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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Serum Insulin, Glucose, Indices of Insulin Resistance, and Risk of Lung Cancer

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Abstract

Background: Although insulin may increase the risk of some cancers, few studies have examined fasting serum insulin and lung cancer risk.

Methods: We examined serum insulin, glucose, and indices of insulin resistance [insulin:glucose molar ratio and homeostasis model assessment of insulin resistance (HOMA-IR)] and lung cancer risk using a case-cohort study within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study of Finnish men. A total of 196 cases and 395 subcohort members were included. Insulin and glucose were measured in fasting serum collected 5 to 12 years before diagnosis. Cox proportional hazards models were utilized to estimate the relative risk of lung cancer.

Results: The average time between blood collection and lung cancer was 9.6 years. Fasting serum insulin levels were 8.7% higher in subcohort members than cases. After multivariable adjustment, men in the fourth quartile of insulin had a significantly higher risk of lung cancer than those in the first quartile [HR = 2.10; 95% confidence interval (CI), 1.12–3.94]. A similar relationship was seen with HOMA-IR (HR = 1.83; 95% CI, 0.99–3.38). Risk was not strongly associated with glucose or the insulin:glucose molar ratio ($P_{trend} = 0.55$ and $P_{trend} = 0.27$, respectively).

Conclusions: Higher fasting serum insulin concentrations, as well as the presence of insulin resistance, appear to be associated with an elevated risk of lung cancer development.

Impact: Although insulin is hypothesized to increase risk of some cancers, insulin and lung cancer remain understudied. Higher insulin levels and insulin resistance were associated with increased lung cancer risk. Although smoking cessation is the best method of lung cancer prevention, other lifestyle changes that affect insulin concentrations and sensitivity may reduce lung cancer risk. *Cancer Epidemiol Biomarkers Prev; 26(10); 1519–24. ©2017 AACR.*

Introduction

Lung cancer is the most common cancer worldwide, accounting for about 12.9% of all cancer incidence and 19.4% of all cancer deaths (1). Affecting men disproportionately more than women, lung cancer remains the leading cause of death for both genders in the United States (2). Despite medical advances in the treatment of lung cancer, 5-year survival rates in the United States remain rather poor at 17.4% (3).

Insulin is a peptide hormone released by pancreatic islet beta cells that is responsible for maintaining homeostatic regulation of glucose and energy metabolism. In response to rising glucose levels, insulin secretion functions in activating cell-membrane insulin receptors (IR), which increase the body's uptake not only of glucose, but also of proteins and various other molecules. Although insulin is crucial in human growth and development, it harbors antiapoptotic properties as well as acts as a growth factor by stimulating mitosis through the Akt pathway (4). Several studies have suggested a positive association between increased serum insulin and various other cancers (5–9), but no studies have examined the insulin association with lung cancer.

In order to study whether fasting serum insulin, glucose, or surrogate indices of insulin resistance [the molar ratio of insulin to glucose and the homeostasis model assessment of insulin resistance (HOMA-IR)] are associated with risk of lung cancer, we conducted a prospective case-cohort analysis of a large cohort of male smokers.

Materials and Methods

Study population

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study was a randomized, double-blind, placebo-controlled, primary prevention trial that was designed to test the efficacy of daily supplementation with α-tocopherol and β-carotene, in reducing lung cancer incidence among male smokers. As a secondary goal, the study was designed to evaluate whether supplementation would prove to have a protective effect against various other cancers, all-cause mortality, and cardiovascular disease (10, 11). Upon inception, the study was approved by the institutional review boards of the U.S. National Cancer Institute as well as the National Public Health Institute in Finland. In total, 29,133 men living in southwestern Finland

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were enrolled in this study between April 1, 1985, and June 30, 1988. Ages of the participants at enrollment ranged between 50 and 69 years, and all were current smokers of 5 or more cigarettes per day as part of the inclusion criteria. Exclusion criteria consisted of previous cancer diagnosis, diagnosis of another serious illness, reported daily supplementation of >20 mg of vitamin E, >20,000 IU of vitamin A, >6 mg of β-carotene, or the use of anticoagulants. Based upon a 2 × 2 factorial design, subjects were randomly assigned to one of four intervention groups for 5 to 8 years (mean, 6.1 years): 50 mg of dl-α-tocopheryl acetate, 20 mg of β-carotene, both, or placebo in one capsule per day. At baseline, written informed consent was obtained from all participants. Although the intervention ended on April 30, 1993, follow-up of the ATBC cohort continues through the Finnish Cancer Registry.

Selection of case and subcohort members

In an attempt to minimize the effect of preclinical disease on serum biochemistry, case subjects were defined as individuals diagnosed with lung cancer at least 5 years after the baseline serum sample was collected (12). Upon randomly selecting 200 men diagnosed with lung cancer, an additional 400 subcohort members were randomly chosen from the entire ATBC Study population who were alive at the beginning of the 5th follow-up year. After exclusion of individuals with missing serum data, 196 case members and 395 subcohort members remained for analysis. Due to the nature of the case-cohort study design, subcohort member selection could include cancer cases that were diagnosed after the 5th follow-up year, and a subject could be selected as both a case and a subcohort member. Thirteen subcohort members developed lung cancer during follow-up and were counted as cases; thus, our final analysis includes 209 cases and 382 noncases. To ensure proper case selection, medical records were evaluated by two oncologists in order to confirm staging and diagnoses through the use of the American Joint Committee on Cancer criteria (13). All 209 cases, with the exception of one individual, had available histology and/or cytology results that were validated by a pathologist. Of these samples, 35% were classified as squamous cell carcinoma, 15% adenocarcinoma, 24% small cell carcinoma, and 26% other; in addition, 22% were categorized as stage 1, 12% stage 2, 24% stage 3, and 42% stage 4.

Data and specimen collection

At baseline, information regarding risk factors and medical history was collected through a self-administered questionnaire. Questions included, but were not limited to, smoking history, physical activity, diabetes status, and family history of cancer. A validated food frequency questionnaire that consisted of inquiries regarding portion size and frequency of consumption of 276 foods and beverages in the past 12 months was used in order to estimate dietary intake (14). In addition to the questionnaires, a fasting serum sample was collected from participants on their first visit and stored at −70°C, height and weight were measured, and body mass index (BMI) calculated [(weight in kilograms)/(height in meters)^2] (11).

Laboratory assays

Insulin concentrations were obtained through the use of a double-antibody immunochemiluminometric assay completed on an Access automated platform (Beckman Instruments). Serum glucose concentrations were ascertained using a hexokinase reaction on a Hitachi 912 Chemistry Analyzer (Boehringer Mannheim); resulting reaction products were assessed via spectrophotometric absorption at 340 nm. Samples obtained from case and subcohort subjects, along with blinded quality control duplicates, were included in each batch. The within-batch and between-batch coefficients of variation for insulin were 3.5% and 3.6%, respectively; for glucose, the coefficients of variation were 1.1% and 2.2%, respectively. The molar ratio of insulin to glucose as well as HOMA-IR, which is calculated as fasting insulin in microunits per milliliter x fasting glucose in millimoles per liter/22.5, was used as surrogate measures of insulin resistance (15).

Statistical analysis

Baseline characteristics reflective of demographic and serum data for both case and subcohort subjects were compared using χ^2 (for categorical variables) and *t* tests (for continuous variables). Correlations among the exposures and suspected confounding variables were assessed using Spearman rank order coefficient (Supplementary Table S1). In an attempt to create a parsimonious model, variable selection was made by first including covariates of greatest biological impact to the outcome of interest using both correlation coefficients and *a priori* knowledge regarding the onset of lung cancer. Cox proportional hazard (HR) was used to model the time to development of lung cancer with adjustment for the following known or suspected confounding factors: age, pack years, BMI, and family history of lung cancer. Because smoking is so strongly associated with lung cancer risk, smoking as a possible confounder was considered carefully. However, as the entire ATBC cohort were smokers, we found that adjustment for smoking had little impact on our results (Supplementary Table S2). In addition to pack-years, cigarettes smoked per day and years smoked were considered individually as potential confounders, but addition of each of these variables individually produced similar results to adjustment for pack-years (Supplementary Table S2). Thus, pack-years was used in the final analysis. Quartiles of insulin, glucose, the molar ratio of insulin to glucose, and HOMA-IR were defined by their distribution among the subcohort subjects and were individually included in the model as exposure variables, with the lowest quartile representing the reference category. All statistical tests were two-sided, and analyses were performed with SAS software version 9.4 (SAS Institute, Inc.).

Results

Baseline characteristics

The mean time between baseline blood serum collection and diagnosis of lung cancer among all cases was 9.6 years, with an average follow-up among noncase subjects of 12.7 years. When compared with those individuals in the subcohort group, case subjects were older, had a lower weight, BMI, and serum cholesterol, smoked more cigarettes per day and had a longer smoking history, and were more likely to have a family history of lung cancer (Table 1).

Serum concentrations of insulin and glucose, molar ratio of insulin to glucose, HOMA-IR, and lung cancer

Age-adjusted models suggested weakly inverse or no associations between levels of insulin, HOMA-IR, and the risk of lung cancer (Table 2). With the exception of glucose, these associations became positive with the addition of the following

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Table 1. Baseline characteristics [mean (SD) or number (percent)] of lung cancer case and subcohort subjects

Characteristic	Case subjects ($n = 196$)	Subcohort subjects ($n = 395$)	*P* value
Age, y	59.5 (5.07)	56.4 (4.99)	<0.0001
Height, cm	173 (6.46)	173.8 (6.00)	0.11
Weight, kg	75.6 (12.77)	80.5 (13.17)	<0.0001
BMI, kg/m^2	25.2 (3.71)	26.6 (3.92)	<0.0001
Number of cigarettes per day	22.9 (9.49)	20.5 (8.45)	0.002
Years of smoking	40.4 (6.91)	34.8 (8.52)	<0.0001
History of diabetes, %	6 (3.06)	17 (4.30)	0.46
Family history of lung cancer, %	24 (12.24)	29 (7.34)	0.03
Physical activity, % active	143 (72.96)	309 (78.23)	0.16
Energy intake, kcal/d	2,684 (754.24)	2,703 (783.45)	0.79
Dietary carbohydrate, g/d	263 (83.51)	266 (82.91)	0.61
Dietary protein, g/d	93.7 (26.2)	94.9 (26.64)	0.63
Serum cholesterol, mmol/L	6.1 (1.05)	6.4 (1.17)	0.02
Insulin, μU/mL	4.7 (3.52)	5.2 (4.11)	0.20
Glucose, mg/dL	99.2 (16.19)	103.4 (23.78)	0.03
Molar ratio of insulin to glucose	0.05 (0.03)	0.05 (0.03)	0.58
HOMA-IR	1.2 (1.02)	1.4 (1.82)	0.09

covariates: BMI, family history of lung cancer, and pack-years of smoking, with BMI being the covariable predominantly responsible for this change. After multivariable adjustment, we observed that individuals in the fourth quartile of insulin were statistically significantly more than twice as likely to develop lung cancer compared with those in the lowest quartile of insulin. Serum glucose was nonsignificantly inversely associated with risk (Table 2). Clinically, a fasting glucose concentration of 100 mg/dL or lower is considered to be within the normal range, and men with higher glucose had a suggestive inverse risk of developing lung cancer compared with men below this threshold [HR, 0.78; 95% confidence interval (CI), 0.58–1.04). In multivariable models, the directionality of the association for the molar ratio of insulin to glucose was similar to that for insulin; men with a higher molar ratio appeared to be at increased risk of lung cancer, although the association was not statistically significant. Similarly, we observed that the association between HOMA-IR and risk of lung cancer was also positive, with a borderline statistically significantly increased risk of lung cancer among men in the highest quartile of HOMA-IR (HR, 1.83; 95% CI, 0.99–3.38). When analyses were repeated to exclude individuals diagnosed with diabetes mellitus, the observed associations remained unchanged.

Both insulin and HOMA-IR were associated with higher risk of lung cancer, regardless of stage, although HRs were stronger for the lower stage cancers (multivariable-adjusted HR for Q4 vs. Q1: insulin HR = 2.85, 95% CI, 1.14–7.15,

Table 2. Association of quartiles of baseline serum insulin, glucose, molar ratio of insulin to glucose and HOMA-IR with lung cancer risk: ATBC Study

	Case subjects ($n = 196$)	Subcohort subjects ($n = 395$)	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[c]
Insulin, μU/mL					
≤2.70	66	100	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
>2.70 to ≤4.10	50	99	0.89 (0.55–1.43)	0.99 (0.61–1.61)	0.99 (0.59–1.67)
>4.10 to ≤6.10	32	101	0.50 (0.30–0.84)	0.71 (0.41–1.24)	0.80 (0.44–1.45)
>6.10	48	95	0.91 (0.56–1.47)	1.87 (1.04–3.36)	2.10 (1.12–3.94)
P_{trend}			0.06	0.01	0.02
Glucose, mg/dL					
≤92	68	99	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
>92 to ≤98	49	99	0.83 (0.52–1.33)	0.87 (0.55–1.39)	0.77 (0.46–1.28)
>98 to ≤107	48	100	0.76 (0.47–1.25)	0.86 (0.52–1.43)	0.86 (0.50–1.50)
>107	31	97	0.52 (0.31–0.88)	0.65 (0.37–1.13)	0.68 (0.38–1.20)
P_{trend}			0.10	0.50	0.55
Molar ratio of insulin to glucose					
≤0.03	60	98	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
>0.03 to ≤0.04	50	100	0.89 (0.55–1.44)	0.98 (0.61–1.60)	0.92 (0.55–1.55)
>0.04 to ≤0.06	46	98	0.72 (0.43–1.18)	0.96 (0.57–1.62)	1.05 (0.60–1.83)
>0.06	40	99	0.81 (0.49–1.32)	1.43 (0.81–2.52)	1.66 (0.89–3.06)
P_{trend}			0.59	0.48	0.27
HOMA-IR					
≤0.67	60	98	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
>0.67 to ≤1.02	50	100	0.91 (0.56–1.46)	0.99 (0.61–1.61)	0.94 (0.56–1.58)
>1.02 to ≤1.53	46	98	0.51 (0.30–0.87)	0.71 (0.41–1.25)	0.78 (0.43–1.44)
>1.53	40	99	0.86 (0.53–1.39)	1.62 (0.92–2.88)	1.83 (0.99–3.38)
P_{trend}			0.08	0.04	0.06

[a]Age-adjusted model.
[b]Age- and BMI-adjusted model.
[c]Model adjusted for age, BMI, family history of lung cancer, and pack-years of smoking.

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Table 3. Baseline serum insulin, glucose, molar ratio of insulin to glucose, and HOMA-IR stratified by lung cancer stage

	Low stage (I–II)		High stage (III–IV)		*P* for heterogeneity by stage
	Number of cases/ number of noncases	HR (95% CI)[a]	Number of cases/ number of noncases	HR (95% CI)[a]	
Insulin, μU/mL					
≤2.70	26/96	1.00 (ref.)	44/96	1.00 (ref.)	0.70
>2.70 to ≤4.10	16/97	0.89 (0.40–2.00)	35/97	1.08 (0.60–1.92)	
>4.10 to ≤6.10	8/100	0.56 (0.22–1.45)	25/100	0.97 (0.51–1.87)	
>6.10	20/89	2.85 (1.14–7.15)	34/89	1.94 (0.93–4.06)	
P_{trend}		0.01		0.23	
Glucose, mg/dL					
≤92	26/96	1.00 (ref.)	45/96	1.00 (ref.)	0.22
>92 to ≤98	18/93	0.63 (0.29–1.37)	37/93	0.85 (0.49–1.49)	
>98 to ≤107	15/99	0.59 (0.26–1.37)	33/99	0.96 (0.52–1.76)	
>107	11/94	0.54 (0.22–1.33)	23/94	0.76 (0.39–1.48)	
P_{trend}		0.48		0.84	
Molar ratio of insulin to glucose					
≤0.03	24/94	1.00 (ref.)	40/94	1.00 (ref.)	0.26
>0.03 to ≤0.04	15/97	0.66 (0.30–1.47)	37/97	1.10 (0.62–1.96)	
>0.04 to ≤0.06	16/98	0.98 (0.44–2.20)	30/98	1.07 (0.58–1.98)	
>0.06	15/93	1.76 (0.69–4.46)	31/93	1.71 (0.84–3.46)	
P_{trend}		0.24		0.46	
HOMA-IR					
≤0.67	26/95	1.00 (ref.)	43/95	1.00 (ref.)	0.89
>0.67 to ≤1.02	18/97	0.87 (0.41–1.85)	36/97	1.00 (0.56–1.80)	
>1.02 to ≤1.53	7/97	0.45 (0.16–1.24)	25/97	1.04 (0.54–2.03)	
>1.53	19/93	2.25 (0.89–5.69)	34/93	1.78 (0.87–3.61)	
P_{trend}		0.02		0.34	

[a]Model adjusted for age, BMI, family history of lung cancer, and pack-years of smoking.

P_{trend} = 0.009; HOMA-IR HR = 2.25, 95% CI, 0.89–5.69, P_{trend}=0.02; Table 3). None of the exposures assessed showed any meaningful differences across histologic subtypes (Supplementary Table S3).

Discussion

In this study, we found a statistically significant association between higher serum insulin and elevated risk of lung cancer. Similar trends were observed for HOMA-IR and the molar ratio of insulin to glucose, indicating an increased risk of lung cancer with greater insulin resistance. Fasting glucose was not associated with lung cancer.

Various studies have analyzed the potential role of insulin-like growth factors on the risk of lung cancer development and progression (16–21), and a few studies have demonstrated a positive association between insulin and lung cancer (21–23). Although insulin and insulin-like growth factor I (IGF-I) are related peptides with similar structure, they have different functions and may cause cancer through different biologic mechanisms. IGF-I is part of a larger IGF system of ligands and receptors that is thought to control growth, reproduction, and metabolism. Produced in the liver, IGF-I is primarily controlled by growth hormone and is involved in cell proliferation, migration, growth, and apoptosis (24). Insulin, on the other hand, is secreted from the β cells in the pancreas and is primarily responsible for the regulation, uptake, and metabolism of glucose in the body (25). That being said, growth hormone sensitivity in the liver is believed to be modulated by insulin, theoretically through the regulation of growth hormone receptor expression (26). Several papers have reported on the presence of IR overexpression in various malignancies, including breast, lung, colon, and thyroid (27–31). The IR is a binding site affiliated with both insulin and IGF-I (32). Increased insulin levels have been shown to potentially stimulate IR isoform-A (IR-A), leading to a reported association between obesity, insulin resistance, type 2 diabetes, and the risk of developing cancer (33).

Insulin resistance is characterized by the decreased responsiveness of target tissues to circulating insulin levels and is often a precursor to type 2 diabetes (34). The original HOMA-IR model was described in 1985 and is still used today in assessing β-cell function. In this study, the impact of HOMA-IR largely reflected that of insulin, with the greatest risk of lung cancer being depicted among the highest quartiles of insulin and HOMA-IR, after adjustment for age, BMI, family history, and pack-years of smoking. Increased levels of fasting serum insulin and HOMA-IR appeared to be more strongly associated with lower stage lung cancer, although this difference was not statistically significant. Whether this indicates a potential role of these factors on lung cancer initiation, rather than progression, requires further study. The association with increased insulin levels did not differ across the primary histologic subtypes of lung cancer (squamous cell carcinoma, adenocarcinoma, and small cell carcinoma). When an analysis was conducted to exclude those patients with diabetes mellitus reported at baseline ($n = 23$), the overall trends remained unchanged.

The ATBC Study provided prospectively collected fasting serum samples as well as other data regarding potential confounders, utilized laboratory quality control procedures, and had relatively long follow-up, which included the use of population-based cancer registry ascertainment of case subjects. In addition, the possibility of reverse causation has been minimized through the use of our study design that excluded cases diagnosed within the first 5 years after blood collection. Our investigation was limited in that the sample size was somewhat small for conducting stratified analyses, and only included white, Finnish male

smokers originally enrolled in a cancer prevention trial aimed at testing the effect of vitamin intervention on cancer incidence and mortality. Therefore, the results depicted in this article may or may not be generalizable to other populations. Nevertheless, we believe that this study provides evidence of the relation between insulin and indices of insulin resistance on lung cancer risk. In order to establish a role for insulin as a risk factor for lung cancer independent of smoking, studies among never smokers are needed.

In conclusion, our findings indicate that increased fasting serum insulin and insulin resistance are associated with higher risk of lung cancer. The associations require confirmation, but may have implications for nutrition, screening, and treatment of higher risk patients that could result in decreasing the burden of lung cancer. Although smoking cessation is the best known method to decrease lung cancer incidence, other lifestyle changes that may limit hyperinsulinemia and increase insulin sensitivity, such as avoiding overweight, healthy dietary changes, and increased physical activity, may affect lung cancer development, as well as reduce the risk of other chronic diseases.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: D. Albanes, A.M. Mondul
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.J. Weinstein, S. Männistö, D. Albanes
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): I. Argirion, S.J. Weinstein, A.M. Mondul
Writing, review, and/or revision of the manuscript: I. Argirion, S.J. Weinstein, S. Männistö, D. Albanes, A.M. Mondul
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S.J. Weinstein, S. Männistö
Study supervision: D. Albanes

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