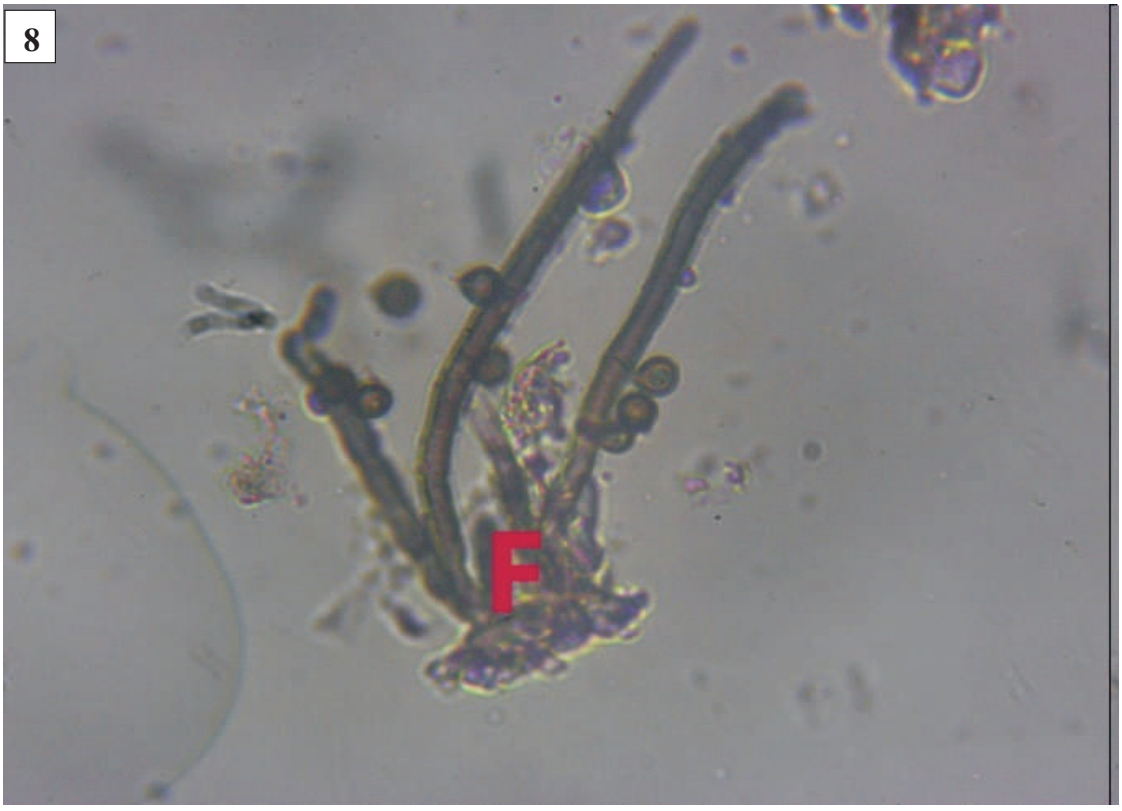

Fig. 8: Cytology smear of marijuana smoker stained with Papanicolaou stain. X400.
F= Fungus

Discussion

The aim of this study was to evaluate the respiratory epithelium of marijuana smokers to detect precancerous or atypical changes. This was done by cytologically assessing the sputum samples obtained from participants that met the inclusion criteria used in the study. Sputum cytology was used in the study for assessment because it has proven to be a simple, non-invasive and reliable method of screening and evaluating the respiratory epithelium of at-risk populations (Ahmed *et al.,* 2021).

From our study, we observed that the highest cannabis smoking age group was 15 to 24 years. This is quite similar to a study done on cannabis consumption among students where data was collected from adolescent age students in more than 4000 schools across the six geopolitical zones of Nigeria. That study placed the mean age of cannabis consumers among students at 15.8 (±1.8) years (Mehanovic *et al*., 2020). Our study also showed a greater percentage of male marijuana smokers compared to females, this observation is correlated by research done by Anyanwu *et al. (*2016) that arrived at a similar conclusion.

From the data obtained in this study, we observed a direct proportionality relationship between increased marijuana smoking duration and severity or increased presence of metaplastic and dysplastic cellular changes. These findings are similar to the result obtained by Prindiville *et al*. (2013). In their research, after conducting cytological assessment of sputum sample obtained from chronic cigarette smokers, they found out that increase duration of cigarette smoking produced progressively worsening cellular abnormalities. Along the same line, another study indicated a higher degree of cellar atypia among long-term smokers (Babiker *et al*., 2012).

The cellular atypical changes observed in our study were mostly squamous metaplasia and dysplasia. Squamous metaplasia results in the transformation of the original pseudostratified columnar epithelium of the lungs to flattened squamous cells. Squamous metaplasia, though a reversible process on cessation of the trigger, may progress to squamous cell carcinoma on continuation of the initial stimulus (Ahmed *et al*., 2021). Metaplasia is not exclusive to marijuana smoking as this effect has also been observed in sputum smears of tobacco smokers (Prindiville *et al.,* 2013; Rigden *et al*., 2016). To further buttress this point, a study found out that the smoke composition of marijuana is comparatively similar to tobacco smoke. They both contain ammonia, tar, nitrosamines and hydrocyanic acid. The major difference between them lies in the presence of nicotine in cigarette and 9-tetrahydrocannabinol (THC) and its derivative compounds found in cannabis (Tashkin, 2013). Hence, the cellular atypia effect caused by cigarette/ tobacco smoke is largely similar to that in cannabis/marijuana smoke. The presence of numerous neutrophils and lymphocytes indicated acute and chronic inflammation respectively. This agrees with studies done by Tashkin (2013) and Owen *et al.* (2014), they reported large airway inflammation and chronic bronchitis in marijuana smokers.

Conclusion

In conclusion, marijuana smoking poses a significant risk for development of atypia in epithelial cells of the respiratory system coupled with acute and chronic inflammation. These effects are similar to the effect of tobacco smoking.

Conflict of Interest

The authors declare no conflict of interest

Author's Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgement

The authors acknowledged the contribution of Mr. Stanley Efewamgbe, a Chief Medical Laboratory Scientist, Department of Pathology, University of Calabar, Calabar, who anchored the practical aspect of this research.

Authors' contribution

ASO conceptualized the topic of this research. The design of the study was done by ASO, AEC and EA. ASO and PAJ carried out the practical while the data analysis and drafting of the manuscript were done by ASO and AEC. ASO is the guarantor of the paper.

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Citation: Anyanwu Stanley O, Akwiwu Euphoria C, Egbe, Agala, Patrick Anifiok J. Cytological Changes in Respiratory Epithelium in Association with Marijuana Smoking. ***Sokoto Journal of Medical Laboratory Science*; 8(3): 61 - 72.** https://dx.doi.org/10.4314/sokjmls.v8i3.8