5-2007

Bronchioalveolar Carcinoma in Jefferson and McCracken Counties, Kentucky: Gender Differences in Survival.

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A thesis

presented to

the faculty of the Department of Public Health

East Tennessee State University

In partial fulfillment

of the requirements for the degree

Master of Public Health

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by

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May 2007

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Keywords: Bronchioalveolar Carcinoma, Survival, Female patients

ABSTRACT

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Bronchioalveolar carcinoma (BAC), a rare lung cancer, is more common in women, has a high proportion of non-smokers, and better survival, especially in women, than other lung cancers. Study subjects were 83 BAC patients from two Kentucky counties. Mean survival differences were compared by selected variables. The results showed better survival for females (6.5 years) than males (3.0 years, p-value 0.02); for urban (4.3 years) compared to rural residents (2.6 years, p-value 0.04); and for females with history of hysterectomy (5.1 years) compared to females without such history (3.3 years, p-value 0.02); the last finding supports a hormonal role in survival. Study results support the previous findings of a female survival advantage in BAC. Additional research is needed to determine reasons for this female survival advantage.

DEDICATION

I dedicate this thesis to my family for their continuing love and support in all my pursuits.

ACKNOWLEDGEMENTS

Foremost, I thank God for giving me the opportunity to realize my dreams and aspirations. This thesis topic came out of a casual conversation with my professor Dr. Timothy Aldrich. I am grateful to him for all his continuing support and guidance. I would like to thank him for inculcating in me a dedication and passion towards the practice of epidemiology. I am greatly indebted to Dr. Anderson, my advisor, for all his precious time spent in editing my paper and trying to improve my writing style. I feel lucky to have him as my committee chair and hope a few years down the line I can make him proud. I would also like to thank Dr. Wu and Dr. Flowers for their support and good suggestions in improving my thesis.

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CHAPTER 1

INTRODUCTION AND OBJECTIVES

Introduction

Lung cancer is the leading cause of cancer mortality for both men and women in the United States, accounting for 13% of all new cases and 29% of all cancer deaths. In 2006, there will be over 174,470 cases and 162,460 deaths (Jemal et al., 2006). The incidence is declining in men from a high of 102 cases per 100,000 in 1984 to 62.3 cases per 100,000 in 2000; whereas the rates have just begun to stabilize in women after years of steady increase. In stark contrast, Kentucky's lung cancer incidence is still increasing. Kentucky has one of the highest incidence rates for lung cancer in the nation; the incidence for the year 2000 was 97.5 cases per 100,000 (American Cancer Society, Cancer Statistics 2004).

Lung cancer is broadly divided into non-small cell carcinomas (75%-80%) and small cell carcinoma (20%-25%). Non-small cell lung carcinoma (NSCLC) is further divided into the following histologic subtypes: squamous cell carcinoma, adenocarcinoma, and large cell undifferentiated carcinoma. Historically, squamous cell carcinoma was the most common histologic type accounting for almost 70% of NSCLC (as cited in Read, Page, Tierney, Piccirillo, & Govindan, 2004). However, for the past 2 decades there has been a steady increase in the incidence of adenocarcinoma and at the same time a decrease in squamous cell carcinoma (Field et al., 2004; Read et al.).

A rise in bronchioalveolar carcinoma (BAC), a histologic subtype of adenocarcinoma, is thought to be the major reason for the increased incidence of adenocarcinoma (Barsky, Cameron, Osann, Tomita, & Holmes, 1994). The reasons for this increase are not clearly understood. Various authors (e.g. Auerbach & Garfinkle, 1991; Levi, Franceschi, La Vecchia, Randimibison,

& Te, 1997; Valaitis, Warren, & Gamble, 1981; Zell, Ou, Zigas, & Anton-Culver, 2005) have attributed this shift to changes in the rate and type of cigarette smoking, changes in exposure to new environmental carcinogens, and changes in the criteria for histopathological diagnosis of lung cancer.

Another possible reason for an increase in the number of BAC patients may be the increase in female lung cancer patients over the past 50 years. BAC, contrary to other types of lung cancers, has a female predilection. Therefore, an increase in the overall number of female lung cancer patients accompanied by a decrease in male patients may have lead to an increased incidence of BAC and a decrease in squamous cell carcinoma, which is much more common in men than women (Read et al., 2004).

Objectives

A series of patients with BAC from hospital-based cancer registries located at Jefferson County and McCracken County, Kentucky from 1988-2005 was selected. They were selected for another study evaluating occupational and environmental cancer risk in Kentucky (The Kentucky Lung Cancer project, Aldrich, 2006). In that study, the BAC cases from 1996-2005 were designated to represent the non-smoking lung cancer risk, an attempt to identify the environmental portion of the overall lung cancer risk. Those cases were then provided for analysis in this thesis. The objectives of this study are:

1. To determine overall survival and survival differences for this series of BAC cases by gender, age, residential location, smoking history, and family history of lung cancer.

2. To assess if the reclassification of bronchioalveolar carcinoma by the World Health Organization (WHO) in 1999 has impacted either survival or the proportion of female patients in this series.
3. To compare the results of this series of BAC cases with the Kentucky Cancer Registry (KCR) database and the national Surveillance, Epidemiology, and End Results (SEER) database.
4. To explore whether there may be evidence to indicate that hormone estrogen events/levels affect the length of survival in this series of female BAC patients.

CHAPTER 2

BACKGROUND AND SIGNIFICANCE

Historical Perspective

In 1876, French clinical microscopist Louis Malassez first reported the gross and microscopic description of a newly discovered type of malignant lung tumor that had occurred in a 47-year-old woman. It was a carcinoma with distinct alveolar distribution that presented with numerous fused tumor nodules, central necrosis, and preserved alveolar structure of the lung. The cells of the tumor were well differentiated and spread along the alveoli with little stromal reaction (Liebow, 1960).

During the early part of 20th century numerous prominent pulmonary physicians attempted to distinguish the above mentioned lung tumor from other lung cancers. In 1960 Averill Liebow, professor of pathology at the Yale University School of Medicine, named this tumor bronchioalveolar carcinoma. He defined it as a generally well differentiated adenocarcinoma located primarily in the periphery of the lung well beyond a grossly recognizable bronchus with the walls of the distal air spaces acting as supporting stroma for the neoplastic cells and a tendency to spread chiefly within the confines of the lung by aerogenous and lymphatic routes (Liebow, 1960). Liebow's definition was accepted by the WHO and the American Joint Committee on Cancer (AJCC) in 1967 (as cited in Laskin, Sandler, & Johnson, 2005).

Histology

The most recent WHO definition states that BAC is a lung adenocarcinoma that is diagnosed in the absence of a primary adenocarcinoma at any other site, has no central

bronchogenic source, is peripheral in location, has an intact pulmonary interstitium, and exhibits malignant cells growing along the alveolar septae (as cited in Dumont et al.,1998). The key feature is the preservation of the underlying lung morphology.

BAC shares some features with other lung adenocarcinomas and most of the time two histological patterns are seen together. Pure BAC represents only about 3%-4% of cases of adenocarcinomas. Adenocarcinomas with some BAC features are much more common and include cancers that are predominantly BAC with a small focus of invasive disease (Castro, Coffey, Medeiros, & Cagle, 2001).

The histopathological classification of BAC includes three subtypes (Lamb 1984; Madri & Carter, 1984):

Mucinous: Mucinous BACs arise from the bronchial mucous cells and are characterized by tall columnar cells, with a pale apical cytoplasm that are PAS positive. The nuclei are bland in appearance with occasional nuclear clefts. The tumor cells contain central to apical cytoplasmic vacuoles and abundant microvilli.

Non Mucinous: Non-mucinous BACs arise along the alveolar walls; they exhibit some degree of focal interstitial thickening and lymphocytic infiltration. The malignant cells themselves are cuboidal or columnar with apical snouting and central nuclei. Multinucleated giant cells and eosinophlic nuclear inclusions may be present. There is a predominance of Clara cells.

Sclerotic: This type of BAC appears similar to non-mucinous at light microscopic and ultra structural levels and presents with areas of sclerosis. Sclerotic BACs account for a considerable number of scar carcinomas. Various authors disagree on the origin of the scar.

There is debate whether the scar is because of the carcinoma or if the malignancy develops around scar tissue (Madri & Carter, 1984; Ochs, Katz, Edmunds, Miller, & Epstein, 1982).

Several studies have reported high inter-observer variability especially with regards to BAC subtype (e.g., Dumont et al., 1998; Madri & Carter, 1984). Available literature suggests that mucinous BACs account for 21%, non mucinous for 68%, and sclerotic for 10% of all BAC cases (Madri & Carter, 1984). Non-mucinous BACs have better prognosis as they tend to be more localized and present with a lower tendency of bronchogenic spread (Dumont et al.).

A 21-year retrospective autopsy study conducted in Glasgow concluded that bronchioalveolar carcinoma is a valid classification that describes a specific disease entity. Furthermore, they established that in pathological terms it represents a heterogeneous population of tumors that are amenable to surgical resection at initial stages (as cited in Barsky et al., 1994).

Clinical Features

BAC presents as a slow growing multifocal disease with intrathoracic metastasis, slow rate of growth and progression, longer median survival rates, and a higher prevalence in women compared to men (Grover & Piantadosi, 1989). When the tumor is localized to a single hemithorax, the patient may be asymptomatic. More than 50% of the patients are asymptomatic. When symptoms are present, the most frequent symptoms are coughing (35%), chest pain (25%), dyspnea (15%), weight loss (13%), fever (8%), and hemoptysis (11%). Distant metastases are hardly ever present. In the rare instance of distant metastases the symptoms depend on the site of metastasis (as cited in Axiotis & Jennings, 1988; Barkley & Green, 1996; Edgerton, Rao, Takita, & Vincent, 1981; Lee & Kim 1997).

Bronchorrhea (productive cough with white mucoid or watery expectoration), once considered the clinical hallmark of this disease, is now viewed as an unusual and late manifestation seen only in the diffuse form of the carcinoma. The prevalence of bronchorrhea was reported between 27%-35% in 1953, whereas a later study reports it to be 5% (Edgerton et al., 1981)

Rare symptoms reported are pulmonary hypertension, pneumothorax, or even pericardial temponade (Singh, Nath, Pinkard, & Alexander, 1994). Late stages (III or IV) of BAC are associated with a greater likelihood of symptoms than earlier stages. Therefore, when symptoms are present the prognosis is poor. BAC shows poor response to chemotherapy with an average survival of 9 months. Traditionally, only symptomatic patients with late stage disease are considered for chemotherapy and earlier stages are treated with more aggressive approaches such as surgical resection. This can account for poor survival of patients receiving chemotherapy (Ebright et al., 2002).

Epidemiology

Incidence and Prevalence

Fifty years ago BAC was a rarely diagnosed neoplasm accounting for less than 3% of all lung cancer cases in the United States, with an average age adjusted incidence of 1.5 cases per 100,000 (Laskin et al., 2005). BAC has increased from 5% cases in 1955, 9% in 1978, 20% in 1985, and to 24% of all NSCLCs in 1990 (Fig.1). The average age adjusted incidence rose from 6.5 in 1987 to 10 cases per 100,000 in 2004 (Field et al., 2005). Over the past 50 years there has been a steady increase in BAC diagnosis along with a steady decrease in the frequency of other

histotypes. Incidence of BAC has increased because of an increase in number of female cases, in whom the cancer is more common (65% adenocarcinomas vs. 35% other types) and a shift in male cases from squamous cell carcinomas to adenocarcinomas (Auerbach & Garfinkle, 1991).

Some authors report the increase in adenocarcinoma cases is solely because of an increase in the number of BAC cases (e.g. Jemal et al., 2006; Travis, Garg, & Franklin, 2005), while other studies report an increase in adenocarcinoma cases but no change in pattern of BAC incidence (as cited in Mirtcheva, Vasquez, Yankelevitz, & Henschke, 2005).

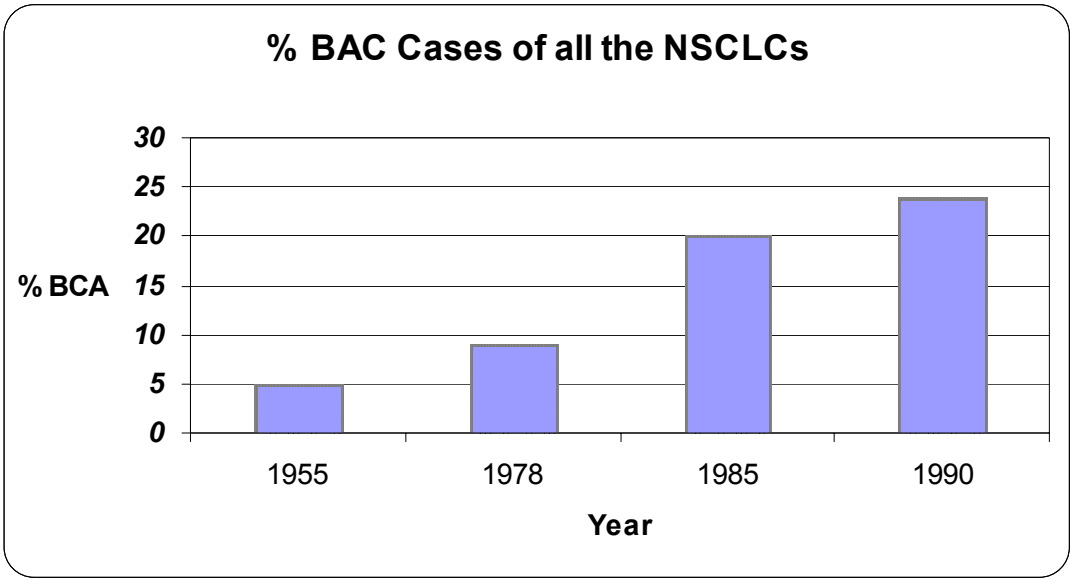

Figure 1. Percentage of BAC Cases by Year.

The mean age-at-diagnosis of BAC patients is lower than that for any other lung cancer type (67 yrs vs. 69 yrs) (Leno, Doyal, & Edelman, 2005). According to Liu, Chen, Huang, and Perng (2000), the average age-at-diagnosis of BAC patients is 66 years with women (63 yrs) being younger than men (68 yrs). The 1-year (65% vs. 42%) as well as 5-year (35% vs. 15%)

survival for BAC is much better than for all other types of lung cancer grouped together (as cited in Jemal et al., 2006; Liu et al.).

Reclassification and Its Impact on Survival

BAC was reclassified at the WHO conference for classification of lung tumors on May 28th 1999. It was the third time the definition of BAC was altered. The earlier two events had been 1967 and 1981 (World Health Organization, 1999). Periodic reclassification has lead to increased recognition that may account for a part of the increase in reported incidence of this cancer. After the revised definition in 1999, the mean overall survival of BAC patients has increased as compared to patients diagnosed before 1999, whereas no significant difference was reported for non-BAC NSCLC patients (Janssen & Coebergh, 2003; Zell et al., 2005). The lack of survival benefit for non-BAC NSCLC patients diagnosed after May 1999 suggests that this positive trend in BAC survival cannot be attributed to an overall improvement in lung cancer management during this time period (Laskin et al., 2005).

According to Zell et al. (2005), changes in the epidemiology of BAC may be attributed solely to the re-classification in 1999. Since 1999, there have been more women patients (63% vs. 55%) and more non-smokers (27% vs. 18%) than before. The survival advantage is reported more in patients with localized disease than in patients with metastatic tumor. They further reported that 41% of patients diagnosed with metastatic BAC before May 1999 died because of the cancer, whereas in cases of localized BAC, 31% of the patients died of the cancer. On the other hand, in patients diagnosed after 1999, 70% with metastatic tumor died because of BAC and less than 10% of patients with localized tumor died because of the cancer indicating that a

survival advantage existed only for localized lesions. The proportion of patients who presented with metastasis was much smaller after 1999 (35% vs. 59%) than before (Laskin, 2004).

Corroborative findings by various authors (e.g. Janssen & Coebergh, 2003; Laskin et al., 2005) indicate that after the reclassification in 1999. BAC presents with a higher proportion of females, more never smokers, earlier stage at presentation, and improved survival compared to other NSCLC and BAC patients before reclassification. As a consequence of these significant changes in epidemiology of BAC, the recent 2005 WHO classification retained all the changes suggested in the 1999 definition (as cited in Zell et al., 2005).

On the other hand, certain authors like Castro et al. (2001) report a 5% discordance rate between the original diagnosis and review diagnosis after reclassification in 1999 when they re-diagnosed the cases by applying the 1999 criteria to earlier cases. Their findings suggested that reclassification alone cannot attribute for all the increase in incidence and survival. Their research consisted of comparing retrospective studies based on autopsy reports to those based on hospital diagnosis. They recognized that the incidence is much higher in the autopsy reports indicating the number of BAC cases that remained un-diagnosed and un-reported is significant.

This is in contrast to findings reported by other studies who reclassified cases diagnosed before 1999 with the post 1999 criteria and found that 41% of their prior BAC cases were other adenocarcinomas and not BAC according to the new definition (as cited in Laskin, 2004). Travis et al. (2005), suggest popularity of screening with low emission helical CT scan as a contributor to the increased identification of clinical cases because of discovery of many relatively smaller tumors that otherwise were difficult to diagnose. This may very well be one of the more important reasons for the early diagnosis and the subsequent increase in survival for true cases of BAC.

Etiology and Risk Factors

The exact etiology of BAC has been aggressively debated (Barkley & Green 1996; Barsky et al., 1994; Dumont et al., 1998; Madri & Carter, 1984). The true burden of smoking as an etiological agent has been controversial (as cited in Laskin, 2004). Various factors implicated as possible etiological agents are listed below.

Smoking**:** It is suggested that the association between BAC and smoking is the weakest for all lung cancer subtypes. Almost 33% of patients with BAC are non-smokers compared to 5% of all other lung cancer patients grouped together. Furthermore, BAC patients who are smokers smoke less (34 vs. 42 pack/years) than patients with other types of lung cancers (Auerbach & Garfinkle, 1997). On the other hand, various studies have shown that smoking low tar filtered cigarettes increases the risk of developing adenocarcinomas like BAC. Filters remove larger particles in cigarette smoke, thus reducing deposition of those particles in central airways but not the smaller peripheral airways. This could lead to a reduction in incidence of the squamous cell carcinomas that develop centrally, but not of BAC that primarily occurs in peripheral areas of the lung (Charloux et al., 1997). Smoking cessation also does not seem to have much of an impact on reduction of risk (as cited in Auerbach & Garfinkle; Radzikowska, Glaz, & Roszkowski, 2002). Environmental tobacco smoke similarly presents with a weaker association as compared to the rest of the lung cancers (Edgerton et al., 1981). Some authors (Leno et al., 2005; Read et al., 2004) fiercely argue that the burden of incidence can be solely placed on smoking. Collectively these studies identify smoking as one of the etiological factors for BAC but it is likely not the only cause. More research needs to be done to evaluate the extent of contribution of cigarette smoking as an etiologic factor for BAC.

Family history: Patients with positive family history for lung cancer are reported to be at a 2.5 times higher risk for developing BAC than patients with no family history. Patients with a parent diagnosed with lung cancer have four times the risk and those with a sibling who has lung cancer are at twice the risk of developing BAC than patients with no family history (Cote, Kardia, Wenzlaff, Ruckdeschel, & Schwartz, 2005; McDoniels-Silvers, Nimri, & Stoner, 2002). This risk is consistent among all histological sub-types.

Viruses: A characteristic diffuse multicentric presentation of the disease has led some investigators to suggest a viral etiological agent. Viral etiology was first suggested in 1940s because similarity both at the histological and gross levels of BAC with Jaagsieke's disease found in sheep. Also known as sheep pulmonary adenomatosis, Jaagsieke's disease is caused by a retrovirus. Retrovirus B and D are suspected to cause BAC in humans (Page, Green, & Lackland, 2000). Because there has never been a case of animal to human transmission and farmers who rear sheep are not reported to be at higher risk of developing BAC, the association between retrovirus and BAC has not been clearly established. Furthermore, no viral component has ever been isolated from BAC tumors. Page et al. further report another virus, the Human Papillomavirus (HPV) types 16 and 18, as an etiological agent. HPV is said to cause BAC in women more than men (OR 10.2). Auerbach and Garfinkle (1997) report that a decrease in adenocarcinomas and an increase in peripheral BAC can be a consequence of HPV. Much research needs to be conducted in this area before anything can be cited with certainty**.**

Other causes: BAC may also arise in lung parenchyma previously destroyed by tuberculosis, infection, or pulmonary fibrosis of any kind (Madri & Carter, 1984; Ochs et al., 1982; Singh et al., 1994). There have been reports of increased risk of BAC in people working in the construction industry, wood and paper mills, motor freights and sugarcane farming

(Rothschild & Mulvey, 1982). Motor freight industry workers show as much as a four-fold increase in risk of developing BAC as compared to general population (as cited in Morton & Treyve, 1982). According to Madri and Carter (1984), these exposures cause epithelial proliferation that subsequently leads to malignant transformation of healthy tissue surrounding these areas of proliferation**.**

Other risk factors implicated are radon and asbestos. Radon was first identified as a risk factor among Uranium miners. It is the most commonly found household carcinogen. Radon decay accounts for 95% of natural radiation exposure of bronchial epithelium. The percentage of BAC cases attributed to radon exposure is between 1-10%. Radon has the same kind of association with BAC as with other lung cancers (as cited in Read et al., 2004).

Asbestos was the first recognized occupational risk factor for lung cancer. The risk presented by asbestos for developing BAC is similar to the risk for developing other histological subtypes of lung cancer (Radzikowska et al., 2002).

In China, where the rate of lung cancer in non-smoking women is one of the highest in the world, indoor pollution because of coal burning has been implicated in the genesis of lung cancer (as cited in Wu, Henderson, Thomas, & Mack, 1986).

Female BAC Risk

The incidence of lung cancer in men plateaued in 1980s and has been steady since. However, the increase in cases of lung cancer in women over the past 50 years has been staggering giving it the name of a "Contemporary Epidemic" (as cited in Patel, Bach, & Kris, 1999). In 1950 women represented less than 10% of lung cancer patients, while in 1990 35% of cases were female (as cited in Leno et al., 2005). The number of cases in women has gone up by

more than 500% in the last 50 years, surpassing breast cancer prevalence since 1984 and by 20,000 cases annually at present. Although lung cancer mortality for men has been steady for the last 15 years, it is projected that the rates for women have only recently begun to stabilize and are expected to show this same trend until 2010 after which they may begin to decrease (Jemal et al., 2006; Radzikowska et al., 2002). Figure 2 shows lung cancer mortality for both sexes from 1989-2003. There were 88,975 male lung cancer patient deaths in 1989 vs. 89,908 deaths in 2003 whereas in case of female patients there were 48,042 deaths in 1989 vs. 68,908 in 2003 (Jemal et al.).

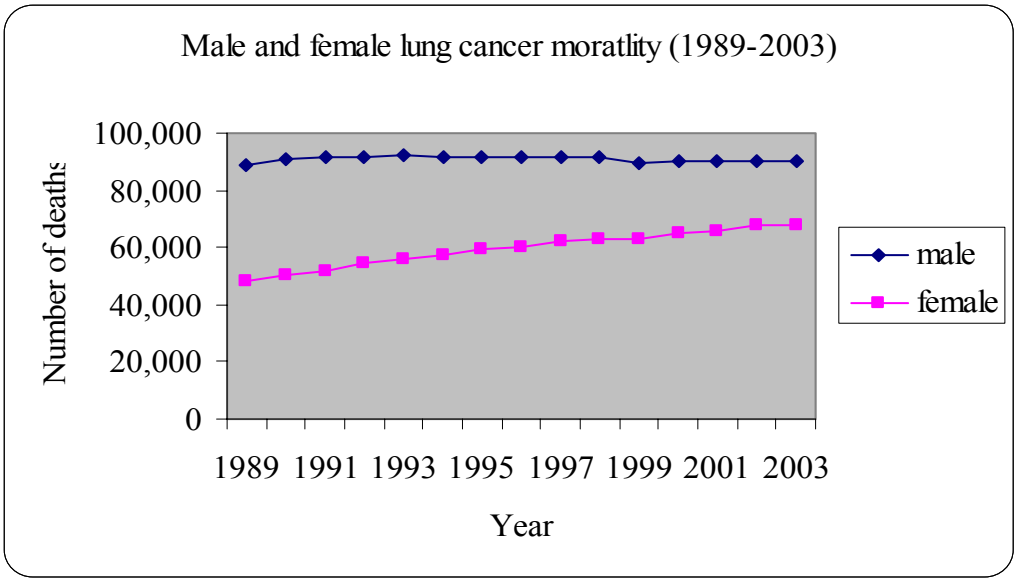

Figure 2. Lung Cancer Mortality by Gender

The rise in overall number of cases of BAC is in part be contributed by the rise in the number of female lung cancer cases. Among all the lung cancer types, BAC has the highest proportion of female non-smokers. Because of its relatively weak association with smoking as compared to other histotypes, an increase in BAC as a consequence of female smoker cohorts

crossing the risk threshold can only explain a small proportion of BAC increase (Clayton 1998; Laskin, 2004; Leno et al., 2005).

Although smoking prevalence has decreased in men by half in the last 40 years, it has decreased only by 25% in women in the same period. Almost a quarter of adult females in the United States are smokers and most of them (85%) started smoking as teenagers (as cited in Leno et al., 2005). It is difficult to assess the true association of smoking as an etiological agent because of a high prevalence of smoking and under-reported environmental smoking (Page et al., 2000). To reduce the effect of smoking as a confounder, Kit et al. (as cited in Page et al.) conducted a study analyzing lung cancer in China and Hong Kong where the prevalence of smoking in women is less than 5%. Per their results, almost 90% of lung cancer cases in mainland China and up to 62% in Hong Kong presented as non-smokers. More than 60% of these cases were adenocarcinomas and BAC contributed the biggest fraction of the adenocarcinoma cases (Page et al.). More research needs to be done to evaluate the causes of increased incidence of BAC with particular emphasis on women.

The survival rates and prognosis for BAC is better in women as compared to men. This has been attributed in part to the fact that women have generally presented younger at the time of diagnosis, but this cannot account for all the cases (Devesa, Bray, Vizcaino, & Parkin 2005; Page, et al., 2000). Emerging evidence indicates that there are differences in the pathogenesis and susceptibility to lung cancer in women. Researchers also believe that women are more susceptible to the carcinogenic effects of smoking than men (Auerbach & Garfinkle, 1991; Radzikowska et al., 2002; Travis et al., 2005).

Possible Reasons for Differences in Women. The rise in lung cancer-related mortality among women accompanied by a decrease in men has significantly altered the male/female ratio

of lung cancer. While much of this altered epidemiology can be attributed to changing patterns of tobacco use, it is becoming increasingly apparent that relative risks (RRs) of specific types of lung cancer, the relationship between smoking and lung cancer, and the response to therapy may not be the same for both sexes (Page et al., 2000; Zang & Wynder, 1996). BAC is a stronger indicator of such differences than other types of lung cancers. There are several differences in men and women with respect to incidence and prevalence of BAC that are of growing importance and may impact diagnosis, treatment, and outcome (Leno et al., 2005).

Higher risk to carcinogenic effects of smoking: Several studies have shown women to be at greater risk than men to carcinogenic effects of smoking. Some studies reported that when compared on the basis of pack years smoked women develop BAC earlier than men (31 vs. 39 packs/years) (as cited in Radzikowska et al., 2002). The reason attributed for this increased susceptibility is the smaller lung volume and body size on average in women compared to men (Devesa et al., 2005). Women are also reported to have higher levels of tobacco-related DNA adducts and DNA transversions than men as a response to carcinogens in cigarettes despite lower exposure levels (as cited in Page et al., 2000). These DNA adducts hamper the DNA repair capacity, therefore, making the lung cells more susceptible to malignant transformation. An increase in BAC is reported to be because of increased smoking of low-tar cigarettes by women that are suspected to cause more DNA transversions and peripheral lung cancers (McDoniels-Silvers et al., 2002; Page et al.). To support these findings additional investigation is required.

Growth factors: Certain growth factors have been shown to stimulate the growth of neoplastic cells in the lung. A receptor for autocrine growth factor called GRPR (gastric releasing peptide receptor) has been identified in various lung cancers, especially BAC. The GRPR gene is on the X chromosome and escapes X inactivation. This gene is expressed more

frequently in female non-smokers than male patients and female smokers and can be activated early in response to tobacco smoke. The presence of these growth factors may account for the younger age at diagnosis of female BAC patients (Didkowska, Manczuk, McNeill, Powles, & Zatonski, 2005; McDoniels-Silvers et al., 2002).

Hormonal influences: More obvious differences between men and women are hormonal. An estrogen driven environment has been recognized in the pathogenesis of breast, endometrial, and ovarian cancers. The reason for the greater predilection of women to the effects of carcinogens of lung cancer may be because of estrogen signaling (Devesa et al., 2005).

Gender and Survival. Over the past 50 years most of the research regarding lung cancer has been done with male patients**.** Most of the treatment modalities and screening procedures such as spiral CT scan are used because of their documented success in men (Travis et al., 2005). Only recently the differences between men and women with respect to lung cancer and more specifically BAC have been properly documented and considered (McDoniels-Silvers et al., 2002; Page et al., 2000).

Women respond better than men to different treatment modalities like chemotherapy and surgical resection .This association is more pronounced in 5-year and longer survival rates. Increased survival in women compared to men is consistent across all age groups and all stages of BAC. Other histological types of adenocarcinoma also show a survival advantage for women compared to men but this trend is much more pronounced in BAC patients (Leno et al., 2005)**.**

The survival advantage of female BAC patients could be because women present younger than men at the time of diagnosis and are more physically resilient than men because of their younger age. Differences in the hormonal milieu in men and women are also suspected to contribute to differences in survival between male and female patients with BAC.

The role of estrogen in lung cancer is not very clearly understood and it remains very controversial (as cited in Falk et al., 1992; Ishibashi et al., 2005; Leno et al., 2005). Some authors (as cited in Leno et al.) suspect estrogen acts as a direct carcinogen via the formation of DNA adducts. Others (Ishibashi et al.) implicate an indirect role in activation of growth factor genes (e.g. epidermal growth factor) or by acting on receptors (e.g. GRPR). There are conflicting data regarding the prognosis of lung tumors that have estrogen receptors. Lung parenchyma has abundant estrogen receptors. Authors report 0% to 96% estrogen receptor expression in lung cancer (Ishibashi et al.). Stabile et al. (as cited in Page et al., 2000) reported a 17-fold increase in proliferation of lung cancer cells as opposed to a 4-fold increase in normal lung parenchyma cells when exposed to estradiol. These findings suggest an increased responsiveness of malignant lung cells to estrogen. According to Yang et al. (as cited in Page et al.), 5-year survival of female patients with active estrogen receptors is significantly lower (9% vs. 70%) than female patients with no estrogen receptors. Another study showed a positive prognosis with respect to male patients with active estrogen receptors as compared to women

The possible association of hormone replacement therapy (HRT) with survival in patients with lung cancer is also a very controversial issue. Adami, Persson, Hooover, Schairer, and Berqkvist (1989) have shown an increased risk (OR 1.7) of lung cancer in women receiving HRT. A case-control study from Texas on the other hand showed a reduced risk of lung cancer (OR 0.6) and an increased survival time in patients receiving HRT (Schabath, Wu, & Vassilopoulou-Sellin, 2005). Early menopause, indicative of decreased levels of estrogen, is associated with a decreased risk (OR 0.3) of BAC (as cited in Minn et al., 2005). Certain studies report that premenopausal women presented with later stages of lung cancer and had higher mortality than postmenopausal women (as cited by Read et al., 2004).

There has been only limited research conducted to evaluate the above mentioned effects and only a very few of those stratified their results according to histological sub-types (Minn et al., 2005). Therefore, more research needs to be conducted with respect to survival advantage provided by HRT before any conclusions can be drawn.

Even with the deficiencies in BAC research it can be stated with certainty that the incidence, prevalence, and mortality of the disease is different for men and women implying that the way the disease is treated in men and women should also be different. A change in the treatment modality by taking into account the possible effects of estrogen on cancer cells can change the way we look at the survival of women with BAC (Falk et al., 1992).

CHAPTER 3

METHODS

Study Design

This descriptive study analyzed 83 patients with BAC from two geographically and demographically distinct locations in Kentucky. One in the city of Louisville, Jefferson County, beale code 2; classified as medium metro and the other in Paducah, McCracken County, beale code 5; classified as non-metro and non-adjacent to metro (The US Census Bureau, American Community Survey Data Profile, 2003). The data were collected from three cancer registries, two located at Louisville and the other located at Paducah. Data analysis was performed in order to obtain a description of the study group. Then, a comparison was made with the state and national data sources to see if the traits seen in the study group were consistent with the former. The source for the state data was the Kentucky Cancer Registry (KCR) dataset from 1996-2000 (issued in 2001) extracted October 1, 2002. The SEER Cancer Incidence Public Use Database 1973-1998 (issued in April 2001) was used to analyze the nationwide data. Lung tumors (site code C33, C34) were extracted and out of those the bronchioalveolar carcinomas (histology code 8250-8254) were used for comparison with the study group (ICD-9-CM: International Classification of Diseases, 1997).

Data Source

This research was done alongside another initiative the 'Kentucky Lung Cancer Project' funded by the State of Kentucky and undertaken by the University of Kentucky, Lexington, KY. The primary objective of 'The Kentucky Lung Cancer Project' was to find possible cancer

clusters located near major petrochemical plants in the regions of McCracken, Jefferson, and Boyd Counties, KY.

Data were extracted as hospital records and discharge sheets of lung cancer patients diagnosed from 1988-2005. The source data were stored either as microfiche files or original (paper) hospital records. Prior to data collection, requests were placed with the registries for records of patients with BAC or mesothelioma. The registries at Louisville provided abstracts of the patients' hospital records and complete records were provided only on further request for specific patients. On the other hand, the registry at Paducah, KY provided excerpts from the hospital records with all relevant information with respect to the variables of interest.

Hospital registrars contact patients annually and review state death certificates periodically to identify deceased registry patients. The last day of follow-up for this study group was either the date of last contact with the patient or the date of death.

Study Sample

The initial study group for this thesis consisted of 88 BAC patients. Twenty-five of these patients were recruited from University of Louisville cancer registry, 30 from Norton hospital registry, and 33 from Western Baptist hospital registry. Five of the original patients were excluded (3 cases from Norton registry and one each from the University of Louisville registry and the Western Baptist registry each). The reasons for exclusion were wrong diagnosis, incomplete records and lack of information on survival status. Demographic characteristics of the study sample are given in Table 1.

Data Management

The data were gathered and recorded in the form of Microsoft Excel spread sheets. The selected variables were entered in the spread sheets after the data were collected. Quality control was performed by the PI of the 'Kentucky Lung Cancer Project', Dr. Timothy Aldrich, in order to minimize errors in data entry, retrieval, etc.

Variables of Interest

The variables taken under consideration were (i) gender, (ii) age at diagnosis, (iii) year of diagnosis, (iv) survival status at the time of data collection, (v) smoking status, (vi) residential location, and (vii) family history of lung cancer. Table 1 gives a detailed description of the variables used for analysis. For the purpose of assessing the possible effect of estrogen on the prognosis of BAC in women, three additional variables were analyzed for the female patients. They were: (a) history of hysterectomy, (b) treatment with hormone replacement, and (c) history of other types of hormone mediated female cancers such as cervical or breast cancers.

Statistical Analysis

The data was analyzed using the statistical software Statistical Software for Social Sciences [SPSS®]. Descriptive statistics were conducted with the variables of interest and graphs were drawn for selected variables. Independent sample t-test, ANOVA, Kaplan Meier survival, and Cox-proportional hazard analyses were applied. Kaplan Meier survival analysis was also used to plot survival curves. Statistical significance was assumed for a two-tailed p-value less than 0.05. Confidence intervals and significance values were reported for the analysis. The study sample and KCR and SEER datasets were analyzed independently.

CHAPTER 4

RESULTS

Description of the Sample

The demographic characteristics of the study sample are presented in Table 1. The study group consisted of 83 patients: 51 women and 32 men. Thirty-one percent of the patients were non-smokers (n=26). Two races were represented out of which only 8.4% (n=7) of the patients were African American and the rest were Caucasian. A total of 61.4% of the patients were from Louisville registries (28.9% from University of Louisville and 32.5% from Norton hospital), whereas 38.6% were from Western Baptist hospital at Paducah. Almost 29% of the patients (n=24) were alive at the time of data collection, 61.4% (n=51) had died because of the cancer itself, and 9.6% (n=8) had died because of other causes. The proportion of patients who had a family history of lung cancer was 20% (n=17). More than half of the patients in the study sample resided in urban areas (61.4%, n=51).

Table 1.
Demographic Characteristics of the Study Sample

Variable		Number (n)	Percentage (%)
Gender	Male Female	32 51	38.6 61.4
Registry	Univ of Louisville Norton hospital Western Baptist	24 27 32	28.9 32.5 38.6
Race	White Black	76 7	91.6 08.4
Smoking	Smoker Non-smoker	57 26	68.7 31.3
Survival status	Alive BAC deaths Other cause deaths	24 51 08	28.9 62.4 09.6
Family History of lung cancer	Present Absent	17 66	20.5 79.5
Rural/Urban	Urban Rural	51 32	61.4 38.6
Age	Younger than 65 Older than 65	30 53	35.4 64.6
Total		83	100

The mean age-at-diagnosis for the cohort was 67 years (Table 2) with the youngest patient being diagnosed at 38 years and the oldest at 85 years. Age-at-diagnosis cross tabulated for variables of interest with 95% CI and p-value calculated using the t-test and ANOVA is presented in Table 2. Men were younger than women at the time of diagnosis (64.7 yrs vs. 68.5 yrs, p-value =0.03) and smokers were diagnosed at younger ages than non-smokers (66 yrs vs. 68 yrs, not significant). African-American patients presented older than Caucasian although this was not a significant finding. Patients who died of BAC were younger than the patients who died of some other cause (67.5 yrs vs. 73.7 yrs, p-value=0.08). The patients in this study who had a

family history of lung cancer were diagnosed at older ages than the patients with no family history (70.8 yrs vs. 66 yrs), but this finding was not significant. Patients from Louisville registries (urban area) were significantly younger at the time of diagnosis than patients from Paducah (64.8 yrs vs. 70.6 yrs, p=0.02).

Table 2.
Age at Diagnosis with Reference to Variables of Interest

Variable		Mean(yrs)	95% Confidence interval (yrs)		p-value
			Lower bound	Upper bound	
Gender	Male Female	64.7 68.5	61.2 65.8	66.3 71.9	0.03
Race	White Black	66.9 68.8	64.3 58.2	69.4 79.5	0.66
Smoking Status	Smoker Non-smoker	66.1 68.1	64.2 63.2	73.7 69.1	0.30
Location	Urban Rural	64.8 70.6	61.4 67.5	68.2 73.7	0.02
Fam Hx	Present Absent	70.7 66.1	65.3 63.3	76.1 68.8	0.13
Survival status	Alive Died of BAC Died other cause	63.8 67.5 73.7	58.5 64.4 68.1	69.1 70.5 79.3	0.08
	Overall Avg. age	67.1			

Mean survival after diagnosis was 5.3 yrs (Table 3) ranging from 0.1 yrs to 16.2 yrs. The mean follow-up time was comparable in alive and dead patients (4.3 yrs vs. 3.9 yrs). Kaplan Meier survival analysis with Wilcoxan chi-square is presented in Table 3. Women survived longer than men (6.5 yrs vs. 3.0 yrs, p-value 0.02), who were 5.2 times more likely to die of the disease than women. Furthermore, 1-year survival for both genders was comparable (71% of male patients vs. 76% of female patients) but 5-year survival was better for women (31% vs.

16%).The survival curve highlighting the difference in cumulative survival between men and women is shown in Figure 3. Non-smokers had longer average survival than smokers (4.2 vs. 3.4) but this difference was not significant on a 0.05 probability. Caucasian patients survived longer than African American patients (5.1 vs. 4.0, not significant). Patients from urban areas survived significantly longer than patients from rural areas (4.3 vs. 2.6, p value 0.04). Patients who had a family history of lung cancer had shorter survival than those who had no history (3.0 vs. 3.8), although not significantly. Patients who died of causes other than the BAC lived longer than patients who died because of the BAC (3.9 yrs vs. 2.3 yrs, p-value 0.04).

Table 3.
Mean Survival of Patients with Respect to Variables of Interest

Variable		Avg. survival(yrs)	95% Confidence interval		Chi-square*	p-value
			Lower	Upper		
Gender	Male Female	3.0 6.5	2.2 4.6	3.8 8.4	5.2	0.02
Race	White Black	5.1 4.0	3.8 2.6	6.5 5.8	0.5	0.48
Smoking status	Smoker Non	4.7 6.2	3.6 3.2	8.8 6.2	0.57	0.44
Location	Urban Rural	5.7 3.5	4.1 2.3	7.4 4.7	1.5	0.04
Fam Hx	Present Absent	3.9 5.3	2.3 3.9	5.4 6.8	1.1	0.90
Age	<65 >65	6.2 3.7	3.9 2.8	8.5 4.5	1.4	0.001
	Overall survival	5.3	3.9	6.6		

* Wilcoxan Chi-square

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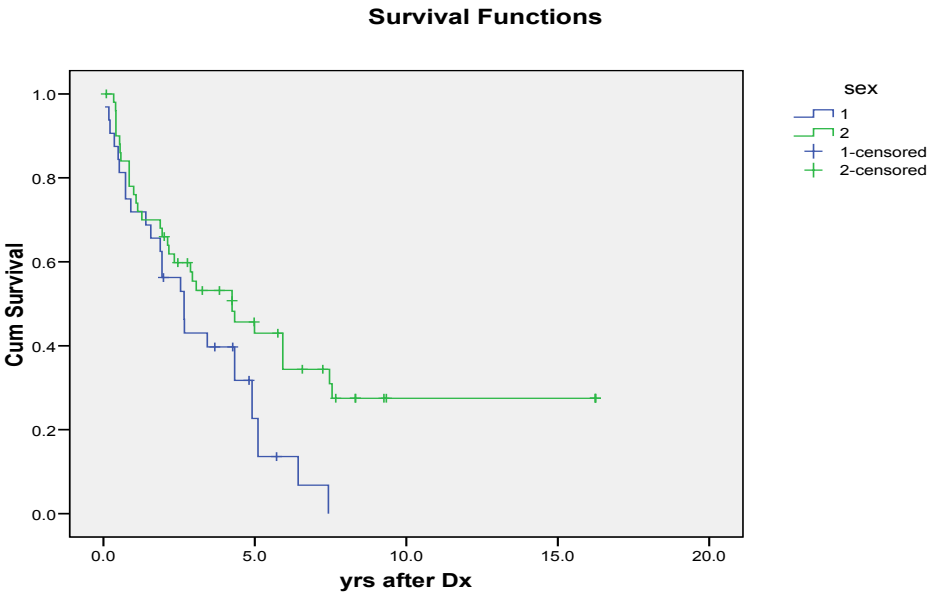

Figure 3. Cumulative Survival Curve by Gender.
sex1: Male patients, sex 2: Female patients.
Survival curve plotted using Kaplan Meier life table programs

Comparisons Between Male and Female Patients

There were more female non-smokers (23 out of 27 non-smokes) than male, but smoking did not have a significant effect on survival or the age-at-diagnosis for women. Gender specific comparisons for survival and age-at-diagnosis are tabulated in Table 4. After stratifying for location both men and women showed significant differences in survival and this difference was more pronounced in men compared to women. In both genders**,** patients in the urban locations survived longer than those in rural settings (6.9 yrs vs. 4.2 yrs for women, p-value 0.05 and 3.6 yrs vs. 2.4 yrs in men, p-value 0.03). Both men and women who had a family history of the disease were diagnosed with the disease later than those who did not have a history of lung cancer, with this difference being more pronounced in women as compared to men (66 yrs vs. 74 yrs in women and 64 yrs vs. 62 yrs in men). Both male and female patients with a family history

of lung cancer had significantly shorter survival time than those with no history. This difference was more pronounced in women (3.2 yrs vs. 7.2 yrs, p-value=0.06) compared to men (2.6 vs. 4.7, p-value=0.08). To further assess the affect of age on survival time, age was dichotomized into groups of patients who were younger than 65 at the time of diagnosis and those who were older. Younger patients survived longer than the older patients and this effect was much more pronounced in women (3.2 yrs vs. 7.2 yrs, p-value 0.01), men on the other hand showed no significant differences.

Table 4.
Gender Specific Comparisons for Survival and Age at Diagnosis

Variables (n= number of patients)		Survival (yrs)	95% CI (yrs)	p-value	Age (yrs)	95% CI (yrs)	p-value
Smoker	Male (n=29)	3.1	2.2 – 4.0	0.80	60.4	43 – 76	0.40
	Female(n=28)	6.3	3.7 – 8.9		70.3	65 – 75	
	Overall(n=57)	4.7	3.6 – 8.8		66.1	64 – 73	
Non	Male (n=3)	2.4	0.6 – 4.7	0.90	65.8	61 – 79	0.30
	Female(n=23)	6.8	1.3 – 3.3		67.2	62 – 71	
	Overall(26)	6.2	3.2 – 6.2		68.1	63 – 69	
		3.6	2.6 – 4.6	0.02	62.6	55 – 66	0.06
Urban	Male (n=18)	6.9	4.5 – 9.2		66.3	63 – 72	
	Female (n=33)	5.7	4.1 – 7.4		64.8	61 – 68	
	Overall(n=51)						
		2.4	1.0 – 3.8	0.06	68.3	61 – 70	0.05
Rural	Male (n=14)	4.2	2.5 – 5.9		72.4	69 – 77	
	Female (n=18)	3.5	2.3 – 4.7		70.6	67 – 74	
	Overall(n=32)						
Fam Hx	Male (n=6)	4.7	2.4 – 7.0	0.08	64.7	53 – 74	0.80
	Female(n=11)	3.2	1.2 – 5.2		64.1	60 – 68	
	Overall(n=17)	3.9	2.3 – 5.4		70.7	65 – 76	
No Hx	Male (n=26)	2.6	1.8 – 3.5	0.06	74.0	67 – 80	0.06
	Female(n=40)	7.2	5.0 – 9.4		66.3	63 – 70	
	Overall(n=66)	5.3	3.9 – 6.8		66.1	63 – 69	
Age<65	Male (n=16)	3.2	2.1 – 4.4	0.01			
	Female(n=16)	8.5	5.1 – 11.0				
	Overall(n=32)	5.9	3.8 – 8.1				
					NA*	NA	NA
Age>65	Male (n=16)	2.8	1.6 – 3.9	0.07			
	Female (n=35)	4.1	2.9 – 5.3				
	Overall(n=52)	3.8	2.8 – 4.7				
Overall Survival		5.3	3.9 – 6.6				

*NA: Not Applicable

Female Hormones and Survival

To assess the affect of an altered female hormonal milieu the following three variables were analyzed: (1) history of hysterectomy, (2) diagnosis of other cancers which disrupt the female hormone production (e.g. cervical carcinoma, ovarian carcinoma, or breast cancer), and (3) positive history of hormone replacement therapy (HRT). Out of 51 female patients in the study sample 24 had undergone hysterectomies, 11 had other types of female cancers, and 7 had positive history of HRT. Survival analysis of female patients using Kaplan Meier life tables is shown in Table 5. Only the patients who had undergone hysterectomies showed a significant difference in survival when compared to patients who had not. Women who had undergone the procedure survived better than those who had not (5.1 yrs vs. 3.3 yrs, p-value=0.02). A survival curve highlighting the difference in cumulative survival between patients who had a history of hysterectomy and those who did not is shown in Figure 4.

Table 5.
Mean Survival for Female Patients with Respect to Variables Affecting Hormonal Milieu

Variable	Average Survival time [in Years]	p-value	(95%CI) [in Years]
HRT No HRT	5.5 6.5	0.80	0.0 – 11.5 4.6 – 08.6
Other cancers No other cancers	6.4 6.5	0.90	2.5 – 10.1 4.3 – 08.6
Hyst* No Hyst	7.1 4.2	0.02	4.3 – 09.9 3.0 – 05.3

*Hyst: Hysterectomy
Survival analysis performed using Kaplan Meier life tables

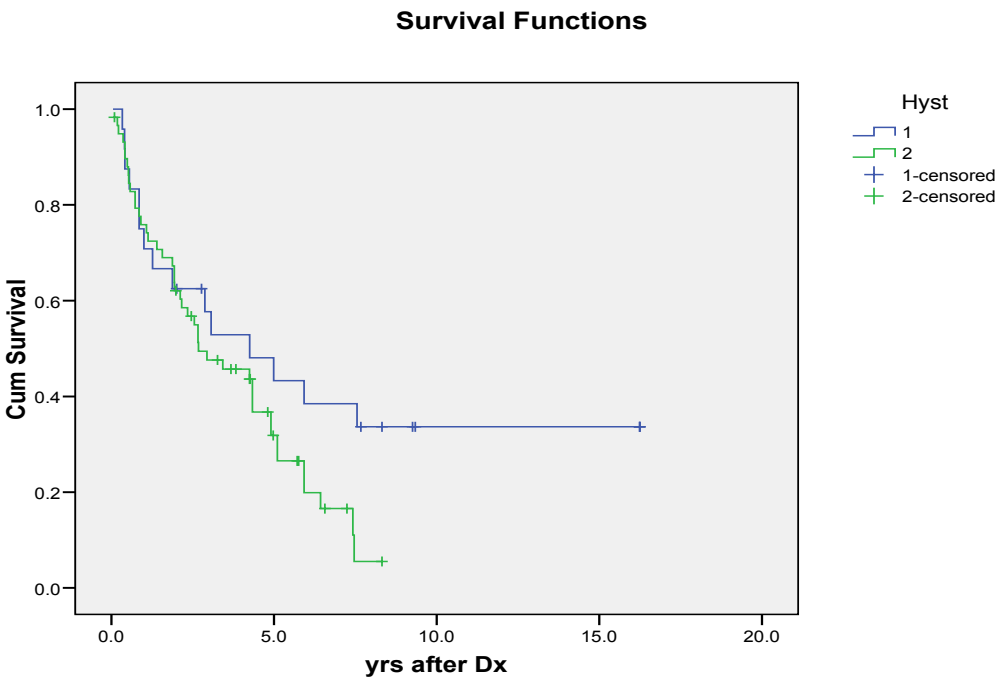

Figure 4. Survival Curve Depicting Differences in Survival by History of Hysterectomy
Hyst 1: hysterectomy performed
Hyst 2: hysterectomy not performed
Survival curve plotted using Kaplan Meier life tables

Comparison Of Patients Diagnosed Before 1999 With Those Diagnosed After 1999

This study group had almost equal number of patients who had been diagnosed after May 1999 as before May 1999 (Table 6). The follow-up period for patients diagnosed before 1999 was much longer than those diagnosed after May 1999, as would be expected for a study comprising subjects from 1988 - 2005.

Table 6.
Descriptive Statistics for Year of Diagnosis

Year of diagnosis	Frequency (n)	Percentage (%)	Avg. years of follow-up
Before May 1999	42	50.6	7.8
After May 1999	41	49.4	3.4

The results of the survival analysis and ANOVA (to assess mean age at diagnosis) are tabulated in Table 7. The mean age at diagnosis after 1999 was higher than for patients diagnosed before 1999 (68 yrs. vs. 64 yrs). This trend was unchanged after stratification by gender. For this patient series, the patients diagnosed before 1999 showed a survival advantage over those diagnosed after 1999 (6 yrs vs. 4.4 yrs). In both the cases (i.e. before and after May 1999) survival was significantly better for female patients as compared to their male counterparts. The lower mean age at diagnosis in patients diagnosed before 1999 can be the confounding factor that contributed to longer mean survival for these patients.

Table 7.
Mean Survival of Patients Diagnosed Before 1999 and After 1999

Variable		Survival (yrs)	95% CI (yrs)	p-value	Age (yrs)	95% CI (yrs)	p-value
Before	Male	3.7	2.3 – 5.1	0.2	60	53 – 76	0.4
	Female	7.0	4.4 – 9.6		65	61 – 69	
	Total	6.0	5.2 – 8.0		64	60 – 74	
After	Male	2.5	1.6 – 3.3	0.06	63	58 – 68	0.3
	Female	5.8	3.1 – 8.6		67	62 – 71	
	Total	4.4	2.7 – 6.2		68	63 – 72	

Comparison Of Study Results with KCR and SEER Datasets

The findings from this study group were compared to analyses performed using the KCR and SEER datasets. The results of this comparison are presented in Table 8. Women constituted 61% of study group, for the state data this percentage was almost 55%, and SEER dataset constituted 53.8% female cases. The mean age at diagnosis for study sample was 67 yrs, which is similar to the pattern noticed in KCR and SEER data (66.4 yrs and 67.1 respectively). Women were older (68.5) than men (64.7) for the study group. This is in contrast to the KY and SEER datasets where women were diagnosed younger than men. The mean length of survival after diagnosis was 5.3 years which was significantly higher than both the state and national datasets (4.0 yrs for KY and 3.5 yrs for SEER). In the study group women presented with a longer survival than men (6.5 yrs vs. 2.8 yrs), this is in contrast with the KCR dataset where this difference in not significant (4.1 vs. 3.9); the SEER dataset on the other hand also presented an increased survival in women compared to men (3.9 yrs vs. 3.4 yrs). As far as increase in survival after reclassification in 1999 was concerned, the study sample suggested a survival advantage for patients diagnosed before 1999. This result could be confounded by younger age of patients diagnosed before 1999 in this patient group. Comparison of survival before and after 1999 could not be performed for the other two datasets because of lack of such information.

Table 8.
Comparison of Regional, State and National Data with Respect to Proportion of Female Patients, Age at Diagnosis and Survival Time

		Study Sample	KCR	SEER
years		1988-2005 (16 yrs)	1996-2000 (5yrs)	1973-1998 (25 yrs)
Total number (N)		83	350	8777
Women (%)		61%	55%	53.8%
Avg. age at Dx* (with 95% CI)	Men Women Overall	64.7 (61.0-66.0) 68.5 (65.8-72.0) 67.1 (63.0-71.5)	67.0 (65.6-73.0) 64.3 (58.0-66.7) 66.4 (62.5-70.8)	67.8 (63.1-69.5) 65.2 (64.4-70.4) 67.1 (65.4-72.1)
Avg. survival (with 95% CI)	Men Women Overall	3.0 (2.2-3.8) 6.5 (4.6-8.4) 5.3 (3.9-6.6)	3.9 (3.6-4.2) 4.1 (3.7-4.5) 4.0 (3.7-4.2)	3.4 (3.0-3.8) 3.9 (3.2- 4.1) 3.5 (2.2-3.8)

*Dx: Diagnosis
Analysis performed using Kaplan Meier survival analysis and ANOVA

Further comparison was made between the study group and the KCR data using Kaplan Meier survival analysis as shown in Table 9. Patients who had undergone hysterectomies in the study sample were compared to pre-and post-menopausal women in the KCR dataset. The results indicated that women who had undergone hysterectomies survived longer than women who had not (7.1 yrs vs. 4.3), while women who were pre-menopausal seemed to be doing better than those who were post-menopausal (4.1 yrs vs. 3.5 yrs). The menopause status data were not available from the SEER dataset. Patients in this study group who lived in urban settings survived better than those in rural settings (4.2 yrs vs. 2.6 yrs); however, there was no significant

difference in the overall survival with respect to the KCR dataset. After stratifying for gender the effect seemed to be more pronounced in men (3.4 yrs vs. 1.9 yrs) in the study group, but no significant differences were seen in the KCR data.

Table 9.
Mean Survival of Study Sample and State Data by Variables of Interest

		Study Sample Survival in yrs (95%CI)	KCR Survival in yrs (95% CI)
Male	Rural	2.4 (1.0-3.0)	3.9 (3.5-4.3)
	Urban	3.6 (2.9-4.8)	3.9(3.4-4.3)
	Overall	2.8 (2.2-3.8)	3.9 (3.6-4.2)
Women	Rural	4.2 (2.5-5.0)	3.7 (3.1-4.2)
	Urban	6.9 (4.5-5.8)	4.5 (4.0-5.0)
	Overall	6.5 (4.6-8.4)	4.1 (3.7-4.5)
Women	No Meno[#]	NA[*]	4.1 (3.7-4.6)
	Meno		3.5 (2.6- 4.0)
	Hyst	7.1 (4.3 – 9.9)	NA[*]
	No Hyst	4.2 (3.0 – 5.3)	

[*]NA: Data Not Available, [#] Meno: Menopause
Analysis performed using Kaplan Meier life tables.

CHAPTER 5

DISCUSSION

The main objective of this research was to highlight the differences in survival between the two genders among patients with BAC. The results of this research indicated that women had an overall survival benefit over men; this survival advantage was observed even after stratifying for age, residential location, family history, and year of diagnosis. This research shows that male patients are at a five-times higher risk of dying from their BAC than female patients. Furthermore, the results of this series of patients showed that the survival advantage was more obvious for 5-year survival than for 1-year survival as noticed by previous authors. Among non-smokers, females constituted a considerable proportion of the BAC patients. Comparing the three datasets (study, KCR, SEER), similar trends were noticed in terms of the gender ratio. All three datasets (study sample, KCR and SEER) presented with female patients constituting more than half of the patients (61%, 55% and 54% respectively).

Furthermore, the mean age-at-diagnosis for this study showed an older age for women compared to men contrasting with the state KCR and national SEER data, where women presented younger. The reason for older age of women at diagnosis cannot be fully explained. A possible reason for later diagnosis could be higher average age of women in the two regions than men (The US Census Bureau, American Community Survey Data Profile, 2003). At the same time the average survival was longer in women than men and even though similar trends were seen in KCR and SEER data, this observation was more pronounced in this study population. BAC is a rare form of lung cancer; our study group of 83 patients represented a reasonable sub-group to use for comparison purposes as there were only 350 patients reported in the whole state of KY during a comparable time period. This research also showed that the patients who were

alive at the time of data retrieval were younger at the time of diagnosis than patients who died of the disease (64 yrs vs. 67 yrs), indicating that younger age-at-diagnosis is a predictor of good prognosis.

Earlier literature reports the younger age-at-diagnosis in women compared to men as one of the possible contributors to longer survival for women (Edgerton et al., 1981; Leno et al., 2005; Page et al., 2000), but this study indicates that the survival advantage in women compared to men is not just a consequence of age. After stratifying survival by age (older than 65 and younger than 65) survival is found to be better for younger patients than older patients. This effect was more pronounced after stratifying for gender. These findings suggest that female gender is a better prognostic factor for survival than male even after taking the effect of age into account.

This research further indicated that the patients who had a family history for lung cancer presented older and with poorer prognosis than patients with no family history. This finding was in contrast with trends reported in literature (as cited in Cote et al., 2005) which suggests that patients with family history presented younger but still had poorer prognosis.

Association Between Smoking History and Survival

Classically, smoking is associated with poorer prognosis when smokers are compared to non-smokers. This trend is suspected to contribute a part of the survival advantage that non-smoker BAC patients have over smokers (Radzikowska et al., 2002). Non-smokers in this study group did not show a significant survival advantage over smokers.

In a study assessing outcomes for histological sub-types of lung cancer, it is very important to analyze the effect of smoking as an etiological agent. Because of the widespread

prevalence of smoking, it becomes very difficult to make such assessments. This study faced similar limitations while analyzing the effect of smoking on survival. There were only three male patients who were non-smokers, so it was not possible to make gender distinction on the effects of smoking. Furthermore, the data included inconsistent coding formats with respect to smoking history. Also, no information was gathered to assess the extent of environmental smoking history (e.g. smoking history of either spouse or other family members).

Recent studies on BAC indicate that the proportion of non-smoker patients of either sex is increasing (Leno et al., 2005). BAC is beginning to gain distinction as a female, non-smoker's lung cancer (as cited by Devasa et al., 2005). It would seem very important to establish the true burden of smoking as an etiology including under-reported environmental smoking before such terminology could be appropriately applied. A good study design to make such assessment could be inspired by the one used by Kit et al. in China who eliminated the confounding effect posed by smoking by conducting their study in non-smoking women (as cited by Page et al., 2000).

The Effect of Geographical Location on Survival

BAC patients in this study who resided in urban areas were significantly younger than those from rural areas. This association with survival was seen in both sexes. Similar trends were noticed in the KCR sample, although not to the same extent as the study group. According to the KCR dataset the survival advantage for urban patients was better in women compared to men. Female urban patients also showed this advantage over rural female patients, but no significant changes were seen for men with BAC in the KCR dataset.

The exact reason for this association by location of residence is difficult to ascertain until further research is conducted. Access-to-care issues for rural populations can be a reason for

such finding. Another reason for better survival reported from the Louisville registries could be because of both registries at Louisville being associated with metropolitan, tertiary care hospitals. Such facilities may be better equipped with infrastructure enabling early diagnosis and proactive treatment when compared to the community hospital configuration at Western Baptist hospital in Paducah. Early age-at-diagnosis may contribute to better survival of urban patients compared to rural patients. A possible contributor to older age-at-diagnosis of patients living in Paducah compared to Louisville could also be the older mean age of residents in Paducah as compared to Louisville (38 yrs vs. 35 yrs) (The US Census Bureau, American Community Survey Data Profile, 2003).

Association Between Female Hormones And Survival

One of the objectives of this research was to assess the effects of estrogen on survival of lung cancer. We examined various variables that can have a possible effect on estrogen production in the body e.g., hysterectomy, HRT, and other cancers such as breast, ovarian, and cervical. Of these variables, only hysterectomy showed a significant effect on survival. There was no difference in mean age-at-diagnosis between the patients who had undergone hysterectomy and those who had not, therefore, suggesting that the patients who underwent hysterectomy clearly showed a survival advantage over those who had not. After hysterectomy the estrogen levels in the body decrease. This increase in survival could be because of a decrease in estrogen levels. More definitive research needs to be performed before any conclusions can be drawn. To make a similar assessment with the KCR data we compared women who were pre-menopausal to those who were post-menopausal. Pre-menopausal women showed a distinct survival advantage over post-menopausal women. A confounder for such observation may be the

fact that premenopausal group was considerably younger than postmenopausal group. Estrogen's affect on lung cancer survival is controversial. Certain studies (Ishibashi et al., 2005) report it to be associated with poor prognosis and others suggest a protective affect (McDoniels-Silvers et al., 2002).

Affect of Reclassification in 1999

This research project also attempted to discern whether or not reclassification in 1999 contributed to an increase in survival of patients with BAC. These study findings indicate that patients who were diagnosed before 1999 were at a survival advantage when compared to those who were diagnosed after 1999. This observation could be a result of confounding by age as patients diagnosed before 1999 were significantly younger than those diagnosed after 1999. These findings should be interpreted very cautiously as the follow-up period of patients who were diagnosed after 1999 was also very small in our group compared to the patients who were diagnosed before 1999. Another confounder in this respect is the 2 year lag that generally exists between the changes in definition and the implementation by the concerned organizations. Because the information of the exact year the updated definition was implemented by these registries is unavailable, these findings cannot be viewed as conclusive.

Limitations

1) One of the biggest limitations of this research is unavailability of data regarding the size of tumor and extent of metastasis. These two variables are the most important predictors of the length of survival in BAC patients (Ebright et al., 2002).

2) An important consideration is the suitability of the study group as a representative of the population of the two counties. African-Americans were underrepresented in this sample. In both these counties African Americans represents 28-33% of the population (The US Census Bureau, American Community Survey Data, 2003) while this sample consisted of only 8.4% African American patients.

3) The data do not provide any information on environmental smoking, which is an important consideration when assessing any lung cancer relationship especially one that presents a lower risk association with respect to smoking. The reason that this cancer type presents with a lower risk with smoking could be an artifact noticed because of under-reported environmental smoking.

4) This study used hospital records as tools of data retrieval. This can result in possible information bias. For example, the records lacked consistent method of coding for smoking status [e.g., not recorded, versus not assessed, versus refused, etc.].

Recommendations for Future Research

BAC is the most common lung cancer cell type in females (smokers or non-smokers) and in non smoking males. Its incidence has been increasing in younger cohorts of males and females until very recent years. Changes in classification and in pathological techniques can account for some of this increase. In females and non-smoker males, the increase could be partly because of a detection bias in former studies. Nevertheless, successive cohorts over time seem more likely to develop adenocarcinoma and less likely to develop squamous cell carcinoma. This probably represents a true increase in incidence of BAC. An explanation for this should be sought in

studies on detailed smoking history and passive smoking exposure, occupational exposure, diet and cooking, pollution, and other environmental factors (Laskin, 2004).

More research needs to be conducted to establish the exact burden of smoking as a risk factor for BAC and to explore the other possible causes of BAC in order to establish multi-modal prevention techniques. A possible direction in this regard may be the exploration of environmental smoking as a risk for BAC and comparing its relationship to other histologic categories of lung cancer.

More research needs to be done on differences in BAC outcomes between the genders and how gender affects the course of the disease. One of the increasingly prominent areas of research is the role that estrogen plays in this regard and how the differences in the male and female physiological makeup can be used with respect to newer treatment modalities. Authors are largely divided on the effects of estrogen (as cited in Ishibashi et al., 2005). Further investigation needs to be done regarding the role of estrogen in the progression of carcinogenesis and for the possibility of productive treatment with HRT.

Furthermore, no research has been performed that has exclusively addressed the possibility of a different line of treatment for BAC patients (Leno et al., 2005).Various studies over the past decade have highlighted differences in the epidemiology and demographics of BAC, but very little work has focused on use of these differences towards improvement of survival (Liu et al., 2000; Zang & Wynder, 1996). BAC patients are still treated the same way as other adenocarcinoma patients. Analyses like the one presented here indicate a definitive survival advantage of female patients over male but no attempts have been made to use this survival advantage by exploring new treatment methods.

In conclusion, it can be stated that BAC is the most common lung cancer cell type in females and a survival advantage exists for female BAC patients as compared to their male counterparts. And, there is much potential for using this advantage for the improvement of prognosis of both male and female patients with BAC.

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