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Mortality Predictors of Small-cell and Non-Small Cell Lung Cancer among Saudi Patients

By

Hatim Alghamdi

[Degree to be awarded: MPH]

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Mortality Predictors of Small-cell and Non-Small Cell Lung Cancer among Saudi Patients

By

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Mortality Predictors of Small-cell and Non-Small Cell Lung Cancer among Saudi Patients

By Hatim Alghamdi

Abstract

Background

Lung cancer ranks as the top cancer worldwide in terms of incidence and constitutes a major health problem. About 90% of lung cancer cases are diagnosed at advance stage where treatment is not available. Despite evidence that lung cancer screening improves survival, guidelines for lung cancer screening are still a subject for debate. In Saudi Arabia, only 14% of lung cancers are diagnosed at early stage and research on survival and its predictors is lacking. This study was conducted to assess predictors of lung cancer mortality according to the two major cancer types, small-cell lung cancers (SCLCs) and non-small cell lung cancers (NSCLCs) in Saudi Arabia.

Material and Methods

A secondary data analysis was performed on small-cell lung cancers (SCLCs) and Non-small cell lung cancers (NSCLCs) registered in the Saudi Cancer Registry (SCR) for the period 2009-2013 to estimate predictors of mortality for both lung cancer types. A total of 404 cases (197 SCLC and 207 NSCLC) were included in the analysis, all Saudi nationals.

Result

A total of 213 (52.75%) deaths occurred among lung cancer patients, 108 (54.82%) among SCLCs and 105 (50.72%) among NCSLCs. Around 75% of patients were diagnosed with advanced disease stage for both SCLC & NSCLC. Univariate analysis revealed higher mean age at diagnosis in dead patients compared to alive patients for SCLCs ($p=0.04$); but not NSCLCs, a lower mortality for NSCLCs diagnosed in 2013 ($p=0.025$) and a significant difference in stage of tumor ($p=0.006$) and ($p=0.035$) for both SCLC and NSCLC respectively. In multiple logistic regression, stage of tumor was a strong predictor of mortality, where distant metastasis increased morality by 6-fold (OR=5.87, 95% CI: 2.01 – 17.19) in SCLC and by 3-fold (OR= 3.29, 95% CI: 1.22 – 8.85) in NSCLC, compared to localized tumors. Those with NSCLC who were diagnosed in 2013 were less likely to die by 64% compared to NSCLC diagnosed in 2009 (OR=0.36, 95% CI: 0.14 – 0.93). Age, sex, topography and laterality were not associated with mortality for both cancer types.

Conclusion

We observed that the stage of the tumor is the strongest predictor of mortality for both SCLCs and NSCLs. This confirms the impact of diagnostic stage on survival. Because the majority of lung cancers were diagnosed at an advanced stage, introducing lung cancer screening and early detection in Saudi Arabia will likely confer a survival advantage in lung cancer.

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Chapter 1: Introduction

Lung cancer is the most commonly diagnosed cancer in the world [1]. According to GLOBACAN, a total of 1.8 million cases of lung cancer were registered during 2012, making up 13% of all cancer deaths. Although cancers along with other non-communicable diseases have been identified by the United Nation General Assembly as an important element in sustainable development and recognized as priority in national planning, respiratory health particularly has been proposed as a neglected topic, even with the high cost-effectiveness of its preventive measures [2-4]

Lung cancer incidence has tracked historically since the beginning of the 20th century and has shown a trend of growth globally given that in 2002 the number of registered cases was 1.35 million which increased to 1.6 million cases by 2008 [5] . This change in incidence contributed to changes in exposure to risk factors, especially smoking, as well as an increase in lifespan and population size [5, 6]. Moreover, the increase in lung cancer trends in recent years has been mostly attributed by developing countries, given that in 1980, the proportion of lung cancer from developing countries was 31%, whereas in 2002, it has increased to 50%. It is important to note that, developed countries have reached their peak incidence at mid of 1980s, as rate begun to decline since then [5].

The mortality rate of lung cancer is relatively close to its incidence rate, with the global mortality-to-incidence ratio being 0.88 and 0.84 for males and females, respectively [6, 7]. As a leading cause of death, lung cancer was responsible for 2.3% of total deaths worldwide during 2004 and ranked as the 8th leading cause of death. However, due to the growing trend, lung cancer is projected to be the 6th leading cause of death during 2030, making up nearly 3.1% of total global deaths [8, 9].

Saudi Arabia has a low incidence rate of lung cancer compared to global incidence. In 2013, the age-standardized ratio (ASR) was 5.5 per 100,000 for males and 1.8 per 100,000 for females [10]. In contrast, the average global ASR during 2008 was 33.8 per 100,000 for males and 13.5 for females [11]. But, the growing population size in Saudi Arabia along with improvement in health services and a decreasing overall mortality rate will most likely result in a larger elderly population size [12], as the elderly population size in Saudi Arabia is expected to increase by sevenfold in the next 25 years [13]. Besides aging as a risk factor for cancer, smoking as primary risk factor for lung cancer; showed a significant increase in its prevalence among Saudis during the 1980-2012 period by at least 1.5% per year for males and 2.0% per year for females [14]. However, age-standardized prevalence of smoking during 2013 was 26.8% for males and 3.0% for females [15]

Global trends of lung cancers staging shows that only 15% of cases are diagnosed at an early stage [11]. In Canada, only 20-30% of cases are diagnosed at early stages [16]. Saudi Arabia fall within the global range, with only 14% of cases diagnosed early with localized tumors [10].

According to the American Cancer Society (ACS), the average age at the time of lung cancer diagnosis is 70 years old, which is 8.8 years below the life expectancy in the U.S. [17, 18]. Where, the actual burden of lung cancer is reflected by premature mortality instead of total mortality. In 2002, lung cancer was responsible for 11 million years of life lost in the world and 233,000 years lost due to disability. The reason behind that is the very low survival rate of lung cancer, as the highest survival rate found in Japan with 5-year survival rate of 20.7% for males and 27.6% for females. In the U.S., the 5-year survival rate is 17.7%. However, in developing countries, the 5-year survival rate is 9% for both genders [5, 19].

Annual lung cancer screening has been recommended since 2012 by several health organizations and expert panels, including; ACS, National Comprehensive Cancer Network (NCCN) and US Preventive Service Task Force (USPSTF) using Low dose-CT scanning, which showed a significant decrease in lung cancer mortality by 20.0% (95% CI: 6.8 - 26.7) (P=0.004) [20]. Besides that, Lung screening program is better to be a supplementary to smoking cessation programs to support cessation and abstinent continuity among smokers [21].

Despite the introduction of lung cancer screening guidelines and the progress has been made in this topic, other features like applications of such a guideline, follow-up protocol, cost-effectiveness, safety, and complication are still subjected to discussion [22].

In Saudi Arabia, there is a shortage of research regarding lung cancer. Although of the effort conducted by Saudi Lung Cancer Association, but from a public health prospective, lung cancer is a neglected topic in Saudi Arabia. Hence, main question of this paper is focused on the predictors of mortality among lung cancer patients, both small-cell and non-small cell, in Saudi Arabia for the period of 2009 to 2013.

Chapter2: Literature Review

Lung Cancer: Definition, Histology, Grading and Staging

The term lung cancer, or bronchogenic carcinoma, refers to malignancies that originate in the airways or pulmonary parenchyma [23]. The International Classification of Disease, tenth revision (ICD-10), classifies lung cancer as a malignant neoplasm of the bronchus and lung with code C34, found under chapter 2: Neoplasms. Lung cancer is characterized by its topography, histology (morphology), grade, extension (staging), and behavior.

To understand lung cancer epidemiology, the World Health Organization (WHO) introduced lung cancer classification in 1967, which is based mainly on resection specimens. In 2004, the WHO updated the lung cancer classification to add histological characteristics to the classification methods. The most recent update to WHO classification was made in 2015 to additionally include the immunohistochemical characteristics [24, 25]. In our study, the 2004 WHO classification will be used along with International Classification of Oncology (ICD-O), 3rd edition, which is considered an extension of chapter 2 of ICD-10. Furthermore, and for the purpose clinical practice, lung cancer histology can be described by using the National Comprehensive Cancer Network (NCCN) grouping which divides lung cancer into two main types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) [26]. NSCLC has four major subclasses: adenocarcinoma, squamous cell carcinoma, large cell carcinoma and NSCLS not otherwise specified. SCLC on some occasions may contain some components of other histological types and be classified as a combined small-cell carcinoma. Additional subtypes of lung cancer occur less commonly, including lung carcinoid tumors and adenoid cystic carcinoma. NSCLC is the most common type, constituting 80%-90% of lung cancers. In particular, squamous cell carcinoma constitutes 44% of lung cancer in men and 25% in women,

followed by adenocarcinoma which constitutes 28% of lung cancer in men and 42% in women and large cell carcinoma which contributes 9% of lung cancer for both genders. On the other hand, SCLC accounts for about 20% of lung cancer in both genders [7, 27]. Besides that, strength of association between different histological type and smoking had been studied frequently. Khudar conduct meta-analysis of 48 published studies, and find a stronger association for squamous cell Carcinoma and small cell carcinoma compared to large cell cancer and adenocarcinoma [28]. Finding in this study supported by other study retrospective study conducted by Govindan et al. where they track the change of SCLC in US over period from 1973 to 2002, they find a gradual decrease of SCLC proportion from 17.26 in 1986 to 12.95 in 2002. Meanwhile, this change in SCLC explained to be reflection of decreased smoking prevalence during same period or change in cigarette composition [29].

According to the WHO, tumor grading is "qualitative assessment of tumor differentiation and it has prognostic implication"[24]. The tumor grade extends from grade I (well-differentiated), grade II (moderately-differentiated) to grade III or IV (poorly-differentiated) [30]. In fact, tumor grading indicates the growth and spreading ability of the tumor cell, as a poorly-differentiated tumor can spread at a higher rate compared to moderately and well differentiated tumors [31]. Besides that, grading is a predictor of survival and also a predictor of the benefits of the therapeutic approach. However, lung cancer does not have a widely accepted grading system in contrast to other cancers, like those of the breast and prostate. For example, some histological types of lung cancer, like large cell carcinoma, are always graded as poorly differentiated. Hence, engaging in research aimed to develop a widely-accepted grading system for lung cancer is highly recommended by the WHO [30, 32].

The extension (or staging) of tumors, the distance the tumor spreads from its point of

origin, has been classified into defined levels. Analyzing tumor extension plays an important role in cancer reporting, and is used as a measurement tool when evaluating cancer prevention programs. Summary Staging or Surveillance, Epidemiology, and End Results Program (SEER) Staging is the required tool by the National Program of Cancer Registry (NPCR). According to the SEER Summary Staging Manual-2000, tumors have seven categories of extension: "in situ, localized, regional by direct extension only, regional lymph node involved only, regional by both direct extension and lymph node involvement, regional not otherwise specified and distant sit(s)/node(s) involved" [33]. In fact, this staging system is not based purely on clinical methods, but rather, is a mix of pathological and clinical information aimed at defining tumor extension.

In addition, lung cancer is described by the anatomical site of its origin with the code C34, which indicates bronchus and lung and is followed by a sub-site code to differentiate between main bronchus and lower, middle, and upper lobes. Laterality is also used to determine the side of origin. Furthermore, the behavior of tumors are part of the reporting requirement in which a tumor is characterized as benign, borderline malignant, in situ or malignant [33].

Lung Cancer Incidence, Mortality and Survival

Global Status

Lung cancer ranks as the top cancer worldwide in terms of incidence and constitutes a major health problem. According to the latest data available from International Agency for Research on Cancer's (IARC) GLOBACAN project, the number of lung cancer cases in 2012 exceeded the number of breast and colorectal cancer cases for both genders worldwide; additionally, the number of lung cancer cases was found to exceed prostate cancer cases for the male gender and to exceed breast cancer as the leading cause of cancer deaths among females

worldwide [1]. A total of 1.8 million cases of lung cancer were registered in 2012, making up 13% of all cancers, with a majority of cases among males 1.242 million male cases (68%) versus 583 thousand female cases (32%)) [34]. In fact, when looking over previous global lung cancer statistics, the 2008 statistics showed some increase in the global incidence of lung cancer, with 1.6 million cases occurring in 2008 [35], while in 2002, 1.35 million cases of lung cancer were registered [5]. Besides that, the 2008 age-standardized rate (ASR) of lung cancer incidence among male was 33.8 per 100,000 and among female was 13.5 per 100,000 worldwide [11].

Although lung cancer was a rare disease at the beginning of the 20th century [6], changes in exposure to causative agents along with the increase in lifespan, have made lung cancer one of the most commonly diagnosed cancers since 1985 [5]. The pattern and trends of lung cancer show global variations, with higher rates in developed countries and lower rates in less developed countries [35]. However, it is important to note that in more developed countries such as North America, New-Zeeland and Australia, the lung cancer rate reached its peak during 1980s and has begun to decline since then. Also important to keep in mind is the shifting trend in rates, given that in 1980, less developed countries constituted 31% of lung cancer cases worldwide, whereas in 2002 this number increased to 50% [5].

Lung cancer mortality rate is not different from its incidence rate given that 90% of lung cancer cases are usually diagnosed at the advanced stage where treatment is not available [6]. In 2012, the number of deaths due to lung cancer was estimated to be 1.59 million cases, with 1.099 million deaths for men and 491 thousand deaths for women [34]; this indicates a mortality-to-incidence ratio of 0.87 for both genders worldwide, with the ratio for females (0.84) being lower compared to that for males (0.88) [24]. Lung cancer is projected to become the 6th leading cause of death in the year 2030, accounting for 3.1% of total deaths by 2030, compared to it being the

8th leading cause of death in 2004, accounting for 2.3% of total deaths [8, 9]. However, the actual burden of lung cancer is reflected by premature mortality rather than total mortality or long-term morbidity; in 2002 lung cancer was responsible for 11 million years of life lost and 233,000 years lost due to disability. However, lung cancer causes a very low premature mortality in developing countries like Africa, and this is mostly due to a shorter life expectancy and higher infectious-related mortality in comparison to developed countries [5].

Lung cancer is characterized by a very low survival rate compared to other cancers. According to the American Lung Association (ALA), the 5-year survival rate of lung cancer is 17.7%, which is very low compared to colon cancer (64.4%), breast cancer (89.7)% and prostate cancer (98.9%) [19]. However, the 5-year survival rate in lung cancer has shown a marginal increase in the U.S. since 1970, according to data from the Surveillance, Epidemiology, and End Results (SEER) program which shows that the 5-year survival rate was 12% from 1975-1977, compared to 18% from 2003-2009 [1]. Besides that, the survival rate shows a variation between countries, with Japan having the highest survival rate (20.7% for males and 27.6% for females), followed by Canada (13.3% for males and 18.5% for females). On the other hand, in developing countries the 5-year survival rate is estimated as an average of 9% combined for both genders [5]. Lung cancer survival is determined mainly based on staging at time of diagnosis. Data from SEER demonstrates the impact of diagnostic stage on the survival rate, where localized tumors have a 55.2% chance of 5-year survival, compared to 28% for regional and 4.3% for distant tumors. However, only 16% of cases are diagnosed at the localized stage while 22% and 57% are diagnosed at regional and distant stages, respectively [36]. Furthermore, histological type has an impact on survival rate, although therapeutic strategy varies based upon histological classification; generally the NSCLC has a better survival than SCLC [37-39].

Status in the Middle East and North Africa Region

The Middle East and North Africa (MENA) region, consisting mostly of low- and middle-income countries, has experienced a rapid population growth since 1950, with the population size increasing from 100 million to 350 million by 2000. This rapid growth in population size is associated with health improvement, an increase in lifespan and an increase in elderly population. For Example, the population of elderly in Egypt is expected to increase from 4.3 million in 2000 to 23.7 million by 2050, and the population of Saudi elderly is expected to increase from 1 million in 2000 to 7.7 million in 2050 [12, 40]. Hence, in regards to cancer, this region is expected to encounter a health challenge, as aging is a risk factor for cancers. Additionally, increasing urbanization levels along with socioeconomic changes are also contributing to making cancer one of the major health challenges in this region [41].

In spite of these factors, the current trend in lung cancer in the MENA region is low, as in other developing countries [41]. In fact, a total of 16,632 cases of lung cancer were registered by Arab League countries (which constitute the majority of MENA countries) during 2008, with 13,826 (79.7%) cases registered for males, compared to 2,806 (20.3%) for females. Furthermore, the estimated ASR incidence in Arab league countries during 2008 was 13.44 per 100,000 for males, which is less than half compared to the world ASR (34.2 per 100,000 males); the female ASR in Arab countries was 2.91 per 100,000, which is also very low compared to the world ASR (13.9 per 100,000 females). The mortality-to-incidence ratio is not much different in Arab countries than in the world, with 15,421 lung cancer deaths registered during 2008 in Arab League countries, resulting in a mortality-to-incidence ratio of 0.93. Mortality ASR for lung cancer in Arab countries was estimated in 2008 to be 12.59 per 100,000 for males and 2.7 per 100,000 for females; this is relatively close to the incidence ASR. However, variations between

Arab countries exist. In males, the highest mortality rate was registered in Tunisia (33.5 per 100,000), and the lowest was in Sudan (2.4 per 100,000). In females, the highest rate was registered in Bahrain (10.5 per 100,000), and the lowest was in Comoros (0.00 per 100,000) [42].

Status in Saudi Arabia

In Saudi Arabia, the incidence of registered lung cancer is lower than the world estimate, and even lower than that of Arab League countries. Based on the 2013 Saudi Cancer Registry report, a total of 435 cases have been registered among Saudis; 329 (75.9%) were male and 106 (25.1%) were female. The ASR incidence among males was 5.5 per 100,000, and 1.8 per 100,000 for females. The incidence variation between regions inside Saudi Arabia shows that for males, the highest ASR was registered in the eastern region, at 12.4 per 100,000, followed by Tabuk, at 12.1 per 100,000; the highest rate for females was also registered in the eastern region and followed by Baha at 2.8 per 100,000[10]. However, the lowest ASR was found in Najran at 0.0 and 0.6 for male and female respectively, followed by Hail with ASR at 0.9 and 1.0 for males and females respectively. Estimates form Globocan 2012 indicate that age-standardized mortality rate for lung cancer (4.7 per 100,000, both sexes combined) is very similar to its incidence rate (4.1 per 100,000).

Risk Factors of Lung Cancer

Tobacco smoking is considered a main cause of lung cancer, as demonstrated by the evidence accumulated since the mid 20th century. One of the earliest pieces of scientific evidence that linked lung cancer to smoking was a case-control study conducted by Wynder and Graham (1950), where a total of 684 individuals with bronchogenic carcinoma were matched with 780 controls, according to their age and smoking intensity. The study showed a higher rate of smoking among bronchogenic cancer groups compared to the control group, indicating that;

"smoking has effect on the induction of lung cancer" [43, 44]. In fact, 90% of lung cancer cases among males and 79% of cases among females are caused by smoking. In addition, evidence indicates that the risk of lung cancer among smokers is 20-40 times higher than non-smokers [45]. In addition to active smoking, a rigorous evaluation of the health consequence related to passive smoking made by the US Surgeon General concluded that; "exposure of adults to secondhand smoke has immediate adverse effects on lung cancer" [46].

Compared to the burden of tobacco-related lung cancer, the occupational-related lung cancer burden is considered low. However, lung cancer is the most common cancer found in occupational-related cancers. A systematic review published by Steenland et al. (1996) calculated the relative risk (RR) for specific carcinogenic agents and found the highest relative risk to be associated with chromium (RR= 2.78) and the estimated number of exposed workers to chromium to be 551,000; however, the review estimated that more than half of occupational lung cancers are related to asbestos with a relative risk of 2.00, with 700,00 exposed workers to asbestos [47].

A small proportion of lung cancer cases (estimated at 1-2%) are due to air pollution. In a study of six U.S. cities, people who were exposed to the highest level of fine particles had a risk of 1.4 (95% CI: 0.8 – 2.4) of lung cancer mortality. Indoor air pollution as a cause of lung cancer has a variation between developed countries and developing countries,. In developed countries, lung cancer cases related to indoor air pollution are mostly due to passive smoking and radon; however, in developing countries, the concern emerges from solid fuels and coal use [48].

To date, multiple genetic abnormalities associated with lung cancer have been discovered, whether inherited or acquired. Timeofeeva et al. (2012) conducted a large meta-analysis on 16 genome-wide association studies (GWAS) of lung cancer and included data of

14,900 cases of lung cancer and 29,485 controls; findings supported an association between lung cancer incidence and chromosomal abnormality at region 5p15 and 6p21 [49]. On the other hand, abnormality of the tumor suppressor gene, TP53, is a commonly acquired mutation of lung cancer, which occurs in 50% of NSCLC, and occurs more frequently among tobacco-related lung cancer compared to non-smoker lung cancer [50].

Prognostic Factors for Lung Cancer

Tumor Characteristics

The lung cancer survival rate shows a difference by histological type, with NSCLC having a better prognosis compared to SCLC [51]. However, the staging of a tumor is the strongest determinant factor of lung cancer survival and the Tumor, Node, Metastasis (TNM) system is most commonly used. Chansky et al. (2009) conducted a retrospective study on 9,137 patients and observed a strong correlation between cancer stage and survival, where the median survival for patients at stage IIIA was 19 months, compared to 95 months for patients at stage IA [52].

Genetic markers

TP53 mutations also play a role in lung cancer prognosis. As demonstrated in Kandioler et al. (2008) clinical trial which tested the role of TP53 as a predictive marker for response to induction chemotherapy, a significant survival advantage was observed for patients with a normal TP53 gene compared to those with gene abnormality [53]. Additionally, an abnormality in the tumor suppressor protein p16 gene has been studied by Esteller et al. (1999) by examining over 22 patients with NSCLC using methylation-specific polymerase chain reaction. Their results showed abnormal hyper-methylation in the gene encoding p16 among 41% of patients across all disease stages [54]. However, Tong et al. (2011) conducted a meta-analysis to examine the prognostic effect of p16 on the survival of NSCLC patients. Twenty trials with 1995 patients

were included in the study and found that a high expression of p16 has a survival advantage with a combined hazard ratio (HR) of 0.69 [95% CI: 0.59 -0.81] [55]. Moreover, KRAS gene mutation is another abnormality found frequently in NSCLC, which has prognostic role [55]. Rosell et al. (1995) examined 192 patients with NSCLCand identified abnormal KARS in 51 (27%) of them. Adjusting for cancer stage, patients with KRAS mutation showed a lower survival time compared to patients with normal KRAS. In stage I, the median survival time for patients without KRAS mutation was 46 months compare to 21 months for those with KRAS mutation; in stage III, the median survival time for patients without KRAS mutation was 16, compared to 7 months for patient with KRAS mutation [56].

Additional Prognostic Factors

In addition, performance status (PS), which is an "assessment of patient actual level of function and capability of self-care", is an important prognostic factor and is used to guide treatment among lung cancer patients [57, 58]. PS is commonly measured by the Eastern Cooperative Oncology Group (ECOG) scale and ranges from 0 to 4 [0= normal activity; 1= symptomatic but nearly fully ambulatory, 2= some bed time but need to be in bed for less than 50% of normal day time, 3= need to be in bed for greater than 50% of normal day time and 4= unable to get out of bed] [59]. Sculier et al. (2008) conducted a study among over 81,015 cases to identify prognostic factors that are independent of clinical stage. The study found a significant effect of PS on lung cancer survival for both NSLC and SCLC. For limited disease stage, the hazard ratio (HR) of survival among patients with a PS=1 was 1.42 (95% CI: 1.3-1.55), PS=3 & 4 was 3.69 (95% CI: 3.03-4.47) in comparison to PS=0. For extensive disease stage, the HR for patients with a PS=1 was 1.32 (95% CI: 1.20-1.38), and that for patients with a PS=3 & 4 was 3.32 (95% CI: 2.84-3.88) compared to PS=0 [57].

Beside PS, the Sculier et al. study identified age and gender as significant prognostic factors independent of disease stage. According to Cancer Research UK, from 2009-2013, the 5-year survival of lung cancer was inversely correlated with age. The 5-year net survival rates for males in the age groups 40-49, 50-59, 60-69 and 70-79 were 15.9, 13.1, 12.7, 9.8, respectively. However, across all age groups, the female 5-year survival rate was better compared to males: the 5-year net survival rates for females in the age groups 40-49, 50-59, 60-69 and 70-79 were 23.2, 18.7, 17.2, 13.2, respectively [60].

To determine whether smoking status has a prognostic effect in NSCLC, Kawaguchi et al. (2010) conducted a retrospective analysis on 26,957 patients with NSCLC in Japan; a Kaplan-Meier survival curve was constructed for never smokers and ever smokers. Results showed a better median overall survival for patients who never smoked (29.9 month) compared to those who ever smoked (19 months; $p<0.0001$); however results were unadjusted for age, stage and gender [61]. To assess the effect of smoking on prognosis of SCLC, OU et al. (2009) conducted a retrospective study of 4,782 patients with SCLC, registered at the Cancer Surveillance Programs of Orang, San Diego and Imperial counties in south California. The study shows that the HR was 31% higher in those with a positive smoking history compared to those who have never smoked, with a statistically significant result ($P=0.01$) [62].

Lung Cancer Screening

Annual lung cancer screening has been recommended since 2012 by several health organizations and expert panels, including; ACS, National Comprehensive Cancer Network (NCCN) and US Preventive Service Task Force (USPSTF). Most recommendations have been made based on the National Lung Screening Trial (NLST), which is a multi-center clinical trial with sufficient power to detect a reduction in lung cancer mortality compared to other smaller

trials. The NLST recruited 50,000 asymptomatic participants who had a smoking history of 30 packs/year and who were aged between 55 and 74 years; exclusion criteria included those who were symptomatic or who had quit smoking within the past 15 years. Participants were assigned randomly to low-dose CT arm and to chest radiography arm. Those assigned to low-dose CT saw a reduction of lung cancer mortality by 20.0% (95% CI: 6.8 - 26.7) (P=0.004). Although the recommendations of lung cancer screening have been introduced mainly based on strong evidence provided by NLST, some organizations restrict their recommendation to same setting of NLST, but others make some modulation NLST setting. For example, the American Association of Thoracic Surgery extend the screening age of the at-risk population to 79 years (with 30 packs/year of smoking history), and NCCN add persons who have an extra risk factor in addition to smoking of 20 pack-year smoking and aged >50 years [20, 63]. In Saudi Arabia, there are currently no uniform guidelines for lung cancer screening.

Problem Statement

Lung cancer is characterized by very low survival rate worldwide. However, rates are even lower in developing countries as opposed to developed countries. For example, in Japan, considered to be a developed country, the highest survival rate is found, with 20.7% for males and 27.6% for females. In the U.S., the 5-year survival rate is 17.7%. However, in developing countries, the 5-year survival rate is 9% for both genders [5, 19].

Only a small portion of lung cancers are diagnosed at an early stage in Saudi Arabia, and approximately three quarter of the cases are diagnosed at an advanced stage [10]. Reserach regarding lung cancer mortality and survival rate, for overall cancers and specific types, is lacking in Saudi Arabia.

The Saudi Lung Cancer Association developed lung cancer management guidelines in 2008 and updated them later in 2012, by efforts of the Saudi lung cancer guidelines committee. These guidelines aim to enhance the overall survival rate among cancer patients, as studies have shown that more variation in lung cancer management leads to a lower overall survival rate. These guidelines were adopted form North American and European guidelines, Developing Saudi-specific management guideline may better contribute in improving the overall survival rate [64]; however, this is hampered by the absence of research to characterize lung cancer survival and its predictors according to different cancer types.

Currently, Saudi Arabia does not have national screening guidelines for lung cancer. Developing country-specific screening guidelines requires a strong research base on lung cancer mortality to offer more evidence for decision makers about the value of instituting and implementing national screening guidelines.

Therefore, the existing gap in research on lung cancer mortality needs to be offset to provide information-for-action for the development of Saudi-customized screening and management guidelines for this malignancy.

Research question

To address the above-mentioned gaps, we conducted a study using data from the Saudi Cancer Registry to identify predictors of lung cancer mortality for both small-cell and non-small cell cancers in Saudi Arabia for the period of 2009 to 2013.

Significance

Saudi Arabia, has a shortage of research regarding lung cancer and this study attempts to

help filling this gap. This study, conducted retrospectively, aims to examine mortality predictors for lung cancer in Saudi patients. Currently, Saudi Arabia does not have national screening guidelines for lung cancer. This research will offer more evidence for decision makers about the value of instituting and implementing national screening guidelines. This study will also provide baseline data that can be used to evaluate the effect of the newly introduced recommendations on lung cancer mortality.

Chapter 3 – Manuscript

Abstract

Background
Lung cancer ranks as the top cancer worldwide in terms of incidence and constitutes a major health problem. About 90% of lung cancer cases are diagnosed at advance stage where treatment is not available. Despite evidence that lung cancer screening improves survival, guidelines for lung cancer screening are still a subject for debate. In Saudi Arabia, only 14% of lung cancers are diagnosed at early stage and research on survival and its predictors is lacking. This study was conducted to assess predictors of lung cancer mortality according to the two major cancer types, small-cell lung cancers (SCLCs) and non-small cell lung cancers (NSCLCs) in Saudi Arabia.

Material and Methods
A secondary data analysis was performed on small-cell lung cancers (SCLCs) and Non-small cell lung cancers (NSCLCs) registered in the Saudi Cancer Registry (SCR) for the period 2009-2013 to estimate predictors of mortality for both lung cancer types. A total of 404 cases (197 SCLC and 207 NSCLC) were included in the analysis, all Saudi nationals.

Result
A total of 213 (52.75%) deaths occurred among lung cancer patients, 108 (54.82%) among SCLCs and 105 (50.72%) among NCSLCs. Around 75% of patients were diagnosed with advanced disease stage for both SCLC & NSCLC. Univariate analysis revealed higher mean age at diagnosis in dead patients compared to alive patients for SCLCs (p=0.04); but not NSCLCs, a lower mortality for NSCLCs diagnosed in 2013 (p=0.025) and a significant difference in stage of tumor (p=0.006) and (p=0.035) for both SCLC and NSCLC respectively. In multiple logistic regression, stage of tumor was a strong predictor of mortality, where distant metastasis increased morality by 6-fold (OR=5.87, 95% CI: 2.01 – 17.19) in SCLC and by 3-fold (OR= 3.29, 95% CI: 1.22 – 8.85) in NSCLC, compared to localized tumors. Those with NSCLC who were diagnosed in 2013 were less likely to die by 64% compared to NSCLC diagnosed in 2009 (OR=0.36, 95% CI: 0.14 – 0.93). Age, sex, topography and laterality were not associated with mortality for both cancer types.

Conclusion
We observed that the stage of the tumor is the strongest predictor of mortality for both SCLCs and NSCLs. This confirms the impact of diagnostic stage on survival. Because the majority of lung cancers were diagnosed at an advanced stage, introducing lung cancer screening and early detection in Saudi Arabia will likely confer a survival advantage in lung cancer.

Introduction

Lung cancer is the most commonly diagnosed cancer in the world accounting for 13% of all cancer deaths [1]. According to GLOBOCAN, a total of 1.8 million cases of lung cancer were registered during 2012, marking an increase from 1.35 million cases in 2002 and 1.6 million cases in 2008 [5, 65]. The increasing trend in lung cancer incidence is attributed to changes in exposure to risk factors, especially smoking, as well as an increase in lifespan and population size [5, 6]. Moreover, the increase in lung cancer trends in recent years has been mostly contributed by developing countries, given that in 1980, the proportion of lung cancer occurring in developing countries was 31%, whereas in 2002, it increased to 50%. It is important to note that, developed countries have reached their peak incidence at mid of 1980s, and rates have begun to decline since then [5].

The mortality rate of lung cancer is relatively close to its incidence rate, with the global mortality-to-incidence ratio being 0.88 and 0.84 for males and females, respectively [6, 7]. As a leading cause of death, lung cancer was responsible for 2.3% of total deaths worldwide during 2004 and ranked as the 8^{th} leading cause of death. However, due to the growing trend, lung cancer is projected to be the 6^{th} leading cause of death during 2030, making up nearly 3.1% of total global deaths [8, 9].

Global trends of lung cancers staging shows that only 15% of cases are diagnosed at an early stage [11]. In Canada, only 20-30% of cases are diagnosed at early stages [16]. Saudi Arabia fall within the global range, with only 14% of cases diagnosed early with localized tumors [10].

According to the American Cancer Society (ACS), the average age at the time of lung cancer diagnosis is 70 years, which is 8.8 years below the life expectancy in the U.S. [17, 18].

Where, the actual burden of lung cancer is reflected by premature mortality instead of total mortality. In 2002, lung cancer was responsible for 11 million years of life lost in the world and 233,000 years lost due to disability. The reason behind that is the very low survival rate of lung cancer, where the highest 5-year overall-survival rate in the world stands at 20.7% for males and 27.6% for females in Japan. In the U.S., the 5-year overall-survival rate is 17.7%. However, in developing countries, the 5-year overall-survival rate is 9% for both genders [5, 19].

Annual lung cancer screening has been recommended since 2012 by several health organizations and expert panels, including; the ACS, the National Comprehensive Cancer Network (NCCN) and the US Preventive Service Task Force (USPSTF) using low dose-CT scanning, which showed a decrease in lung cancer mortality by 20.0% (95% CI: 6.8 - 26.7) (P=0.004) [20].

Despite the introduction of lung cancer screening guidelines, progress is yet to be made on the implementation of guidelines and follow-up protocols and further assessment of cost-effectiveness, safety, and complications of screening [22].

Saudi Arabia has a low incidence rate of lung cancer compared to global estimates. In 2013, the age-standardized ratio (ASR) was 5.5 per 100,000 for males and 1.8 per 100,000 for females [10]. In contrast, the average global ASR during 2008 was 33.8 per 100,000 for males and 13.5 for females [11]. But, the growing population size in Saudi Arabia along with improvement in health services and a decreasing overall mortality rate will most likely result in a larger elderly population size [12], as the elderly population size in Saudi Arabia is expected to increase by sevenfold in the next 25 years [13]. Besides aging, smoking as a primary risk factor for lung cancer showed a significant increase in its prevalence among Saudis during the 1980-2012 period by at least 1.5% per year for males and 2.0% per year for females [14]. However,

age-standardized prevalence of smoking during 2013 was 26.8% for males and 3.0% for females [15]

There is a shortage of research on lung cancer in Saudi Arabia. Despite the efforts by the Saudi Lung Cancer Association to bring emphasis on the topic, lung cancer is a neglected area of research in Saudi Arabia. This study aims at examining predictors of lung cancer mortality in Saudi patients, evaluating SCLCs and NSCLCs separately. Currently, Saudi Arabia does not have national screening guidelines for lung cancer. This research will offer more evidence for decision makers about the value of instituting and implementing national screening guidelines. This study will also provide baseline data that can be used to evaluate the effect of the newly introduced recommendations on lung cancer mortality.

Methods

Study Design

We performed a secondary data analysis on lung cancer cases reported to the Saudi Cancer Registry (SCR) during the period of 2009 to 2013.

Setting and Data Source

Data was requested and readily available from the SCR, as part of their mission to support dissemination and utilization of registry data. The main objective of SCR is to identify the population-based incidence of cancers in Saudi Arabia. However, in 2004 the registry began to collect data on cancer mortality indicators beside the incidence.

SCR was established in 1992 by the Ministry of Health (MoH) of Saudi Arabia and its coverage spanned public health facilities, including those under MoH and others that are affiliated with the military and education sectors, as well as private health facilities. Five regional

hospital-based offices were founded to ensure coverage of all regions in the country. Regional coverage of SCR is largely complete, but completeness and accuracy of SCR's data cannot be determined due to the unavailability of assessment studies in this regard. However, it should be noted that the MoH classifies cancers as a mandatory notifiable disease; for both government and private sectors, which may facilitate the completeness and accuracy of SCR's data.

Data collection in SCR is conducted by trained registered staff under the direct supervision of the regional office. Data is gathered from patient medical records and entered into a customized web-based program. The program connects all regional offices in order to facilitate data filtering and cleaning and to avoid duplicate entry of data. SCR publish all incidence data for all cancer in annual reports.

Lung Cancer Case Definition

In this research, lung cancer, or bronchogenic carcinoma, refers to malignancies that originate in the airways or pulmonary parenchyma. By using International Classification of disease, tenth revision (ICD-10), lung cancer has been classified as malignant neoplasm of the bronchus and lung with the code C34, as described under Chapter 2 of ICD-10; Neoplasms. The database was restricted to NSSLC and SCLC types of lung cancer. The database included 453 cases of invasive NSCLC and SCLC registered between 2009 to 2013. SCLC included five categories: small cell carcinoma- NOS, oat cell carcinoma, small cell carcinoma, fusiform cell, small cell carcinoma, intermediate cell and combined small cell carcinoma. However, all subtypes of NSCLCs were recorded under a single category coded as NSCLC [10].

Study Variables

Data obtained by the SCR was restricted to patients of Saudi nationality. Information collected on patients included demographic data (sex, age, nationality), date of diagnosis, tumor characteristics (topography, morphology, behavior, grade, extension, and laterality), date of last contact and mortality indicators (status and cause of death).

Tumor Characteristics

The variables topography (primary site) and morphology (histology) were recorded according to the International Classification of Disease for Oncology, 3rd edition. Topography was recorded into six categories; main bronchus, upper lobe, middle lobe, lower lobe, overlapping lesion of lung, lung not otherwise specified (NOS). Morphology was restricted into SCLC and NSCLC according to the SEER histology validation list [66].

Tumor stage (extension) which describes the spread of the tumor from its point of origin had eight categories: in situ, localized, regional by direct extension, regional by lymph node, regional by both direct extension and lymph node, regional-NOS, distance metastasis systematic disease and unknown.

Tumor grade, which describes tumor aggressiveness, had five categories: well differentiated/ differentiated NOS, moderately/moderately well differentiated, poorly differentiated, undifferentiated/ anaplastic and unknown.

Tumor behavior was coded with two codes: in situ or malignant/invasive; however, all 452 observations in our analysis were malignant/invasive behavior. Laterality of tumor was described in eight categories: organ is not a paired site, origin of primary is right, origin of primary is left, only one sides involved, right or left origin not specified, bilateral involvement, paired site: midline tumor, paired site, no information on laterality.

Mortality Indicators

The vital status variable was recorded as dead, live and unknown, with only one observation coded as unknown and has excluded. The cause of death was recorded in three categories; not applicable for alive case, cancer for those who died because of cancer and unknown if the cause of death was not cancer-related. One observation only recorded as unknown cause of death and was excluded.

Data Management

The dataset included 452 registered cases of lung cancer during 2009-2013, all of which were of Saudi nationality. Diagnoses were restricted to NSCLC and SCLC types of lung cancers.

We excluded from analysis cases without a valid vital status (N= 1), known cause of death (N= 1) or reported data on cancer extension (N= 47; 23 dead and 24 alive). Therefore, the final dataset included 404 observations with total exclusion of 48 observations.

For the grading variable, 309 observations out of 452 are coded as an unknown grade, hence, grade was not included in the analysis.

Statistical Analysis

All analyses were done separately for SCLCs and NSCLCs. We examined the distribution of variables and conduced a univariate analysis stratified by SCLC and NSCLC to find differences for each variable. Differences in continuous variables between alive and dead patients were done by T-test. Differences in categorical variables were done by Chi-square test or via Fisher's exact test in cases where expected counts were less than five (e.g. topography, grade, stage and laterality).

To estimate predictors of mortality for each histological subtype, logistic regression was performed. A dichotomous mortality indicator variable was regressed on age, sex, topography, extension, laterality and year of diagnosis. Odd ratios (OR) and 95% confidence intervals (95% CI) were calculated for each predictor. Tumor grade was not included in our model due to the large number of missing data (N=272) and due to the lack of a widely accepted grading system for lung cancer that is used consistently by all health facilities. Tumor behavior variable also was not included in the model due to collinearity, where all observations are recorded as malignant behavior. The level of statistical significance was set at 0.05. Stata (version SE64, Stata Corporation, College Station, TX) was used for analysis.

Results

Demographic and Tumor Characteristics for SCLC and NSCLC

A total of 404 lung cancer cases were diagnosed during the period 2009-2013 and included in our final analysis. SCLC composed 48.8% (N= 197) with mortality recorded for 108 (54.8%) among them and NSCLC composed 51.2% of observations (N= 207) with mortality recorded for 105 (50.7%) among them [table 1]. Out of a total of 404 cases, there were 337 (83.4%) cases in males and 67 (16.6%) in females. The overall mean age of lung cancer diagnosis was 63.3 year (SD 12.46 years). The mean age of diagnosis was 63.7 years (SD 12.4 years) in males and 61.02 (SD12.37) in females (p= 0.10). Mean age of diagnosis was 62.19 years (SD 12.52 years) for NSCLC and 64.39 years (SD 12.33 years) for SCLC (P= 0.08). The majority of patients were diagnosed at advanced stage; 74.1% of SCLC and 76.8% of NSCLC had metastasis at the time of diagnosis [Table 1].

Of the 404 cases, 213 (52.8%) were dead and 191 (47.3%) were alive. SCLC had mortality recorded for 108 (54.8%) among them and NSCLC had mortality recorded for 105 (50.7%) among them. In patients with SCLC, age at diagnosis was higher in patients who were dead compared to those who were alive (p=0.04); however, in NSCLC, age showed no significant difference between alive and dead patients (p=0.38). For SCLC, year of diagnosis was not statistically significant different between alive and dead patients (p=0.43), but it showed a statistically significant difference for NSCLCs (p=0.025), where a lower mortality showed in 2013 compared to previous years. Stage of tumor showed a significant difference for both, SCLC and NSCLC, (p=0.006) (p=0.035) respectively, higher mortality for advance stage compared to localized [Table 1].

SCLC Mortality

Multiple logistic regression analysis for SCLC, extension was found to be the strongest predictor of mortality. Having regional extension by both direct extension and lymph node increase the odd of mortality by 6-fold compared to having localized disease (OR= 6.08, 95% CI: 1.05 – 35.18), and having distance metastasis increased the odds of mortality by 5-fold compared to having localized disease (OR=5.87, 95% CI: 2.01 – 17.19).

None of the other variables were found to be statistically significantly associated with mortality in SCLC, including age (OR= 1.02, 95% CI 1.00-1.03) gender (OR= 2.30, 95% CI: 0.90 - 5.89) and year of diagnosis [Table 2].

NSCLC Mortality

The multiple regression model for NSCLC showed a statistically significant increase in mortality among cases with distance metastasis extension compared to local disease (OR= 3.29 95% CI: 1.22 – 8.85). However, in contrast to SCLC, regional extension by both direct and lymph node extension did not increase the odds of mortality. Besides that, year of diagnosis in case showed decrease in odds of mortality for those who were diagnosed in 2013 compared to those who were diagnosed in 2009 (OR 0.36 95% CI: 0.14 – 0.93).

None of the other variables were found to be statistically significantly associated with mortality in NSCLC, including age (OR= 1.01, 95% CI 0.99-1.04) gender (OR= 1.26, 95% CI: 0.59 - 2.69) [Table 3].

Discussion

In this secondary data analysis, the overall mortality rate of lung cancer among Saudi national patients in the period 2009—2013 for both SCLC and NSCLC was 52.75% (54.82% in SCLC and 50.72% in NSCLC). Mortality was strongly predicted by tumor extension. In SCLC, regional extension by both direct and lymph node extension increase mortality by 6-folds compared to localized tumor and distance metastasis/systematic increase mortality by 5-fold compared to localized tumor. In NSCLC, distance metastasis/systematic disease increased mortality by 3-fold compared to localized tumor.

The lung cancer survival rate shows a difference by histological type, with NSCLC having a better prognosis compared to SCLC [19]. However, the staging of a tumor was the strongest determinant factor of lung cancer survival. Chansky et al. (2009) conducted a retrospective study on 9,137 patients and observed a strong correlation between Tumor, Node, Metastasis (TNM) stage and survival, where the median survival for patients at stage IIIA was 19

months, compared to 95 months for patients at stage IA [20]. Our study, confirms the strong effect of disease stage on mortality for both NSCLC and SCLC.

Several efforts have tried to develop an accurate prediction model for lung cancer prognosis by adding further factors to tumor staging, although, tumor staging is still the major mortality predictor [25]. Other factors that showed a prognostic effect independent of disease stage include performance status (PS), age and gender [26, 27]. Additionally, several genetic biomarkers associated with lung cancer were found to have a prognostic effect [28-31]. Other factors like obesity [32] and smoking history [33] were also found to impact survival in lung cancer. Hence, to achieve higher prediction accuracy, a more complex approach that integrates individual, pathological markers and genetics factors is needed [34]. Our study did not allow for a full investigation of important prognostic factors because of the limited nature of data collected within cancer registries.

Analysis of mortality by year of diagnosis showed significantly lower odds for those diagnosed in 2013 compared to 2009 for NSCLC but not for SCLC. It is unclear whether any significant improvements were introduced in clinical management of lung cancer during 2013 [64]. However, the observed drop in mortality in 2013 and the reason why it applied to NSCLCs but not SCLCs requires further investigation.

The overall mean age of diagnosis for both SCLC and NSCLC was 63.27 years (SD= 12.46), which is 6.73 years younger than the average age at diagnosis in the United States. Additionally, the age range in our study overlapped with the age range of lung cancer screening (55-74 years) used in the NLST. The NLST age range was determined by the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial's 2012 prediction model ($PLCO_{m2012}$) which determined that the 55-74 year age range as an inclusion criterion in the trial [21]. It is

worth noting that the screening recommendations of the USPTF recommended an age range for screening of 55-80 years. For Saudi Arabia, it is not clearly evident whether screening beyond the range of 55-74 years could be an advantage or not, especially when viewing this issue from the angle of premature mortality impact of lung cancer, and by taking into consideration the expected age difference between the US and Saudi Arabia.

Various studies revealed that the effect of cigarette smoking on lung cancer varies by histological types, where cigarette smoking and early initiation of smoking show a stronger association with SCLC compared to NSCLC [22, 23]. In the US, the proportion of SCLC was tracked over from 1973—2002 and showed a gradual decrease from 17.26% in 1986 to 12.95% in 2002; this decrease in SCLC proportion is potentially a result of strengthened in tobacco control policies during the 1980s [24]. However, the histological distribution of lung cancer in Saudi Arabia supports this association. Our study showed that SCLC constituted 50% of lung cancer cases among males and 37% among females. This could be explained, in part, by differences in smoking prevalence rates between men and women in Saudi Arabia, where the age-standardized smoking prevalence rate among males during 2013 was 26.8%, compared to 3% among women [12].

A main limitation of this study is the unavailability of time-to-event data which prevented the use of survival analysis methods and the ascertainment of an accurate estimate of survival rates for each cancer type. Another limitation is the restricted data on predictors. For a better characterization of lung cancer mortality, a prediction model that integrates pathological variables, biological markers, genetics and patient physical status is needed [68]. The lack of such factors is assumed to have a residual confounding role in the results. Lastly, the study

population is restricted to Saudi nationals, and the results may not be generalizable to other populations.

A major strength of our study is the use of data from the SCR, which is a population-based registry with nation-wide coverage of diagnosed cancers that uses standardized methods for data collection.

As a conclusion, this study showed a strong effect of disease stage on mortality, especially in SCLC. It also showed that the majority of lung cancer patients in Saudi Arabia are diagnosed at an advanced stage. Therefore, introducing lung cancer screening and early detection program will likely improve lung cancer survival. However, establishing Saudi-specific lung cancer screening guidelines will require further research on the benefits and harms of screening modalities in the Saudi population.

Table 1. Characteristics of lung cancer patients stratified by histological type

		Small Cell Lung Cancer N= 197				Non-Small Cell Lung Cancer (N= 207			
		Alive (N= 89)	Dead (N= 108)	Total	P-value	Alive 102 (49.28%)	Dead 105 (50.72%)	Total	P-value
Age at diagnosis, mean (SD)		62.39 (SD 13.26)	66.04 (SD 11.30)	64.39 (SD 12.33)	0.04 *	61.42 (SD 12.09)	62.94 (SD 12.94)	62.19 (SD 12.52)	0.3833*
Sex	Male	73 (42.69%)	98 (57.31%)	171 (86.80%)		79 (77.45%)	87 (82.86%)	166 (80.19%)	
	Female	16 (61.54%)	10 (38.46%)	26 (13.20%)	0.07**	23 (22.55%)	18 (17.14%)	41 (19.81%)	0.329**
Year of diagnosis	2009	16 (17.98%)	21 (19.44%)	37 (18.78%)		29 (28.43%)	30 (28.57%)	59 (28.5%)	
	2010	19 (21.35%)	28 (25.93%)	47 (23.86%)		22 (21.57%)	22 (20.95%)	44 (21.26%)	
	2011	17 (19.10%)	19 (17.59%)	36 (18.27%)	0.433 **	9 (8.82%)	22 (20.95%)	31 (14.98%)	0.025**

	2012	14 (15.73%)	23 (21.30%)	37 (18.78%)		17 (16.67%)	20 (19.05%)	37 (17.87%)	
	2013	23 (25.84%)	17 (15.74%)	47 (20.30%)		25 (24.51%)	11 (10.48%)	36 (17.39%)	
Topography	Main Bronchus	7 (7.87%)	12 (11.11%)	19 (9.64%)		6 (5.88%)	4 (3.81%)	10 (4.83%)	
	Upper lobe	24 (26.97%)	27 (25%)	51 (25.89%)		33 (32.35%)	34 (32.38%)	67 (32.37%)	
	Middle lobe	4 (4.49%)	5 (4.63%)	9 (4.57%)		3 (2.94%)	6 (5.71%)	9 (4.35%)	
	Lower lobe	19 (21.35%)	14 (12.96%)	33 (16.75%)		21 (20.59%)	20 (19.05%)	41 (19.81%)	
	Overlapped lesion	3 (3.37%)	7 (6.48%)	10 (5.08%)		5 (4.90%)	3 (2.86%)	8 (3.86%)	
	Not otherwise specified	32 (35.96%)	43 (39.81%)	75 (38.07%)		34 (33.33)	38 (36.19%)	72 (34.78%)	
	Carcinoma Of other ill-defined sites	0	0	0	0.597***	0	0	0	0.851***
Grade	Well differentiated/ differentiated NOS	0	1 (0.93%)	1 (0.51%)		1 (0.98%)	0	1 (0.48%)	
	Moderately/Moderately well differentiated	1 (1.12%)	0	1 (0.51%)		3 (2.94%)	2 (1.90%)	5 (2.42%)	
	Poorly differentiated	8 (8.99%)	10 (9.26%)	18 (9.14%)		31 (30.39%)	46 (43.81%)	77 (37.20%)	
	Undifferentiated/ anaplastic	12 (13.48%)	4 (3.70%)	16 (8.12%)		7 (6.86%)	6 (5.71%)	13 (6.28%)	
	Unknown	68 (76.40%)	93 (86.11%)	161 (81.73%)	0.043***	60 (58.82%)	51 (48.57%)	111 (53.62)	0.264***
Stage	In situ	0	0	0		0	0	0	
	Localized	16 (17.98%)	6 (5.56%)	22 (11.17)		16 (15.69%)	7 (6.67%)	23 (11.11%)	
	Regional by direct extension	7 (7.87%)	2 (1.85 %)	9 (4.54%)		7 (6.86%)	3 (2.86%)	10 (4.83%)	
	Regional by lymph node	6 (6.74%)	4 (3.7 %)	10 (5.08%)		7 (6.86%)	2 (1.9%)	9 (4.35%)	
	Rregional by both direct extension and lymph node	4 (4.49%)	5 (4.63%)	9 (4.57%)		2 (1.96%)	2 (1.9%)	4 (1.93%)	
	Rregional-NOS	0	1 (0.93%)	1 (0.51%)		1 (0.98%)	1 (0.95%)	2 (0.97%)	
	Distance metastasis/Systematic disease	56 (62.92)	90 (83.33%	146 (74.11)	0.006 ***	69 (67.65%)	90 (85.71%)	159 (76.81%)	0.035***
Laterality	Not paired	1 (1.12%)	1 (0.93%)	2 (1.02%)		0	0	0	
	Right origin	44 (49.44%)	51 (47.22%)	95 (48.22%)		57 (55.88%)	64 (60.95%)	121 (58.45%)	
	Left origin	32 (35.96%)	35 (32.41%)	67 (34.01%)		34 (33.33%)	32 (30.48%)	66 (31.88%)	
	Only one side involved (right or left) unspecified	0	0	0		6 (5.88%)	2 (1.90%)	8 (3.86%)	
	Bilateral (side of origin unknown or single primary)	2 (2.25%)	4(3.70%)	6 (3.05%)		5 (4.90%)	7 (6.67%)	12 (5.80%)	
	Midline origin	0	0	0		0	0	0	
	paired no information concerning laterality	10 (11.24%)	17 (15.74%)	27 (13.71%)	0.876 ***	0	0	0	0.453***

- * T-test ** Chi-square test *** Fisher's exact test

Table 2. Mortality Predictors among Small Cell Lung Cancers			
Mortality	Odds Ratio	95% Confidence Interval	P-value
Age	1.02	1.00 - 1.05	0.10
Sex			
Female (Ref.)	1		
Male	2.30	0.90 - 5.89	0.08
Extension			
Localized (Ref.)	1		
Regional By direct extension	0.84	0.12 - 5.82	0.86
Regional by lymph node	1.62	0.29 - 9.13	0.58
Regional by both direct extension and lymph node	6.08	1.05 - 35.18	0.04
Regional, Not Otherwise Specified	-§	-	-
Distant Metastasis/systematic disease	5.87	2.01 - 17.19	0.00
Topography			
Main Bronchus (Ref.)	1		
Upper Lobe	0.41	0.11 - 1.61	0.20
Middle Lobe	0.67	0.09 - 5.32	0.71
Lower lobe	0.29	0.07 - 1.23	0.09
Overlapped lesion	0.56	0.08 - 3.76	0.55
Not otherwise specified	0.41	0.11 - 1.52	0.18
Laterality			
Left (Ref.)			
Not paired	0.18	0.01 - 4.12	0.28
Right origin	0.86	0.42 - 1.75	0.68
Bilateral (side of origin unknown or single primary)	2.20	0.32 - 15.24	0.43
Paired no information concerning laterality	1.48	0.51 - 4.31	0.47
Year of Diagnosis			
2009 (Ref.)	1.00		
2010	1.29	0.48 - 3.44	0.61
2011	0.83	0.30 - 2.30	0.71
2012	1.59	0.57 - 4.50	0.38
2013	0.54	0.20 - 1.48	0.23

§ Estimates for this category could not be obtained because number of observations = 1

Table 3. Mortality Predictors among Non-Small Cell Lung Cancers			
Mortality	Odd Ratio	95% Confidence Interval	P-value
Age	1.01	0.99 - 1.04	0.31
Sex			
Female (Ref.)			
Male	1.26	0.59 - 2.69	0.56
Extension			
Localized (Ref.)	1		
Regional By direct extension	0.77	0.14 - 4.16	0.76
Regional by lymph node	0.81	0.12 - 5.22	0.82
Regional by both direct extension and lymph node	2.15	0.22 - 20.70	0.51
Regional NOS	1.26	0.06 - 27.56	0.88
Distan**t** Metastasis/systematic disease	3.29	1.22 - 8.85	0.02
Topography			
Main Bronchus (Ref.)	1		
Upper Lobe	1.67	0.38 - 7.29	0.50
Middle Lobe	2.67	0.34 - 21.08	0.35
Lower lobe	1.42	0.31 -6.58	0.65
Overlapped lesion	1.45	0.17 - 12.25	0.73
Not otherwise specified	2.23	0.50 - 10.01	0.30
Laterality			
Left (Ref.)	1.00		
Not paired	-§	-	-
Right origin	1.04	0.54 - 2.03	0.90
Bilateral (side of origin unknown or single primary)	0.25	0.04 - 1.51	0.13
Paired no information concerning laterality	0.84	0.20 - 3.55	0.81
Year of Diagnosis			
2009 (Ref.)	1.00		
2010	0.96	0.41 - 2.23	0.92
2011	2.14	0.77 - 5.95	0.14
2012	1.10	0.45 - 2.67	0.83
2013	0.36	0.14 - 0.93	0.04

§ Estimates for this category could not be obtained because of low counts

Chapter 4 – Conclusion and Recommendations

As tumor stage is one of the strongest determinants of mortality among lung cancer patients, and with lung cancer having a high incidence-to-mortality ratio, the implementation of lung cancer screening programs can significantly improve the survival rate and therefore reduce the impact of lung cancer premature mortality in Saudi Arabia and globally.

Recommendations for Future Research in Saudi Arabia

- Conduct further studies to assess lung cancer survival and its predictors.
- Conduct risk prediction studies to inform the development of risk-tailored lung cancer screening guidelines.
- Conduct research on the cost-effectiveness of lung cancer screening.

Recommendations for Practice and Policy

- Expand the Saudi Cancer Registry data to include more detailed risk factors and follow-up time.
- Improve the timeliness of data collection and reporting to the Saudi Cancer Registry
- Establish Saudi-specific lung cancer screening guidelines and follow-up protocols and identify an appropriate age of screening for the Saudi population.
- Integrate lung cancer screening in existing smoking cessation programs.
- Sustain implementation of tobacco control measures.

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