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Case-Control Study of Nutrition and Lung Cancer in Appalachian Kentucky

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Case-Control Study of Nutrition and Lung Cancer in Appalachian Kentucky

CAPSTONE PROJECT PAPER

A paper submitted in partial fulfillment of the requirement for the degree of Master of Public Health in the University of Kentucky - College of Public Health

By

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Lexington, Kentucky

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I. ABSTRACT

Background and Objectives

Lung cancer is the most common cause of cancer-related deaths world-wide. Recent studies suggest a possible association between nutrition and risk for specific histological subtypes of cancer. We examined the relationship between nutrition and lung cancer histology in Kentucky, a largely rural U.S. state that ranks among the highest in the nation in lung cancer rates, as well as diseases related to diet, such as diabetes and obesity. The objective of this study was to examine the impact of nutrition on lung cancer risk and histology in Kentucky. More specifically, we wanted to investigate potential associations with high sugar foods using their responses to a brief food frequency questionnaire

Methods

In this case-control study, we used secondary data from a previous population-based case-control study that examined possible environmental exposures to trace elements such as arsenic, chromium, and radon. The original data consisted of 520 surveys completed by 150 cases and 370 controls, and linked data from the Kentucky Cancer Registry. The original study enrolled subjects from January 2012 to August 2014 who resided in the 5th Congressional District and had eligibility requirements for selecting both cases and controls. We tabulated median and interquartile ranges by participant characteristics and by histological type (including controls) to examine consumption patterns for specific types of foods. We also created a logistic model to compare odds of significant covariates from our bivariate analysis and lung cancer among cases and controls while controlling for smoking. Our tertiles for the high sugar variable was based on the distribution of number of times eaten per month.

Results

Our findings show controls ate higher amounts of fruits, vegetables, and whole grains compared to cases, and to cases in each histology group. Cases tended to eat high-sugar and highly processed foods more often than controls. This relationship was mostly similar when examined separately for each specific histological type. The results of this study suggest a possible association between lung cancer risk and high-sugar and highly processed foods.

Conclusion

Our study showed that controls generally had healthier diets, consuming fewer sugary foods and more fruits and vegetables per month compared to cases, though much of this effect was attenuated by controlling for confounding. Future research in this area could benefit from a more comprehensive dietary survey and a larger sample size to enable stratification by histological type.

II. INTRODUCTION

As the most common cause of cancer-related death worldwide, lung cancer affects millions of people each year (Betticher & Heighway, 2004). Roughly 6.4% of men and women will be diagnosed with lung cancer at some point in their life. Cigarette smoking is the most common risk factor for lung cancer, linked to about 90% of lung cancer cases in the United States (Alberg, Brock, Ford, Samet, & Spivack, 2013). There are only about 10-15% of lung cancer cases in which the persons are lifetime never smokers (McCarthy, Meza, Jeon, & Moolgavkar, 2012). Exposure to secondhand smoke, also known as environmental tobacco smoke (ETS) is also a significant risk for developing lung cancer. In 2015, there were approximately 541,000 people estimated to be living with lung cancer in the United States (National Cancer Institute, 2018). The number of new lung cancer cases is estimated to be 54.6 per 100,000 for both men and women. In 2018, there were about 234,000 new cases and an estimated 228,150 new cases in 2019 (American Cancer Society, 2019). In 2017, there was an estimated 154,000 lung cancer deaths, accounting for almost 26% of all cancer deaths. Lung cancer mortality in the United States is estimated to be 43.4 per 100,000 per year for both men and women with the 5-year survival rate being about 18% (National Cancer Institute, 2018). In the United States, much of the south-east has higher incidence and mortality rates of lung cancer when compared to the rest of the country.

In the United States, Kentucky has one of the highest incidence rates of lung cancer, specifically in south-eastern Kentucky (CDC, 2017b). Populations, such as the Appalachian coal-mining region have shown an increase risk to lung cancer (Christian, Huang, Rinehart, & Hopenhayen, 2011). In Kentucky, the percentage of adults who smoke is almost 26% compared to the national rate of almost 17% (American Lung Association, 2018). Kentucky's age-adjusted

lung cancer incidence rate is higher than the national average at 93.5 per 100,000 as well as the age-adjusted mortality rate, which is 60.5 per 100,000 (CDC, 2017b). Compared to the national average, Kentucky's mortality rate from lung cancer is 37% higher (Kentucky Cancer Consortium, 2017). While it is critical to diagnose lung cancer as soon as possible, in Kentucky, only 18.1% of lung cancer cases were diagnosed at early stages, when it is more likely to be curable (American Lung Association, 2018). The low survival rate of patients with lung cancer is related to the stage of lung cancer at diagnosis (Cheng, et al., 2016). Furthermore, some histological types of lung cancer have poorer survival rates (American Cancer Society, 2019). Therefore, it is crucial to be able to predict and diagnose not only lung cancer but also, it's histological group in order to manage treatment for the best possible outcome.

Lung Cancer Histology

Histology is the study of cells, tissues, and organs as seen with a microscope (Singh, 2011), including all aspects of tissue biology, with the focus on how cell' structure and arrangement optimize functions specific to each organ. Lung tumors can be divided into two broad categories by their histology, or the types of cells they comprise: small cell lung cancer and non-small cell lung cancer. Small cell lung cancer (SCLC) makes up approximately 10-15% of lung cancer cases while non-small cell lung cancer (NSCLC) makes up approximately 80-85% of lung cancer cases. Non-small cell lung cancer is often further classified into four principal subgroups: adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and not otherwise specified (NOS). The NOS classification is used when the non-small cell cannot be clearly diagnosed to be in the other three subgroups. Overall, 90% to 95% of NSCLCs are adenocarcinomas, squamous cell carcinomas, or large cell carcinomas, with 3% to 4% being mixed tumors (Movsas, Brahmer, Forde, Kernstine, & Frederic, 2016). In the past few decades, rates of adenocarcinoma have

increased dramatically with corresponding decreases in squamous cell and small cell (Harris, 2013). A 2013 study also attributed this increase to changes in cigarette design and associated smoking behavior, including a greater depth of inhalation (Harris, 2013).

Treatment for SCLC and NSCLC are managed quite differently. Treatment for SCLC includes chemotherapy and radiation (American Cancer Society, 2017e). Treatment for NSCLC includes surgery, adjuvant, chemotherapy, radiotherapy, and biomarker testing. Patients who have stage I, II, and IIIA NSCLC typically have surgery to remove the tumor if the tumor is found to be resectable and the patient is able to tolerate surgery (Zappa & Mousa, 2016). Adjuvant therapy may include radiation, chemotherapy, and/or targeted therapy. Mortality rates also vary by histological subtype. On average, SCLC has a five-year mortality of 90% or more where NSCLC has a five-year mortality rate of about 83%.

Nutrition and Lung Cancer

Recently, studies have shown that cancer cells are heavily dependent on sugar as their energy supply. All cells use sugar, in the form of glucose, to one degree or another, but some use more than others (Fox, 2017). Previous studies on nutrition and lung cancer, though limited, suggest that eating a diet high in complex sugars such as fruits and vegetables compared to simple or processed sugars, could be protective factors against the development of lung cancer. Fruits and vegetables contain important micronutrients which have been shown to have an inverse association between lung cancer and increased consumption. In addition to micronutrients which could be preventative in lung cancer, macronutrients such as healthy fats have also been studied to determine their effect on lung cancer.

In 2002, a study in the American Journal of Epidemiology revealed that carotenoids may have the potential for lung cancer prevention and that the consumption of fruits and vegetables was significantly inversely associated with lung cancer risk (Holick, et al., 2002). This inverse association with lung cancer risk may occur due to the antioxidant activity. More specifically, the stimulation of gap junction intercellular communication, induction of detoxifying enzymes, and inhibition of cellular proliferation (Cooper, AL, & JC, 1999). In Taiwan, researchers studied the intake of vitamin A-rich foods and lung cancer risk. The study found that there was a significantly lower risk of lung cancer was associated with the higher intake of vitamin A, alpha-carotene, and beta-carotene from local common vitamin A-rich foods. However, there was not an inverse association between lung cancer development and the intake of fruits or vitamin A supplements (Jin, et al., 2007).

Other studies have shown that eating a diet high in crucifers; including broccoli, brussels sprouts, and cabbage provides even greater protection against cancer compared to a diet high in a general mixture of fruits and vegetables (Keck & Finley, 2004). Keck and Finley suggested that the micronutrients of both fruits and vegetables, specifically cruciferous vegetables can alter how the body is able to detox. The detoxification leads to decreased activation of procarcinogens and increased excretion of carcinogens. The detoxification elements stem from the anticarcinogenic properties of isothiocyanates (Keck & Finley, 2004). In addition, flavonoids in vegetables, which scavenge free radicals, have been added to the list of protective compounds. In addition to vitamin A, vitamin D has recently been investigated to determine if it could be a protective factor in lung cancer prevention. Previous research has suggested that low vitamin D levels are a risk factor for certain cancer types (Norton & O'Connell, 2012). Not only does vitamin D help to maintain calcium for good bone health but it also helps with immune system functioning,

neuronal communication, and muscle functioning. Vitamin D also exhibits numerous immunomodulatory properties, including inhibition of prostaglandins, proteases and pro-inflammatory cytokines (Norton & O'Connell, 2012). Excessive inflammation is central to COPD and is a key underlying process in the progression of lung cancer; therefore, agents that can reduce inflammation may be of benefit in lung cancer prevention and treatment (Norton & O'Connell, 2012). Ultimately, more studies are needed to determine the impact of vitamin D and lung cancer due to the conflicting data and findings from previous studies on this matter.

Dietary fat intake has been of interest in its role in lung carcinogenesis. A pooled analysis of 10 prospective cohort studies found that a high intake of saturated fat and a low intake of polyunsaturated fat are associated with an increased risk of lung cancer. Substituting saturated fat with polyunsaturated fat may reduce lung cancer risk, especially among smokers and for squamous cell and small cell carcinoma (Yang, et al., 2017). A case-control study in Iran found that vegetables, fruits, and sunflower oil could be protective factors against lung cancer. The same study showed that phytoestrogens and glucosinolate hydrolysis products are other potential micronutrients in vegetables and fruits that may be preventive against lung cancer (Hosseini, et al., 2014). Finally, a case-control study within Japan found that the consumption of cooked or raw fish reduced the risk of lung cancer in both men and women by about 50%. Since eating fresh fish provides an excellent source of complex polyunsaturated fatty acids that are known to have potent anti-inflammatory effects, it is possible that regular fish consumption by Japanese smokers inhibits or delays lung carcinogenesis by tobacco smoke (Stellman, et al., 2001). In relation to exposure time period and food consumption, it is unknown whether there is any relevant impact.

In summary, the previous research and studies show that fruits, vegetables, and certain oils can be protective against lung cancer. Specifically, foods high in vitamin A, which has been shown to lower the risk of lung cancer and also cruciferous vegetables which has shown to have an inverse relation to lung cancer due to its detoxification properties of carcinogens in the body. Flavonoids in vegetables are protective compounds due to their antioxidant properties. Moreover, fish consumption has shown to possibly inhibit or delay lung carcinogenesis.

Nutrition and Cancer Histology

Few studies have been conducted to examine the relationship between nutrition and histological subtypes in lung cancer patients. One such study was published in 2010, which examined the association between fruit and vegetable consumption in relation to the risk of different histological subtypes of lung cancer (Buchner, et al., 2010). The findings observed inverse associations between the consumption of vegetables and fruits and the risk of lung cancer, but without a clear effect on specific histological subtypes of cancer (Buchner, et al., 2010). More recently, a 2016 case-control study in the U.S. used dietary pattern analysis to examine the effect of diet on lung cancer (Tu, et al., 2016). Three dietary patterns were analyzed for this study: one high in fruits and vegetables, an American/Western diet, and a Texas-Mexican cuisine diet. These three dietary patterns were selected due to their associations with lung cancer. A healthy diet of fruits and vegetables were associated with a decreased risk of lung cancer, the Western diet (high in fats and red meat) was associated with an increased risk in lung cancer, and the Texas-Mexican cuisine had never before been examined on its impact on lung cancer (Tu, et al., 2016). Results found that the “Tex-Mex” pattern was associated with a reduced risk of lung cancer. The “fruits and vegetable” patterns were associated with a reduced risk of lung cancer and the protective effects were more evident for squamous cell carcinoma specifically. Finally,

the “Western” pattern was associated with an increased risk of lung cancer, and the harmful effects were more pronounced for NSCLCs other than squamous cell carcinoma.

Lycopene showed significant inverse associations with risk of small cell, squamous cell, and other carcinomas, but not adenocarcinoma. B-Cryptoxanthin and total carotenoids showed significant inverse associations with squamous cell carcinoma only (Holick, et al., 2002).

Recently, a study found that one specific histological type, squamous cell carcinoma is more dependent on sugar than other histology groups as its energy supply. The GLUT1 expression is markedly and specifically elevated in human squamous cell carcinoma, and is associated with enhanced glucose uptake and glycolytic dependency. Conversely, GLUT1 and glycolytic enzyme expression remain relatively low in the majority of adenocarcinoma when compared to squamous cell carcinoma, suggesting that adenocarcinoma may be significantly less reliant on glucose metabolism (Goodwin, et al., 2017).

Previous studies have thus shown that vegetable and fruit consumption can influence the risk of lung cancer and the survival rate among lung cancer patients. Additionally, there have even been a few studies which demonstrated that nutrition might play a stronger role in development of some histological subtypes of lung cancer.

Objective

The objective of this study was to examine the impact of nutrition on lung cancer histology in Kentucky. We aimed to look at differences between cases and controls in regards to population characteristics and nutritional intake. More specifically, we wanted to investigate the association between high sugar foods and the risk of different histological subtypes of lung cancer, since these foods have not been addressed specifically in previous studies. The foods examined in this

study include high sugar and processed foods such as cookies, doughnuts, ice cream, and other sweets. Based on the high burden of lung cancer in Kentucky and the U.S., and the limited number of human studies in the literature concerning nutrition and cancer histological subtypes, there is a need for further investigation of this relationship. We aimed to describe potential relationships between these highly processed foods and lung cancer histology, while controlling for other important covariates.

III. METHODS

Study Population

Our study was conducted using secondary data. The data came from a previous population-based case-control study of lung cancer patients in south-eastern Kentucky; "A Population-based Case-control Study of Lung Cancer in Appalachian Kentucky: The Role of Environmental Carcinogens". The previous study had collected dietary history and information from all participants at the individual level, including histological type and other information pertaining to each case patient from the KCR. Subjects were enrolled in this study between January 2012 to August 2014. Eligibility criteria included: (i) residence in southeastern Kentucky (5^{th} Congressional District) at the time of enrollment; (ii) a working phone; (iii) English speaking; (iv)age greater than 17; (v) no prior history of other cancers. There were 520 participants: 150 cases and 370 controls. Histology was determined by the KCR. The KCR helped to identify incident cases through rapid case ascertainment within three months of diagnosis. The aim of the population-based study was to explore the relationship between lung cancer and environmental risk factors, particularly exposure to trace elements such as arsenic, chromium, and radon on the development of lung cancer.

Study Design

This was a case-control study which analyzed nutrition data previously collected for both cases (n=150) and controls (n=370). The objective of this study was to examine the impact of nutrition on lung cancer histology in Kentucky. We aimed to look at differences between cases and controls in regards to population characteristics and nutritional intake. More specifically, we wanted to investigate the association between high sugar foods and the risk of different histological subtypes of lung cancer while controlling for potential confounding variables. We also compared odds of high-sugar diet between cases and controls to determine if this was associated with developing lung cancer.

Data Collection

Data for lung cancer cases were obtained from the Kentucky Cancer Registry (KCR). Diet was assessed via a self-reported dietary screener from the National Health and Nutrition Examination Survey (NHANES). This was one of eight sections in the original study, the others being demographics, occupational history, residential history, personal tobacco use, physical activity, family history, and health views. For our study, we utilized the dietary questionnaire to analyze participant's answers in regards to participant characteristics, case/control status, and histological type. Covariates were identified based on the literature review.

Variables Examined

Dietary variables that were examined included fruit, spinach, fried potatoes, other potatoes, other vegetables, whole grain, processed meat, red meat, pure juice, sweetened drinks, sugar soda, sugar in coffee, cereal, cereal with milk, candy, cookies, doughnuts, and ice cream. We also created two new variables which combined existing variables. We created a variable to

characterize intake of all sugary foods that included the following items: sweetened drinks, sugar soda, sugar coffee, candy, cookies, doughnuts, and ice cream. Our second created variable was "fruits and vegetables" which combined the existing variables: fruit, spinach, and other vegetables. Participants were also asked to answer based on how they usually ate or drank during a typical month when they were feeling healthy and were asked to input how many times per month each food item was eaten. Participants could answer as "never", "refused to answer", or they could write in their answer.

Histology information was obtained from the KCR. For our study, histology was broken down into 4 groups: adenocarcinoma, small cell, squamous cell, and other types. Cancer of the lung was defined by. Relevant codes from the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) included: adenocarcinoma (8015, 8050, 8140, 8141, 8143-8145, 8147, 8190, 8201, 8211, 8250-8255, 8260, 8290, 8310, 8320, 8323, 8333, 8401, 8440, 8470, 8471, 8480, 8481, 8490, 8503, 8507, 8550, 8570, 8571, 8572, 8574, 8576), squamous cell: (8051, 8052, 8070-8078, 8083, 8084, 8090, 8094, 8120, 8123), small cell: (8002, 8041-8045) and others: (all remaining types).

Demographic Covariates

Several covariates available from survey data could potentially confound the association between nutrition and lung cancer histology. Potentially confounding demographic covariates included in our analysis were gender (male or female), age (<55, 55-64, 65-74, 75+), BMI (<18.5 or "underweight", 18.5-24.9 or "healthy", 25.0-29.9 or "overweight", and 30.0+ or "obese"), marital status (married, previously married, or never married), education status (< high school, high school, college and beyond), health care status (has no healthcare, has health care, or

refused to answer), race (non-Hispanic white or other), and smoking status (never, former, or current).

We created low, medium, and high tertiles for the high sugar frequency variable. Low frequency was defined as high-sugar foods were consumed less than 30 times per month, medium was between 30-89 times per month, and high was explained as if a participant consumed a high-sugar food 90 times or more per month. The tertiles for frequency of high sugar consumption was based on the distribution of high sugar food consumption per month.

Statistical Methods

We first examined participant characteristics in relation to lung cancer to identify important covariates, using a chi-squared test. Next, we examined the median, interquartile range, and range for consumption of each food item of interest. P-values for examining the difference between cases (stratified by histology and all together) and controls were based on the Kruskal-Wallis test since the dietary data were not normally distributed. We also computed unadjusted odds ratios and 95% confidence intervals for the association between high-sugar food consumption and lung cancer. Lastly, we conducted a logistic regression analysis to examine the relationship between high-sugar food consumption and lung cancer while adjusting for covariates. For all analyses, a $p < 0.05$ for a two-tailed test was considered significant.

Data were analyzed using SAS V9.4. Study protocol was ruled exempt by the IRB at the University of Kentucky since all data were already existing and de-identified.

IV. RESULTS

Table 1 displays the descriptive statistics for participants. Of 150 cases, about 41% were male and 59% were female, compared to 48% male and 52% female among controls. P-values showed that gender, age, health care status, and race were not significantly associated with lung cancer. Body mass index was significantly different between cases and controls (p=0.001) with cases less likely to be overweight (30% vs. 38%) or obese (31% vs. 42%). Marital status and educational attainment were both significantly (p=<0.001) associated with lung cancer with cases less likely to be married compared to controls (52% vs. 75%). The majority of cases reported having not completed high school while the number was much lower for controls (41% vs. 15%). It was less likely that cases had completed a college education or beyond compared to controls (26% vs. 47%). Smoking status was significant (p=<.0001) showing that the majority (50%) of controls were never smokers where the majority of cases (51%) identified as current smokers.

Table 2 shows the participant's demographic and histology information. We examined four main histology types for cases: adenocarcinoma, small cell carcinoma, squamous cell carcinoma, and other types. There were 61 (40%) of cases identified as adenocarcinoma, 19 (13%) as small cell carcinoma, 45 (30%) as squamous cell carcinoma, and 25 (17%) of other types. P-values show that out of the eight demographic categories, five showed statistical differences between histological subgroups: BMI (p=0.002), marital status (p=<0.001), education status (p=<0.001), race (p=0.014), and smoking status (p=<0.001). In regards to BMI, underweight is consistent in having the fewest participants in all histology subgroups with normal, overweight, and obese being spread throughout the subgroups. For marital status, "Other" has the highest married percentage at 72% while the other histology types are more evenly distributed between married

and previously married. Education status showed that adeno participants had received the highest percentage (34%) of attaining a college education or beyond compared to histological subgroups. Between, small cell, squamous cell, and other types, education status of less than high school is the highest percentage in all three categories. Non-Hispanic white was the predominant race among all histological subgroups. Squamous cell and other had no participants who identified as never smokers. All histological groups (adeno 48%, small cell 78%, and other 64%), with the exception of squamous cell (40%), had the majority of participants identify as current smokers.

Table 3 compares dietary intake of cases (by histological type) and controls. P-values showed significant differences between cases and controls with in regards to frequency intake of fruit ($p=0.016$), all vegetables ($p=0.0235$), fruits and vegetables combined ($p=0.004$), fried potatoes ($p=0.006$), whole grains ($p=0.004$), and processed meat ($p=0.011$). The median intake of fruit for controls was 16 (IQR=22) times per month, which was higher than for each of the histological types. All vegetable intake was consistent between all subgroups and controls with a frequency of between 30-34 times per month. Fruit and vegetable intake combined was highest in controls with a median intake of 53.5 (IQR=25.8) and lowest median for small cell (44, IQR=45). Small cell, squamous cell, and other types IQR=15, 9, and 11 respectively) shared the highest median score of 8 for fried potatoes, while controls had the lowest median score (4, IQR=8) for fried potatoes. Controls have the highest median value of 7 (IRQ=30) for whole grains, while small cell and squamous cell have the lowest median values of 0 (IQR=2 and 4, respectively). Controls have the lowest median value for processed meat at 5 (IQR=10). “Other” has the highest median value for processed meat at 11 (IQR=12).

Table 4 compares the frequency intake of sugary foods (high sugar and high processed) for cases and controls. P-values for significant differences between combined cases and controls include sugar soda (p=0.031), sweetened drinks (p=0.008), sugar coffee (p=0.005), doughnuts (p=0.001), and all sugary foods combined (p=<.001). Cases have the lowest median value for sugar soda; 1 (IQR=30) and other has the highest value at 30 (IQR 30). The median value for sweetened drinks is 0 for all of our groups. Controls have the lowest median of 2 (IQR=30) in regards to sugar coffee, while adeno, squamous cell, small cell, and other all have a median value of 30 (IQR=30, 60, 30, 30, respectively). Controls and small cell both have the lowest median value of 2 (IQR=6 and 8) for doughnuts while adeno, squamous, and "other" all have a value of 4 (IQR=14, 7, and 14). All sugary combined had a high median of 101 (IQR=65) for adeno and controls had the lowest frequency with a median of 76.5 (IQR=62.5).

Table 5 shows the distribution of participants in the high sugar category. Among cases, 66 (44%) self-reported to have a medium sugar intake per month. Controls self-reported a high sugar intake per month as the lowest percentage for the tertiles at 20%. Case's lowest tertile percentage was low frequency at 18%. Participants who consumed sugar at a high frequency per month were 2.2 times (95% CI: 1.292-3.927) more likely to have developed lung cancer than those who consumed sugar at a low frequency.

Table 6 shows our logistic regression model of lung cancer in relation to previously identified significant covariates from our bivariate analysis among cases and controls. The analysis showed that there were significant differences with gender, BMI, marital status, education status, and smoking status. Females were 1.6 times more likely (95% CI: 1.045-2.493) of having developed

cancer than males. Participants with a BMI classified as underweight were 1.2 (95% CI: 0.377-4.105) times more likely than other classifications compared to a normal weight classification of developing lung cancer. Being previously married showed to be 2.4 (95% CI: 1.511-3.801) times greater of having lung cancer compared to those who were currently married. Having attained less than a high school level education had a higher chance of participants having developed lung cancer (OR=1.000), compared to those who had attained a higher level of education or beyond. If a participant was a current smoker, their chance of developing lung cancer compared to a never smoker was 35.4 times higher (95% CI: 14.750-85.131). Finally, participants consuming high sugared foods at a high frequency per month had a 1.1 times greater chance (95%CI: 0.599-2.105) of developing lung cancer compared to those who consumed high sugary foods at a low frequency. A goodness of fit test based on Pearson's Chi-square (deviance = 1.000 and Pearson = 0.6701) showed that there is no evidence to reject the null hypothesis, which is that the fitted model is correct.

V. DISCUSSION

Primary Findings

The purpose of this study was to first examine the impact of nutrition on lung cancer risk and histology for patients in Kentucky. We also wanted to investigate potential associations with consumption frequency of high sugar foods in relation to lung cancer. In our study, we classified histology into 4 groups: adeno, small cell, squamous cell, and other. Between cases (N=150) and controls (N=370), our primary findings show that in regards to healthful foods, controls tended to have a more nutrient dense food intake and more frequently ate fruit, vegetables, fruit and vegetables combined, and whole grains per month compared to all histological groups. Controls

also less often consumed processed meat and fried potatoes compared to all histological groups. Significant differences among combined cases and controls include fruit (p=0.016), vegetables (p=0.0235), fruit and vegetables combined (p=0.004), fried potatoes (p=0.006), whole grains (p=0.004), and processed meat (p=0.011). In regards to high sugar and high processed foods, cases tended to more frequently eat sugary food items compared to controls per month. Controls consumed less frequently sugar soda, coffee with sugar added in, and all sugary foods combined compared to all histological types. There were significant differences among combined cases and controls in regards to sugar soda (p=0.031), sweetened drinks (p=0.008), coffee with sugar added in (p=0.005), doughnuts (p=0.001), and all sugary foods combined (p=<.001). We saw that in regards to the distribution of participants in the high sugar category, that consuming sugar intake at a high frequency per month was 2.2 times (95% CI: 1.292-3.927) more likely to have developed lung cancer. Finally, our logistic regression showed that among cases and controls, those who had a BMI classified as underweight were 1.2 times more likely (95% CI: 0.377-4.105; p=0.0198) of having lung cancer compared to those who had a BMI within a normal range. Participants who were previously married were 2.4 times more likely (95% CI: 1.511-3.801; p=<0.0010 of having lung cancer compared to those who were married. Education status showed that those who had attained a high school education (95% CI: 0.225-0.657) or a college education and beyond (95% CI: 0.208-0.631) were more likely to not have lung cancer compared to those who had achieved less than a high school education (p=<.001). For smoking status, those who were either former or current smokers were 17.6 (95% CI: 7.422-42.006) and 35.4 (95% CI: 14.750-85.131) respectively more likely to have developed lung cancer compared to those who had never smoked (p=<.001). Finally, with frequency of sugar intake, those who had

frequently consumed high sugar were 1.1 times more likely (95% CI: 0.599-2.105) to have lung cancer compared to those who had consumed sugar at a low frequency per month (p=0.0987).

Comparisons with Other Studies

Our study was unique because we examined high sugar and highly processed foods in our analysis, but we can still make comparisons to previous studies. Previous studies have shown that fruits and vegetables are a protective factor against lung cancer development and that consumption is inversely associated with lung cancer risk (Buchner, et al., 2010). We can see in our study that controls generally ate more fruits and vegetables than cases. Like our study, Buchner et al. (2010) relied on extensive self-administered lifestyle and dietary questionnaires. Their study differed from ours in use of the multivariable cox proportional hazard models to analyze the data. Generally, our results were similar to that of other studies.

Strength and Limitations

Our study has several limitations. First, our study is subject to recall bias. Participants answered the dietary questionnaire on their own regarding their demographics and food consumption. It is possible that participants may not have recalled accurately or honestly. Secondly, our study has small numbers, which hindered our ability to detect significant differences between the different histological subtypes. Our analysis was limited mostly to non-Hispanic white residents of Appalachia, with others races/ethnicities accounting for only about 3% of participants. Therefore, our results may not be generalizable to other populations. Finally, it is unknown whether time period of exposure has any effect on lung cancer development or histological type. This could be an area of interest for future work and studies. Despite the above-mentioned limitations, a great strength was that our study examined an area of lung cancer

histology that had not yet been analyzed. This information will be helpful to future research and studies. This was also a population-based study which makes this more powerful.

Conclusion

In summary, our study showed that controls who had not developed lung cancer consumed more nutrient dense, less sugary foods per month compared to cases who had developed lung cancer. Future research in this area could benefit from a more comprehensive dietary survey, since the NHANES Dietary Screener only features a few dozen types of foods, and is designed to be completed in a short amount of time. Furthermore, a larger sample size would enable stratification by histological type. This is an important consideration, since various histological types of lung cancer might result from differences in exposures.

VI. TABLES

Table 1: Participant characteristics

Demographics	Cases	Controls	P-Values
Gender	150 (28.85%)	370 (71.15%)	0.196
Men	62 (41.33%)	176 (47.57%)	
Women	88 (58.67%)	194 (52.43%)	
Age			0.922
<55 yrs.	33 (22.00%)	81 (21.90%)	
55-64 yrs.	53 (35.33%)	126 (34.05%)	
65-74 yrs.	45 (30.00%)	120 (32.43%)	
75+ yrs.	19 (12.67%)	43 (11.62%)	
BMI			0.001
Underweight	8 (5.33%)	8 (2.16%)	
Normal	51 (34.00%)	67 (18.11%)	
Overweight	45 (30.00%)	140 (37.84%)	
Obese	46 (30.67%)	155 (41.89%)	
Marital Status			<0.001
Married	78 (52.00%)	280 (75.68%)	
Previously Married	66 (44.00%)	80 (21.62%)	
Never Married	5 (3.33%)	10 (2.70%)	
MISSING	1 (0.67%)	0	
Education Status			<.001
<High School	62 (41.33%)	56 (15.14%)	
High School	48 (32.00%)	138 (37.29%)	
College+	39 (26.00%)	175 (47.30%)	
MISSING	1 (0.67%)	1 (0.27%)	
Health Insurance Status			0.961
No health insurance	11 (7.33%)	29 (7.84%)	
Has health insurance	129 (86.00%)	334 (90.27%)	
Refused to answer	0	1 (0.27%)	
MISSING	10 (6.67%)	6 (1.62%)	
Race			0.321
White, non-Hispanic	145 (96.67%)	363 (98.11%)	
Other*	5 (3.33%)	7 (1.89%)	
Smoking Status			<0.001
Never	6 (4.00%)	185 (50.00%)	
Former	67 (44.67%)	117 (31.62%)	
Current	77 (51.33%)	67 (18.11%)	
MISSING	0	1 (0.27%)	

Note: P-values are based on Chi-squared test.
*Other category includes: African-American, Asian, and Hispanic.

Table 2: Participant's Demographic and Histology Information

Demographics	Adeno N (%)	Small Cell N (%)	Squamous Cell N (%)	Other N (%)	P-Values
Gender	61 (40.67)	19 (12.67)	45 (30.00)	25 (16.67)	0.117
Men	20 (32.79)	6 (31.58)	22 (48.89)	14 (56.00)	
Women	41 (67.21)	13 (68.42)	23 (51.11)	11 (44.00)	
Age					0.5808
<55 yrs.	14 (22.95)	6 (31.58)	7 (15.56)	6 (24.00)	
55-64 yrs.	20 (32.79)	7 (36.84)	16 (35.56)	10 (40.00)	
65-74 yrs.	18 (29.51)	5 (26.32)	16 (35.56)	6 (24.00)	
75+ yrs.	9 (14.75)	1 (5.26)	6 (13.33)	3 (12.00)	
BMI					0.002
Underweight	4 (6.56)	1 (5.26)	1 (2.22)	2 (8.00)	
Normal	25 (40.98)	1 (5.26)	13 (28.89)	12 (48.00)	
Overweight	14 (22.95)	11 (57.89)	14 (31.11)	6 (24.00)	
Obese	18 (29.51)	6 (31.58)	17 (37.78)	5 (20.00)	
Marital Status					<0.001
Married	30 (49.18)	9 (47.37)	21 (46.67)	18 (72.00)	
Previously Married	28 (45.90)	9 (47.37)	22 (48.89)	7 (28.00)	
Never Married	3 (4.92)	1 (5.26)	1 (2.22)	0	
MISSING	0	0	1(2.22)	0	
Education Status					<0.001
<High School	20 (32.79)	9 (47.37)	23 (51.11)	10 (40.00)	
High School	20 (32.79)	6 (31.58)	15 (33.33)	7 (28.00)	
College+	21 (34.43)	4 (21.05)	6 (13.33)	8 (32.00)	
MISSING	0	0	1 (2.22)	0	
Health Insurance Status					0.2539
No health insurance	7 (11.48)	0	4 (8.89)	0	
Has health insurance	49 (80.33)	18 (94.74)	38 (84.44)	24 (96.00)	
Refused to answer	0	0	0	0	
MISSING	5 (8.20)	1 (5.26)	3 (6.67)	1 (4.00)	
Race					0.014
White, non-Hispanic	59 (96.72)	19 (100)	45 (100)	22 (88.00)	
Other*	2 (3.28)	0	0	3 (12.00)	
Smoking Status					<0.001
Never	5 (8.20)	0	1 (2.22)	0	
Former	27 (44.26)	5 (26.32)	26 (57.78)	9 (36.00)	
Current	29 (47.54)	14 (73.68)	18 (40.00)	16 (64.00)	

Note: P-values are based on Kruskal-Wallis test.
*Other category includes: African-American, Asian, and Hispanic

Table 3: Fruit, vegetable, and whole grain intake for cases by histology and controls

Food Item	Adeno	Small Cell	Squamous Cell	Other	Cases Combined	Controls	P-Value
Fruit							0.016
Median	15	12	11	15	15	16	
IQR (Q1-Q3)	26 (4-30)	16 (4-20)	27 (3-30)	10 (10-20)	26 (4-30)	22 (8-30)	
Range (Min-Max)	60 (0-60)	29 (1-30)	60 (0-60)	30 (0-30)	60 (0-60)	90 (0-90)	
Missing	0	0	3	0	3	2	
Pure Juice							0.306
Median	4	1	2	1.5	2	2	
IQR (Q1-Q3)	30 (0-30)	12 (0-12)	16 (0-16)	20 (0-20)	20 (0-20)	12 (0-12)	
Range (Min-Max)	90 (0-90)	30 (0-30)	30 (0-30)	84 (0-84)	90 (0-90)	60 (0-60)	
Missing	2	0	6	1	9	19	
All Vegetables							0.0235
Median	31	30	32	32	31	34	
IQR (Q1-Q3)	15 (23-38)	25 (9-34)	24 (18-42)	14 (24-38)	18 (20-38)	16 (26-40)	
Range (Min-Max)	58 (2-60)	43 (2-45)	58 (2-60)	52 (8-60)	58 (8-60)	120 (0-120)	
Missing	0	0	3	0	3	2	
Fruit and Vegetables Combined							0.004
Median	50	44	46	48	47	53.5	
IQR (Q1-Q3)	28 (33-61)	45 (13-58)	30 (32-62)	26 (36-62)	29 (32-61)	28.5 (36-64.5)	
Range (Min-Max)	87 (3-90)	69 (3-72)	117 (3-120)	65 (10-75)	117 (3-120)	170 (0-170)	
Missing	0	0	3	0	3	2	
Fried Potatoes							0.006
Median	6	8	8	8	8	4	
IQR (Q1-Q3)	10 (3.5-13.5)	15 (0-15)	9 (3-12)	11 (4-15)	9 (3-12)	8 (2-10)	
Range (Min-Max)	30 (0-30)	30 (0-30)	30 (0-30)	30 (0-30)	30 (0-30)	30 (0-30)	
Missing	1	0	5	1	7	12	
Other Potatoes							0.840
Median	8	10	8	8	8	8	
IQR (Q1-Q3)	11 (2.5-13.5)	12 (3-15)	8 (4-12)	11 (4-15)	8 (4-12)	8 (4-12)	
Range (Min-Max)	30 (0-30)	30 (0-30)	124 (0-124)	30 (0-30)	124 (0-124)	30 (0-30)	
Missing	1	0	5	1	7	6	
Whole Grain							0.004
Median	4	0	0	4	1	7	
IQR (Q1-Q3)	30 (0-30)	2 (0-2)	4 (0-4)	30 (0-30)	16 (0-16)	30 (0-30)	
Range (Min-Max)	30 (0-30)	30 (0-30)	30 (0-30)	30 (0-30)	30 (0-30)	60 (0-60)	
Missing	2	0	9	2	13	12	
Processed Meat							0.011
Median	8	8	8	11	8	5	
IQR (Q1-Q3)	13 (2-15)	11 (4-15)	11 (4-15)	12 (4-16)	11 (4-15)	10 (2-12)	
Range (Min-Max)	30 (0-30)	30 (0-30)	30 (0-30)	30 (0-30)	30 (0-30)	30 (0-30)	
Missing	1	0	4	1	6	9	
Red Meat							0.195
Median	8	15	12	8	10	10	
IQR (Q1-Q3)	16 (4-20)	12 (8-20)	26 (4-30)	26 (4-30)	26 (4-30)	12 (4-16)	
Range (Min-Max)	40 (0-40)	28 (2-30)	30 (0-30)	29 (1-30)	40 (0-40)	60 (0-60)	
Missing	0	0	4	0	4	4	

Note: Median, IQR, and Range for number of times food eaten per month. P-values for combined cases and controls are based on the Kruskal-Wallis test.

Table 4: High-sugar food intake for cases by histology and controls

Food Item	Adeno	Small Cell	Squamous Cell	Other	Cases Combined	Controls	P-Value
Sugar Soda							0.031
Median	8	5	2	30	4	1	
IQR (Q1-Q3)	30 (0-30)	30 (0-30)	23 (0-23)	30 (0-30)	30 (0-30)	30 (0-30)	
Range (Min-Max)	90 (0-90)	60 (0-60)	120 (0-120)	90 (0-90)	120 (0-120)	299 (0-299)	
Missing	1	0	5	2	8	26	
Sweetened Drinks							0.008
Median	0	0	0	0	0	0	
IQR (Q1-Q3)	5.5 (0-5.5)	4 (0-4)	2 (0-2)	1.5 (0-1.5)	4 (0-4)	0	
Range (Min-Max)	60 (0-60)	30 (0-30)	90 (0-90)	20 (0-20)	90 (0-90)	60 (0-60)	
Missing	3	0	9	3	15	39	
Sugar Coffee							0.005
Median	30	30	30	30	6	2	
IQR (Q1-Q3)	30 (0-30)	60 (0-60)	30 (0-30)	30 (0-30)	30 (0-30)	30 (0-30)	
Range (Min-Max)	90 (0-90)	299 (0-299)	299 (0-299)	240 (0-240)	299 (0-299)	150 (0-150)	
Missing	0	0	9	2	11	11	
Candy							0.078
Median	4	2	4	15.5	4	8	
IQR (Q1-Q3)	13 (2-15)	15 (0-15)	9.5 (0.5-10)	28 (2-30)	14 (1-15)	14 (2-16)	
Range (Min-Max)	30 (0-30)	30 (0-30)	30 (0-30)	30 (0-30)	30 (0-30)	90 (0-90)	
Missing	1	0	5	1	7	15	
Cookies							0.237
Median	5	4	4	8	4	4	
IQR (Q1-Q3)	13 (2-15)	13 (2-15)	18 (2-20)	18 (2-20)	13 (2-15)	10 (2-12)	
Range (Min-Max)	30 (0-30)	30 (0-30)	30 (0-30)	30 (0-30)	30 (0-30)	30 (0-30)	
Missing	1	0	4	0	5	16	
Doughnuts							0.001
Median	4	2	4	4	4	2	
IQR (Q1-Q3)	14 (1-15)	8 (0-8)	7 (1-8)	14 (1-15)	11 (1-12)	6 (0-6)	
Range (Min-Max)	30 (0-30)	30 (0-30)	30 (0-30)	30 (0-30)	30 (0-30)	30 (0-30)	
Missing	1	0	4	0	5	17	
Ice Cream							0.788
Median	2	4	3.5	4	4	4	
IQR (Q1-Q3)	9 (1-10)	3 (1-4)	7 (1-8)	11 (1-12)	7 (1-8)	7 (1-8)	
Range (Min-Max)	30 (0-30)	30 (0-30)	20 (0-20)	30 (0-30)	30 (0-30)	30 (0-30)	
Missing	2	0	7	0	9	13	
All Sugary Foods Combined							<.001
Median	101	84	97.5	116	100	76.5	
IQR (Q1-Q3)	65 (67-132)	61 (59-120)	66 (66-132)	51 (81-132)	63 (67-130)	62.5 (48-110.5)	
Range (Min-Max)	202 (24-226)	422 (3-425)	450 (3-453)	297 (16-313)	450 (3-453)	349 (1-350)	
Missing	0	0	3	0	3	2	

Note: Median, IQR, and Range for number of times food eaten per month. P-values for combined cases and controls were based on the Kruskal-Wallis test.

Table 5: Distribution of participants in high sugar category and unadjusted odds ratio

Sugar Intake	Cases	Controls	Unadjusted Odds Ratio	95% Confidence Interval
Low	27 (18%)	80 (21.62%)	1.000 (ref.)	-
Medium	66 (44%)	215 (58.11%)	0.910	0.543-1.524
High	57 (38%)	75 (20.27%)	2.252	1.292-3.927

Table 6: Logistic regression model of lung cancer and significant covariates among cases and controls

Demographics	Adjusted Odds Ratio	95%Confidence Interval	P-Value
Gender			0.0309
Male	1.000 (ref.)	-	
Female	1.614	1.045-2.493	
BMI			0.0198
Underweight	1.245	0.377-4.105	
Normal	1.000 (ref.)	-	
Overweight	0.474	0.271-0.830	
Obese	0.500	0.288-0.869	
Marital Status			0.0010
Married	1.000 (ref.)	-	
Previously married	2.397	1.511-3.801	
Never married	1.423	0.419-4.828	
Education Status			<.0001
<High School	1.000 (ref.)	-	
High School	0.385	0.225-0.657	
College+	0.362	0.208-0.631	
Smoking Status			0.0003
Never	1.000 (ref.)	-	
Former	17.657	7.422-42.006	
Current	35.435	14.750-85.131	
Sugar Intake			0.0987
Low	1.000 (ref.)	-	
Medium	0.674	0.380-1.199	
High	1.123	0.599-2.105	

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IX. BIOGRAPHICAL SKETCH

Afton N. Wright earned a Bachelor of Science degree in Nutrition and Dietetics from Marywood University, in Scranton, PA in June of 2012. Upon graduation, Afton spent the next two years working in Seoul, South Korea and Auckland, New Zealand. In 2014, Afton came to the University of Kentucky as a candidate for the Masters of Public Health degree with an epidemiology concentration. During her time at the University of Kentucky, Afton served as a graduate assistant for Wellness Initiatives for Student Empowerment. In 2016, Afton moved to Montreal, Canada while continuing to work on her capstone. Finally, in 2018, she moved back to Pennsylvania and finished up her capstone.