



Risk factors for adenocarcinoma and squamous cell carcinoma of the esophagus and lung

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Background: The incidence of adenocarcinoma of the esophagus and lung has been rising in the USA along with a parallel rise in obesity. This study was conducted to investigate possible common risk factors for these two types of cancer.

Methods: Retrospective chart review was done and electronic medical records (EMR) of patients with a diagnosis of esophageal and lung cancer for the last 20 years were reviewed and data analyses done.

Results: Esophageal and lung adenocarcinoma patients shared some common risk factors such as higher body mass index (BMI), diabetes mellitus (DM), hypertension, hyperlipidemia and gastroesophageal reflux disease (GERD).

Conclusions: This study shows that obesity, GERD and metabolic syndrome are common risk factors for adenocarcinoma of esophagus and lung. Obesity may be contributing to the increasing incidence of these two types of cancer.

Keywords: Esophageal neoplasms; lung neoplasms; obesity

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Introduction

The incidence of adenocarcinoma of the esophagus and lung has been rising in developed countries and surpassing the occurrence of its squamous cell counterpart (1-4). The only confirmed risk factor for esophageal adenocarcinoma is Barrett's esophagus, which is a consequence of gastroesophageal reflux disease (GERD). No risk factor has been found to be predictive of adenocarcinoma of the lung in non-smokers. Since the incidence of both these cancers is rising in the US along with a parallel increase in obesity and the metabolic syndrome, we investigated possible risk factors for these two types of cancer.

Methods

A retrospective chart review using electronic medical records (EMR) was performed after Institutional Review Board (IRB) approval. EMR of patients with a confirmed diagnosis of esophageal and lung cancer at the Dayton Veterans Affairs Medical Center (DVAMC) between 1995 and 2015 (20 years) were reviewed. The following data were collected from the patients' charts: age, sex, race, BMI (body mass index), smoker or not, history of alcohol abuse, personal health history, list of medications, type of cancer, and year of diagnosis. The information was collected on a Microsoft Excel spread sheet.

The cohort was divided into four groups:

Table 1 Characteristics of patients with esophageal adenocarcinoma and squamous cell carcinoma

Characteristic	EA (n=102)	ESCC (n=50)	P value
Age, years (mean \pm SD)	66.65 \pm 9.79	66.86 \pm 8.98	0.86
BMI (mean \pm SD)	25.08 \pm 6.46	20.70 \pm 6.56	<0.001
Males (%)	100	96	0.11
White race (%)	95	56	<0.001
Current or ex-smokers (%)	87	100	0.01
Current or ex-alcoholic (%)	38	64	0.008
Diabetes mellitus (%)	33	14	0.012
Hypertension (%)	61	46	0.09
Hyperlipidemia (%)	55	24	<0.001
Coronary artery disease (%)	29	14	0.038
GERD (%)	60	24	<0.001
COPD (%)	23	42	0.013
Statin (%)	42	14	0.001
PPI (%)	55	18	<0.001
ASA (%)	45	15	0.07
Metformin (%)	15	2	0.016

EA, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GERD, gastroesophageal reflux disease; COPD, chronic obstructive pulmonary disease; PPI, proton pump inhibitors; ASA, aspirin.

- (I) Esophageal adenocarcinoma;
- (II) Esophageal squamous cell carcinoma;
- (III) Lung adenocarcinoma;
- (IV) Lung squamous cell carcinoma.

Patients with metastatic lung cancer, small cell lung cancer (SCLC), and large cell lung cancer were excluded from the study.

Statistical analysis

Baseline demographic and clinical data were analyzed with the independent samples Mann-Whitney test for continuous variables and the chi square test or Fisher's Exact test for categorical variables.

Results

A total of 152 patients were identified with a diagnosis of esophageal cancer. Of these, 102 were found to have esophageal adenocarcinoma and 50 had esophageal squamous cell carcinoma. Compared to esophageal

squamous cell carcinoma cases, esophageal adenocarcinoma patients were more likely to be white (95% *vs.* 56%, $P<0.001$), have a higher BMI (25.08 \pm 6.46 *vs.* 20.70 \pm 6.56, $P<0.001$), diabetes mellitus (DM) (33% *vs.* 14%, $P=0.012$), hyperlipidemia (55% *vs.* 24%, $P<0.001$), coronary artery disease (29% *vs.* 14%, $P=0.038$), and GERD (60% *vs.* 24%, $P<0.001$). They were also more likely to be taking proton pump inhibitors (PPI) (55% *vs.* 18%, $P<0.001$), statins (42% *vs.* 14%, $P=0.001$), and metformin (15% *vs.* 2%, $P=0.016$). Esophageal squamous cell carcinoma patients were more likely to be smokers or ex-smokers (100% *vs.* 87%, $P=0.01$), alcoholics or ex-alcoholics (64% *vs.* 38%, $P=0.008$), and have chronic obstructive pulmonary disease (COPD) (42% *vs.* 23%, $P=0.013$) compared to esophageal adenocarcinoma patients (see *Table 1*).

A total of 314 patients were identified with a diagnosis of lung cancer. Twenty-eight patients were excluded from the study because they had metastatic adenocarcinoma of the lung, SCLC, or large cell lung cancer. Of the eligible 286 patients, 162 had primary adenocarcinoma of the lung and 124 had squamous cell carcinoma of the lung.

Table 2 Characteristics of patients with lung adenocarcinoma and squamous cell carcinoma

Characteristic	LA (n=162)	LSCC (n=124)	P value
Age, years (mean \pm SD)	65.87 \pm 8.37	68.63 \pm 8.51	0.007
BMI (mean \pm SD)	26.25 \pm 6.11	23.29 \pm 5.29	<0.001
Males (%)	97.5	98.4	0.7
White race (%)	85.2	81.5	0.4
Current or ex-smokers (%)	98.1	100	0.15
Current or ex-alcoholic (%)	40.1	29.8	0.008
Diabetes mellitus (%)	27.2	22.6	0.38
Hypertension (%)	73.5	64.5	0.1
Hyperlipidemia (%)	50.6	40.3	0.08
Coronary artery disease (%)	34	27.4	0.24
GERD (%)	43.8	20.2	<0.001
COPD (%)	50.6	91.9	<0.001
Statin (%)	46.9	38.7	0.17
PPI (%)	32.7	15.3	0.001
ASA (%)	63	56.5	0.27
Metformin (%)	9.9	3.2	0.029

LA, lung adenocarcinoma; LSCC, lung squamous cell carcinoma; GERD, gastroesophageal reflux disease; COPD, chronic obstructive pulmonary disease; PPI, proton pump inhibitors; ASA, aspirin.

Compared to lung squamous cell carcinoma patients, lung adenocarcinoma patients were more likely to be younger at the time of diagnosis (mean age in years 65.87 \pm 8.37 *vs.* 68.63 \pm 8.51, $P=0.007$), have a higher BMI (26.25 \pm 6.11 *vs.* 23.29 \pm 5.29, $P<0.001$), be a current or ex-alcoholic (40.1% *vs.* 29.8%, $P=0.008$), have GERD (43.8% *vs.* 20.2%, $P<0.001$), and use PPI (32.7% *vs.* 15.3%, $P=0.001$) and metformin (9.9% *vs.* 3.2%, $P=0.029$). The squamous cell cancer of the lung group was more likely to have COPD (91.9% *vs.* 50.6%, $P<0.001$) (see *Table 2*).

We then grouped the adenocarcinoma patients (esophagus and lung) (n=264) and the squamous cell carcinoma patients (esophagus and lung) (n=174) to examine common risk factors. The adenocarcinoma group was younger (mean age in years 66.17 \pm 8.93 *vs.* 68.12 \pm 8.65, $P=0.02$) and more likely to be white (89% *vs.* 74.1%, $P<0.001$), have higher BMI (25.8 \pm 6.25 *vs.* 22.55 \pm 5.78, $P<0.001$), DM (29.5% *vs.* 20.1%, $P=0.027$), hypertension (68.6% *vs.* 59.2%, $P=0.045$), hyperlipidemia (52.3% *vs.* 35.6%, $P=0.001$), GERD (50% *vs.* 21.3%, $P<0.001$), and more likely to be on PPI (41.3% *vs.* 16.1%, $P<0.001$),

statins (45.1% *vs.* 31.6%, $P=0.005$), and metformin (11.7% *vs.* 2.9%, $P=0.001$). The squamous cell group was more likely to have COPD (77.6% *vs.* 39.8%, $P<0.001$), and be a current or ex-smoker (100% *vs.* 95.5%, $P<0.001$) (see *Table 3*).

Discussion

In our study, esophageal and lung adenocarcinoma groups share some common risk factors that include obesity and its associated metabolic syndrome (diabetes, hypertension, hyperlipidemia) and GERD.

The association between GERD, obesity, and esophageal adenocarcinoma is well known (5-8). It is interesting to note the association between lung adenocarcinoma and these risk factors. To date GERD has been linked to different lung diseases but not to lung cancer. GERD can cause or worsen asthma, bronchitis, pneumonia, and pulmonary fibrosis (9). A single pilot study found an association between GERD and lung cancer but not specifically adenocarcinoma of the lung (10). Our study shows an association between

Table 3 Characteristics of patients with adenocarcinoma (esophagus and lung) and squamous cell carcinoma (esophagus and lung)

Characteristic	Adenoca (n=264)	SSC (n=174)	P value
Age, years (mean ± SD)	66.17±8.93	68.12±8.65	0.02
BMI (mean ± SD)	25.8±6.25	22.55±5.78	<0.001
Males (%)	98.5	97.7	0.72
White race (%)	89	74.1	<0.001
Current or ex-smokers (%)	95.5	100	<0.001
Current or ex-alcoholic (%)	39.4	39.7	0.99
Diabetes mellitus (%)	29.5	20.1	0.027
Hypertension (%)	68.6	59.2	0.045
Hyperlipidemia (%)	52.3	35.6	0.001
Coronary artery disease (%)	32.2	23.6	0.051
GERD (%)	50	21.3	<0.001
COPD (%)	39.8	77.6	<0.001
Statin (%)	45.1	31.6	0.005
PPI (%)	41.3	16.1	<0.001
ASA (%)	56.1	48.9	0.14
Metformin (%)	11.7	2.9	0.001

Adenoca, esophageal and lung adenocarcinoma; SSC, esophageal and lung squamous cell carcinoma; GERD, gastroesophageal reflux disease; COPD, chronic obstructive pulmonary disease; PPI, proton pump inhibitors; ASA, aspirin.

GERD and lung adenocarcinoma, which in part may explain the rising incidence of both esophageal and lung adenocarcinoma.

Our study shows that GERD, obesity, and metabolic syndrome are common risk factors for adenocarcinoma of lung and esophagus. Since obesity is the common predictor that contributes to and exacerbates GERD and other metabolic syndromes, it has become the costliest disease in the US.

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Footnote

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/amj.2018.02.04>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of Wright State University (No. SC # 6025). Informed consent was waived due to the retrospective nature of the study.

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References

1. Hur C, Miller M, Kong CY, et al. Trends in esophageal adenocarcinoma incidence and mortality. *Cancer*

- 2013;119:1149-58.
2. Zhang Y. Epidemiology of esophageal cancer. *World J Gastroenterol* 2013;19:5598-606.
 3. Dela Cruz CS, Tanoue LT, Matthy RA. Lung cancer: epidemiology, etiology, and prevention. *Clin Chest Med* 2011;32:605-44.
 4. Nakamura H, Saji H. Worldwide trend of increasing primary adenocarcinoma of the lung. *Surg Today* 2014;44:1004-12.
 5. Rubenstein JH, Scheiman JM, Sadeghi S, et al. Esophageal adenocarcinoma incidence in individuals with gastroesophageal reflux: synthesis and estimates from population studies. *Am J Gastroenterol* 2011;106:254-60.
 6. Hoyo C, Cook MB, Kamangar F, et al. Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled analysis from the International BEACON Consortium. *Int J Epidemiol* 2012;41:1706-18.
 7. Singh S, Sharma AN, Murad MH, et al. Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2013;11:1399-412.e7.
 8. Duggan C, Onstad L, Hardikar S, et al. Association between markers of obesity and progression from Barrett's esophagus to esophageal adenocarcinoma. *Clin Gastroenterol Hepatol* 2013;11:934-43.
 9. Gaude GS. Pulmonary manifestations of gastroesophageal reflux disease. *Ann Thorac Med* 2009;4:115-23.
 10. Vereczkei A, Horvath OP, Varga G, et al. Gastroesophageal reflux disease and non-small cell lung cancer. Results of a pilot study. *Dis Esophagus* 2008;21:457-60.

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