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Cohort Study

Epidemiology and histopathological classification of lung cancer: A study from Jordan, retrospective observational study

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ABSTRACT

Background: Lung cancer is a major health burden in Jordan. With the failure of tobacco control policies and the evolution of new smoking methods like water pipes and e-cigarettes, lung cancer is projected to further increase. This study investigates the epidemiology and the different histopathological subtypes of lung cancer in correlation with age, sex and smoking.

Material and methods: 434 tumors diagnosed in the main tertiary hospital in Northern Jordan throughout the period of 2004–2017 were included. Specimens were tested by H&E and immunohistochemical stains. Clinical data were collected from patients' medical files. IRB approval number 310/2016 was granted by Jordan University of Science and Technology review board.

Results: 86.9% of cases were males compared to 13.1% in females obtaining a male:female ratio of 6.6:1. The mean age was 63.8 years with a range of 28–103 years. Prevalence of cases increased with increasing age and smoking. Histopathologically, adenocarcinoma accounted for over half of the cases followed by Squamous cell carcinoma (SCC) and neuroendocrine tumors (NET) in both sexes. Adenocarcinoma had the lowest mean age; 62.74 years, while SCC had the highest mean age with 65.42 years. All subtypes increased with age but in different degrees. The increase was more pronounced in SCC and NET and less with adenocarcinoma. Adenocarcinoma was more common in both smokers and non-smokers. However, smokers to non-smokers ratio differed; where it was the highest in NET (6:1) compared to 4:1 in SCC and 2:1 in adenocarcinoma.

Conclusion: Median age of our patients was slightly lower than that previously reported in Jordan. This study also showed an increase in the relative incidence of adenocarcinoma compared to SCC.

1. Introduction

Cancer is a worldwide public health problem. Currently, cancer is second only to cardiovascular disease as the leading cause of death. Indeed, recent estimates by the World Health Organization (WHO) indicated that cancer accounts for 9.6 million deaths annually [1]. With current disease trends, it is expected that 38.4% of the world population will be diagnosed with cancer during their lifetime [2]. Disease trends also showed clear geographic disparity in the distribution of cancer cases. Incidence and mortality of the most common types of cancer are declining in the United States and many other western countries [3]. On the other hand, it is estimated that cancer in underdeveloped countries will account for more than 60% of the total cases worldwide by the year 2030. This will represent a 4% increase in cancer cases from figures estimated in 2008 [4].

Worldwide, lung cancer is the most diagnosed cancer among men,

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and the third most diagnosed cancer among women [5]. With around 2 million cases and 1.76 million deaths per year, lung cancer is the leading cause of cancer morbidity and mortality [6]. The 5-year survival rate of lung cancer is only 19.4% for newly diagnosed cases which makes it among the lowest of all cancers. Unfortunately, 5-year survival rates of lung cancer have only minimally declined over the last forty years [7]. Tobacco smoking remains the most strongly linked risk factor of lung cancer [6]. For example, in view of an increasing number of female tobacco smokers, lung cancer incidence has been increasing since the beginning of the 21st century and in 2017 has surpassed breast cancer as the leading cause of cancer related death in some countries [8].

Lung epithelial tumors arise from the respiratory epithelium and are commonly divided into adenocarcinoma, squamous cell carcinoma, small cell carcinoma, large cell carcinoma and large cell neuroendocrine carcinoma as classified by the 2015 WHO classification of Lung tumors [9]. Adenocarcinoma, squamous cell carcinoma and large cell carcinomas are subtypes of non-small-cell lung carcinoma (NSCLC) which account for 85% of all lung cancer cases [10]. Among NSCLC, adenocarcinoma is the most common classification comprising 40% of all lung cancers. It has higher chances of being detected in earlier stages before spreading outside the lung [11]. The other two subtypes; squamous cell carcinoma and large cell carcinoma, are strongly associated with smoking and are found in around 30% and 10% of all lung cancer cases, respectively [11,12].

Similar to global prevalence, cancer is the second leading cause of death in Jordan following cardiovascular disease [5]. Studies of cancer trends in Jordan over a period of 14 years (from 2000 to 2013) demonstrated a 60% increase in cancer incidence with a higher incidence rate in females [13]. Over 5000 new cases of cancers were registered over the study period [14]. With recent estimates indicating an increase in the prevalence of smoking among male and female population in Jordan [15], lung cancer is expected to be a burden on public health. Indeed, although lung cancer is the third most common cancer and accounts for 6.8% of new cancer cases in both sexes, lung cancer is the most lethal cancer in Jordan [14]. In Jordan, a number of tobacco control policies were implemented in the shape of legislations addressing smoke-free places, tobacco advertising, labelling, packaging and promotion in addition to imposing a 200% tax on electronic cigarettes, vapes, and their products in 2019 [16]. Despite that, the lack of strict implementation and the increasing use of electronic nicotine delivery systems led to the failure of such policies.

Although several studies reported lung cancer disease trends in Jordan, none of the studies included a comprehensive overview of the histopathological classification of main primary lung cancer and its correlation with tobacco smoking and other risk factors. Given this current gap in knowledge, we retrospectively reviewed the histopathological specimens and reports of all primary epithelial lung cancer cases diagnosed over a 14-year period correlating it with age, sex and smoking status.

2. Materials and methods

King Abdullah University Hospital (KAUH) is a major medical health care facility that serves the north province of Jordan. All cases from the 3 main categories of primary epithelial lung cancer diagnosed at KAUH pathology department were collected throughout the period of 2004–2017. Cases that did not fall under the categories of adenocarcinoma, squamous cell carcinoma or neuroendocrine carcinoma of primary lung origin were excluded, including all non-epithelial or metastatic tumors. The demographic data and tumor histology information for all cases were extracted retrospectively.

All cases included in the study were reviewed by three pathologists independently (consultant pathologist, specialist pathologist, and senior resident pathologist). Four micrometer sections were stained with H&E and different immunohistochemical stains. Cases that showed the proper tumor morphology and were positive for P63 and CK 5/6 immunostains were considered squamous cell carcinoma. Cases that were positive for TTF-1 and CK 7 immunostains were considered as adenocarcinoma. Cases that showed positivity for CD56 or synaptophysin or chromogranin immunostains were considered small cell carcinoma or large cell neuroendocrine carcinoma. All immunohistochemical stains were performed by Ventana v12.32 (Tucson, USA) fully automated system.

All personal identification information were omitted to ensure patient confidentiality. The study was approved by the IRB committee at KAUH and Deanship of Research at Jordan University of Science and Technology (Research proposal number 310/2016). This work has been in line with STROCSS criteria [17]. It was also registered with research registry (unique identification number "researchregistry6734"). Using IBM SPSS V.24, the chi square test was employed to measure the significance of association using a statistical significance threshold of $p = 0.05$.

3. Results

Records showed that in the period from January-2004 until December-2017, a total of 434 consecutive primary lung epithelial tumors met the eligibility criteria. The majority of the patients were males (86.9%), while only 13.1% of the patients were females; p value < 0.001 (Table 1). This translated into a male to female ratio of 6.6:1.

The age range of the patients was 28–103 years with a mean age of 63.8 ± 11.8 years at the time of diagnosis with no significant difference in age between males and females. Significant differences existed in the distribution of primary lung tumors among the different age groups ($p < 0.001$). The highest frequency of tumors was among individuals 70 years or older (36.9%), while the lowest frequency was among patients younger than 50 years (12.03%).

Findings demonstrated that the majority of the patients were smokers (66.4% vs.24.0%; $p < 0.001$). Significant differences existed in the smoking status of the patients between genders with male patients more likely to be smokers than female patients (83.0% vs 18.8%; $p < 0.001$). Lung cancer patients who were smokers were slightly younger than those who were non-smokers at the time of their diagnosis (63.2 ± 11.0 vs. 64.8 ± 14.1; $p = 0.312$) (Table 2).

Adenocarcinoma was the most frequently diagnosed primary lung tumor accounting for 55.3% of all the cases, followed by squamous cell carcinoma (30.2%) and neuroendocrine carcinomas (14.3%). The relative frequency of histologic subtype remained constant between males and females with adenocarcinoma being the most frequently diagnosed tumor in male and female patients (Table 3). The mean age at diagnosis differed among the different histological types; patients with adenocarcinoma were the youngest (62.74 ± 11.9) while patients with squamous cell carcinoma were the oldest (65.42 ± 11.6). All histopathological subtypes of lung cancer showed an increase in frequency with increasing age. This trend was the strongest in squamous cell carcinoma (Table 4).

Adenocarcinoma was the most common histopathological subtype regardless of the age group. However, the relative frequency of adenocarcinoma compared to other histopathological subtypes differed

Table 1
Baseline characteristics of all primary lung cancer tumors diagnosed at KAUH from January-2014 to December-2017.

Variable		Number of cases (Percentages)	P-value
Gender	Male	377 (86.9%)	<0.001
	Female	57 (13.1%)	
Age (in years)	70 or older	160 (36.9%)	<0.001
	60–69	122 (28.1%)	
	50–59	95 (21.9%)	
	Below 50	52 (12.0%)	
Smoking status	Smoker	288 (66.4%)	<0.001
	Non-smoker	104 (24.0%)	

Table 2
Mean age among smoking status in both sexes.

		Age (Mean ± SD)
Males	Smokers	63.0 ± 10.9
	Non-smokers	65.5 ± 13.9
Females	Smokers	69.4 ± 13.1
	Non-smokers	63.5 ± 14.7
Total	Smokers	63.2 ± 11.0
	Non-smokers	64.8 ± 14.1

Table 3
Histopathological classification among males and females.

	Adenocarcinoma	Squamous Cell Carcinoma	Neuroendocrine tumors
Total cases (n (%)	240 (55.3%)	131 (30.2%)	62 (14.3%)
Males (percentage (%))	194 (51.6%)	125 (33.2%)	57 (15.2%)
Females percentage (%))	46 (80.7%)	6 (10.5%)	5 (8.8%)
Male: female ratio	0.6:1	3.2:1	1.7:1
Age at diagnosis (Mean ± SD)	62.7 ± 11.9	65.4 ± 11.6	64.5 ± 11.6

Table 4
Distribution of histological classification by different age groups.

Histological classification	Below 50 years	50–59 years	60–69 years	Over 70 years
Adenocarcinoma	30 (12.6%)	63 (26.4%)	69 (28.9%)	77 (32.3%)
Squamous Cell Carcinoma	14 (10.9%)	20 (15.6%)	36 (28.1%)	58 (45.3%)
Neuroendocrine tumor	8 (13.1%)	11 (18.0%)	17 (27.9%)	25 (41.0%)

between the age groups. In general, compared to other subtypes, adenocarcinoma was more frequent in younger age groups. Adenocarcinoma accounted for 57.7% of lung cancer cases in patients younger than 50 years of age and 67.0% in those aged 50–59 years. However, adenocarcinoma only accounted for 48.1% of the cases in patients older than 70 years ($p < 0.05$). On the other hand, compared to other subtypes, the relative frequency of squamous cell carcinoma was significantly higher in older age groups. The frequency of squamous cell carcinoma was 36.3% in patients older than 70 years while it accounted only for 21.3% of the cases in patients younger than 50 years ($p < 0.05$). Meanwhile, neuroendocrine carcinoma showed no significant age-related pattern (Table 5).

Adenocarcinoma was also the most common histopathological subtype in both smokers and non-smokers; 69.90% and 51.0% respectively (Table 6). Regardless of the histopathological subtype, lung cancer was always more common among smokers compared to non-smokers. However, the ratio of lung cancer patients who were smokers to those who were non-smokers differed between the different histopathological subtypes. This ratio was the highest in patients with neuroendocrine carcinoma (6:1), followed by squamous cell carcinoma (4:1) and was the lowest among patients with adenocarcinoma (2:1) (see Table 7).

Table 5
Number of cases and percentages breakdown of cases in different histopathological classification by age groups.

Histological classification	Adenocarcinoma	Squamous Cell Carcinoma	Neuroendocrine tumor
Below 50 years	30 (57.7%)	14 (26.9%)	8 (15.4%)
50–59 years	63 (67.0%)	20 (21.3%)	11 (11.7%)
60–69 years	69 (56.6%)	36 (29.5%)	17 (13.9%)
Over 70 years	77 (48.1%)	58 (36.3%)	25 (15.6%)

Moreover, adenocarcinoma incidence was almost as common as all other primary lung tumors combined among smokers, whereas it was almost double the incidence of all other subtypes among non-smokers. Thus, despite being a major causative risk factor, the consequences of smoking varies between different subtypes with adenocarcinoma having less pronounced relation to smoking compared to other histopathological subtypes.

4. Discussion

Despite not being the most commonly diagnosed cancer in Jordan, lung cancer is the most lethal similar to global trends [14,18]. Although Jordan cancer registry reports examine cancer disease trends periodically, studies that examined histopathological classification of lung cancer and its relationship with established risk factors of the disease such as age and smoking are scarce. To our knowledge, this report is the first in Jordan to provide a comprehensive overview of primary lung cancer including its histopathological subtypes and their relationship with established risk factors such as male gender, smoking and age.

A common trend of lung cancer worldwide is the presence of a strong gender bias where lung cancer is more common among males [19,20]. In this cohort of patients of predominantly Arab ethnicity, male to female ratio was consistent with epidemiological findings reported in populations of other ethnicities. Lung cancer was over six times more frequent in males compared to females. This ratio is higher than the ratio previously reported by Jordan cancer registry (JCR) which was published in 2015. In the above document, JCR reported a male and female incidence of 79.6% and 20.4% respectively which translates into a male to female ratio of 3.9:1 [14]. Despite the strong male gender bias of lung cancer observed worldwide, current global trends are increasingly showing an increased prevalence of lung cancer among females accompanied with a decreasing prevalence among males. Several factors were put forward to explain this trend. A common explanation is the increasing prevalence of female smokers worldwide despite some studies suggesting other contributing factors [19–21]. Interestingly, the above trend was not observed in this study cohort. On the contrary, the percentage of female lung cancer cases in this cohort was lower than previously reported findings from other patient cohorts in Jordan [13,14,22]. Thus, it appears that a holistic approach to study the changing smoking trends and its effect on lung cancer incidence in males and females is required to address this issue. This becomes particularly important in view of several reports showing that females are more susceptible than males to a plethora of carcinogenic chemicals present in cigarette smoke [23].

Age is another important determinant of lung cancer. This study reported a slightly lower age of lung cancer patients at the time of their diagnosis compared to results reported by JCR. Herein, we report a median age at diagnosis of 65 years while JCR reported a median age of 66 years [14]. Based on the findings of this report and previously published reports of JCR, ethnic differences exist in the age of lung cancer patients at the time of their diagnosis. For example, lung cancer in Jordan is diagnosed at an older age compared to cohorts in Poland and China where the age of lung cancer patients at the time of their diagnosis is 62 and 59 years, respectively. However, the age of lung cancer patients in this report is similar to results reported from several cohorts in the United States [19,24,25].

A previous report published by JCR noted that male patients are diagnosed with lung cancer at a younger age than female patients [26]. However, this finding was not observed in this cohort and is similar to cohorts from the United States which reported no differences in the age of lung cancer patients between the two genders [20].

Age is a well-established risk factor of lung cancer. Most study cohorts of lung cancer have a median age of 60–70 years which makes lung cancer predominantly a disease of the elderly. Nonetheless, lung cancer could be diagnosed in age groups younger than 40 years old.

Table 6
Histological classifications mean age, gender and smoking status distribution.

	Mean age	Gender		Smoking status Number of cases (percentages among the histopathological classification)		Smoking status (Percentages among smoking status)	
		Male	Female	Smoker	Nonsmoker	Smoker	Nonsmoker
Adenocarcinoma	62.7 ± 11.9	194 (80.8%)	46 (19.2%)	147 (67.1%)	72 (32.9%)	51.0%	69.9%
Squamous Cell Carcinoma	65.4 ± 11.6	125 (95.4%)	6 (4.6%)	92 (80.0%)	23 (20.0%)	31.9%	22.3%
Neuroendocrine Carcinoma	64.5 ± 11.6	57 (91.9%)	5 (8.1%)	49 (86.0%)	8 (14.0%)	17.0%	7.8%

Table 7
Adenocarcinoma cases in smoker and non-smokers.

		Number of cases (percentage)
Adenocarcinoma	Smoker	147 (67.1%)
	Non-smoker	72 (32.9%)
Others	Smoker	141 (81.5%)
	Non-smoker	32 (18.5%)

Interestingly, lung cancer diagnosed in these younger age groups has different disease trends. Lung cancer in younger age groups are more likely to affect females with a higher percentage of the adenocarcinoma subtype [27]. In this cohort, a total of 11 lung cancer cases were diagnosed at ages lower than 40 years constituting 2.9% of the total sample population. From those, 63.6% of the cases were classified as adenocarcinoma. If these findings are compared with figures of lung cancer patients of the older age group where lung cancer of the adenocarcinoma subtype constituted 52.4% of the population; it can be realized that this finding agrees with previous studies linking lung cancer cases in younger age groups with a higher percentage of adenocarcinoma. However, these findings need to be confirmed in cohorts of a larger sample size [27–29].

Multiple lung cancer patient cohorts demonstrated that adenocarcinoma is more frequently diagnosed in female lung cancer patients while squamous cell carcinoma is more frequent in males. The results of this cohort are consistent with the above findings; adenocarcinoma was diagnosed in 79.6% of female lung cancer patients compared to only 48.3% of male cases. Additionally, squamous cell carcinoma was only diagnosed in 11.1% of female patients while it was diagnosed in 34% of male lung cancer patients. The cause of this disparity in the distribution of adenocarcinoma between the genders is unknown. It could be related to differences in smoking behaviour between males and females; adenocarcinoma is less strongly linked with cigarette which is less common among female lung cancer patients including females of this cohort [30,31].

In this cohort, adenocarcinoma was the most commonly diagnosed histopathological type of lung cancer accounting for almost half of the cases. In an earlier report published by JCR in 2012, it was found that adenocarcinoma constituted less than one third of the total cases of lung cancer. Accordingly, findings of this cohort demonstrate a marked increase in the incidence of adenocarcinoma. This observation is in agreement with a worldwide trend reported from several cohorts demonstrating a decrease in the prevalence of squamous cell carcinoma. The exact cause of this trend is currently unknown but could be related to new techniques in use in tobacco industry that include a reduction in tar content and the introduction of better filters. It could also be related to smoking cessation efforts [26,30].

This investigation suffers from several limitations. Firstly, it only represents data collected from a single institution in Jordan and further studies from multiple institutions are required to validate our findings. Secondly, the dataset lacks survival data of the patients which prevented us from performing relevant analysis that examines the relationship between different risk factors and patient survival. Finally, information on other potential risk factors such as water pipe smoking, occupational exposure to potential carcinogens or the use of electronic nicotine delivery systems was not collected in this investigation.

Despite that, this study can serve as a baseline indicating the incidence and patterns of lung cancer and its histopathology in Jordan. The changes in smoking patterns and the shift towards alternative smoking habits; waterpipe and e-cigarette smoking, can dramatically impact the status of lung cancer in the next years.

5. Conclusion

In Jordan, the disease trends of primary lung cancer were generally not different than other populations. Given the findings of this and other investigations, we recommend the implementation of stricter tobacco control regulations and programs.

Ethical approval

The study was approved by the IRB committee at KAUH and Deanship of Research at Jordan University of Science and Technology (Research proposal number 310/2016).

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Author contribution

All authors contributed significantly.

Mohammad AlQudah and Shadi Hammouri were involved in study design.

Mahmoud Alfaqieh and Ala'a Al-Shaikh were involved in data analysis and writing the paper.

Husam Haddad, Wejdan Al-Quran, Mohanad ALebbini, Nama' Bany Amer and Haifa Al-Smadi were involved in data collection.

Mohammad ALQudah and Karem ALzoubi were included in paper review.

Research registration number

1. Name of the registry:
2. Unique Identifying number or registration ID:
3. Hyperlink to your specific registration (must be publicly accessible and will be checked):

Guarantor

Mohammad A. AlQudah.

Data availability

Data available on request from the corresponding author.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.amsu.2021.102330.

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